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Altered anatomical connections of associative and limbic cortico-basal-ganglia circuits in obsessive-compulsive disorder

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ABSTRACT

Background: Current neurocognitive models suppose dysfunctions of associative and limbic cortico-basal ganglia circuits to be at the core of obsessive-compulsive disorder (OCD). As little is known about the state of underlying anatomical connections, we investigated whether these connections were reduced and/or not properly organised in OCD patients compared to control.

Methods: Diffusion magnetic resonance images were obtained in 37 OCD patients with predominant checking symptoms and 37 matched healthy controls. We developed indices to characterise the quantity (spatial extent and density) and the organisation (topography and segregation) of 24 anatomical connections between associative and limbic cortical (anterior cingulate, dorsolateral prefrontal, orbitofrontal cortices and the frontal pole), and subcortical (caudate nucleus, putamen and thalamus) areas in each hemisphere.

Results: Associative and limbic cortico-basal-ganglia connections were reduced in OCD patients compared to controls: 19/24 connections had a reduced subcortical spatial extent, 9/24 had a reduced density. Moreover, while the general topography was conserved, the different cortical projection fields in the striatum and thalamus were hyper-segregated in OCD patients compared to controls.

Conclusion: These quantitative and qualitative differences of anatomical connections go beyond the current model of a reduced cortical control of automatic behaviour stored in the basal ganglia. The hyper-segregation in OCD could also impair the integration of cortical information in the thalamus and striatum and distort the subsequent behavioural selection process. This provides new working hypotheses for functional and behavioural studies on OCD.

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1. Introduction

Obsessive-compulsive disorder (OCD) is characterised by intrusive, persistent thoughts that cause distress (obsessions), and/or irrepressible, repetitive behaviour (compulsions). Those cardinal features are seen as a pathology of cognitive control over habits/automated behaviour [1–3]. In line with these behavioural characteristics, neurobiological models hypothesise that OCD is based on a dysfunction of cortical control over basal ganglia circuits, in which automated behaviour is thought to be stored [4–

6]. Indeed, neuro-imaging functional studies and meta-analyses have mostly found pathological activations in the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorso-lateral prefrontal cortex (DLPFC), and the ventral striatum and thalamus of OCD patients [7–9].

These cortical areas, dysfunctional in OCD, send projections to the ventral striatum then back to the cortex via the thalamus, constituting several loops which are involved in associativolimbic processes such as decision-making, selection of behaviour based on expected reward, and repetitive stereotyped behaviour [1,10–12]. The effect of the neuromodulation of the associative and limbic territories of the basal ganglia on the symptoms of patients [13–15] and animals [16,17] also supports the crucial role of these loops in the pathophysiology of OCD. An involvement of the motor loop in OCD could be supported by dysfunctional

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activities found in the supplementary motor area (SMA) or pre-SMA of OCD patients [18,19], but these results are inconsistent and not confirmed by meta-analyses [7–9] nor included in neurocognitive models [4–6].

Neuroanatomical studies have demonstrated that each connection within the cortico-basal ganglia loops (e.g. cortico-striatal [20] or pallido-thalamic [21]) have a functional topography [22–27]: the medial and ventral part of the loop processes limbic information, the central part associative one, and the lateral and dorsal part processes motor information. This division is supported functionally [17,28,29]. However, while the organisation is topographic, the anatomo-functional channels are not segregated but overlap partially, possibly allowing an integrated control of behaviour [20,22,28,30].

We hypothesized that, in OCD, a disturbance in the selection of appropriate behaviour could be linked to a pathological organisation of these anatomo-functional channels. Indeed, most functional connectivity studies using MRI have shown an increased (although some a decreased) correlation of the blood oxygenation levels between cortico-basal ganglia-thalamic nodes in OCD [7–9]. However, modifications of the anatomical connections are not known.

While a direct access to the anatomical connectivity of cortico-basal ganglia-thalamic circuits is impossible in humans (it involves *ex vivo* axonal tracing), probabilistic tractography seems to provide a non-invasive and reliable estimate *in vivo* [31–35]. This method, based on diffusion MRI, follows the orientation of water molecules from one voxel to the next as a proxy for fibre orientation, thus modelling the path of axons through the white matter [36,37].

