Animal models of obsessive–compulsive disorder: utility and limitations

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Abstract: Obsessive–compulsive disorder (OCD) is a disabling and common neuropsychiatric condition of poorly known etiology. Many attempts have been made in the last few years to develop animal models of OCD with the aim of clarifying the genetic, neurochemical, and neuroanatomical basis of the disorder, as well as of developing novel pharmacological and neurosurgical treatments that may help to improve the prognosis of the illness. The latter goal is particularly important given that around 40% of patients with OCD do not respond to currently available therapies. This article summarizes strengths and limitations of the leading animal models of OCD including genetic, pharmacologically induced, behavioral manipulation-based, and neurodevelopmental models according to their face, construct, and predictive validity. On the basis of this evaluation, we discuss that currently labeled “animal models of OCD” should be regarded not as models of OCD but, rather, as animal models of different psychopathological processes, such as compulsivity, stereotypy, or perseverance, that are present not only in OCD but also in other psychiatric or neurological disorders. Animal models might constitute a challenging approach to study the neural and genetic mechanism of these phenomena from a trans-diagnostic perspective. Animal models are also of particular interest as tools for developing new therapeutic options for OCD, with the greatest convergence focusing on the glutamatergic system, the role of ovarian and related hormones, and the exploration of new potential targets for deep brain stimulation. Finally, future research on neurocognitive deficits associated with OCD through the use of analogous animal tasks could also provide a genuine opportunity to disentangle the complex etiology of the disorder.

Keywords: obsessive–compulsive disorder (OCD), genetic model, behavioral model, pharmacological model, compulsivity, perseverance

Introduction

Obsessive–compulsive disorder (OCD) is a disabling psychiatric condition characterized by the presence of upsetting, persistent thoughts, images, or impulses that are experienced as intrusive and senseless, and which cause marked distress or anxiety (obsessions) and/or excessive repetitive intentional behaviors or mental acts (compulsions) intended to neutralize this distress.¹ The disorder has a lifetime prevalence of 2.3%,² and it significantly interferes with social adjustment, employment, marriage, family relationships, and socioeconomic status.^{3,4}

OCD is a clinically heterogeneous and etiologically complex condition,⁵ whose underlying pathophysiological mechanisms are still unknown. Successful treatment with selective serotonin reuptake inhibitors (SSRIs) alone or in combination with atypical antipsychotics suggests a role for serotonin and dopamine in the pathophysiology of OCD.^{6,7} Abnormalities in the dopaminergic system are also supported by the observation of obsessions and compulsions in basal ganglia-related

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disorders such as Tourette's syndrome.⁸ The glutamatergic system has also been implicated in the pathophysiology of OCD, especially due to the observed association between the glutamate transporter gene *SLC11A1* and OCD⁹ (the most consistent and replicated finding of candidate gene studies in OCD), as well as due to the fact that OCD symptoms seem to improve in response to glutamatergic agents such as d-cycloserine^{10,11} (a partial *N*-methyl-d-aspartate [NMDA] agonist that facilitates the response to cognitive-behavioral therapy), riluzole^{12,13} (a glutamatergic antagonist), or memantine¹⁴ (a noncompetitive NMDA antagonist). Ovarian hormones have also been hypothesized to play a modulatory role in OCD, based on multiple reports of life events related to the female hormonal cycle triggering or exacerbating OCD symptomatology.^{15–18} Finally, genetic studies have broadened the number of neurotransmission systems implicated in susceptibility to OCD, with candidates including genes for the opioid system,^{19,20} as well as for growth-inducing messengers such as brain-derived neurotrophic factor.^{21,22}

From a neuroanatomical point of view, neuroimaging research points to the involvement of parallel, partly segregated, cortico-striato-thalamo-cortical (CSTC) circuits in the pathophysiology of OCD. Milad and Rauch²³ proposed three important CSTC circuits for OCD: the “affective circuit”, the “ventral cognitive circuit”, and the “dorsal cognitive circuit”. The affective circuit, connecting the ventromedial prefrontal cortex (PFC) and anterior cingulate cortex (ACC) with the nucleus accumbens (NAC) and the thalamus, plays a role in affective and reward processing. The dorsal cognitive circuit, connecting the dorsolateral PFC, the caudate nucleus, and the thalamus, is crucial for executive functions such as working memory and planning. Finally, the ventral cognitive circuit, connecting the anterolateral orbitofrontal cortex (OFC), the anterior part of the putamen, and the thalamus, is involved in motor preparation and response inhibition. The OCD model proposes an imbalance between hyper-activated affective and ventral cognitive circuits (with dominance of the “direct pathway” that sends excitatory glutamatergic signals to the striatum, resulting in disinhibition of the thalamus and an increased excitatory effect on the cortex) and a hypo-activated dorsal cognitive circuit (with dominance of the indirect pathway, leading to increased inhibition of the thalamus and decreased excitation in the cortex).²⁴ According to this model, hyper-activated ventral cognitive and affective circuits would be responsible for the increased anxiety and repetitive behaviors, while the hypo-activated dorsal cognitive circuit would explain the cognitive control deficits and inability to modulate emotional

and behavioral responses present in OCD.²⁵ Moreover, frontoparietal connections, mainly between the lateral prefrontal cortices and the inferior parietal lobe, are also important for optimal high-order cognitive processing, and both structural and functional abnormalities in parietal areas have been described in OCD samples.²⁶

Stereotactic lesional procedures, mainly anterior capsulotomy and anterior cingulotomy, significantly improve OCD symptoms in patients refractory to pharmacological and cognitive-behavioral treatments.²⁷ The effectiveness of these ablative techniques is attributed to their modulatory effect upon the dysfunctional CSTC circuit described above.²⁸ Recently, electrical high-frequency brain stimulation at the ventral capsule/ventral striatum (VC/VS), the NAC, the subthalamic nucleus (STN), or the inferior thalamic peduncle has demonstrated similar effectivity in reducing OCD symptomatology in severely resistant patients.²⁹

Animal models of OCD

Over the last 30 years, many attempts have been made to develop animal models of OCD under the hypothesis that, as in other neuropsychiatric disorders, they could be useful to disentangle the genetic, neurochemical, and neuroanatomical substrates of the disorder, as well as helping to develop novel treatments and to characterize the mechanism by which these treatments exert their beneficial influences.

