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## ARTICLE OPEN



# The thalamus and its subnuclei—a gateway to obsessive-compulsive disorder

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Larger thalamic volume has been found in children with obsessive-compulsive disorder (OCD) and children with clinical-level symptoms within the general population. Particular thalamic subregions may drive these differences. The ENIGMA-OCD working group conducted mega- and meta-analyses to study thalamic subregional volume in OCD across the lifespan. Structural T<sub>1</sub>-weighted brain magnetic resonance imaging (MRI) scans from 2649 OCD patients and 2774 healthy controls across 29 sites (50 datasets) were processed using the FreeSurfer built-in *ThalamicNuclei* pipeline to extract five thalamic subregions. Volume measures were harmonized for site effects using ComBat before running separate multiple linear regression models for children, adolescents, and adults to estimate volumetric group differences. All analyses were pre-registered (<https://osf.io/73dvy>) and adjusted for age, sex and intracranial volume. Unmedicated pediatric OCD patients (<12 years) had larger lateral ( $d = 0.46$ ), pulvinar ( $d = 0.33$ ), ventral ( $d = 0.35$ ) and whole thalamus ( $d = 0.40$ ) volumes at unadjusted  $p$ -values <0.05. Adolescent patients showed no volumetric differences. Adult OCD patients compared with controls had smaller volumes across all subregions (anterior, lateral, pulvinar, medial, and ventral) and smaller whole thalamic volume ( $d = -0.15$  to  $-0.07$ ) after multiple comparisons correction, mostly driven by medicated patients and associated with symptom severity. The anterior thalamus was also significantly smaller in patients after adjusting for thalamus size. Our results suggest that OCD-related thalamic volume differences are global and not driven by particular subregions and that the direction of effects are driven by both age and medication status.

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## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a debilitating mental disorder with a lifetime prevalence of 1.3% that often starts during childhood and follows a chronic course [1]. Structural and functional differences in cortico-striato-thalamo-cortical (CSTC) circuits have been linked to commonly observed affective and cognitive deficits, including fear conditioning and extinction,

planning ability, response inhibition, habitual behaviour, and emotion regulation [2]. The thalamus lies at the core of these functionally segregated CSTC circuits. Previous work from the ENIGMA-OCD Working Group revealed that the thalamus is larger in unmedicated pediatric OCD patients compared with controls [3] and shows more leftward asymmetry [4]. The former finding was corroborated in the population-based Generation R study,

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showing that school-aged children with symptoms above a clinical cut-off had a larger thalamus than symptom-free children [5].

Thalamus structure is not uniform and consists of several nuclei with distinct connectivity and functions [6]. The anterior nucleus connects fronto-limbic regions including the medial orbitofrontal and ventromedial prefrontal cortex [7]. The mediodorsal nucleus is involved in both emotional and cognitive processing, including reward devaluation, fear extinction, working memory, behavioural flexibility, and goal-directed behaviour [8, 9]. The pulvinar nucleus functions as an association nucleus involved in attributing salience to visual stimuli and modulating attention and behaviour accordingly [9, 10]. The ventral thalamus includes the ventral anterior and ventral lateral nucleus, which are involved in motor control [9]. Functional deficits in all of the aforementioned domains and their associated circuits have been implicated in the neurobiological model of OCD [2]. Therefore, larger thalamus volume in OCD may reflect structural or functional changes within these circuits that are expressed in enlarged volume of specific nuclei.

Few studies have investigated OCD-related morphological differences of the thalamus at the subregional level. Shape analysis has found increased surface area of the anterior and pulvinar nuclei in adult OCD patients compared with controls [11]. Within school-aged children from the Generation R study, all thalamic nuclei except the pulvinar trended towards larger volumes in the clinical symptom group compared with children without symptoms [12]. The ventral nucleus group showed the largest difference, though this was no longer significant after correction for multiple comparisons [12]. Another recent study found that adult patients compared with controls had lower volumes of the left posterior thalamus, which includes the pulvinar and geniculate nuclei, and smaller posterior thalamus volume was also associated with a later age of onset of OCD [13]. A limitation of previous literature is the focus on a specific age group, limiting the ability to explore differences across the lifespan. The datasets of ENIGMA-OCD allow comparison across a larger age range, including children, adolescents and adults.

We performed mega- and meta-analyses comparing thalamic nuclei volume between OCD patients and healthy controls across 29 sites worldwide. We used the automated segmentation algorithm implemented in FreeSurfer 7.1.1 that uses a histology-based probabilistic atlas created by Iglesias and colleagues [14]. We also examined the effects of medication status, age, sex, age of

disease onset, and symptom severity. Based on the literature, we expected that pediatric OCD patients would show larger nuclei volumes compared with healthy controls, mostly driven by larger volume of the anterior and ventral thalamus. Furthermore, adult OCD patients were expected to have lower pulvinar volumes compared with healthy controls [13]. Based on our previous analyses on subcortical and cortical morphology, we expected that volume enlargement in children would be driven by unmedicated patients and lower volume in adults by medicated patients [3, 15]. We also expected that adult OCD patients with a childhood onset would show larger nuclei volumes than patients with adult-onset OCD.