Some studies have already used a diffusion-based approach to white matter with fractional anisotropy (FA). They found modification consistent with the pathophysiological hypotheses of OCD (e.g. in the cingulum which carries fibres to and from the ACC) [38–42]. However, FA can only identify punctual modifications of the white matter, and cannot provide information about the state of anatomical connections between regions of interest (ROI), unlike probabilistic tractography [31,43,44]. Therefore, our goal was to investigate anatomical connections in OCD using probabilistic tractography.

To our knowledge, this method has not yet been used in OCD. Nevertheless, it has been used to explore anatomical connections in relation to personality traits [45] and neurological disorders of the basal ganglia [46–48]. Those studies were performed at the single voxel level, but animal experiments have shown that the relationship between tractographic metrics and *ex-vivo* anatomical connectivity is stronger at the macroscopic scale [32]. Therefore, we opted for an ROI approach instead of a voxel-by-voxel approach.

Overall, a dysfunction of cortico-basal-ganglia associative and limbic loops in OCD [4–6] could be supported anatomically by decreased and/or not properly organised connections. To test this hypothesis, we compared the anatomical connections between limbic and associative cortical (OFC, ACC, DLPFC and the frontal pole) and subcortical (caudate nucleus, putamen and thalamus) ROIs in OCD and healthy controls, using probabilistic tractography. We developed connectivity indices (spatial spread and density) as well as an index of segregation to test 1/a decrease in the strength of connections and 2/a modification of their organisation in OCD compared to controls.

2. Methods

2.1. Participants

We included 37 OCD patients with predominant checking symptoms and 37 healthy controls matched for age and sex. We

recruited through a clinical trial (clinicaltrials.gov NCT01331876, Ethics Committee approval 2009-A00652-55) [49] and a pathophysiology study (Ethics Committee approval 2007-A00488-45). Only the data at inclusion were used. For both protocols, patients were recruited from outpatient units and through an advertisement on the website of the French OCD association (AFTOC). A clinical psychologist conducted a full interview of each participant and used the Mini International Neuropsychiatric Interview [50] as a standardised assessment. Diagnosis of OCD was made according to the Diagnostic and Statistical Manual of mental disorders, 4th edition, revised text (DSM-IV-TR). OCD severity and clinical subtypes were assessed using the Yale-Brown Obsessive-Compulsive Scale (YBOCS), which has an obsession (YBOCS-O) and a compulsion (YBOCS-C) subscale, as well as a checklist which we used to identify the predominant subtype of symptoms (e.g. checking) [51,52]. Participants completed the Padua Inventory to quantify these subtypes. The inventory comprises four factors, the factor 3 being specific of checking (Padua3) [53]. Inclusion criteria for patients were: YBOCS score >16/40, predominant checking symptoms, no axis 1 comorbidity and a stable treatment for at least two months. Controls were free of any axis 1 diagnosis and had no psychotropic medication.

All participants were legal adults and gave a written, informed consent after a complete description of the study by an investigator. The local ethics committee approved all procedures. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008.

2.2. MRI apparatus and procedures

MRI were acquired using a 3T scanner (Siemens TRIO 32 channel TIM) and a 12 channels head coil, including T1 weighted images and diffusion tensor imaging (DTI). Anatomical scans were acquired using axial three-dimensional inversion recovery MP-RAGE (magnetisation-prepared rapid gradient echo) sequences (TR/TE/flip angle: 2.3s/4.18 ms/9°, 208 axial slices, voxel size: 1 × 1 × 1 mm). DTI was performed using echo-planar imaging (TR/TE/flip angle: 12s/86 ms/90°, matrix size: 128 × 128 mm, field of view: 256 × 256 mm, slice thickness: 2 mm, 80 contiguous axial slices, voxel size: 2 × 2 × 2 mm). Diffusion weighting was performed along 50 independent directions, with a b-value of 1000s/mm², in addition to one reference image (b = 0).

2.3. DTI image processing

Raw DTI images were processed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (<http://www.fmrib.ox.ac.uk/fsl/index.html>) [54,55], specifically its Diffusion Toolbox (FDT) [37]. Images were corrected for head motion and eddy currents.