In spite of these efforts, some authors have questioned whether it is actually possible to develop a true animal model of OCD.³⁰ Their argument is based on the premise that the primary phenomena in OCD are obsessions, defined as recurrent, persistent, intrusive, and unwanted thoughts, ideas, or images that are subjectively resisted because they provoke marked anxiety or distress. As such, this kind of intrusive obsessional thoughts, about uniquely human topics (eg, being responsible for harm or mistakes, religion, morality, the fear of contamination), could never be accessed via animal models. However, animal models might be adequate for studying other aspects of OCD phenomenology, such as compulsivity, stereotypy, or perseveration. Compulsivity can be defined as the performance of repetitive, unwanted, and functionally impairing overt or covert behavior without adaptive function that is performed in a habitual or stereotyped fashion, either according to rigid rules or as a means of avoiding perceived negative consequences.^{31,32} In this sense, locomotion along relatively fixed paths and the display of specific motor rituals in specific locations are ingrained in the normal behavior of many animals including rodents, horses, pigs, cats, or dogs.^{33–35} This behavioral rigidity allows faster

performance and requires less attention, thus enabling more attention to be directed to other aspects of the environment, which may be crucial for the animal's survival.³⁶ Stereotypy, defined as the constancy of form in behavior produced through ritualization or uniform repetition of motor patterns, is also typically observed in wild animals in captivity, in farm animals, and after the administration of certain psychoactive drugs.³⁶ However, authors critical of animal models point out that compulsive urges in OCD are not spontaneous phenomena but, rather, provoked by obsessions. This implies that compulsive rituals are phenomenologically distinguishable from other repetitive, stereotypic behaviors, such as the stereotypies observed in pervasive developmental disorders, the tics observed in Tourette's syndrome, and perseverative behaviors observed in patients with head injuries. It would therefore be difficult to determine, on the basis of behavioral observations alone, whether repetitive behaviors constitute true compulsions.³⁰

Finally, some authors argue that notwithstanding the presence of obsessions and compulsions, OCD can be better conceptualized as a consequence of overactive striatal habit-forming circuitry coupled with a lack of sufficient top-down control over these habits by higher cortical regions responsible for salient executive functions, including response inhibition and cognitive flexibility.^{37–39} According to this conception, animal models might provide the opportunity to analyze patterns of response and executive dysfunctions through the use of analogous neuropsychological tests across species.⁴⁰

Criteria for the validation and evaluation of animal models of psychiatric disorders

Animal models are experimental preparations developed in one species for the purpose of studying phenomena occurring in another species.⁴¹ According to McKinney and Bunney,⁴² the minimum requirements for an animal model are that symptoms induced in the model must be reasonably analogous to those seen in the modeled disease (what is referred to as face validity), that treatment modalities effective in the modeled disease reverse the symptoms seen in animals (predictive validity), and that the neural systems involved and the mechanism, whether physiological or psychological, underlying the behavioral symptoms observed in animals are similar to those responsible for the modeled disease (construct validity). Animal models can also be assessed in terms of reliability, defined as behavioral outputs of the model being robust and reproducible across

laboratories.⁴³ Some authors consider that the evaluation of animal models should principally rely on reliability and predictive validity, since face and construct validity are highly subjective and sometimes difficult or even impossible to test in animals.⁴³ Moreover, even predictive validity is sometimes limited because of the lack of specificity of many medications in human patients.

An important issue to consider is the fact that an animal model will never mimic a psychiatric syndrome in its entirety. Therefore, the criteria that an animal model must satisfy to establish its validity will depend on the purpose of the model. For example, construct validity would be important for neurobiological research, whereas a model with predictive validity will be useful as a potential drug-screening tool.

Animal models can be classified according to different criteria. McKinney⁴¹ defined three groups: those designed to simulate a specific sign or symptom of a human disorder (behavioral similarity models), those designed to permit preclinical drug evaluations (empirical validity models), and those designed to evaluate a specific etiological theory (theory-driven models). Matthysse⁴⁴ described four types based on principles of symptom similarity, pharmacological isomorphism, cross-species psychological processes, and gene transfer. Finally, Willner⁴⁵ classified them into screening tests, behavioral bioassays, and simulations.

Face validity

Face validity is defined as the phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition. Face validity of animal models of OCD is based, by definition, on the induction of behaviors that are proposed to be similar to compulsions, that is, that are repetitive, excessive, and inappropriate. However, as already noted, some animal models can mimic other aspects of OCD such as perseveration. The most notable in this regard is the 8-hydroxy-2-(di-*n*-propylamino)-tetalin hydrobromide (8-OHDPAT) model. Only 8-OHDPAT-induced perseveration has shown pharmacological similarity with OCD, whereas perseveration in other tasks, such as the stop-signal reaction time task⁴⁶ or the reversal learning task,⁴⁷ has not shown this property. It should be noted, however, that perseveration is common in neurological and psychiatric conditions other than OCD, notably Parkinson's disease, schizophrenia, or depression.

Construct validity

An animal model is considered to show proper construct validity if the physiological or psychological mechanisms

responsible for the behavioral symptoms observed in animals and the neural systems involved in them are similar to those known to be implicated in the human illness that is intended to be modeled. For animal models of OCD, this would imply demonstrating the involvement of the OFC, ACC, or basal ganglia, as well as the serotonergic, dopaminergic, and glutamatergic systems and ovarian hormones in the appearance or modulation of the behavioral symptoms in animals. However, this is a complex issue in the context of OCD, since despite the numerous genetic, neurochemical, and neuroimaging studies that have been carried out in patients with OCD, the etiopathogenic basis of the disorder remains poorly understood. Consequently, an alternative way of generating new animal models of OCD with adequate construct validity has been proposed from the perspective of recent cognitive theories. This approach would involve consideration of the cognitive deficits typical of OCD (ie, flexibility, reversal learning) by means of neuropsychological tasks that could be analyzed by creating equivalent versions for animals and humans, for example, the stop-signal reaction time task or the intradimensional/extradimensional shift task.^{37–39}

Predictive validity

For animal models of OCD, predictive validity is established by demonstrating selective alleviation of symptoms by administration of SSRIs and non-selective serotonin reuptake inhibitors (SRIs), as well as by demonstrating the efficacy of high-frequency stimulation of the STN and VC/VS. However, given that 40% of OCD patients do not respond to SSRIs, the demonstration of a lack of effect of drugs such as non-serotonergic antidepressants or benzodiazepines, which are not effective in OCD but are effective in other conditions that are responsive to SSRI treatment, such as depression, generalized anxiety disorder, or panic disorder, is more critical than is the demonstration of an effect of SSRIs for establishing a model's predictive validity. Moreover, a lack of effect of SSRIs in a model does not necessarily demonstrate that it is not a model of OCD, since it might still be a model of compulsive behavior in the subgroup of OCD patients who do not respond to SSRIs.

