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Grey matter volume differences in pediatric obsessive–compulsive disorder: a meta-analysis of voxel-based morphometry studies

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Abstract

Background Obsessive–compulsive disorder (OCD) is one of the most commonly seen mental disorders onset from childhood. The neural mechanisms underlying OCD development and maintenance remain poorly understood. Various empirical evidence from structural magnetic resonance imaging (MRI) studies has reported structural differences in grey matter (GM) among pediatric OCD patients. However, some of the findings diverge from others, and the association between GM and individual differences in pediatric OCD remains inconclusive. To address this gap, we conducted a meta-analysis to synthesize findings quantitatively.

Methods The current research conducted a quantitative meta-analysis of voxel-based GM studies to elucidate existence of neural correlates in pediatric OCD. A whole brain-based d-mapping approach was utilized to explore GM changes and further analyze the relationship between GM and individual differences in pediatric OCD patients.

Results Thirteen studies were included with 288 patients and 273 controls. Compared with controls, pediatric OCD demonstrated significantly greater GM volume in the left insula (SDM value = 1.72, $p < 0.005$) and left superior frontal gyrus (SFG) (orbital part) (SDM value = 1.47, $p < 0.005$), whereas we showed lower GM volume in the right superior temporal gyrus (STG) (SDM value = -1.87, $p < 0.005$), left inferior parietal gyri (IPG) (SDM value = -1.60, $p < 0.005$), left middle occipital gyrus (MOG) (SDM value = -1.66, $p < 0.005$), and left inferior frontal gyrus (IFG) (SDM value = -1.69, $p < 0.005$). The increase in SFG (orbital part) and decrease IPG was commonly found in those without psychiatric comorbidities and treatment-naive subgroup. Meta-regression analysis revealed that longer OCD duration was associated with less GM volume in IPG (SDM value = -3.057, $p < 0.005$). Finally, the onset age and the OCD symptoms severity were positively associated with GM volume in the SFG (SDM z = 2.387, $p < 0.005$).

Conclusions Our findings confirmed the most consistent GM differences in pediatric OCD, particularly in the MOG, IPG and SFG (orbital part), suggesting they are potential markers in pediatric OCD. Larger SFG (orbital part) and smaller IPG volumes are specific to those without comorbidities and untreated patients. The duration of OCD, symptom severity and onset age also influence GM structure. This research provides evidence of the underlying neuroanatomical characteristics of pediatric OCD.

Trial registration PROSPERO CRD42024601906.

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Keywords Obsessive–compulsive disorder, Childhood psychiatric disorders, Voxel-based morphometry, Grey matter, Meta-analysis

Background

Obsessive–compulsive disorder (OCD) is a neuropsychiatric disorder characterized by repetitive thoughts (obsessions) and behaviours (compulsions) that are experienced as unwanted [1] and commonly seen in children and adolescents with an estimated prevalence of 1% to 3% [2]. Furthermore, it demonstrates significant continuity from childhood into adulthood, with approximately 80% of adult OCD patients reporting the onset of their first OCD symptoms before the age of 18 years [3]. The symptoms of OCD significantly interfere with the daily activities of children or adolescents, leading to maladjustment in academic performance and social relationships. The abnormal feedback loops in the cortical-striatal-thalamic-cortical(CSTC) circuits have been implicated as crucial in the pathophysiology of OCD [4]. Those findings have been observed in both adult and pediatric OCD patients [5–7].

However, some differences may exist between adult and pediatric OCD patients, which may attributed to brain maturity [8, 9]. Pediatric OCD patients differ from adults in terms of sex ratio, with pediatric studies often reporting a higher proportion of males compared to adult studies [10]. Additionally, pediatric OCD patients with an earlier onset age may be less responsive to treatments, increasing their susceptibility to comorbid mental disorders and resulting in poor prognosis [11, 12]. Specifically, these young patients are more prone to concurrent tic disorders, depression and attention-deficit hyperactivity disorders (ADHD) [10]. These factors could potentially influence brain volume. Furthermore, the age of symptom onset and symptom severity vary considerably among OCD patients, suggesting that both general and specific etiological factors contribute to the observed phenotypic heterogeneity [13]. This underscores the importance of giving special attention to children with OCD. Nonetheless, the neuroimaging characteristics of pediatric OCD in this specific population have not been thoroughly investigated.

Voxel-based morphometry (VBM) analysis using structural magnetic resonance imaging (MRI) techniques has provided valuable evidence. The meta-analyses synthesizing mixed pediatric and adult OCD samples identified consistent GM reductions in the inferior frontal gyrus, and GM increases in the striatum [9, 14]. Notably, these findings have predominantly relied on mixed adult-pediatric samples, potentially obscuring developmental distinctions in brain abnormalities. Furthermore, the previous meta-analysis [9] included fewer than 10 pediatric studies and reported differences in GM with respect to the lenticular nucleus, medial frontal cortex and inferior frontal gyrus in pediatric OCD patients compared to controls. However, this analysis possessed only a limited number of studies focused solely on pediatric populations. Additionally, some studies have reported that GM volumes decreased in the superior and medial frontal gyrus [15], occipital and parietal cortex [16, 17], while GM increased in the orbitofrontal cortex, anterior cingulate cortex, putamen [17], and thalamus [18] in pediatric patients with OCD. In contrast, smaller GM volumes in the anterior cingulate gyrus and greater GM volumes in the cerebellum were observed only in adult patients with OCD [9]. These inconsistencies may reflect methodological variability or developmental heterogeneity not captured in meta-analyses. Despite growing evidence from structural MRI studies, few meta-analysis has yet focused exclusively on pediatric OCD. Existing meta-analyses either combine pediatric and adult samples [9, 14] or are limited by small pediatric subsamples [9], leading to inconclusive and potentially confounded findings. This gap underscores the need for a dedicated synthesis of pediatric OCD neuroimaging data.

Differences in brain volume reported in pediatric OCD from previous studies may be confounded by various factors, such as treatment response (e.g. medication or cognitive behavioural therapy) [16, 19, 20] or long-term effects of the disease itself [21, 22]. Specifically, the study of Lázaro et al. [16] reported increased GM in parietal regions after medication treatment in pediatric OCD patients, while the study of Huyser et al. [20] found that GM increased in orbital frontal gyrus following cognitive behavioral therapy (CBT). Brain abnormalities have also been associated with different ages at onset, which may act as a moderator of some GM and white matter differences in pediatric OCD [23]. Early-onset OCD demonstrates greater heritability and familial loading compared to adult-onset OCD, suggesting a stronger genetic component [24]. The studies of Carmona et al. [25] and Valente et al. [26] have found negative associations between OCD severity of symptoms and GM in the hippocampus and medial thalamus, respectively. However, Pujol et al. [27] did not find any correlation with disease severity. Considering the inconsistency of previous evidence,

the current study also aimed to quantitatively explore the association between structural imaging results and related clinical characteristics that may influence these outcomes.

