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Striatal circuits, habits, and implications for obsessive–compulsive disorder

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Increasing evidence implicates abnormalities in corticostriatal circuits in the pathophysiology of obsessive–compulsive disorder (OCD) and OC-spectrum disorders. Parallels between the emergence of repetitive, compulsive behaviors and the acquisition of automated behaviors suggest that the expression of compulsions could in part involve loss of control of such habitual behaviors. The view that striatal circuit dysfunction is involved in OC-spectrum disorders is strengthened by imaging and other evidence in humans, by discovery of genes related to OCD syndromes, and by functional studies in animal models of these disorders. We highlight this growing concordance of work in genetics and neurobiology suggesting that frontostriatal circuits, and their links with basal ganglia, thalamus and brainstem, are promising candidates for therapeutic intervention in OCD.

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Introduction

OCD is a neuropsychiatric disorder characterized by obsessions (intrusive thoughts) and compulsions (physical or mental rituals such as washing or checking), often associated with high levels of anxiety. OCD has an estimated lifetime prevalence of 2–3% worldwide. In recognition of the core clustering of symptoms in OCD, and in the light of neurological findings, OCD has newly been separated from the class of anxiety disorders in the revised Diagnostic and Statistical Manual of Mental Disorders [1]. Among the heterogeneous symptoms observed in OCD patients, four clusters have been identified in this new classification: symmetry/ordering, hoarding, contamination/cleaning, and obsessions/checking. These symptom-clusters all have features of repetitive thought and action, expressed in relation to external and internal stimuli, and often appear in ritualized form. Here we emphasize emerging evidence that the striatum is critical to the establishment of such ritualized sequences of actions [2–5], and that the striatal connections of anterior cingulate and orbitofrontal cortical regions are linked to OCD and OC-spectrum disorders, based on physiological, genetic and neuroimaging evidence. We point to remaining challenges to characterize the endophenotypes of OCD in relation to a reconsideration of the central role of the striatum in the emergence of this complex neuropsychiatric pathophysiology.

Striatum-based circuitry and the pathophysiology of OCD: insights from studies in human

New neuroimaging studies are helping to characterize both the circuits implicated in OCD and the potential circuit functions that might contribute, when disturbed, to the symptoms of OCD and related disorders. These studies highlight a special relationship between the caudate nucleus, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). At a morphological level, differences in volumes between OCD patients and healthy controls have been reported for the putamen [6,7] and, especially, for the caudate nucleus [8], but the results reported have not been consistent. Meta-analyses have not yet indicated clear volumetric differences in striatal grey matter in the striatum of OCD patients [9]. By contrast, there is concordance in work estimating coordinate activities of the striatum relative to those of the OFC and ACC. Studies done with functional magnetic resonance imaging (fMRI) indicate that activities in the striatum and these two cortical regions are altered during resting-state and during expression of symptoms [10,11]. fMRI has been employed extensively to study functional relationships across these regions as indicated by correlations of spontaneous metabolic fluctuations during cognitive tasks or symptom provocation in frontostriatal circuits. These studies have consistently shown altered functional connectivity between striatum and prefrontal regions in OCD patients [12–15]. These results have been supported by the use of diffusion tensor imaging tractography in studies that report abnormalities in white

matter (e.g., fiber tracts) in the caudate nucleus and its associated frontal regions [16,17].

Clinical work early on suggested that dysfunction of the striatum might be important in the emergence of OCD symptoms. Comorbid OCD symptoms were identified in neurodegenerative disorders such as Parkinson's disease and Huntington's disease [18–20], and in the wake of focal lesions in the caudate nucleus produced by infarcts [21]. New clinical evidence supports this connection between striatum-related circuits and OCD symptoms. For example, the most widely applied treatments for OCD patients are pharmacologic therapy with selective serotonin-reuptake inhibitors (SSRI) and cognitive behavioral therapy (CBT). Neuroimaging studies reported differentially decreased activity in the striatum and associated cortical regions including the OFC after these treatments [21,22].

