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Structural and resting-state connection abnormalities of habenula in obsessive-compulsive disorder

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Original Article

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Abstract

Background. Previous studies have suggested that the habenula (Hb) may be involved in the mechanism of obsessive-compulsive disorder (OCD). However, the specific role of Hb in OCD remains unclear. This study aimed to explore the structural and functional abnormalities of Hb in OCD and their relationship with the clinical symptoms.

Methods. Eighty patients with OCD and 85 healthy controls (HCs) were recruited as the primary dataset. The grey matter volume, resting-state functional connectivity (FC), and effective connectivity (EC) of the Hb were calculated and compared between OCD group and HCs. An independent replication dataset was used to verify the stability and robustness of the results.

Results. Patients with OCD exhibited smaller Hb volume and increased FC of right Hb-left hippocampus than HCs. Dynamic causal model revealed an increased EC from left hippocampus to right Hb and a less inhibitory causal influence from the right Hb to left hippocampus in the OCD group compared to HCs. Similar results were found in the replication dataset.

Conclusions. This study suggested that abnormal structure of Hb and hippocampus-Hb connectivity may contribute to the pathological basis of OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a common mental disorder characterized by reoccurred intrusive obsessive thoughts or repetitive compulsive behaviors (APA, 2013). OCD has a high lifetime prevalence of 2–3%, and there are still lacking effective treatments because the pathological mechanism of OCD remains unclear.

Neuroimaging studies showed consistent evidence for the dysfunction of cortico-striato-thalamo-cortical (CSTC) circuit in OCD (Shephard et al., 2022). Besides, the alterations in frontolimbic, frontoparietal, and cerebellar networks were also implicated in patients with OCD (van den Heuvel et al., 2016; van Velzen, Vriend, de Wit, & van den Heuvel, 2014). However, current models do not fully explain all symptoms of OCD. The thalamus (and its subnuclei) was regarded as a gateway to OCD, and previous studies have yielded inconsistent results regarding abnormal functional connections of thalamus (Weeland et al., 2022). Since thalamus is highly heterogeneous, it may be necessary to investigate this brain region in a more specific aspect to further expand and refine the pathological model of OCD.

Among the various nuclei in the thalamus, habenula (Hb) is a key node located in the dorsal thalamus and its potential link to the pathology of OCD has been garnering increased attention recently. A previous study suggested that the neurons in the Hb-projecting globus pallidus (GPh) were proposed to play an important role in the typical repetition of obsessions and compulsions (Loonen & Ivanova, 2019). A past study focusing on the Hb in patients with OCD found that targeting the Hb in deep brain stimulation therapy can significantly reduce obsessive-compulsive symptoms and negative emotions in patients with OCD (Zhang et al., 2020). Previous animal models found that selective genetic ablation of neurons in the Hb would induce hyperactive, impulsive, and compulsive behaviors in mice (Okamoto, Agetsuma, & Aizawa, 2012). These results raised the possibility that Hb may be also involved in the psychopathology of OCD. Considering that the structural and functional abnormalities of Hb still remain to be investigated in OCD, it is necessary to study the role of specific habenular nucleus to gain a more in-depth understanding of the etiology of OCD.

The Hb is a pair of small nuclei located in the middle posterior part of the dorsal thalamus near the third ventricle (see Supplementary materials Fig. S2), and can be divided into the medial habenula and lateral habenula (LHb) regions. As a key hub, the Hb connects the

forebrain and midbrain (Fakhoury, 2017), among which at least four different loops were distinguished: first, the GPh-LHb loop is involved in the evaluation of the validity of cognitive and motor processes (Baker et al., 2016; Stephenson-Jones et al., 2016); second, the Hb is an important component of the reward circuit, along with amygdala, ventral tegmental area (VTA), and nucleus accumbens (NAcc); third, the hippocampus-medial prefrontal cortex (mPFC)-LHb loop was reported to play a critical role in response (Fakhoury, 2017) flexibility and adaptive behaviors in a number of studies (Baker et al., 2016; Hones & Mizumori, 2022; Mizumori & Baker, 2017; Stephenson-Jones et al., 2016); fourth, Hb, along with ventromedial prefrontal cortex (vmPFC), amygdala, and periaqueductal gray (PAG) were associated with the process of Pavlovian fear acquisition and extinction (Roy & Parhar, 2022; Sachella et al., 2022; Tovote, Fadok, & Lüthi, 2015). It is possible that the Hb is linked to the pathological mechanism of OCD by participating in these loops. However, few studies have explored the role of Hb in OCD, and which specific loop of Hb was involved in OCD remains unknown and need to be clarified.