The VBM analysis allowed standardized synthesis of whole-brain GM volume differences. The cortical volume encompasses information from both cortical thickness and cortical surface area [28]. This measurement integrates the combined influences of genetic factors and structural phenotypes on cortical thickness and surface area [29]. Therefore, we posit that GM volume may represent the most optimal metric for assessing brain morphological characteristics. Consequently, in the current review, we aimed to conduct a VBM analysis for pediatric OCD patients using anisotropic effect size-signed differential mapping (AES-SDM) software [30]. We will also perform jackknife sensitivity analyses to evaluate the robustness and heterogeneity of the main results. Specifically, we would carry out subgroup analyses based on treatment status (treatment-naïve or treated pediatric OCD) and the presence of psychiatric comorbidities (with or without). However, direct statistical comparisons between these subgroups (e.g., treated vs. treatment-naïve; comorbidity vs. non-comorbidity) were not feasible due to methodological constraints of coordinate-based meta-analyses and insufficient overlap in reported data across studies. Finally, meta-regression analyses will be conducted to investigate the potential moderating effects of other relevant clinical factors, including sample age, age of OCD onset, sex (male ratio), OCD duration, and symptom severity (assessed by Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS] score) on the reported GM abnormalities. Based on previous evidence, we hypothesized that, firstly, the GM of pediatric OCD would significantly differ from the controls; Secondly, specific GM volume differences would be associated with treatment status, psychiatric comorbidities, and clinical characteristics (e.g., symptom severity, illness duration).

Methods

Data source

Systematic and comprehensive searches were conducted in the PubMed, Google Scholar, Embase, and Cochrane Library databases to identify studies published up to July 2024, following the PRISMA guideline [31]. This quantitative meta-analysis adhered to a prospectively registered protocol (PROSPERO, CRD42024601906). The search keywords included: obsessive–compulsive disorder, VBM, grey matter, voxel-based morphometry; volumetry, morphometry or structural MRI. The reference lists of identified articles and relevant theoretical reviews were manually scrutinized to obtain additional papers.

Inclusion/exclusion criteria

Studies were included if they: (1) involved subjects with a primary diagnosis of OCD meeting the DSM diagnostic criteria; (2) reported whole-brain GM alterations in MNI space; (3) use of VBM to explore GM differences between OCD patients and controls; (4) included participants aged < 18, with informed consent provided by all participants; (5) were peer-reviewed original studies; (6) were published in English (for quality assurance purposes).

Studies were excluded if they: (1) only reported a region-of-interest or non-whole-brain approaches (e.g., hypothesis-driven analyses restricted to predefined brain regions) instead of unbiased whole-brain VBM results; (2) included participants aged ≥ 18 years; (3) original coordinates were unavailable, and the author did not respond to email inquiries; (4) were not published in English; (5) consisted of animal experimental studies, review or theoretical articles; (6) only reported results based on small volume correction without whole-brain findings; (7) analyzed white matter differences or cortical thickness only (Fig. 1).

Quality assessment

To evaluate the quality of selected studies, we utilized a checklist (used in other studies [32]) to estimate each included study based on the reported demographic and clinical characteristics of the subjects, as well as the imaging methodology. The criteria were as follows: (1) sample size; (2) demographic matching (e.g., age, sex) minimizes confounding bias in case–control VBM studies; (3) comparison between healthy controls and OCD patients; (4) method of diagnosis; (5) whole brain analysis; (6) use of GM volume covariates; (7) MRI machines and smooth kernels; (8) standard spatial coordinates (e.g., MNI coordinates or TL coordinates); (9) correction of statistical results for multiple comparisons. Each criterion was independently evaluated by two reviewers who scored 2, 1 or 0 if the criterion was fully satisfied, partially satisfied, or otherwise, respectively. Any study scoring above10.0 was included in the meta-analysis. More details are supplemented to Table S1.

AES-SDM

Structural brain differences between patients with OCD and controls were analyzed using AES-SDM (available at http://www.sdmproject.com/). The details of the AES-SDM method have been described previously [14]. In brief, the main steps of AES-SDM were as follows: First, we extracted peak coordinates to create txt files in from the included studies. The effect size, such as P- or Z- values for clusters, were transformed into t-statistics by the SDM online conversion utilities (available at https://www.sdmproject.com/utilities/). Next, txt files containing

