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Lower synaptic density and its association with cognitive dysfunction in patients with obsessive-compulsive disorder

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ABSTRACT

Background Understanding synaptic alteration in obsessive-compulsive disorder (OCD) is crucial for elucidating its pathological mechanisms, but *in vivo* research on this topic remains limited.

Aims This study aimed to identify the synaptic density indicators in OCD and explore the relationship between cognitive dysfunction and synaptic density changes in OCD.

Methods This study enrolled 28 drug-naive adults with OCD aged 18–40 years and 16 healthy controls (HCs). Three-dimensional T1-weighted structural magnetic resonance imaging and ^{18}F-SynVesT-1 positron emission tomography were conducted. Cognitive function was assessed using the Wisconsin Cart Sorting Test (WCST) in patients with OCD and HCs. Correlative analysis was performed to examine the association between synaptic density reduction and cognitive dysfunction.

Results Compared with HCs, patients with OCD showed reduced synaptic density in regions of the cortico-striato-thalamo-cortical circuit such as the bilateral putamen, left caudate, left parahippocampal gyrus, left insula, left parahippocampal gyrus and left middle occipital lobe (voxel $p<0.001$, uncorrected, with cluster level above 50 contiguous voxels). The per cent conceptual-level responses of WCST were positively associated with the synaptic density reduction in the left middle occipital gyrus ($R^2=0.1690$, $p=0.030$), left parahippocampal gyrus ($R^2=0.1464$, $p=0.045$) and left putamen ($R^2=0.1967$, $p=0.018$) in patients with OCD.

Conclusions Adults with OCD demonstrated lower ^{18}F-labelled difluoro analogue of ^{18}F-SynVesT-1 compared with HCs, indicating potentially lower synaptic density. This is the first study to explore the synaptic density in patients with OCD and provides insights into potential biological targets for cognitive dysfunctions in OCD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research acknowledges the importance of investigating synaptic alterations in obsessive-compulsive disorder (OCD), but there is a lack of *in vivo* studies.

WHAT THIS STUDY ADDS

⇒ This study adds to the existing knowledge by identifying reduced synaptic density in specific brain regions of drug-naive adults with OCD and establishing a positive association between cognitive dysfunction and synaptic density reduction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study contributes to understanding OCD's neurobiological basis, potentially guiding future research and informing the development of targeted interventions and treatment strategies.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterised by recurring, intrusive thoughts, impulses or images, commonly accompanied by repetitive behaviours or psychological rituals.[1] Previous studies have proposed that the cortico-striato-thalamo-cortical (CSTC) circuit including the cortical regions, striatum (putamen and caudate), thalamus and other areas of limbic system (insula, parahippocampal gyrus) may be the neuropathological basis of OCD.[1] Previous studies have found brain volume loss/atrophy in the CSTC circuit in patients with OCD.[2]

Synaptic loss is associated with a variety of neurodegenerative diseases and mental disorders, and is correlated with the clinical severity assessed by positron emission tomography (PET) imaging of synaptic vesicular glycoprotein 2A (SV2A) *in vivo*.[3] There is limited research on the loss of synaptic protein markers in OCD. Postmortem research has found lower numbers of synapses in the CSTC circuit and lower expression of corresponding synaptic function genes in patients with OCD.[4] Preclinical research further demonstrated synaptic dysfunction in the CSTC circuit in OCD mouse models.[5] Also, emerging genetic evidence suggests synaptic pathology as a characteristic feature in the progression of OCD.[6] A recent preclinical study used a new PET radiotracer to explore synaptic density change in an OCD mouse model and found a strong correlation between synaptic density reduction in the

CSTC circuit and OCD development.[7] However, investigations into synaptic density have been confined to small-cohort preclinical and postmortem studies, with no exploration in patients with OCD so far.

Patients with OCD exhibit cognitive dysfunction, especially conceptualisation, abstract thinking and impulse control.[8] This cognitive function disturbance is the underlying mechanism of the clinical features of OCD and is associated with imaging abnormalities.[1] The Wisconsin Cart Sorting Test (WCST) can measure subjects' conceptualisation and other cognitive features, and is widely used in the cognitive function measurement of OCD. Previous research has found that patients with OCD exhibit deficits in cognitive set-shifting, as evidenced by their WCST performance.[9]

This is the first study to use SV2A-PET imaging using (R)−1-((3-(18F) fluoropyridin-4-yl)methyl)−4-(3,4,5-trifluoro-phenyl)pyrrolidin-2-one (^{18}F-SynVesT-1) to examine the difference in synaptic density between patients with OCD and healthy controls (HCs) and its correlation with cognitive dysfunction. The preliminary hypothesis of this study is that synaptic density is lower in adults with OCD and is correlated with the severity of cognitive dysfunction. Based on previous studies, we focused on exploring the reduction of synaptic density in the CSTC circuit.[1 4]

