

OBSESSIVE-COMPULSIVE DISORDER: CIRCUIT-LEVEL PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

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Abstract: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by intrusive, distressing thoughts (obsessions) and repetitive behaviors or mental acts (compulsions) performed to reduce the anxiety these thoughts provoke. Neuroimaging and lesion studies consistently implicate hyperactivity within cortico-striato-thalamo-cortical (CSTC) circuits, particularly loops connecting the orbitofrontal cortex, anterior cingulate cortex, caudate nucleus, and thalamus. Symptom provocation studies demonstrate that this hyperactivity intensifies during active symptom states and normalizes following effective treatment. At the cellular and network level, OCD is associated with imbalance between direct and indirect striatal pathways favoring net cortical excitation, dysregulated glutamatergic and serotonergic signaling, and a shift from goal-directed to habitual behavioral control mediated by relative hyperactivity of the dorsolateral striatum. While selective serotonin reuptake inhibitors and exposure-based cognitive behavioral therapy remain first-line treatments, refractory cases increasingly respond to deep brain stimulation targeting specific nodes within these circuits. This review summarizes the neuroanatomical organization of CSTC loops, the cellular and network mechanisms underlying OCD pathophysiology, circuit correlates of specific symptom dimensions, and clinical and neuromodulatory implications.

Keywords: Obsessive-compulsive disorder, Cortico-striato-thalamo-cortical circuit, Orbitofrontal cortex, Caudate nucleus, Habit formation, Deep brain stimulation

1. Introduction

Obsessive-compulsive disorder affects approximately one to three percent of the general population and is characterized by recurrent, intrusive obsessions accompanied by repetitive compulsive behaviors or mental rituals performed to neutralize the distress the obsessions generate (Pauls, Abramowitz, Rauch, & Geller, 2014). Although OCD has traditionally been conceptualized as a disorder of anxiety, contemporary neurobiological models emphasize dysfunction within specific cortico-striato-thalamo-cortical (CSTC) loops that mediate the integration of affective, motivational, and motor information. Functional neuroimaging studies performed during symptom provocation consistently demonstrate hyperactivity within the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus, and this hyperactivity has been shown to normalize following successful pharmacological or behavioral treatment (Saxena & Rauch, 2000). These findings have positioned CSTC circuit dysfunction, rather than a single neurotransmitter abnormality, as the central organizing framework for understanding OCD pathophysiology, its diverse symptom dimensions, and its response to both pharmacological and neuromodulatory interventions.

2. Neuroanatomical Organization of Cortico-Striato-Thalamo-Cortical Circuits

The basal ganglia-thalamocortical system is organized into several largely parallel, functionally segregated loops, each originating in a specific cortical region, projecting to a corresponding striatal territory, relaying through the globus pallidus and thalamus, and returning to the cortical region of origin (Milad & Rauch, 2012). The loop most consistently implicated in OCD originates in the orbitofrontal cortex and anterior cingulate cortex, projects to the ventromedial caudate nucleus, and relays through the medial globus pallidus and mediodorsal thalamus before returning to the same cortical regions. As in other basal ganglia circuits, striatal medium spiny neurons are organized into direct and indirect pathways: the direct pathway disinhibits the thalamus and facilitates cortical drive, whereas the indirect pathway enhances basal ganglia output inhibition of the thalamus and suppresses cortical activity. In parallel, a distinct dorsolateral CSTC loop connects the dorsolateral prefrontal cortex and dorsal caudate to motor planning and habit-related circuitry, while a further loop involving the dorsal putamen and sensorimotor cortex is more directly implicated in the execution of learned, automatic motor sequences. This anatomical segregation provides a framework for understanding how the diverse cognitive, affective, and motor features of OCD may map onto distinguishable, though interacting, neural circuits.

