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Current animal models of obsessive compulsive disorder: A critical review

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Abstract

During the last 30 years there have been many attempts to develop animal models of obsessive compulsive disorder (OCD), in the hope that they may provide a route for furthering our understanding and treatment of this disorder. The present paper reviews current genetic, pharmacological and behavioral animal models of OCD, and evaluates their face validity (derived from phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition), predictive validity (derived from similarity in response to treatment) and construct validity (derived from similarity in the underlying mechanisms—physiological or psychological).

Keywords: Behavioral model; Genetic model; Mice; Obsessive compulsive disorder; Pharmacological model; Rat

1. Introduction

During the last 30 years there have been many attempts to develop animal models of obsessive compulsive disorder (OCD), and these have been reviewed quite extensively (e.g., Insel et al., 1994; Man et al., 2004; Pitman, 1989; Ricciardi and Hurley, 1990; Stein et al., 1994; Winslow and Insel, 1991). Most of these animal models have been abandoned during the years, and others have emerged. The aim of the present paper is to provide a critical review of *currently used* animal models of OCD. To this end, some features of OCD will be shortly described (these features are reviewed extensively in other papers in this issue); the criteria for validating animal models of psychopathology in general will be discussed, and several points which are specific to the modeling of OCD will be highlighted; on this basis, current animal models of OCD, divided according to the method used to induce 'compulsive' behavior (i.e., genetic, pharmacological, or behavioral manipulation) will be reviewed, and their validity evaluated.

OCD is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). According to the Diagnostic and Statistical Manual of Mental Disorders (4th ed; DSM IV; American Psychiatric Association, 1994), the essential features of OCD are recurrent obsessions or compulsions (e.g., doubting, checking, washing) that are time consuming (i.e., they take more than 1 h a day) or cause marked distress or significant impairment (see Bartz and Hollander, this issue).

Several neural systems have been implicated in the pathophysiology of OCD. Dysregulation of the serotonergic (5-HT) system has been suggested primarily on the basis of the effectiveness of serotonin reuptake inhibitors (SRIs) in alleviating obsessions and compulsions in patients (Zohar and Insel, 1987; Zohar et al., 1992), and has received further support from neurobiological, pharmacological and more recently genetic data (for review see Murphy et al., 2001; Ozaki et al., 2003; Sasson and Zohar, 1996; Stein, 2000, but see Baumgarten and Grozdanovic, 1998). Abnormalities of the dopaminergic (DA) system have also been implicated in the pathophysiology of OCD (see a paper by Blier, this issue), based on surplus therapeutic benefits obtained with co-administration of SRIs and DA blockers (McDougle et al., 1990, 1994; Sasson and Zohar, 1996) as well as on clinical observations of obsessions and compulsions in basal ganglia-

Abbreviations: 5-HT, serotonin; 5-MeODMT, 5-methoxy-*N*,*N*-dimethyltryptamine; 8-OHDPAT, 8-hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide; ADHA, attention deficit hyperactivity disorder; DA, dopamine; DAT, dopamine transporter; DSM IV, Diagnostic and Statistical Manual of Mental Disorders (4th ed.); ELP-C, excessive lever-presses in completed trials; ELP-U, excessive lever-presses in uncompleted trials; KD, knockdown; KO, knockout; OCD, obsessive compulsive disorder; SRIs, serotonin reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor; VTE, vicarious trial and error.

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related disorders, such as Tourette's syndrome (Frankel et al., 1986; Grad et al., 1987; Pitman, 1987). In parallel, the results of neuroimaging studies in OCD patients have implicated most consistently the orbitofrontal cortex, the cingulate cortex and the basal ganglia in the pathophysiology of obsessions and compulsions (for review see Saxena et al., 1998; Stein, 2000). These regions are interconnected and are densely innervated by dopaminergic and serotonergic terminals. However, the nature of the dysfunction of these regions or the relation between their malfunction and the disturbance in the neurotransmitter systems postulated to be involved in OCD is still unknown.