METHODS

Participants

In this study, 28 drug-naive patients with OCD were recruited from the Mental Health Centre of Xiangya Hospital in China from January 2021 to April 2022. Additionally, 16 HCs were enrolled as the control group. Inclusion criteria for patients with OCD were as follows: (1) aged between 18 and 40 years and meeting the diagnostic criteria for OCD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[10]; and (2) right handed. The Structured Clinical Interview for DSM-5 Disorders-Research Version was used in this study.[11] None of the participants had been taking antidepressants or other psychoactive medication for at least 4 months. Exclusion criteria included contraindications to PET or magnetic resonance imaging (MRI), loss of consciousness for over 5 min, major medical conditions, neurodevelopmental disorders, neurocognitive disorders, schizophrenia spectrum, bipolar and related disorders, and substance use disorders. The exclusion criteria for the control group were the same, with neither the participant nor a first-degree relative currently or historically meeting any DSM-5 diagnosis. The detailed enrolment process is shown in figure 1.

Psychological assessment

Demographic and clinical characteristics, including age of onset and disease course, were recorded for all participants (table 1). Clinical symptoms were evaluated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[12] the Hamilton Anxiety Scale (HAMA)[13] and the Hamilton Depression Scale (HAMD).[14] Y-BOCS was used to assess obsessive-compulsive symptoms.[12] Total Y-BOCS score of 6–15 indicates mild severity, 16–25 indicates moderate severity and >25 indicates severe obsessive-compulsive symptoms. Right or left handedness was assessed by the

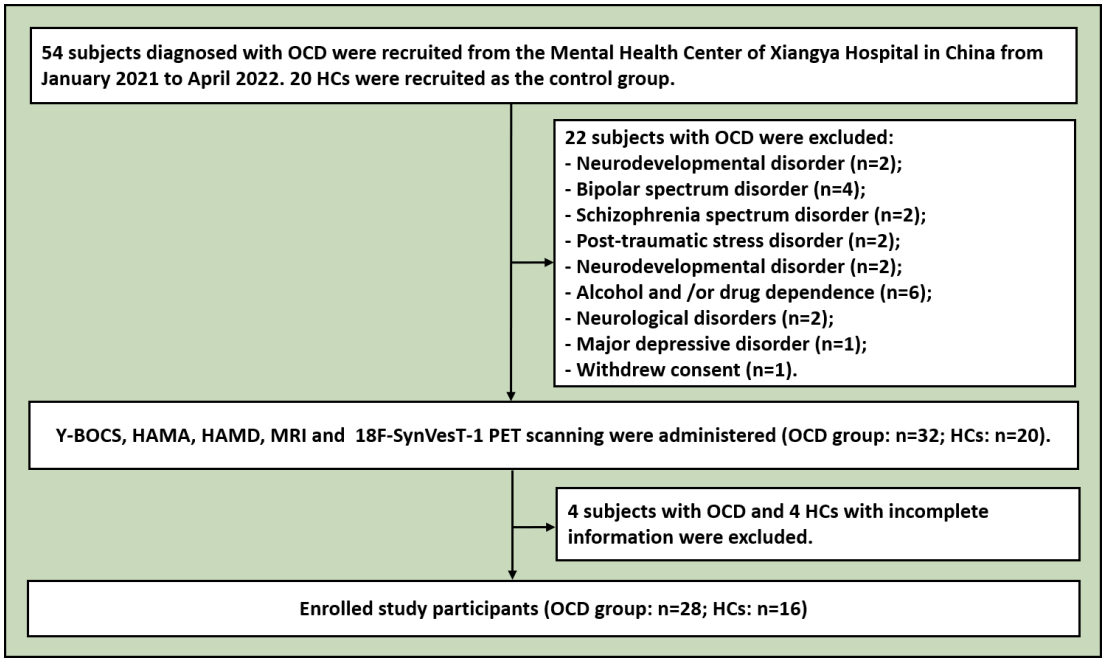

Figure 1 Flowchart illustrating the enrolment process. HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HCs, healthy controls; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PET, positron emission tomography; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 1 Demographic and scale scores of patients with obsessive-compulsive disorder (OCD) and healthy controls (HCs)

