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CROSS-SPECIES MODELS OF OBSESSIVE-COMPULSIVE SPECTRUM DISORDERS

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Advances in our understanding of the genetic and neural substrates of obsessive-compulsive disorder (OCD) and related spectrum disorders such as trichotillomania, as well as their characteristic behavioral and cognitive symptoms, render the search and evaluation of appropriate animal models especially timely. Such modeling in neurology and neuropsychiatry generally occurs on at least two levels: the etiological, in terms of genetics and molecular pathology, and the symptomatic, in terms of identifying suitable neurocognitive endophenotypes that encompass the range of behavioral and psychiatric manifestations of particular disorders in the

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context of altered brain circuitry. The former is generally difficult in psychiatry as distinct from neurogenetic disorders such as Huntington's disease or where the molecular pathology is well defined, as in the case of Alzheimer's disease. Although there are a number of candidate genes for obsessive-compulsive spectrum disorders (OCSDs), it is probable that multiple genes confer vulnerability, each with small effect, thus making it especially difficult to model disease in a suitable transgenic preparation. Even if such a preparation was feasible, there would be questions about the extent to which its behavioral phenotype in the mouse could simulate all of the subtleties of the clinical syndrome. Several studies have provided important information regarding the neural and neurochemical substrates of OCD, and the availability of somewhat effective pharmacological treatments (e.g., selective serotonin reuptake inhibitors [SSRIs], see Fineberg and Gale 2005) provides essential information that in combination with other evidence contributes to criteria to be set for model validation (discussed later).

This review focuses on animal models of OCD based on criteria for model evaluation. Hence, before reviewing these models, it is important to discuss the criteria by which the validity of an animal model might be assessed.

Assessing Animal Models

Validation criteria are general standards that are relevant to the evaluation of any model. Although there have been several attempts to discuss criteria for the evaluation of animal models (Geyer and Markou 1995; Matthysse 1986; McKinney and Bunney 1969; Segal and Geyer 1985), most of these discussions are based on the assumption that it is not always made explicit. Probably the most widespread classification system is the one proposed by Willner (1984). Willner grouped the different criteria for assessing animal models into criteria used to establish face, predictive, and construct validity. *Face validity* concerns the phenomenological similarity between the animal model and the disorder it models. The model should resemble the human phenomenon in terms of its etiology, symptomatology, treatment, and physiological basis. *Predictive validity* generally means that performance in the experimental test predicts performance in the modeled human phenomenon. Although predictive validity in principle can rely on etiological factors, physiological mechanism, and pharmacological isomorphism, Willner (1991) added that in practice predictive validity usually relies on the latter. *Construct validity* means that the model should be logical in itself and is based 1) on the degree of functional homology between the modeled behavior and the behavior in the model that depends on the two behaviors sharing a similar physiological basis, and 2) on the significance of the modeled behavior in the clinical setting.

Unfortunately, this validation system is very rigid in its definitions and is highly subjective. An additional attempt to describe and classify the criteria for

evaluating the validity of animal models has been made by Geyer and Markou (1995, 2002). Working from Willner's definitions, Geyer and Markou restricted face validity to the phenomenological similarity between inducing conditions and specific symptoms of the human phenomenon, while defining predictive validity as the extent to which an animal model allows accurate predictions about the human phenomenon based on the performance of the model. Moreover, *reliability* means that the behavioral outputs of the model are robust and reliable between laboratories. Based on these definitions, Geyer and Markou (1995, 2002) concluded that the evaluation of experimental models in neurobiological research should rely solely on reliability and predictive validity, face similarity being considered a subjective, and therefore secondary, criterion. In other words, every proposed model has to offer a specific, measurable behavior that is pharmacologically analogous with the clinical disorder under study, in order to predict the response of the disorder to new pharmacological treatments.

Although there is a longstanding debate over terminology and classification, it is widely recognized that no one animal model can account for the psychiatric syndrome it mimics in its entirety and that the validation criteria that each model has to fulfill to demonstrate its validity are determined by the defined purpose of the model (Geyer and Markou 1995; Matthysse 1986; Willner 1991).

