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Using Mice to Model Obsessive Compulsive Disorder: From Genes to Circuits

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1. Introduction

Obsessive Compulsive Disorder (OCD) is a severe, chronic, and highly prevalent psychiatric disorder that affects between 1.5–3% of people worldwide, independent of ethnicity and cultural group studied[1]. According to the 1996 report by the World Health Organization, it was listed as the world's 10th leading cause of illness-related disability[2]. In the US alone, the costs associated with treatment of OCD and work loss due to symptoms are estimated at up to 10 billion dollars annually[3]. Yet despite its severity, high prevalence, and clear societal cost, current OCD therapies are only partially effective. This is in part because OCD remains under-diagnosed, under-treated, and understudied due to lack of recognition by health care providers, stigma associated with symptoms by patients, and lack of understanding of the seriousness of the illness by the general public and research organizations. In order to ultimately develop improved treatments for this severe mental illness, we need further research to gain an improved understanding of the pathophysiology that underlies obsessions and compulsions.

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Though studies in OCD patients can provide some insight into the disease process, studies in humans are inherently limited in their ability to dissect pathologic processes because of their non-invasive nature. The recent development of strategies for genetic and circuit-specific manipulation in rodent models finally allows us to identify the molecular, cellular, and circuit events that lead to abnormal repetitive behaviors and affect dysregulation relevant to OCD. This review will highlight recent studies in mouse model systems that have used transgenic and optogenetic tools in combination with classic pharmacology and behavioral techniques to advance our understanding of these pathologic processes.

1.1. Clinical Features of OCD

Despite recent changes to the Diagnostic and Statistical Manual (DSM-5), the core clinical features of OCD remain the same[4,5]. OCD consists of obsessions, which are recurrent, persistent, intrusive thoughts, impulses, or images; or compulsions, which are repetitive behaviors or mental acts that patients typically engage in to reduce the severe anxiety or dread that is associated with the obsessions[6–8]. Though both obsessions and compulsions are not required to meet diagnostic criteria for OCD, both are typically present[9] and tend to be linked together, such that a compulsion is performed in response to a particular obsessive thought. Notably, although OCD is no longer classified as an anxiety disorder according to DSM-5, anxiety symptoms are a prominent feature in many OCD patients[10,11]. Specifically, obsessions are often associated with significant distress, and compulsions are typically performed in a conscious attempt to reduce this severe distress. For example, an intrusive thought about one's hands being contaminated would typically be accompanied by a spike in anxiety followed by a compulsive hand-washing ritual, and completion of the ritual would lead to a temporary decrease in anxiety. Although performing compulsions can provide immediate relief, it is typically fleeting. In fact, execution of these rituals is actually believed to strengthen dysfunctional neural circuits that underlie OCD, leading ultimately to increased anxiety and symptom persistence. These illness features are important to consider when developing neurobiological models of the disorder.

It is clear that OCD is a heterogeneous disorder[12], but it is less clear how the illness should be divided into subgroups. This is an active area of investigation, and therefore many metrics currently exist for 'carving the joints'. First, there is strong evidence that tic-related OCD is neurobiologically distinct, with different neurochemical features, distinct striatal pathophysiology, and higher prevalence in males[13]. There have also been suggestions that early-onset OCD (mean age of onset between 7.5 and 12.5 years[14]) may correspond to a distinct subtype with different genetic and environmental underpinnings[15]. Variations in level of insight into OCD symptoms may also represent biologically meaningful differences[16], and are now delineated by specifiers in DSM-5. Finally, differences in specific content of obsessions and compulsions may potentially correspond to distinct neurobiological substrates[17], as most clearly demonstrated for hoarding (now a separate disorder in DSM-5)[18,19].

1.2. Neural Circuit Abnormalities Associated with OCD

Over the past 20 years, functional and structural neuroimaging studies have led to the discovery of aberrant neural circuits in OCD patients. A remarkable convergence of findings

from neuroanatomical and functional studies collectively implicates cortico-striato-thalamo-cortical (CSTC) circuits in OCD pathophysiology[20–23]. Though discrepancies are found in the directionality of findings, this is typically attributed to either heterogeneity of illness, or differences in stage of development or illness course. These findings are described in detail below.

1.2.1. Structural neuroimaging—Although exact findings have varied across studies, structural abnormalities in CSTC circuits involving orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum have been repeatedly demonstrated in OCD[24–26]. The largest structural MRI study to date reported reduced medial OFC gray matter and increased gray matter in the highly-connected[27,28] ventral striatum (i.e. ventral putamen, nucleus accumbens, and olfactory tubercle)[29]. In addition, a recent meta-analysis reported reduced volumes of left ACC and bilateral OFC, and increased thalamic volumes bilaterally, but no differences in basal ganglia volumes relative to control samples[30]. However, another meta-analysis demonstrated changes in basal ganglia (i.e. increased bilateral caudate gray matter volume) as well as decreased bilateral ACC volume, in OCD patients[31], while a recent mega-analysis demonstrated a reduction in ACC, dorsomedial PFC, and inferior frontal gyrus volumes, with group-by-age interactions in putamen, OFC, and insula[26]. Finally, a study combining structural MRI and behavioral testing demonstrated that impairment on a response inhibition task (Stop-Signal Task) in both OCD patients and unaffected first-degree relatives was correlated with decreased grey matter in OFC and right inferior frontal cortex, and increased grey matter in cingulate cortex, parietal cortex, and striatum[32]. Thus, structural imaging studies in OCD have collectively demonstrated changes in ACC, OFC, and striatal volume, although there are inconsistencies in directionality of findings between studies, particularly in the striatum.

It is important to consider the potential reasons for these inconsistencies in order to develop pathophysiologic models of OCD. Likely key contributors to variation between structural imaging studies are relatively small samples, inclusion of heterogeneous patient populations (i.e. different ages, comorbidities, medication status, and length of illness course), and methodological differences, including exact brain regions studied. For example, older region of interest studies focused exclusively on areas that were thought a priori to be involved in OCD pathophysiology, and tended to use more subjective manual and semi-automatic methods to measure brain volumes. To overcome these limitations, more recent studies have used unbiased automated whole-brain voxel-based morphometry approaches; however, these have tended to be limited by small sample sizes, potentially rendering them prone to the generation of false positives. In an attempt to correct these deficiencies, the two meta-analyses discussed briefly above attempted to synthesize discrepant findings in region-of-interest studies[30] and voxel-based morphometry studies[33], respectively. Synthesizing region-of-interest studies which had highly variable divisions for particular brain regions in the original articles, Rotge et al reported reduced volumes in left ACC and bilateral OFC in OCD, and increased thalamic volumes bilaterally, but no changes in caudate volume. However, of the 14 studies examined, caudate volume was examined in only 3 studies, 2 of which were from pediatric samples. When the remaining adult study was examined, a decrease in caudate volume was observed, but the ability to generalize findings from this

single study is limited. In contrast, by examining voxel-based morphometry studies in an attempt to reduce a priori bias, Radua et al found evidence for increased bilateral caudate gray matter volume, as well as decreased bilateral ACC volume in OCD patients. Additionally, they showed that more severe OCD patients were more likely to report increased caudate volumes, which could have accounted for the discrepancies with Rotge et al, which had significant heterogeneity in terms of illness length, medication status, and treatment-refractory nature of patients.