Therefore, this study aimed to investigate the role of Hb in the pathological mechanism of OCD. We first investigated whether there was structural abnormality in the Hb of patients with OCD through comparing its gray matter volume with healthy controls (HCs). Then, functional connectivity (FC) and effective connectivity (EC) were estimated by resting-state functional magnetic resonance data to explain which Hb circuit was involved in the development of OCD. Finally, the relationship between structural and functional features of the Hb and clinical symptoms in OCD was explored. In addition, we also examined the role of medication status on the results. It is expected to find the abnormalities of Hb in OCD. However, few studies have explored the role of Hb in OCD, and no specific hypothesis has been established as to the mechanism by which the Hb-related circuit is involved. This study is expected to provide evidence for further expanding and refining the pathological model of OCD.

Methods

Participants

Eighty-four patients with OCD were recruited from outpatient clinics affiliated with the Second Xiangya Hospital of Central South University in Changsha, Hunan, China. All patients met DSM-V criteria for OCD and were diagnosed by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV. The inclusion criteria for the OCD group were (1) having a Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) score of ⩾16; (2) no other psychiatric diagnoses meeting the DSM-V criteria except for OCD. Eighty-nine HCs were also recruited from community matched for age, gender, and years of education. The inclusion criteria for HCs were (1) having no current or history of any psychiatric disorders; (2) aged 18–35 years old; (3) right-handed; (4) having at least 9 years of education. Participants were excluded if they had: (1) a history of major medical or neurological problems (e.g. hypothyroidism, seizure disorder, or brain injury); (2) MRI contraindication; (3) being pregnant, lactating, or preparing for pregnancy; (4) inability to cooperate with the MRI procedure. During the study, 35 patients were drug naïve, 11 patients hadn't taken any psychotropic medicine for at least 1 month prior to enrollment, and 34 patients were taking medicine during brain image acquisition. Eight subjects (4 OCD patients and 4 HCs) were excluded due to excessive head motion in any direction more than 1.5 mm or/and 1.5°. The independent replication dataset included 38 patients with OCD and 34 HCs. Detailed descriptions of the replication dataset are presented in the online Supplementary materials.

This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All participants learned about the study procedure and signed the informed consent form.

Measures

The Edinburgh Handedness Inventory (EHI) confirmed the handedness of participants (Oldfield, 1971). The Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), and Obsessive-Compulsive Inventory-Revised (OCI-R) assessed the depression, anxiety, and obsessive-compulsive symptoms of all participants (Chasson, Tang, Gray, Sun, & Wang, 2013). The Y-BOCS assessed the severity of obsessive-compulsive symptoms of patients with OCD (Goodman et al., 1989).

MRI acquisition

The MRI data of all the subjects were collected from the Second Xiangya Hospital of Central South University. All participants were scanned on a Siemens Skyra 3-T MRI system (Siemens Magnetom Skyra 3.0-T scanner) with foam padding to minimize head motion. The three-dimensional T1-weighted scans were acquired with a T1-weighted gradient echo sequence (T1-weighted image). The parameters were as follows: repetition time (TR) = 1900 ms, echo time (TE) = 2.01 ms, flip angle (FA) = 9°, slice thickness = 1.0 mm, voxel size = $1 \times 1 \times 1$ mm^3, field of view (FOV) = 256×256 mm^2, slice numbers = 176. The resting-state functional images were acquired with echo planar imaging sequence with the following parameters: TR = 2500 ms, TE = 25 ms, FA = 90°, voxel size = $3.8 \times 3.8 \times 3.5$ mm^3, matrix = 64×64, FOV = 240×240 mm^2, slice thickness = 3.5 mm, slice numbers = 39. The functional scan lasted for 8 min 33 s and 176 volumes were obtained in total.