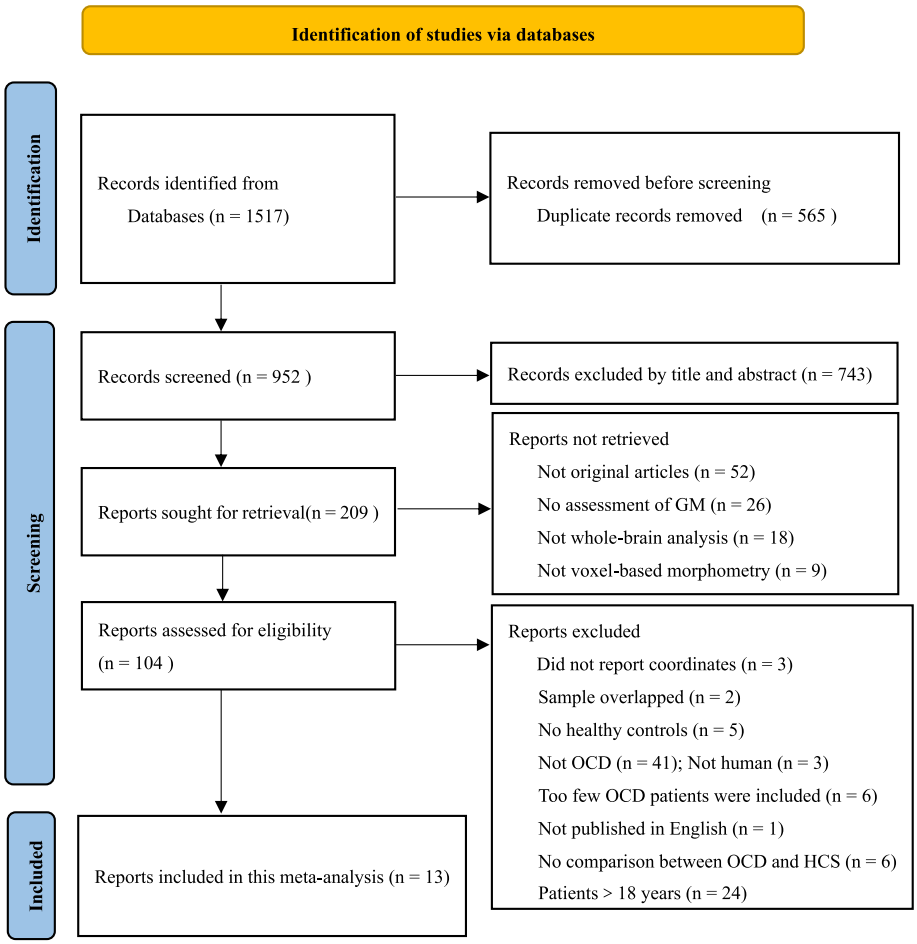

Fig. 1 Flowchart of the selection of VBM studies in patients with OCD for meta-analysis

peak coordinates were imported into the SDM software to collect raw information and the main outcomes of the included research, resulting in the creation of a sdm_table. Finally, we conducted pre-processing (including conversion of statistical values (e.g., t-statistics) to standardized effect sizes, and reconstruction of effect size maps), mean analysis (denoting the primary meta-analysis comparing GM volume differences between pediatric OCD patients and healthy controls, the statistical combination of data from multiple studies to identify consistent patterns of brain differences), sensitivity analysis, heterogeneity analyses, subgroup meta-analysis based on treatment (e.g., without and with other medications or cognitive behavioural therapy) and comorbidity status (without and with other psychiatry comorbidities, such as tic disorders, depression and ADHD). The non-comorbidity was this determination based mainly on declarations by the original authors (Table S2). Subgroup analyses for psychiatric comorbidities were conducted at the study level. Specifically, studies were classified into “comorbid” or “non-comorbid” subgroups based on whether they explicitly included or excluded participants with concurrent psychiatric diagnoses (e.g., ADHD, depression). Individual patient data were unavailable for most studies, precluding within-study subgroup analyses. Treatment status was also grouped in this way. We also performed meta-regression analyses for mean age, the proportion of males, CYBOCS total score, CYBOCS obsessions score, CYBOCS compulsions score, duration of illness, and age at onset. The studies were assgned different weights based on the number of participants and quality of the research, with weights calculated as the square root of the sample size multiplied by the quality score of each study [30].

A whole brain voxel-based jackknife sensitivity analysis was performed on meta-analysis to assess the reproducibility of the results using the same threshold as meta-analysis. We repeated the main analysis 13 times, each time leaving out one different study, to determine whether the results of the meta-analysis remained significant. Conclusions can be drawn if differences for a brain region remain significant in more than 75% of the

sensitivity analyses, which used in previous neuroimaging meta-analysis [33, 34]. Furthermore, between-study heterogeneity of brain abnormalities from meta-analysis results was analyzed using a random effects model with Q statistics. We used the default threshold in SDM, which included a voxel threshold of $P<0.005$, peak $Z>1$, and a cluster extent of 10 voxels. Lastly, for each significant peak, Egger tests were conducted to examine the possibility of publication bias to identify the asymmetry in the funnel plots.

Results

Included studies and sample characteristics

As illustrated in Fig. 1, the search strategy yielded 13 studies for inclusion in the meta-analysis. The total sample comprised 288 patients with OCD (156 males and 132 females; mean age range: 10.8–16.6 years) and 273 controls (147 males and 126 females; mean age range: 10.5–16.5 years). The demographic details of all included studies are presented in Table 1.

Regional GM differences

In the pooled AES-SDM meta-analysis, pediatric OCD patients exhibited significantly greater GM volume in the left insula and left superior frontal gyrus (SFG) (orbital part) compared to controls. Additionally, these patients had significantly lower GM volume in the right superior temporal gyrus (STG), left inferior parietal gyri (IPG), left middle occipital gyrus (MOG), left inferior frontal gyrus (IFG) compared to controls (Fig. 2a and b). Table 2 displays the peak coordinates and cluster breakdown.

Sensitivity, heterogeneity analyses and publication bias

As shown in Table 2, a whole-brain jackknife sensitivity analysis of the findings indicated that GM volume differences in the left insula and left SFG were highly replicable and persisted when each study was individually removed. GM volume differences in the right STG (orbital part) remained significant in 12 out of 13 combinations. Results in the left IPG and left MOG remained significant in 11 out of 13 combinations. The result in the left IFG remained significant in 10 out of 13 combinations. Heterogeneity was detected in a few regions with GM volume differences in the left insula and left SFG ($P<0.05$) (Table S3). To examine potential publication bias, funnel plots and Egge's tests were conducted, the Egger tests of funnel plot asymmetry did not reveal any statistically significant in all clusters except the left IFG (Figure S1).

Subgroup meta-analyses

Treatment-naive pediatric OCD patients showed greater GM volume in the left SFG (orbital part) and smaller GM volume in the left IPG and left MOG (Table 3 and Fig. 2c). Treated pediatric OCD patients (eg., those receiving selective serotonin reuptake inhibitors or tricyclic antidepressants or mood stabilizers or stimulants or Desyrel or clonidine or memantine or atomoxetine or lorazepam or CBT etc.) exhibited greater GM volume in the left SFG (medial orbital), and smaller GM volume in right rolandic operculum and left median cingulate/paracingulate gyri (Table 3 and Fig. 2d).

Pediatric OCD patients in studies without psychiatric comorbidities showed greater GM volume in the left SFG (orbital part) (Table 3 and Fig. 2e). Pediatric OCD patients with any other psychiatry comorbidities (eg., generalized anxiety disorder, simple phobia, agoraphobia, major depression, tourette's or ADHD, etc.) showed greater GM volume in the left insula and right striatum, and smaller GM in the right cingulate gyrus (Table 3 and Fig. 2f).