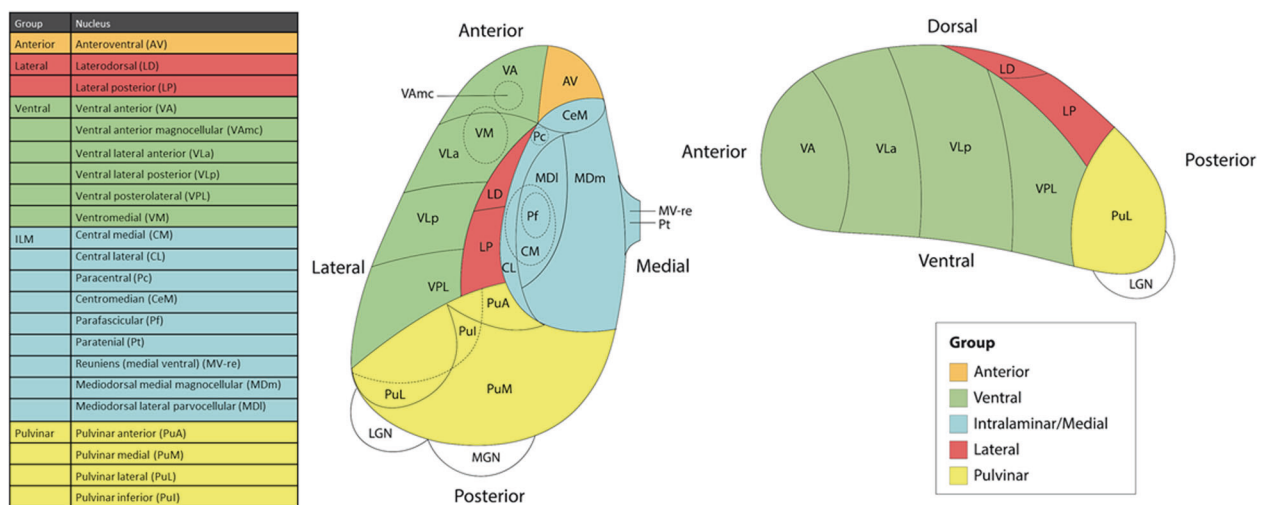
## MATERIALS AND METHODS

### Samples

The ENIGMA-OCD working group is a collaboration of 29 international research institutes that provided in total 50 samples of structural brain imaging and clinical data from OCD patients and control participants without psychopathology. These samples partly overlap with the previous cortical and subcortical mega-analyses performed by this group [3, 15]. We divided the participants into three age groups: children under 12 years, adolescents aged 12–17 years, and adults aged 18 years and older. After excluding 45 participants based on poor segmentations, the dataset included 5423 participants, among which 2678 OCD patients (96 children, 317 adolescents, 2265 adults) and 2746 healthy controls (90 children, 254 adolescents, 2402 adults). The institutional review boards of each participating site permitted the analysis of measures extracted from coded, de-identified individual participant data.

### Image acquisition and processing

T<sub>1</sub>-weighted structural brain magnetic resonance imaging (MRI) scans of the participants were acquired at each site and processed using the latest stable release of FreeSurfer (version 7.1.1) for segmentation of the whole thalamus. Next, the pipeline of Iglesias and colleagues [14] was used to segment the thalamus into 25 nuclei, which we grouped into five different subregions per hemisphere: anterior, lateral, ventral, intralaminar/medial and pulvinar (see Fig. 1 for an overview of the subdivision and Fig. S1 for an in vivo example). A containerized version (Singularity) of the pipeline was created to facilitate cross-platform compatibility at each site ([http://datasets.datalad.org/?dir=/shub/chrisvriend/ENIGMA\\_subthal](http://datasets.datalad.org/?dir=/shub/chrisvriend/ENIGMA_subthal)) and allow standardized quality inspection of the segmentation by means of custom-made Python and shell scripts. All segmentations were visually inspected and investigated for statistical outliers. Full details of the image exclusion criteria and quality assessments are described in Supplementary Section S1.



