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Shared and distinct alterations of thalamic subregional functional connectivity in early- and late-onset obsessive-compulsive disorder

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Original Article

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Abstract

Background. Studies highlight the thalamus as a key region distinguishing early- from late-onset obsessive-compulsive disorder (OCD). While structural thalamic correlates with OCD onset age are well-studied, resting-state functional connectivity (rsFC) remains largely unexplored. This study examines thalamic subregional rsFC to elucidate pathophysiological differences in OCD based on different onset times.

Methods. The study comprised 85 early-onset OCD (EO-OCD) patients, 94 late-onset OCD (LO-OCD) patients, and 94 age- and sex-matched healthy controls (HCs). rsFC analysis was conducted to assess thalamic connectivity across seven subdivisions among the groups.

Results. Both EO-OCD and LO-OCD patients exhibited increased rsFC between the primary motor thalamus and the posterior central gyrus and between the thalamic premotor and the supplementary motor areas. EO-OCD patients showed significantly stronger rsFC between the prefrontal thalamus (Ptha) and the middle frontal gyrus (MFG) compared to both LO-OCD patients and HCs. In contrast, LO-OCD patients demonstrated reduced rsFC between the Ptha and the inferior parietal lobule (IPL) compared to EO-OCD patients and HCs. Additionally, the rsFC between the Ptha and both the MFG and IPL was negatively correlated with age of onset, with earlier onset linked to stronger connectivity.

Conclusion. These findings reveal both shared and distinct thalamic connectivity patterns in EO-OCD and LO-OCD patients. Sensory-motor networks exhibiting thalamic hyperconnectivity are critical for the manifestation of OCD, regardless of age of onset. The frontal–parietal network and thalamic hyperconnectivity may present a compensatory mechanism in EO-OCD patients, while hypoconnectivity with the frontoparietal network may reflect a neural mechanism underlying LO-OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a mental disorder characterized by obsessions and/or compulsions, with a 2–4% prevalence in the general population (Huang et al., 2019). A notable feature of OCD is its bimodal distribution in age of onset, with one peak occurring in childhood and early adolescence and another during early adulthood (Heyman, Mataix-Cols, & Fineberg, 2006). Emerging evidence indicates that early-onset OCD (EO-OCD) and late-onset OCD (LO-OCD) differ in clinical and neuropsychological profiles (Albert et al., 2015; Do Rosario-Campos et al., 2001; Taylor, 2011). Specifically, EO-OCD is associated with a higher prevalence in males (Stewart et al., 2004; Torresan et al., 2013), greater genetic heritability (Bolton, Rijsdijk, O'Connor, Perrin, & Eley, 2007; Narayanaswamy et al., 2012), higher comorbidity with neurodevelopmental disorders such as Tourette's syndrome (De Mathis et al., 2008; Janowitz et al., 2009; Taylor, 2011), and have poorer treatment responses (Ravi Kishore, Samar, Janardhan Reddy, Chandrasekhar, & Thennarasu, 2004; Van Roessel et al., 2023). EO-OCD is also more commonly linked to sexual and symmetry obsessions, along with compulsions such as checking and hoarding (Millet et al., 2004; Wang et al., 2012). In contrast, LO-OCD is more frequently characterized by washing-related compulsions, a more abrupt onset, and heightened comorbidity with anxiety disorder and depression (Girone et al., 2024). Additionally, LO-OCD patients demonstrate greater impairments in executive function and auditory attention than EO-OCD patients (Hwang et al., 2007; Kim et al., 2020; Roth, Milovan, Baribeau, & O'Connor, 2005). These observed differences in clinical and neuropsychological features between EO-OCD and LO-OCD underscore the critical role of age onset in elucidating the heterogeneity of OCD. Consequently, EO-OCD and LO-OCD may represent different

subtypes of the disorder, and the underlying neural mechanisms driving these differences remain poorly understood, necessitating further empirical investigation.

Although the neural distinctions between EO-OCD and LO-OCD are not yet fully elucidated, a growing body of research has explored potential neural differences in structural and functional impairments across various brain regions, including the thalamus, frontal lobe, parietal lobe, temporal lobe, and amygdala (Cao et al., 2022; Hauser et al., 2017; Kim et al., 2020; Park et al., 2023; Vriend, de Joode, Pouwels, & Liu, 2024). Among these regions, the thalamus has emerged as a critical node within the cortico-striato-thalamo-cortical circuits, which are central to the neuropathology of OCD and significantly shape its neurobiology underpinnings (Arend, Henik, & Okon-Singer, 2015; Van Den Heuvel et al., 2016; Weeland, Vriend, van der Werf, Huyser, & van den Heuvel, 2022; Zhang et al., 2019). Importantly, several studies have consistently highlighted the pivotal role of the thalamus in elucidating the distinct neural mechanisms underlying EO-OCD and LO-OCD. For instance, Weeland et al. (2021) identified whole-brain morphological differences between children with probable OCD and healthy controls (HCs), revealing that only the thalamus exhibited increased volume in the OCD group. A follow-up study by the same team further demonstrated that children with probable OCD had larger ventral nuclei of the thalamus and smaller pulvinar volume compared with those without obsessive-compulsive symptoms (Weeland et al., 2022). The specificity of the thalamus in differentiating EO-OCD and LO-OCD has also been supported by additional studies. For example, Jurng et al. (2021) reported that reduced volume in the left posterior thalamic nuclei among OCD patients was significantly negatively correlated with age of onset (Jurng et al., 2021). Similarly, Vriend et al. (2024) found that microstructural integrity in the thalamo-parietal/occipital tract was significantly reduced in LO-OCD patients as compared with EO-OCD patients, indicating that the age of onset influences the integrity of this tract and the efficiency of associated brain networks. Meta-regression analyses have further corroborated these findings, demonstrating that connectivity between the thalamus and putamen was negatively correlated with age of onset in OCD (Liu et al., 2022). Collectively, these findings underscore the thalamus as a key region for understanding the divergent pathophysiological mechanisms underlying OCD subtypes based on age of onset. In addition, these findings indicate that the thalamus in patients with EO-OCD tends to exhibit a characteristic pattern of compensatory changes, evident at both structural volume increase and functional hyperactivation. Nevertheless, the precise role of the thalamus in OCD with varying onset ages remains an area of ongoing investigation, warranting further research to clarify its contributions to the heterogeneity of the disorder.