Structural MRI data analysis

Structural Hb definition

The Hb masks of each subject were segmented by one rater (LQ) blinded to the diagnosis by using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron) to color individual voxels based on the geometric method (Lawson, Drevets, & Roiser, 2013), outlined in the Supplementary material (online Supplementary Fig. S1). A second rater (CYY) manually delineated the Hb masks of 20 participants (10 patients and 10 HCs) to examine the reliability of the manual Hb masks. To quantify intra-rater reliability, the intraclass correlation coefficient (ICC) was calculated and was good enough for subsequent analysis. ($ICC_{left\ Hb} = 0.937$, $ICC_{right\ Hb} = 0.901$) (Lawson et al., 2013).

Voxel-based morphometry analysis

Voxel-based morphometry analysis was implemented using FMRIB Software Library 5.0 (FSL) (Smith et al., 2004). The structural images were segmented, modulated, and normalized

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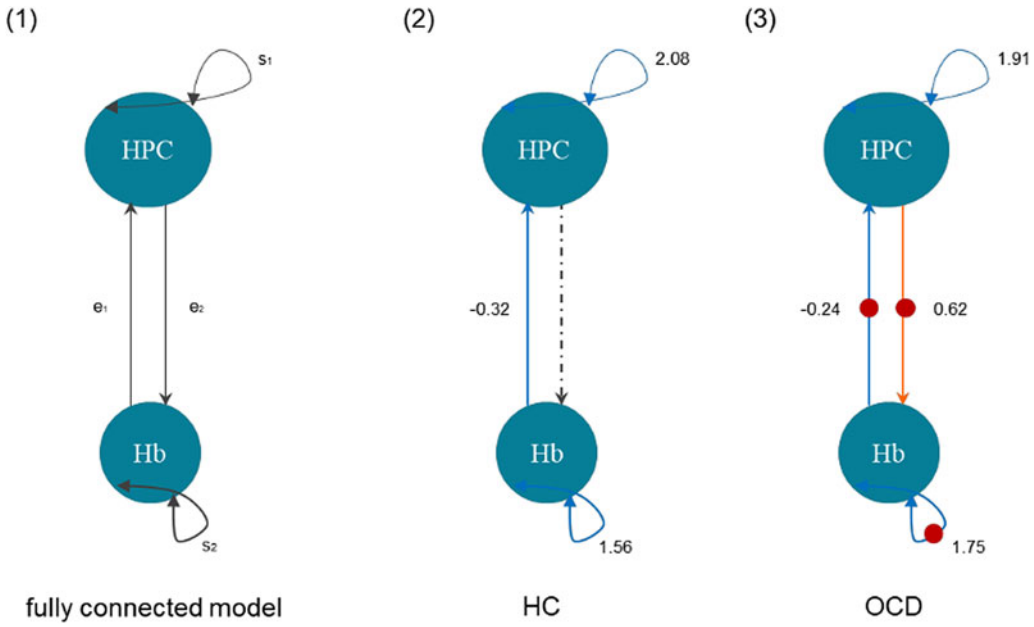

Figure 1. The DCM models. (1) The fully connected model between the habenula and hippocampus was established in the DCM analysis. (2) The DCM model in healthy controls. Blue one-way arrows and values are inhibitory modulation. Blue bidirectional arrows and values are self-inhibition. The dashed line indicates that there is no significant effective connectivity. (3) The DCM model in patients with OCD. Blue one-way arrows and values are inhibitory modulation. Orange one-way arrows indicate decreased inhibition. The red dots represent the significant group difference between healthy controls and patients with OCD. The between-group comparisons revealed that patients with OCD had an increased effective connectivity from the left hippocampus to the right habenula, less inhibition from right habenula to left hippocampus, and increased self-inhibition of the right habenula. These models were thresholded at 0.95 posterior probability after exhaustive Bayesian model reduction (BMR) and Bayesian model averaging (BMA). OCD, obsessive-compulsive disorder; HC, healthy controls; HPC, hippocampus; Hb, habenula.

following the standard procedure using FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) to generate gray matter, white matter, and cerebrospinal fluid images. Lastly, we smoothed the gray matter images using full-width-half-maximum (FWHM) of 3 mm. Besides, we mapped each individualized Hb to the MNI and DARTEL template space with DARTEL estimated deformations to extract gray matter volume.