Meta-regression analysis

As shown in Fig. 3, meta-regression analysis revealed that the age of the entire sample was negatively associated with GM volume in the left IFG (MNI coordinates: −48,26,18; SDM $z=-2.113$; $P=0.00124$; 284peak voxels (Fig. 3a). The male ratio of the sample was negatively associated with GM volume in the left MOG (MNI coordinates: −26, −82, 12; SDM $z=-2.153$; $P=0.0004$; 124 peak voxels) (Fig. 3b). GM volume in the left SFG (orbital part) was positively associated with CYBOCS total score (MNI coordinates: −16, 60, −10; SDM $z=3.684$; $P=\sim 0$; 1140 peak voxels) and CYBOCS compulsion score (MNI coordinates: −18, −58,−8; SDM $z=2.688$; $P=\sim 0$; 1641 peak voxels) in the pediatric patients with OCD (Fig. 3c and d). CYBOCS obsessions score from pediatric patients with OCD were not linearly correlated with GM volume. Studies included subjects with longer OCD duration reported less GM volume in the left IPG (MNI coordinates: −54, −44,42; SDM $z=-3.057$; $P=0.00006$; 1094 peak voxels) (Fig. 3e). Finally, we found that the age of onset in pediatric OCD symptoms was positively association with GM volume in the left SFG (orbital part) (MNI coordinates: −20, 58, −6; SDM $z=2.387$; $P=0.00023$; 221 peak voxels) (Fig. 3f), with the older age of the onset corresponding to larger GM volume in the left SFG (orbital part).

Table 1 Demographic and clinical characteristics of the pediatric OCD participants in the study in the meta-analysis

Study	OCD patients									HCS		Methodology	
	No.(males)	Mean age, yr	Duration of illness, yr	Age of onset	CYBOCS total	CYBOCS obsessions	CYBOCS compulsion	treatment (%)	Comorbidity (%)	No.(males)	Mean age, yr	MRI scanner	Smooth kernel
Britton et al. (2010) [35]	15(9)	13.5(2.4)	4.1(2.0)	8.4	15.4(5.7)	6.6(3.9)	8.8(5.5)	Y (100%)	Y (73%)	20(13)	13.6(2.4)	3.0 T	6
Cabrera et al. (2019) [36]	14(10)	11.14(1.72)	Ns	Ns	Ns	Ns	Ns	Ns	Y (64%)	14(10)	11.14(1.72)	3.0 T	10
Carmona et al.(2007) [25]	18(13)	12.86(2.76)	Ns	Ns	21.39(5.88)	10.28(4.28)	10.94(4.27)	Y (55%)	Y (94.40%)	18(13)	13.03(3.04)	1.5 T	8
Chen et al. (2013) [37]	8(4)	11.7(2.7)	0.67	11.03	31.1(4.3)	Ns	Ns	N	N	12(6)	11.8(2.2)	3.0 T	8
Cheng et al. (2016) [38]	30(18)	10.8(2.1)	0	10.8	18.3(5.5)	11.1(3.5)	10.2(4.1)	N	N	30(18)	10.5(2.2)	3.0 T	8
Gilbert et al. (2008) [15]	10(6)	12.9(2.7)	Ns	Ns	26.5(5.4)	13.7(2.9)	12.7(3.1)	N	N	10(6)	13.4(2.6)	1.5 T	Ns
Huyser et al. (2013) [20]	29(11)	13.78(2.58)	2.6(2.3)	12.17(3.0)	24.86(4.95)	12.34(2.64)	13.03(2.5)	N	Y (80%)	29(11)	13.6(2.73)	3.0 T	8
Jayarajan et al.(2015) [39]	15(8)	14.13(1.79)	1.4(1.04)	12.73(1.87)	21.47(7.41)	10.87(3.76)	10.6(3.72)	Y (87%)	Y (40%)	15(8)	14.31(2.15)	3.0 T	Ns
Lázaro et al. (2009) [16]	15(8)	13.7(2.5)	1.77	11.9(2.7)	25.9(5.6)	11.9(4.3)	14(2.8)	N	N	15(8)	14.3(2.5)	1.5 T	12
Lázaro et al. (2014) [40]	62(36)	15.4(2.1)	2.36	12.91	18.0(8.2)	Ns	Ns	Y (83.90%)	N	46(22)	15.3(2.1)	3.0 T	8
Mirabella et al.(2020) [41]	9(5)	11.29	Ns	Ns	18.4	Ns	Ns	N	N	12(9)	10.5(1.1)	3.0 T	8
Szeszko et al. (2008) [17]	37(14)	13.0(2.7)	3.6	9.4	24.9(6.0)	12.8(4.4)	12.0(3.2)	N	Y (37.80%)	26(9)	13.0(2.6)	1.5 T	8
Zarei et al. (2011) [10]	26(14)	16.6(1.5)	5.3(3.4)	11.2(2.8)	19.5(7.6)	9.7(3.9)	9.8(3.9)	Y (65%)	N	26(14)	16.5(1.4)	1.5 T	Ns

OCD obsessive–compulsive disorder, *HCS* healthy controls, *CYBOCS* Children's Yale-Brown Obsessive Compulsive Scale, *Ns* not specified