For obvious reasons, the understanding and treatment of diseases such as OCD, must rely heavily on appropriate animal models that closely mimic their behavioral and if possible their neural manifestations. Before reviewing animal models of OCD that are currently in use, we discuss the criteria for the validation and evaluation of animal models.

2. Assessing the validity of animal models

Animal models are "experimental preparations developed in one species for the purpose of studying phenomena occurring in another species" (McKinney, 1988, p. 20). Although there has been an expansion in the development and use of animal models in psychiatry, and several papers aiming at providing a conceptual framework for guiding the development of this field have been published (Geyer and Markou, 1995; Matthysse, 1986; McKinney, 1988; McKinney and Bunney, 1969; Willner, 1984, 1986, 1991), there is still a lack of clarity regarding the terminology and classification of animal models and their validation criteria. McKinney and Bunney (1969) suggested that the minimum requirements for an animal model are that the symptoms induced in the model be reasonably analogous to those seen in the modeled disease, and that treatment modalities effective in the modeled disease reverse the symptoms seen in animals. McKinney (1988) later separated the two requirements to describe animal models designed to simulate a specific sign or symptom of the human disorder (behavioral similarity models), and those designed to permit preclinical drug evaluations (empirical validity models). He also added a third type of animal models, those designed to evaluate a specific etiological theory (theory-driven models). A similar classification can be found in Matthysse (1986), who described four types of animal models, based on principles of symptom similarity, pharmacological isomorphism, cross-species psychological processes, and gene transfer. The validity of behavioral (symptom) similarity models is judged by how closely the model approximates the human condition, and the validity of empirical validity (pharmacological isomorphism) models is evaluated by how well drugs that work in humans also work in the model and how well the effects of drugs in the model predict clinical effects (Matthysse, 1986; McKinney, 1988). The methods for evaluating the third type of models, theory-driven models, were not described by Matthysse (1986) and McKinney (1988), but according to both authors, such models do not rely on a priori assumptions about the validity of the theory; rather, they are developed to test the theory (see also Rapoport et al., 1992).

Willner (1986, 1991) advanced a somewhat different classification of animal models into screening tests, behavioral bioassays and simulations. In addition, he grouped the different criteria for assessing animal models into criteria used to establish face, predictive and construct validity (Willner, 1984, 1986, 1991). Face validity refers to a phenomenological similarity between the model and the disorder it simulates. Ideally, the model should resemble the condition it models in its etiology, symptomatology, treatment and physiological basis. Predictive validity means that performance in the test predicts performance in the modeled condition. In principle, predictive validity can rely on etiology, physiology and response to treatment, but Willner (1991) notes that in practice, predictive validity is usually based on the latter. Construct validity means that the model has a sound theoretical rationale, and depends on the degree of homology between the behavior that is being modeled and the behavior in the model (two behaviors are considered homologous if they share a similar physiological basis), and on the significance of the modeled behavior in the clinical picture [see also Matthysse's, 1986 emphasis of the latter].

An additional attempt to describe and classify the criteria for assessing the validity of animal models has been made by Geyer and Markou (1995). Their major departure from the classification of Willner lies in narrowing the definition of face validity and broadening that of predictive validity. Thus, the use of the term face validity is restricted to the phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition. Predictive validity is defined as the degree to which performance in the model allows accurate predictions about the human condition. According to this definition, the identification of any variable that influences the animal model and the modeled phenomenon in similar ways strengthens the model's predictive validity. Based on this definition, Geyer and Markou (1995) conclude that the only necessary and sufficient validation criterion for animal models in neurobiological research is predictive validity.

