ARTICLE

Aberrant cortico-striatal white matter connectivity and associated subregional microstructure of the striatum in obsessive-compulsive disorder

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The striatum and its cortical circuits play central roles in the pathophysiology of obsessive-compulsive disorder (OCD). The striatum is subdivided by cortical connections and functions; however, the anatomical aberrations in different cortico-striatal connections and coexisting microstructural anomalies in striatal subregions of OCD patients are poorly understood. Thus, we aimed to elucidate the aberrations in cortico-striatal white matter (WM) connectivity and the associated subregional microstructure of the striatum in patients with OCD. From diffusion tensor/kurtosis imaging of 107 unmedicated OCD patients and 110 matched healthy controls (HCs), we calculated the cortico-striatal WM connectivity and segmented the striatum using probabilistic tractography. For the segmented striatal subregions, we measured average diffusion kurtosis values, which represent microstructural complexity. Connectivity and mean kurtosis values in each cortical target and associated striatal subregions were compared between groups. We identified significantly reduced orbitofrontal WM connectivity with its associated striatal subregion in patients with OCD compared to that in HCs. However, OCD patients exhibited significantly increased caudal-motor and parietal connectivity with the associated striatal subregions. The mean kurtosis values of the striatal subregions connected to the caudal-motor and parietal cortex were significantly decreased in OCD patients. Our results highlighted contrasting patterns of striatal WM connections with the orbitofrontal and caudal-motor/parietal cortices, thus supporting the cortico-striatal circuitry imbalance model of OCD. We suggest that aberrations in WM connections and the microstructure of their downstream regions in the caudal-motor-/parietal-striatal circuits may underlie OCD pathophysiology and further provide potential neuromodulation targets for the treatment of OCD.

Molecular Psychiatry; https://doi.org/10.1038/s41380-022-01588-6

INTRODUCTION

Accumulating evidence highlights cortico-striatal circuitry as one of the neural bases of obsessive-compulsive disorder (OCD), a prevalent psychiatric disorder characterized by intrusive thoughts or images (i.e., obsessions) and repetitive behaviors (i.e., compulsions) [1–3]. Specifically, the striatum, a principal input structure of cortical information, is involved in reward, executive, self-regulatory, and motor processing, and impairments in these processes underlie obsessive-compulsive symptoms [3–5]. Therefore, early neuroimaging studies have suggested that the striatum is an important neural substrate of OCD by investigating its abnormal metabolic activity [6, 7], the presence of lesions [8, 9], its increased volume [10, 11], and its altered activation [12, 13].

Rather than a unitary and homogeneous structure, the striatum is a complex of topographical divisions defined by cortical projections, and those cortico-striatal connections distinctly underpin cognitive and behavioral processes [5, 14]. In particular, the clinical symptoms or behavioral impairments of patients with OCD might be mediated by alterations in specific cortico-striatal circuits [15–17]. Recent functional magnetic resonance imaging (fMRI) studies have shown abnormal connectivity or network patterns between distinct cortical and striatal regions, such as decreased connectivity between the orbitofrontal [18, 19] and other prefrontal regions with the striatum [20, 21] or increased parietal connectivity [22] to the striatum, in OCD patients. Expanding on those insights, neuroimaging studies have suggested imbalanced functioning between different cortico-striatal circuits as a pathophysiological mechanism of OCD [15–17]. For instance, fMRI approaches revealed hypoactive ventral affective (i.e., the orbitofrontal cortex and caudate nucleus) and hyperactive sensorimotor (i.e., the sensory/motor cortices and putamen) regions in patients with OCD [23–26], but these results are somewhat inconsistent with emotional processing [13].

Despite the accumulating insights into functional alterations, an understanding of aberrant white matter (WM) structural connections that underlie imbalanced functioning of cortico-striatal

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Received: 27 September 2021 Revised: 12 April 2022 Accepted: 14 April 2022
Published online: 26 May 2022

circuitry is also necessary [27, 28]. Altered integrity in several WM regions, including portions of the internal capsules and corona radiata, has been reported in OCD patients [29–32]. Because the observations are derived from hypothesis-free whole-brain comparisons, however, these findings might not have been sufficient to examine WM connectivity in specific cortico-striatal pathways. Probabilistic tractography is a fiber-tracking technique that depends on the probability density function [33, 34] and is relatively appropriate for reconstructing the fan-shaped WM architecture [35, 36]. Using this technique, increased fiber integrity between the orbitofrontal cortex and the striatum has been reported in patients with OCD [37]. However, based on WM connectivity to cortical regions, not limited to the orbitofrontal cortex, a subcortical segmentation approach should be further investigated [35, 38] because connectivity-based segmentation provides valuable insights into distinct cortical projections to subcortical structures [39–41]. Several studies have applied this method to explore connectivity between cortical and subcortical regions in patients with psychotic disorders [40, 41], but no study has been conducted in patients with OCD.

