Review

Biological Psychiatry

Learning From Animal Models of Obsessive-Compulsive Disorder

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ABSTRACT

Obsessive-compulsive disorder (OCD) affects 2%–3% of the population worldwide and can cause significant distress and disability. Substantial challenges remain in the field of OCD research and therapeutics. Approved interventions alleviate symptoms only partially, with 30%–40% of patients being resistant to treatment. Although the etiology of OCD is still unknown, research evidence points toward the involvement of cortico-striato-thalamocortical circuitry. This review focuses on the most recent behavioral, genetics, and neurophysiologic 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 researchers define and test new hypotheses and facilitate the development of targeted therapies based on disease-specific mechanisms.

Keywords: Animal models, Basal ganglia, CSTC, Obsessive-compulsive disorder, OCD, Striatum, Synapse

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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. Because of 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 and selective serotonin reuptake inhibitors (3,4). In cases in which patients do not respond to cognitive behavioral therapy or medication or both, other interventions have been used, such as deep brain stimulation (5–7). Because abnormalities in the glutamatergic system also have been proposed in the pathology of OCD, some *N*-methyl-D-aspartate receptor antagonists including ketamine and memantine are being tested as possible therapies (4,8).

Previously considered under the spectrum of anxiety disorders, OCD is now categorized in the recently revised DSM-5 with other obsessive-compulsive–related disorders, including trichotillomania, body dysmorphic disorder, skin picking disorder, and hoarding disorder. The reclassification is based on behavioral similarities and common features of these disorders —obsessive preoccupations and repetitive actions. Such categorization is thought to help guide diagnostic criteria and ensure consistency among health care providers. However, a more "biologically valid framework" for mental disorders has been proposed by the U.S. National Institute of Mental Health. This new research framework, designated Research Domain Criteria, aspires to emphasize mental disorders as biological constructs that span specific domains of behavior, emotion, and cognition (e.g., social interactions, mood) 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 target therapeutically 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 discusses several areas of research including 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-striato-thalamocortical Circuitry

One of the most replicated findings in human OCD studies is the involvement of cortico-striato-thalamocortical 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 most 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

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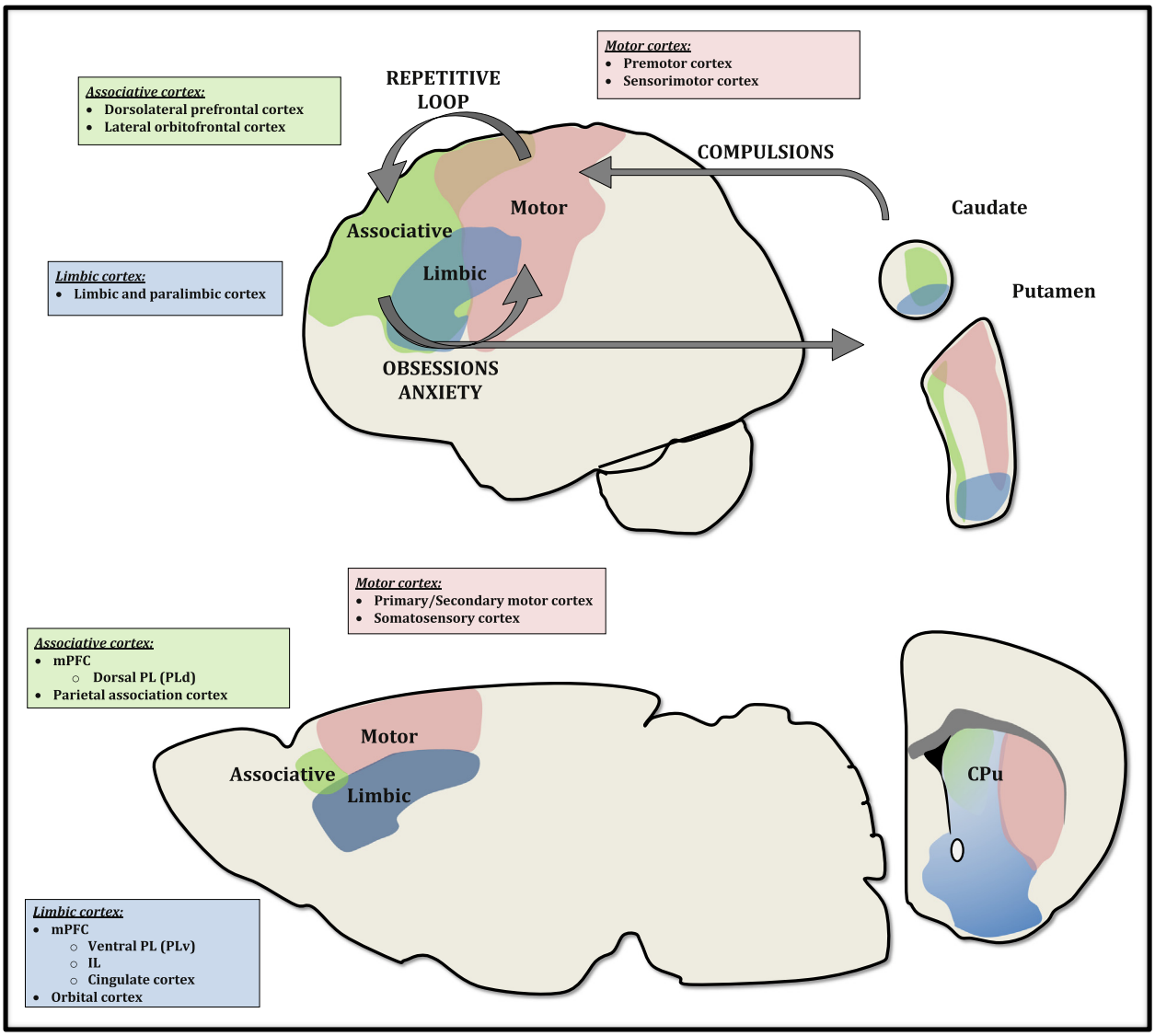