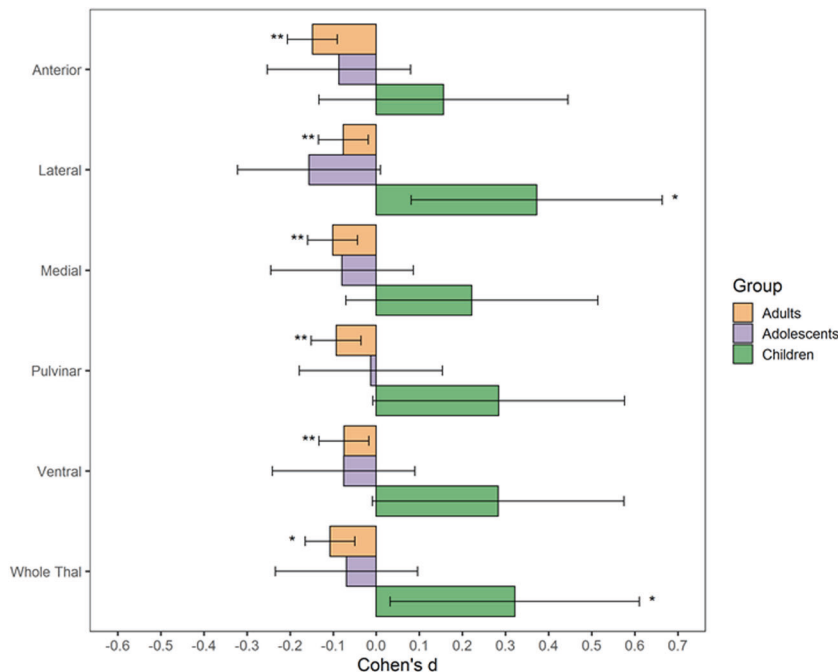
**Fig. 1 Schematic representation of thalamic nuclei grouping.** Figure adapted from Thalamic Subregions and Obsessive-Compulsive Symptoms in 2500 Children From the General Population by Weeland et al., 2021, *Journal of the American Academy of Child and Adolescent Psychiatry*.

**Table 1.** Pooled descriptive statistics of obsessive-compulsive patients and healthy control participants for the adult (age 18 or higher), adolescent (age 12–17) and child (age under 12) age groups.

Variables		Adult OCD <i>n</i> = 2265	Adult HC <i>n</i> = 2402	Adolescent OCD <i>n</i> = 317	Adolescent HC <i>n</i> = 254	Pediatric OCD <i>n</i> = 96	Pediatric HC <i>n</i> = 90
Age (y)	Mean, SD	31.9 (9.9)*	30.7 (9.9)	14.8 (1.7)	14.6 (1.7)	10.0 (1.3)	9.6 (1.4)
	Range	18–67	18–69	12–17.9	12–17.5	5–11.6	6–11.9
(C)Y-BOCS	Mean, SD	24.5 (6.6)	–	22.7 (7.2)	–	21.9 (6.9)	–
	Range	3–46	–	0–40	–	0–36	–
Education (y)	Mean, SD	13.6 (3.1)*	15.1 (3.0)	9.2 (1.8)	8.8 (1.9)	5.0 (1.5)	4.1 (1.6)
	Range	0–26	0–28	5–14	4–14	0–9	0–7
Female (%)		50.3%	50.4%	45.3%	48.6%	47.9%	55.6%
Medicated (%)		52.4%	–	40.6%	–	19.8%	–
Child-onset (%)		45.4%	–	–	–	–	–
Comorbid depressive disorder (%)		26.8%	–	35.9%	–	17.5%	–
Comorbid anxiety disorder (%)		24.7.0%	–	46.4%	–	41.7%	–

OCD obsessive-compulsive disorder, HC healthy control, y years, SD standard deviation, (C)Y-BOCS (Child version) Yale-Brown Obsessive-Compulsive Scale.

\*Statistically significant group difference ( $p < 0.05$ ).

**Fig. 2** Volumetric differences between obsessive-compulsive patients and healthy controls by age group. \* $p_{\text{Uncorrected}} < 0.05$ ; \*\* $p_{\text{FDR}} < 0.05$ ; volumetric differences are adjusted for age, sex and intracranial volume. Thal Thalamus.

### Statistical analysis

We conducted both mega- and meta-analyses. Statistical analyses were conducted in accordance with statistical protocols of the ENIGMA Consortium (<http://enigma.ini.usc.edu/>). We pre-registered our analysis plan and hypotheses prior to conducting any analyses (<https://osf.io/73dvy>). Mega-analyses were performed by pooling the extracted volume measures for each participant across all sites. The data were harmonized to adjust for possible cross-site batch effects using a modified version of the ComBat function [16]. Multiple linear regression models were run on the harmonized data. We conducted separate analyses for children, adolescents and adults. The bilateral mean volumes of the five subregions served as the main outcome measures. Diagnosis was used as a binary predictor in all analyses. All models were adjusted for age, sex, and total intracranial volume (ICV). We additionally investigated the interaction of age, age-squared, sex or sex-by-age. Details of the meta-analysis are described in Supplementary Section S2.