Considering input profiles in the circuitry, an important goal is to determine whether structural anomalies in striatal subregions are accompanied by aberrations in their upstream cortico-striatal connections. Studies using OCD mouse models suggested that microstructural defects in specific striatal subregions and their associated cortico-striatal projections underlie behavioral impairments associated with OCD [42, 43]. In OCD patients, voxelwise studies have reported an increased volume [10, 11, 29] and abnormal morphology [44, 45] of the striatum. However, these approaches did not reflect striatal subregions defined by their cortical connectivity, nor did they indicate whether structural alterations originate in its defective microstructure, such as cell death or abnormal proliferation of the cell and organelle membranes. Diffusion kurtosis imaging (DKI) measures the "tailedness" of a probability distribution in the diffusion of water molecules [46, 47]. DKI also provides meaningful information on the brain apart from structural volume or connectivity, such as microstructural alterations in brain tissue, with higher kurtosis values suggesting increased microstructural complexity [46, 47]. Mean kurtosis (MK) in the human brain is reported to steadily increase during the first 4 years of life in several regions, including the cerebral WM and striatum, whose circuits are involved in neurodevelopmental models of OCD [48, 49].

Hence, in this study, we applied probabilistic tractography to investigate whether WM connectivity of the striatal subregions with their associated cortical area is altered in accordance with the imbalanced cortico-striatal circuitry observed in fMRI studies of medication-free patients with OCD. We further examined microstructural changes in striatal subregions obtained from connectivity-based segmentation. Based on findings from fMRI [18, 19, 22, 26] and animal [42, 43] studies, we hypothesized that striatal WM connectivity would be altered and show imbalanced patterns, specifically weak connections to the orbitofrontal cortex and strong connections to motor cortices, in patients with OCD. Concurrent with aberrations in upstream WM connections, a less complex microstructure of their associated striatal subregions in patients with OCD compared to healthy controls (HCs) was expected.

MATERIALS AND METHODS

Participants

One hundred seven medication-free patients with OCD and 110 age-, sex-, and handedness-matched HCs participated in this study. OCD patients were recruited from the OCD clinic at Seoul National University Hospital (SNUH), of which 45 patients were drug-naïve, and 62 had been unmedicated for more than four weeks prior to the study [50]. Further information on the participants is described in the Supplementary Materials and Methods in the Supplementary Information.

Written informed consent was received from all participants after they were provided a thorough explanation of the study procedure (IRB no. H-1201-008-392). For minors, informed consent was obtained from both the participants themselves and their parents. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of SNUH (IRB no. H-2012-126-1183).

Image acquisition, preprocessing, and connectivity calculation

We describe details of the imaging acquisition and preprocessing steps in the Supplementary Materials and Methods in the Supplementary Information. Probabilistic tractography was used to segment the whole striatum based on connectivity with the different cortical target regions of interest (ROIs) and calculate cortico-striatal connectivity values [34, 39]. For ROI preparation, the frontal lobe was divided into four anatomical subregions, namely, the orbitofrontal, executive, rostral-motor, and caudal-motor subregions. Together with the 4 frontal subregions, the parietal, occipital, and temporal lobes were used as cortical target ROIs projecting bilaterally to the striatum seed (Fig. S1 in the Supplementary Information). All cortical target and striatum seed ROIs were provided by Tziortzi and colleagues [39] and defined in $2 \times 2 \times 2\,mm^3$ Montreal Neurological Institute (MNI) space.

Specifically, using probabilistic tractography, connectivity values were quantified between every voxel in the striatum and each cortical ROI (out of the 5000 initially seeded). These outputs represent the probability of connection between the striatum seed and the corresponding cortical targets [40, 41]. The connectivity values were then commonly thresholded at the 10th percentile to eliminate deviant connections resulting from noise and errors [39–41]. Relative connectivity was then calculated by dividing each striatal connectivity value from different cortices by the sum of connectivity values from 7 cortical target ROIs, and eventually, mean relative connectivity extracted from each bilateral cortical target was used in subsequent statistical analyses. This approach considers individual variances in connectivity values between the striatum and the whole cortex, as described in our previous studies [41].