First is that previous studies typically treated the thalamus as a homogeneous region when selecting it as a region of interest (ROI) (Anticevic et al., 2014). Recent research, however, has highlighted the heterogeneous nature of the thalamus, which is composed of multiple nuclei, each characterized by distinct anatomical and functional connectivity (FC) patterns with cortical and subcortical regions (Behrens et al., 2003a; Johansen-Berg et al., 2005). For instance, the mediodorsal nucleus primarily receives afferent projections from the prefrontal cortex and plays a pivotal role in modulating frontal lobe activity associated with cognitive functions (Pergola et al., 2018). In contrast, the ventral lateral and ventral posteromedial/lateral nuclei are involved in processing sensory information and project to primary sensory and motor cortical areas (Giraldo-Chica & Woodward, 2017; Johansen-Berg et al., 2005). Given the intricate interplay between structural connectivity and FC in the brain (Fan et al., 2015), a subregional analysis of the thalamus may provide critical insights into its role in the pathophysiology of OCD. Using diffusion tensor imaging and functional magnetic resonance imaging (fMRI), Behrens et al. (2003a) and Behrens et al. (2003b) delineated seven distinct subdivisions within the thalamus: the primary motor thalamus (PMtha) (projecting to primary motor cortex), somatosensory thalamus (Stha) (to somatosensory cortex), occipital thalamus (Otha) (to occipital cortex), prefrontal thalamus (Ptha) (to prefrontal cortex), premotor thalamus (PreTha) (to premotor cortex), posterior parietal thalamus (Pptha) (to posterior parietal cortex), and temporal thalamus (Ttha) (to temporal cortex) (Behrens et al., 2003a; Behrens et al., 2003b; Johansen-Berg et al., 2005). Fair (2010) demonstrated that in healthy individuals, the FC of the frontal cortex to the dorsal/anterior subdivisions of the thalamus strengthens with age, whereas connectivity between the temporal lobe and ventral/midline/posterior thalamic subdivisions weakens. Similarly, connectivity of the premotor and somatosensory cortices to the lateral/inferior thalamus strengthens over time, while connectivity to the medial/dorsal thalamus diminishes. In individuals with OCD, altered FC patterns have been observed, including decreased connectivity between the Pptha and the middle frontal gyrus (MFG), as well as increased connectivity between the Pptha and the middle temporal gyrus. Additionally, reduced FC has been reported between the Otha and the inferior parietal lobule (IPL), while increased FC has been noted between the Otha and the middle occipital gyrus (Li et al., 2019). These findings suggest that thalamic subregions show heterogeneous developmental trajectories in FC across the lifespan. In OCD, even within the same thalamic nucleus, connectivity patterns to different cortical targets vary significantly. Consequently, investigating thalamic connectivity, particularly in age-related analyses, necessitates a subregion-specific approach to account for this complexity and advance understanding of the thalamus's role in OCD pathophysiology.

Second is that most prior studies investigating the thalamus in EO-OCD versus LO-OCD have predominantly focused on structural brain abnormalities, with a notable paucity of research adopting a functional brain perspective. FC provides valuable insights into the integration of neural activity and more accurately captures the degree of synchronization between brain regions in neuroimaging studies (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Gao et al., 2019; Wu, Caprihan, Bustillo, Mayer, & Calhoun, 2018). While existing research on thalamic subregion FC in OCD has identified associations between caudate-thalamic hypoconnectivity in OCD with low childhood trauma and prefrontal-thalamic hyperconnectivity in OCD with high childhood trauma, the influence of age of onset remains unexplored in this context (Chu et al., 2022). Consequently, the present study seeks to address this gap by examining FC differences between EO-OCD and LO-OCD across various thalamic subregions.

In conclusion, the present study aimed to delineate distinct resting-state FC (rsFC) patterns within thalamic subregions in EO-OCD and LO-OCD using seed-based FC analysis. It was hypothesized that, relative to LO-OCD patients, EO-OCD patients would demonstrate enhanced rsFC between the frontal thalamus and frontal cortex, the Stha and somatosensory cortex, and the Ttha and temporal cortex.

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Methods

Participants

A total of 179 patients with OCD were recruited from the Second Xiangya Hospital of Central South University, China. The inclusion criteria required a diagnosis of OCD based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (SCID), a Yale-Brown Obsessive-Compulsive Scale (YBOCS) score of 16 or higher, and an age range of 18–45 years. Exclusion criteria included the presence of neurological or other psychiatric disorders (e.g., brain injury, tic disorder, and schizophrenia), a history of substance abuse or dependence, and any contraindications to MRI scanning. Of the 179 patients, 91 were unmedicated, and 88 medicated. A total of 94 age- and sex-matched HCs were also recruited. These controls were interviewed using the nonpatient version of the SCID by two psychiatrists. The inclusion criteria for HCs were normal hearing and vision (or corrected vision), and an age range of 18–45 years. The exclusion criteria for the HCs were the same as those of the OCD patients. All participants provided written informed consent, and the study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All participants were right-handed, as assessed by Oldfield (1971).

Clinical assessment and group classification

Following diagnosis, OCD participants underwent a semi-structured interview to collect sociodemographic and clinical information. The YBOCS, including its checklist, was used to evaluate the severity and profile of OCD symptoms (Goodman et al., 1989). The State–Trait Anxiety Inventory (STAI) (Spielbergerd, Gorsuch, Lushene, & Vagg, 1983) and the Beck Depression Inventory (BDI) (Beck, 1961) were used to assess anxiety and depression severity, respectively. Participants also self-reported their OCD symptoms using the Obsessive-Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002). Verbal Intelligence Quotient (IQ), employed for group matching, was calculated according to the four subtests (information, arithmetic, similarities, and digit span) of the Wechsler Adult Intelligence Scale-Revised in China (Gong, 1983).

We defined the cutoff for age of onset to be 18 years, which aligns with the threshold applied in most previous studies (Cao et al., 2022; Delorme et al., 2005; Girone et al., 2024; Grover et al., 2018; Vriend et al., 2024; Wang et al., 2012). In addition to being widely recognized as the onset age of adulthood, an age of 18 years is considered a threshold for strong familial aggregation of OCD (Taylor, 2011) and is hypothesized to mark distinct etiologic variants of the disorder. Thus, based on the age of onset, we divided OCD patients into two subgroups: EO-OCD (age of onset <18 years, $n = 85$) and LO-OCD (age of onset ≥18 years, $n = 94$). The age of onset was determined during the structured interview, in which patients were asked to recall the initial onset of their obsessive-compulsive symptoms that caused significant distress, and this information was then reverified several weeks later in a follow-up interview. All patients reported the same age of onset in both interviews, suggesting high reliability of recall. The age of onset was also considered as a continuous variable in subsequent data analysis. Duration of illness and medication history were recorded.

