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REVIEW ARTICLE

Animal models of obsessive-compulsive spectrum disorders

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Obsessive-compulsive disorder (OCD) and related conditions (trichotillomania, pathological skin-picking, pathological nail-biting) are common and disabling. Current treatment approaches fail to help a significant proportion of patients. Multiple tiers of evidence link these conditions with underlying dysregulation of particular cortico-subcortical circuitry and monoamine systems, which represent targets for treatment. Animal models designed to capture aspects of these conditions are critical for several reasons. First, they help in furthering our understanding of neuroanatomical and neurochemical underpinnings of the obsessive-compulsive (OC) spectrum. Second, they help to account for the brain mechanisms by which existing treatments (pharmacotherapy, psychotherapy, deep brain stimulation) exert their beneficial effects on patients. Third, they inform the search for novel treatments. This article provides a critique of key animal models for selected OC spectrum disorders, beginning with initial work relating to anxiety, but moving on to recent developments in domains of genetic, pharmacological, cognitive, and ethological models. We find that there is a burgeoning literature in these areas with important ramifications, which are considered, along with salient future lines of research.

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Introduction

Obsessive-compulsive disorder (OCD) is a widespread and debilitating neuropsychiatric disorder with lifetime prevalence of 2–3% worldwide.[1,2] It is characterized by the presence of obsessions (repetitive intrusive thoughts entering into the stream of consciousness that are difficult to suppress) and/or compulsions (repetitive mental or physical rituals undertaken according to rigid rules or in response to obsessions).[3] Several other conditions, less well studied, share phenomenological and comorbid overlap with OCD and thus have been argued to constitute related "obsessive-compulsive (OC) spectrum conditions."[4–7] Key examples include grooming disorders (trichotillomania, ie, pathological hair-pulling; pathological skin-picking; pathological nail-biting), body dysmorphic disorder (BDD), Tourette syndrome, and pathological gambling (PG).[6,8,9]

Animal models represent a useful means of studying behavioral phenomena of relevance to human OC spectrum conditions, including genetic, neurochemical, and neuroanatomical substrates. They are also of potential utility in identifying novel treatments, before they are put forward into human clinical trials, and in characterizing the mechanisms by which treatments exert their beneficial influences on overt symptomatology. This is important because major limitations exist, not only in our understanding of the genetic and neurobiological underpinnings of these disorders, but also in terms of treatments. For OCD, 30–40% of patients do not achieve an adequate treatment response, while some 10% of patients manifest a severe, chronic form of the condition that is refractory to all usual first-line interventions.[10] First-line treatment for OCD comprises serotonin reuptake inhibitors (SRIs) and/or cognitive behavioral therapy (eg, exposure and response prevention, or ERP). In some cases, neurosurgery, including deep brain stimulation (DBS), targeting key neural nodes (eg, striatum), has been deployed with success in alleviating symptoms. Even in such rare

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instances, knowledge of the key "targets" has been gleaned from animal research and translational models (see Pharmacological Models; Behavioural Models). For most OC spectrum conditions besides OCD, rigorous controlled trials are often so few in number that there are no established treatment algorithms.[11]

Early animal models of OC spectrum conditions focused on anxiety (or presumed anxiety for animals) and conditioning. Solomon *et al*[12] paired electric shocks with a light, thereby conditioning dogs to become anxious and exhibit escape behavior when lights were turned on. Solomon *et al*, subsequently, were able to demonstrate extinction of conditioned anxiety and of the urge to escape when the light was presented repeatedly without shock. Models such as these contributed to the development of exposure and response prevention (ERP),[13] a key first-line psychological treatment for OCD, in which patients are exposed—with the support of a therapist—to specific OCD-relevant anxiety-provoking situations for sustained periods of time, during which they are dissuaded from undertaking compulsions. With time, the OCD relevant triggers no longer elicit the same degree of anxiety, and the cycle of repetitive rituals is in some instances broken.

However, there has been a shift in emphasis in terms of how OCD is conceptualized: While considered an anxiety disorder in *The Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), *The Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-V) sees OCD shifted out of this category into "Obsessive-Compulsive and Related Disorders." This shift in focus has been paralleled by new conceptualizations regarding the underlying neurobiology of OC spectrum disorders, which are now considered in terms of overactive striatal habit-forming circuitry coupled with lack of sufficient top-down control over these habits by higher cortical regions responsible for salient executive functions, including response inhibition and cognitive flexibility.[14–16] Significant advances have been made in developing animal models germane to these processes, which cut across the spectrum. While the intrusive obsessional thoughts occurring in patients with OCD are inaccessible in animal models, and it is arguable whether "anxiety" can truly be captured in animal models, ingrained habitual patterns of responding and executive dyscontrol are readily amenable to translation and back-translation across species.

This review provides a concise critique of animal models purporting to capture aspects of select OC spectrum conditions in humans, focusing on OCD and grooming conditions, but also incorporating models of Tourette syndrome of potential relevance (see Table 1 for summary overview). We consider strengths and weaknesses of each model in relation to existing validation criteria, and where relevant, we draw parallels with findings in humans. By synergizing the literature, we highlight key directions for future translational and treatment studies.

Validation Criteria for Animal Models

Animal models of disease are useful for advancing our understanding of pathophysiology and in the development of new treatments.[17] It is impossible to develop an animal model that mimics a human psychiatric syndrome in its entirety, and so the validation criteria that an animal model must satisfy in order to establish its validity largely depend on the defined purpose of the model.[18–21] Models that fulfill different validities have different uses, for instance, construct validity is important for neurobiological research, whereas a model with predictive validity will be useful as a potential drug-screening tool. Animal models are traditionally evaluated on the basis of three criteria proposed by Willner[22,23]:

1. *Face* validity refers to the phenomenological similarity between the model and the disorder it models. The model should resemble the human condition in terms of its etiology, symptomatology, treatment, and physiological basis.
2. *Predictive* validity is the extent to which an animal model allows accurate predictions about the human condition based on the performance of the model. In practice, predictive validity usually describes the ability of a model to accurately predict treatment efficacy.
3. *Construct* validity refers to the similarity in underlying physiological and psychological mechanisms.

In addition, models are assessed for *reliability*, which means that the behavioral outputs of the model are robust and reproducible between laboratories.[20,21] Recently, *etiological* validity, which is defined as the similarity in early environmental and triggering factors, has also been proposed.[20] Based on these definitions, Geyer and Markou recommend that the evaluation of experimental models in neurobiological research should principally rely on reliability and predictive validity, with face and construct validity being highly subjective and sometimes difficult or even impossible to assess in animals.