In the Supplementary Materials and Methods in the Supplementary Information, we provided descriptions for visualizing the process and the results of cortical connectivity maps in each striatal subregion, as well as information about image processing to calculate the fractional anisotropy (FA) data (Figs. S2–S5).

Connectivity-based segmentation

Connectivity maps representing the probability of striatal connections with each cortical target were thresholded at the 50th percentile to minimize overlapping voxels between striatal segment ROIs. We calculated the averaged percent overlap between each striatal segment ROI and conventional striatal subdivisions, namely, the caudate, putamen, and nucleus accumbens (the Supplementary Materials and Methods in the Supplementary Information). These striatal ROIs from individual subjects were subsequently used to extract their microstructural complexity from the MK maps.

MK calculation

From the total sample of participants, 102 patients with OCD and 107 HCs were included for MK calculation because DKI data were missing from the other subjects during image acquisition. The DKI data were preprocessed for skull removal [51], eddy-current correction, and head motion correction [52, 53] with FMRIB Software Library (FSL). The Diffusional Kurtosis Estimator [54] was used to generate individual MK parametric maps. Following registration to match the space using FLIRT, MK values were calculated for each segmented striatal subregion, and the mean of the bilateral MK values was eventually used in the subsequent statistical analysis. Volumes of the whole striatum and its subregions were also extracted.

Statistical analysis

All statistical analyses were conducted using R version 3.6.2 [55]. The demographics were tested using independent *t* tests and tests of equality of proportions to determine their differences between the patients with OCD and HCs.

The striatal connections with 7 cortical ROIs were tested with separate analyses of covariance (ANCOVAs) to identify group effects while controlling

for age and sex. These results were corrected for multiple comparisons of the 7 connectivities using the Bonferroni test. In the Supplementary Materials and Methods in the Supplementary Information, we provided details about the correlation analysis between connectivities and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores and the statistical analyses of the FA values in each cortico-striatal connection.

The group differences in MK values of segmented striatal subregions displaying the strongest connection with each cortical ROI were tested with ANCOVAs while controlling for age, sex, relative connectivity between the striatum and each cortical ROI, and each subregional volume. ANCOVA results were corrected for multiple comparisons of the 7 MK values of the striatal subregions using the Bonferroni test. We described the statistical analyses of the volumes of the striatum and its subregions in the Supplementary Materials and Methods in the Supplementary Information.

Considering the effects of comorbid depressive disorder, we divided the OCD group into 37 patients with OCD and depressive disorder and 70 patients with OCD but without depressive disorder (Table 1). To identify those group effects, all values of connectivity and MK were tested following the ANCOVA and correction approaches described above (Supplementary Materials and Methods in the Supplementary Information).

RESULTS

No significant differences in demographic characteristics were observed between patients with OCD and HCs in either the connectivity (Table 1) or DKI microstructural analyses (Table S1 in the Supplementary Information).

ANCOVA results indicating group effects on cortico-striatal connectivity are summarized in Table 2. Relative connectivity between the orbitofrontal target and its corresponding striatal region was significantly reduced in patients with OCD compared to HCs ($F_{1,\ 213} = 12.69$, $p < 0.001$) (Fig. 1B). However, in patients with OCD, significant increases in caudal-motor ($F_{1,\ 213} = 11.62$, $p = 0.001$) (Fig. 1C) and parietal ($F_{1,\ 213} = 14.39$, $p < 0.001$) (Fig. 1D) connectivity with each associated striatal region were observed. These three differences remained significant after correcting for multiple comparisons.

ANCOVA results for identifying group differences in mean FA values for striatal WM tracts associated with each cortical target are also presented in Table 2. Mean FA values for the striatal WM connection to the parietal target were increased in patients with OCD compared to HCs ($F_{1,\ 213} = 11.73$, $p = 0.001$) (Fig. S5 in the Supplementary Information). The group effects on FA values for other striatal WM tracts did not remain significant after correcting for multiple comparisons.

Regarding microstructural complexity, ANCOVA results comparing MK values between OCD patients and HCs are summarized in Table 2. A significant difference in the MK values was observed between the groups; patients with OCD showed reduced MK values for striatal subregions with the strongest connections to the caudal-motor ($F_{1,\ 203} = 9.39$, $p = 0.002$), parietal ($F_{1,\ 203} = 10.73$, $p = 0.001$), occipital ($F_{1,\ 203} = 9.48$, $p = 0.002$), and temporal ($F_{1,\ 203} = 16.46$, $p < 0.001$) targets. The group differences in other striatal subregions did not remain significant after correcting for multiple comparisons. The results for striatal subregions with the strongest connections to the caudal-motor and parietal targets are shown as a violin plot in Fig. 2. In addition, we specified that orbitofrontal portions of the striatum overlapped with the entire striatal structure. The striatal subregion corresponding to executive targets overlapped with the caudate and the putamen; striatal subregions associated with rostral-motor, caudal-motor, parietal, occipital, and temporal targets overlapped predominantly with the putamen (Table 3).