MRI acquisition

MRI data were collected using a Siemens Skyra 3T MRI scanner at the Second Xiangya Hospital of Central South University. Participants were instructed to lie supine, keep their eyes closed, stay still, and avoid falling asleep. Foam pads and straps were used to minimize head movement. Resting-state fMRI images were acquired with the following parameters: 39 axial slices, 3.5-mm slice thickness, 2,500-ms repetition time (TR), 25-ms echo time (TE), 3.8 × 3.8 × 3.5-mm voxel size, 90° flip angle, 240-mm field of view, 64 × 64 matrix, and 200 volumes. Additionally, high-resolution T1-weighted sagittal images were acquired with 176 slices, 1,900-ms TR, 2.01-ms TE, 1.00-mm slice thickness, 1.0 × 1.0 × 1.0-mm voxel size, 9° flip angle, 900-ms inversion time, 256-mm field of view, and 256 × 256 matrix.

Image preprocessing

fMRI data were processed using the Data Processing Assistant for resting-state fMRI (Yan, Wang, Zuo, & Zang, 2016) (DPARSF V5.4, http://rfmri.org/DPARSF). After discarding the first 10 volumes of each time series, slice timing correction and head motion realignment were performed. Eight subjects (five EO-OCD and three HCs) were excluded due to excessive head motion (translation >1 mm or rotation >1°), leaving 179 OCD patients (EO-OCD = 85; LO-OCD = 94) and 94 HCs for analysis. To account for subtle head movement, head motion scrubbing regression was applied, with frames exhibiting framewise displacement (FD) >0.2 mm, along with their adjacent frames flagged for regression. No significant differences in mean absolute FD were found between the remaining EO-OCD, LO-OCD, and HC groups.

The images were spatially normalized to the Montreal Neurological Institute (MNI) atlas space, with T1-weighted images coregistered to the mean functional image. These images were then segmented into gray matter, white matter, and cerebrospinal fluid. Functional volumes were normalized to MNI space and resampled to 3 × 3 × 3 mm voxels. Following normalization, images were smoothed with 6 × 6 × 6 mm Gaussian kernel, linear detrending was performed, and nuisance covariates (head motion parameters, white matter, and cerebrospinal fluid signals) were regressed out. Temporal band-pass filtering (0.01–0.1 Hz) was applied.

FC analysis

A whole-brain rsFC analysis was conducted, leveraging thalamic probabilistic mapping from the Oxford-FSL (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), which delineates the thalamus into seven distinct subregions: PMtha (ROI1), Stha (ROI2), Otha (ROI3), Ptha (ROI4), PreTha (ROI5), Pptha (ROI6), and Ttha (ROI7) (Behrens, Johansen-Berg, et al., 2003) (see Figure 1 and Supplementary Figure S1). To achieve a more accurate delineation of thalamic subregions, we applied the 75% probability threshold of the Oxford Thalamic Atlas (see Supplementary Figure S2). rsFC between these thalamic subdivisions and the whole brain was analyzed. The mean time series for each seed region was correlated with the time series of all other brain voxels, and correlation maps were converted to Z-maps using Fisher's r–z transformation.

Statistical analysis

Demographic, clinical, and symptom severity measures (YBOCS, OCI-R, STAI, and BDI) were compared among EO-OCD, LO-OCD, and HC groups using χ^2 tests, independent samples t-tests, or analysis of variance (ANOVA), with SPSS version 20.0. All variables were normally distributed.

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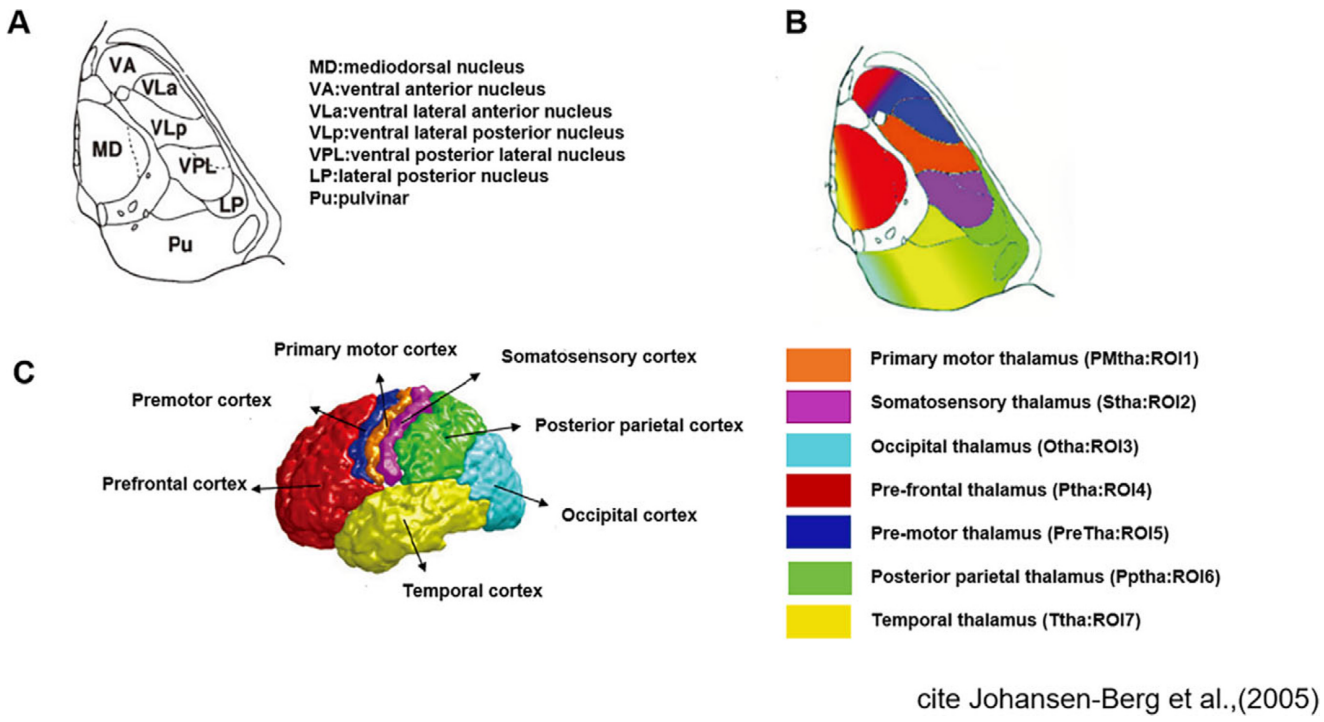

Figure 1. Thalamic subdivisions correspond to the anatomical location of the thalamus and the cortical regions connected to it. (A) Partitioning of thalamic slices in cytoarchitectonic spectra. (B) Each color indicates the major cell nuclei that carry out information exchange in different cortical regions of the brain. (C) The main cortical areas of information exchange carried out by different thalamic subdivisions. ROI, region of interest.