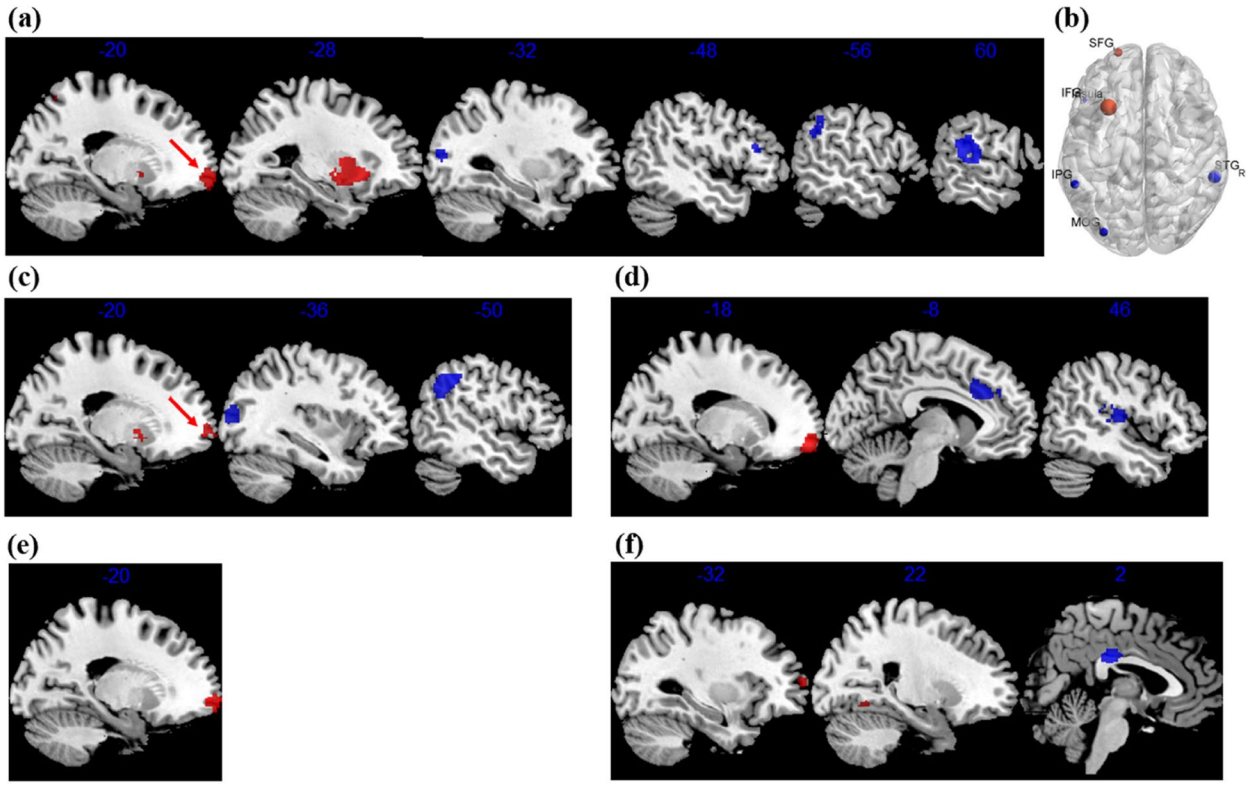

Fig. 2 Meta-analysis results. GM volume differences in pediatric patients with OCD relative to HCS. **a** pediatric OCD patients vs. HCS (GM from left to right: SFG (orbital part), insula, MOG, IFG, IPG, STG); **b** Spatial visualization of the differential GM; **c** Treatment-naive pediatric OCD patients vs. HCS (GM from left to right: SFG (orbital part), MOG, IPG); **d** Treatment pediatric OCD patients vs. HCS (GM from left to right: SFG (medial orbital), rolandic operculum, median cingulate / paracingulate gyri); **e** pediatric OCD patients without other psychiatry comorbidities (GM difference in SFG (orbital part)); **f** pediatric OCD patients with other psychiatry comorbidities (GM from left to right: insula, striatum, cingulate gyrus); GM enlargements are indicated in red and GM reductions in blue. Abbreviations: GM, grey matter; OCD, obsessive–compulsive disorder; HCS, healthy controls; SFG, superior frontal gyrus; STG, superior temporal gyrus; IPG, inferior parietal gyrus; MOG, middle occipital gyrus; IFG, inferior frontal gyrus

Table 2 Grey matter alterations in pediatric patients with OCD compared with controls in the pooled meta-analysis

Anatomical regions	MNI coordinates x, y, z	SDM value	*p*-value	Number of voxels	Breakdown	Jackknife sensitivity analysis
OCD > HCS						
Left insula, BA 48	−28,20,6	1.72	0.00004	1176	Left insula, BA 48; Left striatum; Left lenticular nucleus, putamen, BA 48	13/13
Left superior frontal gyrus, orbital part, BA 11	−20,66, −4	1.47	0.00038	152	Left superior frontal gyrus, orbital part, BA 11, BA10	13/13
OCD < HCS						
Right superior temporal gyrus, BA 48	60, −38,18	−1.87	0.00063	614	Right superior temporal gyrus, BA 42,48; Right rolandic operculum, BA 48	12/13
Left inferior parietal gyrus, BA 40	−56, −44,42	−1.60	0.00282	148	Left inferior parietal gyri, BA 40; Left angular gyrus, BA 39	11/13
Left middle occipital gyrus, BA 19	−32, −84,14	−1.66	0.00205	118	Left middle occipital gyrus, BA 19,18	11/13
Left inferior frontal gyrus, BA 45	−48,26,20	−1.69	0.00183	43	Left inferior frontal gyrus, BA 45,48	10/13

OCD obsessive–compulsive disorder, *HCS* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *BA* Brodmann area

Table 3 Regional differences of grey matter changes between pediatric patients with OCD and HCS in the subgroup meta-analysis

Anatomical regions	MNI coordinates x, y, z	SDM value	*p*-value	Number of voxels	Breakdown	Jackknife sensitivity analysis
Samples from treatment-naive ($n=7$)						
GM greater (OCD > HCS)						
Left striatum	−20,6,4	1.897	0.0001	350	Left striatum; Left insula, BA 48, BA47	5/7
Left superior frontal gyrus, orbital part, BA 11	−20, 62, −4	1.529	0.0006	106	Left superior frontal gyrus, orbital part, BA 11, BA10	5/7
GM smaller (OCD < HCS)						
Left inferior parietal gyri, BA 40	−50, −44,44	−1.936	0.00004	874	Left inferior parietal gyri, BA 40, BA39	6/7
Left middle occipital gyrus	−36, −84,12	−1.552	0.00117	220	Left middle occipital gyrus, BA 19, BA18	6/7
Samples from treatment OCD ($n=5$)						
GM greater (OCD > HCS)						
Left superior frontal gyrus, medial orbital, BA 11	−18, 58, −8	1.004	~0	917	Left superior frontal gyrus, medial orbital, BA 11	4/5
GM smaller (OCD < HCS)						
Right rolandic operculum, BA 48	46, −18,14	−2.033	0.00032	567	Right rolandic operculum, BA 48, BA42, BA22; Right superior temporal gyrus, BA 22, BA42, BA48	4/5
Left median cingulate / paracingulate gyri, BA 32	−8,28,30	−2.288	0.00011	596	Left median cingulate / paracingulate gyri, BA 24	5/5
Samples without other psychiatry comorbidities ($n=7$)						
GM greater (OCD > HCS)						
Left superior frontal gyrus, orbital part, BA 11	−20,60, −6	1.161	0.00009	155	Left superior frontal gyrus, orbital part, BA 11	6/7
GM smaller (OCD < HCS)						
Left inferior parietal gyri, BA 40	−54, −42,42	−1836	0.0015	344	Left inferior parietal gyri,BA40	4/7
Samples with other psychiatry comorbidities ($n=6$)						
GM greater (OCD > HCS)						
Left insula, BA 48	−32, 12, 2	2.251	0.00056	353	Left insula, BA 48; Left lenticular nucleus, putamen, BA 48; Left striatum	5/6
Right striatum	22, 12, −2	1.558	0.00139	76	Right striatum; right lenticular nucleus, putamen, BA 48	5/6
GM smaller (OCD < HCS)						
Right cingulate gyrus, BA23	2, −26, 32	−1.620	0.00062	164	Right cingulate gyrus, BA23; Left cingulate gyrus, BA23	5/6