2.4. Segmentation of regions of interest

As written in the Introduction, we aimed to test the anatomical connections within the associative and limbic cortico-basal ganglia circuits in OCD. Based on the results of functional imaging studies and meta-analyses in OCD [7–9], we segmented four cortical ROIs: ACC, DLPFC, OFC and the frontal pole (Fpole – anterior part of the frontal cortex – BA10, sometimes included in the OFC or DLPFC [56]). As subcortical ROIs we individualised two parts of the striatum (the Caudate nucleus and Putamen) and the Thalamus. While the caudate nucleus and putamen form a single anatomo-functional unit (the striatum), they have a different location; therefore different tracts, with different shapes, connecting them to the cortex. Shape and length of a tract are important parameters in the output of quantitative tracking, thus in the comparison of

tracts. Therefore, we studied these two parts of the striatum separately to obtain the most robust results.

Segmentation was performed automatically on the T1 images using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>). Cortical segmentation was based on the Destrieux Atlas [57], subcortical segmentation on the Fischl parcellation [58]. Masks were binned at 0.5 to avoid overlap. The list of the FreeSurfer labels for each mask is reported in STable 1. The mean volume for each mask was not significantly different between groups (two-tailed *t*-tests, data not shown).

2.5. Probabilistic tracking

We applied the *probtrackx* function of FDT [37] with default parameters (5000 samples per voxel, path length of 2000 × 0.5 mm steps, curvature threshold of |80|° and loop-checking criteria enabled). It was run in each subject’s native space, from each seed (Caudate nucleus, Putamen and Thalamus) to each target (ACC, OFC, DLPFC and Fpole) (12 connections per hemisphere). This direction is a strictly methodological consideration and makes no assumption about the anatomical direction of the axons [31,43]. The smallest ROI is used as the seed for maximum efficacy and robustness [37,47]. We only investigated ipsilateral connections, and each connection was investigated in one direction only. We checked streamlines visually for anatomical plausibility. This produced a connectivity map for each connection (i.e. 24 maps, 4 maps for each seed), in which each seed voxel had for value the number of streamlines connecting it to the target (0–5000).

2.6. Statistical analyses

2.6.1. Connectivity: spatial spread and density

Spatial spread of projections was defined as the proportion of seed voxels connected to the target: $PVox = \frac{Connected\ Voxels}{Total\ Voxels}$. For each of the 24 connections, we tested the difference of mean *PVox* between groups using permutation tests with 10⁶ iterations and $\alpha = 5\%$. We corrected for multiple comparisons using a False Discovery Rate (FDR) of 10% for mathematical reasons [59,60], and *P*-values were adjusted according to Benjamini & Hochberg [60–62] (detailed results are also presented with FDR=5%). For OCD patients, we investigated the relationship of *PVox* with YBOCS,

YBOCS-O, YBOCS-C, Padua3 and disease duration using Spearman’s rank correlation. Likewise, we used permutation tests and FDR correction.

Second, we investigated whether the density of connections amongst the connected voxels was modified. Indeed, if *PVox* is decreased but the total number of connections is unchanged, one might expect an increase in *Density*. *Density* was defined, for each connection, as the total number of streamlines from the seed to the target, divided by the number of connected seed voxels: $Density = \frac{Total\ streamlines}{Nb\ connected\ voxels}$. Statistical tests were the same as *PVox*.

2.6.2. Segregation of the connections

Having established the conserved topography of the connections (details in Supplementary material), we tested a difference in the segregation of cortical projections in each seed between OCD and controls. For each seed-voxel, we derived an index of segregation: $I_{seg} = \frac{Nb\ connections\ to\ most\ connected\ target}{Sum\ of\ connections\ to\ all\ targets}$. Higher values (max=1) indicate high segregation, and lower values (0.25) indicate evenly distributed connections from/to the four cortical targets (Fig. 1). We tested the difference of means between groups using a permutation test and FDR correction.

All statistical analyses were performed using MATLAB (The MathWorks, Inc., MA, USA) and additional toolboxes where so indicated.

3. Results

3.1. Participants

Thirty-seven OCD patients and 37 healthy controls, matched for age and sex were included in the study (see Table 1 for demographic and clinical data). Patients had predominant checking symptoms and had a mean score of 22.49 on the YBOCS (max 40, >16 is pathological). Fifteen OCD patients had no medication, other patients received psychotropic medications which are reported, with detailed clinical scores, in STable 2.