Clinical Profile and Neurobiological Substrate of Obsessive-Compulsive Disorder

OCD is characterized by intrusive and unwanted ideas, thoughts, urges, and images known as *obsessions,* together with repetitive ritualistic cognitive and physical activities comprising *compulsions.* OCD is heterogeneous in terms of its symptomatology, which appears to reflect different pathophysiological mechanisms. Based on specific analytic methods, OCD symptoms have been split into four categories (Cavallini et al. 2002; Leckman et al. 1997; Summerfeldt et al. 1999): 1) aggressive sexual and religious obsessions with checking compulsions; 2) symmetry obsessions with compulsions of classification, sorting, and repetitiveness; 3) obsessions of contamination with cleaning compulsions; and 4) hoarding. There is some evidence that these symptom clusters differ in terms of treatment response (Black et al. 1998; Mataix-Cols et al. 1999, 2002; Winsberg et al. 1999), comorbidity with other psychiatric disorders (Samuels et al. 2002), and genetic predisposition (Leckman et al. 2003).

The essential features of OCD and related spectrum disorders capable of being captured by animal models are the maladaptive and perseverative behavioral or cognitive output, mediated by dysfunctional nodes within the frontostriatal circuitry, probably modulated by altered dopaminergic or serotoninergic influences, for example, the repetitive rituals in OCD, or hair-pulling in trichotillomania. Hu-

man neuroimaging studies have implicated in particular the orbitofrontal cortex and the caudate nucleus in OCD, and cingulotomy has had a limited therapeutic success (see Baxter 1999). However, there may be grounds for considering OCSDs as reflecting impaired functioning of several distinct frontostriatal "loops" (Chamberlain et al. 2005, 2007a; Choi et al. 2007; Graybiel and Rauch 2000; Menzies et al. 2008; Nakao et al. 2005; Whiteside et al. 2006). Animal models of OCSDs have generally fulfilled the criteria of face validity but have sometimes been based on psychological theorizing about the nature of OCD, thus attempting the deeper level of modeling, construct validity. Predictive validity can therefore be employed to a limited extent in OCD, given the known but largely unexplained efficacy of the SSRIs (beginning with fluoxetine) and other less widely evaluated candidate treatments such as dopamine D_1 receptor antagonists and specific serotonin receptor agents.

Current Ethological and Laboratory Animal Models of Obsessive-Compulsive Disorder

ETHOLOGICAL ANIMAL MODELS

The animal literature has approached OCD from two angles, namely ethological models and laboratory models (genetic, pharmacological, and behavioral). Ethological models (see Table 8–1) focus on spontaneous persistent behaviors with genetic components reminiscent of OCD, offering good face similarity and predictive validity but low practicality. Such behaviors include tail-chasing (Brown et al. 1987) and fur-chewing, acral lick dermatitis (paw licking) in dogs (Rapoport et al. 1992), psychogenic alopecia (hair-pulling) in cats (Swanepoel et al. 1998), feather picking in birds (Grindlinger and Ramsay 1991), cribbing in horses (Luescher et al. 1998), schedule-induced polydipsia (which can be considered as a form of displacement behavior in the face of the thwarting of goal-directed behavior, e.g., Robbins and Koob 1980; Woods et al. 1993) and food-restriction-induced hyperactivity (Altemus et al. 1996). Other responses in animals that have been likened to OCD-like behavior include wheel-running, allogrooming (or "barbering," cf. trichotillomania) in mice (Garner et al. 2004), and marble-burying (the use of bedding material to bury noxious/harmless objects, behavior that may be induced by basic fear avoidance mechanisms; Ichimaru et al. 1995). Some of these models have tested the effects of SSRIs and also compared them with the effects of drugs ineffective in OCD (Altemus et al. 1996; Nurnberg et al. 1997; Rapoport et al. 1992; Winslow and Insel 1991; Woods et al. 1993). It is worth noting that the reported efficacy of clomipramine in OCD and trichotillomania was predicated by observations of its remediating effects on canine lick dermatitis (Rapoport et al. 1992; Swedo et al. 1989) and similar abnormal behavior elicited in veterinary con-

texts. For example, psychogenic alopecia in cats (Swanepoel et al. 1998), cribbing in horses (Luescher et al. 1998), and repetitive pacing in several species, often elicited by stressful environments, continue to be a valid source of naturalistic stereotypies that may be informative about OCSDs (Stein et al. 1994). Both stereotypies and schedule-induced polydipsia have been considered as "coping responses" that hypothetically reduce stress. This hypothesis, however, has proved difficult to test experimentally and may well not apply to all forms of stereotypy.

