NEW RESEARCH

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Thalamic Subregions and Obsessive-Compulsive Symptoms in 2,500 Children From the General Population

Cees J. Weeland, MD, Chris Vriend, PhD, Ysbrand van der Werf, PhD, Chaim Huyser, MD, PhD, Manon Hillegers, MD, PhD, Henning Tiemeier, PhD, Tonya White, MD, PhD, Odile A. van den Heuvel, MD, PhD

Objective: Pediatric obsessive-compulsive disorder (OCD) and clinically relevant obsessive-compulsive symptoms in the general population are associated with increased thalamic volume. It is unknown whether this enlargement is explained by specific thalamic subregions. The relation between obsessive-compulsive symptoms and volume of thalamic subregions was investigated in a population-based sample of children.

Method: Obsessive-compulsive symptoms were measured in children (9-12 years of age) from the Generation R Study using the Short Obsessive-Compulsive Disorder Screener (SOCS). Thalamic nuclei volumes were extracted from structural 3T magnetic resonance imaging scans using the ThalamicNuclei pipeline and regrouped into anterior, ventral, intralaminar/medial, lateral, and pulvinar subregions. Volumes were compared between children with symptoms above clinical cutoff (probable OCD cases, SOCS ≥ 6, n = 156) and matched children without symptoms (n = 156). Linear regression models were fitted to investigate the association between continuous SOCS score and subregional volume in the whole sample (N = 2500).

Results: Children with probable OCD had larger ventral nuclei compared with children without symptoms ($d = 0.25$, $p = .025$, false discovery rate adjusted $p = .126$). SOCS score showed a negative association with pulvinar volume when accounting for overall thalamic volume ($\beta = -0.057$, $p = .009$, false discovery rate adjusted $p = .09$). However, these associations did not survive multiple testing correction.

Conclusion: The results suggest that individual nuclei groups contribute in varying degrees to overall thalamic volume in children with probable OCD, although this did not survive multiple comparisons correction. Understanding the role of thalamic nuclei and their associated circuits in pediatric OCD could lead toward treatment strategies targeting these circuits.

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

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Obsessive-compulsive disorder (OCD) is a neurodevelopmental disorder associated with subtle structural brain abnormalities. It affects approximately 0.5%-1% of children and has a lifetime prevalence of 2%-3%.[1,2] Previous large-scale case-control analyses have found that children with OCD have a larger thalamic volume compared with children in a control group.[3] Recently, we replicated this finding in children with probable OCD (scoring above a clinical cutoff) compared with children without symptoms in a population-based sample from the Generation R Study.[4]

As a larger thalamus was found only in children and not adults, this could signify a trait specific to childhood-onset OCD and early stage of disease.[3] It could also indicate that developmental differences in thalamus structure and function play a role in the manifestation of the OCD phenotype in children. Indeed, the thalamus forms an integral part of the cortico-striato-thalamo-cortical (CSTC) circuits that govern various affective, cognitive, and sensorimotor functions implicated in the disorder, including fear extinction, response inhibition, and cognitive control.[5,6]

However, the thalamus is organized into functionally segregated nuclei, each with different projections and fulfilling different roles within the CSTC circuits. Given this organization, whole thalamic volume differences do not inform us about the functional significance in relation to the cognitive, sensorimotor, and emotional processes underlying the phenotype of OCD. Identifying whether thalamic differences are primarily driven by specific nuclei could pinpoint specific circuits that are more affected than others during early stages of the disorder. This provides a potential avenue for targeted treatment strategies, for instance, by applying cognitive-behavioral therapy, cognitive training, or neuromodulation tailored to target these circuits. In that way, this approach

forms a necessary incremental step in the translation of crude neuroimaging findings to their clinical applications.[5]

Few animal and human studies have investigated thalamic subregions in the context of OCD. Experimental work in monkeys demonstrated that overactivation of the ventral anterior and medial dorsal nuclei of the thalamus provokes compulsive behavior and anxiety-like states.[7] A recent study (N = 88) in humans found that adult OCD is associated with altered functional connectivity between posterior, occipital, and sensory regions of the thalamus and cortical connections.[8] Shape analysis in adult humans has revealed increased surface area in anterior and pulvinar nuclei in participants with OCD compared with participants in the control group.[9]

In vivo assessment of thalamic nuclei volumes in humans is challenging because most images from structural magnetic resonance imaging (MRI) scans provide limited contrast to enable accurate delineation of the internuclear borders. Nevertheless, recent advances in automated thalamus segmentation have enabled large-scale volumetric analysis of individual nuclei.[10] Iglesias *et al.*[10] created a histology-based probabilistic atlas within the FreeSurfer pipeline that enables automated segmentation of the thalamus into 25 nuclei.