Figure 1. Simplified neuroanatomic models of corticostriatal circuitry within the human (top) and mouse (bottom) brain. Human motor cortex is represented by premotor and sensorimotor cortical regions that mainly project to the posterolateral putamen (11). Mouse motor cortex is represented by somatosensory and motor cortex that mainly project to the dorsolateral striatum region (16). Human associative cortex, represented by the dorsolateral prefrontal cortex and lateral orbitofrontal cortex, projects to the caudate and anteromedial portion of the putamen (11). Mouse associative cortex is represented by dorsal prelimbic and parietal association cortices that mainly project to the dorsomedial striatum region (15). Human limbic cortex, represented by the paralimbic and limbic cortices (including entorhinal cortex [area 28], perirhinal cortex [area 35], medial orbitofrontal cortex [area 11], and anterior cingulate cortex [area 24]) (11,101), projects to the ventral striatum (ventral region of the caudate nucleus and putamen, including nucleus accumbens). Mouse limbic cortex is represented by orbitofrontal cortex and prefrontal cortex (ventral prelimbic, infralimbic, and cingulate cortices) that mainly project to the ventromedial striatum region (including nucleus accumbens) (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 lead to execution of compulsive actions. 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 anatomic locations. CPu, caudate putamen; IL, infralimbic; mPFC, medial prefrontal cortex; PL, prelimbic.

findings with behavioral manifestations in OCD? A major advantage of studying animal models is the ability to manipulate neural circuits directly and test behavioral outcomes. It is important to define neuroanatomic parallels between CSTC structures in humans and mice so that their (dys)function and relevance to OCD can be tested (Figure 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 medial prefrontal cortex seems to be organized in a dorsal-ventral gradient of connectivity such that dorsal-prelimbic input projects to dorsomedial regions of striatum (DMS; associative striatum), and ventral-

prelimbic input 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). However, despite some functional resemblance, there are important species-specific differences, with mice lacking certain neuroanatomic connectivity possessed by primates (14–17,19,20).