Functional image analysis

Preprocessing and functional connectivity calculation

DPARSF 5.2 based on the SPM12 software was used for all resting-state functional MRI (rs-fMRI) preprocessing (Yan, Wang, Zuo, & Zang, 2016). For the preprocessing, the first 10 time points were discarded. The fMRI BOLD data were slice-time corrected, realigned, normalized to each subject's T1 image, and smoothed with a 6 mm isotropic FWHM Gaussian kernel. Region of interest (ROI) timeseries of Hb were separately extracted from unsmoothed but otherwise fully preprocessed rs-fMRI data in MNI space. Following removal of linear trends and band-pass filtering (0.01–0.08 Hz), several nuisance covariates including white matter and cerebrospinal fluid signals and Friston-24 head motion parameters were regressed. Scrubbing was performed if the head motion measured by frame-wise displacement (FD) (power) was greater than 0.2 (Chen, Zhang, Zhang, Qiao, & Shen, 2021; Yan et al., 2013). The resampled voxel size was $2 \times 2 \times 2$ mm. The mean FD (Jenkinson, Bannister, Brady, & Smith, 2002) was calculated for each participant and was controlled as a covariate in all group-level analyses.

FC analyses were conducted in the DPARSF 5.2. The seeds for the left and right Hb were obtained from the Automated Human Habenula Segmentation Program (Kim et al., 2016) (see online Supplementary Fig. S2). The time course of the FC is computed by linear correlation. We first calculated the correlation coefficient between the Hb and the whole brain, controlled for two nearby thalamic ROIs approximately corresponding to the dorsomedial and centromedian nuclei (Ely, Stern, Kim, Gabbay, & Xu, 2019; Ely et al., 2016). Then, Fisher's z-transformation was used to transform the correlation values into z-values.

Dynamic causal modeling

The DCM12 implemented in SPM12 was applied to perform the spectral dynamic causal model (DCM) analyses (Friston, Kahan, Biswal, & Razi, 2014). The right Hb mask and left hippocampus clusters obtained from FC analyses were used to extract time series. Fixed-effects Bayesian Model Reduction (BMR) was used to determine the best model for each subject based on the fully connected model (Fig. 1(1)). To analyze the connectivity parameters, Bayesian Model Averaging (BMA) was performed (Penny et al., 2010). The covariates were mean-centered and entered in the following order: group (HCs *v*. OCD), age, gender, education, and head motion parameters. For group-based model reduction and comparison, a Parametric Empirical Bayes (PEB) analysis was applied. Besides, a groupwise EC PEB analysis within OCD group was performed to investigate the correlation between obsessive-compulsive symptoms and connectivity parameters. Based on BMA, we also obtained probability-weighted values for the model parameters. Only effects with a posterior probability >0.95 are reported.

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Statistical analysis

Two-sample *t* tests or χ^2 tests were used to compare the demographic and clinical characteristics between OCD and HC group. Covariance analyses were conducted to compare the Hb volume between two groups with age, gender, and education as covariables.

For the FC analysis, two-sample *t* test was performed to determine significant alterations in OCD, controlling the age, gender, education, and head motion parameters. The bilateral globus pallidus internus (Gpi), mPFC, dorsomedial prefrontal cortex, vmPFC, hippocampus, amygdala, PAG, VTA, and NAcc were chosen as ROIs (see online Supplementary materials for details) for small volume correction (SVC, family-wise error corrected (FWEp <0.05)), with an initial threshold of $p < 0.001$. Pearson correlations were performed to test the relationship between the MRI-based Hb alterations and the obsessive-compulsive symptoms using false discovery rate corrected (FDR). The effect of medication status was also explored (see online Supplementary materials). The same analyses were conducted in the replication dataset.

Results

Demographic and clinical characteristics of HC and OCD

There was no significant difference in age, gender, and years of education between OCD and HC group. Patients with OCD had higher BDI, STAI, and OCI-R scores than HCs (see Table 1).