We computed Cohen's  $d$  effect sizes using the  $t$ -statistic of the main predictor variable in the regression models. Medication effects were investigated by conducting stratified analyses comparing medicated versus unmedicated OCD patients with the healthy control group. Similarly, we conducted stratified analyses for the adult-onset and child-onset (onset before age 18 years) groups to study the influence of time of onset (age at diagnosis). We also investigated the continuous association of subregional volume with illness severity, expressed in terms of the total severity score of the adult and child versions of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [17, 18]. In post hoc (i.e. not pre-registered) analyses, lateralization of volume differences was assessed in children and adults by computing an asymmetry index  $([L - R]/([L + R]/2))$  for each subregion [4]. We further explored subregional volume differences relative to the whole thalamus by post hoc adjustment for whole thalamus volume. Since subregions and whole thalamus are highly correlated, we evaluated variance inflation factors to rule out any

**Table 2.** Multiple linear regression output of volumetric difference between obsessive-compulsive patients and healthy controls for children (<12 years), adolescents (12–17 years) and adults (age 18 or higher).

	Cohen's <i>d</i> [95% CI]	<i>p</i> -value	<i>p</i> -value (FDR)	<i>n</i> (OCD)	<i>n</i> (HC)
<i>Children</i>					
Ventral	0.28 [−0.009, 0.575]	0.061	0.102	94	88
Pulvinar	0.28 [−0.008, 0.576]	0.060	0.102	94	88
Medial	0.22 [−0.07, 0.515]	0.143	0.178	94	87
Lateral	0.37 [0.081, 0.664]	0.014	0.068	95	89
Anterior	0.16 [−0.133, 0.445]	0.297	0.297	95	90
Whole Thal	0.32 [0.032, 0.611]	0.032	–	96	90
<i>Adolescents</i>					
Ventral	−0.076 [−0.241, 0.09]	0.374	0.467	314	253
Pulvinar	−0.012 [−0.178, 0.154]	0.884	0.884	312	252
Medial	−0.08 [−0.245, 0.086]	0.348	0.467	316	253
Lateral	−0.16 [−0.322, 0.01]	0.067	0.334	316	252
Anterior	−0.086 [−0.253, 0.08]	0.311	0.467	311	251
Whole Thal	−0.069 [−0.234, 0.096]	0.416	–	317	254
<i>Adults</i>					
Ventral	−0.075 [−0.133, −0.017]	0.011	0.011	2200	2383
Pulvinar	−0.093 [−0.151, −0.035]	0.002	0.003	2211	2381
Medial	−0.10 [−0.159, −0.043]	0.001	0.002	2198	2390
Lateral	−0.08 [−0.134, −0.019]	0.010	0.011	2201	2402
Anterior	−0.15 [−0.206, −0.09]	5.66E−07	2.82E−06	2195	2400
Whole Thal	−0.11 [−0.165, −0.05]	0.0003	–	2265	2402

Models were adjusted for age, sex, and intracranial volume.

95% CI 95% confidence interval, FDR false discovery rate, *n* number of participants, OCD obsessive-compulsive disorder, HC healthy controls, Thal Thalamus.

multicollinearity in the models. Here, we also statistically compared effect sizes between subregions using Z-tests. The main analyses were corrected for multiple comparisons by applying a Benjamini–Hochberg false discovery rate correction ( $q=0.05$ ) across the five subregions tested. We also report uncorrected results throughout the manuscript.

## RESULTS

Table 1 provides an overview of the demographic and clinical characteristics of the pooled samples for each age group. The demographic and clinical characteristics of the separate samples are displayed in Table S1 in the data supplement.

### Mega-analysis

#### Thalamic subregional volume differences between OCD patients and controls

**Children (<12 years):** Consistent with previous findings, larger volume between children with OCD ( $n=96$ ) compared with controls ( $n=90$ ) of the whole thalamus ( $d=0.32$  [0.03, 0.61],  $p=0.03$ ). Larger volume was observed in children with OCD compared with healthy controls in the lateral subregion ( $d=0.37$  [0.08, 0.66],  $p=0.01$ ,  $p_{FDR}=0.08$ ), but the difference did not survive correction for multiple comparisons. The other subregions trended towards increased volume in OCD patients compared with controls ( $d=0.16$  [−0.133, 0.445] to 0.28 [−0.008, 0.576], unadjusted  $p=0.06$  to 0.30,  $p_{FDR}=0.10$  to 0.30) (see Fig. 2 and Table 2). We found no significant differences in subregional volume after adjusting for whole thalamus volume (see Table S2).