GENETIC AND PHARMACOLOGICAL MODELS

In terms of genetic models (see Table 8–1), these have largely been based on face validity and include the *hoxb8* mutant (Greer and Cappechi 2002) as well as genetic manipulations of both dopamine and serotonin functioning leading to similar behavior. Greer and Cappechi (2002) reported that mice with mutations of the *Hoxb8* gene (expressed in the orbital cortex, the striatum and the limbic system, all of which are implicated in OCD pathophysiology) groomed excessively to the point of hair removal and skin lesions compared with their control counterparts. In terms of genetic manipulations of dopamine and serotonin, boosting D_1 receptor function by a neuropotentiating cholera toxin expressed in the pyriform cortex and amygdala produces perseveration and repetitive jumping behavior in mice, named D1CT-7 mice, probably mediated ultimately via striatal mechanisms (Campbell et al. 1999a, 1999b, 1999c). It should also be noted that this repetitive jumping behavior was exacerbated by the administration of yohimbine, an anxiogenic drug (McGrath et al. 1999). Knockdown of the dopamine transporter (DAT) produces "sequential super-stereotypy" in mice, named "DAT KD" mice, with the perseverative performance of quite complex chains of grooming behavior (Berridge et al. 2005). A knockdown of the 5-HT_{2C} receptor similarly leads to perseverative "head-dipping" or the excessively orderly chewing of screen material (Chou-Green et al. 2003), a compulsive behavior (accompanied by other like responses such as stereotypic locomotion and excessive self-aggressive grooming) that has also been shown in rats following chronic lesions of median raphe nucleus (Hoshino et al. 2004). Some of these responses obviously have clear superficial parallels to some of the elaborative rituals in OCD, possibly related to hygiene and checking. However, it is of course essentially impossible to know in fact how closely related they are. It seems likely that these examples of stereotyped behavior are mediated by striatal structures, given the known role of the caudate–putamen in stereotyped behavior produced by psychomotor stimulant drugs (Creese and Iversen 1975) and in normal grooming sequences (Aldridge and Berridge 1998).

It is tempting to utilize pharmacological models based on the stereotypy produced by stimulants such as amphetamine at high dosages (Lyon and Robbins 1975). Although stereotypies in rodents typically consist of gnawing and licking with repetitive sideways movements of the head that may represent vestiges of ori-

enting behavior, they can be elaborated in many ways, for example, to include grooming (including allogrooming, Sahakian and Robbins 1975) and perseverative operant behavior in which rats may continue to work for food they do not eat (Robbins and Sahakian 1983). These responses are dopamine mediated, but it may be a mistake to consider them as being directly related to OCSD because, for example, treatment of mice receiving the D_1 receptor potentiation treatment actually exhibit reduced stereotypy after treatment with cocaine, showing that drug-induced stereotypy and the behavior produced by enhanced D_1 receptor overexpression do not necessarily lie on the same continuum (Campbell et al. 1999b). This may also be reflected in clinical experience. For example, D-amphetamine has actually been shown to ameliorate OCD symptoms in certain circumstances (Insel et al. 1983). Nevertheless, Szechtman et al. (1998) have shown that the D_2/D_3 agonist quinpirole leads to behavior that can be analyzed as a form of repetitive "checking" behavior in rats. Specifically, after drug administration (0.5 mg/kg twice weekly for 5 weeks), rats were placed individually into an open field with four objects at fixed locations, and their activity was recorded for 55 minutes. Analysis of quinpirole- and saline-treated rats revealed that quinpirole-treated rats stopped at two locales more frequently than control rats and exhibited a "ritual-like" set of motor activities at these places (Szechtman et al. 1998). This behavior is reduced by treatment with clomipramine.

