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Learning from Animal Models of Obsessive-Compulsive Disorder

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Abstract

Obsessive-Compulsive Disorder (OCD) affects 2–3% of the worldwide population and can cause significant distress and disability to its sufferers. Substantial challenges remain in the field of OCD research and therapeutics. Approved interventions only partially alleviate symptoms, with 30–40% of patients being resistant to treatment. Research evidence points towards the involvement of cortico-striato-thalamocortical circuitry (CSTC) although OCD's etiology is still unknown. This review will focus on the most recent behavior, genetics and neurophysiological findings from animal models of OCD. Based on evidence from these models and parallels with human studies, we discuss the circuit hyperactivity hypothesis for OCD, a potential circuitry dysfunction of action termination, and the involvement of candidate genes. Adding a more biologically-valid framework to OCD will help us define and test new hypotheses and facilitate the development of targeted therapies based on disease-specific mechanisms.

Keywords

Obsessive-Compulsive Disorder; OCD; animal models; striatum; CSTC; basal ganglia; synapse

Text

Neuropsychiatric disorders encompass a wide range of diseases that manifest as one or many altered behaviors, including but not limited to self-injurious behavior, impaired social-emotional communication and cognitive deficits. Due to the lack of biomarkers and

overlapping behavioral symptoms, diagnosis of neuropsychiatric disorders sometimes relies on exclusion of other underlying conditions.

Obsessive-Compulsive Disorder (OCD) has a 2–3% worldwide prevalence [1], [2] and is characterized by excessive preoccupations (obsessions) associated with specific rituals (compulsions). Current treatments to alleviate symptoms include cognitive behavioral therapy (CBT) and SSRIs (selective serotonin re-uptake inhibitors) [3], [4]. In cases where patients do not respond to CBT and/or medication, other interventions have been used, such as deep brain stimulation (DBS) [5]–[7]. Since abnormalities in the glutamatergic system have also been proposed in the pathology of OCD, some NMDA receptor antagonists, namely ketamine and memantine, are being tested as possible therapies [4], [8].

Previously considered under the spectrum of anxiety disorders, OCD is now categorized with other obsessive-compulsive related disorders, including trichotillomania (TTM), body dysmorphic disorder, skinpicking, and hoarding disorder, in the recently revised DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, 2013*). Re-classification is based on behavioral similarities and common features of these disorders, namely obsessive preoccupations and repetitive actions. Such categorization is thought to help guide diagnostic criteria and ensure consistency among healthcare providers. However, a more "biologically-valid framework" for mental disorders has been proposed by the US National Institute of Mental Health (NIMH). This new research framework, designated Research Domain Criteria (RDoC), aspires to emphasize mental disorders as biological constructs that span specific domains of behavior, emotion, and cognition (*e.g.*, social interactions, mood, etc.) that can co-occur in a range from normal to extreme. Future goals include using brain mapping, genetic studies, and modeling of cognitive aspects of mental disorders to help understand and therapeutically target the biological bases of complex neuropsychiatric diseases, including OCD. Animal models can contribute to this dimensional approach by providing means to test biological causality.

This review will discuss several areas of research □ neurophysiology, behavior, and genetics □ in animal models of compulsive/repetitive behavior that can serve as foundations for understanding the basic biology of such behavior.

Neurophysiology of OCD – insights from animal models

- CORTICO-STRIATAL-THALAMO-CORTICAL CIRCUITRY (CSTC)

One of the most replicated findings in human OCD studies is the involvement of cortico-striatalthalamo-cortical circuitry (CSTC) [9], [10]. Human striatum is anatomically subdivided by the internal capsule into caudate nucleus and putamen. Caudate nucleus receives mostly excitatory inputs from orbitofrontal, prefrontal and cingulate cortex areas, whereas putamen receives the majority of its cortical inputs from sensorimotor areas [11], [12]. Increased activity in the anterior cingulate/caudal medial prefrontal cortex, orbitofrontal cortex (OFC) and caudate region (areas implicated in some aspects of executive function and evaluation of significance [12]) has been reported in OCD [13]. How can we connect these findings with behavioral manifestations in OCD? A major advantage of studying animal models is the ability to directly manipulate neural circuits and test

behavioral outcomes. Therefore, it is important to define neuroanatomical parallels between CSTC structures in humans and mice so that their (dys)function and relevance to OCD can be tested (Fig.1).

Based on behavioral studies in mice, a loose definition of limbic, associative and motor striatal territories can be adopted, as well as definition of their respective sources of cortical inputs [14], [15]. Mouse mPFC seems organized in a dorsal–ventral gradient of connectivity such that dorsal-PL projects to dorsomedial regions of striatum (DMS, associative striatum) and ventral-PL projects mainly to ventral striatum (limbic striatum)[16]. These ventromedial striatum regions are considered to be caudate-like in rodents [15], [17], [18]. Finally, motor cortex projects mainly to the mouse dorsolateral striatum (DLS), a region considered similar to the primate putamen [15], [17]. It should be emphasized, however, that despite some functional resemblance, there are important species-specific differences, with mice lacking certain neuroanatomical connectivity possessed by primates (for detailed review please see [14]–[17], [19], [20]).

Like the connectivity patterns observed between cortex and striatum, it is believed that downstream basal ganglia (BG) territories are equally well-organized into associative, limbic and sensorimotor regions. Evidence for this cognitive, emotional and motor organization of BG has been made clear through groundbreaking monkey studies [21], [22]. Bicuculline injections into limbic regions of *globus pallidus* (GP) can induce stereotypies, whereas injections into associative regions can lead to attention deficit and/or hyperactivity. Abnormal movements are not observed unless injections occur within sensorimotor regions of GP, suggesting a particular role for associative and limbic territories in the etiology of compulsive behaviors [21].

In rats, DLS is known to be required for grooming syntax [23]–[26], a normal physiological behavior that appears hyperactive in some OCD-mouse models with self-injurious over-grooming [27], [28]. Can dysfunction of the rodent putamen-like structure, DLS, and seemingly purposeless repetitive routines/stereotypies be related to caudate dysfunction and compulsive behaviors in human OCD? Neurophysiology and behavior studies suggest that DLS and DMS regions support an important behavioral transition in rodents: intentional goal-directed actions, encoded by DMS, that, upon repetition, become habitual automated responses, encoded by DLS [16]–[18], [29]–[33]. A dynamic competition is thought to take place between these two striatal regions during habit acquisition. DMS activation likely guides the expression of behaviors as they transform into habits, but once this DMS activity drops, DLS circuits assume control over behaviors [34]. Evidence has emerged from DMS lesioned mice that show tendencies for action generalization strategies □ *i.e*., habitual responses □ indicating that DLS guides behavioral performance when DMS function is compromised [29]. This might help to explain results from a recent clinical study where a deficit in goal-directed control and an overreliance on habits is observed in OCD patients [35]. Dysfunctional associative circuitry could hence be affecting the performance of related sensorimotor circuits.

- STRIATUM MICROCIRCUITRY

Medium spiny neurons (MSNs) are the major cell type within the striatum and can be classified into two main subtypes: striatonigral (D1+ direct-pathway cells; project to SNr) and striatopallidal (D2+ indirectpathway cells; project to GP) [36], [37]. The classical model of basal ganglia motor output function postulates that direct-pathway activation facilitates movement and indirect-pathway activation suppresses movement [38]–[41]. Validity of this model has been called into question through recent mouse studies showing concurrent activation of both pathways during action initiation [42], while other recent mouse studies substantiate the classical model [43]. One possible unifying explanation for these disparate results is that activation of both pathways could be important for specific action selection and initiation: direct-pathway cells could be activated to promote a specifically intended motor program, whereas indirect-pathway cells could be concomitantly activated in order to inhibit specific competing motor programs. In this scenario, one could imagine that nonspecific activation of all indirect-pathway cells could lead to inhibition of all motor programs, as in bradykinesia, whereas overall ablation or silencing of all indirect-pathway cells could lead to hyperkinesia.