In the current study, we used this atlas to investigate volumetric differences in 5 thalamic subregions (anterior, ventral, lateral, intralaminar/medial, pulvinar) between children with probable OCD and children without symptoms in a large population-based sample.[10] We also studied whether there is a linear relation between the number of obsessive-compulsive symptoms (OCS) and volume of these thalamic subregions. As this is the first study of volumetric differences within thalamic nuclei in the context of OCS among children and all subregions are potentially relevant from a functional perspective, we did not postulate an a priori hypothesis regarding which subregions show differences.

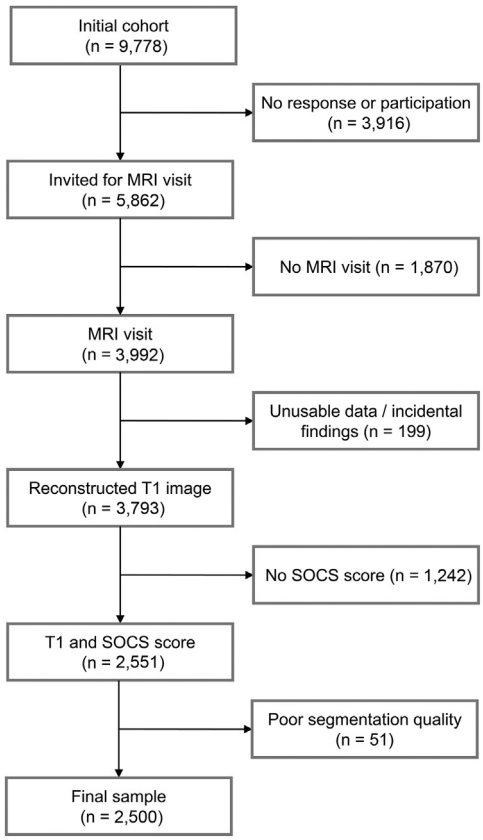
We conducted both a case-control and a dimensional analysis. The case-control analysis was performed to emulate previous clinical case-control studies such as the ENIGMA-OCD meta-analyses[3,11] and to align with our previous findings from the Generation R Study.[4] We complemented this with the continuous analysis to assess whether any structural findings related to OCS show a continuous association with severity and to align with previous studies that include subclinical OCS.[12]

METHOD

Participants

This study was embedded in the Generation R Study, a population-based birth cohort based in Rotterdam, The Netherlands.[13] In the Generation R Study, 9,778 pregnant women from Rotterdam were enrolled, and a total of 9,749 children were born between April 2002 and January 2006. Various health- and mental health–related aspects of pediatric development have been investigated from fetal life onward. Of this cohort, 3,992 children aged 9-12 years underwent an MRI scan of the brain between March 2013 and November 2015, from which 3,966 whole-brain structural T1-weighted images were obtained.[14] We excluded participants with an incomplete T1-weighted scan or failed FreeSurfer reconstruction, scanning artifacts from dental braces, major incidental findings in the brain,[15] or poor quality of the segmentation of the thalamic nuclei. Furthermore, participants without available data on OCS were excluded. The final sample comprised 2,500 children (Figure 1). The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre in and was conducted according to the Declaration of Helsinki. We obtained written informed consent from the legal representatives of the children.

FIGURE 1 Flowchart of Exclusion Steps Toward Final Sample



Note: *MRI = magnetic resonance imaging; SOCS = Short Obsessive-Compulsive Disorder Screener. Please note color figures are available online.*

Obsessive-Compulsive Symptoms and Diagnosis

We measured OCS with the Short Obsessive-Compulsive Disorder Screener (SOCS), rated by the primary caregiver.[16] The SOCS is a 7-item scale and includes items on compulsive behaviors measured on a 3-point Likert scale. A probable OCD cutoff of 6 or higher has good specificity (0.84) and high sensitivity (0.94) for detecting OCD in the general pediatric population.[16] We used the validated cutoff point to identify a probable OCD group for the case-control analysis and the continuous sum score for the test of linear association. Weighted sum scores were calculated in case of one missing item by multiplying the sum of the items by 7/6 (= 1.17). Participants with more than one missing item were excluded.

MRI Data Acquisition

We obtained structural MRI scans on a 3T Discovery MR750w GEM scanner (General Electric, Milwaukee, Wisconsin). Using an 8-channel head coil, a whole-brain high-resolution T1-weighted inversion recovery fast spoiled gradient recalled sequence was obtained. Raw T1-weighted images were manually quality checked during scanning and before preprocessing (see Supplement 1, available online, for details). Preprocessing and subcortical segmentation were performed using the subcortical pipeline within FreeSurfer, version 6.0.[17] The thalamus was segmented into 25 nuclei using the ThalamicNuclei pipeline in FreeSurfer (version 6.0.1 development).