While different authors may disagree on terminology and classification, there seems to be a wide agreement that it is impossible to develop an animal model that mimics a psychiatric syndrome in its entirety, and that therefore the criteria that an animal model must satisfy to establish its validity depend on the purpose of the model (Geyer and Markou, 1995; McKinney, 1988; Matthysse, 1986; Willner, 1991). In the context of neurobiological research, in which the aim of animal models is to promote our understanding of the modeled condition by elucidating its neurobiological mechanisms (Geyer and Markou, 1995), it is widely agreed that a common physiological basis of the model and the modeled condition contributes greatly to the model's validity, although authors disagree on whether this contributes to the model's face, predictive, and/or construct validity (Altemus et al., 1996; Bourin et al., 2001; Geyer et al., 2001; Nurnberg et al., 1997; Rapoport et al., 1992; Sagvolden, 2000; Szechtman et al., 2001; Yadin et al., 1991). It should be noted that a critical component in the demonstration of a common physiological

basis is the demonstration of a similar response to treatment, because the latter suggests similarity in the neurotransmitter systems involved. This makes pharmacological isomorphism an important factor in assessing the validity of an animal model, and indeed, the validation process of most animal models of psychopathology involves testing the effects of relevant pharmacological treatments.

In the present paper we treat similarity in the inducing mechanism (physiological or psychological) and in the neural systems involved as contributing to the construct validity of a model; similarity in response to treatment as contributing to the predictive validity of the model and to its construct validity; and phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition, as contributing to face validity.

3. Assessing the validity of animal models of OCD

Several points should be raised with respect to the assessment of predictive validity in animal models of OCD. First, although SRIs are, to date, the only effective pharmacological treatment of OCD, they are effective in several other psychiatric disorders, including depression, generalized anxiety disorder, panic disorder and social phobia (for recent reviews, see Argyropoulos et al., 2000; Vaswani et al., 2003). Animal models of OCD should therefore demonstrate both sensitivity to SRIs and insensitivity to other classes of drugs, which are not effective in OCD but are effective in these other conditions (e.g., non-serotonergic antidepressants such as desipramine, anxiolytic agents such as diazepam). Second, SRIs are not effective in all OCD patients [see also Insel et al.'s, 1994 emphasis of this point]. Therefore, a lack of effect of SRIs in a model may suggest that it is a model of compulsive behavior in the subgroup of OCD patients that do not respond to SRI treatment, rather than demonstrate that it is not a model of OCD. Importantly, such a model should still demonstrate insensitivity to other types of pharmacological treatment, because there is currently no other effective monotherapy for this subgroup of OCD patients.

Third, SRIs are effective in patients only after several weeks of repeated administration. There is currently disagreement on the importance of demonstrating similarity in treatment regime (acute versus chronic) in the animal model and the modeled disease. Bourin et al. (2001) stated that a demonstration of a "therapeutic" effect in a model after acute treatment undermines the model's predictive validity. Willner (1991) argued that the demonstration of drug effects in a model after a period of chronic administration is important for establishing its face validity, but is not relevant to the model's predictive validity and therefore to its ability to serve as a screening test for treatments for the modeled disease. Matthysse (1986) included a demonstration that the pharmacological effect grows stronger with time among the requirements for establishing pharmacological isomorphism. He pointed out, however, some difficulties with the notion of delayed drug effects in psychiatric disorders, which may also be relevant to OCD (for a recent criticism of the notion of delayed-onset action, see Agid et al., 2003). In practice, although this issue is relevant for animal models of many psychiatric disorders (in which response to pharmacological treatment is evident only after several weeks of treatment), whether emphasis is placed on treatment regime is greatly field-dependent. Thus, the predictive validity of the leading animal models of schizophrenia (latent inhibition and prepulse inhibition) is based primarily on acute drug effects (for reviews see Geyer et al., 2001; Moser et al., 2000). This is also true for most animal models of depression, but is usually taken as a weakness of the model (for review see Bourin et al., 2001). In the filed of animal models of OCD, most early models have used chronic rather that acute administration to establish predictive validity (e.g., Altemus et al., 1996; Nurnberg et al., 1997; Rapoport et al., 1992; Szechtman et al., 1998; Woods et al., 1993, but see Winslow and Insel, 1991), whereas more recently developed behavioral models, namely, marble burying and signal attenuation, have mainly used acute administration (see below).