Characteristics	Patients with OCD, n (%) (n=28)	HCs, n (%) (n=16)	t	P value
Gender				0.735
Male, n (%)	16 (57.14)	10 (62.50)		
Female, n (%)	12 (42.86)	6 (37.50)		
Age (years)	21.00 (19.00–23.75)	21.00 (18.25–25.00)	−0.01	0.995
Age at onset (years)	16.00 (15.00–18.00)	—		
Duration of illness (years)	5.00 (4.00–7.00)	—		
Education (years)	14.00 (13.00–15.00)	13.50 (13.00–15.00)	0.19	0.849
IQ	115.00 (108.00–123.00)	110.00 (107.25–121.75)	0.64	0.532
Y-BOCS	21.50 (16.50–25.75)	0		<0.001***
Obsessional thoughts	14.00 (9.00–16.00)	0	11.32	<0.001***
Compulsive behaviour	10.00 (3.00–16.00)	0	4.92	<0.001***
HAMD	20.50 (12.75–25.75)	2.0 (0.00–6.50)	7.36	<0.001***
HAMA	17.50 (12.25–20.75)	2.00 (0.25–3.75)	7.00	<0.001***
Comorbidity				
GAD (%)				
Yes	3 (10.71)	—		
No	25 (89.29)	—		
MDD (%)				
Yes	2 (7.14)	—		
No	26 (92.86)	—		
Family history (%)				0.001***
Yes	20 (71.43)	0 (0.00)		
No	7 (25.00)	16 (100.00)		
WCST				
PCLR (%)	40.00 (36.00–54.00)	75.50 (65.00–77.50)	−56.20	<0.001***
PCR (%)	63.33 (40.42–70.00)	74.41 (72.85–78.13)	−3.16	0.003**
TCFC	7.50 (6.00–18.00)	9.00 (7.25–9.75)	1.04	0.306
CC	5.00 (2.00–6.00)	6.00 (6.00–6.00)	−2.67	0.011*
TE	21.00 (17.25–35.75)	13.00 (11.00–15.75)	3.49	0.001**

Data are presented as median (IQR).
*p<0.05, **p<0.01, ***p<0.001.
CC, categories completed; GAD, generalised anxiety disorder; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HCs, healthy controls; IQ, intelligence quotient; IQR, interquartile range; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PCLR, per cent conceptual-level response; PCR, per cent correct response; TCFC, trials to compete first category; TE, total errors; WCST, Wisconsin Cart Sorting Test; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Edinburgh Handedness Inventory.[15] All interviews and evaluations were conducted on the day of PET scans.

Psychological assessment

We used the computerised version of the 52-card WCST to assess cognitive function in both OCD and HC groups. The WCST evaluates various aspects of cognitive function, such as the level of conceptualisation (per cent conceptual-level responses (PCLRs)), abstract generalisation ability (per cent correct responses (PCRs)), concept formation ability (trials to compete first category (TCFC)), categorisation ability (categories completed (CC)) and cognitive transfer ability (total errors (TE)). A lower PCLR indicates a lower abstract conceptualisation.

MRI data acquisition

We used the GE Healthcare 3.0 T MRI scanner to capture MRI data. For PET image registration and structural abnormality assessment, sagittal three-dimensional (3D) T1 bravo was employed (Echo Time (TE)=3.2 ms, Repetition Time (TR)=8.5 ms, matrix=256×256 mm^2, phase field of view (FOV)=1, voxel size 1.0×1.0×1.0 mm^3, slice thickness=1.0 mm). All MRI data were inspected by an experienced neuroradiologist to ensure MRI quality.

PET imaging

^{18}F-SynVesT-1 was synthesised as previously described with radiochemical purity of >99%. All participants refrained from medication intake for at least 24 hours before PET examination. The PET/Computed Tomography (CT) was carried out with a General Electric PET/CT scanner (Discovery 690 Elite, General Electric Healthcare, Waukesha, Wisconsin, USA). ^{18}F-SynVesT-1 PET/CT imaging was performed 60 min after the radiotracer was intravenously injected at a dose of 3.7–4.44 MBq (0.1–0.12 mCi) per kg of body weight. Static PET images were acquired in three dimensions for 30 min, starting at approximately 60 min after intravenous ^{18}F-SynVesT-1 injection. First, a low-dose CT scan (120 kV; automatic mAs; pitch, 1:1; slice thickness, 3.75 mm; matrix, 512×512) was performed for attenuation correction. Next, all PET images were reconstructed as a 256×256 transaxial matrix (35 cm FOV) using the 3D VUE Point (GE Healthcare) ordered-subset expectation-maximisation algorithm with six iterations and six subsets, which produced 47 transaxial images at 3.25 mm intervals.