In addition to MSNs, the striatum contains three main classes of interneurons that regulate striatal function: fast-spiking (FS) interneurons that are cytochemically PV+ and project to both MSN types but are more likely to target D1+ cells; low-threshold spiking (LTS) interneurons; and cholinergic (ChAT+) interneurons [36], [37], [44], [45] (Fig.2). Despite their relative sparsity, these interneurons can strongly modulate MSNs, thereby greatly influencing final output of the striatum [46]. In fact, in patients with Tourette's syndrom (TS), a disorder often comorbid with OCD, histology of post-mortem striatal tissues revealed decreased density of PV+ and ChAT+ interneurons in caudate and putamen regions [47], [48]. A potential bridge between TS, OCD, and striatal interneuron dysfunction is also suggested by a study, summarized below, where increased MSN activity and lower striatal PV+ cell density were observed in a mouse model of OCD [49]. Although interneuron dysfunction is a less commonly explored hypothesis in animal models of OCD, it is possible that defective interneuron activity might result in or contribute to abnormal striatum activation associated with pathology. It will be important to define in future studies exactly how these interneuron populations modulate striatum output and how, if at all, they are relevant to OCD.

- HYPERACTIVE CIRCUITRY IN OCD

Among the variety of tools that have recently become available to study neural circuits, one holds great promise: optogenetics [50], [51]. Using this strategy, a recent study directly tested the CSTC hyperactivity hypothesis of OCD [52]. The authors expressed and activated ChR2 in mouse *medial*OFC excitatory neurons that project to ventro-medial striatum. Surprisingly, repeated direct hyperactivation of these cells over five consecutive days led to a progressive increase in repetitive grooming. Acute stimulation, however, was not sufficient to induce increased grooming patterns, suggesting the need for a reinforcing circuitry loop in repetitive OCD-like behaviors.

Another finding in support of the CSTC hyperactivity hypothesis is derived from the *Slitrk5*-knockout mouse model. Staining for FosB, a cellular marker of sustained neuronal activity [53], showed its levels to be increased specifically at OFC, suggesting hyperactivity of this brain region. These results may be particularly relevant to understanding the increased metabolic activity observed in OFC and caudate nucleus of OCD patients [54].

A recent study from Thomas Südhof's lab shows that imbalanced basal ganglia activity can clearly influence the formation of repetitive motor routines [55]. In this study, the authors showed that disinhibition of direct-pathway MSNs in ventral striatum can enhance the formation of repetitive motor routines, observed as increased rotarod learning. Even though direct-pathway MSNs in dorsal striatum are important for overall motor coordination, the observed phenotype is independent of cerebellum or dorsal striatum. Such studies support the idea that different symptom dimensions might be associated with distinct neural substrates [56]. Proper balance between direct- and indirect-pathway activity along with proper dynamic interaction between different striatal subregions seem crucial for normal behavior. Repetitive behaviors observed in OCD may arise from brief but repeated bursts of neuronal activity in specific brain areas, facilitating their re-activation by subsequent stimuli.

- A DYSFUNCTION OF TERMINATION (STOP SIGNAL) IN OCD?

CSTC hyperactivity in OCD and consequent propagation of positive-feedback loops could emerge from augmented sensitivity to initial triggering stimuli (too much START signal) or due to deficiency in motivation to break the initiated behavioral ritual (too little STOP signal). Recent work tried to address this question by studying security-related behaviors that arise from exposure to contamination cues [57]. Results indicate that the cause of patients' symptoms relies on dysfunctional termination (STOP signal) rather than dysfunctional activation (START signal). The root cause of this improper action termination may be weakened "motivational satiety". In line with this hypothesis, a recent report from Ann Graybiel's lab corroborates an insufficiency of the STOP signal and reinforces the importance of the OFC-striatal pathway in the genesis of compulsive behaviors [49]. Chronic electrophysiological recordings in *Sapap3*-KO mice, an established model of OCD-like behaviors (see below), reveal abnormally high spontaneous MSN activity in the centromedial striatum, in further support of the hyperexcitability hypothesis. These mice not only show deficits in adaptive grooming response during a conditioned grooming task (tone-delay-water), but also show impaired striatal physiology, where MSNs are incapable of adapting and refining their activity during task shaping. These findings point towards acquired maladaptive behavior to an initially neutral stimulus. *Sapap3*-KO mice further show reduced striatal FS interneuron density, suggesting that deficient inhibition within striatum might contribute to MSN hyperactivity [58]. Interestingly, optogenetic stimulation of lOFC somata or afferent terminals in the striatum can successfully alleviate conditioned over-grooming as well as naturally occurring compulsive grooming in the *Sapap3*-KO mice [49]. *In vivo* recording data demonstrates that stimulation of lOFC-striatal pathway increases FS-MSN inhibitory efficacy and helps to restore behavioral inhibition, presumably through increasing striatal inhibitory tone. Given that FS interneurons synapse onto both MSN subtypes but are more likely to target direct-pathway MSNs [45], it is tempting to speculate

that the altered feed-forward inhibition of striatal MSNs observed in *Sapap3*-KO mice more profoundly affects the direct-pathway to lead to disinhibition of specific motor compulsions.

Although the aforementioned animal studies from the Hen [52] and Graybiel labs [49] might at first appear discrepant □ MO stimulation increases grooming while LO stimulation reduces grooming □ it is critical to note that results are derived from different cell populations. Importantly, both these studies implicate OFC dysregulation in compulsive behaviors and suggest that *lateral* OFC and *medial* OFC might be playing different roles in OCD, as earlier hypothesized by Rauch, *et al* [59].

Behavioral studies in OCD-animal models

To evaluate OCD-like behaviors in animal models, specific behavioral paradigms have been developed in the last decades to assess multiple factors, such as anxiety and compulsivity. Tests of anxiety include open field and elevated zero or plus mazes, where patterns of exploratory activity can be evaluated by quantifying time spent in typically anxiogenic open areas *versus* time spent in perimeter or protected areas. Despite the relevance of anxiety in OCD, it is important to emphasize that anxiety is an equally relevant trait to other non-OCD spectrum disorders. Similarly, it is important to emphasize that OCD itself shares important links with other anxiety disorders, although this is not true for all other OC-spectrum disorders [60]. Additional behavioral paradigms focus on compulsive behaviors, considering them as closer translational manifestations of the human condition. Time spent in repetitive tasks, such as non-nutritive chewing, grooming, or shifting/digging in bedding as in the marble burying test, can be simply observed. Other more complex tests involve learned tasks where presence of compulsive traits can be tested under specific conditioning paradigms. The delayed reinforcement task helps to dissociate impulsive choices from the motor impulsivity observed in OCD. In addition, reversal learning tasks or serial reaction time tasks, in which duration, frequency and perseverance of choices is assessed, can distinguish between impulsive and compulsive responses (for detailed reviews, please see [14], [61]).

