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Corresponding author:
Behcet Ayyildiz;
Email: behcetayyildizz@gmail.com

Exploring connectivity and volume alterations in the Pulvinar's subnuclei: insights into the neuropathological role in obsessive-compulsive disorder (OCD)

Behcet Ayyildiz[1], Daniela Rodriguez-Manrique[2,3], Sevilay Ayyildiz[1,2,4], Tuncay Colak[5] and Kathrin Koch[2,3,4]

[1]Graduate School of Health Sciences, Anatomy PhD Program, Kocaeli University, Kocaeli, Turkey; [2]School of Medicine, Department of Neuroradiology, Technical University of Munich, Munich, Germany; [3]Graduate School of Systemic Neurosciences, Ludwig Maximilians Universität München, Martinsried, Germany; [4]School of Medicine, TUM-NIC Neuroimaging Center, Technical University of Munich, Munich Germany and [5]School of Medicine, Department of Anatomy, Kocaeli University, Kocaeli, Turkey

Abstract

Background. Previous research has highlighted abnormalities in the pulvinar region of the brain among individuals diagnosed with obsessive-compulsive disorder (OCD). Nevertheless, given the pulvinar's complex structure, comprising four distinct subnuclei (PuA, PuI, PuL, and PuM), inconsistencies persist regarding both structural and connectivity alterations within this region.
Methods. 3D T1-weighted magnetic resonance imaging (MRI) and resting-state functional magnetic resonance imaging (rs-fMRI) were used on a cohort consisting of 41 healthy controls and 51 individuals with OCD in order to compare pulvinar connectivity and gray matter volume. Our aim was to compare both connectivity patterns and gray matter volume (GMV) within the PuA, PuI, PuL, and PuM subnuclei between the two groups. First, we examined resting-state connectivity differences in these subnuclei, followed by an analysis of GMV discrepancies to elucidate the potential neuropathological role of the pulvinar in OCD.
Results. Our findings revealed significant connectivity differences in the left PuL, the right PuA, and the left PuA between OCD patients and healthy controls ($p < 0.05$). Furthermore, the left PuA exhibited both connectivity differences and increased GMV in the OCD group after applying multiple comparison corrections ($p = 0.002$).
Conclusions. Our study identified functional connectivity alterations within specific subnuclei, including the left and right PuA, and the left PuL, alongside GMV changes in the left PuA. These observations suggest that these distinct regions of the pulvinar may contribute to the pathophysiology of OCD through differences in both functional connectivity and GMV compared to healthy controls.

Introduction

Obsessive-compulsive disorder (OCD) is a neurodevelopmental condition characterized by persistent obsessions and compulsions, affecting 2–3% of all individuals (Shaw et al., 2015; Weeland, Vriend, et al., 2022). Obsessions involve disturbing preoccupations, such as fear of contamination, while compulsions are repetitive behaviors performed in response. If lasting over 1 hour a day and significantly disrupting daily life, individuals meet the criteria for an OCD diagnosis (Li et al., 2019; den Braber et al., 2008).

Symptoms of OCD can lead to interpersonal difficulties, unemployment, substance abuse, criminal justice issues, and physical injuries. The heterogeneity of OCD encompasses various themes of obsessions, types of rituals, and presence or absence of tics. The epidemiology of the disorder displays variability in factors such as etiology, genetics, and response to pharmacotherapy (Diedrich & Voderholzer, 2015). Despite these classifications, the pathological mechanism of the disorder still requires clarification.

The cortico-striato-thalamo-cortical (CSTC) circuit is assumed to play a relevant role in the psychopathology of OCD. It projects from the cortex to the striatum, through the thalamus (via globus pallidus), and back to the cortex (Haynes et al., 2018; Tang et al., 2015). The direct and indirect pathways within the circuit exert opposing effects on the thalamus, leading to either heightened (direct pathway) or reduced (indirect pathway) cortical excitation. An imbalance between these pathways is believed to play a role in OCD pathology. Specifically, increased activity in the direct pathway, crucial for initiating and suppressing behavior, sets off a positive feedback loop, resulting in hyperactivity in the CSTC circuit (Jalal, Chamberlain, & Sahakian, 2023).

The thalamus forms an essential part of the CSTC circuit. Previous findings indicate that the thalamus is a key structure in the pathophysiology of OCD. Alterations in both gray matter volume as well as functional connectivity (FC) of the thalamus have been reported in earlier OCD studies (Atmaca, Korucu, Tabara, Yildirim, & Kılıç, 2019; Atmaca, Yildirim, Ozdemir, Tezcan, & Kursad Poyraz, 2007; Jurng et al., 2021; Li et al., 2019; Weeland, Kasprzak, et al., 2022). However, taken together, especially the findings on thalamic volume alterations in OCD patients have been rather inconsistent (Jurng et al., 2021) with some studies reporting increases (Atmaca et al., 2007; 2019; Li et al., 2019) and other studies reporting decreases (Jurng et al., 2021; Weeland, Kasprzak, et al., 2022) in thalamic gray matter volume or FC. An explanation for these inconsistencies might be the fact that the thalamus is organized into functionally segregated nuclei, each with different projections and fulfilling different roles in the context of cognitive, sensorimotor, and emotional processing. Given this organization, volumetric analyses of the entire thalamus may not provide sufficient information about its functional significance with regard to cognitive, sensorimotor, and emotional processes known to be relevant for the pathophysiology of OCD (Weeland, Vriend, et al., 2022).