Grouping of Thalamic Nuclei and Segmentation Quality

We divided the nuclei into 5 groups, based on functional and anatomical overlap: anterior, lateral, ventral, intralaminar/medial, and pulvinar (Table 1 and Figure 2) in accordance with the grouping used in the ThalamicNuclei pipeline that is based on the parcellation by Jones.[18] We combined the intralaminar/midline and medial group into one group because the nuclei within these groups show similar thalamocortical connection patterns.[19,20] We derived the volume of each nucleus group by computing the sum of the nuclei belonging to a group. Each image was visually inspected to assess whether the segmentation of the whole thalamus followed proper boundaries, as was done for our previous analysis.[4] The lateral and medial geniculate nuclei were excluded from the analyses owing to poor segmentation quality. We subsequently assessed the segmentation quality of the nuclei groups in three steps. First, we calculated the statistical outliers (below $Q_1 - 1.5 \times$ interquartile range or above $Q_3 + 1.5 \times$ interquartile range) of each nuclei group. Second, we compared the segmentation of the whole thalamic volume derived from the aseg and ThalamicNuclei pipelines by calculating the difference between the aseg derived volumes and the sum of the ThalamicNuclei derived nuclei volumes and identifying statistical outliers of these differences. Third, we quantified the degree of overlap between voxels labeled as white matter in the aseg segmentations and voxels labeled as thalamus in the ThalamicNuclei segmentations. High overlap may represent erroneously labeled tissue. We identified the statistical outliers with the highest overlap. Together, these 3 steps provided a group of statistical outliers suspect of segmentation errors. The segmentations of these participants were visually inspected (n = 262). During visual inspection, we excluded only participants in case of nuclei groups with a biologically implausible segmentation (n = 51). The resulting participants were eligible for analysis (N = 2,500).

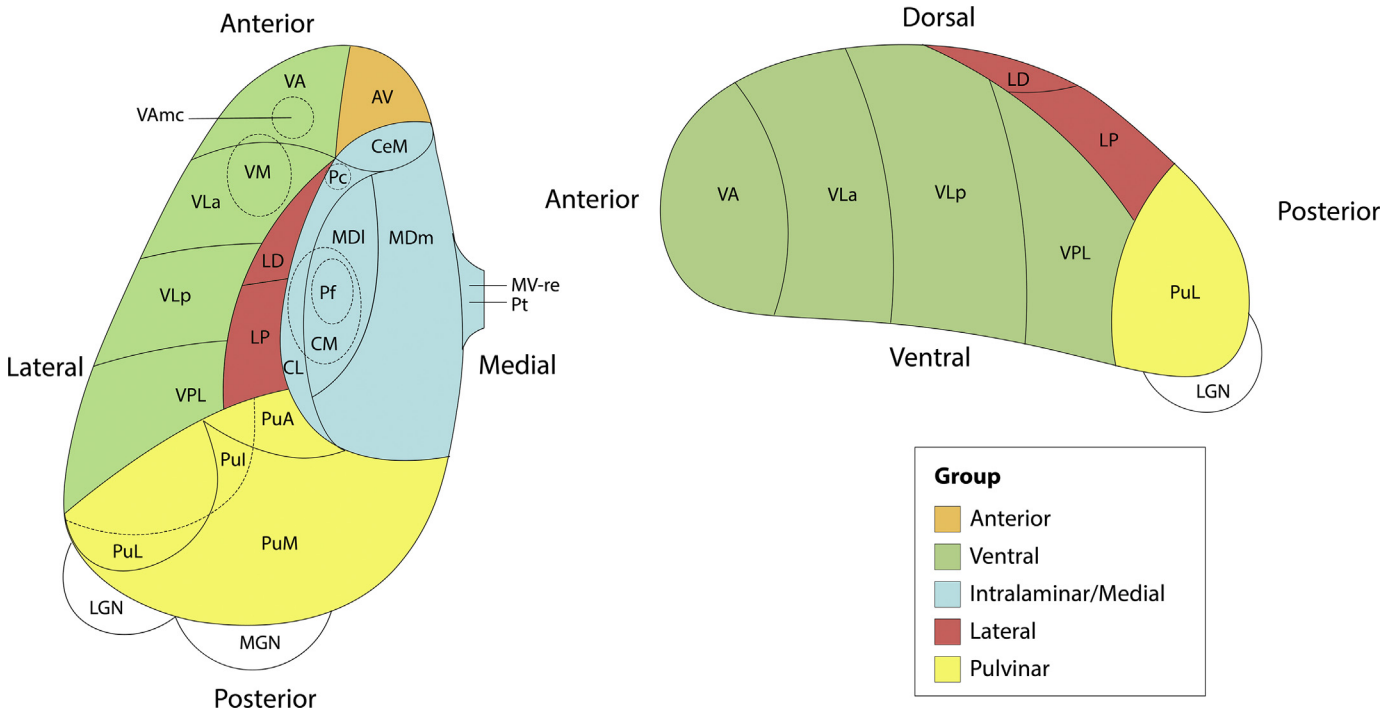
Covariates

Covariates were defined a priori to adjust for possible confounding effects. 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,