Thus, to predict the response of a mental disorder to a new pharmacological treatment, a proposed animal model should produce a specific, measurable behavior reliably, which is pharmacologically analogous with the clinical disorder. However, predictive validity is limited by the lack of specificity of certain medications in human patients (ie, heterogeneity of response), and

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Table 1. *Summary of animal models of OC spectrum disorders*

Type	Model (key references)	Description	Face validity (modeled behavior)	Construct validity (neurotransmitter/anatomy)	Predictive validity
Genetic models	HoxB8 knockout mice[31,195]	Hoxb8 involved in neuronal development. Mice with knock-out show excessive auto-grooming.	++ (trichotillomania);+(OCD)	+ (gene expression in brain areas implicated in OCD)	? (Model suggestive of immune involvement in trichotillomania—ramifications for human research)
	Slitrk5 knockout mice[58]	Slitrk5 involved in development. Mice with knockout show excessive auto-grooming and increased anxiety-like behaviors.	++ (trichotillomania); ++ (OCD)	++ (increased FosB expression in OFC; anatomical abnormalities in striatum)	+ (response to fluoxetine)
	Sapap3 gene mice[53]	Sapap3 is a postsynaptic scaffolding protein. Mice with knockout show excessive auto-grooming and increased anxiety-like behaviors.	++ (trichotillomania); ++ (OCD)	++ (involvement of striatum and glutamatergic system)	+ (response to fluoxetine)
	Serotonin 2c receptor knockout mice[39]	Knockout leads to a range of compulsive-like behaviors	+/− (OCD; mimics behaviors relevant to other disorders as well)	+ (5-HT2c receptor involvement in OCD; 5-HT abnormalities)	?
	Dopamine transporter knock-down mice[40]	Express elevated free brain dopamine levels	+/− (OCD, TS; hyperdopaminergic tone relevant to other disorders as well)	++ (elevated free dopamine levels; may bear parallels with likely striatal dopamine involvement in OCD, trichotillomania)	?
	D1CT mice[33]	Transgenic mice expressing intracellular cholera toxin within subgroup of dopamine D1 receptor expressing neurons	+ (OCD, TS)	+ (transgene expressed in regions implicated in OCD)	?
	Aromatase knock-out mice[60]	The aromatase knockout mouse lacks a functioning aromatase enzyme and is therefore estrogen deficient	+ (trichotillomania); +/− (OCD). Mice display behaviors relevant to other disorders as well.	+ (associated with low COMT activity; evidence for involvement of estradiol in OCD)	?
Pharmacological models	Pharmacologically induced checking[78]	Chronic quinpirole or 8-OH-DPAT leads to excessive checking of a "home base" site in an open field	++ (OCD)	++ (involvement of dopamine, 5-HT) + (reduced by HFS of subthalamic nucleus, nucleus accumbens shell and core) - (no effect of OFC lesions)	+ (partial attenuation by clomipramine)
	8-Hydroxy-2-(di-ni-polylamino)-tetraline hydrobromide (8-OHDPAT)–induced decreased alternation[66]	Acute 8-OH-DPAT leads to perseveration of goal arm choice in a T-maze	+/− (OCD; motor perseveration relevant to others disorders as well)	+ (5-HT1a receptor involvement in OCD; involvement of 5-HT, modulation by sex steroids) - (no effect of OFC lesions, HFS of thalamic reticular nucleus)	+ (response to fluoxetine)
	Meta-chlorophenylpiperazine (mCPP)–induced directional persistence in reinforced spatial alternation[48]	Acute mCPP promotes expression of a side bias of a goal arm in a T maze	+/− (OCD; motor perseveration relevant to other disorders as well	+ (5-HT involvement; 5-HT2c receptor involvement in OCD)	++ (response to fluoxetine but not to desipramine or diazepam)

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Table 1. Continued

Type	Model (key references)	Description	Face validity (modeled behavior)	Construct validity (neurotransmitter/anatomy)	Predictive validity
	Neonatal clomipramine[87]	Neonatal rats administered repeated clomipramine injections develop compulsive-like behaviors later in life	++ (OCD)	++ (increased 5-HT2c mRNA expression in the OFC; increased D2 mRNA expression in the striatum)	?
	5-HT1b agonist-induced compulsive-like behavior[92]	Acute 5-HT1b agonist leads to range of compulsive-like behaviors	+ (OCD; behaviors relevant to other disorders as well)	++ (involvement of OFC; 5-HT1b receptor involvement in OCD; 5-HT involvement)	++ (response to fluoxetine and clomipramine but not to desipramine)
	Quinpirole-induced water contrafreeloading[79]	Rats show excessive lever pressing for water despite it being available for free	++ (OCD)	+ (involvement of dopamine)	++ (response to clomipramine but not to haloperidol or aripiprazole)
Behavioral models					
Ethological					
Naturally occurring behaviors	Acral lick dermatitis,[100] hair-pulling in cats,[98] feather picking in birds[99]	Repetitive, relatively simplistic habits observed in animals especially following neglect/sensory deprivation	++ (trichotillomania)	++ (spontaneous development)	Evidence for selectivity to medications known to be useful in OCD, ie, SRIs (fluoxetine, clomipramine) Evidence for lack of effects of drugs not useful in OCD (eg, desipramine, fenfluramine in ALD)
	Dogs with compulsive behaviors (tail-chasing, biting, and circling)[95,96]	Repetitive, relatively simplistic motor habits	+ (OCD)	+ (involvement of striatum, frontal cortex, thalamus) ++ (involvement of 5-HT, dopamine)	+++ (response to clomipramine, fluoxetine, and memantine)
	Cribbing and weaving in horses[97]	Repetitive, relatively simplistic habits usually observed following neglect/sensory deprivation	+ (OCD)	?	?
	Barbering in mice[101]	Mice with abnormal whisker- and fur-plucking behaviour	+++ (trichotillomania)	++ (spontaneous development)	?
	Spontaneous stereotypy in deer mice[104]	Stereotypic behaviors consisting of vertical jumping, backward somersaulting, and patterned running	+/− (OCD; stereotypy relevant to other disorders as well)	++ (spontaneous development) ++ (involvement of frontal cortex and striatum)	++ (response to fluoxetine but not to desipramine) - (stereotypy decreased by mCPP and quinpirole)
	Nest building in house mice[112]	Nest-building house mice use large amounts of cotton to build a nest	++ (OCD)	++ (spontaneous development)	++ (response to fluoxetine and clomipramine but not to desipramine)
	Nest building in female rabbits[113]	Nest building in the female domestic rabbit comprises stereotyped and repeated components, and is carried out in a rigid manner	++ (OCD)	++ (spontaneous development) + (involvement of dopamine)	?