Imaging data analysis

Images were processed with statistical parametric mapping software (SPM V.12, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB V.R2016b (MathWorks). ^{18}F-SynVesT-1 PET images were co-registered with the subject's T1-weighted MRI. The image volume of the individual ^{18}F-SynVesT-1-PET was normalised into a standard stereotactic space. The internal ^{18}F-SynVesT-1-PET template was used, and the voxel size was 2×2×2.

The height threshold for synaptic density changes was set at an uncorrected probability value of 0.001 with a cluster level above 50 contiguous voxels. After data preprocessing with SPM, xjView MATLAB toolbox was used to visualise anatomically label significant clusters.

Computational Anatomy Toolbox V.12 is used to provide computational anatomy as a free extension to SPM V.12. The SPM V.12 Automated Anatomical Labeling V.3 map[16] was used to extract regions of interest (ROIs). The standard uptake value ratio (SUVR) of each ROI was calculated with the centrum semiovale as the reference area.[17] In our study, there were no significant differences between patients with OCD and HCs in centrum semiovale (1.69 (0.26) vs 1.71 (0.23), p=0.765). The SUVR values of each ROI between groups were also compared.

Demographic and clinical data analysis

Data are shown as the median (interquartile range (IQR)) or mean (SD). We analysed the demographic and psychological data using SPSS V.22.0. Mann-Whitney U test or Student's t-test was used to test the continuous variables. χ^2 test was used to test the categorical variables.

Spearman correlation was applied for analysing the associations between SUVR and clinical variables and p<0.05 was considered statistically significant.

RESULT

Clinical characteristics

Demographic characteristics and clinical symptoms of patients with OCD and HCs are shown in table 1. No significant differences in age, gender, intelligence quotient (IQ) or length of education were observed between patients with OCD and HCs (p>0.05). The median age of the OCD group was 21.00 years (IQR 19.00–23.75 years), while that of the HCs was 21.00 years (IQR 18.25–25.00 years). However, the OCD group had higher Y-BOCS, HAMA and HAMD scores compared with the HCs (p<0.001). All enrolled patients with OCD had moderate or higher severity of OCD and mood symptoms (Y-BOCS total score, median 21.50 (IQR 16.50–25.75); HAMA total score, median 17.50 (IQR 12.25–20.75); HAMD total score, median 20.50 (IQR 12.75–25.75)). In addition, 71.43% of patients had a family history of mental illness (10 with OCD, 4 with impulse control disorders and 6 with general anxiety disorders). Comorbidities were present in 17.86% of patients, including three with general anxiety disorder and two with major depressive disorder.

Cognitive dysfunction

As shown in table 1, significant differences were observed in multiple indicators in the WCST between the OCD group and the HCs. As expected, cognitive abnormalities were more pronounced in the OCD group. Patients with OCD showed lower levels of abstract conceptualisation, as indicated by a lower median PCLR (%) (40.00, IQR 36.00–54.00) compared with HCs (75.50, IQR 65.00–77.50). Decreased abstract generalisation ability was seen in the OCD group with a lower median PCR (%) (63.33, IQR 40.42–70.00) compared with HCs (74.41, IQR 72.85–78.13). Additionally, patients with OCD exhibited poorer concept formation ability and categorisation ability with a lower median TCFC (7.50, IQR 6.00–18.00) and CC (5.00, IQR 2.00–6.00) compared with HCs (9.00, IQR 7.25–9.75 and 6.00, IQR 6.00–6.00, respectively). Furthermore, patients with OCD demonstrated impaired cognitive transfer ability with a higher median TE (21.00, IQR 17.25–35.75) compared with HCs (13.00, IQR 11.00–15.75).

Synaptic density reduction

In our study, there were no differences between the OCD group and HCs in total intracranial volume (1597.00 (141.70) vs 1610.00 (120.90) cm^3, p=0.763). However, patients with OCD exhibited a decrease in synaptic density compared with HCs. Voxel-based group analysis showed that patients with OCD had