Animal models of neuropsychiatric disorders should exhibit at least one of the following characteristics: atypical behaviors that resemble human symptomatology (face validity); shared biological grounds with human conditions, such as mutation of a specific gene (construct validity); or successful respose to the same therapeutic agents prescribed to patients, allowing outcome predictability (predictive validity). Several animal models exhibit OCD-like behaviors and have been useful in underpinning distinct aspects of the neurobiology of OCD. The first genetic mouse model presenting face, construct, and predictive validity for OCD was published in 2007 [28]. These mice lack SAPAP3, a scaffolding protein normally enriched at cortico-striatal glutamatergic synapses. Besides impaired cortico-striatal transmission, these mice display self-injurious grooming and increased anxiety as assessed by the open field, elevated zero maze and dark light emergence tests. Both anxiety and compulsive grooming can be partially alleviated by fluoxetine treatment. An interesting key finding is that restoring SAPAP3 expression in the striatum alone can rescue self-injurious grooming and cortico-striatal transmission, further emphasizing the striatum's role in compulsive behaviors. A more recent study in this OCD mouse model suggests exaggerated stimulus-response habit formation. When mice are

conditioned to groom in response to delivery of a water-drop to the forehead preceded by a tone, *Sapap3*-KO mice promptly groom in response to the tone and are unable to re-shape this acquired behavior, even when water-drop delivery is subsequently omitted. This behavior contrasts sharply with wild-type mice that respond primarily to the water-drop rather than the tone, suggesting an abnormal adaptive process to conditioned stimuli in OCD.

Other interesting findings have emerged from the deletion of the *Slitrk5* gene in mice. SLITRK family proteins are involved in neurite outgrowth [62] and absence of SLITRK5 protein in mice leads to increased anxiety, as assessed by elevated plus-maze and open field tests, and compulsivity, as assessed by increased marble burying behavior and self-injurious grooming [27]. Chronic fluoxetine treatment can alleviate this phenotype. Thus, *Slitrk5*-KO mice provide researchers with another promising mouse model for studying OCD-like behaviors.

Genetic studies of OCD – insights from human patients and animal models

Common acts carried out by OCD patients involve actions such as checking, washing and ordering. The fact that these themes are not random and occur consistently in patients across distinct socio-cultural backgrounds worldwide raises the possibility of common genetic bases [63], [64]. In fact, twin studies of obsessive-compulsive disorder also support this prediction, yielding the strongest evidence for genetic contribution in OCD. An extensive review work published by van Grootheest, *et al.* [65] concluded that, using a dimensional approach for twin studies, OCD symptoms are highly heritable, ranging from 45–65% in childhood-onset OCD and 27–47% in adult-onset OCD.

- SLC1A1/EAAC1

The first genome-wide linkage study for OCD was carried out in 2002 to identify susceptible chromosomal regions for early-onset OCD [66]. The results suggest a link to chromosomal region 9p24 with the closest gene being *SLC1A1* (Solute Carrier Family 1, Member 1), a glutamate transporter also known as *EAAC1* [67]. Since then, several linkage studies have supported OCD association with this genomic region, but with modest cross-validation, as different studies support different single nucleotide polymorphisms (SNPs) associated with the disease [68]–[70]. An *EAAC1*-KO mouse was first generated and published in 1997, albeit with apparently nominal relevance to the study of OCD neurobiology and behavior [71]. *EAAC1*-KO mice develop dicarboxylic aminoaciduria and show reduced spontaneous locomotion in the open field. Later studies report reduced neuronal glutathione levels and age-dependent neurodegeneration, evidenced by cortical thinning and ventricular enlargement [72], [73]. Despite the absence of a strong OCD-like phenotype in *EAAC1*-KO mice, there remain several studies implicating the human *EAAC1* gene in at least some cases of OCD [68], [74]. It is plausible that EAAC-1 functional deficits are not well recapitulated in mice or that this gene is involved, rather, in polygenic susceptibility to OCD by interacting with other factors.

- SAPAP AND SLITRK

Recently, an effort has been made to search for common SNPs predisposing individuals to OCD. More than twenty research groups have collaborated to accomplish the first Genome-Wide Association Study (GWAS) for human OCD [75]. Results from this study suggest the involvement of two SNPs located within the *DLGAP1* gene that encodes the SAPAP1 protein. Previously, another member from the same family of proteins, SAPAP3, had been implicated in the *Sapap3*-KO mouse model that exhibits OCD-like behavior (see above) [28], [76]–[78]. Smaller association studies have supported a role for SAPAP3 in human TTM and OCD [79]–[81], reinforcing the idea that proteins from this family might play a role in OCD-related behaviors.

Another group, the OCD Collaborative Genetics Association Study (OCGAS) [82], found association of a marker on chromosome 9 near the *PTPRD* gene, although no genome-wide significance was achieved. The PTPRD protein seems to play a role in regulating development of inhibitory synapses through its interaction with SLITRK3. SLITRKs (SLITRK1-6) are a relatively recently discovered family of proteins [62] that have emerged as candidate genes in neuropsychiatric disorders [83]. Human genetic studies have suggested an association link between *SLITRK1* and Tourette's syndrome, a neuropsychiatric disorder characterized by motor and vocal tics [84]. *Slitrk1*-KO mice display increased anxiety and noradrenergic abnormalities [85], consistent with reports of increased norepinephrine levels in cerebrospinal fluid of TS patients [86]. The hypothesis of SLITRK1 involvement in TS and the fact that SLITRKs are highly expressed in mammalian CNS [87] motivated the generation of a *Slitrk5*-KO mouse to explore possible phenotypes [27]. As described earlier in this review, *Slitrk5*-KO mice display OCD-like behaviors and impaired cortico-striatal circuitry. Given that both *Slitrk5*- and *Sapap3*-KO mice display impaired cortico-striatal transmission and OCD-like behaviors that are responsive to treatment with fluoxetine, one of the pharmacological agents used in OCD patients, it would be interesting to address whether these mutations of these genes lead to a common defects in molecular pathway or circuitry function.

- HOXB8

Another interesting hypothesis concerning OCD etiology comes from genetic deletion of the *Hoxb8* gene in mice, which suggests a link between the immune system and OCD expression [88]. This transcription factor is detected in the adult brain, being expressed in bone marrow-derived microglia cells that migrate into the brain's OFC, cingulate cortex, limbic system, and other regions, during the postnatal period [88], [89]. *Hoxb8*-KO mice display self-injurious and cage-mate excessive grooming that can be rescued by bone marrow transplantation from wild-type mice. Although this link between the immune system and OCD might seem puzzling at first, it has previously been shown that microglia play roles in regulating neuronal cell death and in modulating neural networks [90], [91]. In fact, a subset of children with OCD can experience worsening of symptoms following Streptococcal infection. One brain region that is affected in Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) is the basal ganglia (for recent review on immunobiology of OCD and PANDAS, please see [92]). Although expressed brain-wide in the mouse, HOXB8 is predominantly found in adult

brainstem, olfactory bulb, cortex and striatum [88], [89], the latter two regions being highly implicated in OCD, as discussed earlier.

Although *Hoxb8-*, *Sapap3-* and *Slitrk5*-KO mice have grooming phenotypes that are unique in their biological origins, all genes share an enriched cortico-striatal expression. In regards to human OCD, these mice studies suggest that a commonly shared pathological behavior, compulsivity, may arise from different causal insults that impact the same brain circuits.