For comorbid effects of depressive disorder in patients with OCD, there were no significant differences in either the cortico-striatal connectivity or MK values between patients with OCD presenting with depressive disorder and those presenting without depressive disorder (Table S4 in the Supplementary Information). Accordingly, altered cortico-striatal WM connectivities and their associated striatal MK values may not be affected significantly by comorbid depressive disorder in patients with OCD.

Table 1. Demographic and clinical characteristics of the participants.

Variable	OCD ($n = 107$)	HCs ($n = 110$)	χ^2/t	p
Age (y)	25.2 ± 2.1	25.0 ± 4.9	−0.28	0.783
Sex (M/F)	72/35	69/41	0.70	0.484
IQ	110.7 ± 11.6	112.8 ± 12.3	1.35	0.180
Handedness (L/R)	8/99	6/104	−0.60	0.547
Education (y)	14.2 ± 2.1	14.3 ± 1.8	0.63	0.529
Duration of illness (y)	6.8 ± 0.7			
Y-BOCS				
Total	26.6 ± 6.3			
Obsession	14.1 ± 3.0			
Compulsion	12.6 ± 4.3			
HAM-D	11.8 ± 6.1			
HAM-A	10.9 ± 6.0			
Comorbidity				
None	61 (57.0%)			
Depressive disorder	37 (34.6%)			
Bipolar disorder	6 (5.6%)			
Personality disorder	3 (2.8%)			

OCD patients with obsessive-compulsive disorder, *HCs* healthy controls, *Y-BOCS* Yale–Brown Obsessive Compulsive Scale, *HAM-D* Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale.

DISCUSSION

To our knowledge, this study is the first to identify aberrations in distinct cortico-striatal WM connectivity and microstructural changes in striatal subregions in patients with OCD. We indicate decreased orbitofrontal WM connectivity to the associated striatal subregion and increased caudal-motor/parietal WM connectivity to the corresponding striatal subregions in OCD patients compared to HCs. Moreover, OCD patients showed lower MK values for striatal subregions strongly connected with caudal-motor and parietal cortices. This study demonstrates aberrations in both cortico-striatal WM connections and the microstructure of the associated striatal subregions, thus providing an integrated view that different anatomical profiles support the circuitry imbalance model of OCD pathophysiology.

Orbitofronto-striatal functional connectivity is altered [18, 19, 56, 57] and associated with clinical symptomatology in patients with OCD [56, 57]. While these findings have been inconsistent [58], they highlighted dysconnectivity between the orbitofrontal cortex and the striatum, as well as their individual functional abnormalities, in OCD patients. Based on this suggestion, Nakamae et al. used probabilistic tractography and observed higher FA in orbitofronto-striatal connections in patients with OCD, showing possible WM abnormalities in cortico-striatal circuitry [37]. However, the striatum is subdivided based on different cortical projections [5, 14], and thus, their topographical organization must be considered. Using connectivity-based segmentation [39], we defined 7 striatal subregions strongly connected with each cortical region and subsequently revealed lower orbitofronto-striatal connectivity compared to other cortices in OCD patients. Accordingly, our study not only reflects the dissociable cortico-striatal architecture but also emphasizes WM pathology that may underlie reduced functional connectivity between the orbitofrontal-striatal regions [18, 19].

Despite a lack of clear evidence for striatal connectivity with motor cortices, alterations in sensory-motor regions are related to

Table 2. Comparisons of mean connectivity, fractional anisotropy, and mean kurtosis values for striatal white matter regions connected to cortical targets and their associated subregions of the striatum.

