Frontostriatal dynamics modelling obsessions and compulsions

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Abstract

The frontostriatal system support several processes related to attention, habits, emotional regulation and goal directed behaviours. Preclinical and clinical work suggests that obsessive-compulsive disorder (OCD) maps onto a functional imbalance in the ventral and dorsal frontostriatal circuits. However, the neural mechanisms supporting these dysregulations remain elusive, their association with symptom severity is unclear, and therapeutic interventions are limited. We here combined neuroimaging and behavioural data from individuals with OCD and controls with computational modelling. We found that bidirectionally decreasing neural coupling in the ventromedial circuit while concurrently increasing dorsolateral cortico-striatal coupling delivered the highest functional improvements in OCD. The analysis of longitudinal changes in obsessions and compulsions with respect to modelled neural interventions supported our predictions. This study highlights behaviourally meaningful neural mechanisms hidden from traditional neuroimaging analysis to better understand the neural basis of OCD and provide new therapeutic targets for obsessions and compulsions.

Keywords: corticostriatal, striatocortical, OCD, dynamical systems, Bayesian optimization

Introduction

Deregulation of frontostriatal brain circuit activity has been reliably associated with the emergence of obsessive thoughts and compulsive actions associated to obsessive-compulsive disorder (OCD) (Robbins et al., 2019). Biophysical models provide a viable way to link preclinical advances at the microscale with clinical findings at the macroscale (Breakspear, 2017; Shine, 2021; Wang et al., 2023). Here, we develop a biophysical model of OCD frontostriatal pathology using dynamical systems theory, Bayesian inference, and a unique longitudinal dataset comprising clinical and neuroimaging information (Cocchi et al., 2023). We simulate ventral and dorsal frontostriatal circuits, capturing essential aspects of local neural activity and cross-region coupling, explaining macroscopic patterns of resting-state functional connectivity measured via functional magnetic resonance imaging (fMRI).

Methods

Dataset. Functional MRI (3T, 2mm^3 voxels, TR=820ms, TE=30ms, 12 mins eyes open) and behavioural score (Y-BOCS) were collected from 52 OCD subjects and 45 matched healthy controls (average age of 31 years, 42% female), all recruited from within Australia and assessed by board certified psychiatrists (see (Naze et al., 2023) and (Cocchi et al., 2023) for inclusion criteria and clinical trial procedure).

Functional connectivity. Pearson's correlations were extracted voxel-wise between the orbitofrontal cortex, the lateral prefrontal cortex, the nucleus accumbens, and the dorsal putamen areas following seed regions previously shown to be impacted in OCD (Naze et al., 2023), and then averaged within regions.

Neural model. We adapted a widely used model of resting state activity (Deco et al., 2013) to account for striato-pallido-thalamic dynamic couplings. A mean-reversal stochastic term is introduced to model the interplay between direct and indirect pathways of the basal ganglia in each circuit (Graybiel & Rauch, 2000). The drift η and volatility σ of this dynamic coupling affect the switching probability of cortical states based on striatal activity, and the magnitude C denote the coupling strength.

Bayesian optimization. We performed parameter inference using the Approximate Bayesian Computation framework with a sequential Monte-Carlo algorithm (ABC-SMC), using 10 generations of 1000 particles with adative acceptance thresholds. ABC-SMC has been shown to outperform other Bayesian frameworks for model-based inference with unknown likelihoods (Toni et al., 2008).

Digital twins. We create digital twins from empirical subjects by first densely sampling the parameter space for OCD and controls conditions (1.5M digital

subjects for each condition). Then, each empirical subject is matched to its closest simulation in frontostriatal functional connectivity space (minimal Euclidian distance) to obtain their digital twin.

Results

Frontostriatal changes in ventral and dorsal circuits activity. The posterior distributions of parameters after running the optimization reveal increased bidirectional couplings in the ventromedial circuits and decreased dorsolateral couplings in the dorsolateral circuit in OCD compared to controls (Figure 1).