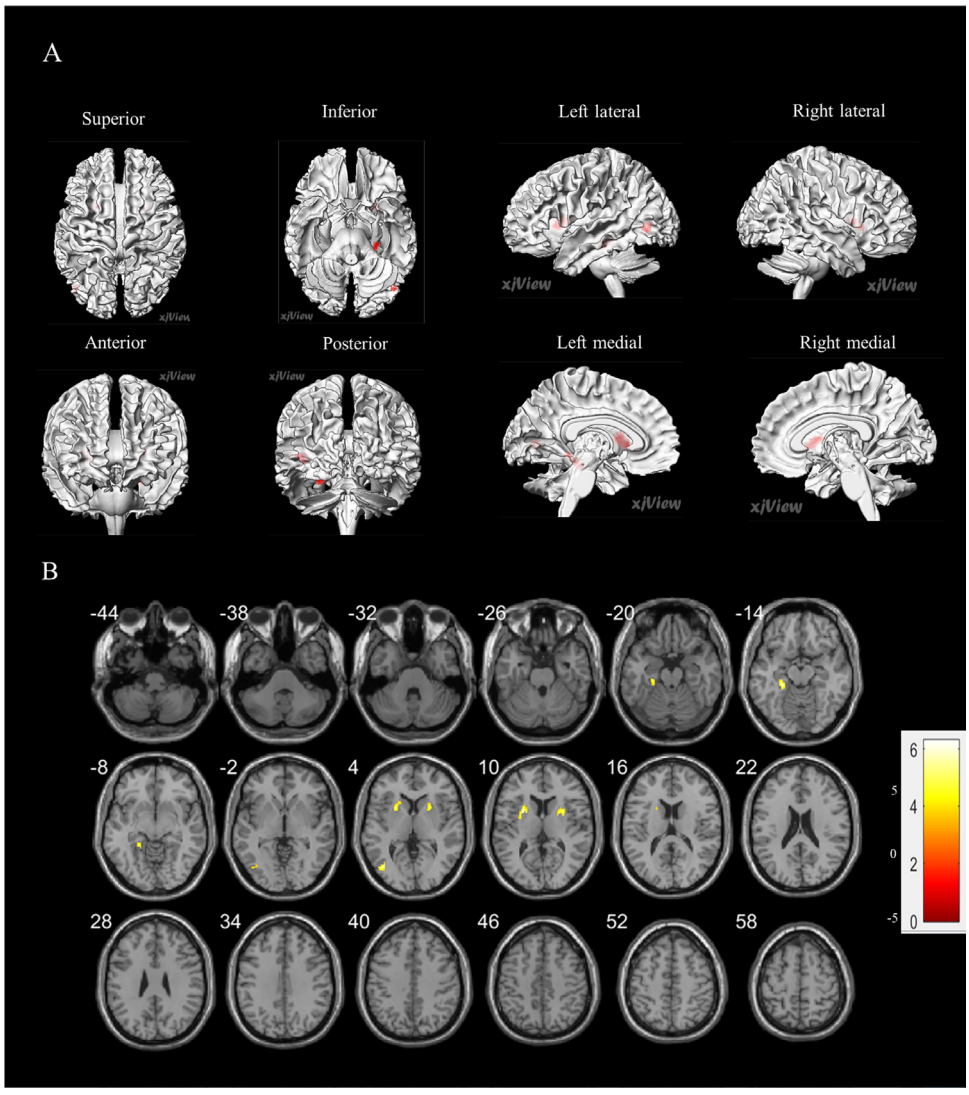

Figure 2 Comparison of patients with OCD versus HCs was performed in (A) render view and (B) slice view (p<0.001 with cluster thresholding, k=50 voxels). Voxels with significantly low uptake are shown in red. HCs, healthy controls; OCD, obsessive-compulsive disorder.

significantly low uptake in the CSTC circuit, including the bilateral putamen, left caudate, left parahippocampal gyrus, left insula and left middle occipital gyrus compared with HCs (the height threshold was set at p< 0.001, corrected at cluster above 50; figure 2). Coordinate and regional details are presented in

Table 2 Location and peaks of significant reduction in synaptic density in patients with OCD compared with HCs

Cluster-level k_E	Voxel-level T	Z-score	P value	Peak coordinates (x, y, z) (mm)			Anatomical region	BA
179	5.51	4.75	<0.001	−26	8	10	Left putamen	
	4.17	3.79	<0.001	−30	0	10	Left sublobar	
	4.14	3.77	<0.001	−18	18	4	Left caudate	
107	5.49	4.74	<0.001	−24	−32	−14	Left parahippocampal gyrus	
71	5.42	4.69	<0.001	−40	4	10	Left insula	13
121	4.66	4.16	<0.001	30	8	10	Right putamen	
	4.47	4.02	<0.001	22	12	4	Right putamen	
53	4.62	4.13	<0.001	−42	−72	4	Left middle occipital gyrus	

BA, Brodmann area; HCs, healthy controls; OCD, obsessive-compulsive disorder.

table 2. The SUVR analyses based on ^{18}F-SynVesT-1 PET found that the SUVR of patients with OCD was lower than HCs in the left middle occipital gyrus (4.16 (0.69) vs 5.26 (0.92), p<0.001), left parahippocampal gyrus (4.20 (0.50) vs 4.68 (0.57), p=0.006), right putamen (4.20 (0.63) vs 4.92 (0.86), p=0.003), left putamen (3.68 (0.49) vs 4.29 (0.69), p=0.001) and left precentral gyrus (3.74 (0.40) vs 4.40 (0.86), p=0.001).