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Table 1. Continued

Type	Model (key references)	Description	Face validity (modeled behavior)	Construct validity (neurotransmitter/anatomy)	Predictive validity
Experimentally induced behaviors	Marble burying in mice and rats[196,197]	Rodents use bedding material to bury marbles	+/− (OCD; marble burying cannot differentiate between anti-compulsive and anxiolytic activity)	++ (modulation by sex steroids; involvement of 5-HT, dopamine; involvement of NMDA receptors, nitric oxide)	+++ (response to SSRIs, memantine, aripiprazole but not to desipramine) — (response to anxiolytics) - (no response to riluzole)
	Food-restriction induced hyperactivity[116]	Displacement behavior in response to stress/frustration	+/− (OCD; exercise has not been defined as a variant of OCD)	?	++ (response to fluoxetine but not to desipramine) — (response to reboxetine)
	Schedule-induced polydipsia[115]	Displacement behavior in response to stress/frustration	++ (OCD)	+ (decreased by 5-HT2c agonist)	+++ (response to clomipramine, fluoxetine, and fluvoxamine but no response to diazepam, desipramine, or haloperidol) + (response to HFS of nucleus accumbens shell, mediodorsal thalamic nucleus and bed nucleus of the stria terminalis)
Cognitive	Signal attenuation[130]	Attenuation of a feedback cue signaling reward delivery leads to excessive lever pressing not followed by attempts to collect the reward	++ (OCD)	+ (deficient psychological process implicated in OCD) ++ (involvement of OFC, striatum) ++ (involvement of 5-HT, dopamine, glutamate; modulation by sex steroids)	+++ (response to fluoxetine and D-cycloserine but not to diazepam, desipramine, or haloperidol; response to HFS of subthalamic nucleus)
	Perseveration in the 5-CSRTT[140]	Repeated response to a specific magazine after it has been rewarded	+/− (OCD; motor perseveration relevant to other disorders as well)	+ (OFC lesions increase perseveration)	+ (no response to atomoxetine)
	Perseveration in reversal learning[49,143,147,198]	Repeated response to the previously reinforced lever	+/− (OCD: motor perseveration relevant to other disorders as well)	+ (OFC lesions increase perseveration) ++ (OCD associated candidate endophenotype) +++ (5-HT involvement)	+ (response to citalopram) — (response to atomoxetine and desipramine)
	Set-shift deficit[152,199,200]	Impaired shifting of attentional focus between stimulus dimensions	++ (OCD)	++ (deficient psychological process implicated in OCD) ++ (OCD associated candidate endophenotype) + (brain areas implicated in OCD) - (no involvement of 5-HT) - (noradrenaline involved)	+ (response to escitalopram, quetiapine) - (response to atomoxetine)

Table 1. Continued

Type	Model (key references)	Description	Face validity (modeled behavior)	Construct validity (neurotransmitter/anatomy)	Predictive validity
	Response inhibition deficit[153,176,177,201–203]	Impaired suppression of pre-potent motor responses	++ (OCD, trichotillomania)	+ (deficient psychological process implicated in OC spectrum) ++ (OCD associated candidate endophenotype) + (brain areas implicated in OCD, trichotillomania) - (no involvement of 5-HT; involvement of noradrenaline)	– (response to atomoxetine; no response to citalopram)
	Aberrant habit learning[178,179,185,190,191,204]	Deficit in goal-directed control and an overreliance on habits	++ (OCD, trichotillomania)	+ (deficient psychological process implicated in OCD) + (brain areas implicated in OCD, trichotillomania)	?

so the ability of such a medication to mitigate a behavioral effect in an animal model is therefore not necessarily a reliable guide to the model's validity. This certainly holds true for animal models of OCD, as 40–60% of patients do not show a significant clinical improvement when treated with an adequate course of SRI treatment, which represents the first-line pharmacological intervention.[24] Moreover, in the case of animal models of OCD, there is currently disagreement as to whether similarity in treatment regime (chronic versus acute) is important in establishing predictive validity. Construct validity, on the other hand, though limited by the paucity of theories about the pathophysiology of most disorders, does offer enhanced understanding and capacity for innovation. Therefore, an understanding of the psychological and physiological mechanisms underlying OCD symptoms may, ultimately, be critical to the development of accurate animal models of this disorder.

Genetic Models

OCD has a complex etiology: As with many psychiatric disorders, it is likely that multiple genes confer risk, each with small effect size. Heritability estimates for OCD vary, but genes are likely to play an important predisposing role.[25,26] Candidate genes found as possible risk factors for OCD include genes for the serotonergic, dopaminergic, glutamatergic, and opioid systems, as well as for growth-inducing messengers such as brain-derived neurotrophic factor, although the only candidate gene for which positive findings have been consistently replicated is the glutamate transporter gene *SLCL1A1*.[27] It is also worth noting that while little is known of the epidemiology and genetics of grooming disorders, the only twin study to date in trichotillomania supported a role for genetic factors, with a concordance rate of 38% in monozygotic twins as compared to 0% in dizygotic twins.[28]

Several putative genetic mouse models have been developed to date, in which compulsive-like behavior appears in mice following a known genetic manipulation. Genetic models tend to rely on behavioral similarity (ie, face validity) rather than construct validity, because they were not created on the basis of any established OC-symptom inducing mutation in humans.

Earlier models show behavioral similarity to OCD and related compulsive behavioral disorders (for reviews, see Wang *et al*,[27] Joel,[29] and Boulougouris *et al*[30]). For instance *Hoxb8* mutant mice show excessive grooming behavior that resembles trichotillomania.[31] D1CT-7 mice exhibit a range of compulsive-like behaviors that are characteristic of human OC spectrum disorders, including episodes of perseverance or repetition of any and all normal behaviors, repetitive leaping and repetitive nonaggressive

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biting of siblings during grooming, as well as tics reminiscent of comorbid Tourette syndrome–like behaviors.[32–37] The increased anxiety-related behaviors support the relevance of the compulsive phenotype to OCD.[35,36] DAT knockdown mice display excessively stereotyped and predictable grooming sequences, termed "sequential super stereotypy," that superficially resemble the overly rigid sequential patterns of action, language, or thought displayed by patients with OCD and Tourette syndrome.[38] 5HT2c knockout mice exhibit a range of compulsive-like behaviors, including increased chewing of non-nutritive kaolin clay, organized chewing of a plastic screen, and either increased perseveration or reduced long-term habituation of head-dipping behavior, not secondary to motoric or sensory disruption.[39]

While most of these models show some relevance (construct validity) to OCD, eg, by demonstrating involvement of cortico-limbic regions, which have been consistently implicated in compulsive behaviors in humans, none of them have demonstrated pharmacological predictive validity, which could have strengthened their relevance to OCD.

An additional limitation of most of the early genetic models is that the genetically modified mice typically exhibit additional behavioral and neural abnormalities that are not related to OCD. For example, DAT KD mice may, more generally, model disease states characterized by a hyperdopaminergic tone, such as bipolar disorder and ADHD.[40,41] 5-HT2c knockout mice are obese and hyperphagic with impaired satiety mechanisms.[42–44] They exhibit reduced anxiety-related symptoms compared to wild-type mice,[45,46] which is inconsistent with anxiety symptoms reported in OCD. These 5-HT2c knockouts also show behaviors that may be related to cocaine dependence[47] and Alzheimer's disease.[45] Moreover, data obtained from this genetic preparation do not match with other data investigating the same receptor, as pharmacological evidence in both rats and humans suggests that 5HT2c receptor activation is associated with increased, rather than decreased, compulsivity.[48,49] Therefore, in general, many of the older genetic models of OCD have limitations, but might prove useful as tools for neurobiological investigations in a wider sense.

In the newer models, which are described below, genetic alteration in regional glutamate signaling induces compulsive-like behaviors redolent of human OCD. These models offer behavioral similarities with OCD, as well as better construct and predictive validity.

Sapap3 knockout mice

In the mouse, SAP90/PSD95-associated protein 3 (SAPAP3) is a post-synaptic scaffolding protein that is highly expressed in glutamatergic synapses of the striatum, a region that is implicated across OC spectrum disorders.[50–52] Welch *et al*[53] found that, from the age of 4–6 months, *Sapap3* knockout mice show OC-like behaviors, including excessive self-grooming and increased anxiety-like behaviors, which are alleviated by repeated (6 days), but not acute, treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine. This result is akin to OCD, in which symptomatic improvement requires chronic SSRI treatment, although the timelines do differ (4 or more weeks are needed in human patients for a response). *Sapap3* knockout mice also exhibit cortico-striatal synaptic defects, including reduced cortico-striatal synaptic transmission and defects in the functioning of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamate receptors. Lentiviral-mediated selective expression of SAPAP3 in the striatum reversed the synaptic and behavioral abnormalities, suggesting that the absence of SAPAP3 in the striatum causes the synaptic and behavioral phenotypes.