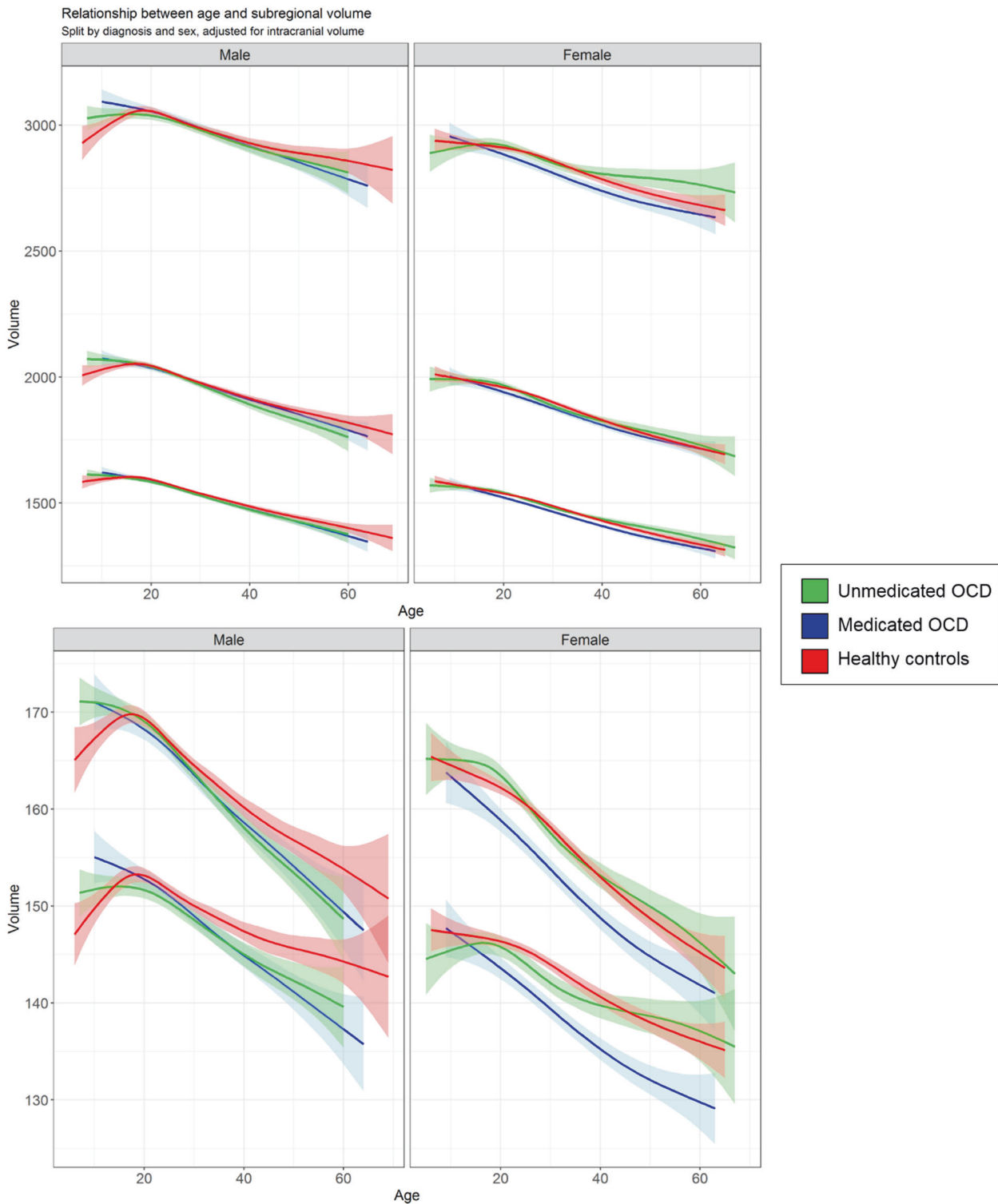
**Adolescents (12–17 years):** There were no significant volume differences of the thalamus as a whole or subregions between adolescent OCD patients ( $n=317$ ) and healthy controls ( $n=354$ ) (see Fig. 2 and Table 2). There was also no group differences in relative thalamus volume (Table S3).

**Adults (18–69 years):** Whole thalamus volume was smaller in adult OCD patients ( $n=2265$ ) compared with controls ( $n=2402$ ) ( $d=-0.11$  [−0.17, −0.05],  $p=0.001$ ). All subregions had smaller volume in adult OCD patients compared with healthy controls ( $d=-0.08$  [−0.133, −0.017] to  $-0.15$  [−0.21, −0.09],  $p_{FDR}<0.001$  to 0.011, Fig. 2 and Table 2) and in the whole thalamus. In addition, anterior volume relative to whole thalamus volume was significantly smaller in adults patients ( $d=-0.10$  [−0.16, −0.05],  $p_{FDR}=0.003$ , Table S4). We ruled out multicollinearity of these models by inspecting variance inflation factors, which all remained below 2. Formal comparisons of effect sizes between the anterior thalamus and other subregions revealed statistically significant or nearly significant differences with the pulvinar ( $Z=-2.45$ ,  $p=0.0144$ ), ventral ( $Z=-3.75$ ,  $p<0.001$ ), lateral ( $Z=-1.92$ ,  $p=0.0546$ ) and medial ( $Z=-1.94$ ,  $p=0.0658$ ) thalamus.

**Influence of medication status.** Figure 3 visualizes the volumetric differences between medicated patients, unmedicated patients and healthy controls in relation to age and sex.