Correlation between synaptic density and cognitive dysfunction in OCD

Correlation analysis revealed positive associations between PCLR and synaptic density reduction in specific brain regions of patients with OCD, such as the left middle occipital gyrus (R^2=0.1690, p=0.030) (figure 3A), left parahippocampal gyrus (R^2=0.1464, p=0.045) (figure 3B) and left putamen (R^2=0.1967, p=0.018) (figure 3C).

DISCUSSION

Main findings

OCD is a common mental disorder and significant research has been trying to understand its neurobiological mechanism. While previous MRI studies have indicated abnormal activity and volume within the CSTC circuit in OCD neurobiology,[1] the underlying molecular mechanisms remain elusive. This is the first study to investigate radioligand binding to SV2A in patients with OCD, and the first *in vivo* evidence of reduced synaptic density in association with cognitive dysfunction in OCD. Our findings suggest a lower synaptic density in the CSTC circuit in patients with OCD, aligning with the 'network degeneration hypothesis' which suggests that OCD pathology affects specific neural networks rather than being diffuse or random.

Several studies have linked OCD-like behaviours with synaptic changes.[7] The relationship between synaptic density/dysfunction in the CSTC circuit and OCD-like behaviours has been demonstrated in preclinical models.[7] Research found lower excitatory synaptic gene expression in the CSTC circuit in postmortem patients with OCD.[4] Another study showed that patients with epilepsy treated with the SV2A-targeting antiepileptic drug levetiracetam exhibited obsessive-compulsive behaviour.[18] Given the emerging evidence of synaptic abnormalities in OCD,[6] evaluating SV2A availability in patients with OCD could be of importance in this study.

This study revealed that patients with OCD had various cognitive dysfunctions compared with HCs, as evidenced by their performance on the WCST. Specifically, patients with OCD showed significant impairment in conceptualisation (shown in PCLR), abstract generalisation ability (shown in PCR), categorisation ability (shown in CC) and cognitive transfer ability (shown in TE) when compared with HCs. Our findings are consistent with prior studies highlighting cognitive dysfunction across multiple domains in patients with OCD.[19] Furthermore, we observed a positive association between reduced conceptualisation and decreased synaptic density in the left putamen, left hippocampus and left middle occipital gyrus.

The striatum is the core node of the CSTC circuit, including the putamen and caudate. The caudate and putamen play a key role in impulse control, abstraction and conceptualisation. Dysfunction of the caudate and putamen ultimately leads to OCD symptoms.[20] Our results suggest that synaptic reduction in the bilateral putamen and left caudate may have downstream effects on the structural volume of the CSTC circuit, as previous research has indicated.[20] We also found a positive correlation between synaptic density in the left putamen and cognitive dysfunction in patients with OCD, with lower synaptic density corresponding to reduced ability in abstract conceptualisation. In both structural MRI[21] and PET imaging,[22] abnormal volume and metabolic increases of caudate and putamen were found in patients with OCD. This demonstrates the significance of the striatum in OCD pathology, with synaptic density reduction potentially reflecting compromised neurotransmitter delivery and contributing to degenerative changes in the neural network. Clinical imaging studies suggest abnormal synaptic pruning patterns in the striatum structures as a possible explanation for a volumetric reduction in patients with OCD.[23] A decrease in synaptic density in the striatum was found in a preclinical mouse model of OCD,[7] corroborating our findings in human OCD.

We observed a significant decrease in synaptic density in the left insula and left parahippocampal gyrus in patients with OCD compared with HCs. These regions are part of the limbic/affective circuit within the CSTC, which regulates reward anticipation and motivation. Impairment in these circuits can reduce reward response by altering sensitivity to the expected reward, exaggerate the response to threat and decrease incentive drive, resulting in obsessive-compulsive symptoms.[24] In addition, the insula is an important treatment target for deep brain stimulation in OCD.[25] MRI studies have reported that patients with OCD have abnormal neural activity in the insula,[26] and a PET study also showed increased metabolism in this region.[27]

In this study, synaptic density reduction in OCD was observed in widespread neural regions, including the left middle occipital lobe. Our results demonstrated a positive correlation between synaptic density in the left parahippocampal gyrus and abstract conceptualisation ability, suggesting that lower synaptic density is associated with reduced conceptualisation ability. Similarly, we found that synaptic density in the left middle occipital gyrus positively correlated with abstract conceptualisation ability in patients with OCD. This suggests that reduced synaptic density in the middle occipital gyrus may exacerbate cognitive dysfunction, consistent with findings in the left putamen and left parahippocampal gyrus. Recent studies have highlighted the importance of the occipital lobe in OCD pathology.[28] Reductions in synaptic density in the middle occipital gyrus may contribute to deficits in 'posterior' cognitive functions such as memory and perceptual ability observed in patients with OCD.[29]