The involvement of the striatum and glutamatergic system in the compulsive behaviors observed in *Sapap3* knockout mice is consistent with evidence implicating both cortico-striatal circuitry and glutamate systems in the pathophysiology of OCD. Moreover, recent studies have implicated variants in the *Sapap3* gene in OC spectrum disorders, including grooming disorders (trichotillomania, pathologic nail-biting, and pathologic skin-picking) and OCD,[54,55] further establishing the model's relevance to OCD and rendering it useful in further investigating the role of SAPAP3 in the development of grooming disorders.

Slitrk5 knockout mice

The Slitrk family of proteins is a family of integral membrane proteins that are thought to control neurite outgrowth during development.[56,57] Shmelkov *et al*[58] found that, starting at the age of 3 months, loss of the neuron-specific transmembrane protein SLIT and NTRK-like protein-5 (Slitrk5) leads to OC-like behaviors in mice, including excessive self-grooming, increased anxiety-like behaviors, and increased marble burying, with no gross motor deficits. Over-grooming behavior was alleviated by chronic fluoxetine, which supports the relevance of this behavior to OCD. *Slitrk5* knockout mice also show elevated neuronal activity (indicated by upregulation of FosB) selectively in the orbitofrontal cortex (OFC), as well as anatomical deficits in the striatum, including decreased volume, decreased medium spiny neuron dendritic complexity, and down-regulation of glutamate receptors, leading to a reduction in corticostriatal neurotransmission. Neuroimaging studies have consistently implicated

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the orbitofrontal cortex in OFC pathophysiology, and evidence suggests that dysfunction of the striatum may also underlie behavioral deficits in individuals with OCD.[15] Although there is no genetic evidence in humans to date linking the *Slitrk5* gene with OCD or related disorders, the *Slitrk5* model may prove useful in further investigating the role of Slitrk5 in the development of compulsive behaviors.

Aromatase knockout mice

The aromatase knockout (ArKO) mouse lacks a functioning aromatase enzyme and is therefore estrogen-deficient.[59] Hill *et al*[60] reported that 6-month-old male, but not female, ArKO mice develop compulsive behaviors such as excessive barbering, grooming, and wheel running but reduced locomotion in the home cage environment, all of which were normalized by chronic treatment with 17β-estradiol. This was paralleled by a significant decrease in catechol-*O*-methyltransferase (COMT) protein expression in the hypothalamus in male knockouts. COMT is one of the major enzymes involved in the metabolic degradation of catecholamines across species. This is relevant to evidence in male OCD patients that low COMT activity is associated with higher risk of developing OCD.[61,62] Earlier studies demonstrated that male, but not female, ArKO mice showed disruptions in pre-pulse inhibition (PPI), a measure of sensorimotor gating that is impaired in several neuropsychiatric disorders including OCD,[63] and increased amphetamine-induced locomotor activity.[64] The aromatase model describes a possible link between estrogen, COMT, and development of compulsive behaviors in male animals, which may have therapeutic implications in OCD patients.

The ArKO mouse model is of interest to the study of OC spectrum disorders because excessive grooming/barbering has superficial similarity to the symptomatology of some OC spectrum disorders, such a trichotillomania; also, hormonal influences on OCD have been reported,[65] and have been speculated to be involved in trichotillomania.

Pharmacological Models

Pharmacological models tend to be based on drug-induced behavioral alterations that resemble specific OCD symptoms in humans, such as perseveration, indecision, and compulsive checking, as well as increased anxiety. Moreover, in each of the models, the relevant behavior is induced by manipulations of neurotransmitter systems that are thought to be dysfunctional in OCD. The fact that dopaminergic and serotonergic manipulations lead to compulsive-like behaviors is consistent with evidence implicating altered function of these neurotransmitters in OC spectrum conditions. However, it is not clear what roles dopamine and serotonin play in the pathogenesis of these conditions, and thus whether their involvement contributes to the construct validity of the models described below.

Although the behavioral phenotypes of many pharmacological models, such as motor perseveration, working memory impairment, and anxiety, are common in neurological and psychiatric conditions other than OCD (eg, Parkinson's disease, schizophrenia, autistic spectrum disorders), this does not necessarily undermine the validity of these models as plausible proxies for compulsive behavior in OCD. Translational research accommodates such phenotypic heterogeneity by investigating from a trans-diagnostic perspective to identify the neural mechanisms contributing to specific aspects of mental disorder.

Motor perseveration following serotonergic manipulations has been suggested to model compulsive behavior in OCD. Spontaneous alternation in a T-maze is reduced following administration of the 5-HT1a agonist 8-hydroxy-2 (di-n-propylamino)-tetralin (8-OH-DPAT).[66] In a reinforced delayed alternation task, administration of the nonspecific serotonin agonist (mainly at the 5-HT2c, 5HT1d, and 5-HT1a receptors) meta-chlorophenylpiperazine (mCPP) increased directional persistence.[48] The claim of these preparations as animal models of OCD rests mainly on the sensitivity of motor perseveration to the effects of drugs used in the treatment of OCD. Thus, 8-OH-DPAT-induced decreased alternation is reduced by chronic (3 weeks) fluoxetine[66] and by subchronic (3 administrations) clomipramine (serotonergic tricyclic)[67] but not by subchronic desipramine (noradrenergic tricyclic).[67] mCPP-induced persistence is reduced by chronic (20 days) fluoxetine but not by desipramine or a benzodiazepine.[48] While these models show overlap between the neural systems affected and those implicated in OCD (eg, involvement of the serotonergic system), it is not yet entirely clear what role serotonin plays in the pathogenesis of OCD and thus whether its involvement contributes to the construct validity of these models. Increased perseveration after mCPP is consistent with evidence that acute pharmacological challenge with mCPP exacerbates OCD symptoms in patients—an effect that is attenuated by pre-treatment with fluoxetine[68] and clomipramine.[69] Evidence also points to a role for 5-HT2c receptors in modulating mCPP-induced persistent behavior, since challenge with a 5-HT2c antagonist, but not a 5-HT2a antagonist or the 5-HT1b agonist naratriptan, reduced mCPP-induced persistence.[48,70] Consistent with these results, Boulougouris *et al*[49] found that a 5-HT2c antagonist improved perseverative responding during

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reversal learning in a serial spatial reversal learning task. Moreover, activation of the 5-HT2c receptor has also been shown to induce self-grooming in rats, further supporting the hypothesis that selective stimulation of central 5-HT2c receptors exacerbates OC-relevant symptoms.[71]