Similar to the connectivity patterns observed between cortex and striatum, it is believed that downstream basal ganglia territories are equally well organized into associative, limbic, and sensorimotor regions. Evidence for this cognitive, emotional, and motor organization of basal ganglia has been clarified through groundbreaking studies in monkeys (21,22). Bicuculline injections into limbic regions of globus pallidus (GP) can induce stereotypies, whereas injections into associative regions can lead to attention deficit/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 physiologic behavior that appears hyperactive in some OCD mouse models with self-injurious overgrooming (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, on repetition, become habitual automated responses, encoded by DLS (16–18,29–33). A dynamic competition is thought to occur 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 decreases, DLS circuits assume control over behaviors (34). Evidence 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 evidence might help to explain results from a clinical study in which a deficit in goal-directed control and an overreliance on habits were observed in patients with OCD (35). Dysfunctional associative circuitry could 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 (dopamine 1 receptor–positive direct-pathway cells; project to substantia nigra pars reticulata) and striatopallidal (dopamine 2 receptor–positive indirect-pathway cells; project to GP) (36,37). The classic 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 was called into question through more recent mouse studies showing concurrent activation of both pathways during action initiation (42), whereas other mouse studies substantiated the classic 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 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 parvalbumin-positive and project to both MSN types but are more likely to target dopamine 1 receptor–positive cells; low-threshold–spiking interneurons; and choline acetyltransferase–positive interneurons (Figure 2) (36,37,44,45). Despite their relative sparsity, these interneurons can strongly modulate MSNs, greatly influencing final output of the striatum (46). In patients with Tourette's syndrome, a disorder often comorbid with OCD, histology of postmortem striatal tissues revealed decreased density of parvalbumin-positive and choline acetyltransferase–positive interneurons in caudate and putamen regions (47,48). A potential bridge between Tourette's syndrome, OCD, and striatal interneuron dysfunction is also suggested by a study, summarized subsequently, in which increased MSN activity and lower striatal parvalbumin-positive 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. In future studies, it will be important to define exactly how these interneuron populations modulate striatum output and how, if at all, they are relevant to OCD.

Hyperactive Circuitry in OCD

Among the various tools that have become available to study neural circuits, one holds great promise: optogenetics (50,51). Using this strategy, a 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 ventromedial striatum. Repeated direct hyperactivation of these cells over 5 consecutive days led to a progressive increase in repetitive grooming. However, acute stimulation was insufficient 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 (KO) 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 patients with OCD (54).