In an attempt to overcome the limitations of both of these meta-analyses, de Wit et al [26] performed a voxel-based morphometry mega-analysis, in which they obtained raw data from 780 participants and re-analyzed it using a uniform pipeline for pre-processing and analysis. This again demonstrated a reduction in ACC volume, consistent with the prior two meta-analyses. However, in contrast, this mega-analysis showed a relative preservation of both OFC and putamen with aging compared to healthy controls, suggesting possible activation-mediated neural plasticity leading to a relative volume increase as patients age. They suggest that the lack of findings in the caudate may be due to differences in age, treatment history, and medication status, and also note that data for 530 out of 780 participants in this study has not been published before; differences from past studies could therefore be due to increased power in the mega-analysis. Whether methodological differences also contribute to these differences will only become clear when the original source data are published.

1.2.2. Functional neuroimaging—Similar to findings from structural studies, OFC, ACC, and caudate (specifically the head) have likewise been implicated in OCD using PET and fMRI; functional studies also highlight anterior thalamus[17,20,34]. These brain regions are linked by well-described neuroanatomical connections[24]. Notably, OCD subjects demonstrate hyperactivity in these areas both at rest and with symptom provocation, though OFC shows the most robust activation[20]. In further support of the role of this regional hyperactivity in symptom generation, most studies have found that successful serotonin reuptake inhibitor (SRI) or cognitive behavioral therapy treatment was associated with reduced activity in OFC or caudate, with decreased ACC activity being less prominent[35,36]. Finally, recent fMRI studies of resting state connectivity have also generally supported a role for cortical-basal ganglia circuit dysfunction in OCD, demonstrating abnormal connectivity of orbitofrontal cortex[37–40], anterior cingulate[39,41], ventral striatum[37,39–41], dorsal striatum[40,41], putamen[38,41], and anterior thalamus[41]. However, other regions including subthalamic nucleus[38], cerebellum[41,42], and temporal cortex[42] have also been implicated, and directionality of findings varies across studies. Discrepancies in resting state data are less prominent than those seen in structural imaging studies, likely because fewer studies exist. While three prior studies have demonstrated increased resting state connectivity between striatum and OFC (using both seed-based[37,40] and graph theory[38] approaches), one recent seed-based study found the opposite result– i.e., reduced functional connectivity between OFC and ventral striatum in OCD[39]. One theory for this discrepancy is that Posner et al exclusively examined unmedicated patients, and that observations of increased functional connectivity in the other studies could stem from medication effects. This theory is called into question by Beucke et al's study, which used different methodology (graph theory) to show reduced local connectivity in ventral striatum in an unmedicated patient

subgroup; however, in addition to the methodological differences, Posner et al's subjects were extremely clean (almost half of patients medication naïve; average of 94 weeks off medication in other patients; very little co-morbidity). Determining how medication status, illness course, and potential compensatory changes may relate to resting state fMRI findings in OCD is a key direction for future studies.

1.2.3. Cognitive activation studies—Based on the theory that circuit dysfunction in particular mental illnesses may only be unmasked during performance of neurocognitive tasks, there has been a recent shift towards performing OCD imaging studies during cognitive activation paradigms. Many tasks have been used, though executive functions have been particularly emphasized[23]. First, several studies have shown hyperactivity of dorsal ACC (dACC) in OCD patients during performance of tasks involving error monitoring and/or conflict resolution, suggesting that dACC and connected regions might function differently in OCD[43]; these findings correlate well with baseline functional studies. In addition, studies have used Go/NoGo tasks to assess inhibitory control in OCD, both of which report decreased activation of OFC[44,45]. Similarly, greater frontostriatal activation has been demonstrated in unmedicated OCD patients during engagement of control and conflict resolution on the Simon task[46]. Finally, decreased activation of the lateral OFC, as well as the lateral PFC and parietal cortex, has been demonstrated in both OCD patients and their unaffected first-degree relatives in a reversal learning task[47]. Overall, these findings support the idea that cortical-basal ganglia circuits are dysfunctional in OCD, and may contribute to symptom generation.

1.2.4. Working Model of OCD Pathophysiology—By synthesizing the studies reviewed above, several models of OCD pathophysiology have been proposed[22,48]. Though models differ in details, they consistently share the idea that obsessions and compulsions somehow result from malfunctioning neural circuits that include OFC, ACC, caudate, anterior thalamus, and/or ventral striatum. However, as discussed in detail above, it is important to consider the fact that some structural and resting state fMRI studies have shown differential effects, leading to challenges in developing a fully integrated model of circuit-based OCD pathophysiology. Potential factors include methodological differences between studies, inclusion of heterogeneous patient populations, and exact brain regions studied. Although further study is warranted to tease out the key factors that account for these differences, in aggregate, these findings can be synthesized by an integrative model which prioritizes functional, rather than structural, neuroimaging findings. PET and fMRI studies have consistently demonstrated hyperactivity in OFC, striatum, and thalamus at baseline and with symptom provocation; this meshes well with the increased OFC-striatal connectivity seen in most resting state fMRI studies in OCD. Though structural studies have been less consistent, this could be explained both by the methodological differences described in detail above, and by the fact that either decreases or increases in volume of individual brain structures could potentially lead to similar functional outcomes by disrupting normal inter-regional communication. Finally, the specific brain regions affected may depend on the particular OCD subtype. For example, based on functional imaging studies, it has been proposed that different OCD symptom dimensions (e.g., symmetry/ordering vs. washing/cleaning) may have different underlying neural substrates within CSTC circuits[12]. Thus,

different OCD subtypes could have distinct core neurobiologic deficits leading to differences in both neuroimaging findings and neurocognitive task performance. However, as discussed above (see Section 1.1), the most accurate way to segregate OCD into different subtypes is still a matter of active investigation and debate. For example, symptom dimensions frequently change over time in individuals with OCD[49], suggesting either that the functional status of the underlying neural substrates is also fluctuating, or that it may not be possible to broadly delineate subtypes using symptom dimensions.

In line with models of CSTC dysfunction in OCD, evidence from recent human studies suggests that OCD patients have dysfunction in core neural processes mapped onto CSTC circuits, such as response inhibition e.g., response inhibition; [50,51,52], sensorimotor gating[53], and fear-learning[54], as will be discussed further in Section 3. In addition, a group of studies that examined the balance between goal-directed versus habitual behavior in OCD patients is particularly interesting. Although the ways in which goal-directed and habitual performance cooperate and/or interfere with each other in healthy subjects is still an area of active investigation (see Balleine & O'Doherty for comprehensive review[55]), there is growing evidence that patients with OCD are biased to perform habits, sometimes at the expense of performance goal-directed actions, which may be impaired at baseline[56]. Interestingly, this bias towards increased habit formation in OCD not only applies to appetitive habits, it also extends to avoidant habits that may be more relevant to the clinical symptoms seen in patients[57,58]. Though it is challenging in general to make direct links between dysfunctional neural processes and symptoms in patients (highlighted by Gillan et al's finding that avoidance habits did not correlate with the YBOCS compulsion subscale[57]), the possibility that impaired regulation of the goal-directed behavior/habit balance contributes to symptom generation is intriguing.