Further evidence implicating striatal circuitry in OCD is being obtained with the therapeutic use of deep brain stimulation (DBS) targeting subcortical structures to treat severely ill OCD patients for whom conventional treatments have proved ineffective. About a quarter (20–30%) of OCD patients are resistant to conventional treatments, but some receive benefit from the DBS [23]. To date, the main DBS targets include the anterior limb of the internal capsule, also referred to as the ventral capsule/ventral striatum region [24–26], the nucleus accumbens and anterior caudate nucleus [27,28], and the anterior ventral part of the subthalamic nucleus, a nucleus embedded in striatopallidal output pathways [29].

Despite encouraging results of DBS therapy in these different targets (at least half of the patients showed a diminution of symptoms from 25% to total remission [23]), the physiological mechanisms through which therapeutic effects are achieved remain unclear, given that electrical DBS can have varying effects depending on local cell and fiber types. However, neuronal single-unit recording can be performed during surgery, prior to the insertion of the stimulating electrode, to verify the electrophysiological signature of the targeted structures. Abnormally high firing rates and variability in firing of putative medium spiny neurons (the main population of projection neurons in the striatum, MSNs) have been reported for the caudate nucleus of OCD patients during the expression of symptoms compared to features of firing recorded during resting-state conditions [30].

This finding is notable in light of evidence in the related disorder of Tourette syndrome. In two studies of postmortem striatal tissue from patients who suffered from Tourette syndrome, characterized by tics and overexpression of ritualized motor and/or vocal behaviors, the authors observed a significant decrease of parvalbumin (PV)-immunoreactive interneurons and cholinergic interneurons relative to their incidence in normal striatum [31•,32]. Each of these neuronal types has been found in animal studies to exert powerful effects on striatal circuitry, and the PV interneurons, which are GABAergic and thought to be striatal fast-spiking or 'high-firing' interneurons, have been shown capable of inhibiting up to ~100 nearby MSNs apiece. They can be broadly activated by microstimulation of small regions of the motor cortex, and so could be suited to control corticostriatal flow [33] through fast feed-forward inhibition. Work on an animal model of OCD, summarized below, reports both increased firing rates of MSNs and lowered counts of PV interneurons in the striatum, suggesting potential bridges between findings related to Tourette and OCD syndromes.

Genetic evidence for the involvement of striatal circuitry in OCD

Genetically engineered mice that exhibit both corticostriatal dysfunction and OCD-like behaviors support a function for candidate OCD-related genes in the pathogenesis of OCD and point toward a common dysfunction in glutamatergic signaling, including dysfunction within the striatum, as a major contributor to the OCD-like behaviors. These mouse models include the transgenic *D1CT-7* model (over-activation of glutamatergic input to the striatum produced by chronic potentiation of dopamine D1-receptor expressing neurons); the *Sapap3/Dlgap3* deletion model (defective corticostriatal glutamatergic transmission) and the *Slitrk5* deletion model (increased OFC activity, reduced striatal volume and defective corticostriatal transmission), among others [34–38].

A recently published genome-wide association study (GWAS) in dogs further identified genomic loci associated with OCD, with four genes having the most case-only variation: neuronal cadherin (CDH2), catenin alpha2 (CTNNA2), ataxin-1 (ATXN1), and plasma glutamate carboxypeptidase (PGCP)—all of which have functions at synapses [39•]. In human studies using magnetic resonance spectroscopy (^{1}H-MRS), strong associations between genes involved in glutamate signaling and pediatric OCD have been found [40]. However, despite this consensus between basic research and human studies, a comprehensive understanding of the genetics of OCD has remained elusive.

The first GWAS study of OCD in human patients, involving more than 20 research groups, has provided new data that support the central involvement of glutamate signaling in OCD [41•]. In this case-control analysis, the top two single-nucleotide polymorphisms (SNPs) were located within DLGAP1, a gene that influences glutamate signaling and encodes SAPAP1, a protein from the same super-family as SAPAP3 that is not striatum-enriched, but is strongly expressed in cerebellum, hippocampus and neocortex. Another study led by the OCD

Collaborative Genetics Association Study (OCGAS) observed significance of a marker on chromosome 9, near PTPRD. This protein promotes the pre-synaptic differentiation of glutamatergic synapses and interacts with SLITRK3 to regulate the development of inhibitory GABAergic synapses [42••]. These results from genetic studies pointed toward genes implicated in glutamatergic synaptic transmission, suggesting that imbalances in excitation/inhibition signaling within frontostriatal circuitry could be one of the etiologic factors leading to OCD and OC-spectrum disorders.