3.2. Connectivity: spatial spread (*PVox*) and density

PVox for OCD patients was reduced in 12/12 connections in the left hemisphere and 7/12 in the right hemisphere compared to

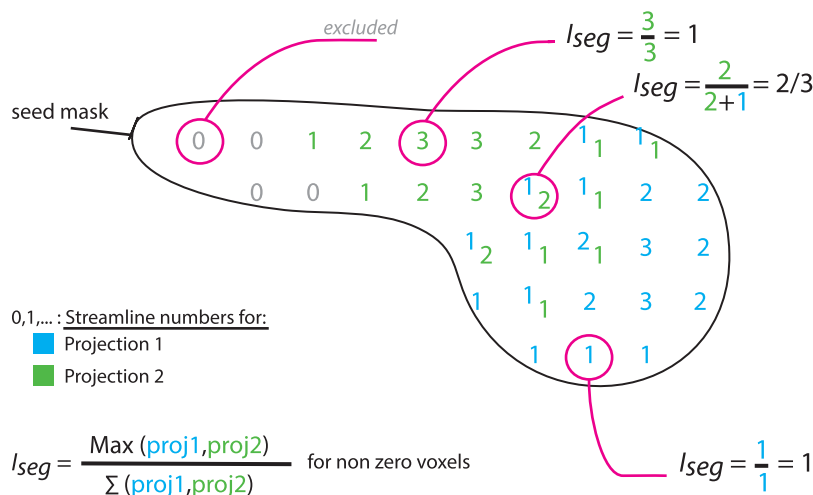


Fig. 1. *I_{seg}*, index of segregation. Schematic sagittal section of a caudate nucleus, one of the seed ROIs. Each number represents the number of streamlines made from the underlying seed voxel to region 1 (blue) or region 2 (green). Some voxels have streamlines connecting them to both region 1 and 2. Voxels with no connections (0) are excluded. Different examples of *I_{seg}* calculations are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Demographic and clinical characteristics of the two groups.

	Controls	OCD	2-tailed <i>t</i> -test
Age (mean ± SD)	34.03 ± 11.26	37.54 ± 9.91	<i>t</i> =1.4234, P=0.159
Sex (M/F)	16/21	16/21	
Y-BOCS score/40 (mean ± SD)	/	22.49 ± 4.96	
Y-BOCS O/20 (mean ± SD)	/	10.84 ± 3.15	
Y-BOCS C/20 (mean ± SD)	/	11.62 ± 2.67	
Padua 3 (mean ± SD)	/	19.03 ± 9.41	
Duration of illness (mean years ± SD)	/	20.34 ± 10.08	

controls (Fig. 2, darker bars). There was a non-significant trend towards a reduction for the other connections. Detailed means, standard deviations, *p*-values and FDR-adjusted *p*-values are provided in STable 3.

Density was reduced in OCD in 7/12 connections in the left hemisphere and 2/12 in the right hemisphere. In addition, *Density* was increased in OCD for the right ACC-Caudate connection compared to controls (Fig. 2, lighter bars). Detailed means, standard deviations, raw *p*-values and FDR-adjusted *p*-values are provided in STable 4.

3.3. Clinical correlations

No clinical correlation (YBOCS, YBOCS-O, YBOCS-C, Padua3 scores and duration of illness) was statistically significant after correction for multiple comparisons with any of our connectivity or segregation measures. Moreover, we identified no trend as ρ was generally small (max $\rho^2 = .17$) and indiscriminately positive or negative.

3.4. Topography and segregation of the connections

The topography of cortical basal ganglia/thalamic connections was the same in OCD patients and controls with ACC, OFC, Fpole and DLPFC connections organised in this order (regression equations, ρ^2 and *P*-values in Table S5).

I_{seg} was increased bilaterally in the putamen and thalamus in OCD compared to controls. A trend was also observed for the caudate nuclei (Table 2). This increase seemed characterised, visually, by a marked increase of subcortical voxels connected to only one cortical area ($I_{seg} = 1$, Fig. 3).

4. Discussion

We found altered associative and limbic cortico-basal-ganglia-thalamic anatomical connections in OCD patients compared to healthy controls: their spatial spread was reduced for 19/24 connections, so was the density of about half (9/24) of these connections. In addition, we showed that these connections were hyper-segregated in OCD.