Mean connectivity	OCD	HCs	*F*	*p*	Bonferroni-corrected *p*
Cortical target					
Orbitofrontal	0.339 ± 0.071	0.375 ± 0.080	12.69	0.000	0.003**
Executive	0.125 ± 0.053	0.126 ± 0.062	0.05	0.815	1.000
Rostral Motor	0.072 ± 0.026	0.068 ± 0.026	1.51	0.221	1.000
Caudal Motor	0.065 ± 0.018	0.056 ± 0.019	11.62	0.001	0.005*
Parietal	0.205 ± 0.035	0.183 ± 0.048	14.39	0.000	0.001**
Occipital	0.025 ± 0.010	0.025 ± 0.014	0.00	0.991	1.000
Temporal	0.170 ± 0.040	0.166 ± 0.035	0.61	0.435	1.000
Fractional Anisotropy					
Cortical Target					
Orbitofrontal	0.247 ± 0.015	0.245 ± 0.015	0.70	0.403	1
Executive	0.272 ± 0.016	0.266 ± 0.021	5.44	0.021	0.144
Rostral Motor	0.309 ± 0.014	0.303 ± 0.028	5.18	0.024	0.167
Caudal Motor	0.331 ± 0.016	0.325 ± 0.024	4.48	0.036	0.249
Parietal	0.331 ± 0.012	0.323 ± 0.020	11.73	0.001	0.005*
Occipital	0.229 ± 0.012	0.227 ± 0.012	1.38	0.242	1
Temporal	0.267 ± 0.012	0.264 ± 0.018	2.41	0.122	0.856
Mean Kurtosis					
Cortical Target Strongly Connected with the Striatal Subregion					
Orbitofrontal	0.746 ± 0.047	0.763 ± 0.067	5.77	0.017	0.120
Executive	0.806 ± 0.065	0.819 ± 0.067	2.87	0.092	0.642
Rostral Motor	0.853 ± 0.069	0.871 ± 0.087	3.42	0.066	0.461
Caudal Motor	0.844 ± 0.075	0.879 ± 0.010	9.67	0.002	0.015*
Parietal	0.845 ± 0.072	0.879 ± 0.091	10.67	0.001	0.009*
Occipital	0.870 ± 0.061	0.898 ± 0.083	9.48	0.002	0.017*
Temporal	0.821 ± 0.058	0.860 ± 0.084	16.46	0.000	0.000***

Data are presented as means ± standard deviations. * Bonferroni-corrected $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$.
OCD patients with obsessive-compulsive disorder, *HCs* healthy controls.

behavioral impairments in patients with OCD. Recent neuroimaging studies have suggested that the sensorimotor cortex is a structural [59] and functional [23] neural correlate in OCD patients experiencing aversive bodily and mental sensations (i.e., sensory phenomena). In relation to motor processing, de Wit et al. identified activity patterns in motor and parietal cortices during a response inhibition task in patients with OCD [24]. This study notably showed overactivation in the presupplementary motor area in patients during successful inhibition, thus suggesting excessive neural functioning in motor cortices. Specifying projections from the caudal-motor target (primary motor cortex and caudal premotor area) to the postcommissural striatum (posterior putamen), our results revealed higher WM connectivity between those regions in OCD patients. While the caudal-motor target is not correctly matched with cortical regions, as reported in previous studies [23, 24], we speculate that increased caudal-motor-striatal WM connectivity may underlie inefficient neural processing during sensory and inhibitory control in patients with OCD.

In the current study, patients with OCD also showed greater WM connectivity and mean FA between the parietal cortex and its associated striatal subregion (the posterior putamen). Although the parietal lobe has attracted little attention, several studies have reported functional [22, 60] and structural anomalies [31, 32, 61, 62] in the parietal regions of OCD patients. Marsh et al., for instance, identified greater functional connectivity between the parietal area and the putamen in patients with OCD during inhibitory control and conflict processing relative to the resting state [20], suggesting a neural correlate of patients' cognitive inflexibility [22]. Considering our findings, increased parietal WM connectivity to the putamen might underlie its functional hyperconnectivity during attention loading in OCD patients. Regarding WM integrity in parietal regions, studies have shown reduced FA values in patients with OCD and their relatives [31, 32]. Compared to whole-brain analyses, our tractography-based approach might indicate finer parieto-striatal WM connections, and thus some inconsistencies may have been derived from differences in methods and specific target regions.

Concurrent with higher WM connectivity, we observed disrupted microstructure of striatal subregions associated with caudal-motor, parietal, occipital, and temporal cortices. Although previous approaches showed structural anomalies in the putamen, such as increased volume [29] or decreased gray matter density [63], in OCD patients, these changes were not related to the intrinsic anatomy of the putamen and its topographical distinctions. Regarding those limitations, the DKI approach might add information about the subregional microstructure of the striatum in patients with OCD. Diffusion kurtosis models are sensitive to shorter distances between water molecules, and therefore, the reduced MK derived from fewer diffusion barriers would reflect a less complex microstructure of tissues [47]. Despite a lack of evidence from patients with OCD, previous DKI studies revealed decreased MK values in the putamen of people with drug addiction [64] and rodents subjected to chronic mild stress [65].