TABLE 1 Thalamic Nuclei and Nuclei Groups Used for Analyses

Group	Nucleus
Anterior	Anteroventral
Lateral	Laterodorsal
	Lateral posterior
Ventral	Ventral anterior
	Ventral anterior magnocellular
	Ventral lateral anterior
	Ventral lateral posterior
	Ventral posterolateral
	Ventromedial
Intralaminar/medial	Central medial
	Central lateral
	Paracentral
	Centromedian
	Parafascicular
	Paratenial
	Reuniens (medial ventral)
	Mediodorsal medial magnocellular
	Mediodorsal lateral parvocellular
Pulvinar	Pulvinar anterior
	Pulvinar medial
	Pulvinar lateral
	Pulvinar inferior

FIGURE 2 Schematic Depiction of Individual Thalamic Nuclei Derived From the Segmentation Pipeline Colored by Thalamic Nuclei Group



Note: *On the left is a transverse see-through top view of the left thalamus, with dashed lines indicating deeper lying nuclei. On the right is a sagittal view from a lateral perspective. AV = anteroventral; CeM = central medial; CL = central lateral; CM = centromedian; LD = laterodorsal; LGN = lateral geniculate nucleus; LP = lateral posterior; MGN = medial geniculate nucleus; MDm = mediodorsal medial; MDl = mediodorsal lateral; MV-re = reuniens; Pc = paracentral; Pf = parafascicular; Pt = paratenial; PuA = pulvinar anterior; Pul = pulvinar inferior; PuL = pulvinar lateral; PuM = pulvinar medial; VA = ventral anterior; VAmc = ventral anterior magnocellular; VLa = ventral lateral anterior; VLp = ventral lateral posterior; VM = ventral medial; VPL = ventral posterolateral. Please note color figures are available online.*

Asian Non-Western, Cape Verdean)—in accordance with the categorization of Statistics Netherlands.[14,21] We used maternal education level as a proxy for socioeconomic status, which was defined as highest education level finished 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.[22] To avoid overcorrection, the items from the CBCL Obsessive-Compulsive Scale were excluded.[23] Nonverbal IQ was assessed at age 5-8 years using the Snijders-Oomen Nonverbal Intelligence Test–Revision (SON-R 2.5-7).[24] Missing data of covariates were imputed using the mice package in R for multiple imputation.[25]

Statistical Analyses

We preregistered our research plan on the Open Science Framework (https://osf.io/28a43) before conducting any analysis. All analyses were performed using R statistical software version 3.6 (R Foundation for Statistical Computing, Vienna, Austria). We performed a nonresponse analysis to compare the sample in the study with the excluded children who participated in the previous wave of data collection (at the age of 6).

Building on our previous work showing larger thalamic volume in probable OCD cases compared with controls, we compared thalamic nuclei group volumes between a probable OCD group with OCS severity above the clinical cutoff (SOCS $\geq$ 6, n = 156, 6.2%) and a 1:1 nearest-neighbor matched control group (SOCS = 0), matched on sex, age, ethnicity, maternal education level, and handedness. We performed a paired *t* test for group comparison of the nuclei group volumes. We chose this matching procedure to align with clinical case-control studies where participants are well matched on key variables, in line with our own previous work. We chose to apply 1:1 matching ratio because adding more participants in the control group resulted in suboptimal matching between the cases and controls. To adjust for possible confounding effects, we residualized the group volumes for the CBCL score and

intracranial volume to control for head size in all models. To assess whether significant differences would persist relative to whole thalamic volume and thus relative to the other thalamic substructures, we additionally constructed a ratio measure between the substructure and whole thalamic volume in another analysis. We calculated *d* effect sizes for the group differences.

In a second analysis, we conducted linear regressions with SOCS sum scores as continuous predictors of the mean bilateral volume of the 5 thalamic subregions. All regression models were hierarchically adjusted for age, sex, maternal ethnicity, maternal education level, handedness, and intracranial volume (model 1) and total child behavioral problems (model 2). For significant nuclei groups, we investigated the association between volume and OCS of the individual nuclei within the group. We also performed a post hoc analysis using the ratio between substructure volume and whole thalamic volume to assess whether the associations would persist relative to overall thalamus size. We used a ratio variable because including whole thalamus in the volume resulted in strong collinearity. In a post hoc analysis, we tested for quadratic and cubic associations between OCS and nuclei group volumes. We also tested for interaction effects between age and OCS severity.

All analyses were corrected for multiple testing using false discovery rate correction (Benjamini-Hochberg) for each of the 5 thalamic subregions. Finally, to compare with our previous results of higher overall thalamic volume in children with probable OCD compared with children without symptoms,[4] we performed the case-control analysis for the whole thalamus using the new ThalamicNuclei pipeline derived volume data. Because the thalamus segmentation we used from the subcortical pipeline does not include the lateral and medial geniculate nuclei in the thalamus segmentation, we subtracted the lateral and medial geniculate nuclei volumes from the ThalamicNuclei pipeline derived total thalamic volume metric for consistency with our previous analysis.