**Children:** Unmedicated children with OCD ( $n=75$ ) compared with healthy controls ( $n=88$ ) had a larger lateral volume ( $d=0.46$  [0.15, 0.77],  $p_{FDR}=0.02$ ). At an unadjusted significance threshold, patients had a larger ventral subregion ( $d=0.35$  [0.04, 0.66],  $p=0.03$ ,  $p_{FDR}=0.07$ ) and pulvinar ( $d=0.33$  [0.02, 0.64],  $p=0.03$ ,  $p_{FDR}=0.07$ ) (see Table S5). We found no significant volume differences between medicated children with OCD and healthy controls or between medicated and unmedicated children with OCD (see Tables S6 and S7).

**Adolescents:** We found no significant differences between medicated adolescents with OCD ( $n=186$ ), unmedicated



**Fig. 3** Age trajectory of thalamus subregion volume for medicated obsessive-compulsive patients, unmedicated patients and healthy controls, split by sex and diagnosis. Adjusted for intracranial volume. Shading represents error margins. OCD obsessive-compulsive disorder.

adolescent OCD patients ( $n = 128$ ) and healthy controls ( $n = 254$ ) (see Tables S8–S10).

Adults: Medicated adults with OCD ( $n = 1091$ ) compared with healthy controls ( $n = 2402$ ) exhibited a significantly smaller volume of all thalamic subregions ( $d = -0.09 [-0.16, -0.01]$  to  $-0.17 [-0.24, -0.10]$ ,  $p_{FDR} = <0.001$  to  $0.02$ ) (Table S11), but there

were no significant differences between unmedicated adult OCD patients ( $n = 1000$ ) and healthy controls ( $n = 2402$ ) (Table S12) or between medicated and unmedicated patients (Table S13).

*Influence of age and sex on OCD-related differences in thalamic nuclei volume.* Results of the interaction models are displayed in Tables S14–S25. In children, we found an age-by-diagnosis

interaction for the medial (Cohen's  $d = 0.30$  [0.01, 0.60],  $p = 0.046$ ,  $p_{FDR} = 0.076$ ), pulvinar ( $d = 0.31$  [0.02, 0.60],  $p = 0.041$ ,  $p_{FDR} = 0.076$ ), ventral ( $d = 0.36$  [0.07, 0.65],  $p = 0.018$ ,  $p_{FDR} = 0.076$ ) nuclei and for the whole thalamus ( $d = 0.36$  [0.07, 0.65],  $p = 0.017$ ). This indicates larger volume with age in patients versus lower volume with age in controls (see Table S15). We also found an age-by-sex-by-diagnosis interaction in the anterior ( $d = -0.32$  [-0.61, -0.03],  $p_{FDR} = 0.045$ ), medial ( $d = -0.40$  [-0.70, -0.11],  $p_{FDR} = 0.026$ ), pulvinar ( $d = -0.39$  [-0.69, -0.10],  $p_{FDR} = 0.026$ ), ventral ( $d = -0.34$  [-0.63, -0.05],  $p_{FDR} = 0.045$ ) subregions and for the whole thalamus ( $d = -0.42$  [-0.71, -0.13],  $p = 0.006$ ) (see Table S17), indicative of larger volume in male pediatric OCD patients with age, but lower volume with age in female OCD patients and healthy controls. We found no such interactions in adolescents (Table S18–S21).

In adults, we found a sex-by-diagnosis interaction in the anterior subregion ( $d = -0.07$  [-0.12, -0.01];  $p = 0.03$ ,  $p_{FDR} = 0.13$ ) (see Table S22), indicating stronger volume differences between OCD patients and healthy controls among females. We found no other interactions (see Tables S23–S25).

*Influence of time of disease onset on thalamic subregional volume in adults.* Compared with healthy controls ( $n = 2402$ ), adult-onset OCD patients ( $n = 1000$ ) had a smaller medial ( $d = -0.10$  [-0.17, -0.02],  $p_{FDR} = 0.026$ ) and anterior ( $d = -0.14$  [-0.21, -0.07],  $p_{FDR} = 0.001$ ) thalamic volume. The ventral and lateral subregions were smaller at unadjusted  $p$ -value  $< 0.05$  (see Table S26). There were no differences between adult patients with a child-onset ( $n = 850$ ) and controls (see Table S27) or between child-onset and adult-onset patients (see Table S28).

*Association between illness severity and thalamic subregional volume.* Medication use was associated with higher YBOCS scores ( $t = 2.23$ ,  $p = 0.026$ ) and the presence of comorbid depressive disorders ( $t = 3.13$ ,  $p = 0.002$ ) but not comorbid anxiety disorders ( $t = 0.59$ ,  $p = 0.56$ ). We therefore additionally adjusted the severity analyses for medication use and comorbid depressive disorders. There was no relationship between symptom severity and subregional volume in pediatric ( $n = 83$ ) and adolescent OCD patients ( $n = 301$ ) (see Table S29 and S30). Conversely, symptom severity in adult OCD patients ( $n = 2106$ ) was negatively associated with volume in all subregions ( $r = -0.04$  and  $-0.06$ ) and whole thalamus volume ( $r = -0.07$ ) (see Table S31).