Support for construct validity comes from the finding that ovarian and related hormones modulate 8-OH-DPAT-induced decreased alternation,[72,73] which is consistent with reported sex differences in the responsiveness to 8-OH-DPAT[74] and with dysregulation of neurosteroids in OCD patients.[75] In contrast, high-frequency stimulation (HFS) of the thalamic reticular nucleus had no effect on 8-OH-DPAT-induced decreased alternation,[76] which is inconsistent with preliminary evidence that HFS of this nucleus may have a therapeutic effect in treatment-refractory OCD patients with severe illness.[77]

Several models use the D2/D3 dopamine agonist quinpirole to induce compulsive-like behaviors in rats. Szechtman *et al*[78] have shown that chronic administration of quinpirole leads to behavior that can be analyzed as a form of repetitive "checking" in rats. In another model, chronic quinpirole was found to elicit high levels of contrafreeloading (CFL), a behavioral strategy in which animals continue to respond for a reward in an operant setting even after the same reward becomes available at no cost.[79,80] Quinpirole thus appears to reduce behavioral flexibility in coping with environmental stimuli by exaggerating adaptive strategies, which is in line with a proposed model of OCD as a disturbance of security motivation.[81]

Both models have tested the effects of drugs known to be effective in OCD; thus quinpirole-induced checking is partially attenuated by treatment with chronic clomipramine,[78] and CFL is inhibited by acute clomipramine, but not by haloperidol or aripiprazole.[82] Quinpirole-induced checking also shows predictive validity regarding HFS (subthalamic nucleus and core and shell subregions of the nucleus accumbens), which is consistent with reports on the beneficial effects of HFS of these regions from studies in otherwise severely unwell and treatment-refractory OCD patients.[83,84]

Quinpirole-induced checking also demonstrates similarity in the neural systems involved. In saline-treated rats, lesions to the nucleus accumbens and OFC had distinct effects on checking behavior. Specifically, although they did not increase checking behavior, nucleus accumbens lesions affected the intensity or vigor of checking, while OFC lesions affected the concentration on checking.[85] Recently, 8-OH-DPAT, a 5-HT1a agonist, was also found to induce compulsive checking in an open field, and the authors suggest that it may have a stronger effect on this behavior compared with quinpirole.[86]

Neonatal clomipramine

In this model, neonatal rats are exposed to repeated injections of the serotonergic tricyclic clomipramine (15 mg/kg, twice daily between postnatal days 9–16), and their behavior is assessed at adulthood.[87] Although the model currently lacks predictive validity, clomipramine-treated adult male rats show a behavioral phenotype that is consistent with an OCD-like profile in humans. Specifically, these rats show enhanced anxiety, increased marble burying (which may reflect increased anxiety and/or increased compulsivity), behavioral inflexibility (less spontaneous alternation and impaired reversal learning in a T-maze), delay in working memory-related tasks (assessed in a win-shift task in an 8-arm radial maze), and increased hoarding. These deficits draw remarkable parallels with cognitive dysfunction reported in OCD, eg, reversal learning-related hypofunction,[88] which provides an endophenotype for OCD, increased perseveration,[89] and working memory impairments.[90]

The behavioral features of clomipramine treatment are associated with biochemical alterations in cortico-striatal regions implicated in OCD, which strengthens the relevance of the behavior to OCD. Specifically, clomipramine-treated rats show increased mRNA for 5-HT2c receptors in the OFC and for D2 receptors in the striatum compared with vehicle-treated rats.

The model also has the advantage of inducing a permanent behavioral phenotype, which is consistent with the chronic nature of OCD for many patients. The paradoxical OCD-like behavior produced in healthy rats by neonatal exposure to a drug used to treat OCD is consistent with evidence suggesting that early exposure to a pharmacological agent can sometimes produce long-term effects opposite to those observed following adult drug exposure.[91] This raises the possibility that anti-compulsive drugs may have unique effects in disease states, since SRIs are effectively used to treat childhood OCD.

5-HT1bR agonist-induced behavior

Acute treatment with a serotonin 1b (5-HT1bR) receptor agonist induces OCD-like behaviors in female Balb/cJ mice, including reduced PPI, hyperlocomotion, and perseverative spatial locomotion patterns, which are reduced by chronic (4 week) treatment with the SRIs fluoxetine and clomipramine but not by desipramine.[92,93] This is the first mouse model to show strong predictive validity for the time course of action of effective treatments, as the reduction of OCD-like behaviors required about 4 weeks of SRI treatment, which is more in line with the time course of the human therapeutic response to SRIs.

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Several lines of evidence support the construct validity of this model. In the clinic, pharmacologic challenge with 5-HT1b agonists exacerbates symptoms in OCD patients,[94] and so the 5-HT1b agonist-induced phenotype in mice is likely to be mechanistically similar to 5-HT1bR-induced worsening of symptoms in OCD patients. Chronic SRI but not noradrenaline reuptake inhibitor (NRI) treatment specifically reduced 5-HT1b receptor expression in the OFC, the brain region most consistently implicated in OCD.[15] Furthermore, OFC 5-HT1b receptors appear to be necessary for the expression of OCD-like behaviors in this model. Whereas infusion of a 5-HT1b antagonist specifically into the OFC blocked the behavioral effects of systemic administration of an agonist, control infusion of the antagonist into the infralimbic cortex did not. Additionally, infusion of the 5-HT1b agonist specifically into the OFC, but not into the infralimbic cortex, was able to recapitulate some of the behavioral effects of systemic treatment.

An advantage of this drug-induced model is that OCD-like behavior is induced temporarily through a known neural substrate, 5-HT1b receptor, in the OFC. The model thus links orbitofrontal 5-HT1bRs to certain features of OCD and identifies the 5-HT1b receptor pathway as a potential therapeutic target for novel OCD treatments.

Behavioral Models

Behavioral models of OC spectrum conditions comprise the following: (i) models that focus on overt behaviors that represent more extreme forms of what would otherwise constitute normal behaviors, including those brought about by stress ("ethological models"); and (ii) models that attempt to capture specific cognitive features of the OC spectrum and their neurochemical and neuroanatomical correlates ("cognitive models"). The latter have advantages in terms of being relatively more translatable across species, with relative ease of objective measurement using laboratory-based paradigms, while ethological models are useful in terms of considering relationships between "normal" and "extreme" behavioral patterns, but involve behaviors that are in many instances more difficult to quantify. This section will consider each category of model in turn. We survey cognitive models only briefly, as they are covered elsewhere in this special issue.