Another leading pathophysiologic model that is not mutually exclusive is based on the fact that different populations of striatal spiny projection neurons differentially regulate the direct and indirect basal ganglia pathways. Given the known functions of the direct pathway (i.e. striatum→globus pallidus interna→substantia nigra) and indirect pathway (i.e. striatum→globus pallidus externa→subthalamic nucleus) in modulating thalamic input to cortex and in generating motor patterns, this has led to the hypothesis that OCD symptoms result from excess activity in direct versus indirect OFC-subcortical pathways[59]. This imbalance could lead to OCD symptoms in a variety of ways. For example, increased direct pathway activity could lead to decreased inhibition of thalamus, which in turn would decrease filtering of intrusive thoughts and images to cortex, thus triggering compulsions. Alternatively, it is possible that OCD symptoms stem from increased firing of excitatory neurons in cortical areas including mOFC, ACC, or supplementary motor area, ultimately generating intrusive thoughts and images that override other sensorimotor input [60]. In turn, this could trigger ritualistic compulsions driven by striatum through persistent activation of the direct pathway. However, it is important to note that many different models could be proposed to synthesize findings from neuroimaging and neurocognitive studies in OCD, and that no single proposal can provide an explanatory model for all findings in the literature–in part because of heterogeneity of patients, as well as heterogeneity of tasks used, measurement parameters, and specific brain regions studied. This is highlighted by two recent animal studies discussed further below, which indicate it is possible that hyperactivity

in medial OFC regions connected to limbic structures may lead to OCD-relevant symptoms[61], while hyperactivity in lateral OFC regions important for inhibitory control may lead to symptom reduction[62]. As described below, studies in rodents can be used to directly tease out these differences and test these models.

1.2.5. Other candidate regions—Though current models suggest that dysfunctional CSTC circuits are important in generation and/or maintenance of OCD symptoms, evidence for involvement of other structures is beginning to accumulate[43]. For example, while CSTC models do not currently provide a clear explanation for increased anxiety observed in OCD, exaggerated responses in amygdala observed after presentation of OCD-specific stimuli could be responsible[63]. Furthermore, although dACC has been classically linked to conflict monitoring/obsessions in OCD, there is evidence that it also plays a role in expression of fear responses[64]. dACC hyperactivation could therefore explain increased anxiety observed in OCD patients. Finally, recent studies have demonstrated that OCD patients have impaired extinction recall in a fear-conditioning paradigm, with accompanying alterations in cerebellum, posterior cingulate, and putamen activity during extinction recall, and reduced hippocampus and caudate activation during fear extinction[54]. Integration of other brain structures may therefore be necessary to generate a satisfying explanatory model of OCD pathophysiology and symptom generation.

2. Testing Proposed Etiologies in Animal Model Systems

2.1. Transgenic Models of OCD

A role for genetics in OCD is supported by evidence from both twin and family studies[65], and increased heritability in pediatric-onset OCD suggests an even greater genetic contribution[66]. In many other complex psychiatric disorders, investigation of etiology using transgenic technology has been aided by the identification of families with highly penetrant gene abnormalities. For example, microdeletions in chromosomal region 22q11.2 are associated with a 20–30 fold increased risk for schizophrenia[67], and mouse models of the 22q11.2 deletion syndrome have led to significant insights into the potential role of this region in generating cognitive deficits in schizophrenia[68]. Similarly, a family was recently identified in which Tourette's Syndrome was linked with a rare but highly penetrant mutation in histidine decarboxylase, the key enzyme required for biosynthesis of histidine[69,70]. Parallel studies were then performed in histidine decarboxylase knockout mice to attempt to identify pathophysiologic mechanisms of Tourette's syndrome, and dopaminergic abnormalities in the striatum were observed[71]. In contrast to these examples, the field of OCD research has been hindered by the lack of identification of families carrying rare genetic variants of large effect. In addition, genome-wide association studies (GWAS) in OCD have failed to identify common variants that reach genome-wide significance, though this is still an active area of investigation since it is most likely that common variants provide the most important genetic contribution in OCD[72,73,74]. This has limited the investigation of OCD pathophysiology using transgenic technology. Despite this fact, several transgenic mouse models have serendipitously yielded significant insights into pathophysiologic mechanisms underlying abnormal repetitive behaviors, and are now providing potential links

back to the human disorder via targeted genetic screens in OCD patients. In this section, we will present findings from these models, as well as discuss potential future directions.

2.1.1. Hoxb8 knockout mice—One of the first transgenic models suggested to have relevance for OCD was the Hoxb8 knockout (KO). These knockout mice were initially generated to pursue the investigation of the role of Hox genes in neurodevelopmental patterning. After constitutive knockout of Hoxb8, a striking behavioral pattern emerged. Mice began to over-groom themselves, and persisted in this behavior even after developing severe facial and body lesions[75]. Because Hoxb8 is also located in the periphery and Hoxb8 KOs demonstrated defects in nociception (which could theoretically drive excessive grooming behavior due to lack of peripheral sensory feedback), a follow-up study was performed to localize the cells responsible for the phenotype[76]. In this study, Chen et al observed that the only cells in the brain labeled by the Hoxb8 lineage were bone-marrow derived microglia[76]. Strikingly, when they performed bone marrow transplants in HoxB8 KOs whose brains had been irradiated to remove all resident knockout microglia, they observed a complete reversal of the abnormal grooming behavior accompanied by repopulation of the brain with microglia from the healthy transplant donor mouse. This intervention did not rescue the nociceptive deficits, suggesting that the grooming abnormalities were not linked to peripheral nervous system defects. Though future studies will be needed to further specify the locus of these effects in the brain, together, these two studies generally highlighted the potential importance of perseverative grooming as a mouse behavior relevant to OCD, and raised the intriguing possibility that microglial pathology could be relevant to this disorder. Though further work needs to be performed, this finding is of particular clinical interest because of the potential link between pediatric-onset OCD and autoimmune dysregulation, which has been proposed as a factor in PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection)[77,78]. Additional human genetic studies will also be necessary to clarify the link between Hoxb8 gene disruption and the human OCD phenotype.

2.1.2. Slc1A1 knockout mice—One of the more consistently replicated genetic findings in OCD is an association with the neuronal glutamate transporter *SLC1A1* (protein: EAAT3 or EAAC1)[79–85], although a recent meta-analysis showed only a modest association of 2/9 SNPs with OCD[86], and *SLC1A1* has not emerged as a probable locus from recent GWAS studies[72,73]. Findings cluster in the 3′ region, with most evidence for association with the rs301430C allele. In cell models and brain tissue, this allele is associated with increased *SLC1A1* expression, suggesting that overexpression contributes to OCD susceptibility[80]. Coding variants are very rare (3/1400 subjects screened) and do not clearly segregate with OCD[87,88]. Thus, noncoding polymorphisms most likely account for the association of *SLC1A1* with OCD.