*Volume asymmetry group differences between patients and controls.* We found no significant thalamic subregional volume asymmetry in child, adolescent and adult OCD patients compared with controls (see Tables S32–S34).

### Meta-analysis

Methods and results of the meta-analysis are displayed in Supplementary Section S1 and Table S35 and Fig. S1. The results of the meta-analysis corroborate the mega-analysis results.

### DISCUSSION

We performed a mega- and meta-analysis investigating differences in thalamic subregion volume between OCD patients and healthy controls across the lifespan. While unmedicated pediatric patients had significantly *larger* lateral volumes and larger pulvinar, ventral and whole thalamus volumes at uncorrected significance thresholds compared with controls, adult OCD patients had *smaller* volumes across all subregions, which was mostly driven by medicated and adult-onset patients. No volume differences were found in adolescent OCD patients. Furthermore, most subregional group differences did not persist after adjusting for whole thalamus volume. Together, this provides new insight

that OCD-related thalamic volume differences are global and not driven by particular subregions and that the direction of effects are explained by both age and medication status.

The current study further elucidates the strongly age-dependent nature of the link between OCD and thalamic morphology. In line with our prior work, we found the whole thalamus was larger in the pediatric patient group [3]. However, a crucial difference is that we split the pediatric group into children (<12 years) and adolescents (12–17 years). This revealed that OCD-related thalamic volume differences appear during childhood and already attenuate during adolescence. Complementary to the pediatric findings and in contrast with our previous work, we found significantly smaller volumes across all subregions in adult OCD patients compared with controls. This novel finding relative to previous work is likely explained by increased power from the larger sample size and use of the ComBat algorithm to adjust for batch effects [16], as well as the more sensitive thalamic segmentation method [14]. Taken together, we robustly show that thalamic volume differences, regardless of subregions, follow an opposite trajectory from larger to smaller volumes across age in patients compared with controls. This is consistent with the significant interactions with age and age-by-sex we found in the pediatric sample. However, we are cautious to interpret the pediatric interaction analyses due to the low sample size and skewed age distribution in this group. Conversely, the sufficiently powered adult sample size did not show a significant interaction with age or age-by-sex. This could indicate that differences in volume trajectories across age between patients and controls that appear in the plot are challenging to model with formal testing. However, we did find a sex-by-diagnosis interaction in adults for the anterior subregion (see Table S3), indicating that OCD-related volume differences are on average stronger in females than males. We should note that our findings in adults are partly consistent with recent work from Jurg et al. in a sample that was also included in the current analysis [13]. While the current study found lower volumes of all subregions in adult OCD patients, Jurg et al. found significant differences only in the posterior thalamus region that includes the pulvinar [13]. This difference is most likely explained by differences in sample size and the fact that only unmedicated patients were included in the Jurg et al. sample.

Given that specific thalamic subregions play a key role in OCD-relevant circuitry [2], we hypothesized morphometric differences in these subregions in OCD. Thalamic subregions have been more intensively studied in relation to schizophrenia and have repeatedly shown subregional volume differences [19], including recently by using the same Iglesias et al. segmentation tool [20, 21]. Participants at high risk of developing schizophrenia with auditory hallucinations had a smaller volume of the medial geniculate nucleus and a steeper volume decrease over time compared with symptom-free controls, accompanied by functional connectivity differences in related circuits [21]. This suggests that subregional volume changes might be related to specific symptoms. OCD-related symptom dimensions have also been related to distinct structural changes [22]. In the current study, we only had data on global symptom severity and not specific symptom dimensions. Given the heterogeneity of the OCD phenotype and the many circuits involved, this could explain why the shrinkage of the thalamus was distributed across all subregions.

Conversely, thalamus volume was larger rather than smaller in the child sample, suggesting another process may be at play. For instance, the larger overall thalamus volume could reflect broad neurodevelopmental differences between patients and controls that predispose to developing OCD. During early childhood and adolescence, thalamo-cortical circuits undergo a process of myelination, synaptic remodelling and pruning that give rise to a mature thalamus [23]. Recent work showed that compulsivity

and impulsivity are related to reduced myelin-related growth in cortico-striatal regions in adolescents [24]. Although disagreement exists on the trajectory of normative thalamic development, relative thalamus size has been described to increase until 4 years of age [25], followed by either a steady decrease [26] or stabilization [25] during childhood and adolescence. The larger volumes observed in our pediatric OCD patients aged 6–12 years may therefore reflect altered neurodevelopment. The association was strongest in unmedicated children, indicating that medication normalizes thalamic volume. This is consistent with the report by Gilbert et al. [27], that revealed enlargement of the thalamus in pediatric patients that normalized after 12-week-treatment with paroxetine. Since neurodevelopment is governed by both genetic [28] and environmental influences [29], longitudinal studies integrating these aspects can offer insight into the altered neurodevelopment in OCD.