The pulvinar nucleus, comprising approximately 30% of the thalamic volume, is the largest nucleus in the thalamus. Cytoarchitectonically, it is divided into the anterior pulvinar (PuA), the inferior pulvinar (PuI), the medial pulvinar (PuM), and the lateral pulvinar (PuL; Olszewski, 1952). Functioning as a higher-order nucleus, the pulvinar receives its primary inputs from the cortex and projects efferents back to the cortex (Karunakaran et al., 2020). Its extensive and reciprocal connectivity with cortical regions, including the frontal, parietal, temporal, occipital, and cingulate cortex, suggests its involvement in advanced cognitive (Romanski, Giguere, Bates, & Goldman-Rakic, 1997), emotional (Arend, Henik, & Okon-Singer, 2015), and sensorimotor (Karunakaran et al., 2020) functions. Among its subnuclei, PuA is the least explored in humans and is primarily associated with sensorimotor functions (Benarroch, 2015). In this context, Guedj and Vuilleumier recently reported FC between the anterior cluster of the pulvinar and sensorimotor system areas, such as the precentral gyrus, postcentral gyrus, and medial frontal gyrus. Their analysis of brain activation patterns associated with task-induced modulation (through co-activation patterns) revealed additionally, a robust coupling with motor and sensory areas of the brain (Guedj & Vuilleumier, 2020), which have been shown to be impaired in OCD and to be related to symptoms (Russo et al., 2014; Stevens, Hoffman, & Hsia, 1998) Conversely, PuM, being the largest part of the pulvinar, exhibits reciprocal connectivity with the parietal, temporal, cingulate, and prefrontal cortical areas and thus with regions known to be involved in various cognitive processes such as attention, executive functions or working memory. Especially executive functions and working memory processes have repeatedly been shown to be impaired in patients with OCD (Harkin & Kessler, 2011; Manarte et al., 2021). PuI and PuL are interconnected with visual cortical areas and functions, spanning from the occipital lobe to the temporal and parietal lobes, earning them the label 'visual pulvinar' (Kaas & Lyon, 2007). On the other hand, PuL was recently found in networks with brain areas involved in executive control and attention, such as precentral gyrus, postcentral gyrus, middle frontal gyrus, superior and inferior parietal cortex, and precuneus (Guedj & Vuilleumier, 2020). Again, both executive control and specific visual functions, such as visual search processes, have been reported to be affected in patients with OCD (Botta et al., 2018; Manarte et al., 2021).

Against this background, it appears that specific thalamic subnuclei are structurally and functionally altered in OCD. Furthermore, these alterations appear to be closely related to the cognitive, affective, and sensory impairments of the disorder. Considering that several studies have pointed out the pivotal role of the pulvinar in the pathogenesis of OCD (Kang et al., 2008; Shaw et al., 2015), this subnucleus is considered to be of predominant psychopathological relevance. While functional and structural alterations of the entire pulvinar have previously been reported in OCD (Jurng et al., 2021; Li et al., 2019; Weeland, Kasprzak, et al., 2022; Weeland, Vriend, et al., 2022), potential alterations within specific pulvinar subnuclei in patients with OCD have not yet been investigated. Based on these considerations, the first aim of the present study was to investigate potential changes in FC as well as gray matter volume of the different pulvinar sub-regions (i.e. PuA, PuI, PuL, and PuM) in a relatively large sample of patients suffering from OCD using analyses of resting-state FC as well as gray matter volumetric analysis. The second aim was to correlate potential changes in FC as well as gray matter in different pulvinar subregions with clinical Yale–Brown Obsessive Compulsive Scale (YBOC) scores.

Additionally, we aimed to explore whether volumetric alterations are related to changes in functional connectivity. Earlier studies have already investigated such an association between structural and functional changes. For instance, (Wagner et al., 2008) investigated the direct association between altered gray matter volume and altered functional activation in patients with depression. They found that hyperactivation of the rostral anterior cingulate cortex in patients with depression showed an inverse correlation with gray matter reduction in the orbitofrontal cortex.

Another previous study using different models to reveal mediation effects between structural volume alterations and functional connectivity networks has been conducted from a multimodal perspective in patients with OCD (Moreira et al., 2017). Moreover, an association between thalamic volume and reduced thalamus functional connectivity has been identified and linked to a potential cognitive impairment mechanism in diabetes (Jing et al., 2023). Given earlier findings on both direct and indirect associations between brain volume alterations and functional connectivity, we sought to provide further insight into the interplay between functional and anatomical changes in OCD.

Method

Participants

G*power (ver. 3.1.7) software was used to determine the sample size. Based on the parameters in the study reported by Li et al. (2019), at least $n = 35$ subjects per group were needed to detect expected effect sizes with a power of 95% and a significance level of $\alpha = 0.05$. Our power analysis was based on the FC group comparison (i.e. ANCOVA) of the relevant study. In total, 51 patients with OCD and 41 healthy participants were enrolled in the study. Patients were recruited from the Psychosomatic Hospital Windach and the Tagesklinik of Klinikum rechts der Isar. Healthy controls were recruited through online platforms and newspaper advertisements. All patients were assessed and diagnosed with OCD by an experienced psychiatrist based on the criteria of DSM-5 for OCD. Exclusion criteria for all subjects included a history of clinically significant head injuries, seizures, stroke, and neuropsychiatric and neurodegenerative diseases. In addition, all patients were screened for drug use. Patients´ clinical symptoms were assessed using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). All participants were scanned using a 9-minute resting-state fMRI sequence and instructed to keep their eyes closed.

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Ethics approval

Written informed consent was received from all participants after they were given a thorough explanation of the study procedure. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Kocaeli University Ethics Committee and the Ethics Committee of the Klinikum rechts der Isar in München. All participants gave their informed consent to the study.

Image acquisition

All images were acquired on a 3 T Philips Ingenia (Philips Healthcare, Best, The Netherlands) using a 32-channel (SENSE) head coil. T1-weighted images were acquired with the following parameters: 170 slices, sagittal orientation, 240×240 matrix, 1 mm isotropic resolution, TR = 9 ms, TE = 4 ms, flip angle = 8°. T2* weighted functional magnetic resonance imaging (fMRI) resting-state data were acquired using echo-planar imaging (EPI; TR = 2.7 s, TE = 33 ms, flip angle = 90°, matrix size = 96×94, field of view =192×192×141 mm, 64 transverse slices, 2.0 mm slice thickness, whole brain coverage, 2×2×2 mm^3 resolution). A series of 200 whole-brain volumes was recorded. We scanned for a total of 9 minutes during which participants were told to keep their eyes closed and avoid falling asleep.