As mentioned earlier, *perseveration* is a term that can be applied to a variety of behavioral outputs ranging from relatively simple to complex. The "complex" category is where it is not a motor output that is performed repetitively but an approach to a particular goal or the persistence in complex sequences of behavior. We also include in the "complex" category trained operant behavior (in which rats keep on working for food they do not eat) and also both spontaneous (Yadin et al. 1992) and reinforced delayed alternation behavior (Tsaltas et al. 2005), which can become perseverative if the animal continues to make the previous choice following treatment, for example, with dopaminergic or serotoninergic agents. At yet higher levels of organization, we can consider impairments of object reversal behavior to reflect a "higher order" form of perseveration because the animal may perseverate in responding to a formerly reinforced stimulus, even though its spatial position is shifted across trials. Such behavior occurs when serotonin depletion is effected in the orbitofrontal cortex (Clarke et al. 2004, 2005, 2007) in marmoset monkeys. Moreover, this behavior is truly perseverative in the sense that reversal learning is normal if the previously rewarded stimulus is substituted by a novel one (Clarke et al. 2007). However, this form of perseverative responding is probably not the same as that produced by perseveration of a learned rule in the Wisconsin Card Sort Test, following, for example, frontal lobe damage (or OCD), which involves a so-called "extra-dimensional shift." This form of attentional shifting is impaired by lateral frontal lesions in the marmoset and by catecholamine, but not serotonin, depletion (Clarke et al. 2005, 2007; for a review, see also Robbins 2005).

SIGNAL ATTENUATION AND EXTINCTION: BEHAVIORAL MODELS

Another sophisticated model is that of "signal attenuation" (see Table 8–1) in which it is postulated that OCD results when behavior receives weakened response feedback (whether kinaesthetic in nature or in terms of conditioned reinforcers, analogous to sub-goals) that signal when the required contingency has been completed. Joel et al. (2004) developed this model perhaps more fully than any other extant model of OCD. Rats are trained to respond for food that they retrieve at a food magazine, accompanied by a conditioned stimulus functioning as a conditioned reinforcer. The magazine response is then separately extinguished (i.e., undergoes signal attenuation) before the animal is allowed again to respond on the lever, but during extinction. The critical consequence of the signal attenuation procedure is that the rat may continue to respond on the lever but fail to complete the sequence by moving on to the food magazine. The instrumental lever-pressing thus has a perseverative quality that is sensitive to reductions produced by virtually all of the drugs used therapeutically in OCD, but not to those that are less effective, such as diazepam or desipramine. This behavior is also enhanced by lesions of the rat orbitofrontal cortex and sensitive to manipulations of the medial striatum, to which the orbitofrontal cortex projects. Joel and colleagues have thus established many of the validating criteria for a successful model of OCD, although the exact theoretical explanation in terms of signal attenuation may perhaps be queried.

Signal attenuation appears to resemble a special form of extinction in which pavlovian associations of a conditioned stimulus are extinguished differentially with respect to instrumental responding. The perseveration in instrumental behavior arises because the terminal links in the response chain leading to food are extinguished. Extinction itself also depends on an inhibitory process that suppresses associations, which in fact remain intact (Rescorla 2001). Another example of this form of perseveration has been reported in the performance of an attentional task for rats that requires the animals to visit the food magazine after a nose-poke response to detect a target visual stimulus. Perseverative nose-poking, possibly caused by a failure to detect response feedback cues, can arise from lesions to the orbitofrontal cortex in rats (Chudasama et al. 2003).

PUTATIVE BEHAVIORAL ANIMAL MODELS

It would be parsimonious to describe all of these examples of perseverative responding from the level of single response elements to complicated sequences of behavior, to a perseverative attentional focus, as resulting from failures of "behavioral inhibition." However, the fact that they are mediated by both striatal and different prefrontal cortical sectors suggests that these are not the same forms of inhibition and that a generic explanation in terms of behavioral inhibition may lack