4. Current animal models of OCD

4.1. Genetic models

Under this heading there are currently four mice models of OCD. It is important to note that the four models are not genetic models in the sense alluded to by Matthysse (1986), that is, they were not created on the basis of a known mutation in humans that was found to be related to OCD. Rather, these models are based on behavioral similarity, that is, the behavior of genetically modified mice was found to be similar in specific respects to that of OCD patients, and this is the main basis for the claim that they may serve as animal models of this disorder. Regretfully, there are no reports on the effects of different pharmacological treatments in these models, which could have strengthened their relevance to OCD. However, if these models are shown to have predictive validity, they may contribute greatly to our understanding of the neural mechanisms of OCD.

4.1.1 A transgenic mouse model of comorbid Tourette's syndrome and obsessive compulsive disorder

Burton et al. were the first to create a genetic mouse model of OCD (Campbell et al., 1999a,b; McGrath et al., 1999a). They engineered transgenic mice expressing a neuropotentiating protein (cholera toxin A1 subunit) within a cortical-limbic subset of dopamine D1-receptor expressing (D1+) neurons. They found that the transgenic mice (named, D1CT-7 mice) exhibited abnormal behaviors, including episodes of perseverance or repetition of normal behaviors, repetitive leaping and non-aggressive repeated biting of siblings during grooming (Campbell et al., 1999a). These behaviors were shown to be different from the hyperactivity and stereotypy induced by systemic administration of cocaine and from limbic seizure behaviors (Campbell et al., 1999b). D1CT-7 mice were also shown to exhibit an increased basal level of anxiety compared to control non-transgenic siblings (McGrath et al., 1999a). In addition, the administration of the anxiogenic drug yohimbine (McGrath et al., 1999a), as well as the exposure to an

anxiogenic odor (cat urine, McGrath et al., 1999b), potentiated the abnormal repetitive leaping of these transgenic mice. In a later study (Nordstrom and Burton, 2002), D1CT-7 mice were found to also exhibit comorbid Tourette's syndrome-like behaviors, including juvenile-onset tics; increased tic number, complexity and flurries; increased tic severity in males; voluntary tic suppression; and tic responsiveness to a non-cataleptic dose of clonidine, a drug that is being used for the treatment of comorbid OCD and Tourette's syndrome.

On the basis of the similarities between the behaviors exhibited by D1CT-7 mice and those exhibited by patients suffering from OCD, Tourette's syndrome and trichotillomania, Burton et al. suggested that D1CT-7 mice may provide a transgenic mouse model of OCD and related compulsive behavioral disorders. These authors have also pointed out the similarities between the brain regions in which transgene expression was evident in D1CT-7 mice and the neural systems involved in compulsive behaviors in humans, namely, the amygdala and limbic regions of the cortex (Campbell et al., 1999a).

Although the D1CT-7 model is promising in that the behaviors exhibited by the mice bear similarities to the behaviors of OCD patients, and there is some overlap between regions that may be involved in producing abnormal behavior in the model and the neural systems implicated in OCD, the demonstration of a similar pharmacological profile is critical for strengthening the model's relevance to OCD. To date, only the effects of dopaminergic (i.e., cocaine, and D1 and D2 antagonists) and noradrenergic (clonidine) agents have been assessed (Campbell et al., 1999c; Nordstrom and Burton, 2002).