Creating average group-specific pulvinar seeds

The group-specific pulvinar subnuclei (PuA, PuI, PuL, and PuM) were created separately for the healthy group and the OCD group, based on each subject's T1-weighted anatomical images. Each subject's pulvinar subnuclei segmentation was performed using Freesurfer 7.1.1 (https://surfer.nmr.mgh.harvard.edu). For each hemisphere, segmentation outputs (pulvinar subnuclei) were extracted from automatic 'recon-all' and 'thalamic segmentation' modules. The outputs of pulvinar subnuclei were visually inspected. Afterwards, all pulvinar subnuclei across all subjects in each group were selected and converted from Freesurfer (.mgh/.mgz) format to Nifti (.nii/.nii.gz) format, which is suitable for further functional analyses with the CONN toolbox. Subsequently, an in-house MATLAB script was employed, which included the normalization of pulvinar subnuclei, the calculation of group averages using Imcalc in SPM12, and thresholding at 0.2 using FMRIB Software Library (FSL). This process was conducted separately for the healthy group and OCD group, ensuring that the group-specific seeds reflect the structural characteristics of each group. This resulted in group-specific average PuA, PuI, PuL, and PuM subnuclei, which were then selected as seeds using the Freesurfer thalamic segmentation (Figure 1).

fMRI pre-processing

T1-weighted anatomical images and T2*-weighted functional MRI data were first converted from DICOM to NIFTI format. After conversion, anatomical and functional images were edited so the origin would be at the anterior commissure and the anterior–posterior commissure line would pass through the centers of each commissure, using the display module in SPM12 (Kim, Ahn, Chung, & Kim, 2009). Subsequently, all functional and anatomical images were uploaded to the connectivity toolbox (CONN) v21a (http://web.mit.edu/swg/software.htm), implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The default pre-processing steps were conducted in CONN, which included the following steps: (1) functional labeling, (2) functional realignment and unwarping, (3) functional centering to coordinates, (4) slice-timing correction, (5) outlier identification, (6) functional segmentation and normalization to Montreal Neurological Institute (MNI) template, (7) functional smoothing, (8) structural segmentation and normalization, and (9) structural centering to coordinates. The functional images were smoothed with a 6 mm full width at half-maximum (FWHM) Gaussian kernel. After that, the default denoising pipeline provided by (A, 2020) in CONN was used to remove noise components related to motion (3 translation and 3 rotation parameters with their first-order derivatives), white matter, and cerebrospinal fluid signals employing the aCompCor procedure implemented in CONN. Scrubbing was performed by

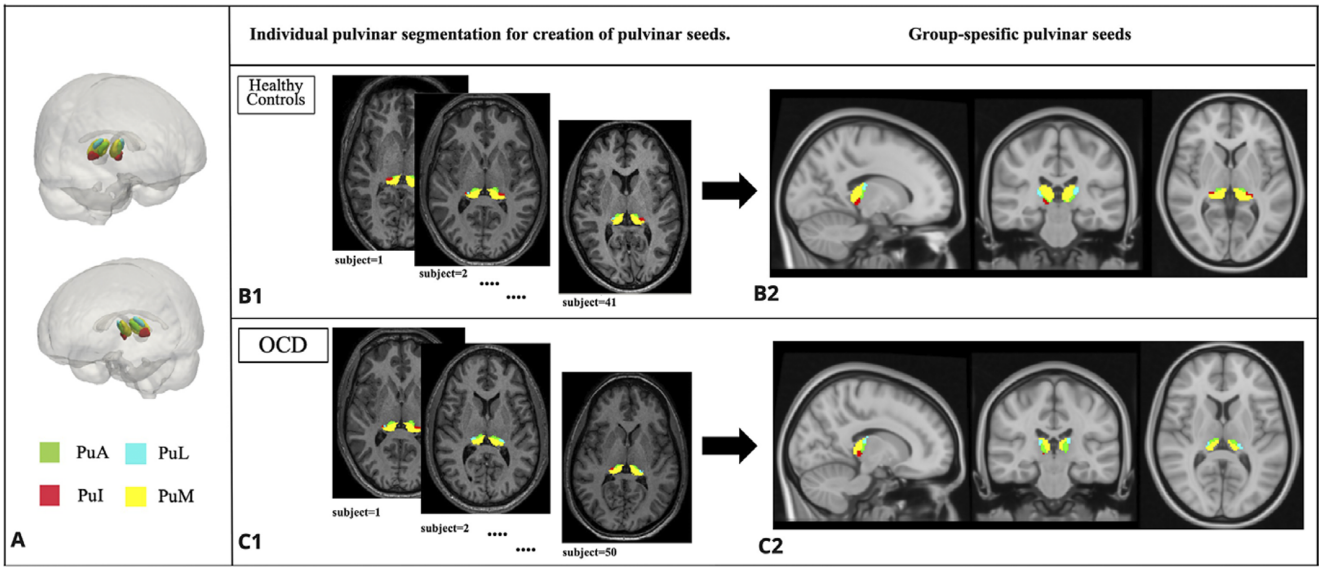

Figure 1. The pulvinar subnuclei seeds. Bilateral pulvinar subnuclei—anterior (PuA, green), medial (PuM, light blue), inferior (PuI, red), and lateral (PuL, yellow)—are visualized in a glass brain (A). Segmentation of T1-weighted MRI images showing individual pulvinar subnuclei in the control (B1) and OCD (C1) groups. Group-specific pulvinar subnuclei seeds were created separately for the control (B2) and OCD (C2) groups, based on the segmented seeds from all individuals within each group.

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incorporating each outlier scan identified in the outlier identification pre-processing step as a noise component. Finally, the images were bandpass filtered with a range of 0.01–0.09 Hz to eliminate temporal frequencies above and below the specified range from the BOLD signal. Additionally, we employed the Artifact Removal Tools (ART) to eliminate the impact of head movements on functional connectivity results during the denoising.

Seed-based resting state fMRI analysis

The previously created group-specific pulvinar seeds for the healthy group and OCD group were separately imported into the CONN toolbox to perform group-specific seed-to-voxel resting state fMRI analysis. On the first level, whole-brain regional blood oxygen-level-dependent (BOLD) time series were estimated by averaging the time series of all voxels within each seed. Seed-based functional connectivity was then computed to explore the connectivity patterns between the respective pulvinar seeds and all other voxels in the brain. This involved calculating bivariate Pearson's correlation measures between the mean BOLD signal time courses extracted from each seed and those of all other voxels. These correlation coefficients were transformed into normally distributed z-scores using Fisher's transformation to fulfill normality assumptions. All ROI z-scores were then compared between the two groups on the second level, by including age and gender as covariates in the group comparison (OCD patients versus controls). All results were thresholded at $P_{unc} < 0.001$ at the voxel level and FWE-adjusted $P_{FWE} < 0.05$ at the cluster level. Clusters were defined based on a minimum cluster size determined using the FWE correction method, in line with previous studies using seed-based resting-state fMRI analysis (Cankaya et al., 2025; Yulug et al., 2023).