FC analyses were conducted using SPM12 (https://www.fil.ion.ucl.ac.uk/spm). A voxel-based one-way ANOVA compared FC maps across groups, controlling for age, sex, FD, and verbal IQ ($p < 0.001$, uncorrected). Post-hoc *t*-tests identified group differences with initial ANOVA results as masks (refer to Supplementary Figure S3 for further details), applying a threshold of $p < 0.05$ with family-wise error correction. To address the potential statistical inflation caused by the two-step thresholding, a cross-validation analysis was performed (refer to Supplementary Table S1). The effects on thalamic connectivity were examined in post hoc tests in the EO- and LO-OCD groups, controlling for drug and disease duration. Partial correlation analyses were conducted to examine the relationships between rsFC and OCD severity, while controlling for potential confounding variables, including age, sex, FD, and verbal IQ.

Results

Demographic and clinical variables

The demographic and clinical characteristics of the participants are detailed in Table 1. The EO-OCD group comprised 42 unmedicated and 43 medicated patients, while the LO-OCD group consisted of 49 unmedicated and 45 medicated patients. No significant difference was found in the proportion of medicated versus unmedicated patients between the groups ($\chi^2 = 0.05$, $p = 0.823$).

No significant differences were observed between the EO-OCD and LO-OCD groups regarding YBOCS scores ($t = 0.17$, $p = 0.47$), obsession scores ($t = -0.48$, $p = 0.62$), or compulsion scores ($t = 1.48$, $p = 0.14$). However, LO-OCD patients exhibited a significantly later age of onset compared to EO-OCD patients ($t = -13.54$, $p < 0.001$), while EO-OCD patients had a significantly longer illness duration ($t = 6.35$, $p < 0.001$).

Compared with HCs, OCD patients scored significantly higher on obsession ($F = 143.8$, $p < 0.001$), washing/cleaning ($F = 55.75$, $p < 0.001$), hoarding/collecting ($F = 10.07$, $p < 0.001$), ordering ($F = 35.01$, $p < 0.001$), checking ($F = 74.65$, $p < 0.001$), and spiritual neutralization ($F = 40.79$, $p < 0.001$) based on the OCI-R. Additionally, LO-OCD patients were significantly older than EO-OCD patients.

Thalamic subregional FC

FC in the EO-OCD patients and HCs

Regarding the EO-OCD group, we observed significantly increased rsFC compared to HCs between: (1) the thalamic primary motor (PMtha) seed and the right postcentral gyrus (PoCG), (2) the thalamic premotor (PreTha) seed and the right supplementary motor area (SMA), (3) the thalamic prefrontal (Ptha) seed and the right MFG, and (4) the thalamic temporal (Ttha) seed and the right medial temporal gyrus (MTG) (see Table 2 and Figures 2 and 3).

FC in the LO-OCD patients and HCs

Compared with HCs, the LO-OCD patients showed significantly decreased rsFC between (1) the Ptha seed and the left IPL and (2) the PreTha seed and the left IPL (see Table 2 and Figure 3). However, LO-OCD patients showed increased rsFC between (1) the PMtha seed and the right PoCG and (2) PreTha seed and the right SMA (see Table 2 and Figure 2).

FC in the EO-OCD and LO-OCD patients

To account for potential medication effects, we included medication status as a covariate in the post-hoc *t*-tests between the two OCD groups. EO-OCD patients showed significantly increased rsFC compared to LO-OCD patients between (1) the Ptha seed

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Table 1. Demographic and clinical variables for EO-OCD patients, LO-OCD patients, and HCs

				Statistics			
	EO-OCD (G1; *n* = 85)	LO-OCD (G2; *n* = 94)	HC (G3; n = 94)	$F/t/\chi^2$	*P*	Cohen's d/η^2	Bonferroni ($p < 0.001$)
Sex (M/F)	45/40	46/48	39/55	0.619	0.431		
Age (years)	21.53 ± 4.78	24.33 ± 5.69	22.06 ± 3.43	9.04	<.001	0.06	G1 < G2
Verbal IQ	48.77 ± 7.12	48.16 ± 8.95	52.41 ± 6.16	8.68	<.001	0.06	G1 < G3; G2 < G3
Mean_FD	.061 ± .043	.054 ± .026	.053 ± .027	1.36	0.058	0.01	
Age of onset	14.85 ± 2.17	21.98 ± 4.39		−13.54	<.001	−2.02	
Duration of illness (years)	6.46 ± 5.53	2.37 ± 2.74		6.35	<.001	0.95	
Unmedicated/ medicated	42/43	49/45		0.05	0.823		
Y-BOCS	23.45 ± 5.07	22.92 ± 4.78		0.71	0.47	0.1	
Obsession score	12.19 ± 2.83	12.39 ± 2.61		−0.48	0.62	−0.07	
Compulsion score	11.25 ± 3.19	10.52 ± 3.36		1.48	0.14	0.22	
OCI-R score	31.96 ± 13.37	30.89 ± 14.49	9.99 ± 5.14	103.22	<.001	0.43	G1 > G3; G2 > G3
Obsession	7.09 ± 2.88	7.13 ± 3.13	1.51 ± 1.47	143.8	<.001	0.51	G1 > G3; G2 > G3
Washing/cleaning	5.82 ± 3.61	4.95 ± 3.75	1.36 ± 1.21	55.75	<.001	0.29	G1 > G3; G2 > G3
Hoarding/collecting	3.79 ± 2.92	3.94 ± 3.18	2.37 ± 1.44	10.07	<.001	0.06	G1 > G3; G2 > G3
Ordering	5.26 ± 3.32	5.04 ± 3.16	2.17 ± 1.63	35.01	<.001	0.2	G1 > G3; G2 > G3
Checking	5.44 ± 3.33	5.96 ± 3.30	1.37 ± 1.36	74.65	<.001	0.35	G1 > G3; G2 > G3
Spiritual neutralization	4.47 ± 3.24	3.88 ± 3.00	1.20 ± 1.10	40.79	<.001	0.23	G1 > G3; G2 > G3
STAI-S	44.29 ± 6.30	43.15 ± 7.57	43.26 ± 6.73	0.73	0.822	0.005	
STAI-T	48.84 ± 6.34	48.02 ± 8.18	43.21 ± 5.33	18.64	<.001	0.12	G1 > G3; G2 > G3
BDI	20.01 ± 9.51	24.01 ± 12.01	4.48 ± 3.42	121.33	<.001	0.47	G1 > G3; G2 > G3