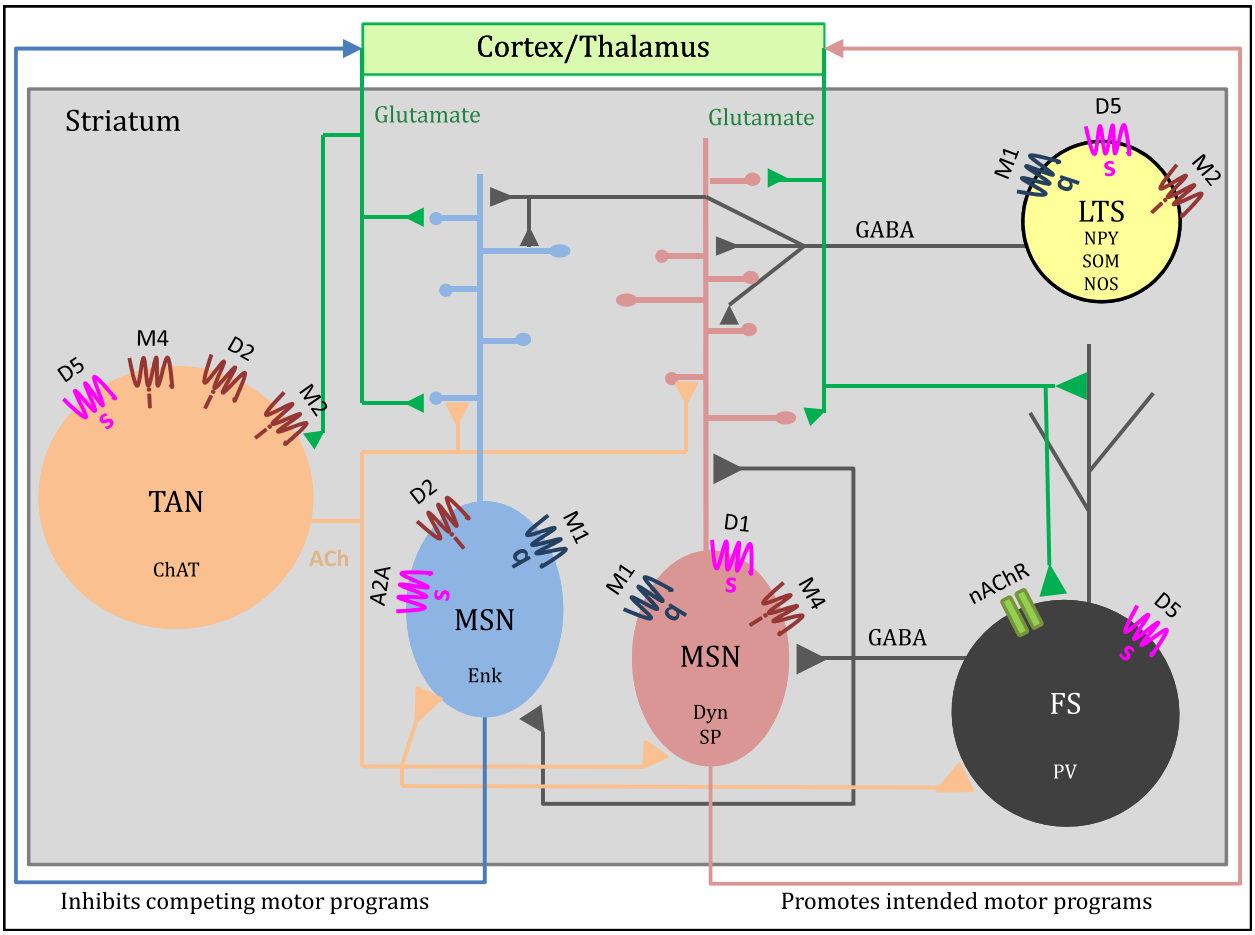

Figure 2. Representation of intrastriatal microcircuitry. Corticostriatal and thalamostriatal excitatory axons target the dendritic spines of medium spiny neurons (MSNs) and dendritic shafts and soma of striatal interneurons. Fast-spiking (FS) interneurons receive more cortical contacts and are more responsive to cortical inputs than MSNs (102,103); FS interneurons synapse proximally onto both MSN types (104) with a bias toward direct-pathway dopamine 1 receptor-positive MSNs (45); FS interneurons also synapse with other FS cells, but not low-threshold spiking neurons or TANs (45). Low-threshold spiking 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). Dopamine 1 receptor-positive MSNs have more elaborate dendritic arbors (110), and their axons project to substantia nigra pars reticulata (37) (not represented); this direct pathway promotes the execution of intended motor programs (42). Dopamine 2 receptor-positive MSNs project to globus pallidus (37) (not represented); this indirect pathway may inhibit the execution of competing motor programs (42). G protein–coupled receptors are depicted with their associated G protein: Gs (pink), Gi (brown), Gq (blue). A2A, A2A adenosine receptor; ChAT, choline acetyltransferase; D, dopamine receptors; Dyn, dynorphin; Enk, enkephalin; LTS, low-threshold spiking; M, muscarinic acetylcholine receptors; nAChR, ionotropic nicotinic acetylcholine receptor; NOS, nitric oxide synthase; NPY, neuropeptide Y; PV, parvalbumin; SOM, somatostatin; SP, substance P; TANS, tonically active neurons.

A recent study by Rothwell *et al.* (55) showed that imbalanced basal ganglia activity can clearly influence the formation of repetitive motor routines. 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. Although 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-pathway and indirect-pathway activity and 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 reactivation by subsequent stimuli.

Dysfunction of Termination (Stop Signal) in OCD?

Hyperactivity of CSTC circuitry in OCD and consequent propagation of positive-feedback loops could be due to augmented sensitivity to initial triggering stimuli (too much start signal) or to deficiency in motivation to break the initiated behavioral ritual (too little stop signal). More recent work tried to address this question by studying security-related behaviors that arise from exposure to contamination cues (57). The results indicated that the cause of patients' symptoms relied 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 report by Burguière *et al.* (49) corroborated an insufficiency of the stop signal and reinforced the importance of the OFC-striatal pathway in the genesis of compulsive behaviors. Electrophysiologic recordings obtained over a long-term period in *Sapap3*-KO mice, an established model of OCD-like behaviors (see later), revealed abnormally high spontaneous MSN activity in the centromedial striatum, in further support of the hyperexcitability hypothesis. These mice not only showed deficits in adaptive grooming response during a conditioned grooming task (tone-delay-water) but also showed impaired striatal physiology, in which MSNs were incapable of adapting and refining their activity during task shaping. These findings point toward acquired maladaptive behavior to an initially neutral stimulus. *Sapap3*-KO mice further showed reduced striatal FS interneuron density, suggesting that deficient inhibition within striatum might contribute to MSN hyperactivity (58). Optogenetic stimulation of lateral OFC somata or afferent terminals in the striatum can successfully alleviate conditioned overgrooming as well as naturally occurring compulsive grooming in *Sapap3*-KO mice (49). In vivo recording data demonstrated that stimulation of the lateral OFC–striatal pathway increased FS-MSN inhibitory efficacy and helped 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 feedforward 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 by Ahmari *et al.* (52) and Burguière *et al.* (49) might at first appear discrepant—medial OFC stimulation increases grooming, while lateral OFC stimulation reduces grooming—it is critical to note that results were derived from different cell populations. Both studies implicated OFC dysregulation in compulsive behaviors and suggested that lateral OFC and medial OFC might be playing different roles in OCD, as hypothesized earlier by Milad and Rauch (59).