For methodological and anatomical reasons, we did not study the connectivity of all the basal ganglia. The pallidum and the nucleus accumbens, both relevant to OCD pathophysiology and part of cortico-basal ganglia circuits, were not included in the analyses. Indeed, DTI cannot access the axonal tracts connecting pallidum to striatum (they are mostly embedded in grey matter), and the pallido-thalamic connection follows a convoluted path that would not be traced accurately. Concerning the nucleus accumbens, we included it in the caudate nucleus ROI as it mostly runs underneath its ventral edge, and because there is no clear morphological criteria to isolate it from the striatum. Also, we did not perform a whole cortex analysis (motor regions included) because we wanted to base our study on strong hypotheses, and

the involvement of non-prefrontal regions is inconsistent across studies and not consensual [4–9].

Concerning the tracking process, basal ganglia were identified as seeds and cortical areas as targets only for methodological reasons [37,47]; indeed, tractography is non-directional [31,43]. Nonetheless, because no striato-cortical projection is known in primates, we will consider hereafter that modifications of the striato-cortical tracts reflects modifications of the cortico-striatal axonal projections.

This change of connections, demonstrated with probabilistic tractography, could provide an anatomical substrate of the dysfunctional cortico-basal-ganglia circuits in OCD. However, probabilistic tractography is an indirect estimate of axonal pathways [31,37], based on algorithms with no anatomical priors. Thus, it could create false-positive pathways through the white matter [31,35]. Here, we studied connections for which there is ample anatomical evidence [20,27] [e.g. 20, 27], and the pathways through the white matter were checked visually for anatomical plausibility. Moreover, the *probtrackx* algorithm which we used has been validated specifically for cortico-striatal and cortico-thalamic pathways by direct comparison to axonal tracing [63–66].

The streamline counts used to assess *PVox* and *Density* are also given by tracking; thereby subject to limitations. They cannot be considered as a direct estimate of the underlying number of axons [31]. Indeed, the streamline count is bounded by the number of iterations of the algorithm (here 5000). Nonetheless, experimentally, the number of streamlines from the cortex has a monotonic relationship to the number of axons and neuronal bodies stained using neuroanatomical tracers [32], or the density of axon terminals [34]. Consequently, a variation in the number of streamlines (and the indices that we derived, *PVox* and *Density*) gives a direction of the variation of the underlying number of axons, but does not quantify this difference. Thus, even if the difference cannot be precisely quantified, our results are in favour of a reduced number of axons in cortico-basal-ganglia connections in OCD.

In light of these methodological considerations, we find that our results can be trusted concerning the validity of the tracts as well as the comparison of streamline counts. Consequently, the reduction of the cortico-striatal connections in OCD demonstrated with tractography is indicative of a reduction in cortico-striatal axonal projections.

Schematically, the cortex is thought to provide voluntary control over learned behaviour stored in and implemented by the basal ganglia. Clinically, OCD patients are unable to inhibit unwanted thoughts and behaviour, even though they can identify their inappropriate character. Therefore, our results provide anatomical support for a lack of cortical voluntary control over habits stored in the basal ganglia [2,4,5,67–70]. One might argue that such a reduction in anatomical connections is contradictory with the increased functional connectivity reported in other studies [71,72]; however, this increased functional connectivity could be a homeostatic attempt to counterbalance the lack of connections.

Among the connectivity parameters, the one that changed for the most connections was the spatial spread (*PVox*). The difference between the two measurements might be explained by the wider variance of *Density*, but could also suggest that the spatial organisation of connections is closer to the core of the pathophysiology.

Indeed, in OCD patients we also found an alteration in the organisation of the cortico-basal-ganglia anatomical connections in the form of a hyper-segregation of the cortical projection fields.