explanatory power. However, it is possible that particular forms of behavioral inhibition are impaired in OCSDs. There are several other theoretical positions that may be especially useful in explaining certain forms of OCD while capturing some of the clinical observations of patients exhibiting these disorders (see Table 8–1). Thus, one set of theoretical constructs suggests that anxiety (e.g., Mowrer 1960) is the prime trigger of OCD, as posited, for example, by Rachman and Hodgson (1980). Active avoidance behavior in animals is well known to be very persistent because it so rarely has the opportunity for extinction, and drugs such as D-amphetamine exacerbate this perseverative tendency. Thus behavior that initially has some adaptive value, for example, in avoiding shocks, apparently loses its rationale after thousands of trials in which shock is never presented. We have previously alluded to the possibility that stereotyped behavior acts as a coping response to reduce stress, and this is essentially the same contingency. A more recent formulation is that by Szechtman and Woody (2004) that OCD-like behavior arises as an aberrant excess of behavior motivated by the need for security. These theories are of obvious clinical interest and will ultimately depend on their validation by the importance assigned to anxiety in producing the persistent symptoms of OCD. A related concept is that of exaggerated habit learning, in which behavior is controlled by stimulus–response links with a generally weakened influence of the ultimate goal. Recent evidence (e.g., Yin and Knowlton 2006) strongly supports the hypothesis that habit learning in the rat is mediated by specific sectors of the rat striatum (those probably homologous to the putamen). However, we have to consider what types of mechanism are brought into play to turn habits into compulsions (for a discussion of compulsive drug taking, which may be governed by similar mechanisms, see Everitt and Robbins 2005). Evidence also indicates that habit learning in the striatum can be influenced by prefrontal cortical mechanisms (e.g., Killcross and Coutureau 2003).

The clinical concept of a continuum of impulsive and compulsive behavior is highly relevant to OCSD, where different aspects of behavior can perhaps be thought of as having impulsive or compulsive features (Hollander and Rosen 2000; Stein and Hollander 1995), or even that impulsive behavior is converted into compulsive responding as a function of its repetition (see Everitt and Robbins 2005). This counterbalancing of impulsive and compulsive responding brings us back to sophisticated notions of behavioral inhibition, which might become disrupted in both cases, possibly while engaging different neural circuitry. These notions have been recruited previously by Gray (2000) in his extensive theory based on behavioral inhibition, in which OCD symptoms are accredited to an overactive "checking" mechanism that compares intended actions with their outcomes: if the hypothetical comparator is constantly detecting mismatches, this will continuously engage the "checking" mechanism possibly dependent on anterior cingulate influences.

The Stop-Signal Reaction Time Task

Another way of explaining this form of perseveration is to suggest that in OCD or related forms there is a failure of "stop-signal inhibition"—an inability to stop an already-initiated response. This notion is compatible with the proposed lateral orbitofrontal cortex dysfunction in OCD, and OCD patients do show decreased behavioral and cognitive inhibition in a variety of tasks (Bannon et al. 2002; Enright and Beech 1993; Rosenberg et al. 1997; Tien et al. 1992; for review, see Chamberlain et al. 2005) in addition to the increased errors they show on the alternation learning task (Abbruzzese et al. 1995; Cavedini et al. 1998). Moreover, Logan and Cowan (1984) have devised a way of measuring the stop-signal reaction time in humans by measuring the response latency required to successfully cancel a response in a choice-reaction time procedure. This can also be conceived as measuring "impulsive" responding, particularly as it is impaired in attention-deficit/hyperactivity disorder (ADHD) and it has been shown for example that methylphenidate normalizes stop-signal reaction time in adult ADHD patients (Aron et al. 2003b). A recent comparative study of OCD and trichotillomania (Chamberlain et al. 2006a) shows an interesting dissociation in which trichotillomania patients had greatly lengthened stop-signal reaction times and that OCD patients were also significantly slowed on this measure, as compared with age- and IQ-matched control subjects. By contrast OCD patients were significantly impaired on the extra-dimensional shift test, whereas trichotillomania patients were not. These data suggest that whereas OCD is accompanied by a general problem in cognitive flexibility, trichotillomania is associated more specifically with a failure to stop motor output. Moreover, recent studies of first-degree relatives of OCD patients (Chamberlain et al. 2007a; Menzies et al. 2008) identified behavioral deficits on these tasks in "at risk" relatives of patients linked with structural abnormalities of frontostriatal circuitry.

In terms of neural substrates, studies of human patients with frontal lobe damage have localized the critical zone for stop-signal reaction time to the right inferior frontal gyrus (Aron et al. 2003a), and other data implicate the striatum in this inhibitory process (Aron et al. 2003c). It is intriguing that precisely the same structure is implicated in the extra-dimensional shift test, according to a recent functional magnetic resonance imaging study (Hampshire and Owen 2006). A method of measuring stop-signal reaction time in rats has been developed that is dependent on possibly homologous structures in the lateral orbitofrontal cortex and medial striatum (Eagle and Robbins 2003; Eagle et al. 2008). Intriguingly, however, the stop-signal reaction time is insensitive to serotoninergic manipulations in both rats (Eagle et al. unpublished data) and humans (Chamberlain et al. 2006b, 2007b; Clark et al. 2005).