BEHAVIORAL STUDIES IN OCD ANIMAL MODELS

To evaluate OCD-like behaviors in animal models, specific behavioral paradigms have been developed in recent 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, anxiety is an equally relevant trait to other non–OCD spectrum disorders. Similarly, OCD itself shares important links with other anxiety disorders, although this is not true for all other OCD 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 nonnutritive chewing, grooming, or shifting/digging in bedding as in the marble burying test, can be simply observed. Other, more complex tests involve learned tasks in which the 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 are assessed, can distinguish between impulsive and compulsive responses (14,61).

Animal models of neuropsychiatric disorders should exhibit at least one of the following characteristics: atypical behaviors that resemble human symptoms (face validity); shared biological grounds with human conditions, such as mutation of a specific gene (construct validity); or successful response 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 corticostriatal glutamatergic synapses. Besides impaired corticostriatal transmission, these mice display self-injurious grooming and increased anxiety as assessed by the open field, elevated zero maze, and dark-light emergence tests. Anxiety and compulsive grooming can be partially alleviated by fluoxetine treatment. A key finding is that restoring SAPAP3 expression in the striatum alone can rescue self-injurious grooming and corticostriatal transmission, further emphasizing the role of the striatum in compulsive behaviors. A more recent study in this OCD mouse model suggested 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 reshape this acquired behavior, even when delivery of the water drop 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). Long-term fluoxetine treatment can alleviate this phenotype. *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 patients with OCD involve actions such as checking, washing, and ordering. The fact that these themes are not random and occur consistently in patients across distinct sociocultural backgrounds worldwide raises the possibility of common genetic bases (63,64). Twin studies of OCD also support this prediction, yielding the strongest evidence for a genetic contribution in OCD. An extensive review published by van Grootheest *et al.* (65) using a dimensional approach for twin studies concluded that 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 suggested 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 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 reported 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, several studies implicated the human *EAAC1* gene in at least some cases of OCD (68,74). It is plausible that *Eaac1* 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*

An effort has been made to search for common single nucleotide polymorphisms predisposing individuals to OCD. More than 20 research groups have collaborated to accomplish the first genome-wide association study for human OCD (75). Results from this study suggested the involvement of two single nucleotide polymorphisms 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 earlier) (28,76–78). Smaller association studies supported a role for *SAPAP3* in human trichotillomania 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 (82), found an 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 through SLITRK6) are a relatively recently discovered family of proteins (62) that have emerged as candidate genes in neuropsychiatric disorders (83). Human genetic studies 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 patients with Tourette's syndrome (86). The hypothesis of *SLITRK1* involvement in Tourette's syndrome and the fact that SLITRKs are highly expressed in mammalian central nervous system (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 corticostriatal circuitry. Given that *Slitrk5*-KO mice and *Sapap3*-KO mice display impaired corticostriatal transmission and OCD-like behaviors that are responsive to treatment with fluoxetine, one of the pharmacologic agents used in patients with OCD, it would be interesting to address whether these mutations of these genes lead to common defects in molecular pathway or circuitry function.

Hoxb8

Another 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 OFC, cingulate cortex, limbic system, and other regions of the brain 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 was previously shown that microglia play roles in regulating neuronal cell death and in modulating neural networks (90,91). A subset of children with OCD can experience worsening of symptoms after streptococcal infection. One brain region that is affected in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections is the basal ganglia (immunobiology of OCD and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections reviewed by Murphy *et al.* (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*-KO mice, *Sapap3*-KO mice, and *Slitrk5*-KO mice have grooming phenotypes that are unique in their biological origins, all genes share an enriched corticostriatal expression. In regard to human OCD, these mice studies suggest that a commonly shared pathologic 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 serotoninergic system. Although the exact mechanisms are unknown, it is thought that 5-hydroxytryptamine 2C serotonin receptor agonism might contribute to therapeutic benefits in OCD (93). Genetic deletion of 5-hydroxytryptamine 2C receptor in mice led to enhanced sensitivity to induced motor stereotypy and compulsive-like behaviors, such as nonnutritive chewing and increased head dipping (94–97), supporting serotoninergic involvement in compulsivity. In contrast to other OCD models, these mice showed 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