Ethological models

Unlike experimentally induced animal models, excessive behavioral patterns in animals that develop spontaneously in a limited subpopulation provide unique insights into the full range of genetic and environmental etiologic factors in humans. Most of the early animal models of OCD fall into this category, and focus on spontaneous persistent behaviors that superficially resemble OCD or trichotillomania. They represent a source of naturalistic stereotypies with genetic components, which may be informative about OC spectrum disorders. Earlier models are based primarily on behavioral similarity, with some offering good predictive validity, although they have low practicality and reliability. These can represent naturally occurring repetitive or stereotypic behaviors, for instance, tail chasing,[95] fur chewing, and circling in dogs,[96] as well as cribbing/weaving in horses.[97] Others represent innate motor behaviors that can be attributed to stressful environments (displacement behaviors), for instance, psychogenic alopecia (hair pulling) in cats,[98] feather picking in birds,[99] acral lick dermatitis (ALD) in dogs,[100] and barbering in laboratory mice.[101,102] Only some of these models have tested the effects of SRIs, as well as drugs known not to be effective in OCD.[98–100] Recently, compulsions in dogs have been associated with imbalanced serotonergic and dopaminergic pathways, supporting the construct validity of dogs with compulsive behaviors as models of OCD.[103]

Spontaneous stereotypy in deer mice

Deer mice (*Peromyscus maniculatus*) develop spontaneous stereotypy, including somersaulting, jumping, and pattern running.[104] The finding that chronic (21 days) fluoxetine, but not desipramine, reduced stereotypic behavior supports the relevance of the behavior to OCD.[105] However, stereotypy was also reduced by mCPP and quinpirole, which detracts from the construct validity of the model, since acute administration of mCPP in the clinic typically exacerbates OCD symptoms,[68,69] and D2 antagonists rather than agonists are used to augment SSRI treatment.[106]

Multiple studies have suggested that spontaneous stereotypy in deer mice is associated with abnormalities of neural systems implicated in OCD. For instance, neurochemical alterations were found in both the striatum[107,108] and frontal cortex[109,110] of deer mice, with evidence suggesting that an imbalance in the direct and indirect pathways may mediate stereotypy.[108] Repetitive behaviors predominate in OCD, and so studying the neural mechanisms of spontaneous stereotypy in deer mice may advance our knowledge of neural circuits relevant to OCD.

Nest building in house mice

Over 55 generations of bidirectional artificial selection in house mice (*Mus musculus*) have resulted in a spontaneous and consistent 40-fold difference between big (BIG) and small (SMALL) nest-building house mice

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in the amount of cotton used for a nest.[111] BIG male mice exhibit compulsive-like nest building and increased marble burying, which superficially resemble OCD-like compulsions.[112] Interestingly, SMALL male mice demonstrated increased anxiety-like behavior compared to BIG male mice, suggesting that increased marble burying by BIG mice reflects increased compulsivity rather than anxiety. Chronic treatment with SRIs (fluoxetine and clomipramine), but not desipramine, reduced both compulsive nest building and marble burying in BIG male mice, without affecting general locomotor activity, which is consistent with it being a plausible model of OCD. Further studies establishing the construct validity of the model will likely prove interesting, considering that the neural alterations in this spontaneous model may more closely resemble the neural alterations seen in OCD.

Nest building in female rabbits

Hoffman and Rueda Morales[113] have suggested that the naturally occurring nest-building behavior in the preparturient female rabbit may be a useful ethological model for understanding neural processes underlying the sense of task incompletion often experienced by patients with OCD and Tourette Syndrome. There is increasing recognition that OCD compulsions can be aimed at preventing or reducing distress, as well as representing harm-avoidant strategies. One form of distress that has been associated with compulsions is incompleteness, or sensations of things not being "just right," which results in a compensatory urge to generate "just right" feelings, thus promoting repetitive behaviors.

In female rabbits, nest-building behavior comprises a cycle of repeated, stereotyped components (collecting straw, entering nest box and depositing the straw there, returning to collect more straw), which itself is repeated 80-plus times in a single bout that lasts approximately 50 minutes. The bout, in turn, is repeated if necessary, according to the rabbit's perception of whether or not the nest is finished. It appears that the transition from perceiving the nest as unfinished to "knowing" that it is finished is promoted by the perception of cues (probably visual) associated with a completed nest as well as the performance of the nest-building behavior itself. Thus, nest building in the female domestic rabbit comprises stereotyped and repeated components, is carried out in a rigid manner, and has a clear point of termination, after which the rabbit behaves as if she "knows" the nest is finished.

D1 and D2 dopamine antagonists selectively reduced bout duration without affecting other components of the nest building ritual.[114] "Incompleteness" OCD appears to be more associated with mechanisms that maintain and terminate a particular behavioral routine, and the present results suggest that these may be modulated by dopaminergic neurotransmission. This is consistent with evidence that tic-related OCD is often associated with sensations of incompleteness and responds well to antipsychotic augmentation.[106]

Natural responses under conditions of stress

Models falling into this section include those that capture displacement behaviors, such as schedule-induced polydipsia (SIP)[115] and food restriction-induced hyperactivity (FRIH),[116] as well as marble burying, which may be induced by basic fear-avoidance mechanisms.[117] Thus, some degree of construct validity for compulsions is inferred, inasmuch as the compulsive behaviors are performed in states assumed to correspond to anxiety.

The SIP model is characterized by the development of excessive drinking in food-deprived animals that are exposed to intermittent food-reinforcement schedules. In FRIH, rats exposed to food deprivation and a running wheel will paradoxically increase wheel-running activity while reducing their food intake, and thus develop weight loss. Both SIP and FRIH demonstrate good predictive validity in terms of drugs known to be effective as well as ineffective in OCD, and may thus serve as useful screening tools for detecting drugs with anti-compulsive activity.[115,116] In addition to being excessive, maladaptive, and purposeless, these behaviors are thought to represent "coping responses" that hypothetically reduce stress, akin to compulsions. Indeed, it has been suggested that OCD symptoms in humans, which are exacerbated by environmental stress, are analogous to displacement behaviors in animals.[118,119]

Acquisition of SIP depends on the integrity of dopaminergic projections to the nucleus accumbens.[120] More recently, HFS of the nucleus accumbens shell, the mediodorsal thalamic nucleus, and the bed nucleus of the stria terminalis was found to reduce polydipsic behavior in male rats,[121] which is consistent with evidence that deep brain stimulation of the nucleus accumbens has proved effective in treatment-refractory OCD patients.[121,122]

Impaired fear extinction

One theoretical construct posits that fear and anxiety may be causal in driving or sustaining some of the compulsions in individuals with OCD.[123] One prominent feature of OCD is the performance of repetitive avoidance behaviors in response to fear-evoking stimuli,[124] and impaired fear-extinction has been implicated as a perpetuating factor in the human disorder.[125] As noted previously, extinction forms the basis of cognitive-behavioral therapy for OCD, known

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as exposure with response prevention.[126] An advantage of the fear extinction model is its cross-species validity, with considerable similarity observed between the neural circuitry that is involved in extinction in the rodent and in the human. Thus, although impaired fear extinction does not attempt to explain the entire complex phenomenology of OCD, it may be beneficial for understanding the pathogenesis, pathophysiology, and treatment of OCD. Indeed, translational fear extinction research has already led to the development of novel therapeutic approaches in OCD, including reconsolidation blockade,[127] and adjuncts to cognitive behavioral therapy such as D-cycloserine.[128] Recent research using a rodent model of fear conditioning found that HFS of the ventral striatum strengthened fear extinction and retention.[129]

Cognitive Models

Signal attenuation

The signal attenuation model is based on the theory that compulsive behaviors may result from a deficit in the feedback associated with performance of normal goal-directed responses.[130] In the model, rats are trained to lever-press for food (the goal-directed behavior), the delivery of which is accompanied by the presentation of a magazine light and tone (feedback stimulus for a successful response). The feedback stimulus is then separately extinguished (ie, undergoes "signal attenuation") before the animal is allowed to respond on the lever again, but this time in extinction (ie, pressing the lever results in the presentation of the stimulus but no food is delivered). Rats that undergo signal attenuation prior to the extinction test show a high number of lever-presses that are not followed by magazine entry, which may be analogous to compulsive behavior.