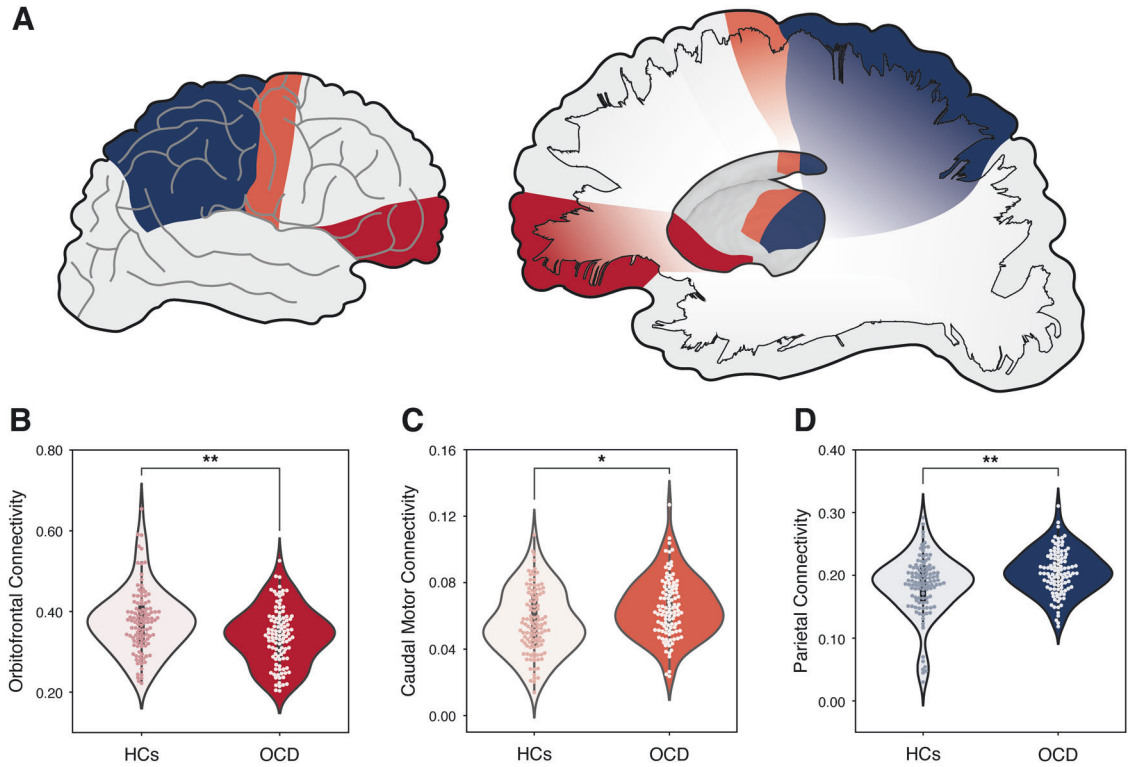

Fig. 1 Group comparison of cortico-striatal white matter (WM) connectivity. A Illustrations of the connections between the cortical targets (red, orbitofrontal; dark orange, caudal motor; dark blue, parietal) and the striatum (gray) that are significantly altered in patients with obsessive-compulsive disorder (OCD). In the bottom, the graphs show group effects on the relative connectivity of (**B**) orbitofrontal-striatal, (**C**) caudal-motor-striatal, and (**D**) parietal-striatal WM tracts between healthy controls (HCs) and patients with OCD. The results from the analysis of covariance (ANCOVA) with age and sex as covariates between each group were corrected with the Bonferroni test and are presented as "*" ($p < 0.05$) and "**" ($p < 0.005$) on the graph.

Moreover, recent mouse studies have suggested that reduced numbers of striatal parvalbumin interneurons may lead to greater excitation by cortical afferents and, consequently, to hyperactivation of cortico-striatal circuits in mice with OCD-like behaviors [3, 42, 43]. Consistent with this evidence, our results of decreased MK values in caudal-motor/parietal portions of the striatum may represent a defective microstructure, specifically a loss of neuronal cell bodies, dendrites, or their connections and an increased extracellular space, underlying putamen dysfunction in patients with OCD. Notably, our findings also highlight contrasting profiles, such as lower microstructural complexity in the caudal-motor, parietal, occipital, and temporal portions of the striatum and higher WM connectivity of their upstream cortical projections, thus suggesting mechanisms underlying the structural alterations in cortical-striatal regions [3, 42, 43] and impaired sensory/motor control in patients with OCD [22–24].