Table 1. Candidate Genes From Animal Models With OCD-like Behaviors

Gene	Genetic Evidence	Behavioral Phenotype	Neurophysiology	Notes	References
Hoxb8	Global *Hoxb8*-KO mice with relevant phenotype	Self-injurious grooming	*Hoxb8* expressed in bone marrow–derived microglia that migrate into brain OFC, cingulate cortex, and basal ganglia regions	WT bone marrow transplantation rescues excessive grooming	(88,89)
	Conditional-KO mice (hematopoietic cells) exhibit global KO phenotype	Cage mate overgrooming		KO bone marrow transplantation induces excessive grooming in WT	
Sapap3	Global *Sapap3*-KO mice with strong phenotype	Self-injurious grooming	*Sapap3* mainly expressed in neocortex, striatum, hippocampus, and thalamus	Striatum infection using lentivirus-*Sapap3* rescues self-injurious grooming and fEPSP	(28,49,75,78)
	Two SNPs located in *Sapap1* (family member) found in human OCD GWAS study	Increased anxiety (open field test, elevated zero maze, and dark-light emergence)	Impaired corticostriatal function (reduced fEPSP, mEPSC and AMPA/NMDA ratio; increased silent synapses and eCB-LTD)	Fluoxetine treatment partially alleviates compulsive grooming and anxiety	
		Deficit in adaptive grooming response during conditioning task	Increased spontaneous MSN firing activity in centromedial striatum		
			Reduced interneuron PV number in centromedial striatum		
Slitrk5	Global *Slitrk5*-KO mice with strong phenotype	Self-injurious grooming	*Slitrk5* mainly expressed in neocortex, striatum, and hippocampus	Fluoxetine alleviates overgrooming	(27)
		Increased anxiety (open field test, elevated plus maze)	Impaired corticostriatal function (reduced fEPSP)		
		Compulsive-like behavior (marble burying test)	OFC hyperactivity (increased FosB staining levels)		
			Decreased striatal volume and decreased MSN dendritic arbor complexity		
Slc1a1/ Eaac1	Human OCD genetic studies	Human OCD	*Slc1a1* is highly expressed in human cortex, striatum, and thalamus	Age-dependent cortical thinning and ventricular enlargement in *Eaac1*-null mice	(67,71–73)
	Eaac1-null mice show modest phenotype	*Eaac1*-KO mice show cognitive and motivational impairment at old age		Dicarboxylic aminoaciduria	
		Reduced spontaneous locomotion in open field test			
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	Nonnutritive chewing	Decreased corticotropin hormone release from extended amygdala in response to anxiogenic stimuli	Midlife obesity (due to hyperphagia)	(94,97)
		Increased head-dipping		Prone to death from spontaneous seizures	
		Reduced anxiety (open field test, elevated plus maze, novel object, mirrored chamber)		Altered sleep homeostasis	

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

AMPA/NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/*N*-methyl-D-aspartate; 5-HT_{2C}-R, 5-hydroxytryptamine 2C receptor; eCB-LTD, endocannabinoid-mediated long-term depression; fEPSP, field excitatory postsynaptic potentials; GWAS, genome-wide association study; KO, knockout; mEPSC, miniature excitatory postsynaptic currents; MSN, medium spiny neuron; ND, not defined; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PV, parvalbumin; SNP, single nucleotide polymorphism; WT, wild-type.

genomic sequencing from animals displaying spontaneously occurring pathologic 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 genome-wide association study was carried out recently, which identified four synaptic genes with case-only variations (*Cdh2*, *Ctnna2*, *Atxn1*, *Pgcp*) (98). Previous studies in mice showed that *Cdh2* gene disruption, although embryonically lethal, caused synaptic dysfunction in cultured neurons (99,100).

Together, the ever-expanding genetic studies of human, mouse, and dog seem to converge toward CSTC synaptic dysfunction in OCD pathology (Table 1). Although animal

models never can fully recapitulate the human OCD spectrum because of species-specific limitations, they do allow us to study precisely 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 AND CONCLUSIONS

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 motor programs of compulsions? What brain areas initiate the obsession-compulsion process?

Human functional imaging data seem to suggest hyperactivity in OFC of patients with OCD. It is possible that this area could be important for generating specific thoughts that in a person without OCD 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 physiologic need. However, patients with OCD 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 toward specific dysregulations that might be relevant as OCD endophenotypes—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 evolutionally conserved CSTC circuitry might be relevant across DSM diagnoses and help to guide future translational studies.

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