Gray matter morphometry analysis procedure

The gray matter volume calculation of the pulvinar's subnuclei was analyzed using Freesurfer v7.1.1 via its default settings. First, the recon-all pipeline was performed using the T1-weighted anatomical images of all participants. The recon-all pipeline comprises several steps: motion correction, signal intensity, Talairach transformation, skull stripping, removal of non-brain tissue, and, finally, cortical and subcortical segmentation. Next, in order to reveal volumetric values of the pulvinar, we implemented an automatic parcellation of the thalamus based on the module by Iglesias et al., which has been developed for this purpose (Iglesias et al., 2018) combining in vivo and ex vivo data in a manual delineation process. Following the thalamus segmentation, a visual inspection was manually performed. Finally, the volumetric values of PuA, PuI, PuL, and PuM across all participants were extracted to compare volumetric alterations between the two groups.

Statistical analysis

All statistical analyses were conducted using JAMOVI Version 2.3.28.0. The normality of the variables was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (M ± SD). To compare the gray matter volume of the pulvinar seeds, separate ANCOVAs with group (OCD patients, healthy controls) as between-subject factor and age, gender, and total intracranial volume (TIV) as covariates were employed for each nucleus. To correct for multiple comparisons across the eight subnuclei, the resulting p-values from these ANCOVAs were Bonferroni-corrected, yielding an adjusted significance threshold of $p < 0.00625$ (0.05/8). Partial correlation analyses in the OCD group were conducted to explore the relationships between functional connectivity values from clusters demonstrating significant group differences and patients' Y-BOCS scores, illness onset, illness duration, and medication usage, while controlling for age and gender. Furthermore, volumes of subnuclei showing significant group differences and patients' Y-BOCS scores, illness onset, illness duration, and medication usage were also partially correlated (controlling for TIV, age, and gender) to assess potential associations between severity of clinical symptoms and volume aberrations in the OCD group. Finally, volumes of subnuclei showing significant group differences and functional connectivity values of clusters showing group differences were correlated in order to determine whether potential volume changes were related to functional connectivity changes. To account for multiple comparisons in these correlation analyses, we applied Bonferroni correction based on the number of tests performed. Since eight independent correlation tests were conducted, the significance threshold was adjusted to $p < 0.00625$ (0.05/8).

Results

Participants

Out of the 51 patients with OCD (20 males, 31 females), one patient had to be excluded based on quality check criteria provided by Morfini, Whitfield-Gabrieli, & Nieto-Castañón (2023). Thus, only 50 patients with OCD were included in the resting-state fMRI analysis. There were no significant differences between the participants in terms of age and gender ($p = 0.592$ and $p = 0.548$, respectively). In the patient group, 18 had comorbidities, including depression, attention-deficit/hyperactivity disorder, general anxiety, and social anxiety. Thirty-five patients were medicated, and the mean duration of illness was 16.9 (± 12.2) years (see Table 1).

Comparison of seed-based resting state fMRI

The resting state fMRI analysis revealed statistically significant connectivity alterations for the left PuL, the right PuA, and the left PuA between the OCD patients and healthy controls. The left PuL showed decreased connectivity to the bilateral superior frontal gyrus in the OCD group compared to the control group (Figure 3). The right PuA showed an increased connectivity, particularly to the left and right precentral gyri, the left postcentral gyrus, the left middle and superior temporal gyrus, and the left central opercular cortex in the OCD group compared to the control group (Figure 4).

Table 1. The demographic features and clinical scores of participants

	Controls	OCD	p value
Age	34.2 ± 10.6	32.90 ± 11.6	0.592
Gender (M/F)	19/22	20/30	0.548
Medication, (yes/no)	*N/A*	35/15	*N/A*
Total Y-BOSCS	*N/A*	20.9 ± 6.02 (8–33)	*N/A*
Obsessions	*N/A*	10.6 ± 3.25 (0–16)	*N/A*
Compulsions	*N/A*	10.3 ± 3.89 (0–18)	*N/A*
Age of onset	*N/A*	17.5 ± 9.02 (5–57)	*N/A*
Duration of illness	*N/A*	16.9 ± 12.2 (1–53)	*N/A*

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Finally, the left PuA showed an increased connectivity to the left superior temporal gyrus, the left central opercular cortex, and the left planum polare (Figure 2), (Table 2).

Gray matter volumetric analysis results

Table 3 displays the individual pulvinar subnuclei volumes of patients and controls. After correction for multiple comparisons, there were no significant volumetric differences between the two groups in the left-PuI, left-PuL, left-PuM, right-PuA, right -PuI, right-PuL, and right-PuM ($p = 0.021$, $p = 0.037$, $p = 0.021$, $p = 0.437$, $p = 0.406$, $p = 0.299$, $p = 0.621$; respectively). However, the volume of the left-PuA subnucleus was found to be greater in participants with OCD compared to healthy controls (Figure 5) ($p = 0.002$).

Clinical correlation

The correlation analysis between connectivity values of those clusters showing significant functional connectivity differences and clinical scores (i.e. Y-BOCS obsessions, Y-BOCS compulsions, Y-BOCS total score, illness onset, illness duration, and medication usage) yielded no significant results ($p > 0.00625$). Furthermore, the gray matter values of the left-PuA were extracted and subjected to correlation analysis with clinical parameters (i.e. Y-BOCS