Our segregation index, I_{seg} , uses the connectivity profiles of voxels in each seed (the relative strengths of each connection for

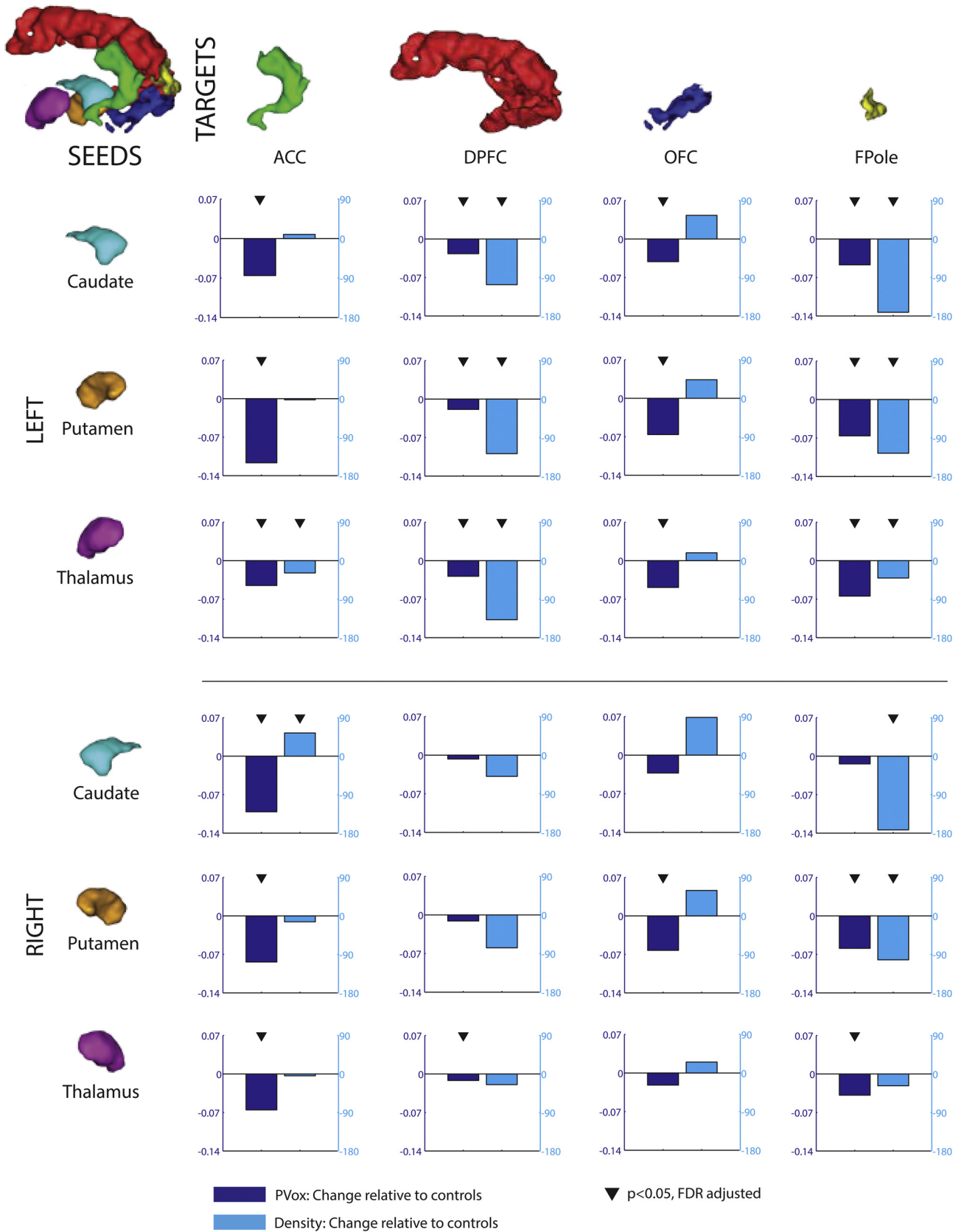


Fig. 2. Connectivity changes in OCD patients. The rows correspond to each seed: Caudate nucleus, Putamen and Thalamus, left and right. An example of the segmented masks is given as row entries. The columns correspond to each target: ACC, DLPFC, OFC, and FPole. Representative segmented masks figure as column entries. A composite of all masks is in the top left corner. Y axes represent the delta absolute value of PVox and Density for patients relative to controls. In each cell, the dark bar is the difference in PVox and the light bar is the difference in Density in patients vs. controls for that connection. Significant changes after FDR adjustment are indicated by the black triangles.

Table 2
Segregation. The segregation index I_{seg} ranges from 0.25 (least segregation) to 1 (most segregation, no overlap, single connection). The criterion p-value was 0.046 for an FDR of 10%.