Our research findings showed a more pronounced decrease in synaptic density in the left brain regions,

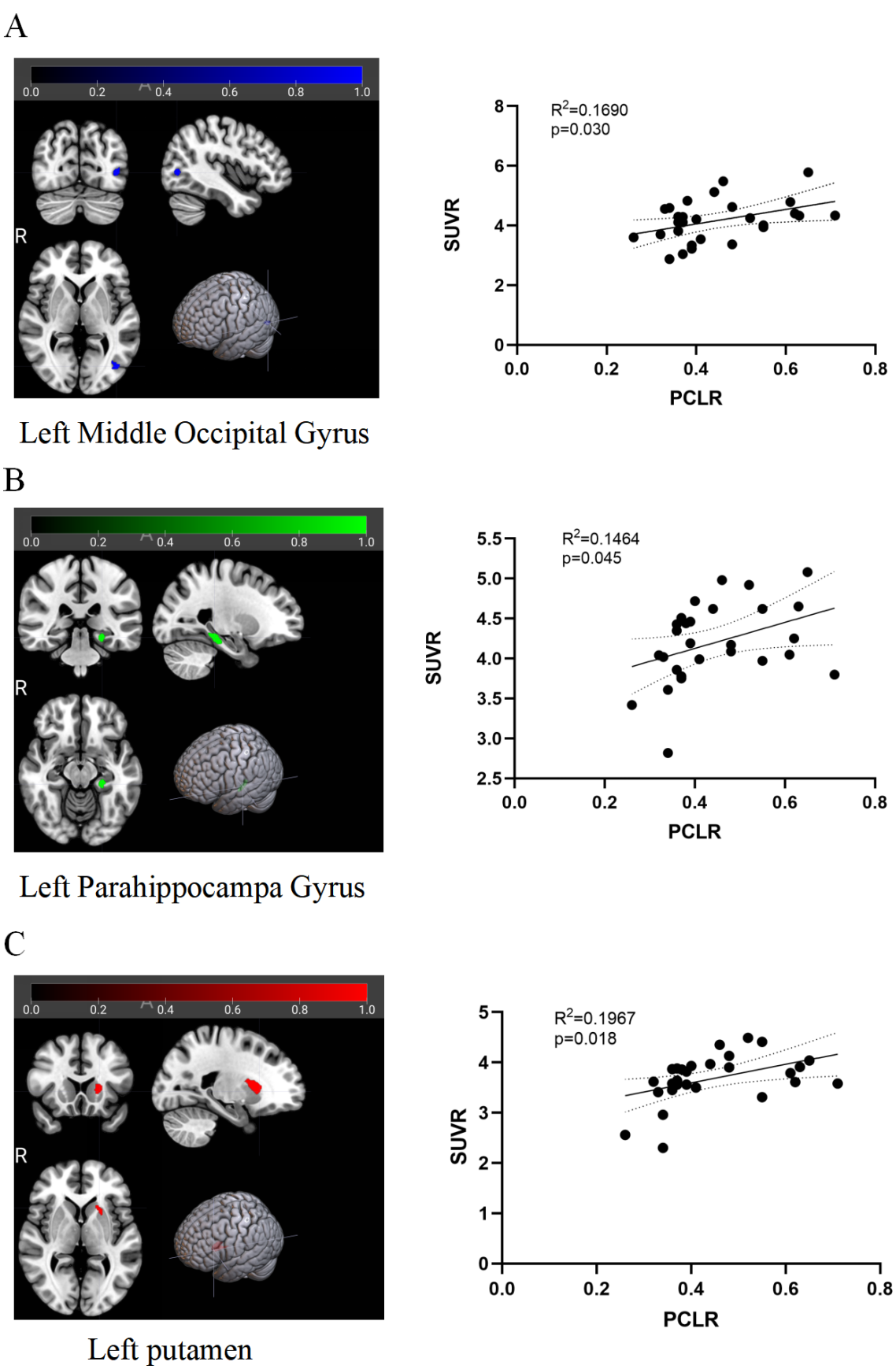

Figure 3 Correlation analysis between synaptic density and cognitive dysfunctions in OCD demonstrating positive correlations between the synaptic density of left middle occipital gyrus (A), left parahippocampal gyrus (B), left putamen (C) and abstract conceptual level. OCD, obsessive-compulsive disorder; PCLR, per cent conceptual-level response; SUVR, standard uptake value ratio.