Though SLC1A1 knockout mice do not demonstrate clear OCD-relevant phenotypes, they have not yet been screened in targeted behavioral tests[89]. In addition, and perhaps more importantly, it is likely that brain-wide deletion is less relevant to OCD pathophysiology than targeted alteration of expression. Given that the SLC1A1 non-coding variants most clearly associated with OCD appear to be associated with increased gene expression, over-

expression of the gene may be more relevant to OCD pathophysiology. Ongoing studies are therefore investigating whether tissue-specific manipulations of *SLC1A1* are more relevant to the human clinical phenotype. Examining the outcome of targeted expression changes in specific neural circuits will allow us to directly address the molecular, cellular, and behavioral impact of this OCD candidate gene.

2.1.3. SAPAP3 knockout mice—More recently, it was serendipitously determined that SAPAP3, a post-synaptic density protein concentrated in cortico-striatal synapses, may be relevant to particular OCD subtypes[90]. Targeted knockout of this gene led to the development of perseverative grooming behavior resulting in facial lesions, generating a phenotype that was strikingly similar to that observed in the Hoxb8 KO model. However, in addition to the abnormally elevated grooming, SAPAP3 KOs also displayed increased anxiety when tested in the elevated zero maze. Interestingly, both of these behaviors were reversed after administration of fluoxetine at 5mg/kg for 6 days, which likely represents a subchronic administration paradigm when compared to human treatment regimens. Lentiviral rescue of SAPAP3 via broad injections in the striatum normalized both the grooming and the anxiety-like behaviors. Furthermore, *in vitro* electrophysiologic investigation began to determine the pathophysiologic mechanisms underlying these abnormal behaviors by demonstrating that SAPAP3 KOs had decreased fEPSP amplitudes compared to controls (dominated by AMPAR transmission in the recording conditions used), and increased NMDAR fEPSPs; this is consistent with their observation of altered NMDA receptor subunit composition reflecting a more immature ‘juvenile’ subtype (i.e. increased levels of NR2B and decreased levels of NR2A subunits). An additional study isolated these disturbances to cortico-striatal, rather than thalamo-striatal, synapses[91]. Though genetic investigation in a relatively small group of patients based on these results found no association of SAPAP3 SNPs with OCD, it did find associations in a subset of OCD patients with grooming disorders (e.g. pathological skin-picking, trichotillomania, nail-biting)[92]. It is important to note that despite these findings, SAPAP3 has not neared genome wide significance in OCD GWAS studies to date. However, the *DLGAP1* gene (alternative name for another SAPAP family member, SAPAP1) appears to be emerging as a leading candidate from GWAS studies (though it has not reached unambiguous genome-wide significance), potentially providing further evidence of a role for this gene family in OCD pathophysiology[93]. Independent of the human studies, the findings from SAPAP3 KO mice clearly demonstrate a link between molecular changes at cortico-striatal synapses and repetitive pathological behaviors.

2.1.4. Slitrk5 knockout mice—In a similar unexpected finding, Shmelkov et al (2010)[94] determined that knockout of the Slitrk5 post-synaptic protein led to abnormal behaviors potentially relevant to OCD. Slitrk5 is a transmembrane protein that is enriched at cortico-striatal synapses, and consists of an extracellular domain that shares homology with the Slit/Robo family of axon guidance molecules, and an intercellular domain that shares homology with the trkB receptor. Though the function of these proteins is still under investigation, they have been implicated in neuronal survival, outgrowth of neuronal processes, and synapse formation[95]. Interestingly, although an *a priori* link was previously established between *Slitrk1* and Tourette’s Syndrome based on genetic studies, knockout of the Slitrk1 gene did

not lead to abnormal repetitive behaviors; rather, it led to increased anxiety measured using the elevated plus maze, and increased immobility time on the forced swim and tail suspension tests[96]. In contrast, targeted inactivation of Slitrk5, which had a comparatively unknown function and no previous link to psychiatric disorders, led to perseverative grooming resulting in lesions and increased anxiety. Both of these behaviors were reversed by treatment with chronic, but not acute, fluoxetine, which is consistent with the pharmacologic response profile seen in OCD patients[97,98]. Notably, Slitrk5 KOs also showed selective overactivation of OFC, as measured by baseline expression of the immediate early gene, FosB, providing another parallel to human fMRI and PET studies demonstrating baseline OFC hyperactivation. In addition, they show decreased expression of striatal glutamate receptors, with decreased levels of GluR1, GluR2, NR2A, and NR2B. Combined with the findings from SAPAP3 KO mice discussed above, this suggests a model whereby disruption of striatal post-synaptic density proteins leads to abnormal trafficking and insertion of glutamate receptors in striatal synapses, and abnormal cortico-striatal communication. Whether these disruptions in synaptic function are specific to particular projections or neuronal subtypes remains to be determined. In an attempt to link these findings back to humans, preliminary evidence indicates the presence of rare Slitrk5 genetic variants in OCD patients; however, these findings must still be validated (F. Lee, personal communication).

2.1.5. Specificity of repetitive behaviors for OCD?—Notably, many transgenic strains billed as animal models of OCD have similar behavioral profiles as those seen in animal models of highly comorbid disorders, such as Tourette's syndrome and autism. For example, the two transgenic OCD animal models most studied to date (SAPAP3 and Slitrk5 KO mice) both demonstrate increased perseverative grooming leading to facial lesions and anxiety, and Hoxb8 KOs similarly demonstrate perseverative, self-destructive grooming. These phenotypes are most strikingly shared with mouse models of autism[99] [e.g. Shank3 KOs[100] and BTBR[101]). It is therefore an increasingly important topic for the field to identify shared versus specific neural circuit abnormalities and behavioral phenotypes that can distinguish animal models of distinct but comorbid complex psychiatric disorders.

2.1.6. Future Directions—The transgenic models described above have been incredibly useful for generating new insights into potential pathophysiologic mechanisms underlying OCD-relevant behaviors. By generating new transgenic models based on more definitive GWAS studies, or combining multiple genes of small effect in a single animal model, the field may be able to better recapitulate the neurodevelopmental progression of OCD in preclinical models.

2.2. Strategies for Testing Function of OCD-related Circuits in Rodent Models

As described above, convergent evidence from human functional and structural imaging studies implicates cortico-striatal-thalamic circuit dysfunction in OCD. However, because causality cannot be directly tested in human studies, it is not possible to determine whether this dysfunction leads to OCD symptoms, is a compensatory response that results from attempts to fight symptoms, or is simply an epiphenomenon. New technologic approaches can now be used to tease these possibilities apart. In this section, we will review advanced

circuit dissection techniques and recent studies from the OCD animal literature that exploit novel approaches to determine whether CSTC circuits are necessary and/or sufficient to either generate or alleviate OCD-like symptoms in mice.