- OTHER GENES

Currently approved treatments to alleviate OCD symptoms include medications that modulate the serotonergic system. Although the exact mechanisms are unknown, it is thought that 5-HT_{2C} serotonin receptor agonism might contribute to therapeutic benefits in OCD [93]. Genetic deletion of 5-HT_{2C}-R in mice leads to enhanced sensitivity to induced motor stereotypy and compulsive-like behaviors, such as nonnutritive chewing and increased head-dipping [94]–[97], supporting a serotonergic involvement in compulsivity. In contrast to other OCD models, these mice show less anxiety than wild-type mice in open field, elevated plus maze, novel object, and mirrored chamber tests, suggesting that compulsivity and anxiety symptoms might be dissociable.

Another useful method to look for candidate genes involved in OCD, besides hypothesis-driven gene deletion in mice, is genomic sequencing from animals displaying spontaneously-occurring pathological behaviors. Some dog breeds display OCD-like behaviors, including incessant tail chasing and relentless paw chewing. Given that the dog genome is less complex than the human genome, the first canine OCD GWAS study was recently carried, identifying four synaptic genes with case-only variations (*CDH2*, *CTNNA2*, *ATXN1*, *PGCP*) [98]. Previous studies in mice have shown that *CDH2* gene disruption, while being embryonically lethal, causes synaptic dysfunction in cultured neurons [99], [100].

Together, the ever-expanding genetic studies of human, mouse, and dog seem to converge towards CSTC synaptic dysfunction in OCD pathology (Table 1). Although animal models can never fully recapitulate the human OCD spectrum due to species-specific limitations, they do allow us to precisely study neurobiological mechanisms of gene-linked phenotypes by limiting some of the many confounds inherent to studies of humans, including variability in one's environment and genetic background.

Future perspectives

Much is still to be unraveled in terms of the detailed neurobiology of CSTC circuits in OCD: What neuromodulators are imbalanced? Are OCD compulsions dissociable from obsessions or anxiety in general? What specific ensemble of neurons encode for compulsions' motor programs? And what brain areas initiate the obsession-compulsion process?

Human functional imaging data seem to suggest hyperactivity in orbito-frontal cortex of OCD patients. It is possible that this area could be important for generating specific thoughts that in a normal person are easily resolved by performing a particular act, such as double-

checking something in case of doubt. This behavioral ritual could serve a perfectly banal physiological need. However, OCD patients might have insufficient "motivational satiety" that prevents resolution and proper termination of the obsession.

To answer the many unresolved questions regarding OCD, continued efforts to understand the circuitry involved need to be undertaken, with particular attention to distinct brain regions, cell types, and the roles of modulatory neurotransmitters. Some OCD animal models discussed in this review point towards specific dysregulations that might be relevant as OCD endophenotypes, namely CSTC hyperactivity and dysfunctional task-specific behavioral performance, including in adaptive switching to novel stimulus-reinforcement associations. Despite the limitations in using animal models to study neuropsychiatric disorders, these findings in the evolutionarily conserved CSTC circuitry might be of relevance across DSM diagnoses and help to guide future translational studies.

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References

1. Fontenelle LF, Mendlowicz MV, Versiani M. The descriptive epidemiology of obsessive-compulsive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2006; 30:327–337. [PubMed: 16412548]

2. Ruscio A, Stein D, Chiu W, Kessler R. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry. 2010; 15:53–63. [PubMed: 18725912]

3. Fineberg, Na; Gale, TM. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int. J. Neuropsychopharmacol. 2005 Mar.8(1):107–129. [PubMed: 15450126]

4. Pallanti S, Hollander E. Pharmacological, experimental therapeutic, and transcranial magnetic stimulation treatments for compulsivity and impulsivity. CNS Spectr. 2014 Feb.19(1):50–61. [PubMed: 24176028]

5. Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. Biol Psychiatry. 2010; 67:535–542. [PubMed: 20116047]

6. Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. 2010

7. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J. The nucleus accumbens: A target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. Journal of Chemical Neuroanatomy. 2003; 26:293–299. [PubMed: 14729131]

8. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol. Ther. 2011 Dec.132(3):314–332. [PubMed: 21963369]

9. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr. Clin. North Am. 2000; 23:563–586. [PubMed: 10986728]

10. Ting JT, Feng G. Neurobiology of obsessive-compulsive disorder: Insights into neural circuitry dysfunction through mouse genetics. Current Opinion in Neurobiology. 2011; 21:842–848. [PubMed: 21605970]

11. Krack P, Hariz MI, Baunez C, Guridi J, Obeso Ja. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci. 2010 Oct.33(10):474–484. [PubMed: 20832128]

12. Graybiel, aM; Rauch, SL. Toward a neurobiology of obsessive-compulsive disorder. Neuron. 2000 Nov.28(2):343–347. [PubMed: 11144344]

13. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. British Journal of Psychiatry. 1998; 173:26–37. [PubMed: 9829024]

14. Dalley JW, Cardinal RN, Robbins TW. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci. Biobehav. Rev. 2004 Nov.28(7):771–784. [PubMed: 15555683]

15. Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. Nat. Rev. Neurosci. 2006 Jun.7(6):464–476. [PubMed: 16715055]

16. Voorn P, Vanderschuren LJMJ, Groenewegen HJ, Robbins TW, Pennartz CMa. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 2004 Aug.27(8):468–474. [PubMed: 15271494]

17. Hilário MRF, Costa RM. High on habits. Front. Neurosci. 2008 Dec.2(2):208–217. [PubMed: 19225594]

18. Yin HH, Ostlund SB, Knowlton BJ, Balleine BW. The role of the dorsomedial striatum in instrumental conditioning. Eur. J. Neurosci. 2005 Jul.22(2):513–523. [PubMed: 16045504]

19. Fuster J. The prefrontal cortex-An update-Time is of the essence. Neuron. 2001; 30:319–333. no. C. [PubMed: 11394996]

20. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. Neuron. 2012 Dec.76(6):1057–1070. [PubMed: 23259943]

21. Grabli D, McCairn K, Hirsch EC, Agid Y, Féger J, François C, Tremblay L. Behavioural disorders induced by external globus pallidus dysfunction in primates: I. Behavioural study. Brain. 2004 Sep.127(Pt 9):2039–2054. [PubMed: 15292053]

22. Mink JW. The basal ganglia: Focused selection and inhibition of competing motor programs. Progress in Neurobiology. 1996; 50:381–425. [PubMed: 9004351]

23. Berridge KC. Comparative Fine Structure of Action: Rules of Form and Sequence in the Grooming Patterns of Six Rodent Species. Behaviour. 1990; 113:21–56.

24. Aldridge JW, Berridge KC. Coding of serial order by neostriatal neurons: a 'natural action' approach to movement sequence. J. Neurosci. 1998; 18:2777–2787. [PubMed: 9502834]

25. Berridge KC, Aldridge JW, Houchard KR, Zhuang X. Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. BMC Biol. 2005 Jan.3:4. [PubMed: 15710042]

26. Joyce EM, Iversen SD. Dissociable effects of 6-OHDA-induced lesions of neostriatum on anorexia, locomotor activity and stereotypy: The role of behavioural competition. Psychopharmacology (Berl). 1984; 83:363–366. [PubMed: 6436865]

27. Shmelkov SV, Hormigo A, Jing D, Proenca CC, Bath KG, Milde T, et al. litrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice. Nat. Med. 2010 May; 16(5):598–602. 1p following 602. [PubMed: 20418887]

28. Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding J-D, et al. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature. 2007 Aug.448(7156):894–900. [PubMed: 17713528]

29. Hilario M, Holloway T, Jin X, Costa RM. Different dorsal striatum circuits mediate action discrimination and action generalization. Eur. J. Neurosci. 2012 Apr.35(7):1105–1114. [PubMed: 22487040]