Seed	Mean (SD) OCD	Mean (SD) Controls	Uncorrected P-values	FDR-adjusted P-values
Left Caudate	0.689 (0.180)	0.681 (0.169)	NS	NS
Right Caudate	0.700 (0.176)	0.686 (0.168)	NS	NS
Left Putamen	0.770 (0.190)	0.746 (0.189)	0.034	0.062
Right Putamen	0.754 (0.193)	0.724 (0.188)	0.011	0.062
Left Thalamus	0.723 (0.196)	0.700 (0.193)	0.041	0.062
Right Thalamus	0.741 (0.191)	0.714 (0.189)	0.025	0.062

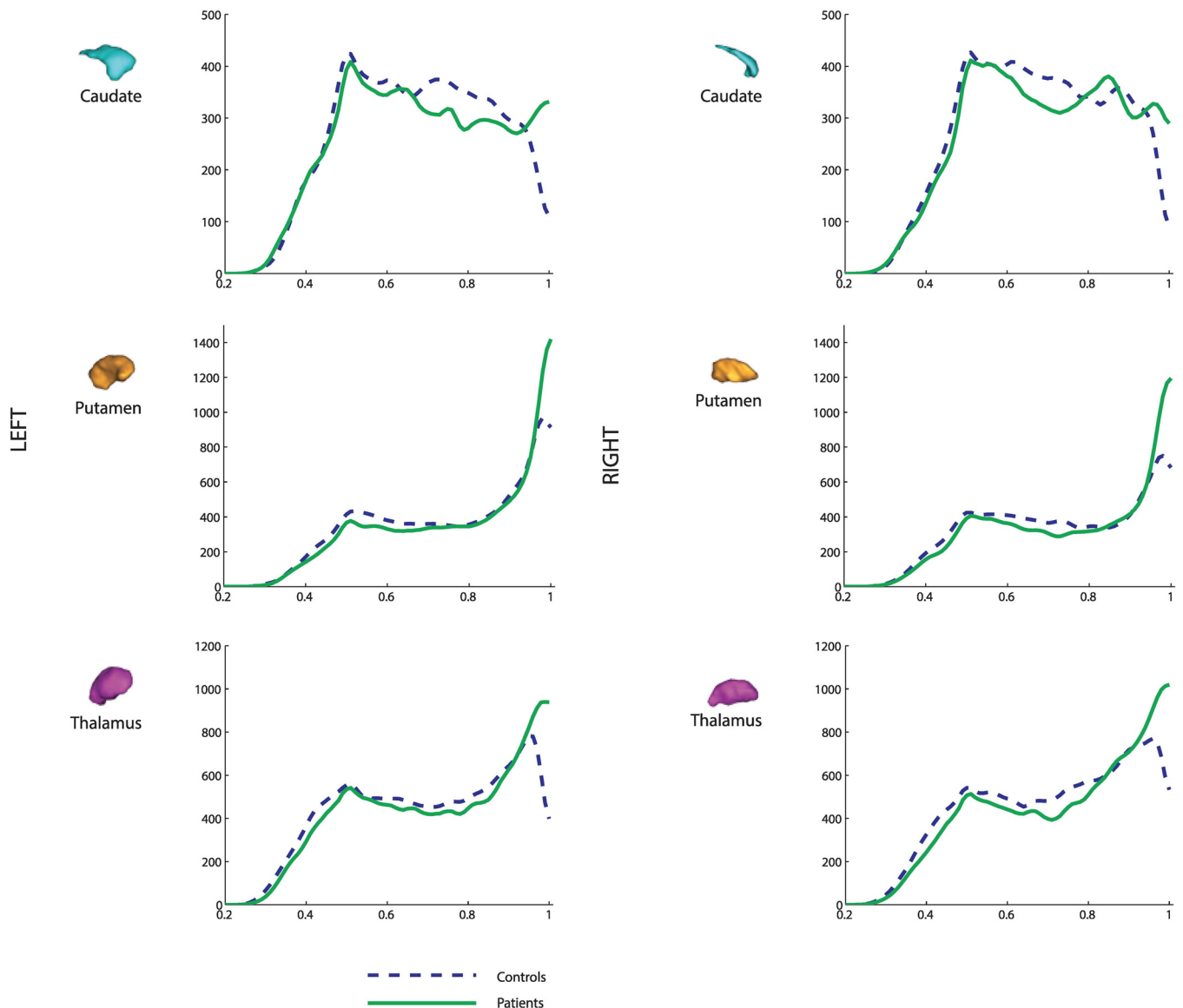


Fig. 3. Distribution of I_{seg} for each seed. Values were sorted into 100 bins of width 0.01. The histogram was smoothed with a sliding boxcar, width of 0.03. X axes represent the index of segregation with higher values (max = 1) for more segregation and minimal values (min = 0.25) evenly distributed connections to the four targets. Y axes represent the number of voxels.