Note: BDI, Beck Depression Inventory; EO-OCD, early-onset OCD; HC, health control; LO-OCD, late-onset OCD; OCI-R, Obsessive-Compulsive Inventory-Revised; STAI-S, Spielberger State–Trait Anxiety Inventory-State Form; STAI-T, Spielberger State–Trait Anxiety Inventory-Trait Form; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale. $F/t/\chi^2$: variables of age, Verbal IQ, education, STAI-T, STAI-S, BDI, and OCI-R were tested by one-way ANOVAs (results were indicated by *F*). Categorical data, such as gender, medication, obsession, and compulsion, were tested using chi-square tests (results were indicated by χ^2). Variables such as age onset, duration of illness and Y-BOCS were statistically tested by two-sample *t*-test (results were indicated by *t*); *p*, statistical significance, significant at $p < 0.05$.

and the right MFG and left IPL; (2) the PreTha seed and the left IPL; and (3) the Ttha seed and the right MTG (see Table 2). A two-sample *t*-test assessed the impact of medication on these results. No significant differences in thalamocortical connectivity were found between medicated and unmedicated EO-OCD patients for the thalamic prefrontal seed and the right MFG ($t = 0.323$, $p = 0.747$) and left IPL ($t = 0.853$, $p = 0.395$), the thalamic premotor seed and the left IPL ($t = 1.34$, $p = 0.182$), and the thalamic temporal seed and the right MTG ($t = 0.827$, $p = 0.409$; see Supplementary Table S4).

In the cross-validation analysis (Supplementary Table S1) and the age-matched sensitivity analyses (Supplementary Tables S2 and S3), the higher rsFC between the Ttha seed and the right MTG in EO-OCD compared with the LO-OCD and HCs disappeared. When we included disease duration as a control variable in the analysis, Ptha was the only thalamic subregion with differences in rsFC with EO- and LO-OCD patients. EO-OCD patients showed significantly increased rsFC compared to LO-OCD patients between the Ptha and the left IPL and right MFG (see Figure 4). The sensitivity analysis comparing EO- and LO-OCD subgroups with matched average disease durations yielded results consistent with those obtained when disease duration was a covariate (see Supplementary Table S5 and Supplementary Figure S4). The failure to replicate the result of rsFC between the Ttha seed and the right MTG may be due to this cluster being located in regions of spatial distortions. To sum up, to ensure confidence when interpreting the results, only results that were robust and unaffected by disease duration are discussed.

Correlations between RSFC and clinical characteristics

We found that the PreTha-IPL rsFC (LO-OCD < HC) was positively correlated with the duration of illness in the LO-OCD patients (see Figure 3). Additionally, the Ptha–MFG and Ptha–IPL rsFCs (EO-OCD > LO-OCD) were negatively correlated with the onset of age in the whole OCD patients (individuals with EO-OCD and LO-OCD combined) (see Figure 4).

Discussion

In the current study, we discovered both shared and distinct patterns of thalamic subregional rsFC alterations in EO- and LO-OCD patients. Two principal findings emerged from our analysis. First, the PMtha–PoCG and PreTha–SMA rsFCs showed stronger connectivity in the EO- and LO-OCD patients than in the HCs. Second, our results demonstrated distinct thalamic connectivity patterns between EO- and LO-OCD patients. Specifically,

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Table 2. Altered thalamic functional connectivity with the whole brain in EO-OCD, LO-OCD, and HCs

Thalamic seeds	Brain region	Voxels	MNI (*X*, *Y*, *Z*)	*t*	p_{FWE}
ROI1: PMtha					
EO-OCD > HC	PoCG. R	29	18 –33 54	4.31	0.001
LO-OCD > HC	PoCG. R	9	15 –30 57	3.98	0.001
ROI4: Ptha					
EO-OCD > HC	MFG. R	10	33 0 51	3.39	0.017
LO-OCD < HC	IPL. L	26	−39 –60 57	−4.22	0.001
EO-OCD > LO-OCD	MFG. R	37	36 3 54	4.08	0.002
	IPL. L	16	−48 –51 51	3.84	0.005
ROI5: PreTha					
EO-OCD > HC	SMA. R	31	7 –16 54	4.12	0.001
LO-OCD < HC	IPL. L	18	−36 –60 57	−4.04	0.002
LO-OCD > HC	SMA. R	9	6 –15 54	3.68	0.046
EO-OCD > LO-OCD	IPL. L	17	−48 –54 51	4.04	0.002
ROI7: Ttha					
EO-OCD > HC	MTG.R	29	39 –69 10	4.43	0.001
EO-OCD > LO-OCD	MTG.R	5	39 –69 10	3.52	0.006

Note: EO-OCD, early-onset OCD; HC, health control; IPL, inferior parietal lobule; LO-OCD, late-onset OCD; MFG, medial frontal gyrus; MTG, medial temporal gyrus; PoCG, postcentral gyrus; SMA, supplementary motor area. Significance threshold was set at $p < 0.05$ with family-wise error corrected

the enhanced connectivity of Ptha–MFG was uniquely associated with EO-OCD patients, whereas the weakened connectivity of IPL–Ptha was characteristic of LO-OCD patients. These findings highlight differences in the underlying neural substrates between EO-OCD and LO-OCD patients, providing empirical evidence that these conditions represent distinct subtypes of OCD, which should be carefully considered when selecting clinical treatment approaches.

Shared alterations of PMtha and PreTha in EO-OCD and LO-OCD patients

Compared to HCs, our study revealed increased rsFCs between the PMtha seed and the right PoCG, as well as between the PreTha seed and the right SMA in both EO- and LO-OCD patients. The thalamic nuclei implicated in these subregions, including the dorsal medial nucleus, ventral lateral posterior nucleus, ventral anterior nucleus, and ventral lateral anterior nucleus, primarily project to the primary motor cortex and premotor cortex (Behrens, Johansen-Berg, et al., 2003; Behrens, Woolrich, et al., 2003; Johansen-Berg et al., 2005). Both the PoCG and SMAs are integral components of the somatomotor network (SMN), which mediates the integration of sensory perception and motor control (Thomas Yeo et al., 2011). These findings suggest that dysfunctional connectivity between the thalamus and the SMN is a hallmark of OCD. Previous research has reported reduced intrinsic connectivity within the SMN but increased thalamic-SMN connectivity in OCD patients (Ping et al., 2013; Sha et al., 2020; Zang, Jiang, Lu, He, & Tian, 2004). Furthermore, abnormalities in the supplementary motor cortex and sensorimotor cortex, including lower regional homogeneity, have been documented in OCD patients (Armstrong, 2016). Ping et al. (2013) suggested impaired modulation of sensory information (Rossi et al., 2005; Stern, 2014). Such sensory gating deficits may underlie motor compulsions and cognitive dysfunction, which are central to OCD symptomatology (Rossi et al., 2005). Sensorimotor gating, which relies on corticothalamic connectivity to filter irrelevant sensory input (Mayer et al., 2009). The elevated thalamic-SMN connectivity observed in our study may reflect impaired sensory integration processes, underscoring the potential role of altered sensory processing in the pathophysiology of OCD.