2.2.1. Transgenic Circuit Dissection—One of the earliest direct investigations testing the potential role of cortico-striatal circuits in OCD-related behaviors was performed by Campbell et al[102]. Hypothesizing that cortico-striatal circuit activation would lead to OCD-like behaviors, they creatively used transgenic technology to drive expression of the active subunit of cholera toxin under the control of the dopamine 1 receptor (D1) promoter (D1-CT mice). This led to excessive stimulation of a random subset of D1-expressing neurons, which were concentrated in layers 2 and 3 of the somatosensory cortex (which stimulate layer V striatal-projecting cortical neurons in motor cortex), the amygdala intercalated nucleus (which ultimately regulates amygdala output to ventral striatum), and layer 2 of the piriform cortex (which stimulates ventral striatum/nucleus accumbens). These animals displayed an interesting and complex phenotype. Whereas normal mice tend to engage in many different behaviors for short periods of time in their natural environment and show frequent behavioral switching, D1-CT mice demonstrated behavioral perseveration independent of the behavior they were engaged in, and were less likely to switch to a new behavior. This general tendency towards perseveration independent of the specific behavior involved may have particular relevance for OCD compared to other disorders demonstrating abnormal repetitive behaviors, because compulsions observed in OCD tend to be composed of multiple behaviors performed in sequence, as opposed to more stereotyped repetitive behaviors such as are typically observed in autism (repetitive hand-flapping, rocking) or Tourette's syndrome (repetitive stereotyped motor or vocal tics). In addition, there is evidence that compulsive rituals in OCD tend to be more flexible over time in comparison to stereotyped repetitive behaviors seen in other disorders[49]; which compulsion is performed in response to an intrusive thought can change depending on context, environmental circumstances, or life stage, suggesting that the abnormal motor programs are not as rigid as those observed in other disorders. Because the cholera toxin was expressed in a random distributed subset of neurons and the systems level effects on circuit activation are therefore complex, the specific neuronal subpopulations responsible for these intriguing behavioral findings remain to be determined. Also, since the D1-CT transgene stimulates cortical layer 2/3 neurons, rather than directly stimulating cortico-striatal afferents, the construct validity for OCD is debatable. As will be seen below, new technologic advances now permit refined manipulation of specific circuits in order to identify which brain subregions and cell types are involved in the generation of abnormal repetitive behaviors.

2.2.2. Optogenetic Dissection—Though many different theories exist regarding the etiology of OCD symptoms, two major models of OCD pathophysiology have recently been investigated using optogenetic technology. First, as discussed briefly above, it is has been suggested that OCD symptoms result from deficits in inhibitory control. This concept is based on a group of studies demonstrating either behavioral deficits in OCD patients during inhibitory control tasks such as the Stop Signal Task (SST) and Go/No-Go, or abnormal activation of cortical and striatal regions during normal performance on these tasks[32,51,103–105]. Although findings in the human literature are not always consistent across

studies (see [106]), this body of work has led to the proposal that compulsive behaviors in OCD emerge during failures of normal inhibitory processes. By extension, this theory suggests that improvements in inhibitory control may decrease the frequency of performance of compulsions.

To investigate this theory in an animal model system, Burguiere et al[62] trained SAPAP3 KOs and wild-type mice in a conditioned grooming task. In response to an unconditioned stimulus (drop of water on the forehead), both SAPAP3 KOs and wild-type controls demonstrated increased grooming. If a conditioned stimulus (tone) was played before the water drop was delivered, both WT and SAPAP3 KOs acquired conditioned responses and groomed in response to the tone early in the training paradigm. However, later in training, when WT mice began to inhibit their response to the tone, instead delaying grooming until the water drop was presented, SAPAP3 KO mice continued to groom both in response to the tone and in response to the water drop. These findings were interpreted as evidence of impaired inhibitory control in the SAPAP3 KO mice. To next determine if inhibitory control could be enhanced in the SAPAP3 KOs via manipulation of cortico-striatal circuit function, the authors expressed the excitatory light-activated ion channel, channelrhodopsin (ChR2), in the lateral orbitofrontal cortex (lOFC) of both SAPAP3 KOs and wild-type controls. Activation of ChR2 (10Hz 473nm blue light) in either lOFC cell bodies or lOFC terminals projecting to the centromedial striatum in SAPAP3 KOs led to a shift in grooming responses away from the tone (conditioned stimulus) towards the water drop (unconditioned stimulus), thus rendering the behavioral profile more like a healthy control. This was accompanied by normalization of the striatal firing rate, which was increased at baseline compared to controls. Further experiments indicated that the impaired behavior and excessive striatal firing resulted from decreased functioning of fast-spiking interneurons in SAPAP3 KO striatum, and that 10Hz stimulation of lOFC to centromedial striatum projections compensated for the impaired interneuron function. This intriguing paper highlighted the potential importance of lOFC activation in overcoming response inhibition deficits, which may provide mechanistic insight into observations of lOFC hypofunction in OCD patients during neurocognitive tasks.

A second (but not mutually exclusive) theory suggests that OCD does not result from primary deficits in inhibitory control, but rather stems from a stronger drive to perform abnormal compulsive behaviors in response to either a greatly increased frequency of intrusive thoughts or increased likelihood that intrusive thoughts will persist. In this scenario, even if cognitive control processes are functioning normally, they may not be sufficient to inhibit the performance of compulsions. In the context of this theory, the etiology of the increased drive is still unknown, but could result from increased baseline activation of the direct vs. indirect pathway [59], abnormal reward processing leading to increased performance of goal-directed behaviors[107], or enhanced motivation to perform avoidance-related behaviors[108].

A second set of optogenetic experiments investigating OCD-relevant behaviors using mouse models may lend support to this theory. To simulate the orbitofrontal cortex and striatal hyperactivity observed in OCD patients in human functional imaging studies, Ahmari et al[61] injected ChR2 into glutamatergic neurons of medial OFC (mOFC). By selectively

stimulating striatal terminals on projections from mOFC to ventromedial striatum (VMS), we were able to activate only mOFC-VMS synapses, and determine the impact of stimulation on OCD-relevant behaviors. While acute optogenetic stimulation of mOFC-VMS projections had no impact on OCD-like behaviors, instead leading to an increase in locomotion, repeated stimulation for only five minutes a day over the course of 5–7 days led to a gradual and progressive increase in grooming behavior. Notably, this increase in grooming was not time-locked to the stimulation, suggesting that neural plasticity changes were required for the development of the abnormal perseverative grooming. Though an alternative interpretation would be that the brain regions responsible for the abnormal behaviors are downstream of the OFC-VMS synapse, the plasticity theory was supported by our finding that repeated stimulation of OFC-VMS projections led to an increase in evoked firing rate at mOFC-VMS synapses as measured by *in vivo* electrophysiology. Further supporting the potential relevance of these findings to OCD, we observed that chronic (but not acute) treatment with high-dose fluoxetine (18mg/kg) normalized both the repetitive grooming behavior and the increase in evoked firing rate induced by repeated optogenetic stimulation. Because serotonin reuptake inhibitors such as fluoxetine are effective in a subset of OCD patients when used chronically at high doses, this further supports the potential relevance of these circuits both in the pathology and the treatment of OCD. Furthermore, these findings support the idea that increased pathologic drive through OFC-striatal circuits can lead to increased selection of pathological actions. Ongoing work is examining the relationship of these processes to reward learning, and further dissecting the molecular and cellular mechanisms underlying the progressive evolution of abnormal repetitive behaviors.