To date, Joel and Albelda[131–133] have characterized the signal attenuation model more comprehensively than any other model of OCD. The surplus lever pressing is reduced by virtually all of the drugs used therapeutically in OCD, but not by those that are less effective, such as diazepam, desipramine, or haloperidol.[134] A disadvantage of the signal attenuation model is that it is not suited to investigating the effects of chronic drug treatment, as prolonged drug administration may contaminate the early stages of the procedure. However, given its ability to differentiate between effective and ineffective treatments, the model may serve as a useful screening tool for anticompulsive drugs.

The model also shows relevance to OCD in all of the neural systems involved [OFC; nuclei of the basal ganglia (striatum, subthalamic nucleus, entopeduncular nucleus, globus pallidus); the serotonergic, dopaminergic, and glutamatergic systems, and ovarian hormones] and is thus well validated for studying the neural mechanisms of OCD.

Joel and colleagues argue that signal attenuation simulates the deficiency in response feedback that is hypothesized to underlie obsessions and compulsions. The signal attenuation model may, however, more closely resemble a special form of extinction, in which the Pavlovian associations of a conditioned stimulus are extinguished differentially with respect to instrumental responding. Thus, the perseveration in instrumental behavior arises because the terminal links in the response chain leading to food are extinguished. The finding that OFC lesions produce excessive lever pressing could be attributable to a deficit in response extinction. Several studies demonstrate enhanced resistance to extinction following OFC damage in rhesus monkeys and rats, which is suggestive of greater difficulty in suppressing strong, habitual modes of responding.[135–138] The process of extinction suppresses response–outcome associations, but does not destroy the original learning.[139] An example of perseveration due to response incompleteness can be observed in the 5-Choice Serial Reaction Time Task (5CSRTT), whereby perseverative nose poking in rats, possibly caused by a failure to detect response feedback cues, can arise from lesions to the OFC.[140]

One major drawback of this model is difficulty in assessing its applicability to findings in human patients: Signal attenuation is problematic to quantify in an equivalent form in humans, which limits the translational utility of this approach.

Perseveration in 5CSRTT and reversal learning tasks

Perseveration occurring spontaneously in the 5CSRTT and during reversal training has been suggested to model compulsive behavior on the basis of studies reporting perseverative behavior during neurocognitive tasks in OCD patients.[89]

In rats, perseverative responding in the 5-CSRTT is increased by lesions to the OFC[140] and the dorsomedial striatum,[141] as well as by transient inactivation of the subthalamic nucleus,[142] thus demonstrating overlap between the neural systems involved and OCD. Such perseveration is possibly caused by a failure to detect response feedback cues and may serve to model compulsive behavior arising from feelings of incompleteness—one of the core dimensions of OCD.[124]

Another form of perseveration that occurs during reversal training also involves neural systems relevant to OCD. Studies in animals have elucidated some of the neural substrates of reversal learning deficits. Specifically, perseveration is increased after lesions to the OFC[143] and dorsomedial striatum in rats and marmosets,[143–145] as well as by selective depletion of

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5-HT from the OFC and lateral prefrontal cortex in marmosets.[146] In rats, perseveration is increased by systemic administration of a 5-HT2a antagonist and a D2 agonist, and is decreased by a 5-HT2c antagonist.[49,147] Thus, serotonergic and dopaminergic mechanisms as well as specific orbitofrontal-striatal loops are implicated in this form of cognitive rigidity.

Importantly, it has been found that patients with OCD and their symptom-free first-degree relatives exhibit hypoactivation of bilateral orbitofrontal cortices during reversal learning, as measured using a functional magnetic resonance imaging (fMRI) paradigm.[88] These data implicate abnormal brain activation during reversal learning as a candidate intermediate biological marker that is likely to indicate vulnerability for OCD (referred to as an "endophenotype").

Impaired set-shifting

Set-shifting refers to the ability to inhibit and shift attention away from a previously relevant stimulus dimension onto a different stimulus dimension that was previously irrelevant.[148,149] Deficient set-shifting commonly occurs in OCD patients,[150–152] but importantly also exists in unaffected first-degree relatives of patients with OCD.[152] As such, impaired set-shifting represents a candidate endophenotype. Set-shifting appears to be generally intact in certain other OC spectrum disorders (trichotillomania and pathological skin-picking).[153,154] Remarkable parallels exist in the neural and likely neurochemical underpinnings of this function across species.[155]

Given the behavioral findings in patients outlined above, impaired set-shifting is a useful model for capturing aspects of OCD. Much is also known about its neuroanatomical substrates across both species and contexts. Thus, in monkeys, damage to lateral sectors of the prefrontal cortex impairs set-shifting[156] (in contrast to damage to orbitofrontal sectors which affects reversal learning), while a probably similar (medial PFC and OFC, respectively) dissociation has been reported in rats.[157] fMRI evidence in healthy volunteers supports a role for the ventrolateral prefrontal cortex in set-shifting.[158] These findings fit well with recent models of OCD neurobiology, which emphasize not only dysfunction within the OFC but also more dorsolateral prefrontal regions.[159]

The model is somewhat conflicting, however, in terms of neurochemical findings versus treatments shown to be effective in OCD (predictive validity).

Serotonin manipulations generally have no effect on set-shifting in animals[160] or in humans,[161] while SRIs represent first-line treatment for OCD.[10] In rats, lesions of the dorsal noradrenergic bundle impair set-shifting,[162] while set-shifting is improved by chronic NRI treatment using desipramine.[163] It is less clear whether noradrenergic manipulations can affect set-shifting in humans,[155] but in any event, OCD is not responsive to desipramine treatment.[164] There is some evidence linking aspects of set-shifting to dopaminergic function.[165] COMT inhibition in rats improved set-shifting and modulated prefrontal dopamine levels during conditions of increased catecholamine transmission.[166] Lack of overt serotonin involvement in set-shifting raises important clinical questions, in that deficits in this domain may predispose one to OCD and contribute to its persistence, but are unlikely to be remediated by current first-line pharmacological intervention.

Impaired response inhibition

Response inhibition refers to the ability to suppress pre-potent motor responses, a cognitive ability that is contingent on a distributed neural network including the right inferior frontal gyrus and basal ganglia.[167] This ability is typically measured across species using stop-signal paradigms. Using diffusion weighted tractography in humans, it has been found that the inferior frontal gyrus and subthalamic nucleus are connected with the presupplementary motor region.[167] The subthalamic nucleus—along with ventral striatum/nucleus accumbens—represent key treatment targets highlighted for deep brain stimulation in the treatment of severe treatment-refractory OCD.[168] Inactivation of the subthalamic nucleus reduces compulsive lever-pressing in rats.[169] Furthermore, this region is clearly implicated in aspects of response inhibition in rats[170]; however, as a result of wide-ranging effects on inhibitory control, its precise role in stop-signal response inhibition is far from clear.[170] Nucleus accumbens[171] lesions did not impact stop-signal response inhibition in rats, while OFC and medial striatum lesions did.[170,172] In a case report, deep brain stimulation to the nucleus accumbens did not affect response inhibition in a human patient with OCD[173] but was associated with symptomatic improvement. Thus, the neural regions implicated in performance of this model overlap considerably with core neural nodes implicated in OCD.