OCD obsessive–compulsive disorder, *HCS* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *BA* Brodmann area

Discussion

The current meta-analysis, utilizing AES-SDM and based on VBM studies with relatively large sample sizes, revealed GM volume alterations in pediatric OCD patients. It was found that, compared to controls, pediatric OCD patients demonstrated GM volume increase in the left insula and left SFG (orbital part), and GM volume decreased in the right STG, left IPG, left MOG and left IFG. Second, the GM increase in SFG (orbital part) volume and GM decrease in IPG volume were observed in those without psychiatric comorbidities and in the treatment-naive subgroup. Meta-regression analysis indicated that GM volume in the IFG decreased with higher mean age, GM volume in the SFG (orbital part) was positively associated with symptom severity and onset age, GM volume in the MOG was negatively associated with percentages of males, OCD duration was associated with reduced GM volume in the IPG. To our knowledge, this is one of the few meta-analyses exclusively focused on pediatric OCD using voxel-based methods. While ENIGMA-OCD consortium studies [42, 43] included pediatric

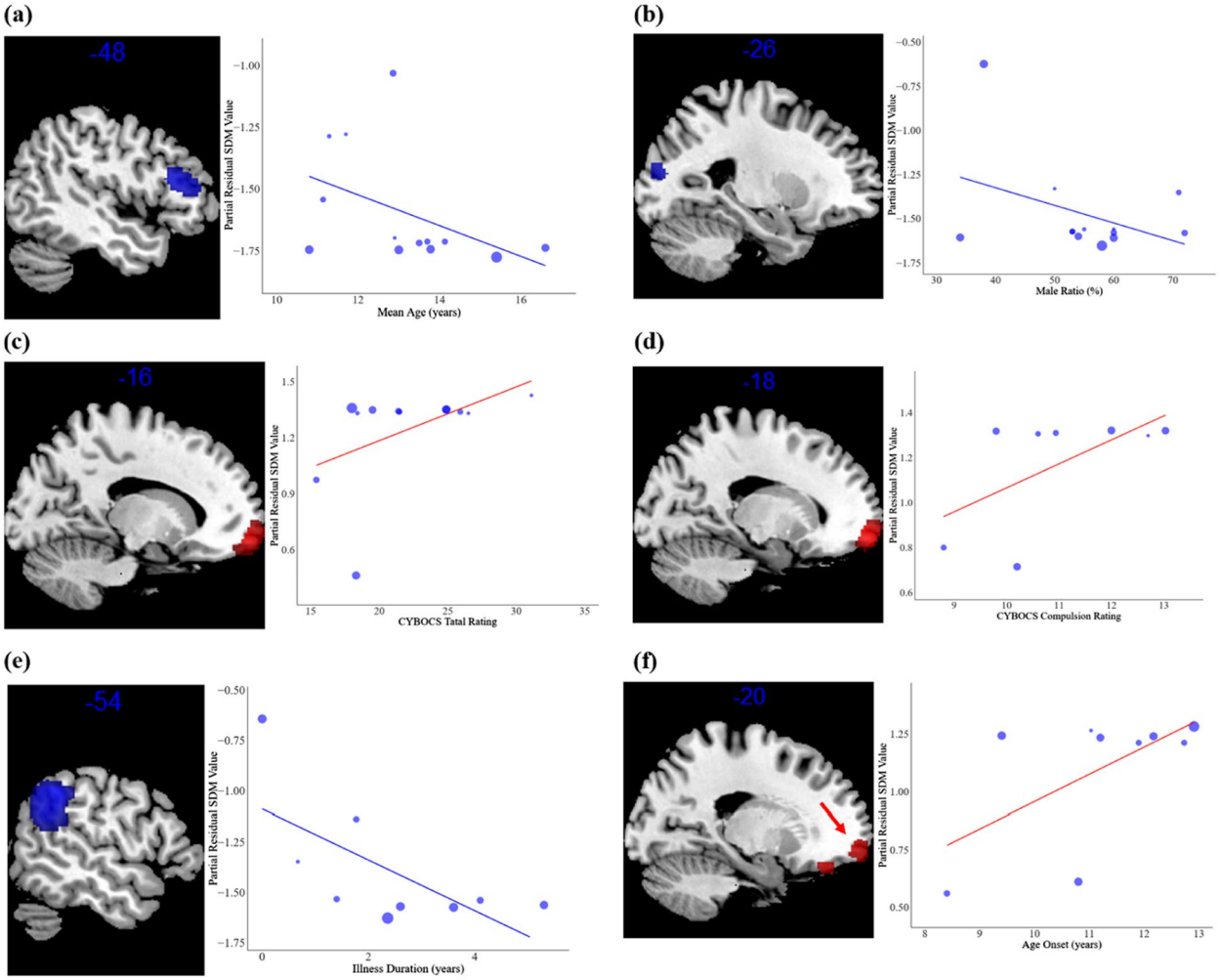

Fig. 3 Meta-regression analysis results. **a** GM volume in the left IFG was significantly negatively associated with the mean age in pediatric OCD patients. **b** GM volume in the left MOG was significantly negatively associated with the male ratio in pediatric OCD patients. **c** GM volume in the left SFG (orbital part) was significantly positively associated with CYBOCS score in pediatric OCD patients. **d** GM volume in the left SFG (orbital part) was significantly positively associated with CYBOCS compulsion score in pediatrics OCD patients. **e** GM volume in the left IPG was significantly negatively associated with duration illness in pediatric OCD patients. **f** GM volume in the left SFG (orbital part) was significantly positively associated with onset age in pediatric OCD patients. The blue color represents GM reduction, and the red color represents GM increase

subsamples, their primary focus on combined adult-pediatric cohorts limits developmental specificity.