that voxel). Such connectivity profiles have been used in other studies to make connectivity-based parcellations of the striatum and cortex [67,69,70]. These parcellations are in agreement with both axonal tracing in non-human primates, and functional data in humans. Thus, connectivity profiles appear to contain anatomically and functionally relevant information. With I_{seg} , we used the same connectivity profiles but instead focused on the information about overlap and segregation which they contain.

Partial overlap of neighbouring cortico-basal-ganglia-thalamic loops is a crucial component of their anatomical and functional organisation [20,22,27]. It allows the convergence and integration of different types of information, which in turn allows a fine-tuning of behavioural output [68,69]. According to models of behavioural selection, each specific combination of cortical inputs – representing an environmental state – elicits activity in a specific striatal cell assembly [73], and thus a specific behaviour [68,69].

Here, we demonstrate an increased segregation of the associative and limbic prefrontal inputs to the striatum in OCD. It follows that their functional integration would also be disturbed in OCD. Because this integration is used to control reinforcement learning [67,74] and behavioural selection in the basal ganglia [69], its disturbance could explain why OCD patients select inappropriate programs for the circumstances. This may be reflected in patients' inability to use new conditions to update behaviour [1,11], leading to the repetition of compulsions and cognitive rigidity [3]. Thus, hyper-segregation provides working hypotheses to be tested in future functional and behavioural studies.

Reduced connectivity and hyper-segregation were also found in prefrontal-thalamic connections. As tractography is non-directional, this can reflect modifications in cortico-thalamic and/or thalamo-cortical axons. The involvement of the thalamus and its cortical connections in OCD has been described in functional studies [9]. One might consider a dysregulation of the balance between the cortico-basal ganglia (supporting implicit/automatic function) and the cortico-thalamic circuit (processing explicit information) in OCD [4]. One might also consider that the hypersegregation is 'simply' carried-on from the cortical-basal ganglia projection throughout the loop. More studies are needed to understand the implication of these two loops in the expression of OCD symptoms.

It would also be of interest to identify the respective role of anatomical alterations in the associative and the limbic loops, in OCD. However, for methodological reasons, we cannot compare the modification of anatomical connectivity between two loops. Indeed, the magnitude of the difference in *PVox* or *Density* cannot be compared between different anatomical connections because streamline counts are influenced by the shape and length of the tract (e.g. one cannot conclude that *PVox* is more reduced for the left caudate-ACC connection than for the left thalamus-OFC connection) [31,36].

While we showed a modification of connections in cortico-basal-ganglia-thalamic loops in OCD, we found no correlation between our connectivity measures and the clinical characteristics of the patients. This could be due partially to the non-linear relationship of streamlines and axon counts [32], but also to the homogeneity of the population in terms of severity. Our OCD group was also homogenous concerning clinical subtype. As neurophysiological differences have been shown between OCD subtypes [75], the inclusion was limited to patients with predominantly checking symptoms. This limits the application of our results to other clinical subtypes; however, checking is one of the most common symptoms in OCD, and dysfunctions of the associative and limbic part of cortico-basal-ganglia circuits (in fMRI) are shared by all the major subtypes [75].

In conclusion, we used probabilistic tractography to demonstrate that the limbic and associative prefrontal-striatal and prefrontal-thalamic loops are anatomically altered in OCD. More specifically, we found a reduction in the spatial extent and density of connections, and a hyper-segregation of the cortical connections with the basal ganglia in OCD. We hypothesise that these quantitative and qualitative differences in anatomical connections might lead to a reduced and ineffective regulation by associative and limbic prefrontal areas of habit learning and expression by the basal ganglia in patients. Clinically, cognitive and behavioural therapy might act through a reorganisation of these connections, by driving plasticity during the reprogramming of pathological habits for appropriate ones [5].

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eurpsy.2018.01.005>.

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