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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.

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 associativo-limbic 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 theanatomical 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: $1 \times 1 \times 1$ 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: $2 \times 2 \times 2$ mm). Diffusion weighting was performed along 50 independent directions, with a b-value of 1000s/mm^2, 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