The results revealed a significantly increased GM volume in the insula in pediatric OCD patients compared to controls, which aligns with previously published studies and reviews [10, 15, 44]. The insula, a region of the brain located deep within the lateral sulcus, is part of the inhibitory network in both children and adults [45, 46]. It is a key component of habit learning, motivation, emotional regulation, interoceptive awareness, and salience-events detection, contributing to activation of target brain regions in generating appropriate behavioural responses to salient stimuli [47]. Those stimuli are regulated by dopaminergic activity, and increased striatal synaptic dopamine has been found in OCD, which may be related to enhanced volumes observed [48–51]. Consequently, dopamine antagonists are effective as augmentation medications in OCD [52]. Another contributing factor may be the consistent evidence for abnormal salience-processing networks in OCD [53]. The enlarged GM in the insula in paediatrics OCD may be a neuroplastic consequence of increased insula activation during symptom provocation [54], which may mediate habitual compulsions, goal-directed action control, and misattributions of behavioural and emotional salience to symptom-provoking stimuli [54]. Enhanced bottom-up detection by the insula in pediatric OCD may increase automatic or habitual responding and heightened interoceptive processing

at the cost of goal-driven behaviour, such as inhibitory control [48]. The insula's GM enlargement may reflect altered salience processing, consistent with its role in OCD pathophysiology [55]. Furthermore, enlarged insula volume has also been found in adult OCD in the previous study [56]. Given that the increase in insula persists from childhood to adulthood, we therefore hypothesize that the larger insula in OCD could be the consequence of illness chronicity.

The SFG is a component of the frontostriatal circuitry, which plays a crucial role in regulating behaviour and cognitive processes [57, 58]. Dysregulation in this circuitry can impair executive functioning in OCD, making it difficult for patients to control obsessive thoughts and compulsive actions effectively [59]. Increased SFG in pediatric OCD also aligns with evidence of GM overgrowth that appears to stabilize later in life [60]. The SFG, involved in higher cognitive functions like decision-making, planning, and self-control, has been identified as a potential region in the pathophysiology of pediatric OCD [15, 57], and is also thought to relate to inhibitory control processes [61]. The increased volume of SFG may reflect the excessive excitation of this circuit, leading to the failure of the control of compulsive behavior [5]. Furthermore, we also identified that positive association between GM in the SFG (orbital part) and the severity of OCD symptoms in pediatric patients. The meta-analysis by Norman et al. [44] indicated that prefrontal structural abnormalities were specifically associated with OCD symptom dimensions such as compulsive behaviors. Possible mechanisms were that severe OCD symptoms might drive excessive activation of SFG, and long-term increased neural activity may lead to increased GM volume through synaptic remodelling or gliosis [20]. The present study found that SFG (orbital part) volume was greater in pediatric OCD patients with a later age of onset. This result supports the hypothesis of neurodevelopmental heterogeneity in OCD [62]. Early-onset OCD and late-onset OCD may have different neural mechanisms. Early-onset OCD is often associated with a stronger genetic burden and family history [1], and its SFG may not fully develop due to abnormal synaptic pruning or delayed myelination, resulting in a smaller SFG [13]. Increased SFG volume in late-onset patients may reflect adaptive changes in neuroplasticity during adolescence, such as compensatory responses to stress or environmental factors [15]. In addition, hormonal changes during puberty (such as dopaminergic system maturation) may affect the developmental trajectory of SFG [17]. Subgroup analysis showed a more significant increase in SFG (orbital part) volume without other psychiatry comorbidities and untreated patients, whereas this difference was attenuated after treatment [16]. For example, Huyser et al. [20] found that CBT reversed orbitofrontal GM abnormalities in adolescents with OCD, suggesting that SFG volume changes may be treatment-sensitive. This plasticity may achieve symptom improvement by regulating the overactivity of the CSTC circuit [63]. The absence of other psychiatric comorbidities can sometimes simplify the clinical presentation. Therefore, SFG volume may be used as a potential biomarker for treatment response. Notably, this pattern was not observed in other regions (e.g., insula, IFG, MOG), which may reflect distinct neuroplastic mechanisms in the SFG. The GM increase in SFG (orbital part) among treatment-naïve and non-comorbid subgroups suggests its potential role in early neurodevelopmental abnormalities, as observed in other neurodevelopmental disorders (e.g., ASD [64] and ADHD [65]). However, whether this reflects compensatory mechanisms or pathological overgrowth requires longitudinal investigation.

Our results also reported the consistent GM volume difference in IPG, which also found in the treatment-naïve and non-comorbid pediatric OCD subgroup. Given that the duration of illness in OCD can significantly affect symptom severity and treatment response [66], our meta-regression linked longer illness duration to reduced IPG volume, aligning with evidence that chronic OCD may accelerate structural decline in regions supporting sensory integration [67]. Patients with a longer duration of OCD may show different responses to treatment compared to those with a shorter duration [66]. Chronic course of illness might require more intensive or prolonged interventions to achieve symptom relief [68]. Comorbidities (e.g., ADHD, tic disorders) are often accompanied by extensive brain structural changes [44], and the reduced IPG in the group without comorbidities is more likely to be specifically associated with sensory integration deficits in OCD. The ENIGMA study by Boedhoe et al. [42] found that parietal abnormalities exist independently of comorbidities in pediatric OCD, which is consistent with the results of this study. Compared to treatment group, we found GM reduction in the IPG disappeared. Thus, we highlight the importance of early intervention and comprehensive treatment approaches to mitigate long-term neural and functional impacts.

In addition, the occipital cortex is believed to be associated with visuospatial function, playing a crucial role in visual-spatial processing and information reception [69]. Alterations in this brain region may affect how pediatric patients with OCD perceive and respond to visual cues [70]. In pediatric OCD, the reduction of GM volume in MOG may reflect abnormalities in the visual processing network, closely related to the patient's excessive attention to detail (such as obsessive checking of contamination or symmetry) [71]. Olatunji et al. [72] found

that patients with OCD have enhanced activation in the occipital cortex when exposed to pollution-related stimuli, and structural abnormalities may impair their adaptive filtering of visual information and exacerbate obsessive anxiety. In addition, visual processing deficits may further sustain compulsive behavior by affecting cognitive flexibility, such as difficulty in moving from local details to global context [69]. Furthermore, our findings found that GM volume in the MOG was negatively correlated with the proportion of males in the sample, suggesting that male patients with OCD may be more prone to structural abnormalities in the brain regions related to visual processing. The male brain undergoes more significant GM pruning during adolescence [29], and the early onset of OCD (with a male predominance) may be associated with an acceleration or disruption of this process. Studies have found that male OCD patients have more significant abnormalities in the prefrontal-striatal circuit [73], and the structural abnormalities of the MOG, as the hub of the visual-prefrontal connection, may exacerbate the symptoms of male patients. Our results also revealed that the GM volume differences in MOG were observed in pediatric OCD in the treatment-naïve groups but not in adult OCD samples in previous studies [9]. Pharmacological treatment (such as SSRIs) or CBT may improve MOG function by modulating visual-prefrontal connectivity, thereby partially reversing structural abnormalities [20]. For example, Lazaro et al. [16] found an increase in occipital GM volume in children with OCD after drug treatment, suggesting that treatment may repaire visual processing networks through neuroplasticity. The reduction in MOG volume in the untreated group may represents pathological progression without intervention, and reflects the abnormality of visual processing network in pediatric OCD, which is different from that in adults, and the structural differences in male patients and untreated subgroups may mark the core pathological mechanism of the disease.