Table 1. Differences of demographic and clinical data between OCD and HC groups

	OCD ($n = 89$)	HC ($n = 84$)	(χ^2/t)	p
Age (years)	22.54 ± 4.00	21.47 ± 4.29	1.69	0.093
Gender (male/female)	43/37	44/41	0.03	0.865
Education (years)	14.42 ± 2.39	14.42 ± 2.05	0.02	0.984
Medication (yes/no)[a]	34/46	-	-	-
BDI	20.49 ± 9.86	6.11 ± 5.58	11.72	<0.001
SAI	54.65 ± 12.43	37.27 ± 9.70	10.18	<0.001
TAI	57.29 ± 8.18	40.20 ± 8.70	13.29	<0.001
OCI-R	31.13 ± 12.31	15.86 ± 10.70	8.72	<0.001
Washing	5.58 ± 3.61	2.29 ± 2.16	7.03	<0.001
Checking	5.76 ± 3.22	2.61 ± 2.27	7.22	<0.001
Ordering	5.31 ± 3.02	3.32 ± 2.26	4.78	<0.001
Hoarding	3.75 ± 2.83	3.29 ± 2.03	1.19	0.236
Obsessing	7.21 ± 2.77	2.41 ± 2.30	12.09	<0.001
Mental neutralizing	4.29 ± 3.07	2.21 ± 2.19	4.97	<0.001
Y-BOCS	22.79 ± 4.07	-	-	-
Obsession	11.81 ± 1.99	-	-	-
Compulsion	10.97 ± 3.07	-	-	-

Note. OCD, obsessive-compulsive disorder; HC, healthy control; BDI, the score of the Beck Depression Scale; SAI, the score of the state anxiety scale; TAI, the score of the trait anxiety scale; OCI-R, the score of the Obsessive-Compulsive Inventory-Revised; Y-BOCS, the score of the Yale–Brown Obsessive-Compulsive Scale.
[a]Medication: number of patients taking psychopharmacology yes/no. 'no' means that the patients were medication-naïve, or they did not take any psychotropic medicine at least for 1 month prior to the day when they were enrolled. 'yes' mean they were using medicine when enrolled.

Volumetric analysis of the habenular nucleus

The volumes of left Hb (HCs = 45.68 ± 20.94 mm^3; OCD = 35.76 ± 16.28 mm^3; $F = 9.312$, $p = 0.001$) and right Hb (HCs = 45.12 ± 17.54 mm^3; OCD = 33.30 ± 17.00 mm^3; $F = 15.014$, $p < 0.001$) were significantly smaller in OCD group than in HCs (see Fig. 2). After controlling for the total intracranial volume (TIV) of each subject, the differences remained ($ps < 0.01$). The decreased volume of bilateral Hb was replicated in the replication dataset as well (see online Supplementary Table S5).

Functional connectivity of the habenula

ROI analysis showed that patients with OCD showed significantly increased FC of right Hb-left hippocampus ([−26, −6, −26], voxels = 19, $T = 4.32$, $p = 0.003$, SVC) (see Fig. 3). No other significant difference in FC between the OCD group and HCs was observed. There was no significant difference in FC between the medicated and unmedicated patients with OCD. The increased FC of right Hb-right hippocampus was replicated in the independent replication dataset (see online Supplementary Fig. S3).

Effective connectivity of the habenula

The fully connected model was established in the DCM analysis. The winning model at the group level was presented in Fig. 1. The between-group comparisons revealed that patients with OCD had an increased EC from the left hippocampus to the right Hb, less inhibition from right Hb to left hippocampus, and increased self-inhibition of the right Hb (see Fig. 1(3)). The increased EC from the hippocampus to the right Hb and increased self-inhibition of the right Hb were also found in the replication dataset (see online Supplementary Fig. S4(3)). There was no significant difference in EC between the medicated and unmedicated patients with OCD in the discovery dataset.