RESULTS

The initial sample consisted of 2,551 participants, of which 51 were excluded owing to poor quality of the segmentations (Figure 1). The final sample thus included 2,500 participants, of which 312 children were included in the case-control analysis (n = 156 with SOCS $\geq$ 6 and n = 156 with SOCS = 0).

Sample Characteristics

Table 2 displays the characteristics of the sample. We performed a nonresponse analysis comparing the demographic characteristics of the current sample (N = 2,500) with participants on which data were collected in a previous wave but did not participate in this data collection wave (n = 4,262). Children in the excluded sample more often had a non-Dutch background ($\chi^2 = 245.52$, $p < .001$), and mothers of the nonparticipating children were more likely to have a lower education level ($\chi^2 = 238.02$, $p < .001$). Children in the excluded group had a lower nonverbal IQ at age 6 (mean difference = –5.36, $p < .001$) and more behavioral problems (CBCL score, mean difference = 1.71, $p < .001$) than children included in the study.

Case-Control Analysis

The results of the case-control analysis of nuclei group volume differences between probable OCD cases (SOCS $\geq$ 6, n = 156) and matched controls (SOCS = 0, n = 156) are displayed in Table 3 and Figure 3. Probable OCD cases had larger ventral nuclei compared with matched symptom-free control children ($d = 0.25$, $p = .025$), adjusted for intracranial volume and behavioral problems. This finding did not survive correction for multiple comparisons (false discovery rate adjusted $p = .126$). No significant differences between cases and controls were found in the other nuclei groups. In a post hoc analysis, there was no significant difference in the ratio of ventral volume and whole thalamic volume ($d = 0.11$, uncorrected $p = .34$). Of the individual nuclei that form the ventral nucleus, significant volume differences were found in the ventral lateral anterior ($d = 0.27$, $p = .015$) and ventral lateral posterior ($d = 0.28$, $p = .016$) nuclei (Table S1, available online).

Continuous Analysis

The results of the continuous analysis of OCS and thalamic nuclei group volume (N = 2,500) are displayed in Table 4. We found a significant negative association between OCS and pulvinar volume after adjusting for age, sex, maternal education level, ethnicity, and intracranial volume ($\beta = -0.039$, $p = .018$). This remained significant after further adjustment for behavioral problems ($\beta = -0.038$, $p = .029$). The association became a trend after correction for multiple comparisons (false discovery rate adjusted $p = .09$). In a post hoc analysis, we found a significant association between OCS and ratio between pulvinar and whole thalamic volume ($\beta = -0.057$, $p = .009$). There were no quadratic or cubic associations between OCS and volume of the nuclei groups (Tables S2 and S3, available online). We found no interaction effects of age and OCS (Tables S4 and S5, available online). Of the individual nuclei that form the pulvinar nucleus, we

TABLE 2 Sample Characteristics

	Whole sample (N = 2,500)	Probable cases (n = 156)	Controls (n = 156)
Child characteristics			
Age at MRI, mean ± SD	10.08 ± 0.57	10.11 ± 0.57	10.15 ± 0.63
Sex, % girls	50.2	55.0	53.0
Nonverbal IQ, mean ± SD	104.23 ± 14.57	98.9 ± 14.7	99.2 ± 13.5
CBCL, mean ± SD[a,b]	15.44 ± 13.49	23.2 ± 18.8	13.5 ± 12.1
SOCS, mean ± SD	1.74 ± 2.18	7.13 ± 1.21	0
Maternal characteristics			
Ethnicity			
Dutch	1,615	52	54
Non-Dutch Western	309	85	88
Non-Dutch Non-Western	554	19	14
Education level			
High	1,379	54	52
Middle	863	71	93
Low	111	31	11
Maternal age at birth, mean ± SD	31.81 ± 4.56	30.45 ± 5.34	30.60 ± 4.96

Note: *CBCL = Child Behavior Checklist; MRI = magnetic resonance imaging; SOCS = Short Obsessive-Compulsive Disorder Screener.*
[a]*CBCL score minus CBCL Obsessive-Compulsive Scale subscale items.*
[b]*Statistically significant differences of CBCL score between groups (t = 5.432, p < .001).*

found a significant negative association between OCS and the medial pulvinar nucleus ($\beta = -0.043$, $p = .016$) (Table S6, available online).

Whole Thalamus

Probable OCD cases had a larger whole thalamic volume compared with matched controls ($d = 0.16$, $p = .044$) when using the aseg pipeline of FreeSurfer version 6.0, as was described in our previous article.[4] We performed the same analysis with the whole thalamus minus medial and lateral geniculate volume from the ThalamicNuclei pipeline showing a slightly larger thalamic volume in probable OCD cases, but this did not reach statistical significance ($d = 0.18$, $p = .10$). The internuclear correlations and volume of all individual nuclei are presented in Tables S7 and S8, available online.