Finally, we found that the IFG volume was significantly negatively associated with the mean age of the samples. Younger patients exhibited greater GM volume in the IFG, a region implicated in cognitive control circuits, potentially reflecting delayed maturation of cognitive control circuits. While prior work links IFG structure to cognitive flexibility [35], our study did not assess this behavior, thus, this association remains speculative. This finding further implies that neurodevelopmental differences during childhood and adolescence can influence the IFG's role in OCD, potentially leading to variations in symptomatology and brain function across different age groups [62].

Above all, GM in the IFG and insula were similarly observed in the previous meta-analysis studies [9, 14, 56], which included across samples of adults and youths, suggesting these regions are stable neural markers of OCD. Our study reported the GM difference in the MOG, while the analysis by Norman et al. [44] did not cover the vision-related regions. This discrepancy may stem from the latter's focus on the frontostriatal-mediated inhibitory control circuit, whereas our whole-brain analysis has unveiled more extensive brain structural abnormalities. Meanwhile, the adult OCD study by Radua et al. [5] did not report GM differences in MOG, SFG and IPG. The possible explanation posits that the pediatric brain is in a dynamic process of maturation, with the prefrontal cortex (e.g., SFG) and visual networks (e.g., MOG) potentially undergoing critical remodelling during adolescence, leading to abnormal patterns that differ from those observed in adults. The current study focused on investigating the GM alterations in pediatric OCD, confirming abnormalities consistent across age groups (e.g., IFG and insula) while uncovering pediatric-specific brain regions (e.g., MOG, SFG and IPG). These findings underscore the importance of dissecting the neural mechanisms of OCD within a developmental framework and provide novel targets for future pediatric research. Finally, our findings in the IPG align with ENIGMA-OCD reports of abnormalities [43]. This cross-method convergence (VBM vs. cortical thickness) strengthens confidence in these regions as transdiagnostic OCD markers. Unlike ENIGMA's report of enlarged thalamus volumes in unmedicated youth [42], we observed SFG/IPG abnormalities. The possible reason is that our VBM approach vs. ENIGMA's region-of-interest focus may prioritize distinct spatial patterns. Furthermore, the predominance of left-hemisphere abnormalities (insula, SFG, IFG, IPG, MOG) aligns with pediatric OCD's association with language-mediated obsessions (e.g., taboo thoughts) and left-lateralized executive networks [62]. The left insula and IFG are hubs for language processing and cognitive control [45], which are developmentally prioritized in early adolescence. Aberrant left-hemisphere growth patterns may reflect disrupted maturation of these circuits, predisposing to compulsive verbal rituals and impaired inhibition [35]. Notably, adult OCD studies report more bilateral changes [5], suggesting pediatric leftward anomalies may spread with ageing.

Limitation

There are several limitations to note. First, the current review only identified and included cross-sectional studies, which limits our ability to determine causal relationships between GM differences and clinical variables. Further longitudinal studies are necessary to establish the relationships. Second, we utilized peak coordinates and effect size from published studies rather than the

original data, potentially overlooking subtle differences in individual studies and potentially result in less accurate findings [74]. Third, the sample size for the subgroup meta-analysis may be significantly reduced due to limited available data, such as treated OCD (less than half of the 13 studies provided this information), necessitating cautious interpretation of these results. Fourth, although voxel-based meta-analysis methods effectively control for false positive results, false negative results remain difficult to avoid [75]. Fifth, heterogeneity analysis revealed significant statistical heterogeneity in many brain regions with altered GM across studies. To explore the factors contributing to this heterogeneity, we conducted subgroup analysis and meta-regression analysis [5] to elucidate these effects. Sixth, due to small sample sizes and imbalanced recruitment in the comorbid/non-comorbid and treated/treatment-naïve subgroups, direct statistical comparisons between these groups were not possible in the current study. Future research with more carefully designed data collection is needed to address this issue. Meanwhile, combining treatments (e.g., CBT vs. medication) and comorbidities (e.g., ADHD vs. depression) into single subgroups may obscure modality or disorder-specific effects. Future studies with larger samples should explore these nuances. In addition, subgroup analyses for comorbidities and treatment status were conducted at the study level due to the lack of individual patient data. This approach assumes homogeneity within studies (e.g., all participants in a "non-comorbid" study were free of comorbidities), which may not fully capture heterogeneity in real-world clinical populations. Finally, in the current research, the GM difference in VBM reflect a combination of cortical thickness, cortical surface area, and cortical folding differences which are closely related to the neurodevelopmental nature of pediatric OCD. Future research should specifically aim to identify these robust cortical imaging markers associated with pediatric OCD.

Conclusion

In conclusion, our findings indicate that GM volume increased in the left insula and left SFG (orbital part), and GM volume decreased in the right STG, left IPG, left MOG and left IFG in pediatric patients with OCD. These brain regions may play an additional role in the pathophysiology of pediatric OCD, with the observed volumetric abnormalities and their associations with clinical variables providing further evidence of their involvement in the disorder. Future longitudinal studies should track the outcomes of pediatric OCD into adulthood to validate the current findings and identify targets for early diagnosis and intervention.

Abbreviations

OCD	Obsessive–compulsive disorder
MRI	Magnetic resonance imaging
GM	Grey matter
VBM	Voxel-based morphometry
CBT	Cognitive behavioural therapy
MNI	Montreal Neurological Institute
CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale
SFG	Superior frontal gyrus
STG	Superior temporal gyrus
IPG	Inferior parietal gyri
MOG	Middle occipital gyrus
IFG	Inferior frontal gyrus
AES-SDM	Anisotropic effect size-signed differential mapping

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
HY, LL, and YL were responsible for the study concept and design. YH, LL, YL, TL, YT, SZ, PL, ZY, YJ, MZ, XD and MS collected, analysed data, and interpreted the results. LL wrote the first draft of the paper. YH and YL provided critical revision of the manuscript. All authors participated in the discussions and revisions of the paper.

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Data availability
The de-identified data are available on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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