Another important issue is that of response to acute versus chronic drug administration. Since, in OCD patients, both SRIs and SSRIs are effective only after some weeks of treatment, the predictive validity of those animal models that show beneficial effects after acute drug administration – as is usual in marble-burying and signal attenuation tests – should be questioned.

Finally, it should be noted that evidence supporting the predictive validity of a model also strengthens its construct

validity by suggesting similarities in the neural systems involved in both symptomatic manifestations.

Leading animal models of OCD

Depending on the method used to induce compulsive-like behavior, animal models of OCD are traditionally divided into four classes: genetic, pharmacological, behavioral manipulation, and neurodevelopmental.

Genetic models of OCD

Genetic animal models of OCD are not based on developing an animal with a known mutation related to OCD in humans, since such a clear genetic mutation has not been established in OCD. Rather, they are based on behavioral similarity, since the behavior of genetically modified mice has been proposed to be similar in specific aspects to that of OCD patients. There are currently seven mouse models of OCD in which compulsive-like behavior appears in mice following a known genetic manipulation, and one model in which compulsive-like behavior developed as a result of selective breeding.⁴⁸ However, these models have several limitations. On the one hand, genetically modified mice typically exhibit additional behavioral and neural abnormalities not related to OCD. For example, 5-HT_{2c} receptor knockout (KO) mice show behavioral and neural abnormalities that may be related to cocaine dependence⁴⁹ and Alzheimer's disease,⁵⁰ and they are obese and hyperphagic with an impaired satiety mechanism.⁵¹ Similarly, dopamine transporter knockdown mice show behavioral abnormalities and response to treatment that may be relevant to attention deficit hyperactivity disorder, bipolar disorder, or substance use disorders.⁵² On the other hand, with the exception of Sapap3-mutant and Slitrk5 KO mice, there are no reports on the effects of pharmacological treatment on compulsive-like behavior of genetically modified mice. Due to these limitations, some authors argue that these models should not be considered real models of OCD, although they may contribute to our understanding of the role of certain genes in compulsive behavior.

DICT-7 transgenic mice

DICT-7 mice, developed by Burton et al⁵³ are transgenic mice expressing a neuropotentiating protein (cholera toxin A1 subunit) within a cortical-limbic subset of dopamine D1-receptor expressing (D1+) neurons. These mice were observed to exhibit abnormal behaviors, including episodes of perseverance or repetition of normal behaviors such as digging, grooming, and climbing, repetitive leaping, and non-aggressive repeated biting of siblings during grooming.⁵⁴

Hoxb8 mutant mice

Hoxb8lox mutant mice, developed by Greer and Capecchi in 2002, have been reported to exhibit OCD-like increased persistence of self-directed grooming and body licking, as well as mutual grooming of other mice.⁵⁵

5-HT2c receptor KO mouse

5-HT2c receptor KO mice were described by Chou-Green et al to display compulsive-like behavior, comprising more chewing of nonnutritive clay, a distinct pattern of neat chewing of plastic-mesh screen, and reduced habituation of head-dipping activity.⁵⁶ These mice also showed enhanced reversal learning with a decrease in trials, correct responses, and omissions to criterion, supporting the involvement of 5-HT2c receptors in the cognitive mechanism underlying spatial reversal learning.⁵⁷

Dopamine transporter knockdown mouse

The dopamine transporter knockdown mouse (*DAT-KD*) is a mutant mouse with a genetic knockdown of the presynaptic dopamine transporter (DAT), which shows 10% normal DAT expression in dopamine neurons.⁵⁸ This reduced expression impairs synaptic reuptake of dopamine, resulting in elevated (170%) levels of extracellular dopamine in the neostriatum (wild-type mice = 100%). *DAT-KD* mutant mice show several types of behavioral evidence for high levels of dopamine activation: they tend to be hyperactive, to walk in perseverative straight paths, and to over-pursue certain incentive stimuli.⁵⁹ Compared with wild-type mice, *DAT-KD* mice exhibit more stereotyped and predictable syntactic grooming chains, designed as sequential super-stereotypy of a complex behavioral pattern, an instinctive fixed action pattern that serially links up to 25 movements into four predictable phases that follow a single syntactic rule.⁵⁸ It has been hypothesized that this phenomenon mimics overly rigid sequential patterns of movements, language, or thoughts that characterize several human brain disorders involving dysfunctional basal ganglia systems (ie, dopamine nigrostriatal projections to the neostriatum and related brain structures), such as pathological repetitions of spoken words in Tourette's syndrome or the tormenting habits and thoughts of OCD.

Aromatase KO mice

Aromatase KO mice were originally developed to study the role of estradiol in the sexual differentiation of the reproductive system.⁶⁰ They lack a functioning aromatase enzyme and are therefore estrogen-deficient. Male, but not female, KO mice exhibited increased wheel-running activity and

grooming but decreased ambulatory activity.⁶¹ They also showed a decrease in catechol-*O*-methyltransferase activity in the hypothalamus. However, in addition to these compulsive-like behaviors, these mice also show other behavioral abnormalities that have been linked with other disorders such as schizophrenia, for example, a decrease in pre-pulse inhibition and an increase in amphetamine-induced activity.⁶²

Sapap3-mutant mice

SAP90/PSD95-associated protein 3 (SAPAP3) is a postsynaptic scaffolding protein expressed mainly in the striatum. Sapap3 KO mice have defects in the structure of the postsynaptic complex of cortico-striatal synapses⁶³ and exhibit reduced cortico-striatal synaptic transmission and defects in the functioning of NMDA and AMPA glutamate receptors. Sapap3 KO mice, both males and females, show at the age of 4–6 months excessive self-grooming and increased anxiety-like behaviors on several tests, with no change in activity levels. These abnormal behaviors reduced with the intra-striatal injection of lentiviruses expressing the SAPAP3 protein.⁶⁴ Interestingly, excessive self-grooming and anxiety-like behaviors in Sapap3 KO mice significantly improve following repeated (for 6 days) but not single injections of fluoxetine, supporting the predictive validity of the model.⁶⁴

Slitrk5 KO mice

The Slitrk family of proteins is a family of integral membrane proteins that are thought to control neurite outgrowth during development.⁶⁵ Slitrk5 KO mice show increased expression of FosB, indicating elevated neuronal activity, restricted to the OFC, as well as anatomical abnormalities in the striatum, including decreased volume, decreased dendritic complexity of striatal neurons, and a reduced number of glutamate receptors. Slitrk5 KO mice develop excessive self-grooming, increased marble burying, and increased anxiety-like behaviors, manifested in the open field test and the elevated plus maze, with no gross motor deficits.⁶⁶ The model has shown predictive value since excessive grooming in Slitrk5 KO mice was ameliorated by repeated administration over 21 days of fluoxetine.