Although segregated topographically, cortico-striatal circuits do not execute their functions independently but communicate across circuits, and imbalanced functioning between those circuits might mediate obsessive-compulsive symptoms [16, 17]. Together with dissociated dopaminergic signaling in the cortico-striatal circuitry [16, 17, 25, 66], accumulating evidence has supported circuitry imbalances, specifically between ventral affective and sensorimotor circuits, in patients with OCD [26]. By assessing functional synaptic inputs in the central striatum, a knockout mouse study also revealed weakened inputs from the lateral orbitofrontal cortex and strengthened inputs from the secondary motor area in mice with OCD-like behaviors, thus suggesting a model of imbalanced cortical inputs to the striatum [67]. Regarding parietal regions, studies have reported increased gray matter density [68] and lower activation [69] in the parietal cortex accompanied by orbitofrontal abnormalities, and these extensive cortical anomalies were correlated with inhibitory control in OCD patients. Considering this evidence, we suggest that the lower orbitofrontal and higher caudal-motor/parietal WM connectivity to the striatum reported in our study might provide an anatomical framework for the imbalanced gray matter structure and activation in cortico-striatal circuitry. Moreover, our study indicated microstructural defects in caudal-motor/parietal portions of the striatum, thus suggesting striatal involvement in the imbalanced circuit mechanism in patients with OCD. Clearly, future research is needed to evaluate how individual cortico-striatal circuits interact with others and how obsessive-compulsive symptoms and cognitive impairments are associated with the circuitry. However, our findings provide an anatomical framework for the imbalance between orbitofronto-striatal and caudal-motor-/parietal-striatal circuits, including microstructural impairments in their associated striatal subregions, and further suggest that these imbalanced profiles may underlie cognitive or behavioral disinhibition in OCD patients [20, 22, 24, 69].

This study has several limitations. The findings may be limited by image acquisition. A single B0 image acquisition and nonisotropic voxel shape might have slightly biased the fiber reconstruction process, depending upon the fiber orientation. Additionally, our study did not control for cardiac pulsation, which might have resulted in body movements. However, we visually inspected the DWI of every participant to ensure that the images of subjects with significant motion artifacts were not included.

In the current study, decreased orbitofrontal and increased caudal-motor/parietal WM connectivity to the striatum were detected in patients with OCD. Reduced MK values in the caudal-motor and parietal portions of the striatum were also