AUTHOR: Please provide more info regarding Eagle et al. unpublished data above (other author names, year/date of data, etc).

Conclusion

We are thus intriguingly close to providing useful theoretically motivated models of OCSDs, particularly with regard to repetitive motoric habits and inhibitory failures. Nonetheless, significant puzzles still remain (Table 8–1). For example, two of the most sensitive of the human tests used to highlight deficits in OCD (the stop-signal and ID/ED tests) appear to be more dependent on the integrity of the inferior frontal cortex rather than the orbitofrontal cortex. Moreover, OCD patients are not markedly impaired on simple reversal learning, which has been associated in animal studies with damage to the orbitofrontal cortex (Boulougouris et al. 2007) and which is sensitive to serotonin manipulations (Boulougouris et al. 2008). Neuroimaging versions of these tasks may yet identify subtle brain dysfunction in patients and unaffected relatives at risk of OCSDs, in the absence of overt behavioral deficits. OCD has received the most research attention to date; it would be of considerable interest to determine whether the more obvious motor manifestations of other conditions such as trichotillomania are associated with structural and/or functional impairments of similar corticostriatal loops, possibly more at striatal than cortical nodes, or whether, as seems likely, these are associated with impairments in other frontostriatal pathways, for example, related to the putamen and its role in the control of motor output.

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AUTHOR: It was very difficult in the format that this book is in (as opposed to the larger format of the original journal) to get table to lay out with brackets as in original. We deleted brackets for ease of layout. OK to go without? We also could repeat entry that applies across entries for utmost clarity.

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD)

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Ethological models	Tail-chasing (Brown et al. 1987), acral lick dermatitis (paw licking) in dogs (Rapoport et al. 1992), psychogenic alopecia (hair pulling) in cats (Swanepoel et al. 1998), feather picking in birds (Grindlinger and Ramsay 1991), cribbing in horses (Luescher et al. 1998), schedule induced polydipsia (Woods et al. 1993), food-restriction-induced hyperactivity (Altemus et al. 1996)	Spontaneous persistent behaviors with genetic components reminiscent of OCD	Although these models offer good face similarity and predictive validity, construct validity is difficult to be tested mainly due to the fact that they focus on spontaneous persistent behaviors	The effects of SSRIs have been tested and compared with the effects of drugs ineffective in OCD, e.g., remediating effects of clomipramine on canine lick dermatitis
Genetic models	*hoxb8* mutant mice (Greer and Cappechi 2002)	Excessive grooming similar to that seen in trichotillomania and OCD	Hoxb8 gene is expressed in orbitofrontal cortex, the anterior cingulate, the striatum, and the limbic system, all of which are implicated in OCD	There are no reports on the isomorphic response of these models with clinical compulsive behavior

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD) *(continued)*

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Genetic models *(continued)*	D1CT-7 mice (Campbell et al. 1999b, 1999c; McGrath et al. 1999)	Perseveration and repetitive leaping Tourette's syndrome-like behaviors	Transgene expression in neural systems hyperactive in human OCD, e.g., amygdala, somatosensory/ insular and orbitofrontal cortical regions	
	DAT KD mice (Berridge et al. 2005)	Sequential super-stereotypy apparent in OCD/ Tourette's syndrome patients in the form of rigid patterns of actions, language, or thought	Dopaminergic involvement in OCD. Basal ganglia are implicated in grooming and OCD	
	5-HT_{2c} KO mice (Chou-Green et al. 2003)	Perseverative "head dipping" and excessively orderly chewing of screen material similar to human obsessive-compulsive symptoms such as ordering, washing, etc.	5-HT_{2C} receptors involvement in OCD pathophysiology	