Distinct alterations regarding the Ptha in EO-OCD and LO-OCD

In a direct comparison of the EO- and LO-OCD patients, the Ptha subregion was the only region to exhibit differences in rsFC independent of medicine use and disease duration. The primary thalamic nuclei within the Ptha include portions of the mediodorsal nucleus, ventral anterior nucleus, and anterior nucleus (Behrens et al., 2003a; Behrens et al., 2003b; Johansen-Berg et al., 2005). Thalamic nuclei can be classified into first-order and higher-order (HO) nuclei based on the direction of information transfer and complexity of processing, with the nuclei comprising the Ptha categorized as HO nuclei (Jones, 2001, 2002). HO nuclei receive inputs from the association cortex, including the prefrontal cortex and posterior parietal regions, and damage to these nuclei has been linked to significant impairments in cognitive functioning in humans, especially executive functions (Guillery, 1995; Jones, 2001; Sherman, 2016).

Further analyses revealed that the rsFC of Ptha-MFG was increased in the EO-OCD compared to both HCs and LO-OCD, whereas the rsFC of Ptha-IPL was decreased in the LO-OCD relative to HCs and EO-OCD. These connectivity patterns were negatively correlated with the age of onset. The MFG and IPL are key components of the prefrontal-cingulo-parietal 'executive control' network, which plays a critical role in cognitive processes such as flexibility, initiation, and inhibition. A meta-analysis of over 190 functional neuroimaging studies identified the thalamus as a central node within this network, supporting executive functions (Niendam et al., 2012). Increasing evidence suggests that functional abnormalities within the frontoparietal network in OCD patients are associated with deficits in executive functioning, particularly cognitive flexibility, initiation, and inhibition (Gonçalves et al., 2016; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Liu et al., 2021). These findings indicate a divergent pattern of Ptha connectivity with the prefrontal-cingulo-parietal network in EO-OCD versus LO-OCD patients. We hypothesize that these differences may reflect varying degrees of executive function impairment between the two groups. Studies have demonstrated that LO-OCD patients exhibit poorer cognitive flexibility, which correlates with reduced MFG volume (Kim et al., 2020). Therefore, the enhanced Ptha-MFG connectivity in EO-OCD may reflect less severe cognitive flexibility deficits, while reduced Ptha-IPL connectivity in LO-OCD may reflect more pronounced impairments. However, since cognitive flexibility was not directly measured in this study, future research should investigate the impact of age of onset on cognitive flexibility in OCD to further elucidate this relationship.

In LO-OCD patients, we observed a reduction in rsFC between the PreTha and the IPL compared to HCs. The main thalamus nuclei within PreTha include the ventral lateral anterior nucleus and portions of the mediodorsal nucleus, which predominantly project to the premotor cortex. Research has shown that the ventral lateral anterior nuclei of the thalamus receive afferent inputs from

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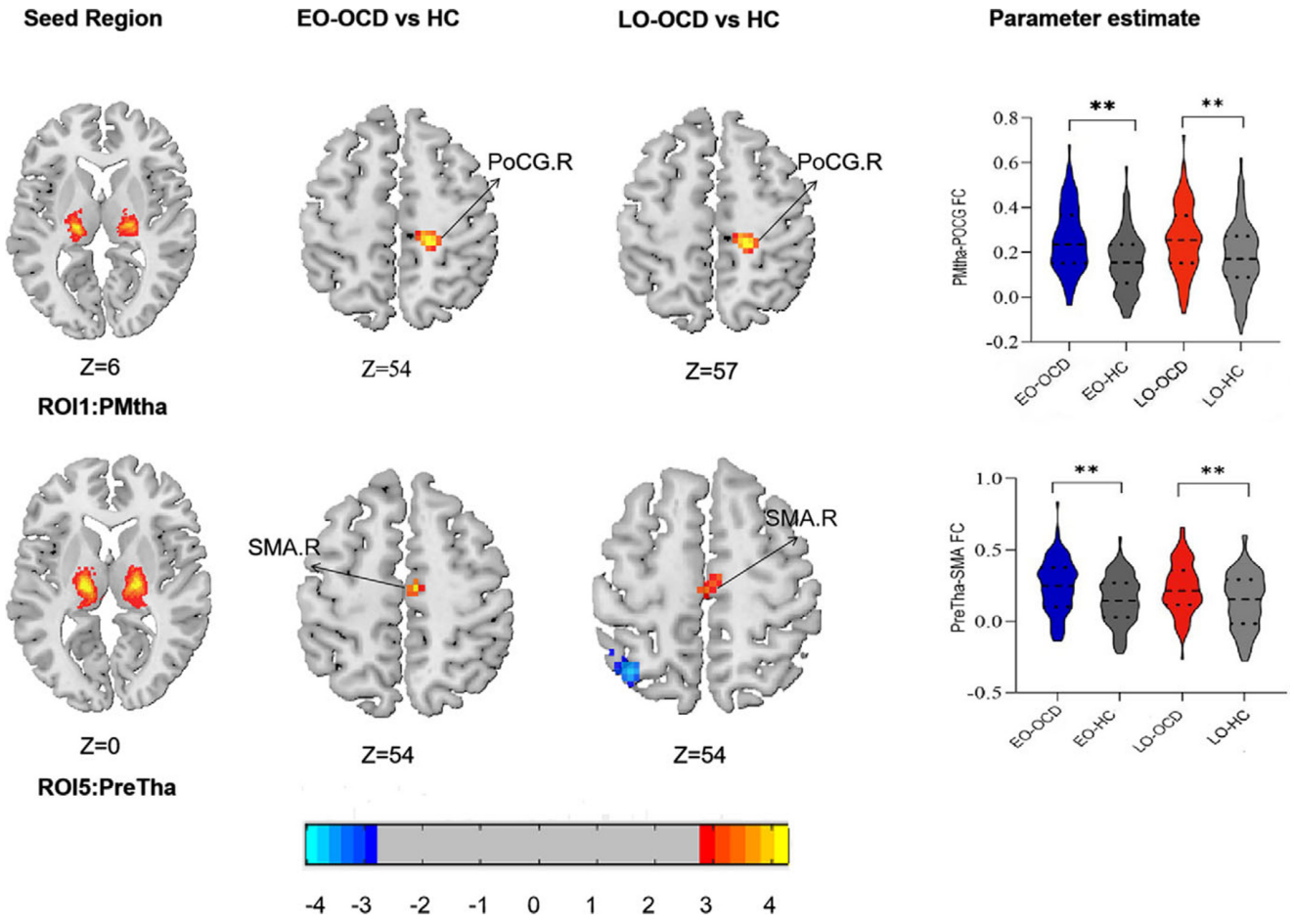