3. Cellular and Network Mechanisms of Circuit Dysfunction

The predominant network model of OCD proposes a relative imbalance between direct and indirect pathway activity within the orbitofrontal-striatal loop, favoring net direct-pathway-mediated disinhibition of the thalamus and consequent hyperexcitability of orbitofrontal and anterior cingulate cortex (Pauls et al., 2014). This model is supported by structural and functional neuroimaging demonstrating increased orbitofrontal-caudate-thalamic activity and connectivity in patients with OCD compared with healthy controls, with the magnitude of hyperactivity in the orbitofrontal cortex and caudate correlating with symptom severity in several studies (Saxena & Rauch, 2000). At the neurochemical level, both glutamatergic and serotonergic dysregulation have been implicated: excessive glutamatergic corticostriatal drive is thought to contribute to circuit hyperactivity, while serotonergic projections from the raphe nuclei modulate cortical and striatal excitability, providing a mechanistic rationale for the therapeutic efficacy of selective serotonin reuptake inhibitors. A complementary and increasingly influential framework proposes that OCD reflects a shift in the balance between goal-directed and habitual modes of behavioral control, mediated respectively by the ventromedial/associative striatum and the dorsolateral/sensorimotor striatum. Behavioral studies demonstrate that individuals with OCD show a relative bias toward habitual responding at the expense of goal-directed action selection, consistent with relative hyperactivity or dominance of dorsolateral striatal circuitry and providing a mechanistic account for the persistence of compulsive behaviors despite their lack of adaptive value (Gillan & Robbins, 2014).

4. Circuit Correlates of Specific Symptom Dimensions

OCD is clinically and neurobiologically heterogeneous, and specific symptom dimensions have been associated with relatively distinguishable, though overlapping, patterns of circuit engagement. Contamination-related obsessions and washing compulsions have been associated with hyperactivity in the orbitofrontal cortex, insula, and ventral striatum, regions implicated in disgust processing and affective evaluation. Checking behaviors and pathological doubt are more strongly associated with dorsolateral prefrontal cortex and dorsal caudate engagement, consistent with a role for working memory and executive monitoring circuitry in this symptom dimension. Symmetry and ordering symptoms have been linked to activity within sensorimotor cortico-striatal circuits involving the putamen, consistent with their close relationship to motor sequencing and automaticity. Hoarding symptoms, now classified separately as hoarding disorder in current diagnostic frameworks, have been associated with a distinct pattern involving the ventromedial prefrontal cortex and anterior cingulate cortex related to decision-making and value assignment rather than classical OCD circuitry. This dimensional mapping supports the broader conceptualization of OCD as

arising from dysfunction distributed across multiple, partially independent CSTC loops rather than a single unified circuit abnormality (Milad & Rauch, 2012).

5. Clinical and Neuromodulatory Implications

First-line treatment for OCD combines selective serotonin reuptake inhibitors, typically requiring higher doses and longer treatment durations than in major depressive disorder, with exposure and response prevention, a form of cognitive behavioral therapy that directly targets pathological threat appraisal and compulsive avoidance behavior. Both interventions have been shown using functional neuroimaging to reduce orbitofrontal-caudate-thalamic hyperactivity, providing convergent evidence that clinical improvement is associated with normalization of CSTC circuit function regardless of treatment modality (Saxena & Rauch, 2000). For patients with treatment-refractory OCD, neurosurgical and neuromodulatory approaches have been developed that directly target nodes within these circuits. Ablative procedures such as anterior capsulotomy and cingulotomy interrupt specific white-matter connections within the orbitofrontal-striatal-thalamic loop. Deep brain stimulation of the ventral capsule/ventral striatum region, targeting fibers connecting the orbitofrontal cortex to the striatum and thalamus, has demonstrated substantial and sustained symptom reduction in patients with severe, treatment-resistant OCD across long-term follow-up studies (Greenberg et al., 2010). Deep brain stimulation of the subthalamic nucleus, a structure that in OCD receives hyperdirect glutamatergic input from associative and limbic cortical regions, has similarly shown efficacy, further supporting the involvement of basal ganglia output structures in the disorder's core pathophysiology.

Conclusion

Obsessive-compulsive disorder arises from dysfunction within specific cortico-striato-thalamo-cortical circuits, particularly the orbitofrontal-caudate-thalamic loop, characterized by a shift toward net cortical hyperexcitability, imbalance between direct and indirect striatal pathways, and a relative dominance of habitual over goal-directed behavioral control mediated by the dorsolateral striatum. Distinct symptom dimensions, including contamination, checking, and symmetry concerns, map onto partially distinguishable circuit territories, providing a framework for understanding the clinical heterogeneity of the disorder. Effective pharmacological and behavioral treatments converge on normalization of this circuit hyperactivity, while neuromodulatory approaches targeting specific nodes within these loops offer additional therapeutic options for treatment-refractory disease. Continued refinement of circuit-based models, informed by advances in functional neuroimaging and neuromodulation, will likely be central to developing more precisely targeted and individualized treatments for OCD.

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