In conclusion, the latter two genetic models of OCD are more valid than the initial ones, since both Sapap3-mutant and Slitrk5 KO mice exhibit a restricted profile of behavioral and neural abnormalities that are relevant to OCD, and these altered behaviors improve in response to chronic administration of SSRIs. However, to increase their predictive validity, it would be important to establish that drugs

without an anti-OCD effect do not significantly change the models. Moreover, due to the limited number of studies conducted so far, one cannot rule out the possibility that future research in these models might demonstrate additional behaviors or neural changes related with other disorders in addition to OCD.

Pharmacologically induced animal models of OCD

Pharmacological models are based on drug-induced behavioral alterations that are similar to specific OCD symptoms in humans, such as perseveration, indecision, or compulsive checking, as well as increased anxiety. Construct validity of these models is based on the fact that these abnormal behaviors are induced by manipulation of neurotransmitter systems that are thought to be related with OCD, mainly the serotonin and dopamine pathways. Two of the most widely studied animal models of OCD, the 8-OHDPAT-induced decreased alternation and quinpirole-induced compulsive checking models, belong to this group.

8-OHDPAT-induced decrease in spontaneous alternation

Yadin et al⁶⁷ were the first to suggest that a pharmacologically induced decrease in the natural tendency of rats to explore novel places sequentially and in succession, what is known as spontaneous alternation, might serve to model two specific aspects of OCD, namely perseveration and indecision. The most common version of this model uses acute administration of the 5-HT_{1A} agonist 8-OHDPAT to decrease spontaneous alternation both in rats and mice.⁶⁸

Face validity of this model has been questioned because decreased alternation is common in neurological and psychiatric conditions other than OCD (eg, Parkinson's disease or schizophrenia), and it has been shown to result from an imbalance in many neurotransmitter systems including serotonin, dopamine, glutamate, gamma-aminobutyric acid, acetylcholine, and norepinephrine,⁶⁹ as well as being linked to many different psychological processes^{70,71} (comprising sensory, attentional, emotional, and motor processes). The model nevertheless shows good predictive validity, supported by the fact that 8-OHDPAT-induced decreased alternation is prevented by both sub-chronic and chronic administration of the SSRI fluoxetine, ranging from three injections over 1 day to 48 injections over 21 days,^{67,72,73} as well as by sub-chronic administration (three injections over 1 day) of the SRI clomipramine but not by sub-chronic administration of the tricyclic antidepressant desipramine.^{67,72} Results from lesions and deep

brain stimulation are, however, controversial. On the one hand, Andrade et al⁷⁴ detected that lesion of the thalamic reticular nucleus was as effective as clomipramine in attenuating the effects of 8-OHDPAT, whereas lesions of the OFC did not affect the model. Similarly, low- but not high-frequency stimulation (HFS) of the thalamic nucleus was effective in reducing 8-OHDPAT-induced perseveration in rats, whereas HFS of the STN has shown anti-OCD effects in humans.⁷⁵

Regarding the construct validity of the model, this is supported by hormonal findings of 8-OHDPAT-induced decreased alternation being clearly modulated by fluctuating levels of endogenous ovarian hormones. In this context, decreased alternation is more robust in prepubertal male than in prepubertal female rats, but it did not differ between mature male and female rats. In mature females, the effect varied across the estrous cycle, it being nonsignificant during estrous and highest during the proestrous phase; it also changes during gestation, being high on day 17, low on day 21, and nonexistent during lactation.⁷⁶ Discrepant findings have been obtained when assessing the interaction between ovarian hormones and the serotonergic system in 8-OHDPAT-induced decreased alternation,⁷⁷ although non-conclusive results have been linked with the use of ovariectomized rats in these experiments, which may not constitute a good model for studying the role of ovarian hormones in females.

Neurosteroids, such as dehydroepiandrosterone (DHEA) or allopregnanolone, have also been proposed to modulate the 8-OHDPAT model, and a dysregulation of neurosteroids, including DHEA, dehydroepiandrosterone sulfate (DHEAS), cortisol, and corticotrophin-releasing factor, has been reported to be associated with OCD.⁷⁸ From a construct validity perspective, but also supporting the predictive value of the model, the acute administration of 8-OHDPAT has been described to cause an 88% reduction in baseline serotonin levels, as assessed by spectrofluorometry, in the frontal cortex of mice. Chronic fluoxetine treatment after the single administration of 8-OHDPAT significantly increases the frontal cortex levels of serotonin, and this effect was dose-dependent, with increases ranging from around 70% for 5 mg/kg of fluoxetine treatment to 94% if the dose rises to 10 mg/kg. This is especially relevant since high – but not low – doses of fluoxetine have shown anti-OCD effect. Similarly, CREB levels in the frontal cortex were decreased by 32% with the acute administration of 8-OHDPAT, whereas chronic administration of fluoxetine raised them again. However, similar changes in both serotonin and CREB levels in the frontal cortex of 8-OHDPAT-treated mice were observed

after the administration of oxcarbamazepine, a drug that has not shown anti-OCD properties.⁶⁸

Thus, although some results suggest that 8-OHDPAT-induced decreased alternation may constitute an interesting animal model for screening anti-compulsive drugs and for studying the role of ovarian hormones in compulsive behavior, controversial findings, mainly from lesional and brain-stimulation studies, partially detract from the predictive and construct validity of the model.

Alkhatib et al⁷⁹ recently reported that acute administration of 8-OHDPAT can also induce compulsive checking behavior in a large open field, as did quinpirole. However, differences in the mechanism of action of the two drugs and the appearance of a distinct profile of effects on the amount and spatial distribution of locomotion suggest that this compulsive-like behavior might stem from dysfunctions in different parts of a specialized neural circuit.