DISCUSSION

We investigated the relation between OCS and volume of thalamic subregions in children aged 9-12 years from a population-based study. Participants with probable OCD showed a larger volume of ventral thalamic areas. In the continuous analysis, we found a negative association between OCS and pulvinar volume. However, these findings did not survive correction for multiple comparisons.

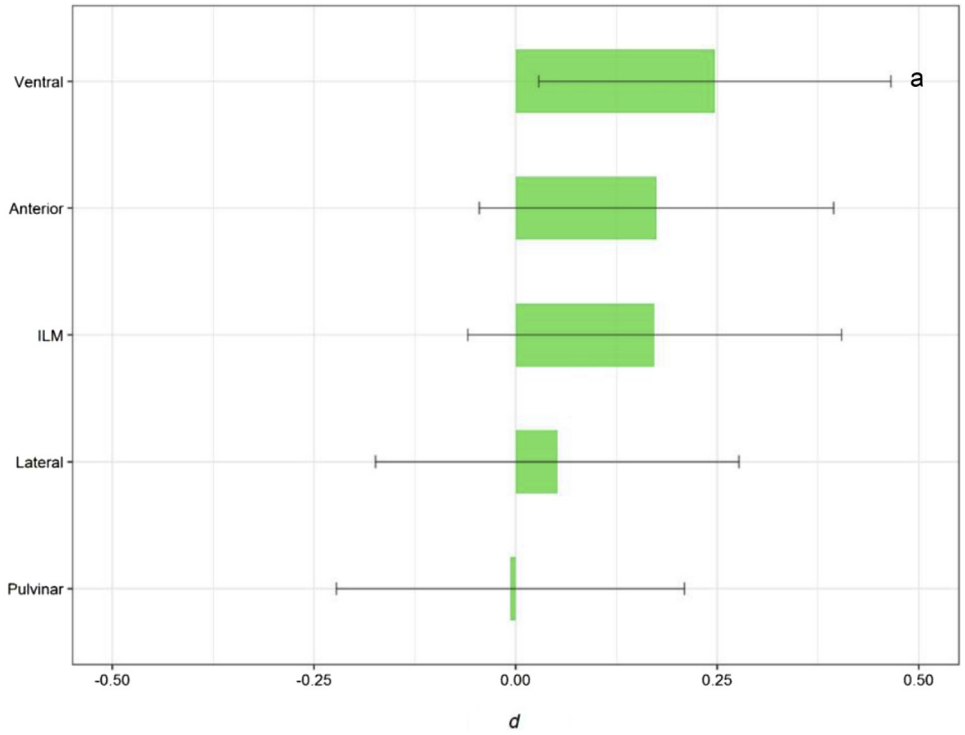
In our analyses, the larger ventral volume was mostly driven by the ventral lateral nucleus. This nucleus receives

TABLE 3 Differences in Mean Between Thalamic Nuclei Group Volumes Between Probable Obsessive-Compulsive Disorder and Control Groups

				95% CI			
Nuclei group	***t***	***p***	p_{FDR}	−	+	**Mean differences**	***d***
Ventral	2.26	.025	.126	4.55	67.39	35.97	0.25
Anterior	1.57	.117	.237	−0.57	5.02	2.23	0.17
ILM	1.47	.142	.237	−6.20	42.63	18.22	0.17
Lateral	0.45	.652	.815	−3.24	5.16	0.96	0.05
Pulvinar	−0.06	.955	.955	−32.48	30.66	−0.91	−0.01

Note: *Volume measures residualized for intracranial volume and the Child Behavior Checklist sum score minus the Obsessive-Compulsive Scale subscale items. ILM = intralaminar/medial; p_{FDR} = adjusted p for false discovery rate q = .05; degrees of freedom = 155.*

FIGURE 3 Differences in Thalamic Nuclei Volume Between Probable Obsessive-Compulsive Disorder Group and Controls



Note: *Thalamic nuclei volumes are residualized for intracranial volume and Child Behavior Checklist sum score minus the Obsessive-Compulsive Scale subscale items. ILM = intralaminar/medial; Please note color figures are available online.*
[a]p = .025.

afferents from the cerebellum and outputs to the primary motor cortex and premotor cortex.[26] The larger ventral lateral volume suggests motor involvement in children with probable OCD, which has been implicated in OCD pathophysiology.[6] Children with OCD often have tics and comorbid tic disorders with involvement of the sensorimotor network.[27,28] In adult OCD, sensorimotor involvement is hypothesized to reflect a shift from goal-directed behaviors toward habitual stimulus-response behaviors as a result of chronic symptoms.[6] So far, no research has reported on thalamic subnuclei in adult OCD. It must be noted that these findings should be

TABLE 4 Linear Association Between Obsessive-Compulsive Symptoms and Nuclei Group Volume