4.1.2. Hoxb8 mutants as a model of the OC-spectrum disorder, trichotillomania

Greer and Capecchi (2002) reported that mice with disruptions of *Hoxb8* show excessive grooming compared to control litermates, manifested in longer time spent grooming, more frequent initiation of grooming, the presence of hair removal and skin lesions and excessive grooming of cage-mates. The mutant mice had normal coetaneous sensation and normal peripheral nerve innervation, and there was no evidence for inflammation of the area where hair has been removed, suggesting that the excessive grooming was not a result of skin or peripheral nervous system abnormality. The excessive grooming exhibited by the mutant mice is similar to the excessive grooming seen in trichotillomania and in OCD. Interestingly, *Hoxb8* is expressed in the orbital cortex, the anterior cingulate, the striatum and the limbic system, all of which are implicated in the pathophysiology of OCD. As is the case with regard to the D1CT model, the *Hoxb8* model is promising in that excessive grooming has face similarity to symptoms observed in OC spectrum disorders and may involve neural systems similar to those involved in compulsive behavior in patients, yet, it currently lacks predictive validity.

4.1.3. 5-HT2c receptor knockout mouse as a model of compulsive behavior in OCD

The 5-HT2c receptor knockout (KO) mouse was originally developed to investigate the functional roles of this receptor subtype in the control of feeding behavior (Nonogaki et al., 1998; Tecott et al., 1995). 5-HT2c KO mice were first described as obese and hyperphagic, with impaired satiety mechanisms (Nonogaki et al., 1998; Tecott et al., 1995; Vickers et al., 1999). Following the observation that these rats also chewed nonedible objects, Chou-Green et al. (2003) tested whether this was a form of compulsive behavior, and whether 5-HT2c KO mice show additional forms of compulsive behaviors. These authors reported that 5-HT2c KO mice showed increased chewing, but not eating, of non-nutritive clay, and a tendency to exhibit increased chewing of a plastic screen. In addition, these rats chewed the plastic screen in a "neat" way, that is, leaving less ragged pieces. In addition to these abnormal oral behaviors, KO mice also exhibited a slower habituation, or perseveration, of head-dipping into a hole located in the center of an elevated square board. Chou-Green et al. (2003) concluded that these behaviors provide evidence for compulsive behavior in the 5-HT2c KO mouse. Specifically, they suggested that the "strikingly organized manner of screen chewing in the KO mouse represents an example of compulsive-like behavior directed at changing something in the environment, similar to the human symptoms of checking, ordering, smoothing, or washing." (p. 646), and that the slower habituation of head-dipping may resemble compulsive checking in OCD patients.

In contrast to the two genetic models described above, in which the relation between the targeted gene and OCD in not clear, there is some clinical evidence suggesting that 5-HT2c receptors may play a role in OCD, as 5-HT2c agonists and antagonists have been shown to exacerbate OC symptoms in patients (Hollander et al., 1992; Khullar et al., 2001; Ramasubbu et al., 2000; Zohar et al., 1987, but see Charney et al., 1988; Ho Pian et al., 1998 which did not find such an effect).

Other work from the same group revealed that 5-HT2c KO mice exhibit an increased responsiveness to novelty and increased sensitivity to the psychostimulant and reinforcing effects of cocaine, as well as enhanced cocaine-induced increase in nucleus accumbens dopamine levels (Rocha et al., 2002). Although these data were discussed mainly in relation to cocaine dependence (Rocha et al., 2002), the finding of abnormalities in the mesolimbic dopaminergic reinforcement system may also be relevant to the modeling of OCD, because dopamine has been suggested to play a role in the pathophysiology of OCD (see a paper by Blier, this issue), and because there are several psychological theories of OCD which emphasize the role of reinforcement in this disorder (for a review and discussion of these theories see Pitman, 1989; Ricciardi and Hurley, 1990). 5-HT2c KO mice were also found to show a dentate gyrus-specific deficit in hippocampal long-term potentiation and hippocampal-related behavioral abnormalities, namely, impaired use of a spatial strategy in the Morris water maze and reduced avoidance of a novel environment (Tecott et al., 1998). These data were discussed with association to Alzheimer's disease (Tecott et al., 1998). However, there is some evidence implicating hippocampal dysfunction in OCD (Kang et al., 2003; Kwon et al., 2003a,b). Regretfully, Chou-Green et al. (2003) have not discussed the

relationship between these findings and OCD in their paper presenting the 5-HT2c mutant mouse as a model of OCD.