Figure 2. Share alterations of PMtha and PreTha in EO-OCD and LO-OCD patients. EO-OCD, early-onset OCD; HC, health control; IPL, inferior parietal lobule; LO-OCD, late-onset OCD; MFG, medial frontal gyrus; PMtha, thalamic primary motor; PoCG, postcentral gyrus; PreTha, thalamic premotor; SMA, supplementary motor area.

the cerebellum and basal ganglia nucleus, subsequently relaying this information to the motor and premotor cortices, thereby supporting motor and speech functions (Berezhnaya, 2003; Bordes et al., 2020). The IPL, located at the junction of the parietal and occipital lobes, consists of the angular gyrus and the parietal marginal gyrus, and plays a crucial role in HO cognitive and perceptual processes, including motor control and attentional regulation (Cheng et al., 2021; J. Zhang et al., 2023). The observed reduction in PreTha–IPL rsFC in LO-OCD patients may result from impaired sensory integration, contributing to deficits in attentional control and cognitive flexibility. Numerous studies have revealed abnormal activity and volumetric alterations in the parietal cortex, particularly the IPL, which are associated with impaired attention and inhibitory control in OCD patients (Boedhoe et al., 2018; Norman et al., 2019; Posner et al., 2017). Additionally, dysfunction in the connectivity between the parietal region and the thalamus has been consistently documented (Li et al., 2019; Snow, Allen, Rafal, & Humphreys, 2009). Furthermore, LO-OCD patients have been shown to exhibit poorer performance on tasks measuring attentional control and cognitive flexibility compared to EO-OCD and HCs (Kim et al., 2020; Roth et al., 2005). These findings emphasize the importance of the parietal cortex in OCD and suggest that functional deficits in attentional control and cognitive flexibility may be more pronounced in LO-OCD. Notably, the FC within this circuit was positively correlated with illness duration but not with symptom severity, indicating that the deterioration of PreTha–IPL connectivity may progress over time independently of illness severity in LO-OCD patients.

Limitations

This study has several limitations that should be acknowledged. (1) Although efforts were made to balance the proportions of patients between EO- and LO-OCD subgroups, the potential influence of medication exposure on the results cannot be entirely excluded. Future research should aim to include a larger cohort of medication-naive patients to further validate these findings. (2) As a cross-sectional study, it provides only a snapshot of brain connectivity characteristics at a single point in time and does not capture how these characteristics may evolve over the course of OCD. Longitudinal studies that track patients from a preclinical stage could offer valuable insights into the role of thalamocortical circuitry in both EO- and LO-OCD. (3) Although the two-step analytical approach employed in this study was adopted in several previous studies and demonstrates methodological rigor (Ming et al., 2017; Nichols et al., 2017; Zhuo et al., 2018), it may inherently introduce a risk of statistical inflation. To address the potential statistical inflation, a cross-validation analysis was performed. Though the results support the robustness of our primary results, future investigations could benefit from exploring alternative statistical methodologies, such as Bayesian frameworks or machine learning algorithms, to further enhance the robustness and

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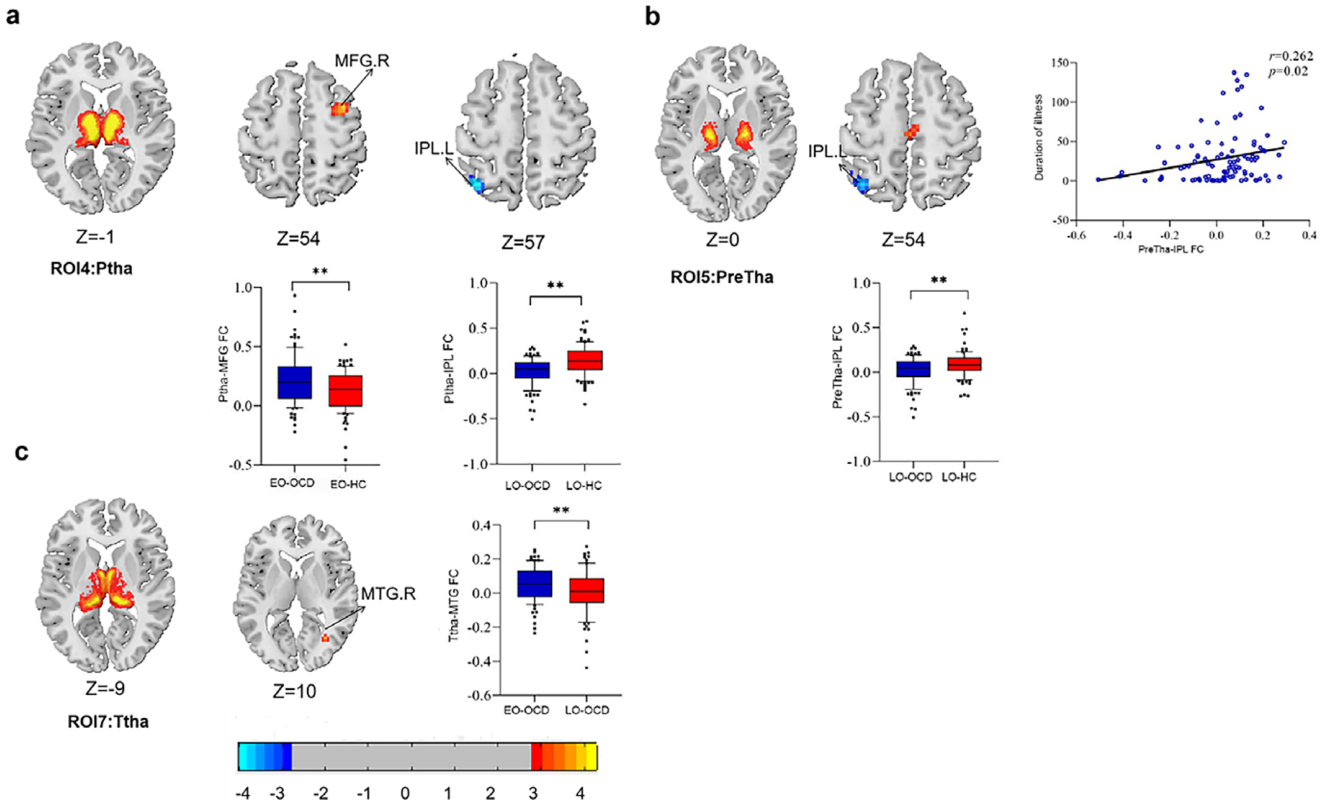