Thalamic volume declines with healthy ageing [30] and shows enhanced decline in various brain disorders [31, 32]. Likewise, OCD patients may exhibit a more rapid decline in thalamic volume through various mechanisms. Glutamatergic neurons fulfil an important role within the CSTC circuits. Several studies have found alterations in glutamatergic systems in OCD, indicating possible glutamatergic dysregulation [33, 34]. Excitotoxic effects of glutamate have been proposed as a mechanism for local structural loss in schizophrenia [35]. Alternatively, the presence of auto-antibodies in conjunction with increased excitatory metabolites in adult OCD suggest activity of autoimmune processes [34].

Our results suggest that medication status largely drives volumetric differences in adult OCD. Selective serotonin reuptake inhibitors (SSRIs) have been reported to induce both neurogenesis and neuronal elimination in the hippocampus [36, 37]. In vitro studies have linked antidepressant exposure to non-neuronal and neuronal apoptosis or death [38, 39], providing a possible mechanism for volume decline of brain structures. However, to our knowledge, such effects have not been described in the thalamus. In another study, a single dose of SSRIs caused widespread decreases in subcortical and cortical connectivity as well as increased thalamic connectivity [40]. Perhaps functional alterations induce structural remodelling of the thalamus that result in volumetric changes. However, causal effects cannot be inferred due to the cross-sectional methodology and lack of detailed information on medication status.

Only the anterior subregion was significantly smaller relative to overall thalamic volume in adult OCD patients, suggesting that this difference is superimposed on the overall thalamic difference. Formal comparison of effect sizes between the anterior region and other subregions using Z-tests showed (near) significant differences across regions. This suggests that on top of a general case-control difference in thalamus volume, the anterior subregion shows the most pronounced contribution to smaller volume in adult OCD. As the variance inflation factors were in the range 1.65–1.66 for the different subregions, there was no evidence of multicollinearity that may have influenced these findings. The ventral anterior nucleus connects to fronto-limbic regions including the medial orbitofrontal and ventromedial prefrontal cortex [7]. Lower relative volume of the anterior nucleus may reflect fronto-limbic disruption, which has been linked to the dysregulated fear responses in OCD, characterized by excessive and poorly controlled fear responses to stimuli [2].

Strengths of our study include the large sample size, the use of a harmonized and containerized processing protocol and quality inspection procedure, as well as adjustment for batch effects that arise from multi-site data. Furthermore, separation into three age groups allowed us to identify stage-specific volume differences. Nevertheless, the cross-sectional nature of the study complicates identifying developmental processes and medication effects that seem to underlie the observed volume effects. Furthermore,

despite adjustment for batch effects, we are not able to overcome all effects that arise from scanner and site differences. Since all sites included both patient and control groups, large effects of site differences are, however, not expected. Despite the large sample size, adults form the majority of participants and pediatric participants are relatively underrepresented. It is important to emphasize that because of this not all findings in the pediatric sample survived multiple comparisons. Fortunately, the ENIGMA-OCD Working Group continues to grow, and future analyses will enable us to balance out the age distribution in favour of younger participants. We should also acknowledge that the internal borders of the thalamus on T1 images are difficult to discern with visual checks and could not be used to visually verify the anatomical correctness of the segmentations. Despite this, the pipeline's validity has been thoroughly evaluated with histological comparison, across different field strengths (1.5T and 3T) and has successfully detected subregional differences across different disorders and age groups [12, 14, 20, 21].

Despite these limitations, our results provide the first robust findings on OCD-related volume differences in the thalamus across different developmental stages. In contrast with our hypotheses, we observed mostly global thalamic rather than region-specific volume differences, suggesting that the relationship with OCD is not driven by changes of a particular subregion but overall thalamus volume. Future endeavours should focus on disentangling longitudinal age-related and medication-related effects to determine what drives these global differences. Furthermore, multimodal approaches including resting-state functional MRI and diffusion-weighted imaging could bolster our understanding of thalamic connectivity and its involvement in OCD, preferably at higher field strengths to attain optimal contrast for high-quality images.

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Cees J. Weeland: Conceptualization, methodology, formal analysis, resources, data curation, writing—original draft, writing—review and editing, visualization; Selina Kasprzak: Conceptualization, methodology, resources, data curation, writing—original draft, writing—review and editing; Niels T. de Jooode, Yoshinari Abe, Pino Alonso, Stephanie H. Ameis, Alan Anticevic, Paul D. Arnold, Srinivas Balachander,

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## COMPETING INTERESTS

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## ADDITIONAL INFORMATION

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