In summary, 5-HT2c KO mice exhibit a number of behavioral and neural abnormalities, which may be relevant to OCD as well as to other disorders. It is therefore unlikely that this model is a mouse model of OCD, although clearly, it may contribute to our understanding of the role of the 5-HT2c gene and receptor in compulsive behaviors. However, pharmacological studies of the effects of drugs which are known to produce beneficial effects in OCD as well as of drugs which are known not to be effective, are still needed to determine the relevance of the behavioral abnormalities of 5-HT2c KO mice to compulsive behaviors in OCD patients.

4.1.4. Dopamine transporter knockdown mouse as a model of obsessive compulsive disorder and Tourette's syndrome

The dopamine transporter (DAT) knockdown (KD) mouse was originally developed in an attempt to model aspects of attention deficit hyperactivity disorder (ADHD), on the basis of reports of an association between ADHD and polymorphisms in the DAT gene, and the fact that DAT is a major target for amphetamine and methylphenidate that are the treatments for ADHD (Zhuang et al., 2001). Indeed, DAT KD mice, which express 10% of wild-type DAT levels and exhibit elevated extracellular dopamine concentration (Zhuang et al., 2001), were found to display hyperactivity (Ralph-Williams et al., 2003; Zhuang et al., 2001), and their hyperactivity was blocked by amphetamine administration (Zhuang et al., 2001). Although these results were taken to support the suggestion that DAT KD mice may serve as a model of ADHD (Zhuang et al., 2001), Ralph-Williams et al. (2003) suggested that they may more generally model disease states characterized by a hyperdopaminergic tone, such as bipolar disorder and ADHD. These authors have shown that valproate, a standard treatment for manic and hypomanic episodes, attenuated the hyperactivity and diminished the degree of perseverative locomotor patterns in DAT KD mice (Ralph-Williams et al., 2003). Still others have found that DAT KD mice demonstrated enhanced acquisition and greater incentive performance for a sweet reward, and suggested that these mice may serve to study motivational features of drug addiction (Pecina et al., 2003).

Berridge et al. (2004) have studied in detail the grooming behavior of DAT KD mice, assessing not only grooming duration but also the sequential pattern of the syntactic grooming chain (a grooming chain contains up to 25 movements serially combined into 4 phases). Berridge et al. (2004) found that DAT KD mice spent more time than wild-type mice in grooming behavior overall, and that this increased grooming time was due to longer grooming bouts (rather than a greater number of bouts) in the mutant compared to the wild-type mice. In addition, DAT KD mice initiated more syntactic grooming chains compared to wild-type mice, and were more likely to complete syntactic chains they had started. Because the behavioral sequence of the mutant mice was more predictable and stereotyped, Berridge et al. (2004) refer to it as *sequential super-stereotypy*.

Berridge et al. (2004) pointed out several similarities between DAT KD mice and patients suffering from OCD and Tourette's syndrome: (i) OCD and Tourette's patients show symptoms of super-stereotypy, in the form of overly rigid sequential patterns of action, language, or thought; (ii) rituals of cleanliness, security behavior or concerns of contamination may all be related to self-grooming; and (iii) the basal ganglia have been implicated in OCD and Tourette's syndrome as well as in the serial pattern of grooming chains. On the basis of these similarities they concluded that "elucidation of the basis for sequential super-stereotypy of instinctive behavior in DAT knockdown mutant mice may offer insights into neural mechanisms of overly rigid sequences of action or thought in human patients with disorders such as Tourette's or OCD." (Berridge et al., 2004, p. 1).

In summary, as was the case for the 5-HT2c KO mouse, DAT KD mice show a number of behavioral abnormalities which may be related to several basal ganglia- and dopamine-related disorders, including OCD and Tourette's syndrome, as well as ADHD and mania. It is therefore unlikely to provide a mouse model of OCD and Tourette's syndrome, although clearly, studying the neural mechanisms of super-stereotypy in this model may further our understanding of the neural mechanisms of compulsive behaviors. Importantly, however, if this model is also to be used for the elucidation of the pathological mechanisms of OCD and for the development of treatments for this disorder, it would seem important for the predictive validity of this model to also be assessed.