					95% CI	
Nuclei group	**Model**	**β**	***p***	**p_{FDR}**	−	+
Anterior	1	0.016	.356	.826	−0.018	0.049
	2	0.016	.381	.740	−0.019	0.050
Lateral	1	−0.004	.839	.839	−0.039	0.032
	2	−0.0056	.767	.767	−0.042	0.032
Ventral	1	0.0058	.661	.826	−0.020	0.032
	2	0.0075	.591	.740	−0.019	0.035
ILM	1	0.0087	.596	.826	−0.023	0.041
	2	0.010	.547	.740	−0.023	0.044
Pulvinar	1	−0.039	.018	.090	−.071	−.0066
	2	−.038	.029	.145	−.072	−.0041

Note: Model 1 is adjusted for age at magnetic resonance imaging, sex, maternal education level, ethnicity, and intracranial volume. Model 2 is additionally adjusted for CBCL score minus CBCL Obsessive-Compulsive Scale subscale items. ILM = intralaminar/medial; p_{FDR} = adjusted p for false discovery rate q = 0.05.

interpreted with caution, as the volumetric differences in ventral thalamic regions did not reach statistical significance after correction for multiple comparisons. However, these results provide insight into how individual thalamic subregions contribute to overall thalamic volume. The ventral lateral nucleus represents approximately 21% of total thalamic volume and showed a 0.91 correlation with the whole thalamus (Tables S7 and S8, available online). This suggests that the trend toward larger thalamic volume is primarily driven by the ventral nuclei. In post hoc analyses, this is supported by the decreased effect estimate and significance after accounting for overall thalamic volume. The anterior, lateral, and intralaminar/medial subregions also showed larger volumes at trend level in the probable OCD group. This could indicate an overall bigger thalamus that is not nuclei specific. In this light, on one hand, the fact that only ventral volume was significantly different between groups may be explained by the large size and low variance of these nuclei. On the other hand, the variability in correlations with total thalamic volume as well as the differences in effect size between the nuclei group, ranging from $d = -0.01$ (for the pulvinar) to $d = 0.25$ (for the ventral region), could suggest that individual subregions contribute to overall thalamus size in different degrees.

The negative association of SOCS score with the volume of the pulvinar region is in direct contrast to the previously described increased volume of the whole thalamus in children with probable OCD[4] and pediatric OCD.[3] As the association strengthened following adjustment for whole thalamic volume, this indeed suggests a relation opposite to a trend of overall thalamic enlargement. This finding also contrasts with an earlier shape analysis, where adults with OCD showed surface expansions at the pulvinar region.[9] We also considered segmentation errors of this region as a possible explanation. For quality control, we assessed the degree of overlap between voxels labeled as white matter in the aseg segmentations and voxels labeled as thalamus in the ThalamicNuclei segmentations. This overlap was most pronounced at the posterior region of the thalamus, where the pulvinar is located. However, there was no association between the degree of overlap and OCS (data not shown). Therefore, it is unlikely that segmentation errors explain the volumetric association with SOCS score.

Despite the inconsistency with overall larger thalamic volume, the findings do suggest that an inverse relation between OCS and pulvinar volume may exist. Previous studies demonstrated altered functional connectivity of the pulvinar during conflict monitoring in childhood-onset OCD. Altered resting-state functional connectivity of the pulvinar has also been observed in adults with OCD.[8] In post hoc analyses, we found that the relation between OCS and pulvinar volume was driven by the medial pulvinar nucleus. This nucleus has efferent connections with cortical regions, including premotor, prefrontal cingulate, and posterior parietal cortices.[29] It is involved in saccadic eye movements as well as visual attention.[26] Visual attention impairments have been found in patients with OCD.[30] The pulvinar is also responsible for integration of multisensory inputs with appropriate motor responses.[29] Abnormal sensorimotor processing could play a role in the aberrant stimulus-response behavior reported in OCD.

The results of the case-control and continuous analyses were only partially consistent. Higher ventral volume was found in the case-control analysis. On one hand, the association with ventral volume showed the same direction in the continuous analysis but did not reach statistical significance. On the other hand, we found a negative association with pulvinar volume in both the case-control and the continuous analysis that reached statistical significance only in the continuous analysis. We assume that children with probable OCD in our sample phenotypically resemble pediatric OCD or are mostly likely to develop OCD. In previous studies, the thalamic volume differences were most profound between cases and controls, rather than related to OCS severity across the spectrum.[3,4] This may explain why the finding of an enlarged ventral region was more pronounced in the case-control analysis. In our continuous analysis, we found a negative association with pulvinar volume, while our previous study showed no significant association with whole thalamic volume.[4] This suggests that the influence of a smaller pulvinar volume on the whole thalamic volume in association with OCS is masked by the variance volume of other nuclei that show an opposite effect. We think that the discrepancy between the case-control and the continuous analysis reveals that (probable) OCD may represent a phenotypical distinction from subclinical OCS, which is reflected by differences in thalamic nuclei structure.