30. Yin HH, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. 2004; 19:181–189. no. August 2003.

31. Yin HH, Knowlton BJ, Balleine BW. Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. Behav. Brain Res. 2006 Jan.166(2):189–196. [PubMed: 16153716]

32. Yin HH, Knowlton BJ. Contributions of striatal subregions to place and response learning. Learn. Mem. 2004; 11(4):459–463. [PubMed: 15286184]

33. Smith KS, Graybiel AM. Investigating habits: strategies, technologies and models. Front. Behav. Neurosci. 2014; 8:39. [PubMed: 24574988]

34. Thorn CA, Atallah H, Howe M, Graybiel AM. Differential Dynamics of Activity Changes in Dorsolateral and Dorsomedial Striatal Loops during Learning. Neuron. 2010; 66(5):781–795. [PubMed: 20547134]

35. Gillan C. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. Am. J. 2011 Jul.:718–726. no.

36. Kreitzer AC, Malenka RC. Striatal plasticity and basal ganglia circuit function. Neuron. 2008 Nov. 60(4):543–554. [PubMed: 19038213]

37. Kreitzer AC. Physiology and pharmacology of striatal neurons. Annu. Rev. Neurosci. 2009 Jan. 32:127–147. [PubMed: 19400717]

38. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990 Jul.13(7):281–285. [PubMed: 1695404]

39. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 1990 Jul.13(7):266–271. [PubMed: 1695401]

40. Albin R, Young A, Penney J. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989; 12(10)

41. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch. Neurol. 2007 Jan.64(1):20–24. [PubMed: 17210805]

42. Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, Costa RM. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature. 2013 Feb.494(7436):238–242. [PubMed: 23354054]

43. Kravitz AV, Freeze BS, Parker PRL, Kay K, Thwin MT, Deisseroth K, Kreitzer AC. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature. 2010 Jul. 466(7306):622–626. [PubMed: 20613723]

44. Bennett BD, Callaway JC, Wilson CJ. Neostriatal Cholinergic Interneurons. 2000; 20(22):8493–8503.

45. Gittis AH, Nelson AB, Thwin MT, Palop JJ, Kreitzer AC. Distinct roles of GABAergic interneurons in the regulation of striatal output pathways. J. Neurosci. 2010 Feb.30(6):2223–2234. [PubMed: 20147549]

46. Tepper JM, Koós T, Wilson CJ. GABAergic microcircuits in the neostriatum. Trends Neurosci. 2004 Nov.27(11):662–669. [PubMed: 15474166]

47. Kalanithi, PS a; Zheng, W.; Kataoka, Y.; DiFiglia, M.; Grantz, H.; Saper, CB., et al. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. Proc. Natl. Acad. Sci. U. S. A. 2005 Sep.102(37):13307–13312. [PubMed: 16131542]

48. Kataoka Y, Kalanithi P. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette syndrome. J. 2010; 518(3):277–291.

49. Burguière E, Monteiro P, Feng G, Graybiel AM. Optogenetic Stimulation of Lateral Orbitofronto-Striatal Pathway Suppresses Compulsive Behaviors. Science (80-.). 2013 Jun.340:1243–1246. no.

50. Tye KM, Deisseroth K. Optogenetic investigation of neural circuits underlying brain disease in animal models. Nat. Rev. Neurosci. 2012 Apr.13(4):251–266. [PubMed: 22430017]

51. Zhang F, Wang L, Boyden ES, Deisseroth K. Channelrhodopsin-2 and optical control of excitable cells. 2006

52. Ahmari SE, Spellman T, Douglass NL, Kheirbek Ma, Simpson HB, Deisseroth K, et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science. 2013 Jun.340(6137): 1234–1239. [PubMed: 23744948]

53. Nestler EJ, Barrot M, Self DW. DeltaFosB: a sustained molecular switch for addiction. Proc. Natl. Acad. Sci. U. S. A. 2001 Sep.98(20):11042–11046. [PubMed: 11572966]

54. Insel TR, Winslow JT. Neurobiology of obsessive compulsive disorder. Psychiatr. Clin. North Am. 1992; 15(4):813–824. [PubMed: 1461798]

55. Rothwell PE, Fuccillo MV, Maxeiner S, Hayton SJ, Gokce O, Lim BK, et al. Autism-associated neuroligin-3 mutations commonly impair striatal circuits to boost repetitive behaviors. Cell. 2014; 158:198–212. [PubMed: 24995986]

56. Pauls DL, Abramovitch A, Rauch SL, Geller Da. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat. Rev. Neurosci. 2014 Jun.15(6):410–424. [PubMed: 24840803]

57. Hinds AL, Woody EZ, Van Ameringen M, Schmidt La, Szechtman H. When too much is not enough: obsessive-compulsive disorder as a pathology of stopping, rather than starting. PLoS One. 2012 Jan.7(1):e30586. [PubMed: 22291994]

58. Burguière E, Monteiro P, Mallet L, Feng G, Graybiel AM. Striatal circuits, habits, and implications for obsessive-compulsive disorder. Curr. Opin. Neurobiol. 2014 Sep.30C:59–65. [PubMed: 25241072]

59. Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn. Sci. 2012 Jan.16(1):43–51. [PubMed: 22138231]

60. Stein DJ, Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G, et al. Should ocd be classified as an anxiety disorder in DSM-V? Depression and Anxiety. 2010; 27:495–506. [PubMed: 20533366]

61. Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A, et al. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacology. 2010; 35:591–604. [PubMed: 19940844]

62. Aruga J, Mikoshiba K. Identification and characterization of Slitrk, a novel neuronal transmembrane protein family controlling neurite outgrowth. Mol. Cell. Neurosci. 2003; 24:117–129. [PubMed: 14550773]

63. Clifford CA, Murray RM, Fulker DW. Genetic and environmental influences on obsessional traits and symptoms. Psychol. Med. 1984; 14:791–800. [PubMed: 6545413]

64. Hollander E, Kim S, Khanna S, Pallanti S. Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. CNS Spectr. 2007:1–10.

65. van Grootheest D. Twin studies on obsessive–compulsive disorder: a review. Twin Res. 2005; 8(5):450–458.

66. Hanna GL, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, et al. Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. Am. J. Med. Genet. - Neuropsychiatr. Genet. 2002; 114:541–552.

67. Rothstein JD, Martin L, Levey AI, Dykes-Hoberg M, Jin L, Wu D, et al. Localization of neuronal and glial glutamate transporters. Neuron. 1994; 13:713–725. [PubMed: 7917301]

68. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. Arch. Gen. Psychiatry. 2006; 63:769–776. [PubMed: 16818866]

69. Wendland JR, Moya PR, Timpano KR, Anavitarte AP, Kruse MR, Wheaton MG, et al. A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder. Arch. Gen. Psychiatry. 2009; 66:408–416. [PubMed: 19349310]

70. Wang Y, Adamczyk A, Shugart YY, Samuels JF, Grados MA, Greenberg BD, et al. A screen of SLC1A1 for OCD-related alleles. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 2010; 153:675–679.

71. Peghini P, Janzen J, Stoffel W. Glutamate transporter EAAC-1-deficient mice develop dicarboxylic aminoaciduria and behavioral abnormalities but no neurodegeneration. EMBO J. 1997; 16:3822–3832. [PubMed: 9233792]

72. Aoyama K, Suh SW, Hamby AM, Liu J, Chan WY, Chen Y, Swanson RA. Neuronal glutathione deficiency and age-dependent neurodegeneration in the EAAC1 deficient mouse. Nat. Neurosci. 2006; 9:119–126. [PubMed: 16311588]

73. Wu K, Hanna G, Rosenberg D, Arnold P. The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder. Biochem. Behav. 2012; 100(4):726–735.