Striatum-based circuitry and the pathophysiology of OCD: insights from studies in animals

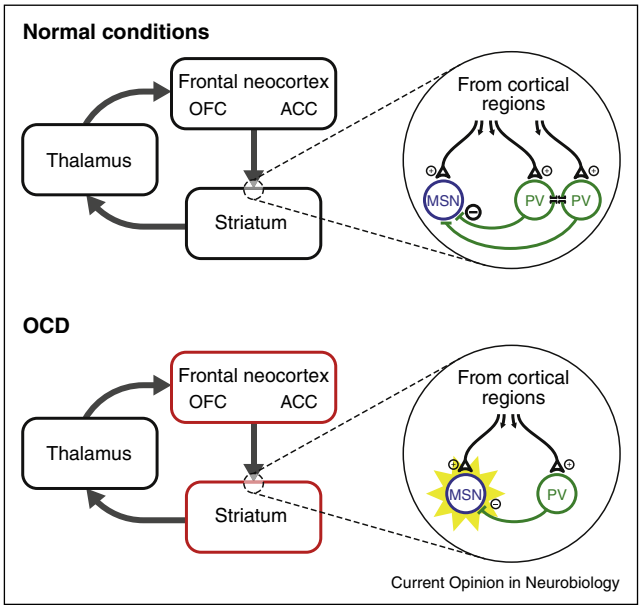
Major advances are coming from the use of genetically engineered models of OCD and OCD-like disorders together with the use of new methods now available to neuroscientists, such as optogenetic. Animal models of OC-spectrum symptoms were originally generated by employing either behavioral conditioning, pharmacological treatment or physical manipulation, and these studies suggested that corticostriatal circuitry contributed to OCD-like symptoms, in keeping with the growing clinical literature (for review see [43,44]). With the new engineered mouse models of OCD-like disorders, it is possible for the first time to link genes implicated in OCD and related disorders to behavioral phenotypes [35,36,45,46].

Several of these mouse models have phenotypes related to excessive grooming behavior, which might be interpreted as a proxy for compulsive behavior in mice. These grooming bouts are expressions of abnormal ritualistic behavior that occur despite their negative consequences (e.g., the production of skin lesions). The validation of these mutant animals as models of OCD and OC-related disorders has depended on their genetic linkage with candidate OCD genes discovered in patient populations (e.g., SAPAP3 variants in trichotillomania [47] and SLITRK1 in Tourette syndrome [48]), and the rescue of the pathological behavior in these animal models with SSRI treatment (fluoxetine, administered to OCD patients) [35,36].

The study of these mouse models has proved striking confirmation of earlier conclusions that the striatum and corticostriatal pathways are related to OCD. Introduction of gene mutations related to OCD and Tourette syndrome have resulted in decreased striatal volume [36] and in dysfunctional corticostriatal synaptic transmission following deletion of genes coding for Sapap3, Slitrk5, and EAAC1, proteins located post-synaptically in striatal neurons [35,36,46]. In the *Sapap3* deletion mutants, chronic electrophysiological recording has demonstrated abnormally high spontaneous activity of MSNs in the dorsomedial striatum, considered as the mouse equivalent of part of the caudate nucleus in primates [49••]. In the Slitrk5-KO mouse model, elevated early-gene activation in MSNs has been found by measuring levels of expression of FosB [36]. Yet another study, done in normal mice, demonstrated that chronic optogenetic stimulation of the medial OFC, activating the orbito-fronto-striatal pathway, could lead to the emergence of compulsive behavior accompanied by sustained increases in the activity of MSNs [50••]. All of these studies indicate overactive striatal activity as a key component of the model phenotypes of OCD and Tourette syndrome.