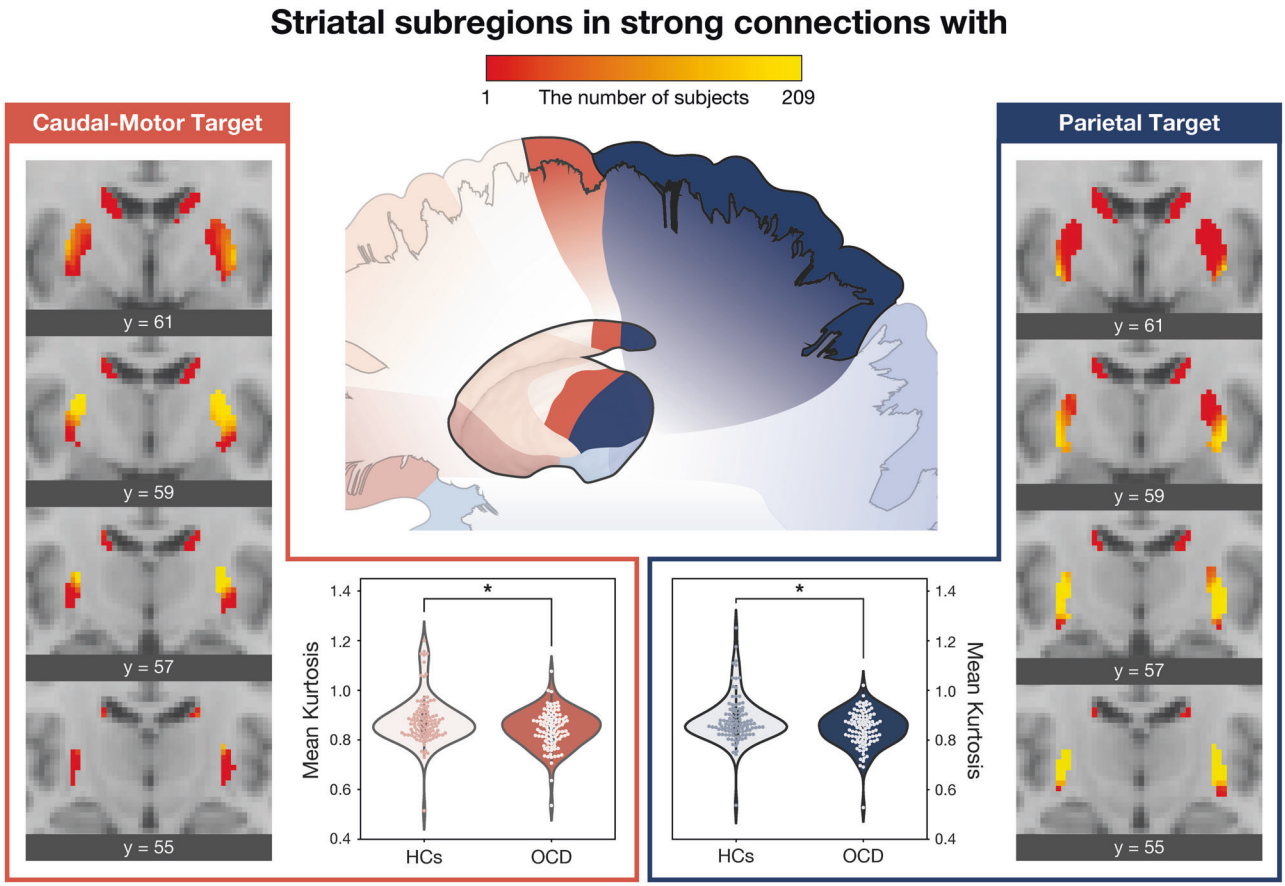

Fig. 2 Visualization of striatal subregions with strong connections to the caudal-motor (in orange column) and parietal (in navy column) targets. Cortical connections and their corresponding striatal subregions are schematically illustrated in the center of this figure. Averaged probabilistic maps of two striatal subregions from 209 subjects are shown in the coronal Montreal Neurological Institute (MNI) space in the left and right columns. Group effects on mean kurtosis (MK) values from two striatal subregions are also shown in the bottom panel. The results from the ANCOVA with age, sex, cortico-striatal relative connectivity, subregional volume as covariates between each group were adjusted with the Bonferroni test and are presented as "*" ($p < 0.05$) on the graph.

Table 3. Percent overlaps between connectivity-based subregions and the conventional distinctions of the striatum: caudate, putamen, and nucleus accumbens.

Striatal structure	Caudate	Nucleus accumbens	Putamen
Cortical target strongly connected with striatal subregions			
Orbitofrontal	0.185 ± 0.093	0.303 ± 0.072	0.352 ± 0.115
Executive	0.433 ± 0.204	0.004 ± 0.016	0.514 ± 0.213
Rostral motor	0.097 ± 0.088	0.000 ± 0.000	0.880 ± 0.100
Caudal motor	0.045 ± 0.070	0.000 ± 0.000	0.947 ± 0.080
Parietal	0.032 ± 0.056	0.000 ± 0.000	0.947 ± 0.069
Occipital	0.008 ± 0.035	0.001 ± 0.009	0.935 ± 0.047
Temporal	0.008 ± 0.019	0.045 ± 0.044	0.862 ± 0.078

Data are presented as means ± standard deviations.

observed in those patients, suggesting that these concurrent aberrations are an anatomical pattern supporting the cortico-striatal imbalance model of OCD pathophysiology. Our integrated approach using tractography and DKI analysis allowed us to segment the striatum more finely in individual subjects and subsequently calculate WM connectivity and striatal microstructural complexity at the same time. We minimized confounding effects of psychotropic medications on WM integrity [70] by only including medication-free patients with OCD. Taken together, the aberrations in WM connectivity and the microstructure within the caudal-motor-striatal and parietal-striatal circuits and their anatomical imbalance with the orbitofrontal-striatal circuit may reflect structural correlates of OCD pathophysiology that underlie the functional imbalance in cortico-striatal circuits, suggesting potential neuromodulatory targets for the treatment of OCD.

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ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program and the Bio & Medical Technology Development Program through National Research Foundation of Korea (NRF) funded by the Ministry of Science & ICT (Grant no. 2019R1C1C1002457 and 2021M3A9E4080784).

AUTHOR CONTRIBUTIONS

HP, MK, and JSK conceived and designed the study. MK, YBK, and JSK supervised all the processes. MK, JL, SYM, SKL, and JSK collected clinical information from the participants. HP, KIKC, and YBK performed image processing and data analysis. HP and MK wrote the manuscript. YBK, KIKC, JL, SYM, SKL, and JSK edited the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-022-01588-6.

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