Correlation analysis

In OCD group, the FC of right Hb-left hippocampus showed positive correlation with the severity of obsessing ($r = 0.225$, $p = 0.045$, uncorrected, Fig. 4a); the EC from right Hb to left

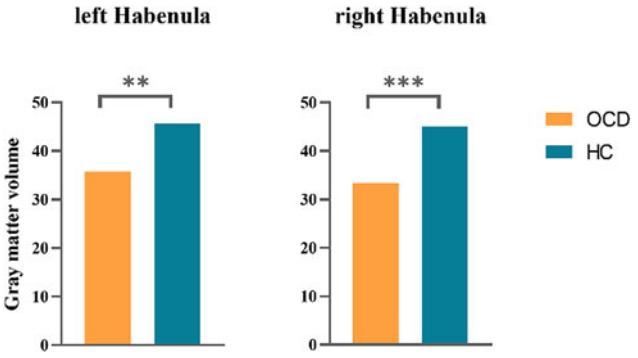

Figure 2. Group difference in gray matter volume of bilateral Hb. **Significance level of 0.05; ***significance level of 0.001. OCD, obsessive-compulsive disorder; HC, healthy controls.

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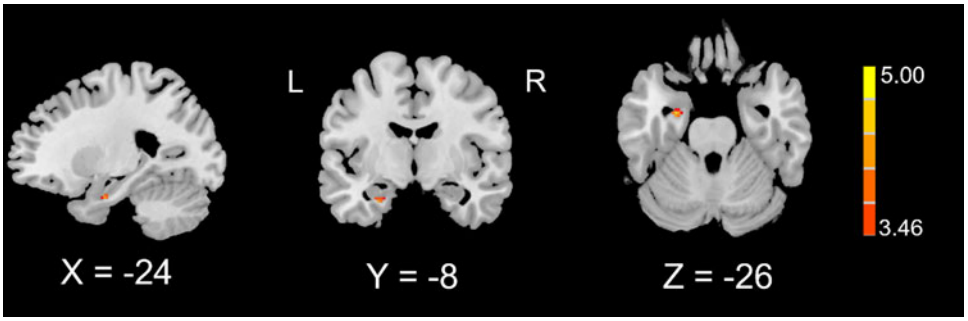

Figure 3. Group difference in functional connectivity of the right Hb by ROI analysis. Enhanced resting-state functional connectivity (rsFC) of the right habenula-left hippocampus were found in patients with obsessive-compulsive disorder (OCD) when compared to healthy controls. The connectivity values were obtained from small-volume correction analyses. L, left; R, right.

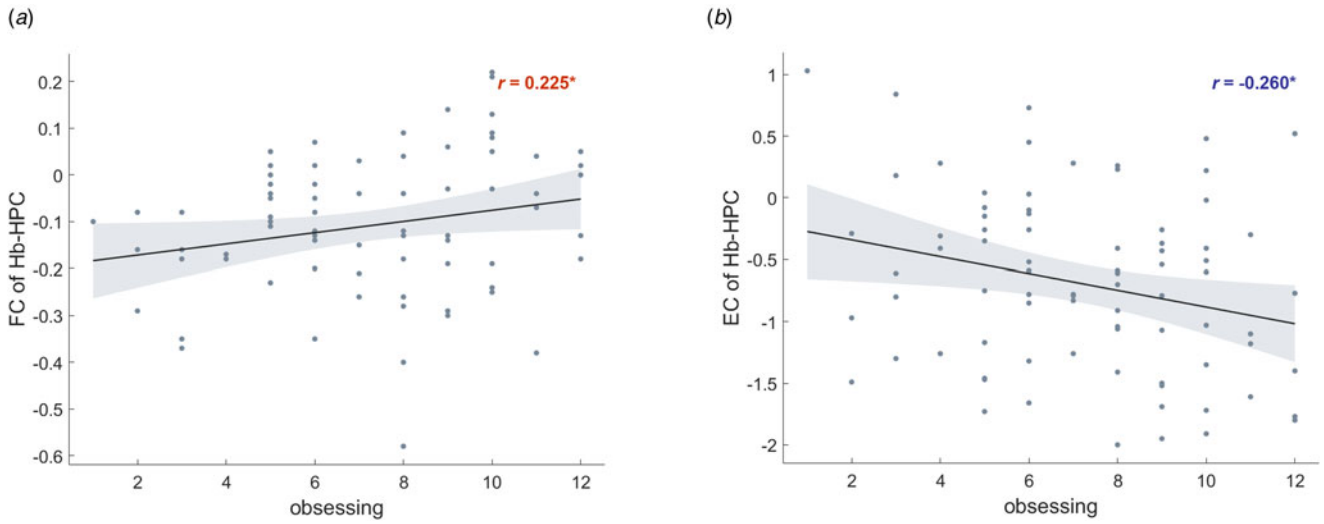

Figure 4. Association of FC and EC with OCD symptom severity.These associations were not corrected by FDR. (a) Correlation between the FC of right habenula-left hippocampus and the severity of obsessing (subscale of OCI-R); (b) correlation between the EC of right habenula-left hippocampus and the severity of obsessing; *r*, correlation coefficient. *Significance level of 0.05. FC, functional connectivity; EC, effective connectivity; FDR, false discovery rate; OCI-R, obsessive-compulsive inventory-revised.