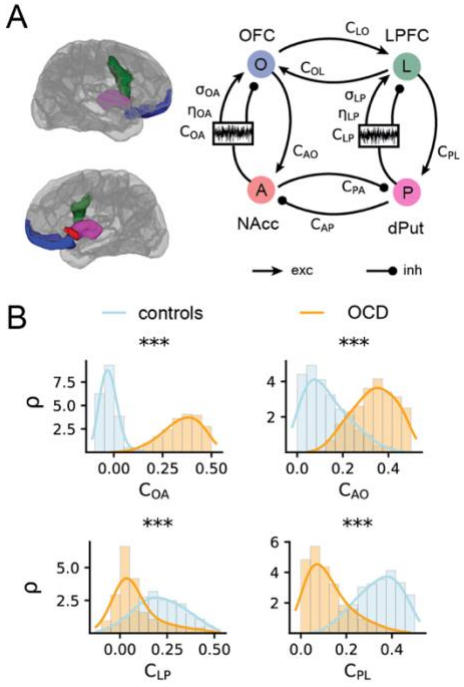

Figure 1: Altered frontostriatal circuits in OCD. A. Schematic of the coupled model (OFC/LPFC: orbitofrontal/lateral prefrontal cortices, NAcc: nucleus accumbens,dPut: dorsal putamen). C terms are coupling strengths, η and σ terms are drift and volatility properties of noise. B. Posteriors and density functions of model parameters after optimization. * p_{FWE}<0.05 (U-test) with ** Cohen's d>0.5 and *** d>0.8.

Restoring healthy functional connectivity. We performed a restoration analysis by permuting model parameters required to bring OCD frontostriatal functional connectivity patterns closer to those observed in healthy controls. We virtually established a hierarchy of interventions targets that would maximally improve the frontostriatal functional connectivity in subjects with OCD, without prior constraint on the feasibility or modality of the intervention.

Validating model predictions. We started by confirming the clinical relevance of the relationship between the severity of OCD symptoms and empirical frontostriatal functional connectivity (Figure 2A). Then, we created "digital twins" of OCD subjects and probed hidden neural parameters associated with the observed changes in symptom severity over time (Figure 2B-C).

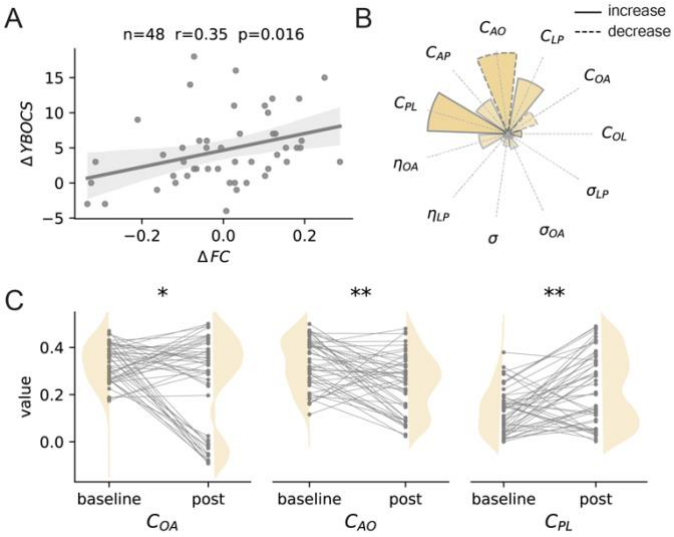

Figure 2: Digital twin analysis supporting changes in frontostriatal functional connectivity and OCD symptoms over time. A. Changes in functional connectivity (FC) and OCD symptoms' severity (Y-BOCS: Yale-Brown Obsessive-Compulsive Scale) over time (baseline *minus* follow-up). B. Dot-product between digital twin's parameter changes and the Y-BOCS changes across OCD subjects. C. Distributions of model parameters in individual digital twins. * $p_{uncorrected}$<0.05, ** p_{FWE}<0.05.

Conclusion

Our work suggests that distinct changes in neural variability and cross-regional coupling play a key role in OCD frontostriatal pathophysiology. The bidirectional reduction of neural coupling between the nucleus accumbens to the orbitofrontal cortex, combined with increased couplings between the lateral prefrontal cortex and the dorsal putamen, supports the improvement of obsessions and compulsions over time. These findings confirm (Apergis-Schoute et al., 2018) and progress the understanding of the neural mechanisms relating key diagnostic and dimensional features of OCD.

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