Response inhibition deficits cut across OC spectrum disorders, including trichotillomania,[153] pathological skin-picking,[154] and OCD itself.[153] With respect to face validity, the model may more closely recapitulate grooming disorders, which are associated with relatively simplistic motoric habits that are difficult to suppress, as opposed to the more complex compulsions characteristic of OCD. This suggestion is supported by the more pronounced response inhibition problems found in trichotillomania versus OCD.[174] Nonetheless, impaired response inhibition has been found in unaffected first-degree relatives of

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patients with OCD, supporting its utility as a candidate endophenotype.[152]

Whilst neuroanatomical evidence supports the usefulness of considering stop-signal response inhibition dysfunction as a model for OC spectrum conditions, the validity is hindered with respect to OCD in that this cognitive function is under neuromodulatory control of the noradrenaline system, but appears to be relatively unaffected by serotonin manipulations.[175–177] As indicated above, OCD is generally regarded to be responsive to serotonin but not noradrenergic interventions. Further work is needed to explore the differential contribution of different brain regions and neurochemical systems to stop-signal and other measures of inhibitory control across species, and the relevance of this to understanding of OCD and related conditions.

Aberrant habit learning

Dual-system theories posit that actions can be supported by either a goal-directed or a habit system.[178] The neural circuits underlying the balance between habitual and goal-directed behavior have been defined quite extensively in both rodents and humans.[179–182] In rats, evidence suggests that the prelimbic cortex, and the dorsomedial striatum to which it projects, have a role in goal-directed learning since lesions to either of these regions prevent the acquisition of goal-directed learning and render performance habitual.[181,183,184] A series of fMRI studies have suggested that likely functional homologues in humans include part of the ventromedial prefrontal cortex[185,186] and one of its target structures, the anterior caudate nucleus.[187,188] Finally, a region of the dorsolateral striatum in rodents[189] and of the putamen in humans[182] is involved in the habitual control of behavior.

The habit hypothesis of OCD suggests that relatively heightened stimulus–response associations coupled with a generally weakened influence of the ultimate goal may underlie compulsive behavior. Initial evidence for this comes from a recent study that demonstrated a deficit in goal-directed control and an overreliance on habits in patients with OCD.[190] Critically, compulsions in OCD are avoidant rather than appetitive, and a recent study provides the first published evidence that OCD patients exhibit a tendency to develop excessive avoidance habits.[191]

Conclusion

It is evident from this review that there exists a variety of intriguing animal models capturing facets of OC spectrum conditions (Table 1). Each of these models has strengths and weaknesses, which impact the needs they can serve, and it is clear that none can fully recapitulate all aspects of the human OC spectrum of symptoms. The critical features of a model will depend on whether it is being used to screen for anticompulsive activity or in elucidating neurobiological mechanisms. Whereas the former requires the model to have good predictive validity and cost-effectiveness, the latter requires similarity in inducing mechanisms. In this sense, while none of the models reviewed here provide an ideal animal model of OCD, they may be useful in studying particular aspects of the disorder. Indeed, rather than focusing on animal models of entire syndromes, it may be more beneficial to focus on well-understood symptoms or symptom clusters. This is especially true for complex neuropsychiatric disorders such as OCD, in which the underlying genetic and molecular pathology is unknown. Moreover, OCD is heterogeneous in terms of symptom presentation, comorbidity, underlying neurocognitive profile, and therapeutic responsiveness.

One approach is the use of "neurocognitive endophenotypes," which allows a deconstruction of the behavioral phenotype into biologically simpler measures that are associated with particular brain systems.[192] This approach is attempted by the cognitive category of OCD models described above; for instance, changes in the capability/substrates for (stop-signal) response inhibition and cognitive flexibility (reversal learning, set-shifting) may provide examples of cognitive endophenotypes for OCD.[88,193,194] Such objective and quantitative measures of deficits will likely provide more accurate means for assessing the efficacy of novel treatments, that have been overlooked perhaps by the understandable initial focus on symptoms alone (rather than vulnerability factors). Importantly, the cross-species validity of neurocognitive endophenotypes will likely improve the use of animal models in psychiatry, by enhancing model specificity and validity. The 8-OH-DPAT and mCPP models, which are based on motor perseveration, may offer a step in this direction.

Given the heterogeneous nature of OCD, which comprises different subtypes (eg, washers and checkers), it would be an immense contribution to our understanding and treatment of OCD if different animal models could be linked to specific subtypes or dimensions of OCD. Our laboratory has attempted to address this issue through the recent development of a translational model of compulsive checking, the Observing Response Task. The rodent version of the observing response task was designed to explore the neural and neuropharmacological substrates of compulsive checking. Unlike the model developed by Szechtman *et al*, which is more ethological in nature, the observing response task was designed to investigate repetitive, compulsive-like behavior in detail, for

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instance, how compulsive checking may evolve from a more "normal" behavioral repertoire, and how this relates to behavioral flexibility and tolerance of uncertainty. To our knowledge, this is the first cognitive model of an OCD-specific symptom that aims to translate directly between rats and humans, and so there are clear translational implications of the findings from this model for clinical research and the development of novel therapeutic strategies for OCD.

While it is unlikely that archetypal forms of OC spectrum conditions in humans are mediated by singular genetic mutations, single-gene animal models are important in highlighting pathological mechanisms that may be relevant to a subset of human sufferers. Particularly intriguing is the *Hoxb8* mouse model, which not only demonstrates a link between cells involved in immune function (microglia expressing HoxB8), brain function, and pathological grooming, but also shows that these symptoms can be reversed via transplantation of normal bone marrow.[195] Indeed, grooming disorders may ultimately prove more tractable to discovery of precise pathological mechanisms than OCD, which is arguably more heterogeneous.

Naturally occurring ethological models of OC spectrum disorders are useful in that they likely represent an extension of "normal behavioral processes" rather than being artificially induced; in some cases they have been shown to have a similar pharmacological response profile to OCD, but relatively little is known about the neurobiological substrates. Experimentally induced (including stress-induced) models give potential insights into environmental factors that may trigger compulsivity, but again are not ideally situated for exploring brain mechanisms. In contrast, cognitive models, such as signal attenuation, and those exploring aspects of flexible responding fit quite well with neural circuitry known to be implicated in OC spectrum conditions, but have given rise to new questions with respect to pharmacological specificity. Signal attenuation and reversal learning models show pharmacological responses akin to OCD, but other cognitive problems are just as pronounced in OCD, such as set-shifting, and appear to be largely unrelated to serotonin function. More recent focus on "habit learning"—both in terms of behavioral quantification and underlying brain substrates—represents a particularly promising and emerging area where animal models may complement human findings quite tightly.

To some extent, animal model limitations are paralleled by what is still a relatively poor understanding of the human manifestation of these conditions: Even within a disorder such as OCD, there exists considerable heterogeneity with respect to behavioral expression of symptoms, treatment response, and underlying neurocognitive and neuroanatomical findings. For other OC spectrum conditions, notably trichotillomania and its relations, very little research has been undertaken even in humans. Far from counting against the utility of animal models, these limitations add to the importance of attempting to fractionate different aspects of these conditions using translational animal models.

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