5. Pharmacological models

Pharmacological models of OCD are based on drug-induced behavioral alterations which bear similarity to some specific characteristics of the behavior of humans diagnosed with OCD, such as perseveration and indecision (Yadin et al., 1991), or compulsive checking (Eilam and Szechtman, 1995; Szechtman et al., 1998, 2001). In addition to behavioral similarity, in both models the relevant behavior is induced by manipulations of a neurotransmitter system whose dysfunction has been implicated in OCD. Thus, in Yadin et al.'s (1991) model, perseveration is induced by manipulations of the serotonergic system, and in Szechtman et al.'s model, compulsive checking is induced by manipulations of the dopaminergic system. Finally, in both models the effects of an SRI (fluoxetine and clomipramine in Yadin et al.'s model (Yadin et al., 1991; Fernandez-Guasti et al., 2003, respectively), and clomipramine in Szechtman et al.'s model (Szechtman et al., 1998)) have been tested.

5.1. Pharmacologically induced decrease in spontaneous alternation

Spontaneous alternation refers to the natural tendency of rats to explore novel places sequentially and in succession. Yadin et al. (1991) were the first to suggest that *pharmacologically-induced decrease in spontaneous alternation* may serve to model a specific aspect of OCD, namely, indecision. Food deprived rats were run in a T-maze in which the two goal boxes

(one black and the other white) were always baited with chocolate milk. Each rat was given 7 trials a day, during which it was placed in the start box and allowed to choose one of the goal arms. The critical measure was the mean number of choices made until an alternation occurred (a score of 1 represents perfect alternation, whereas a score of 7 represents perseveration). Acute administration of the non-selective 5-HT agonist 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) or of the 5-HT1a agonist 8-hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide (8-OHDPAT) led to a reduction in spontaneous alternation (that is, 5-MeODMT-and 8-OHDPAT-treated animals obtained a score of ~3.5 and ~2.5, respectively, compared to ~1.5 in control animals). This reduction was prevented by repeated administration (3 weeks) of the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Yadin et al., 1991). It should be noted that repeated administration of fluoxetine had no effect on spontaneous alternation in rats that were not challenged with a 5-HT agonist (Yadin et al., 1991), indicating that spontaneous alternation per se cannot be used for the screening of anti-compulsive drugs.

Fernandez-Guasti et al. (2003) have shown that 8-OHDPAT-induced decrease in spontaneous alternation is prevented by sub-acute administration (3 injections) of the serotonin reuptake inhibitor clomipramine, but not of the tricyclic antidepressant desipramine, strengthening the predictive validity of this model. This group has also found that the effects of 8-OHDPAT differed in young male and females rats, so that administration of 8-OHDPAT led to decreased alternation in young male but not in young female rats (Ulloa et al., 2004a). The authors have pointed out that this gender difference resembles the greater vulnerability of males to childhood-onset OCD (in which the ratio of males to females is 3:2).

Seibell et al. (2003) have replicated the finding of decreased spontaneous alternation following 8-OHDPAT administration in additional strains of rats and in juvenile rats. They also reported that 8-OHDPAT administration led to an increase in the amount of time animals spent performing vicarious trial and error (VTE) behavior at the T-maze decision point, in line with Yadin et al.'s (1991) suggestion that the behavior of 8-OHDPAT-treated rats may be analogue to indecision in OCD patients. In addition, Seibell et al. (2003) showed that administration of a 5-HT2 agonist (*R*-(−)dimethoxyiodophe-)dimethoxyiodophenylaminoethane, DOI) or a 5-HT3 agonist (*N*-methyl quipazine, NMQ) did not alter alternation scores nor VTE scores, strengthening the specific role of 5-HT1a receptors in decreased alternation/increased VTE behavior. Interestingly, the administration of the partial 5-HT1a agonist/D2 antagonist, buspirone, led to a dramatic increase in VTE behavior, such that rats spent the entire 5 min allocated to them in the choice point performing VTE behavior without actually entering one of the arms of the T-maze (Seibell et al., 2003).