2.2.3. Chemogenetic Dissection—Another recently developed set of technologies, which fall broadly under the category of chemogenetics, are also currently being used in animal models to probe the neural circuits linked to OCD. These tools allow for cell-type specific expression of mutant G-protein coupled receptors (GPCRs) that can be activated by administration of small synthetic molecules; the mutant GPCRs are known as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). The designer drugs can be administered either systemically via drinking water or intraperitoneal injection, or locally via intracerebral infusion, thus maximizing the flexibility of the system. Since these artificially synthesized drugs have been designed to be otherwise inert, after administration they only activate receptors that are localized on the cell populations of interest. Whereas optogenetic technology allows for rapid and specific activation and inhibition, DREADD technology yields more sustained activation and inhibition that may be more consistent with pathophysiologic processes. Though this technology has not yet formally been applied to the investigation of OCD-related behaviors, it is currently being used to investigate the neural circuits underlying behavioral functions that may be relevant to OCD, as further described in Section 3.

3. Leveraging Rodent Behavioral Assays Relevant to OCD

As highlighted in the above discussion, significant progress has been made in identification of genes and circuits whose dysfunction leads to abnormal repetitive behaviors that may have relevance to OCD and related disorders. In order to capitalize on these advances, it is

important to combine these transgenic, optogenetic, and chemogenetic methods with the rich history of rodent behavioral models examining OCD-relevant tasks. While some of these behavioral models have been developed with an eye towards face validity– i.e. tasks which lead to the development of perseverative behaviors that 'look like' compulsive rituals in OCD– others directly translate tasks which show abnormalities in human OCD patients into rodent models. In the sections below, we will first give a brief overview of non-transgenic behaviorally-based animal models that demonstrate face validity for perseverative behaviors, and finish by discussing promising behavioral tasks identified in human OCD studies that are currently being dissected using rodent model systems.

3.1. Spontaneous Perseverative Behaviors

The study of OCD using animal models is grounded in a longstanding literature based on observations of animals engaged in spontaneous, stereotyped, seemingly purposeless or self-destructive behaviors. These include barbering (repetitive hair biting and pulling), acral paw-lick (repetitive paw-licking leading to lesions in dogs), and zoo-related stereotypies (e.g. pacing in stereotyped patterns around cages) (see [109–111] for review). In contrast to these examples, which tend to be observed in captivity or in stressful conditions, deer mice, which have been suggested as an ethological model of OCD, demonstrate repetitive running, jumping, and flipping behaviors at baseline[112]. Though the exact relationship between these spontaneous repetitive behaviors and OCD is unclear, and the role of stress in their generation may be confounding, these models can be used to dissect circuits underlying stereotyped behaviors via either targeted lesions or drug injections through stereotactically-placed cannulae. For example, striatal *in vivo* microdialysis in deer mice showed that increased glutamate directly preceded stereotyped behaviors, lending support to the hypothesis that dysfunction in glutamatergic signaling may lead to OCD symptomatology[113]. This example demonstrates the potential utility of models showing spontaneous repetitive behaviors for both generating and testing hypotheses about pathophysiology.

3.2. Interactions with Physical Objects

Early investigations of non-spontaneous OCD-related behaviors generally observed animal behavior during interactions with artificial objects, and determined the extent of the repetitive or stereotyped nature of these actions. Examples include nestlet shredding[114], screen gnawing[115], digging[116], and marble burying[114], which has gained particular prominence as a tool for genetic screening in recent years. Of note, it is difficult to determine the relevance of findings from these assays to human OCD, because many of these tests are species specific (e.g. screen gnawing and nestlet shredding). In addition, the pharmacologic response profile of digging-related tasks, particularly marble burying, may be more consistent with that of generalized anxiety (i.e. responsive to benzodiazepines) than of OCD[117]; however, there is also evidence that marble burying is not correlated with anxiety measures in the open field and light-dark test, and may be more appropriately considered as a proxy measure of repetitive digging[118]. All told, it is therefore likely that more complex behavioral paradigms may have greater translational relevance for the study of OCD neural circuitry.

3.3. Pharmacologically-induced Perseverative Behaviors

Classic pharmacologic approaches have also been used to study abnormal repetitive behaviors. Though much of this literature focuses on stereotyped behaviors generated by amphetamine administration, two pharmacologic stimulation models have been investigated which may have greater relevance to the abnormal repetitive behaviors observed in OCD.

3.3.1. Quinpirole-induced checking—In the late 1990's, Szechtman et al[119] discovered that chronic administration of the D2/D3 agonist quinpirole led to the development of compulsive checking behavior in rats. Specifically, in an open field environment, rats revisited objects excessively, and performed specific behavioral sequences when revisiting these preferred locations. These behaviors were partially attenuated by clomipramine, the tricyclic antidepressant with the most selectivity for serotonin reuptake inhibition and one of the first-line treatments for OCD. Interestingly, this finding of partial (but not full) attenuation may actually suggest pharmacologic relevance of this model to the majority of OCD patients, who demonstrate partial treatment responses to serotonin reuptake inhibition. Further work has explored the utility of this model for the investigation of the mechanism of action for deep brain stimulation (DBS) treatment in OCD, and has provided preclinical evidence supporting a potential role for high frequency DBS of both STN[120] and nucleus accumbens[121]. Furthermore, recent work has extended these findings by demonstrating that quinipirole also increases checking-like behavior in an operant-based observing response task with uncertain reinforcement[122]. Thus, the quinpirole-induced checking model may yield insights into pathophysiologic mechanisms relevant to OCD, and provide some utility as a preclinical screen for pharmacologic treatments.

3.3.2. Serotonin-1B Receptor (5-HT1B) Agonist Administration—Although the role of the 5-HT1B receptor in aggressive and impulsive behaviors has been more clearly delineated[123–128], some evidence from pharmacologic challenge studies[129] also suggests that abnormalities in 5-HT1B receptor function (sometimes referred to as 5-HT1D-beta in human literature) play a role in OCD. In addition, though weak, some genetic association studies provide tentative aggregate support for a role in OCD[130]; however there was a lack of an association in a recent meta-analysis[74]. Studies based on these findings investigated the potential relationship between 5-HT1B stimulation and the development of abnormal repetitive behaviors. Shanahan *et al* found that injection of a 5-HT1B agonist leads both to perseverative locomotion and prepulse inhibition deficits (also observed in OCD patients), both of which are reversed with chronic, but not acute, fluoxetine treatment[131]. A follow-up study localized the responsible receptors to the orbitofrontal cortex (OFC) [132], providing parallels to the circuit abnormalities seen in OCD patients, and a more recent study indicated that 5-HT1B agonist treatment also led to impaired performance on the delayed alternation task[133], paralleling impaired performance in OCD patients (see Section 3.4.2). A strength of this model is that it exhibits strong predictive validity for the chronic time course and high serotonin reuptake inhibitor dose necessary for effective OCD treatment in the subset of patients who are treatment responders.