Quinpirole-induced compulsive checking

This model, developed by Szechtman et al⁸⁰ refers to the behavioral changes observed in rats after chronic treatment with the D2/D3 dopamine agonist quinpirole (0.5 mg/kg twice weekly for 5 weeks). When placed in a large open field with four small objects present at fixed locations, and over a period of 55 minutes in which they were videotaped, quinpirole-treated rats gradually developed a preference for two locations, at which they stopped more frequently (up to 20 times more) than did saline-treated rats. They exhibited much shorter return times to these places and stopped at fewer places between returns, as compared with control rats.^{80,81} In addition, quinpirole-treated rats perform a characteristic “ritual-like” set of motor actions at these preferred places/objects, which were different from the actions performed at other locations/objects,⁸² and this pattern of activity was altered when the environmental properties of the places/objects were changed. Thus, quinpirole rats are considered to exhibit a specific spatio-temporal organization of behavior with compulsive-like performance limited to certain preferred locations, whereas their behavior does not differ from that of saline-treated rats in other non-preferred locations.⁸³ According to Szechtman et al^{80,81} this behavior shares a formal conceptual framework/etiological criterion with compulsive checking in OCD, including a) a preoccupation with and an exaggerated hesitancy to leave the item(s) of interest, b) a ritual-like motor activity pattern, and c) dependence of checking behavior on the environmental context. Some authors argue that the motivational bases of quinpirole-induced and OCD checking appear to be similar in that both represent an

exaggerated form of normal checking of stimuli related to safety and security (the “home base” in the case of the rat model).^{67,80,83–86}

Besides compulsive checking, quinpirole administration produces other perseverative, time-consuming, excessive, and rigid behaviors such as perseverative operant responding in the absence of reward,⁸⁷ enhancement of excessive lever-pressing in the condition of post-training signal attenuation,⁸⁸ and focusing on the response lever throughout the operant conditioning session.⁸⁹ Intrastriatal injections of quinpirole elicit perseverative non-rewarded instrumental responses,⁹⁰ whereas intra-accumbens injections of the drug cause a general impairment of flexibility in a reversal learning task.⁹¹ Quinpirole thus appears to reduce behavioral flexibility in coping with environmental stimuli by exaggerating adaptive strategies, which is in line with proposed models of OCD.

The model does, however, have some limitations. Behavioral pattern analysis in Sprague Dawley rats revealed that, in comparison with OCD rituals in patients, quinpirole-induced behavior consisted of a smaller behavioral repertoire performed with a high rate of repetition. Behavior in OCD patients is characterized not only by a high rate of repetition but also by the addition of nonfunctional unique acts, together referred to as pessimal behavior.^{92–94} Thus, only part of the behavioral characteristics of OCD (ie, repetition) is seen in quinpirole-induced behavior in rats.⁹⁵ In this context, de Haas et al⁹⁶ demonstrated that long-term quinpirole treatment in C57BL/6J mice and Sprague Dawley rats resulted in increased repetition and a more limited behavioral repertoire, indicating a more stereotypic than compulsive-like behavior in quinpirole-treated rats. Whatever the case, recent data suggest that genetic background might have an impact on the expression of quinpirole-induced compulsive-like behavior, since A/J, but not other, mice show a greater behavioral repertoire and also a high rate of behavioral repetition after the chronic administration of quinpirole, a behavioral pattern that resembles that of OCD rituals.⁹⁶

Quinpirole-induced compulsive checking has been shown to be partially attenuated by chronic administration (daily injections over 5 weeks) of clomipramine,⁸⁰ supporting the predictive validity of the model. Regrettably, no data are available for changes in the model in response to the administration of SSRIs or other antidepressants not effective in OCD. Lesional and stimulation studies also partially support the predictive validity of the quinpirole-induced compulsive checking model. HFS of the STN did not have any influence on checking behavior of saline-treated rats or on their locomotor activity, whereas in quinpirole-treated

rats, it transiently reduced compulsive behavior without affecting locomotion.⁹⁷ Temporary inactivation of the STN after the administration of muscimol decreased locomotion – but not checking – in a dose-dependent way in saline-treated rats, whereas in quinpirole-treated ones, the lowest dose of muscimol had no effect, the intermediate dose decreased compulsive checking without affecting locomotion, and the highest dose decreased both checking and locomotion.⁹⁸ Similar to what has been described for HFS, these effects of the temporary inactivation of the STN on checking behavior were transient.⁹⁷ HFS of the shell and core of the NAC did not have any influence on the checking behavior of saline-treated rats, but it did increase their locomotor activity, whereas in quinpirole-treated ones, it transiently reduced compulsive behavior without affecting locomotion.⁹⁹ Finally, pharmacological inactivation and HFS of the entopeduncularis nucleus, the rodent equivalent of the human globus pallidus (GP) internus, and of the GP, the rodent equivalent of the human GP externus, exerted an anti-compulsive effect on quinpirole-sensitized rats but not on saline-treated ones, without affecting locomotion in any of them.¹⁰⁰

Construct validity studies have demonstrated that activation of kappa receptors by the administration of a kappa opioid agonist, namely (5a,7a,8)-*N*-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69593), facilitated the development of quinpirole-induced compulsive checking, whereas treatment with the kappa agonist on its own had no behavioral effect.¹⁹ Perreault et al¹⁰¹ also found that treatment with either quinpirole or the kappa agonist or both increased the number of D2 and D3 receptors in their high-affinity state in the NAC, as well as the number of high-affinity D2 receptors in the caudate putamen, supporting the role of these receptors and of the striatum in compulsive checking. On the other hand, negative results have been obtained for the effect of pituitary hormones, such as vasopressin, oxytocin, and adrenocorticotropin, on quinpirole-induced compulsive checking,¹⁰² partially compromising the construct validity of the model, since these hormones have been reported to be related with the severity of OCD.

Quinpirole-induced water contrafreeloading

Besides compulsive checking, repeated administration of quinpirole also produces an increase in contrafreeloading (CFL),¹⁰³ a phenomenon that occurs when animals, offered a choice between working for food (for instance, by lever-pressing) and obtaining it for free, consume a high proportion of their food from the source which requires effort.¹⁰⁴

Alongside this increase in the fraction of water obtained by operant responding (percentage of CFL), quinpirole-treated mice show a reduction in the total amount of water intake, that is, hypodipsia. Administration of the serotonergic agent clomipramine prevents the development of both CFL and hypodipsia induced by quinpirole, while haloperidol, a classical antipsychotic with D2 antagonist activity, prevents CFL but not hypodipsia.¹⁰⁵ Aripiprazole, a second-generation antipsychotic that acts as a dopaminergic stabilizer, shows, by contrast, no effect on either quinpirole-induced CFL or hypodipsia.¹⁰⁵ Interestingly, therefore, the effects produced by repeated administration of a dopaminergic D2/D3 agonist seem to be more efficiently addressed by the action of a serotonergic antidepressant, clomipramine, than by drugs that, albeit to a different extent, inhibit dopaminergic tone.