Notably, study of the *Sapap3* deletion model also showed that these mice, compared to control animals, have reduced numbers of PV-immunoreactive interneurons in the dorsomedial striatum. This decrease was accompanied by decreased feed-forward inhibition of MSNs by fast-spiking interneurons (FSIs), putative PV neurons, as shown by paired FSI-MSN spike recordings [49••]. This finding supports the idea that a lack of inhibitory drive in striatal microcircuitry could lead to enhanced MSN spiking in this compulsive mouse model (Figure 1).

Figure 1



Hypothetical dysfunctional corticostriatal circuity in OCD. In normal conditions (top), the excitatory corticostriatal projections modulate striatal activity through a balance between excitation and inhibition. Medium spiny neurons (MSNs) are maintained under tonic inhibition by a network of parvalbumin (PV)-positive interneurons (and possibly other interneuron's not shown here), with the PV interneurons tightly interconnected through gap-junctions. In pathological OCD conditions (bottom), both cortical and striatal regions are hyperactive, possibly due to a decrease in the number and/or function of striatal PV interneurons that could lead to enhancement of MSN excitation by corticostriatal inputs and eventually to an increased activity throughout the affected corticostriatal loops.

Causal evidence for the importance of this interneuron-projection neuron circuitry for compulsive, OCD-like behavioral symptoms was obtained by optogenetically stimulating the OFC corticostriatal pathway in the *Sapap3* deletion mutants [49••]. This treatment blocked compulsive grooming, leaving other motor behaviors unaffected. The treatment also produced inhibition of striatal MSNs by increasing excitation of local interneurons. The involvement of the corticostriatal glutamatergic pathway in behavioral inhibition thus likely includes not only direct effects on corticostriatal (or other glutamatergic) synapses, but also local intrastriatal effects on microcircuits that can modulate the efficacy of corticostriatal glutamatergic drive (Figure 1).

This conclusion is bolstered by recent evidence that selective ablation of striatal PV interneurons in mice can lead to increased stereotypical grooming after stress [51]. Moreover, pharmacologic interference with striatal PV interneurons can lead to behavioral abnormalities as shown in a study in which selective blockade of synaptic excitation of PV interneurons produced dyskinesia-like movement abnormalities [52•].

In search of relevant corticostriatal-dependent behavioral and neurophysiological endophenotypes of OCD

The evidence that we have reviewed points to new opportunities to refine our understanding of both the neural correlates of OCD and the endophenotypes of OCD and OC-spectrum disorders. Many lines of evidence point to the caudate nucleus-anterior putamen and their connected cortical regions, the OFC and the ACC, as important to the disorder (Figure 1). A major current challenge is to identify core functions supported by these corticostriatal loops, circuits likely affected in patients.

The 'habit hypothesis' of OCD suggests that OCD and related disorders reflects dysregulation of neural processes favoring the expression of routinized, habitual sequence of actions triggered by environmental stimuli ([2,53••] and reference therein). Evidence from neural recording experiments in animals suggests that such behavioral routines can be encapsulated in 'chunks' marked by action boundary signals both in the striatum [3,54,55] and in the prefrontal cortex [56••,57]. Such neural beginning-and-end signals, if relevant to the behaviors repeatedly released in compulsive behavior, could be central to the OCD and related disorders. Within the striatum, such signals are dynamically regulated as habits are acquired, and they can be strikingly marked by specific patterns of oscillatory activity as well as specific patterns of spiking activity [58•]. The ventromedial striatum has strong task-end signals involving local field oscillatory activity that entrains the striatal neurons [58•], and in OCD patients, DBS aimed at the ventral striatal region can powerfully ameliorate symptoms [59•]. A recent study involving 70 OCD patients suggests that a dysfunction related to the termination of action could provoke the patients' symptoms [60]. Signals related to successful completion of action sequences are a promising target for further study, as noted below.