including the left caudate, left parahippocampal gyrus, left insula, left parahippocampal gyrus and left middle occipital lobe. This intriguing finding may be due to our selection of right-handed patients with OCD, whose dominant hemisphere is the left brain. This aligns with previous findings that the abnormal brain function in patients with OCD is concentrated in the left brain hemisphere.[30]

Limitation

There are some limitations in this study. First, while the sample size is consistent with PET imaging norms, it remains relatively small. This raises the possibility of false negatives, particularly in the CSTC circuit. Therefore, this study should be considered preliminary, and larger-scale replication is required to solidify our findings. Second, we used a reference region approach (typically using the centrum semiovale as a reference) to estimate the specific binding of tracers. However, these conclusions require careful interpretation, as variable non-specific binding of tracers within the centrum semiovale may exist. So far, the exact correlation between SV2A-PET results and actual pathological severity remains unclear, and the selection of the optimal reference area may be difficult, especially in longitudinal quantitative research. Finally, as ^{18}F-SynVesT-1 PET is sensitive to the presynaptic but not the postsynaptic compartment, any loss of synapses related to dendritic spine atrophy may not be detectable by this measure, potentially underestimating the degree of synaptic loss in relation to OCD. Although few individuals met the diagnostic criteria for major depressive disorder and generalised anxiety disorder through structured interviews, high levels of anxiety and depressive symptoms were observed in the OCD group. This may limit the interpretation of the results, as depression symptoms may lead to decreased synaptic density in these brain regions.[3] Future studies should control for the severity of depression and anxiety in patients with OCD to address this issue. In this study, no relationship was found between SV2A/SynVesT-1 abnormalities of ROI and the severity of negative mood and obsessive-compulsive symptoms in OCD. Therefore, the finding of decreased synaptic density in OCD-related brain regions is preliminary and requires further research to validate the results.

Implications

The study's findings of lower synaptic density, particularly within the CSTC circuit, have significant clinical implications. This synaptic alteration could contribute to the pathophysiology of OCD, suggesting that therapeutic strategies aimed at increasing synaptic density or enhancing synaptic function may be beneficial. This could pave the way for the development of novel pharmacological agents targeting synaptic regeneration or neuroplasticity, potentially offering new treatment avenues for patients who are drug-naive or refractory to current therapeutic options.

Patients with OCD often exhibit disturbances in emotional regulation, such as excessive anxiety or fear responses. This study indicates that reduced synaptic density in these areas may be related to these emotional regulation disturbances. Cognitive dysfunction may be a manifestation of this impaired emotional regulation, or alternatively, the reduced synaptic density could affect both emotional processing and cognitive function, as these brain regions are interconnected in processing emotions and performing cognitive tasks. Understanding these synaptic changes could lead to targeted therapies that address the affective symptoms of OCD by focusing on enhancing synaptic density or modulating the activity within the limbic circuit. Further, this insight may also help predict the course of the disorder or response to treatment based on synaptic density measures in these regions.

The observed synaptic density reduction in the left middle occipital lobe and its association with cognitive dysfunction suggest that these synaptic alterations may contribute to deficits in visual processing and visual memory, which are cognitive domains pertinent to the occipital lobe.[31] Given that the occipital lobe is crucial for visual information processing, synaptic deficits might underlie some of the visual-spatial cognitive deficits observed in patients with OCD. This could inform cognitive remediation strategies that specifically target and strengthen visual processing skills in this population.

Summary

This is the first study to explore the synaptic density in patients with OCD. The combination of ^{18}F-SynVesT-1 PET and structural MRI methods provides new perspective into the molecular mechanism of OCD. We presented evidence that abnormalities in the CSTC circuit in OCD are associated with reduced synaptic density, providing a possible molecular underpinning for OCD. We also demonstrated an obvious correlation between synaptic density in the left putamen, left parahippocampal gyrus and left middle occipital gyrus and level of conceptualisation. In conclusion, our findings add to the growing evidence suggesting synaptic loss in the pathophysiology of OCD, which holds promise for developing novel treatments targeting synaptic function. However, this finding requires confirmation with fully quantitative methods in future studies.

Contributors QX: collection of patients and control groups, experimental design and paper writing. JH: the design of parameters for MRI and PET, guidance of imaging technology and paper writing. LX: imaging data collection and analysis. MZ: imaging data collection. ZH: MRI and PET data analysis. HD: statistical analysis of demographic data and the guidance of paper writing. SH: paper revision, statistical analysis and responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Research Ethics Committee of Xiangya Hospital, Central South University (IRB: 202106134). All participants or their parents signed written informed consent before participating in this research.

Provenance and peer review Not commissioned; externally peer reviewed.

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