mCPP-induced directional persistence in reinforced spatial alternation

Administration of meta-chlorophenylpiperazine (mCPP), a nonspecific serotonin agonist, which mainly acts at the 5-HT_{2c}, 5-HT_{1d}, and 5-HT_{1a} receptors, increased directional persistence in a reinforced delayed alternation task. This mCPP-induced persistence was reduced by chronic administration of fluoxetine for 20 days but not by desipramine or a benzodiazepine. Challenge with a 5-HT_{2c} antagonist, but not a 5-HT_{2a} antagonist or a 5-HT_{1b} agonist, reduced mCPP-induced persistence, thus underlining the importance of 5-HT_{2c} receptors in this compulsive-like behavior.¹⁰⁶

5-HT_{1bR} agonist-induced behavior

Acute treatment with a serotonin 1b (5-HT_{1bR}) 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 treatment (4 weeks) with fluoxetine and clomipramine but not with desipramine.^{107,108} 5-HT_{1b} receptors in the OFC appear to be necessary for the expression of OCD-like behaviors in this animal model. In this regard, whereas infusion of a 5-HT_{1b} antagonist specifically into the OFC blocked the behavioral effects of systemic administration of a 5-HT_{1b} agonist, infusion of the same antagonist into the infralimbic cortex did not. Additionally, infusion of the 5-HT_{1b} agonist into the OFC, but not into the infralimbic cortex, was able to induce some of the behavioral effects observed after systemic treatment.¹⁰⁸ In this context, 5-HT_{1b} agonists have been reported to exacerbate OCD symptoms in patients affected by the disorder.¹⁰⁹ Thus, this model suggests that the 5-HT_{1b}

receptor pathway might be a potential therapeutic target for new OCD treatments.

Behavioral manipulation-based animal models of OCD

This subgroup comprises what have been called “behavioral” and “cognitive” animal models of OCD. Behavioral models include 1) naturally occurring repetitive or stereotypic behaviors, such as fur chewing and weaving, and 2) innate motor behaviors that occur during periods of stress or conflict – displacement behaviors – such as grooming, cleaning, and pecking, or following some behavioral manipulation – adjunctive behaviors – such as schedule-induced polydipsia and food restriction-induced hyperactivity. Cognitive models attempt to capture specific neuropsychological features of OCD – reversal learning, impaired set-shifting and response inhibition, or altered habit learning – as well as their neurochemical and neuroanatomical correlates. Three of the most widely studied animal models of OCD, namely marble burying, signal attenuation, and spontaneous stereotypy in deer mice, belong to this subgroup.

Marble burying in mice and rats

Inhibition of natural rodent behavior involving the burying of both noxious and harmless objects was originally hypothesized to constitute a screening test for anxiolytic activity because the duration and extent of burying objects were reduced by different anxiolytic drugs. However, it was later argued that the model does not mimic anxiety but may rather be related to compulsive behaviors.^{110–114} Mice were found not to avoid marbles when given the opportunity to do so, suggesting that they have no aversive or fear-provoking properties,¹¹³ and repeated exposure to marbles did not lead to habituation of marble burying, indicating that this behavior was not related to novelty or fear.^{112,113}

The marble-burying test is probably the most cost-effective animal model of OCD, since it requires no behavioral training and no pharmacological manipulation. Consequently, it is one of the most widely studied, alongside the 8-OHDPAT-induced decreased alternation model that requires limited behavioral training and acute administration of 8-OHDPAT. There are many reports that burying behavior in male mice and rats is decreased by the administration of SSRIs at doses that do not affect locomotor activity,^{68,73,113,115–121} and there is one study showing that such a suppressive effect is not exerted by desipramine.¹¹⁶ However, the well-documented finding that burying behavior is also reduced by anxiolytic and anticonvulsant drugs that do not have

anti-compulsive activity, such as diazepam, clonazepam, or oxcarbamazepine,^{68,113,117,119,122–125} undermines the predictive validity of the model. Atypical antipsychotics such as olanzapine, quetiapine, and aripiprazole all reduce marble burying, but aripiprazole is the only one to do so without reducing locomotion and impairing motor coordination. Pharmacological manipulation seems to suggest that this effect may be exerted via either activation of 5-HT_{1A} receptors or blockade of D₂ receptors.¹²⁵ This is especially interesting, since aripiprazole has recently demonstrated an anti-obsessional effect significantly greater than that of olanzapine or quetiapine.¹²⁶ The administration of NMDA antagonists such as memantine, amantadine, or MK-801 to male mice also decreased marble burying without concomitantly decreasing locomotion, but the glutamate release inhibitor riluzole showed no effect on marble burying.¹¹⁵ Since both memantine and riluzole have shown anti-obsessional effect in OCD patients, these results again compromise the predictive validity of the model.

Regarding construct validity, ovarian and related hormones have been reported to influence marble-burying behavior. Normally, cycling female rats buried more marbles during the diestrous compared with the proestrous phase.¹¹⁸ Llana and Frye¹²⁷ found that the time spent by cycling rats on marble burying was reduced in the proestrous compared with the diestrous phase, although the number of buried marbles did not differ between phases. Moreover, acute administration of progesterone, alone or in combination with estradiol, to ovariectomized rats decreased this burying time.

Neurosteroids also modified marble burying. Acute administration of allopregalone or progesterone decreased marble burying in male mice, whereas DHEAS increased it, without locomotor activity being affected in any case.⁷³ Gonadotropin-releasing hormone also exerts an effect on marble burying that is mediated by its effect on serotonergic activity, specifically through 5-HT_{2A/2C} receptors.¹²⁸ Other serotonin receptors that seem to be involved in marble-burying behavior include 5-HT₇.¹²⁹ Intracellular Ca²⁺ likewise appears to play an important role in marble burying, since administration of calcium-channel antagonists attenuates marble burying without any effect on locomotion.¹²⁸ Finally, sigma 1 receptors may also be implicated in marble-burying behavior, and it has been hypothesized that they might mediate the effect of fluvoxamine but not of paroxetine on the reduction of this compulsive-like behavior.¹¹⁴

In conclusion, marble burying as an animal model of OCD shows good face validity but poor predictive validity, since it cannot differentiate between anti-compulsive and

anxiolytic drugs. Moreover, marble burying failed to detect the anti-compulsive activity of riluzole, suggesting that it may not be sensitive to all classes of anti-compulsive treatments. Consequently, this is not a suitable model for testing new anti-compulsive drugs.