New evidence obtained by studying OCD patients favors the habit hypothesis of OCD and related disorders. Gillan *et al.* introduced, for the first time, the reward devaluation procedure commonly accepted as distinguishing habits (independent of forthcoming reward) from other behaviors for which acquisition of rewarding outcomes drive the behavior [53••]. Critically, their study focused on avoidance behaviors, the behaviors that are the hallmark of individuals with OCD. Their evidence suggests that individuals with OCD, relative to controls, tend to perseverate in making avoidance responses to external stimuli signaling negative outcomes even after they are informed that the outcome will no longer depend on their action.

In related work, rigid ritualistic behaviors observed in OCD patients have been proposed to be the consequence of diminished behavioral flexibility (i.e., ability to change one's behavior according to contextual cues). Behavioral flexibility can be challenged in experimental tasks such as reversal learning paradigms, which test the ability to adapt behavior in response to a reversal of reinforcement contingencies. Such behavioral flexibility tasks, and reversal learning, in particular, appear to engage differentially frontostriatal circuits including the caudate nucleus, OFC and ACC. In a study of OCD patients, Remijinse *et al.* showed that OCD was associated with reduced response in an OFC-striatal network during adaptive switching to the new stimulus-reinforcement association [61•]. With a different type of behavioral flexibility task, Chamberlain *et al.* have demonstrated that OCD patients, as well as their relatives, exhibit diminished OFC responses to behavioral adaptation triggered by the task, pointing toward the identification of an OCD endophenotype [62•]. Similar results have been obtained in animal studies implicating the medial striatum [63] and the OFC in reversal learning [64].

Compulsive checking represents another core symptom of OCD. It is characterized by the urge to verify repeatedly that an action, usually aimed at preventing a possible harm, has been properly completed beyond doubt [65]. One possibility to account for these problems is, as noted above, defective neural end-signals. The clinical phenomenology of compulsive checking illustrates two further, and potentially related, hypotheses regarding possible psychopathological mechanisms in OCD: compulsive checking may proceed from maladaptive goal-directed behavior toward uncertainty reduction or, in the context of habit-driven behavior, it may result from a failure to control impulses to check.

These two alternatives fit nicely with two lines of research on the behavioral functions of the corticostriatal circuits

[66]. Investigations of repetitive checking in human have employed 'verification task' paradigms based on a working memory protocol in which, on each trial, participants could review the stimuli before proceeding to the feedback. This strategy allowed provocation and assessment of compulsive checking in OCD patients in behavioral studies [67,68] and also the reproduction of this pathological behavior during DBS surgery, in which the patient is awake and can behave [69•]. Despite challenges in designing such tasks for animals, new behavioral paradigms have been developed to assess uncertainty monitoring in animals. These demonstrate that, when given the opportunity, rats can adaptively 'opt-out' and move on to the next, possibly easier, trial of the task [70,71•]. In these tasks, varying uncertainty about stimulus identity (hence decision difficulty) leads the animal to discard trials in which the answer is most uncertain. Simultaneous electrophysiological recordings demonstrated that stimulus-related uncertainty is encoded in the spike rate of OFC neurons. Whether such uncertainty-monitoring signals reach the striatum and participate in the regulation of goal-directed behavior, either to opt-out from a trial or to check back at the stimulus, is a matter of great interest.

Conclusions and perspectives

Converging findings from clinical and experimental work, across anatomical, physiological, genetic and behavioral levels, point to the importance of the striatum and corticostriatal pathways in the pathophysiology of OCD and related OC-spectrum disorders. The strength of these studies comes both from their diversity of approaches and from the increasing specificity with which underlying genetic and neural circuit level mechanisms can be identified. The challenge presented by these studies is to discover which dysfunctional executive functions are embedded within these circuits, and to characterize the behavioral and neurophysiological endophenotypes of OCD and related disorders. This integrative approach could lead to more appropriate treatments for such psychiatric diseases and is supported by a growing number of clinicians [72,73]. To meet this challenge, new methodologies based on circuit neuromodulation in humans and in animal models will offer great support. The examples that we have reviewed here hint at a new era in which dynamic interactions between studies of large genomic data sets, research on genetically engineered animal models and improved study of patient endophenotypes can help to define and to target therapeutically the neural circuits disordered in OCD and related conditions.

Conflict of interest statement

Nothing declared.

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