74. Wu H, Wang X, Xiao Z, Yu S, Zhu L, Wang D, et al. Association between SLC1A1 gene and early-onset OCD in the han chinese population: A case-control study. J. Mol. Neurosci. 2013; 50:353–359. [PubMed: 23564280]

75. Stewart SE, Yu D, Scharf JM, Neale BM, Fagerness Ja, Mathews Ca, et al. Genome-wide association study of obsessive-compulsive disorder. Mol. Psychiatry. 2013 Jul.18(7):788–798. [PubMed: 22889921]

76. Wan Y, Feng G, Calakos N. Sapap3 deletion causes mGluR5-dependent silencing of AMPAR synapses. J. Neurosci. 2011 Nov.31(46):16685–16691. [PubMed: 22090495]

77. Wan Y, Ade KK, Caffall Z, Ilcim Ozlu M, Eroglu C, Feng G, Calakos N. Circuit-selective striatal synaptic dysfunction in the Sapap3 knockout mouse model of obsessive-compulsive disorder. Biol. Psychiatry. 2014 Apr.75(8):623–630. [PubMed: 23414593]

78. Chen M, Wan Y, Ade K, Ting J, Feng G, Calakos N. Sapap3 deletion anomalously activates short-term endocannabinoid-mediated synaptic plasticity. J. Neurosci. 2011 Jun.31(26):9563–9573. [PubMed: 21715621]

79. Züchner S, Wendland JR, Ashley-Koch AE, Collins AL, Tran-Viet KN, Quinn K, et al. Multiple rare SAPAP3 missense variants in trichotillomania and OCD. Molecular psychiatry. 2009; 14(1): 6–9. [PubMed: 19096451]

80. Bienvenu OJ, Wang Y, Shugart YY, Welch JM, Grados MA, Fyer AJ, et al. Sapap3 and pathological grooming in humans: Results from the OCD collaborative genetics study. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 2009; 150(5):710–720.

81. Boardman L, Van Der Merwe L, Lochner C, Kinnear CJ, Seedat S, Stein DJ, et al. Investigating SAPAP3 variants in the etiology of obsessive-compulsive disorder and trichotillomania in the South African white population. Compr. Psychiatry. 2011; 52(2):181–187. [PubMed: 21295225]

82. Mattheisen M, Samuels JF, Wang Y, Greenberg BD, Fyer aJ, McCracken JT, et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol. Psychiatry. 2014 May.:1–8. no. October 2013. [PubMed: 24362539]

83. Proenca C, Gao K, Shmelkov S. Slitrks as emerging candidate genes involved in neuropsychiatric disorders. Trends. 2011; 34(3):143–153.

84. Abelson JF, Kwan KY, O'Roak BJ, Baek DY, Stillman AA, Morgan TM, et al. Sequence variants in SLITRK1 are associated with Tourette's syndrome. 2005; 310:317–320.

85. Katayama K, Yamada K, Ornthanalai VG, Inoue T, Ota M, Murphy NP, Aruga J. Slitrk1-deficient mice display elevated anxiety-like behavior and noradrenergic abnormalities. Mol. Psychiatry. 2010; 15:177–184. [PubMed: 18794888]

86. Leckman JF. Tourette's syndrome. Lancet. 2002 Nov.360(9345):1577–1586. [PubMed: 12443611]

87. Aruga J, Yokota N, Mikoshiba K. Human SLITRK family genes: genomic organization and expression profiling in normal brain and brain tumor tissue. Gene. 2003; 315:87–94. [PubMed: 14557068]

88. Greer JM, Capecchi MR. Hoxb8 is required for normal grooming behavior in mice. Neuron. 2002 Jan.33(1):23–34. [PubMed: 11779477]

89. Chen S-K, Tvrdik P, Peden E, Cho S, Wu S, Spangrude G, Capecchi MR. Hematopoietic origin of pathological grooming in Hoxb8 mutant mice. Cell. 2010 May; 141(5):775–785. [PubMed: 20510925]

90. Stephan AH, Barres BA, Stevens B. The Complement System: An Unexpected Role in Synaptic Pruning During Development and Disease. Annual Review of Neuroscience. 2012; 35(1):369–389.

91. Aguzzi A, Barres BA, Bennett ML. Microglia: Scapegoat, Saboteur, or Something Else? Science (80-.). 2013; 339(6116):156–161.

92. Murphy TK, Kurlan R, Leckman J. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with Streptococcus, and related disorders: a way forward. J. Child Adolesc. Psychopharmacol. 2010 Aug.20(4):317–331. [PubMed: 20807070]

93. Goddard AW, Shekhar A, Whiteman AF, McDougle CJ. Serotoninergic mechanisms in the treatment of obsessive-compulsive disorder. Drug Discov. Today. 2008 Apr.13(7–8):325–332. [PubMed: 18405845]

94. Chou-Green JM, Holscher TD, Dallman MF, Akana SF. Compulsive behavior in the 5-HT2C receptor knockout mouse. Physiol. Behav. 2003 Apr.78(4–5):641–649. [PubMed: 12782219]

95. Abdallah L, Bonasera SJ, Hopf FW, O'Dell L, Giorgetti M, Jongsma M, Carra S, et al. Impact of serotonin 2C receptor null mutation on physiology and behavior associated with nigrostriatal dopamine pathway function. J. Neurosci. 2009; 29:8156–8165. [PubMed: 19553455]

96. Giorgetti M, Tecott LH. Contributions of 5-HT2C receptors to multiple actions of central serotonin systems. European Journal of Pharmacology. 2004; 488:1–9. [PubMed: 15044029]

97. Heisler LK, Zhou L, Bajwa P, Hsu J, Tecott LH. Serotonin 5-HT(2C) receptors regulate anxiety-like behavior. Genes. Brain. Behav. 2007 Jul.6(5):491–496. [PubMed: 17451451]

98. Tang R, Noh H, Wang D, Sigurdsson S, Swofford R, Perloski M, et al. Candidate genes and functional noncoding variants identified in a canine model of obsessive-compulsive disorder. Genome Biol. 2014; 15(3):R25. [PubMed: 24995881]

99. Pielarski KN, van Stegen B, Andreyeva A, Nieweg K, Jüngling K, Redies C, Gottmann K. Asymmetric N-Cadherin Expression Results in Synapse Dysfunction, Synapse Elimination, and Axon Retraction in Cultured Mouse Neurons. PLoS One. 2013; 8

100. Radice GL, Rayburn H, Matsunami H, Knudsen KA, Takeichi M, Hynes RO. Developmental defects in mouse embryos lacking N-cadherin. Dev. Biol. 1997; 181:64–78. [PubMed: 9015265]

101. Alexander G, DeLong MR, Strick P. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. 1986

102. Ramanathan S, Hanley JJ, Deniau J-M, Bolam JP. Synaptic convergence of motor and somatosensory cortical afferents onto GABAergic interneurons in the rat striatum. J. Neurosci. 2002 Sep.22(18):8158–8169. [PubMed: 12223570]

103. Berke JD. Functional properties of striatal fast-spiking interneurons. Front. Syst. Neurosci. 2011 Jan.5:45. no. June. [PubMed: 21743805]

104. Bennett B, Bolam J. Synaptic input and output of parvalbumin-immunoreactive neurons in the neostriatum of the rat. Neuroscience. 1994; 62(3):707–719. [PubMed: 7870301]