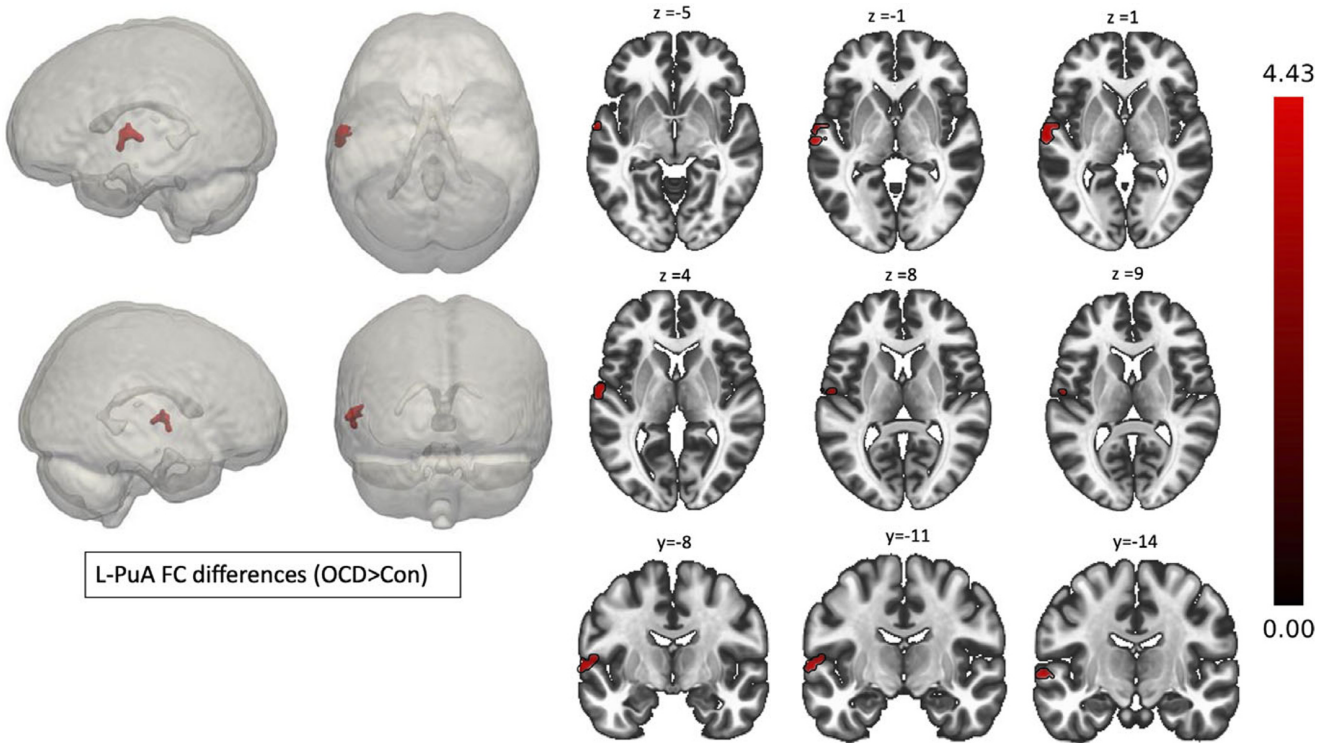

Figure 2. Clusters of voxels showing significant functional connectivity differences between the two groups in L-PuA seed. The red patches indicate that the L-PuA in the OCD group exhibited significantly increased connectivity compared to controls. All maps were family-wise error-corrected at *p-FWE* = 0.008736, with a minimum of 20 voxels for each cluster. The color bar represents the t-statistic. All significant clusters are presented on a standard brain atlas. The corresponding areas are also shown in Table 2.

Table 2. The pulvinar subnuclei that showed significant connectivity differences between the two groups

seeds	MNI coordinate	Region	Cluster size	t-max	*p*-FWE corrected
Left-PuA	−62–04–06	L-Superior Temporal Gyrus L-Central Opercular Cortex L-Planum polare	95	−4.68	0.008736
Left-PuL	14–12–70	R-Superior Frontal Gyrus L-Superior Frontal Gyrus	56	5.17	0.031775
Right-PuA	−52–02–42	L-Precentral Gyrus L-Postcentral Gyrus	111	−5.07	0.024643
	−52–04–16	L-Middle Temporal Gyrus L-Superior Temporal Gyrus	88	−4.96	0.034843
	00–020–68	R-Precentral Gyrus	33	−4.51	0.049603

Note: The left-PuA and the right PuA showed an increased connectivity in the OCD group compared to the healthy controls, while left PuL showed a decreased connectivity in the OCD group. The *p*-value assesses the difference between groups using one-way analyses of covariance ($p < 0.001$ voxel and P-FWE < 0.05 at the cluster level).

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Table 3. Volumes of the pulvinar subnuclei groups in patients with obsessive-compulsive (OCD) and healthy controls

	Controls		OCD		
Pulvinar subnuclei	Mean	Sd	Mean	Sd	Bonferroni-corrected p
Left- PuA	255.345	36.0	271.521	39.6	*0.002**
Left-PuI	296.382	52.7	310.067	56.1	0.984
Left-PuL	253.112	50.4	248.607	59.9	0.037
Left-PuM	1291.191	184	1337.584	189	0.021
Right-PuA	225.690	31.7	217.922	34.9	0.437
Right-PuI	264.411	50.2	252.095	47.0	0.406
Right-PuL	217.294	45.1	205.388	37.6	0.299
Right-PuM	1185.978	160	1155.560	164	0.621

Note: * Significant group difference at $p < 0.00625$, Bonferroni-corrected.