Figure 3. Brain regions with altered thalamic functional connectivity in EO-OCD and LO-OCD and the relationship to clinical characteristics. IPL, inferior parietal lobule; MFG, medial frontal gyrus; MTG, medial temporal gyrus; PreTha, thalamic premotor; Ptha, prefrontal thalamic; Ttha, temporal thalamic.

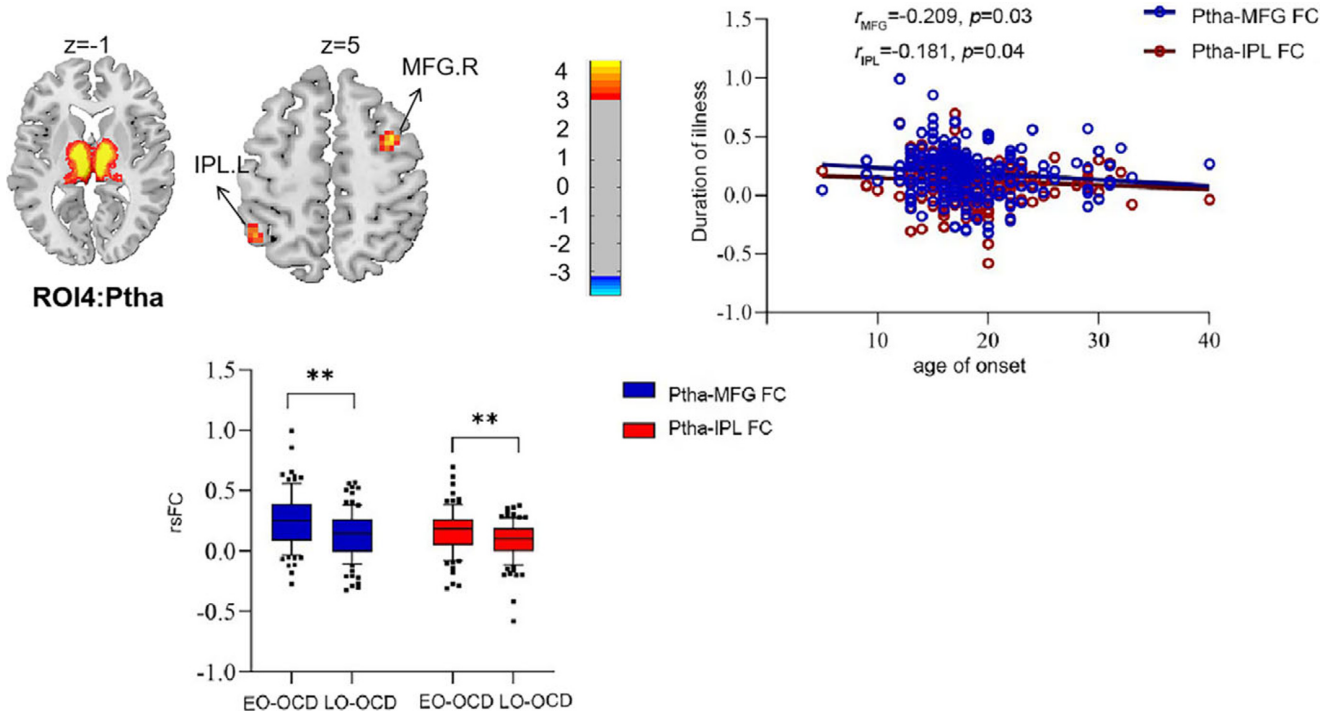

Figure 4. Brain regions with altered functional connectivity in the EO-OCD and LO-OCD thalamus after controlling for the course of the disease duration and the relationship to age of onset. IPL, inferior parietal lobule; MFG, medial frontal gyrus; Ptha, prefrontal thalamic.

reliability of the findings. (4) The absence of Fieldmap correction in our imaging protocol may introduce some spatial distortion in the functional images, particularly in regions susceptible to magnetic field inhomogeneities, such as those near air-tissue interfaces (e.g., the orbitofrontal cortex and temporal poles). However, it is worth emphasizing that the primary regions of interest identified in this study (e.g., MFG, IPL, PoCG, and SMA) are located in areas less affected by such distortions, thereby minimizing the potential

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impact of this limitation on our core findings. (5) The OCD cohort in this study excluded individuals with comorbidities (e.g., schizophrenia and major depressive disorder), which may limit the generalizability of our findings to more heterogeneous, real-world OCD populations. While this exclusion criterion was implemented to isolate the effects of OCD as a distinct clinical entity, it may inadvertently reduce the external validity of the results. Future research should aim to extend these findings to more representative cohorts to enhance their clinical applicability.

Conclusion

In conclusion, our findings provide valuable insights into the impact of age of onset on brain connectivity alterations in OCD. These results reveal both shared and distinct patterns of thalamic connectivity in EO-OCD and LO-OCD patients. Thalamic hyperconnectivity within sensory-motor networks emerges as a central feature of OCD, irrespective of age of onset. In EO-OCD patients, thalamic hyperconnectivity with the frontal–parietal network may serve as a compensatory mechanism, while hypoconnectivity with the same network in LO-OCD patients may reflect a neural mechanism underlying the disorder in this subgroup. These findings underscore the importance of considering the age of onset when investigating the neurobiological basis of OCD and developing targeted therapeutic interventions.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725100548.

Data availability statement. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author contribution. J. Fan, X. Zhu, and Y. Liu conceptualized the study. C. Xiao, Z. Wang, Q. Yu, Y. Han, Q. Kong, F. Gao, and Q. Liu collected the data. Q. Yu and F. Gao analyzed the data. Q. Yu interpreted the data. Q. Yu drafted the manuscript with critical revisions from J. Fan, Y. Liu, X. Wang, and X. Zhu. All authors approved the final manuscript and are accounted for all aspects of the work in ensuring that questions related to the accuracy or any part of the work are appropriately investigated and resolved.

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Competing interests. The authors declare none.

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