3.4. Tasks Demonstrating Abnormal Performance in OCD Patients

With expansion in the number of complex rodent behavioral tasks, and increased availability of animal paradigms that are designed to directly mimic human tasks, we are now better able to directly assess neurocognitive functions relevant to OCD using animal models. Many recent human studies have uncovered either altered performance or abnormal brain activation patterns in OCD patients during behavioral tasks that can be translated into rodents. Though a detailed review of the animal literature related to circuit dissection of each of these paradigms is beyond the scope of this review, we will highlight the findings from the human literature, as well as important next steps in animal models given these results.

3.4.1. Reversal Learning—Reversal learning is an important measure of cognitive flexibility, which is thought to be impaired in OCD patients. This is manifested symptomatically in both the tendency to repeatedly perform compulsive ritualized behaviors, and the difficulty of engaging in alternative behaviors in response to obsessive thoughts. Abnormal reversal learning performance (either impaired learning or slower reaction times) and altered neural activity during reversal learning combine to form one of the more well-replicated neurocognitive findings in OCD patients[47,134–136]. Improved reversal learning has been demonstrated following treatment with a serotonin reuptake inhibitor in rodents[137–139], while serotonin depletion leads to impairments in human subjects[140–142], suggesting that involved neural mechanisms may be relevant to OCD pathophysiology. Dissection of neural circuits underlying reversal learning in rats has made substantial progress, and has focused on the lateral OFC and ventral striatum as key involved regions. Whether similar brain regions are involved in reversal learning in mice remains to be seen, though Gourley and colleagues have demonstrated involvement of mOFC in a mouse instrumental reversal paradigm[143]. Future work will link findings from mice and rats, and leverage new technologies to determine how online manipulation of activity in specific brain regions impacts this cognitive process.

3.4.2. Delayed Alternation—Another translatable behavioral task that has been proposed to measure behavioral reversal in the context of a distinct aspect of set-shifting is the delayed alternation task[144,145]. Though this task shares some similarities with reversal learning tasks described above (i.e. it is thought to measure the ability to learn a rule and then subsequently inhibit and/or reverse it to achieve reward[145]; it has been shown to be dependent on OFC function[146]), and has a distinct structure which may require different learning mechanisms that have different underlying neural substrates. Specifically, it requires immediate shifting of strategy after a correct response, as opposed to learning and maintaining a particular set and then adopting a new strategy when the rule is changed. Deficits on this task have been observed in OCD patients with consistency[147–150], and more recently, have been isolated to perseverative errors following correct responses[147]. Translating the delayed alternation task to mice may therefore yield insight into potential molecular and circuit mechanisms relevant to OCD, as highlighted by Woehrle et al[133], who have shown that 5-HT1B receptor activation leads to impaired delayed alternation task performance, and that this deficit is prevented by chronic fluoxetine pre-treatment.

3.4.3. Habit Learning—As discussed briefly above, exciting new developments in the OCD clinical literature have highlighted the potential importance of abnormal habit learning in the pathophysiology of OCD. Recent studies demonstrated that OCD patients shift towards habitual rather than goal-directed behavior on an instrumental learning task. Although participants with OCD were able to flexibly adjust their behavior during the training phase of the task in order to optimize the likelihood of receiving rewards in response to stimuli, they showed overreliance on habits and impaired flexible goal-directed responding during the subsequent 'slips of action' and outcome devaluation task[56]. Further support for impairments in goal-directed behavior was provided in a subsequent study examining counterfactual decision-making in OCD patients, which is the ability to prospectively compare the expected results of action-outcome scenarios, and use these findings to guide economic choices. Compared to healthy controls, OCD patients had disrupted goal-directed forward modeling, relying instead on current expected value to make their economic decisions; this is consistent with a model of disrupted goal-directed cognitive behavior in OCD[151]. Furthermore, two recent studies in separate cohorts of patients have determined that this overreliance on habit formation also extends to habits formed in avoidance of a feared stimulus, which may be more relevant to the symptoms observed in OCD patients[57,108]. In these studies, subjects were overtrained on a shock-avoidance task. Though a devaluation sensitivity task showed that both OCD patients and controls could inhibit unnecessary behavioral responses before overtraining, OCD patients exhibited greater avoidance habits after overtraining, despite appropriate ratings of shock expectancy. Subsequent fMRI demonstrated hyperactivation of the caudate in OCD patients with excessive habits, as well as hyperactivation of mOFC during the acquisition of avoidance behavior.

These human studies suggest that the switch from goal-directed behaviors to habits is an important area for future investigation in preclinical OCD research. Optogenetic and chemogenetic approaches are now being applied to understand the neural circuit mechanisms underlying this switch. Towards this goal, two recent studies investigated the development of habitual behavior using a combination of optogenetics and in vivo electrophysiology in awake behaving animals. In the first study, rats were overtrained on a maze task to develop habitual behavior. When infralimbic cortex activity was subsequently disrupted using halorhodopsin, online blockade of habitual behavior occurred within an average of 2–3 trials[152]. This led to the suggestion that the manifestation of habits is under cortical control, and that modulation of the involved circuits could potentially serve as a targeted treatment for disorders with excessive habit formation. In the second study, they observed that the shift from goal-directed to habitual behavior was correlated with activation of neural ensembles in the infralimbic cortex and sensorimotor striatum, and that the upper layers of the infralimbic cortex closely tracked habit states late in overtraining. Subsequent optogenetic disruption of infralimbic cortex activity using halorhodopsin during overtraining again prevented habit formation[153].

In a more recent study, a novel instrumental lever-pressing task was developed in which individual mice switched between goal-directed (Random Ratio schedule) and habitual actions (Random Interval schedule), allowing within-subject comparisons. By performing

simultaneous *in vivo* recordings in OFC, dorsomedial striatum, and dorsolateral striatum during this paradigm, they demonstrated that the same neurons have different activity patterns depending on whether an individual lever press is goal-directed or habitual, suggesting the absence of distinct neuronal ensembles that control goal-directed vs habitual actions. They also showed that OFC and dorsomedial striatum become more engaged when lever presses are goal-directed, whereas dorsolateral striatum becomes less active. Reinforcing the importance of the OFC for goal-directed behavior, they found that OFC inhibition using DREADDS led to a disruption of goal-directed lever presses, while selective optogenetic activation of OFC led to increased lever pressing for goal-directed actions (Random Ratio schedule) only in the devalued condition, and did not simply increase the number of lever-presses overall. Notably, optogenetic stimulation did not change habitual actions (Random Interval schedule). The authors suggest that these results reveal an important role for OFC in re-evaluating outcomes to guide appropriate performance of instrumental actions, which may have implications for the generation of behaviors that are compulsively performed even when the outcome is devalued[107]. The relationship of such behaviors to the compulsions observed in OCD remains to be determined.