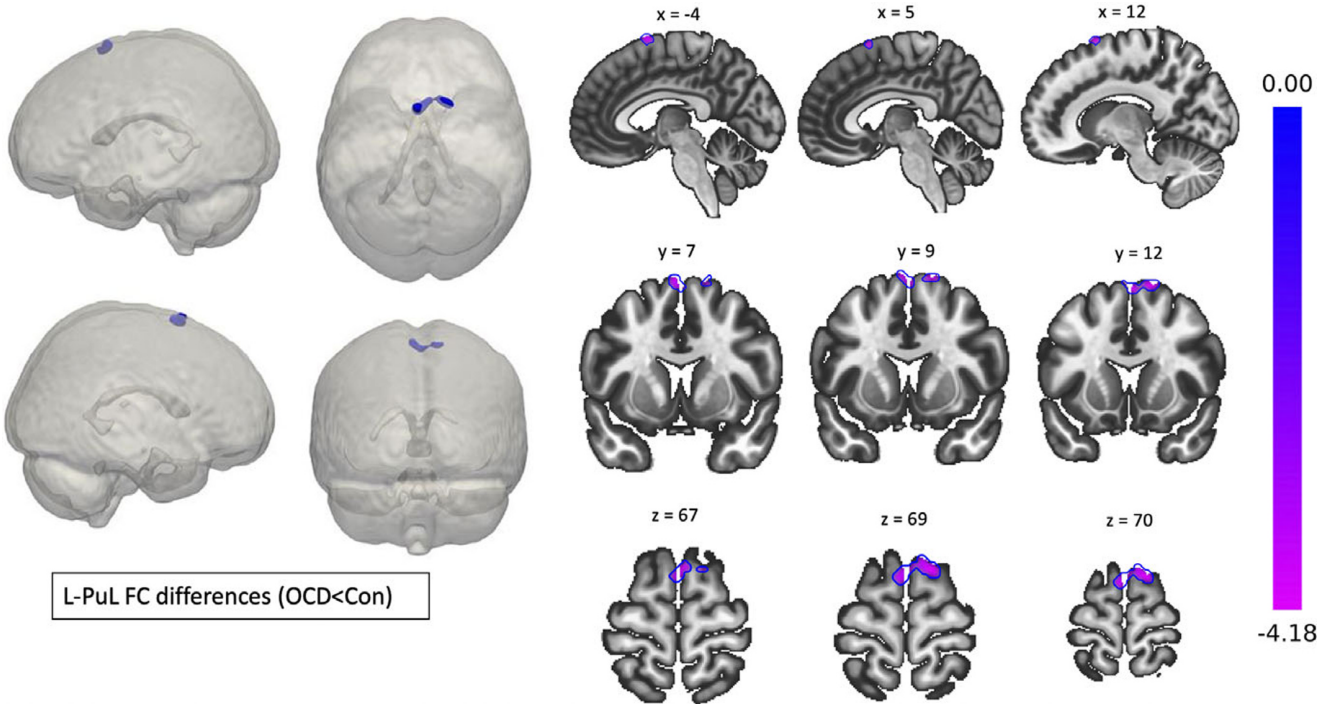

Figure 3. Clusters of voxels showing significant functional connectivity differences between the two groups in L-PuL. The purple patches indicate that the L-PuL in the control group exhibited significantly increased connectivity compared to OCD. All maps were family-wise error-corrected at *p-FWE* = 0.031775, with a minimum of 20 voxels for each cluster. The color bar represents the t-statistic. All significant clusters are presented on a standard brain atlas. The corresponding areas are also shown in Table 2.

obsessions, Y-BOCS compulsions, Y-BOCS total score, illness onset, illness duration, and medication usage). This correlation analysis was conducted while controlling for TIV, age, and gender as covariates. Yet, the analysis revealed no statistically significant correlation ($p > 0.00625$). Finally, we correlated the gray matter values of the structural cluster that showed a significant group difference (i.e. left PuA) with the functional connectivity values of the clusters that showed significant functional differences between the two groups (i.e. left PuL, the right PuA, and the left PuA). However, these correlations did not yield any significant results ($p > 0.00625$).

Discussion

The purpose of the study was to explore the functional and morphometric alterations of the pulvinar's subnuclei in patients with OCD. The pulvinar is an important anatomical structure that plays a critical role in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (Chen et al., 2020; Velioglu et al., 2022) as well as in neuropsychiatric diseases such as schizophrenia, major depressive disorder, and OCD (Penner et al., 2018; Weeland, Vriend, et al., 2022; Yulug et al., 2024). In this respect, the present study provided novel evidence for the crucial role of the pulvinar,

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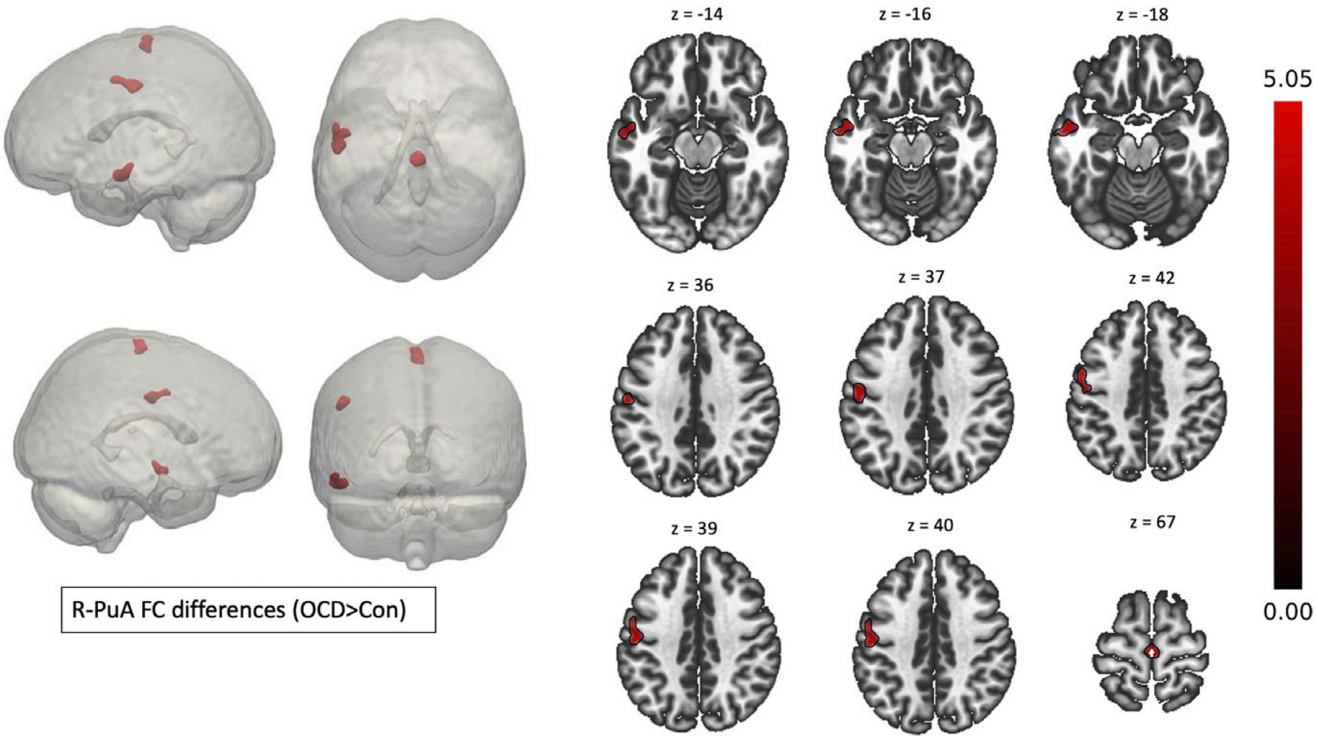

Figure 4. Clusters of voxels showing significant functional connectivity differences between the two groups in R-PuA seed. The red patches indicate that the R-PuA in the OCD group exhibited significantly increased connectivity compared to controls. All maps were family-wise error-corrected at *p-FWE*: 0.024643, *p-FWE*: 0.034843, *p-FWE*: 0.049603, with a minimum of 20 voxels for each cluster. The color bar represents the t-statistic. All significant clusters are presented on a standard brain atlas. The corresponding areas are also shown in Table 2.

particularly the PuA, in the pathophysiological mechanism of OCD by demonstrating functional and gray matter changes in the pulvinar's subnuclei in patients with OCD. To our knowledge, this is the first study to report connectivity and volume alterations in the pulvinar's subnuclei in patients with OCD when compared with age-matched controls.