hippocampus showed a negative correlation with the severity of obsessing ($r = -0.260$, $p = 0.020$, uncorrected, Fig. 4b). However, the above correlations were not significant after FDR correction. Correlation between the volume of Hb/EC of hippocampus-Hb and OCD symptom severity (Y-BOCS total, Y-BOCS obsessions, Y-BOCS compulsions, OCI-R and its subscales) did not yield any significant results in OCD group (see Table 2).

Table 2. Correlation coefficients of the correlation analysis (uncorrected)

	1	2	3	4	5	6	7	8	9	10
Gray matter volume										
lHb	0.001	0.096	−0.062	−0.066	−0.118	−0.017	−0.024	0.128	−0.075	−0.149
rHb	0.059	−0.044	0.107	0.119	0.007	−0.022	0.040	0.172	0.212	0.082
Functional connectivity										
rHb-lHPC	0.073	0.001	0.097	0.200	0.188	0.035	0.145	0.073	0.127	**0.225***
Effective connectivity										
lHPC-rHb	−0.008	−0.089	0.047	0.066	−0.011	0.165	0.016	0.113	0.094	−0.152
rHb-lHPC	−0.094	−0.084	−0.070	−0.046	−0.097	0.053	0.023	−0.002	0.075	**−0.260***

Notes. lHb, left habenula; rHb, right habenula; lHPC; left hippocampus; 1, Y-BOCS total; 2, Y-BOCS obsession; 3, Y-BOCS compulsion; 4, OCI-R total; 5, checking; 6, washing; 7, ordering; 8, hoarding; 9, mental neutralization; 10, obsessing.
*Significance level of 0.05.

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Discussion

This study explored the structural and functional abnormalities and the role of Hb in patients with OCD. Results showed that patients with OCD had decreased gray matter volumes of Hb and increased FC of Hb-hippocampus compared to HCs. DCM revealed an increased EC from left hippocampus to right Hb and less inhibitory causal influence from the right Hb to left hippocampus in the OCD group. Similar results were found in the replication dataset. These findings provided novel insights into the role of Hb in the pathogenesis of OCD.

This study found that patients with OCD had a smaller Hb volume than HCs even after controlling for the TIV, which further indicated the structural abnormalities of Hb in OCD. Previous studies have proposed that abnormalities in serotonin, dopamine, glutamate neurotransmission and homeostasis, and especially in the CSTC circuitry, may contribute to the development of OCD (Bokor & Anderson, 2014; Carlsson, 2000; Pittenger, Bloch, & Williams, 2012), while the Hb is an important relay station for the transmission of these neurotransmitters (Hu, Cui, & Yang, 2020). In addition, increasing evidence suggests that the Hb regulates and connects brain regions associated with divergent motivational and cognitive states (Fakhoury, 2017; Hu et al., 2020; Namboodiri, Rodriguez-Romaguera, & Stuber, 2016). The structural abnormalities of Hb in OCD may be related to its cognitive or motivational dysfunction, which needs to be studied further. In addition, the potential effect of medications on the structure of Hb in patients with OCD was excluded in this study. The smaller Hb volume was also found in the replication dataset, suggesting the stability of this result.