3.4.4. Sensorimotor Gating—Deficits in sensorimotor gating as measured by prepulse inhibition (PPI), a neural process that has been linked to cortico-stratial-pallido-pontine circuits[154], have been observed in many psychiatric disorders. Though PPI deficits are classically associated with schizophrenia, they have also been observed in OCD[53,155,156]. The reflexive PPI response is typically calculated by measuring the amplitude of the eyeblink in response to a startling auditory stimulus, and then determining how much the response is inhibited by presentation of a lower decibel ‘prepulse’ before the startling stimulus. Our recent publication suggests that PPI deficits may be more prominent in patients who have a history of past or current tic disorder[53], which may yield clues regarding differences in the neural circuitry underlying different OCD subtypes–specifically, tic-related vs non-tic-related OCD. This finding may also offer a circuit-level explanation for the extensive comorbidity between schizophrenia, Tourette’s Syndrome, and OCD, all of which demonstrate PPI deficits. Though the neural circuitry of PPI has not yet been explored using optogenetic approaches, further dissection of this important translational endophenotype may help to further address these questions.

3.4.5. Response Inhibition—As discussed in Section 2.2 above, a prominent theory in the OCD human literature suggests that performance of compulsive behaviors may be related to deficits in response inhibition. According to this theory, when presented with a trigger (for example, a stove), someone who suffers from OCD would have difficulty inhibiting their conditioned response to the trigger (for example, checking repeatedly to make sure the stove is turned off in order to prevent the house from burning down). Though this theory contrasts with the idea that OCD may be more related to excessive drive to perform actions (i.e. behavior that is goal-directed but is focused on maladaptive/misdirected actions), these concepts are not mutually exclusive–i.e. subthreshold impairments in response inhibition could couple with an increased propensity towards goal-directed actions, leading to the performance of compulsive behaviors. In keeping with this concept, several studies have now demonstrated impaired response inhibition in adults with OCD and/or first-

degree relatives using a standard Stop Signal Task[32,52,105,157], which assesses the ability to inhibit a prepotent motor response. Similarly, there is evidence for abnormal brain activation in OCD patients during response inhibition measured with other tasks, including the Stroop[36,158,159] and the Simon tasks[160]. Though in sum, a recent meta-analysis suggests that the effect sizes observed across studies of response inhibition in OCD are not clinically significant[106,161], another recent study suggests differently[51]. Thus, sufficient positive data have been reported that more detailed investigation of the neural correlates underlying response inhibition is warranted. Significant inroads have already been made using refined lesion and pharmacologic blockade studies in rats (for example, see[162–164]); future studies will more precisely dissect the neural circuits and specific cell types involved using advanced technologies in mouse model systems.

3.4.6. Fear Learning—Though OCD is no longer classified as an anxiety disorder according to DSM-5, it is widely accepted that anxiety is an important component of the disorder. Though it is still unclear whether anxiety plays an etiologic role in the generation of OCD or instead is a consequence of symptoms, from a clinical perspective, ritualized behaviors are typically performed with the conscious intent of reducing anxiety or dread associated with obsessive thoughts. Notably, this is an effective, albeit temporary, strategy for short-term resolution of anxiety, although it ultimately leads to maintenance or even strengthening of anxiety due to continuous reinforcement of compulsive behaviors.

To further explore the relationship between OCD and anxiety, researchers have recently begun to examine the construct of fear learning in OCD patients. Milad et al (2013)[54] demonstrated that although OCD patients have normal fear learning when compared to healthy controls, they have impaired fear extinction recall when responses are examined 1 day later. This has significant implications for whether there are particular OCD subpopulations that would have difficulty maintaining gains that they obtained while engaged in exposure therapy due to extinction recall impairment.

Another aspect of fear learning which is just beginning to be explored in OCD is the formation of habits in avoidance. As discussed above, there is increasing evidence from the human literature that people with OCD are more prone to forming habits than healthy controls. Recent work by Gillan et al[108] has demonstrated that this does not occur only for appetitive habits, but also for habits in avoidance. In fact, it has been suggested that avoidance habits may have even more direct relevance to OCD than appetitive habits, since compulsions in OCD patients tend to be performed specifically to avoid or diminish the impact of anxiety-provoking stimuli. Paradigms to explore this construct in rodents are now being developed[165] to facilitate dissection of the involved circuits.

3.4.7. Translation from rat to mouse—Though the rich behavioral paradigms described above have classically been developed and used in rats, these complex paradigms are now increasingly being translated into murine models to take advantage of core facilities offering widely-available genetically-based tools for assaying cell-specific functions–e.g. cell- and tissue-specific Cre transgenic lines (Gensat; Allen Brain Atlas; JAX Cre resource); and cell-specific optogenetic and chemogenetic viral vectors (Penn Vector Core; UNC Viral Vector Core). The development of CRISPR technology is beginning to make these cell-specific

interventions more feasible in rats, and will ultimately pave the way towards using similar approaches in primate species such as marmosets. Thus, future studies may be able to identify the cells and circuits underlying higher order cognitive functions relevant to OCD in primate species with cortical development similar to humans.

4. Conclusions

The Future: Application of Findings from Animal Models to Develop Targeted Treatments

The examples described above clearly demonstrate the utility of animal models for investigation of pathologic abnormal repetitive behaviors. However, critical evaluation of transgenic, pharmacologic, optogenetic, and chemogenetic models is crucial to determine their relevance to OCD. As described in Section 3, using translatable probes of neural circuits that are reliably abnormal in OCD patients is one method for validation, to help ensure that dissection of molecular and cellular abnormalities will ultimately yield information relevant for treatment development[166].

Since the development of improved treatments is one of the major goals of preclinical neuropsychiatric research, it is important to consider how the different approaches described above may be useful for development of different types of treatment. For example, transgenic animal models may be particularly useful for drug development where high-throughput screens are required, because of the ability to rapidly generate large cohorts with relatively stable behavioral abnormalities. In contrast, optogenetic and chemogenetic techniques may be more important for the development and refinement of circuit-based treatment approaches, including deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS). Finally, as cumulative evidence begins to highlight abnormalities of particular neurocognitive functions in OCD, such as sensorimotor gating, reversal learning, response inhibition, goal-directed versus habitual behavior, and fear-extinction, we will be able to apply findings from the rich literature investigating the basic neurobiology of these core neural processes to gain improved understanding of circuit dysfunction in OCD, which may be helpful for development of psychotherapeutic approaches. Detailed investigation of these behavioral constructs, which have relevance to both OCD and other psychiatric disorders, may ultimately lead to the development of treatments for symptoms that cross disease boundaries.

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Highlights

- OCD is a severe, chronic, and prevalent disorder that affects 1.5–3% of people
- Animal models can be used to dissect pathologic changes underlying OCD
- Methodologic advances allow precise manipulation of genes and circuits in mice
- Combining these tools with behavior can advance our understanding of OCD pathology