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD) *(continued)*

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Pharmacological models	Quinpirole-induced compulsive checking (Szechtman et al. 1998)	Compulsive checking in OCD patients (e.g., ritual-like motor activities)	Dopaminergic involvement in OCD pathophysiology	Quinpirole-induced compulsive checking is reduced following treatment with clomipramine.
	8-OHDPAT-induced spontaneous alternation (Yadin et al. 1992)		5-HT_{1A} receptors involvement in OCD pathophysiology	Administration of fluoxetine (chronic) and clomipramine (subacute), but not desipramine, offers protection from the 8-OHDPAT-induced decrease in spontaneous alternation
	m-CPP-induced directional persistence in reinforced spatial alternation (Tsaltas et al. 2005)		5-HT_{2C} receptor involvement in OCD pathophysiology	Chronic treatment with fluoxetine, but not with diazepam or desipramine, blocks the mCPP-induced directional persistence.

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD) *(continued)*

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Behavioral models	Barbering (Garner et al. 2004)	Compulsive hair plucking in humans (trichotillomania)	Spontaneous development	No reports
	Marble burying (Ichimaru et al. 1995)	Inability to achieve a sense of task completion	No reports	Marble burying is sensitive to SSRIs and diazepam. However, the effects of diazepam disappear following repeated administration, which is not the case with SSRIs, e.g., fluvoxamine. No response to desipramine
	Signal attenuation (Joel and Avisar 2001; Joel et al. 2004)	Compulsive lever-pressing is both excessive and unreasonable, as are compulsions in OCD patients.	1. Similarities in the compulsivity-inducing mechanism (i.e., attenuation of an external feedback and a deficient response feedback mechanism, respectively) 2. Orbital, but not medial prefrontal or amygdala, lesions induce compulsive lever-pressing	Acute administration of fluoxetine, but not diazepam, desipramine or haloperidol, reduces compulsive lever pressing

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD) *(continued)*

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Other possible behavioral models	Reversal learning (Boulougouris et al. 2007; Chudasama and Robbins 2003; Clarke et al. 2004)	Inability to withhold, modify, or sustain adaptive behavior in response to changing situational demands	Lesions to the orbitofrontal cortex as well as serotonin depletion in this brain region heavily implicated in OCD disrupt reversal learning, manifested as increased perseverative responding to the prepotent stimulus.	The isomorphic response of these models with clinical compulsive behavior needs to be tested.
	Attentional set-shifting (Extradimensional shift) (Birrell and Brown 2000; Clarke et al. 2007)		Sensitive to lateral frontal lesions and catecholamine but not serotonin depletion in monkeys and medial prefrontal cortical lesions in rats.	
	Extinction		No reports but see signal attenuation model	

TABLE 8–1. Animal models of obsessive-compulsive disorder (OCD) *(continued)*

	Model	Modeled behavior (face validity)	Neuroanatomical/ neurochemical substrate (construct validity)	Predictive validity
Other possible behavioral models *(continued)*	Habit-learning (Killcross and Coutureau 2003; Yin and Knowlton 2006)	This behavior is controlled by stimulus–response links with a generally weakened influence of the ultimate goal	Habit learning is mediated by specific sectors of the striatum and can be influenced by prefrontal cortical mechanisms.	
	SSRT (Aron et al 2003a, 2003b, 2003c; Eagle and Robbins 2003; Eagle et al. 2008)	"Impulsive" responding particularly as it is impaired in ADHD	Studies in human patients with frontal lobe damage have localized the critical zone for SSRT to the right inferior gyrus whereas others have localized it to the striatum.	SSRT is insensitive to serotoninergic manipulations both in rats and humans.

Note.<m#>8-OHDPAT<t#>=<t#>8-hydroxy-2-(di-ni-popylamino)-tetralin hydrobromide; ADHD<t#>=<t#>Attention-deficit/hyperactivity disorder; D1CT mice: transgenic mice expressing a neuropotentiating protein (cholera toxin A1 subunit) within a cortical-limbic subset of dopamine D_1-receptor expressing (D_{1+}) neurons; DAT KD mice: dopamine transporter *(DAT)* knockdown (KD) mice, expressing 10% of wild-type *DAT* levels and exhibit elevated extracellular dopamine concentration; KO<t#>=<t#> knockout; *m*-CPP<t#>=<t#>meta-chlorophenylpiperazine; SSRI<t#>=<t#>selective serotonin reuptake inhibitor; SSRT<t#>=<t#>stop-signal reaction time task.