Our study has several strengths and limitations. To our knowledge, this is the first study to investigate thalamic subregions in relation to OCD, and it has paved the way for similar endeavors in the future. If replicated, these findings can reveal which specific CSTC circuits are most affected in early OCD, providing potential targets for tailored treatment strategies. Other strengths of this study include studying OCS in children from the general population to distinguish normative from pathological symptoms, a preregistered hypothesis, a robust sample size, an innovative method for thalamic subsegmentation, and combining case-control with continuous analyses. A limitation is that thalamic nuclei volumes were extracted from a probabilistic

atlas, based on histological segmentation of postmortem brains from adult volunteers. The thalamus is a dense structure in the center of the brain that primarily consists of gray matter, making it difficult to distinguish nuclear borders using a 3T 1-mm^3 isotropic structural scan. Therefore, aside from the outer borders, we could not verify the segmentations by visual inspection.

Another limitation within our sample is that we identified probable OCD based on a screening instrument and therefore did not have certainty of formal OCD diagnoses. It must be noted that the measure we used has excellent test characteristics (sensitivity 0.97, specificity 0.88) for predicting OCD.[16] The SOCS is validated as a parent-rated instrument. The items focus primarily on OCD behavior that is noticeable to the parent. However, its documented validity potentially introduces a degree of observer bias owing to difficulty of assessing obsessions and mental rituals in the child. Another limitation of the SOCS is that it does not provide information on symptom dimensions. Future studies should focus on studying the thalamic morphology in relation to symptom heterogeneity. We should also address the modest effect sizes of our results. Previous studies have established that structural differences in clinical OCD are modest and require substantial sample sizes.[3,11] This need may be even stronger in subclinical/population studies. The screening instrument to identify probable OCD cases tends to slightly overestimate the number of true OCD cases. This could potentially dilute the association with symptoms, reducing power and producing lower effect sizes. That said, subtle yet reproducible findings from neuroimaging studies have proved to yield mechanistic insight into pathophysiological processes and potential treatment targets.[31,32] An additional limitation is that the Generation R dataset does not include all clinical information that may be relevant to OCD, including medication status, history of streptococcal infection, and comorbid tic disorders. Finally, using the new thalamic segmentation pipeline, we were not able to show similar effect estimates from our earlier findings of the volume differences of the whole thalamus. A possible explanation is that the new pipeline does not include the reticular nucleus and therefore produces a different volume estimate. The reticular nucleus, however, forms a relatively thin sheet around the thalamus, so its contribution to overall thalamic volume is probably limited.[33]

Because in vivo assessment of thalamic nuclear morphology using T1-weighted structural MRI is a novel approach, there are considerable strides to be made in the future. Higher field strengths, possibly in a multimodal setting of different MRI sequences, will allow extraction of a much clearer view of thalamic nuclei. Another possibility lies in investigating whether the structural differences between probable cases and controls correspond to functional differences, in particular, whether probable OCD is associated with altered functional connectivity between the ventral subregions and sensorimotor network. Another noteworthy point is the difference in age range used in this study (9-12 years) compared with the ENIGMA-OCD studies (age up to 18 years). It would be interesting to see in future data collection waves of Generation R whether thalamic differences persist with increasing age.

In conclusion, building on our previous work, we conducted a neuroimaging study of OCS and volume of thalamic subregions in children from the general population. Probable OCD cases had larger ventral thalamic nuclei compared with symptom-free controls, which plays a role in the sensorimotor circuit. Overall SOCS score was negatively associated with pulvinar volume. To our knowledge, this is the first study using this novel segmentation approach for OCS in the general population. It invites further research to confirm and better understand these findings.

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Drs. Weeland and Vriend and Prof. Drs. van der Werf and van den Heuvel are with Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands. Drs. Weeland, Hillegers, and White and Prof. Dr. Tiemeier are with Erasmus Medical Center, Rotterdam, the Netherlands. Drs. Weeland and Hillegers are also with the Generation R Study Group, Erasmus Medical Center, Rotterdam, the Netherlands. Prof. Dr. Tiemeier is also with Harvard T.H. Chan School of Public Health, Boston, Massachusetts. Dr. Huyser is with the Academic Center for Child and Adolescent Psychiatry, Amsterdam, the Netherlands.

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Author Contributions
Conceptualization: Weeland, van den Heuvel
Data curation: Weeland
Formal analysis: Weeland
Funding acquisition: Tiemeier, White, van den Heuvel
Methodology: Weeland, Vriend, Hillegers, Tiemeier, White, van den Heuvel
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Resources: Tiemeier, White
Software: Weeland, Vriend
Supervision: van den Heuvel
Visualization: Weeland
Writing — original draft: Weeland, White, van den Heuvel
Writing — review and editing: Weeland, Vriend, van der Werf, Huyser, Hillegers, Tiemeier, White, van den Heuvel

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Correspondence to Cees J. Weeland, MD, Department of Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, PO Box 7057, 1007 MB, Amsterdam, the Netherlands; e-mail: c.j.weeland@amsterdamumc.nl

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