Next, we performed the FC analysis of Hb and revealed aberrant Hb-hippocampus connectivity in the OCD group. Hippocampus is an important part of the limbic system, which is closely related to the pathophysiology of OCD (Boedhoe et al., 2017; Li et al., 2020; Rao et al., 2018). Structural and functional abnormalities in the hippocampus have also been previously reported in adult patients with OCD (Boedhoe et al., 2017; Li et al., 2020; Rao et al., 2018). Moreover, another major function of the hippocampus is to support the creation of new and declarative memories including episodic memory and semantic memory (Knierim, 2015). Previous animal experiments suggested that the FC of Hb-hippocampus would enable adaptive and flexible responding, particularly when established rules must be flexibly applied on a trial-by-trial basis (Baker, Rao, Rivera, Garcia, & Mizumori, 2019). However, patients with OCD are characterized by maladaptive patterns of repetitive and inflexible cognition and behavior, suggesting a lack of cognitive flexibility (Patricia & Christopher, 2018). Furthermore, this study found the abnormal FC of right Hb-left hippocampus was associated with the severity of obsessing. Thus, the functional abnormality of Hb-hippocampus connectivity may contribute to the OCD to a certain extent.

The DCM which was adopted to further analyze the abnormal connectivity found an increased self-inhibition of Hb, increased EC of hippocampus-Hb, and decreased inhibition from Hb to hippocampus in patients with OCD. The connectivity of hippocampus-Hb is essential for the response flexibility and adaptive behaviors (Hones & Mizumori, 2022; Mizumori & Baker, 2017), and it is through this circuit that the hippocampus sends information to the mPFC about impending/recent behavioral events. As a result of its working memory capacities, the mPFC is able to determine whether expected goals were reached based on the previous response. A signal is then sent from the mPFC to the Hb, indicating whether or not the current response should be maintained or adjusted to maximize goal acquisition in the future. The Hb signals would inform the hippocampus to continue processing the spatial and temporal context at hand (Mizumori & Baker, 2017). However, the abnormal FC between the Hb and mPFC was not found in this study. The self-inhibition of Hb was found increased in the OCD group, while self-inhibition in the hippocampus was similar to that in HCs. Therefore, it is possible that the functional abnormality of Hb may play a role in behavioral inflexibility in patients with OCD (Gruner & Pittenger, 2017). Correlation analysis suggested that the abnormal EC of Hb-hippocampus was negatively related to the obsessive-compulsive symptom in OCD, which indicated patients with severe OCD symptoms may exhibit a compensatory neural activity in EC of Hb-hippocampus. Previous neuroimaging studies have identified compensatory neural activity in OCD, finding that the compensatory processes may result in normal or only subtly perturbed performance despite the substantial abnormalities in underlying capacities (Gruner & Pittenger, 2017; Gruner et al., 2012; Henseler et al., 2008; Ullman & Pullman, 2015). The potential effect of medications on the EC of Hb-hippocampus in patients with OCD was also excluded in this study.

In summary, this study focused on the Hb located in the dorsal thalamus and found functional impairment of Hb-hippocampus connectivity in OCD, indicating that Hb may play a crucial role in the pathological mechanism of OCD. A meta-analysis suggested that previous studies focusing on the overall thalamus of OCD have consistently found decreased connections between the thalamus and the striatum. As the thalamus is a heterogeneous brain region, studies focusing on the thalamic subregion of OCD have found abnormal connections between the thalamus and brain regions inside and outside the CSTC circuit. Despite that the Hb is a key node in the thalamus located in the dorsal thalamus, the role of the Hb in the pathological mechanism of OCD still remains unknown and needs to be clarified. The abnormal Hb-hippocampus connectivity in OCD was found in this study and was replicated in the replication dataset as well. In previous pathological models of OCD, the hippocampus is involved in the ventral affective CSTC and played an important role in the process of emotion and motivation (Shephard et al., 2021, 2022). This study further extended the ventral affective CSTC by identifying specific abnormalities in the connection between Hb and hippocampus.

There were several limitations in this study. Firstly, this study is a cross-sectional study which cannot explore the causal relationship. Further longitudinal research should be conducted to address this issue. Secondly, functional abnormalities of the Hb were investigated only in the resting state. Future research is needed to validate the specific functions of Hb in patients with OCD by performing task-state fMRI.

Conclusion

This study found that OCD patients had small Hb volume, and abnormal connectivity of right Hb-left hippocampus. The functional abnormality of Hb was associated with the severity of obsessing. These results provide evidence for the involvement of the Hb in the pathological mechanism of OCD, especially through the connectivity of Hb-hippocampus, which further enhanced our insight into the pathological basis of OCD.

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