105. Koós T, Tepper JM. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. Nat. Neurosci. 1999 May; 2(5):467–472. [PubMed: 10321252]

106. Wilson CJ. GABAergic inhibition in the neostriatum. Prog. Brain Res. 2007 Jan.160:91–110. [PubMed: 17499110]

107. Izzo PN, Bolam JP. Cholinergic synaptic input to different parts of spiny striatonigral neurons in the rat. J. Comp. Neurol. 1988; 269:219–234. [PubMed: 3281983]

108. Koós T, Tepper JM. Dual cholinergic control of fast-spiking interneurons in the neostriatum. J. Neurosci. 2002 Jan.22(2):529–535. [PubMed: 11784799]

109. Tepper JM, Wilson CJ, Koós T. Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons. Brain Res. Rev. 2008 Aug.58(2):272–281. [PubMed: 18054796]

110. Gertler TS, Chan CS, Surmeier DJ. Dichotomous anatomical properties of adult striatal medium spiny neurons. J. Neurosci. 2008 Oct.28(43):10814–10824. [PubMed: 18945889]
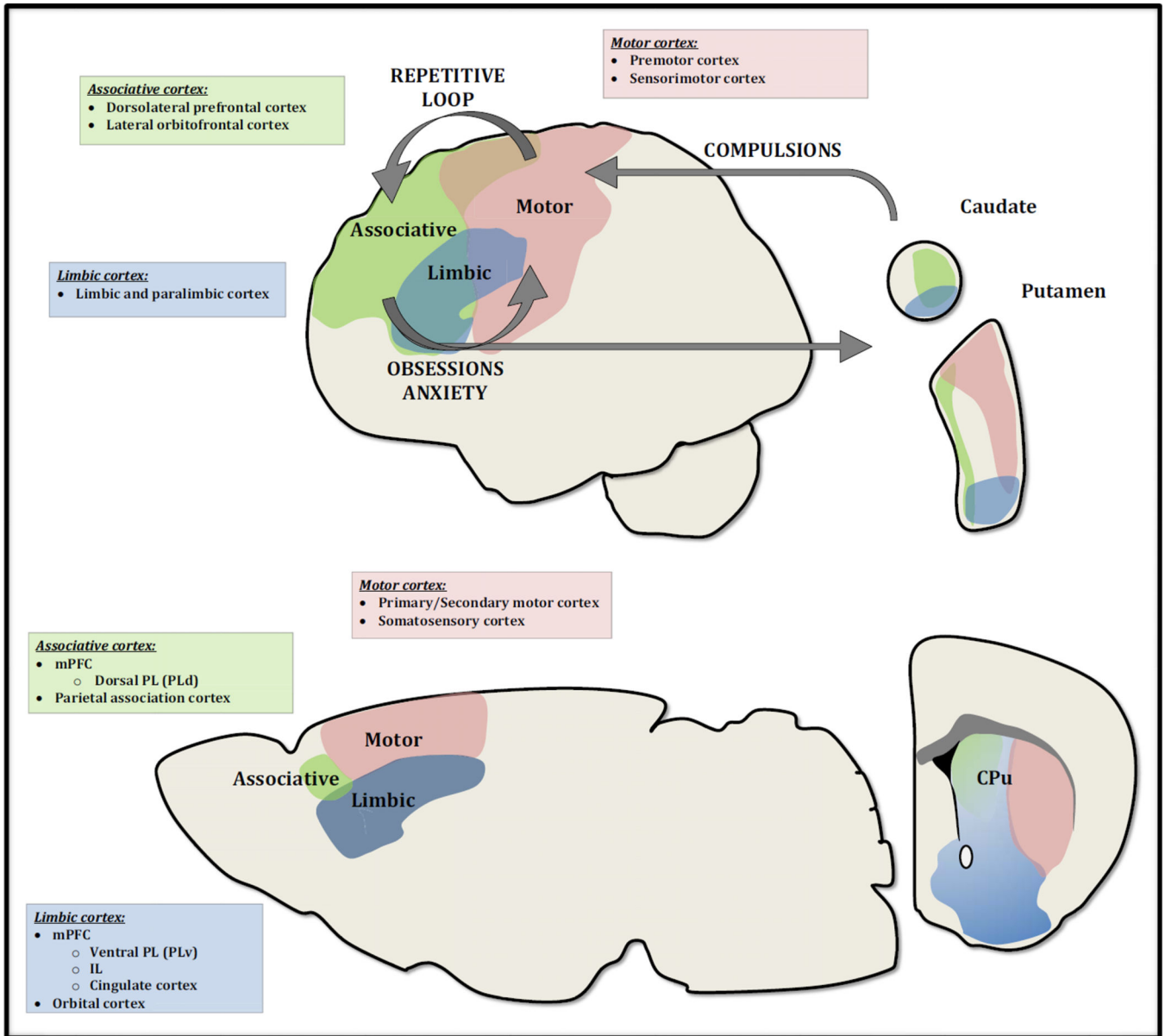
Figure 1. Simplified neuroanatomical model of cortico-striatal circuitry within the human and mouse brain

Motor: Human motor cortex is represented here by premotor and sensorimotor cortical regions that mainly project to posterolateral putamen [11]. Mouse motor cortex is represented here by somatosensory and motor cortex that mainly project to dorso-lateral striatum region [16]. Associative: Human associative cortex, represented here by the dorsolateral PFC and lateral OFC, projects to the caudate and anteromedial portion of the putamen [11]. Mouse associative cortex is represented here by dorsal prelimbic and parietal association cortices that mainly project to dorso-medial striatum region [15]. Limbic: Human limbic cortex, represented here by the paralimbic and limbic cortices (including entorhinal cortexarea28, perirhinal cortex-area35, medial OFC-area11, anterior cingulate cortex-area24) [11], [101], projects to the ventral striatum (ventral region of the caudate