The thalamus is pivotal in the CSTC circuit, which, in turn, is critical in OCD (Shaw et al., 2015; Weeland, Vriend, et al., 2022). Imaging studies highlight its pathophysiological significance, revealing functional connectivity defects in OCD. Given the thalamus's diverse and functionally distinct subnuclei, we focused on the pulvinar, which is the anatomically largest subnucleus in the thalamus, and its role in OCD. Notably, while structural alterations were restricted to the left PuA, alterations in functional connectivity were found between the two groups in the left PuA, the left PuL, and the right PuA seeds.

Our most remarkable finding was an increased connectivity pattern in the right PuA to the left and right precentral gyri, as well as to the left postcentral gyrus in patients with OCD (Figure 4). This is noteworthy due to the well-documented connections of the PuA to sensorimotor cortical areas of the brain (Benarroch, 2015; Guedj & Vuilleumier, 2020). In line with this finding, several previous studies have reported increased FC patterns in the thalamus of OCD groups. First, Lin et al. reported that the bilateral thalamus was among the regions showing a significantly increased fractional amplitude of low-frequency fluctuations (fALFF) in OCD patients (a combination of medicated and unmedicated patients) compared to the controls (Li et al., 2019). Similarly, a hyper-connectivity pattern in the thalamus has been previously reported by Bruin et al. in their large sample size study (Bruin et al., 2023). Interestingly, they emphasized that one of the only significant hyper-connectivity patterns was found in medicated as well as unmedicated OCD patients between the bilateral thalamus and the sensorimotor cortex (Bruin et al., 2023), aligning well with our results. Additionally, higher long-range positive functional connectivity was described in the bilateral thalamus of the OCD group, involving both medicated and unmedicated patients, compared to healthy controls (Lv et al., 2022). We assume that this might result from increased activity in the direct pathway, leading to hyperactivity in the CSTC circuit, which fails to suppress the compulsive behaviors (Jalal et al., 2023). Thus, the observed increased connectivity pattern of the right PuA to the sensorimotor cortices might be related to compulsive, predominantly sensorimotor symptoms in the disorder (such as, e.g. counting one's actions, checking one's sensations, repeatedly researching physical feelings or processes, or adhering to rigid 'rules' about breathing or blinking, for example).

In the past two decades, the superior temporal cortex has emerged as a focal point for researchers investigating the pathophysiology of OCD. Numerous studies have emphasized the pivotal role of the superior temporal gyrus, aligning their findings with the symptomatic manifestations of OCD (Rotge et al., 2008; Tao et al., 2023). Cottraux et al. reported that patients with OCD had higher regional cerebral blood flow in the superior temporal region in a resting state (Cottraux et al., 1996). Along the same line, an fMRI study recently reported an increased amplitude of low-frequency fluctuation (ALFF) in the superior temporal gyrus of patients with OCD compared to controls (Fan et al., 2017), whereas Yu et al. reported a significantly lower ALFF in, among others, the left superior temporal gyrus in patients with OCD (Yu et al., 2021) – a finding which seems to be specifically related to social anhedonia in OCD (Xia et al., 2019). Processing of both obsession-related and

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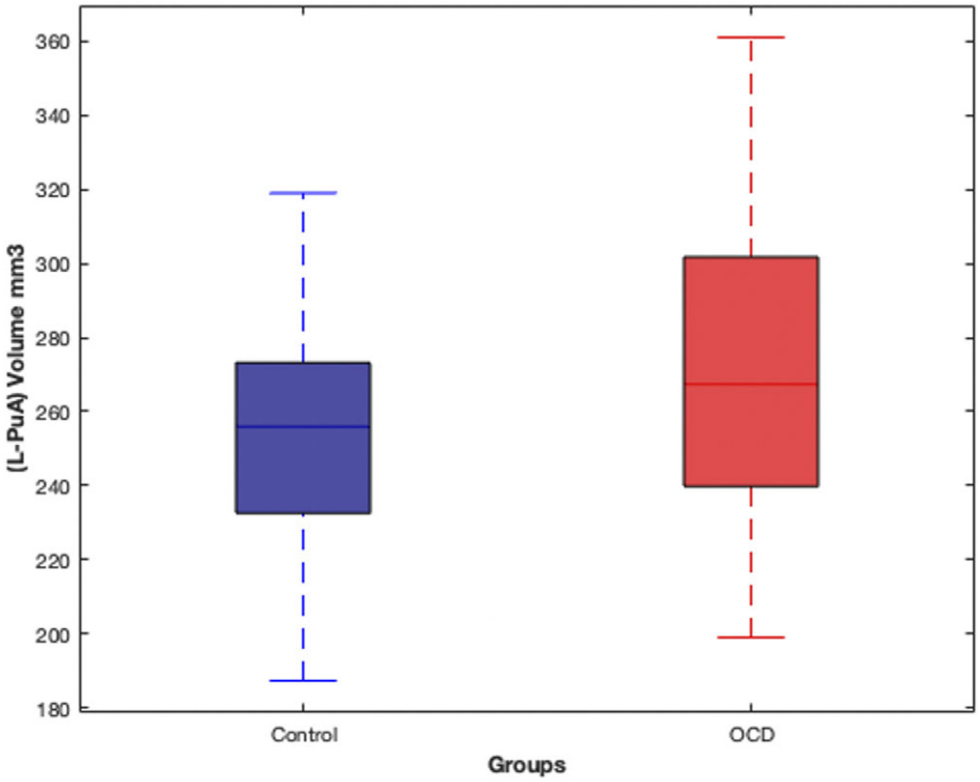

Figure 5. The plot showing the mean gray matter values of the L-PuA in two groups.