The signal attenuation model

The signal attenuation model was developed by Joel in 2006,¹³⁰ based on the premise that compulsive behavior results from a deficit in the feedback associated with the performance of normal goal-directed responses.¹³¹ In this model, the goal-directed behavior is lever-pressing for food, and the feedback cue is a stimulus that accompanies the delivery of food. To attenuate the signaling property of the stimulus, the latter is repeatedly presented without food, and the effects of this signal attenuation are finally assessed under extinction conditions (pressing the lever results in the presentation of the stimulus, but no food is delivered). To control for the effects of extinction per se, the behavior of these rats is compared with that of others in an extinction session that was not preceded by a signal attenuation process (regular extinction). An anti-compulsive effect in this model is evidenced when a decrease in the number of excessive lever presses is detected in rats that had undergone the signal attenuation process but not in those that only underwent regular extinction.

Acute administration of paroxetine and fluvoxamine exerted an anti-compulsive effect on the model, whereas acute administration of desipramine, diazepam, and haloperidol did not.¹³² However, no data are available for the effects of chronic administration of any medication on the signal attenuation process, and hence, the predictive validity of the model remains limited.

Lesional studies showed that manipulation of the rat OFC affected compulsive lever-pressing.¹³³ Specifically, lesions of the OFC were followed by an increase in compulsive lever-pressing that was correlated with an increase in the density of the striatal serotonin transporter¹³⁴ and a decrease in the content of dopamine and serotonin in the striatum. Intra-striatal administration of paroxetine abolishes orbitofrontal lesion-induced increased compulsivity.¹³⁴ Lesions of the STN increased compulsive behavior and decreased dopamine and serotonin content in the striatum.¹³⁵ Post-training temporary inactivation, as well as HFS, of the STN and of the entopeduncular nucleus of the GP also exerted an anti-compulsive effect.^{98,136} Generally, therefore, the results from lesional studies contribute to the predictive and construct validity of the model.

Also, with regard to construct validity, compulsive lever-pressing has been reported to be modulated by ovarian

hormones, with fluctuations in its level across the estrous cycle (higher in the late diestrous and lower during the estrous phase). Acute administration of estradiol to prepubertal female rats attenuates compulsive behavior, whereas withdrawal from chronic administration of estradiol increases it.¹³⁷ Besides hormonal influences, manipulation of serotonergic activity, specifically through antagonism of 5-HT_{2c} receptors, also shows an anti-compulsive effect. This effect was also present when the 5-HT_{2c} antagonist was administered directly into the OFC of the rat, reinforcing the importance of this cortical area for compulsive behavior.¹³⁸ Dopamine receptors are also involved in compulsive lever-pressing, as demonstrated by the fact that withdrawal from repeated administration of a D1 antagonist or the D2 agonist quinpirole led to an increase in compulsive lever-pressing, whereas a D1 agonist or D2 antagonist exerted no effect on the model.¹³⁹ Finally, acute administration of d-cycloserine, a partial NMDA agonist, also decreased compulsive lever-pressing.¹⁴⁰

Unfortunately, the signal attenuation model has a major shortcoming, namely that it is unable to test the effect of repeated administration of drugs, since this would affect the acquisition of the behavior in the early stages of the procedure (ie, lever-pressing training, signal attenuation).

Spontaneous stereotypy in deer mice

This model is based on the fact that deer mice (*Peromyscus maniculatus bairdii*) show spontaneous stereotypic behaviors consisting of vertical jumping, backward somersaulting, and patterned running.¹⁴¹ Depending on the frequency of these behaviors, deer mice can be classified into high-, low-, and non-stereotypic mice. Both high- and low-stereotypic deer mice have been used as models of OCD, in some studies comparing them with non-stereotypic ones. Although both male and female mice were used in the studies, the potential influence of sex on the results was not analyzed.

In terms of predictive validity, stereotypic behaviors in deer mice significantly decreased in response to repeated administration of fluoxetine but not of desipramine.¹⁴² Systemic administration of the 5-HT_{2a/2c} agonist mCPP and of the D2 agonist quinpirole also decreased stereotypic behaviors.¹⁴² This is an intriguing result, since mCPP worsens OCD symptoms in patients, and D2 antagonists (antipsychotics) but not agonists such as quinpirole are used as potentiating strategies in OCD. Finally, the same reduction in stereotypic behavior was observed when blocking striatal D1 and NMDA glutamate receptors.¹⁴³

Regarding construct validity, high- compared with low-stereotypic mice showed decreased enkephalin content

and an increased dynorphin/enkephalin ratio in the striatum. It has been hypothesized that high stereotypy may be related to an imbalance in the functioning of the direct and indirect basal ganglia-thalamo cortical pathways, with a preponderance of the direct one.¹⁴² Low- and high-stereotypic mice, compared with non-stereotypic ones, showed elevated levels of cyclic adenosine monophosphate (cAMP) in the frontal cortex but not in the striatum, suggesting that the frontal cortex is also involved in stereotypic behaviors. In this context, chronic administration of fluoxetine for 21 days decreased these elevated cAMP levels in the frontal cortex of high-stereotypic mice at the same time as reducing stereotypic behaviors.¹⁴⁴

With respect to face validity, however, it is important to note that stereotypic behaviors are present in many neuropsychiatric conditions other than OCD, including schizophrenia, autism, or mental retardation.

Schedule-induced polydipsia

This model is based on the observation that food-deprived rats trained to collect a food reward on a fixed-interval schedule, while having free access to drinking water, develop after 3–5 weeks of training a polydipsic behavior and consume five to ten times more water than control rats that were not exposed to this reinforcement schedule.¹⁴⁵ Since it can be described as repetitive, excessive, and inappropriate, schedule-induced polydipsia could therefore be considered a compulsive-like condition.