nucleus and putamen, including nucleus accumbens - NAcc). Mouse limbic cortex is represented here by OFC and PFC (ventral prelimbic, infralimbic and cingulate cortices), that mainly project to ventromedial striatum region (including NAcc) [15], [16]. Human associative and limbic circuits are implicated in stimuli significance and might generate obsessive thoughts that cause anxiety. Interconnections with motor cortex and basal ganglia circuits then lead to compulsive action execution. Based on the perceived outcome, actions can be reinforced and propagated through this repetitive loop. All regions depicted are representative and are not intended to provide accurate anatomical locations.
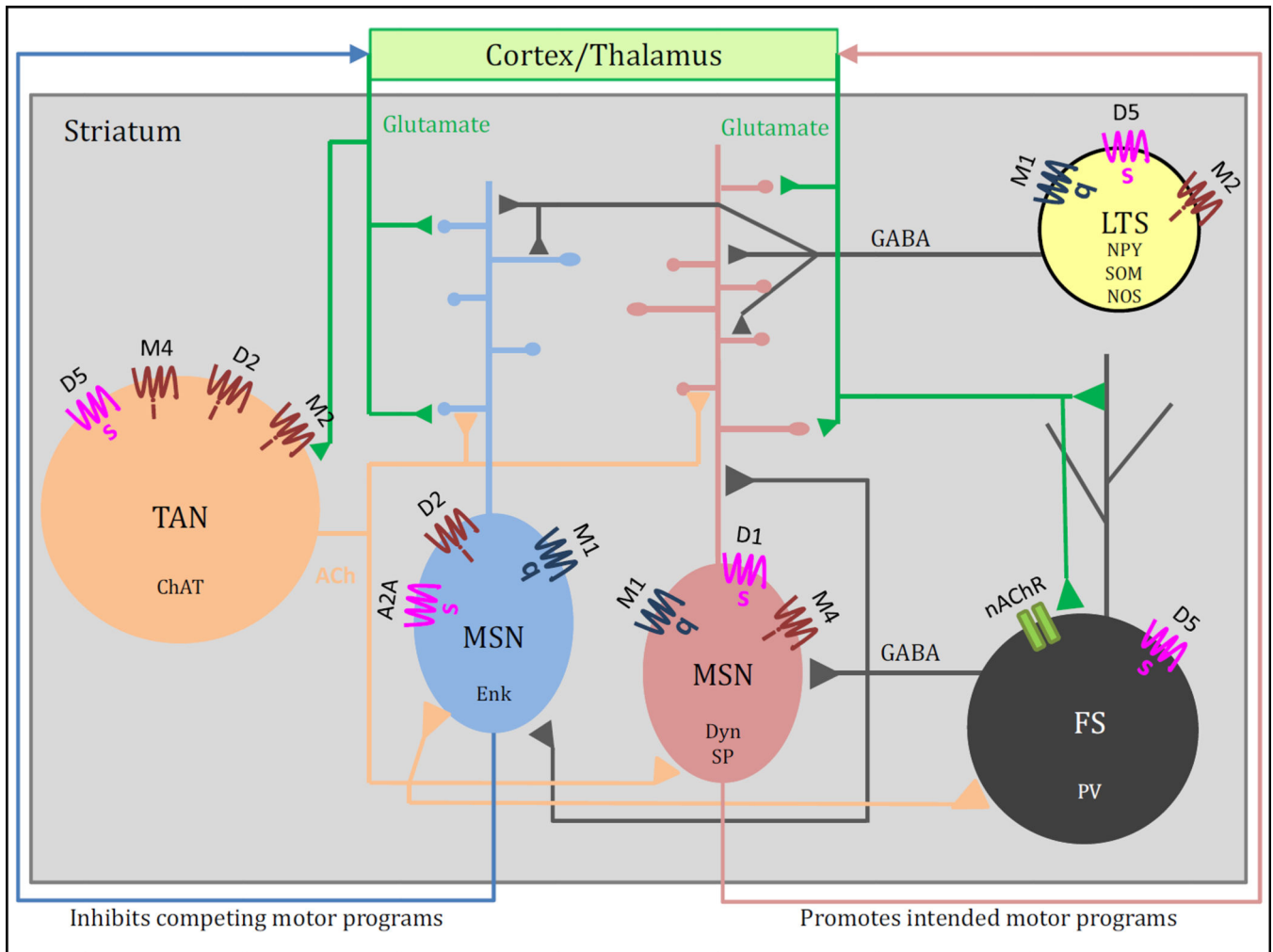
Figure 2. Representation of intrastriatal microcircuitry

Cortico- and thalamo-striatal excitatory axons target the dendritic spines of MSNs as well as dendritic shafts and soma of striatal interneurons. FS interneurons receive more cortical contacts and are more responsive to cortical inputs than MSNs [102], [103]; FS interneurons synapse proximally onto both MSN types [104] with a bias towards direct-pathway D1+MSNs [45]; FS interneurons also synapse with other FS cells but not LTS or TANs [45]. LTS interneurons send sparse inhibitory projections onto MSN dendrites [45], [105], [106]. TANs send inputs to dendritic spines, shafts and somata of MSNs [107] and provide powerful excitatory cholinergic input to FS interneurons [108], [109]. D1+MSNs have more elaborate dendritic arbors [110] and their axons project to SNr [37] (not represented); this direct-pathway promotes the execution of intended motor programs [42]. D2+MSNs project to GP [37] (not represented); this indirect-pathway may inhibit the execution of competing motor programs [42]. GPCRs (G protein–coupled receptors) are depicted with their associated G-protein: Gs (pink), Gi (brown), Gq (blue). M- muscarinic ACh receptors; nAChR- ionotropic nicotinic ACh receptor; D- dopamine receptors; A2A- A2A adenosine receptor; ChAT- choline acetyltransferase; Enk- enkephalin; SP- substance P; Dyn-

dynorphin; PVparvalbumin; SOM- somatostatin; NPY- neuropeptide Y; NOS- nitric oxide synthase.

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Table 1

Candidate genes from animal models with OCD-like behaviors

Genes listed in this table have emerged from human sequencing studies or animal single gene KO studies that resulted in OCD-like phenotypes.

Gene	Genetic evidence	Behavioral phenotype	Neurophysiology	Notes	References
HOXB8	- Global Hoxb8-KO mice with relevant phenotype - Conditional-KO mice (hematopoietic cells) exhibit the global KO phenotype	- Self-injurious grooming - Cage mate over-grooming	- Hoxb8 expressed in bone-marrow derived microglia that migrate into brain OFC, cingulate cortex and basal ganglia regions	-	Wild-type bone marrow transplantation rescues excessive grooming KO bone marrow transplantation induces excessive grooming in WT	[88]–[89]
SAPAP3	- Global Sapap3-KO mice with strong phenotype - Two SNPs located in Sapap1 (family member) found in human OCD GWAS study	- Self-injurious grooming - Increased anxiety (open-field, elevated zero maze and dark light emergence) - Deficit in adaptive grooming response during conditioning task	- Sapap3 mainly expressed in neocortex, striatum, hippocampus and thalamus - Impaired cortico-striatal function (reduced fEPSP, mEPSC and AMPA/NMDA ratio; increased silent synapses and eCB-LTD) - Increased spontaneous MSN firing activity in centromedial striatum - Reduced interneuron PV number in centromedial striatum	-	Striatum infection using lentivirus-Sapap3 rescues self-injurious grooming and fEPSP Fluoxetine treatment partially alleviates compulsive grooming and anxiety	[28], [49], [75]–[78]
SLITRK5	- Global Slitrk5-KO mice with strong phenotype	- Self-injurious grooming - Increased anxiety (open-field, elevated plus maze)	- Slitrk5 mainly expressed in neocortex, striatum and hippocampus	-	Fluoxetine alleviates over-grooming	[27]

Gene	Genetic evidence	Behavioral phenotype	Neurophysiology	Notes	References
SLC1A1/EAAC1	- Human OCD genetic studies - EAAC1-null mice show modest phenotype	- Compulsive-like behavior (marble burying test) - Human OCD - EAAC1-KO mice show cognitive and motivational impairment at old age - Reduced spontaneous locomotion in the open field	- Impaired cortico-striatal function (reduced fEPSP) - OFC hyperactivity (increased FosB staining levels) - Decreased striatal volume and decreased MSN dendritic arbor complexity - SLC1A1 is highly expressed in human cortex, striatum and thalamus	- Age-dependent cortical thinning and ventricular enlargement in EAAC1-null mice - Dicarboxylic aminoaciduria	[67], [71]–[73]
CDH2	- Dog OCD small GWAS	- Canine OCD (incessant tail chasing, relentless paw chewing)	ND in dogs	- CDH2 KO mice die during early embryonic stages	[98]–[100]
HT2RC	- Global 5-HT$_{2C}$R-KO mice show compulsive phenotype	- Non-nutritive chewing - Increased head-dipping - Reduced anxiety (open field, elevated plus maze, novel object, mirrored chamber)	- Decreased corticotrophin hormone release from the extended amygdala in response to anxiogenic stimuli	- Mid-life obesity (due to hyperphagia) - Prone to death from spontaneous seizures - Altered sleep homeostasis	[94], [97]