neutral stimuli additionally increased regional cerebral blood flow in the superior temporal region in OCD patients (Cottraux et al., 1996). Likewise, Choi et al. proposed that the bilateral anterior superior temporal gyrus, particularly the planum polare, may be involved in the pathophysiology of the disorder. This is supported by their findings of volume reduction in the superior temporal gyrus in patients with OCD (Choi et al., 2006). Finally, the left superior temporal gyrus exhibited significantly decreased gray matter volume in an unmedicated OCD group and had a significantly impaired dynamic FC to the left thalamus compared to healthy controls (Ding et al., 2023). This is in line with our results (see Table 2). Studies demonstrating a strong connectivity of the pulvinar with the superior temporal gyrus emphasize that thalamocortical projections of the pulvinar to the superior temporal gyrus relay visuospatial, somatosensory, and auditory information (Huang & Barber, 2021; Romanski et al., 1997). Hence, the increased FC between the left and right PuA and the superior temporal gyrus, planum polare, and the central opercular cortex in the OCD group compared to the controls (Figures 2 and 4, and Table 2) might once more be closely linked to the psychopathological state in our patient group and, maybe more specifically, constitute the neural substrate of mainly somatosensory-affiliated compulsions.

In addition to the observed hyperconnectivity patterns involving the right and left PuA, we also noted decreased FC in the left PuL to the bilateral superior frontal gyrus, a relatively crucial structure in higher cognitive functions (Figure 3). The PuL is generally associated with striate and extra-striate cortices, and often referred to as the 'visual pulvinar' along with its sibling, PuI (Homman-Ludiye & Bourne, 2019). While previous research has indicated that the ventral part of the PuL is functionally connected to visual cortices (Adams, Hof, Gattass, Webster, & Ungerleider, 2000), the medial part of PuL has been shown to be coupled with 'higher' cortical areas, contributing to associative or limbic functions (Romanski et al., 1997). Additionally, recent work by Guedj and Vuilleumier has extended PuL's connections to brain areas involved in higher cognitive functions (Guedj & Vuilleumier, 2020), besides its visual area connections. Furthermore, papers have proposed integrative and executive roles for the PuL, such as planning (Bridge, Leopold, & Bourne, 2016; Guedj & Vuilleumier, 2020). In association with our findings, a thinner cortical thickness in the left superior frontal gyrus was reported in OCD patients with poor insight compared to patients with good insight and controls (Liu et al., 2019). We propose that the observed reduction in connectivity between PuL and the superior frontal gyrus could be associated with executive impairments in OCD (Manarte et al., 2021). However, precision in assessing executive functions was not recorded in our study. Future investigations, incorporating comprehensive tests of executive functions, will be essential to provide a more nuanced understanding of the role of PuL in executive functions.

The volume and shape alterations in the pulvinar have been previously considered in various studies. However, inconsistencies persist across these studies, likely attributed to differences in sample size, participant demographics (children, adolescents, and adults), and medical history. For instance, some studies found a volume reduction across all thalamus subnuclei, including the pulvinar, in medication-free and medicated adult patients with OCD (Jurng et al., 2021; Weeland, Kasprzak, et al., 2022). On the other hand, Shaw et al. reported a noteworthy increase in surface area within the thalamus, particularly in the anterior and pulvinar nuclei, among medicated patients with OCD and their unaffected siblings when

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compared to controls (Shaw et al., 2015). Our gray matter findings align with those reported by Shaw et al. (2015). We identified a greater gray matter volume in the left PuA within the OCD group compared to healthy controls (Figure 5). We believe our observations regarding gray matter are noteworthy, as we focused on individual pulvinar subnuclei rather than exploring alterations in the entire pulvinar. The observed increase in gray matter within the left-PuA suggests a potential mechanism, possibly indicative of neuronal hypertrophy related to illness mechanisms or characteristics, or a neurodevelopmental defect in cortical and/or subcortical pruning (Christian et al., 2008). Moreover, the PuA is recognized for its involvement in somatosensory-associated functions (Benarroch, 2015; Guedj & Vuilleumier, 2020). Thus, the increased gray matter volume observed in individuals with OCD may also, like its increased connectivity, be linked to somatosensory-affiliated compulsions.

Many patients with OCD are exposed to various types of comorbidities such as major depressive disorder, anxiety disorders, and attention deficit disorder/hyperactivity disorder across the lifespan (Sharma et al., 2021). The presence of comorbidities in OCD may also affect brain connectivity and volumetry. For example, OCD patients with depressive comorbidity have been found to exhibit lower cortical volume compared to those with pure OCD (Cardoner et al., 2007). Likewise, OCD patients with comorbidities such as Tourette syndrome and schizophrenia exhibited altered functional connectivity in the brain compared to pure OCD patients (Tikoo et al., 2021; Wang et al., 2019). Hence, future studies should investigate functional connectivity and gray matter volume of the pulvinar subnuclei by considering the comorbidities of OCD patients.

Conclusion

In summary, we focused on the subnuclei of the pulvinar instead of the entire pulvinar in OCD. To the best of our knowledge, this study is unique because it is the first time that pulvinar subnuclei have been considered in patients with OCD. We observed functional connectivity alterations in subnuclei such as the left and right PuA, and the left PuL, as well as gray matter volume alteration in the left PuA. Those subregions of the pulvinar may be involved in the pathophysiology of OCD due to differences in functional connectivity and gray matter volume between the two groups. Our findings invite further research to confirm and better understand these functional and anatomical alterations seen in the pulvinar's subnuclei in patients with OCD.

Limitation

Despite the valuable functional and anatomical findings in this study, several limitations should be acknowledged. Firstly, most of the OCD patients included in this study were receiving medication, which may have an impact on our results. Secondly, while we associated our functional and gray matter results with clinical signs in OCD, we did not identify a significant correlation between them. A more comprehensive study, encompassing a larger sample size and categorizing participants with OCD into unmedicated and medicated groups, may offer a more comprehensive understanding of the role played by the pulvinar's subnuclei in the pathophysiology of OCD.

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Author contribution. BA designed the study, wrote the manuscript, analyzed the resting-state fMRI data, and performed the statistical analysis. DRM collected the resting-state fMRI and clinical data. SA guided and designed the study. TC and KK reviewed and revised the manuscript. All authors contributed to the manuscript and approved the submitted version.

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Competing interests. The authors declare none.

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