Predictive validity of the model is established by the fact that, in male rats, schedule-induced polydipsia, but not drinking in control rats, is reduced by chronic administration of clomipramine, fluoxetine, and fluvoxamine but does not change in response to chronic administration of desipramine, haloperidol, or diazepam.¹⁴⁵ High- but not low-frequency stimulation of the NAC shell, the mediodorsal thalamic nucleus, and the bed nucleus of the stria terminalis also reduced polydipsic behavior in male rats, although the effects of stimulation on drinking in normal rats were not assessed, limiting the interpretation of the results.¹⁴⁶

Schedule-induced polydipsia is modulated by serotonergic agents, a fact that supports the construct validity of the model. Acute administration of different 5-HT_{2c} agonists decreased polydipsic behavior in male and female rats without affecting the amount of water consumed by control rats.¹⁴⁷ Administration of a 5-HT_{1a} antagonist or a 5-HT_{1b} partial agonist with fluoxetine accelerated the effect of the SSRI on reducing polydipsic behavior in male rats, while administration of the serotonergic antagonist or agonist alone had no effect on the model.¹⁴⁸

Neurodevelopmental animal models of OCD

Neonatal clomipramine

In 2010, Andersen et al claimed to have developed a multiple OCD-like behavior model in rats.¹⁴⁹ They compared rats treated with 16 intraperitoneal injections of 15 mg/kg of clomipramine administered across postnatal days 9–16 with those receiving a saline vehicle following the same pattern of administration. Clomipramine-exposed rats showed more anxiety-like behavior in the elevated plus maze and a directed anxiety response in the marble-burying task, burying more foreign/novel objects. They also showed more perseveration in a reversal task, a general impairment of discrimination learning, and increased hoarding behavior. Besides these behavioral changes, regional biochemical differences were also observed in rats exposed to clomipramine, namely increased RNA messenger expression for 5-HT_{2c} receptors in the OFC and D₂ receptors in the striatum. None of these behavioral or biochemical changes were detected if clomipramine was administered in adult rats at postnatal days 50–57.

Animal models and fear conditioning

Recent translational research suggests that dysfunctional fear acquisition and extinction learning may be at the core of many anxiety disorders including OCD as well as of their response to exposure-based therapies.¹⁵⁰ Extensive literature on animal models addressing the neural mechanisms of fear acquisition and extinction has allowed improving our knowledge of the mechanism of action underlying exposition and response prevention (ERP), the first-line treatment for OCD and a psychological therapy based on extinction processes.¹⁵¹ Rodent models have probed that while amygdala plays a critical role in the acquisition and expression of conditioned fear, prefrontal areas including the ventromedial PFC and medial, dorsomedial, and dorsolateral PFC are important for consolidation, retention, and expression of extinction memory.¹⁵² Differences in cortical thickness and volume of these areas have been described to be related to exposure therapy outcome in OCD patients.¹⁵³ Since strong parallels exist between fear circuits in rodents and humans, translational research in the last decade has focused on developing strategies that facilitate extinction of fear, through pharmacological, physical, behavioral, or cognitive treatments that combined with ERP can aid in extinction learning. In terms of pharmacological manipulations, infusion in rat amygdala of an NMDA antagonist blocks extinction,¹⁵⁴ while administration of d-cycloserine, an NMDA partial agonist, seems

to facilitate extinction both in rats¹⁵⁵ and in OCD patients.¹¹ Deep brain stimulation as well as repetitive transcranial magnetic stimulation of the VS in rats during extinction training reduced fear expression and strengthened extinction memory facilitating fear extinction.¹⁵⁶ Future research should address whether these physical techniques might augment the effectiveness of ERP in OCD patients. Behavioral manipulation based on extinction training during the reconsolidation period – through the presentation of an isolated retrieval trial before the extinction session – has also been probed to induce a persistent reduction in learned fear both in rats¹⁵⁷ and healthy subjects¹⁵⁸ and might constitute a challenging option for OCD patients resistant to classical ERP.

Conclusion

Many animal models have been generated in the last decades to explore different aspects associated with OCD from a range of perspectives, including pharmacological manipulation, genetic selection, and the analysis of behavioral patterns or neurocognitive function.¹⁵⁹ The aim of all these approaches is to improve our understanding of the etiopathogenic basis of the disorder and to develop new therapeutic strategies, a particularly important goal considering the high percentage of OCD patients with partial or no response to available therapies. A key aspect to consider in relation to the so-called animal models of OCD is the term itself, since the models presented in this review should, in our view, be regarded not as models of OCD *per se* but, rather, as animal models of certain psychopathological processes that are present not only in OCD but also in other psychiatric or neurological disorders; examples of these processes would be compulsivity, stereotypy, and perseverance. In this regard, animal models might help to study from a trans-diagnostic perspective the neural mechanisms that contribute to common, specific aspects of different mental disorders. With this aim in mind, it should be noted that researchers have yet to develop an optimum animal model of compulsivity or perseverance, that is, one that shows a sufficient degree of construct, predictive, and face validity. In genetic models, for instance, compulsive-like symptoms are associated with other symptoms not characteristic of OCD, such as obesity or hyperphagia, and very little is known about how these symptoms might be modified by the administration of drugs with or without an anti-obsessive action. One of the limitations of models based on pharmacological manipulation – which include two of the most well-known animal models of OCD, namely the 8-OHDPAT-induced decreased alternation model and the quinpirole-induced compulsive checking model – is that they

mainly mimic just one specific aspect of compulsive-like behavior: perseverance. The issue here is that perseverant behavior is also frequently observed in other neurological and psychiatric disorders such as Parkinson's disease and schizophrenia, which are distinct from OCD. A further problem is that lesional studies have produced contradictory findings, thus limiting both the construct and the predictive validity of the models. Finally, the subgroup of behavioral models includes what is probably the most cost-effective animal model of OCD, the marble-burying test. However, from a translational point of view, this model has proved to be of very limited value when it comes to developing new pharmacological strategies, whether due to its inability to discriminate between the effect of anxiolytic drugs or due to the methodological impossibility of analyzing the repeated administration of drugs. It should be highlighted, however, that behavioral models have shed some light on certain etiopathogenic aspects of compulsive-like behavior, especially as regards the effect which hormonal factors have on it. Combining several animal models of OCD in order to detect anti-compulsive activity of new drugs might therefore constitute an interesting therapeutic option. The area of research where convergence is greatest involves the role of ovarian and related hormones in compulsive behavior. Fluctuations in compulsive behavior during the estrous cycle show an opposite pattern in the marble-burying and 8-OHDPAT models, but the administration of exogenous sex hormones exerted similar effects in the two models in ovariectomized females and in intact males. Therefore, new treatment strategies for OCD could explore the role of sex hormones in compulsive behavior. Some recent results suggest that the blockade of D1 and NMDA receptors might also constitute a good alternative focus for research. Animal models can likewise be used to detect new brain regions whose electrical stimulation may produce an anti-compulsive effect, thus paving the way for the development of a promising new technique that is still at the early stages of implementation: deep brain stimulation.

Finally, although behavioral similarities between animals and humans will be always limited and partial, animal models may constitute a unique opportunity to assess neurocognitive deficits that have been hypothesized to underlie the etiopathogenesis of OCD. Indeed, the use of suitable animal models designed especially to assess tasks that can be evaluated both in humans and rats, such as the stop-signal reaction time and the intradimensional/extradimensional shift tasks, could constitute a genuine alternative approach to disentangling the complex etiology of OCD.

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