Einat and Szechtman (1993, 1995) demonstrated that chronic administration of the D2/D3 agonist quinpirole led to a reduction in spontaneous alternation in a T-maze, and suggested that quinpirole-induced decreased alternation may model 'compulsive checking' (Einat and Szechtman, 1995). Ulloa et al. (2004b) have later found that in adult male rats, quinpirole-induced decreased alternation, like 8-OHDPAT-induced decreased alternation, was prevented by a sub-acute administration (3 injections) of clomipramine. These authors showed that male juvenile rats were less responsive to the effects of both quinpirole and clomipramine than adult rats, and suggested that the latter finding may be relevant to the observation that in OCD, the response to SRI treatment is weaker in children than in adults. It should be pointed out, however, that the lack of significant effect of clomipramine in quinpirole-treated juvenile rats may have been a result of a floor effect, because in these rats quinpirole did not alter significantly the alternation score (i.e., the baseline alternation score in both groups was around 1.4 [a score of 1 reflects perfect alternation]; the alternation score following 11 quinpirole administrations was ~2 for juvenile rats and ~3 for adult rats, and it was reduced to about 1.6 in both groups following clomipramine administration).

It is clear that studies using 8-OHDPAT- and quinpirole-induced decreased alternation have yielded interesting findings, some of which seem to bear relevance to OCD. It is not at all clear, however, what the decrease in spontaneous alternation is a model of, because motor perseveration is common in neurological and psychiatric conditions other than OCD (e.g., Parkinson's disease, schizophrenia). Indeed, decreased alternation has been suggested to model indecision in OCD (Yadin et al., 1991), 'compulsive checking' in OCD (Einat and Szechtman, 1995), repetitive behaviors and need for sameness in autism (Kahne et al., 2002), and some aspects of Parkinson's disease (Taghzouti et al., 1988). The question of the relevance of pharmacologically induced decreased alternation to OCD becomes even more critical when considering the fact that spontaneous alternation is highly sensitive to neurochemical interference, with decreased alternation found following manipulations to all of the major neurotransmitter systems, including glutamate, GABA, acetylcholine, norepinephrine, serotonin and dopamine (for review see Myhrer, 2003).

It follows that the specific pharmacological manipulation used to induce decreased alternation is critical for establishing the relevance of this behavior to OCD. The fact that decreased alternation is induced by a serotonergic manipulation has been taken by Yadin et al. (1991) as a strength of the model, because the serotonergic system has been implicated in the pathophysiology of OCD. However, as pointed out recently by Man et al. (2004), although it is clear that SRIs have a therapeutic effect in OCD, it is less clear that abnormalities in the serotonergic system cause OCD (but see the recent genetic study of Ozaki et al., 2003). It is also not clear what role dopamine plays in the pathogenesis of OCD, and therefore whether quinpirole-induced decreased alternation is relevant to OCD. It should be noted that there are some differences between the two models (e.g., age differences in response to the pharmacological manipulation, see above) suggesting that they do not model the same clinical condition.

The fact that decreased alternation may result from interference with many neurotransmitter systems (Myhrer, 2003) as well as with many different psychological processes, including sensory, attentional, emotional and motor (Richman

et al., 1986/1987), not only weakens the face and construct validity of pharmacologically-induced decreased alternation as a model of OCD, but questions its usefulness for neurobiological research, as many neural systems are likely to be involved in the mediation of spontaneous alternation.

In summary, as a model of OCD, 8-OHDPAT- and quinpirole-induced decrease in spontaneous alternation may lack in face and construct validity and may not be very useful for understanding the neurobiological mechanisms of compulsive behaviors. As a screening test for anti-compulsive drugs, this procedure has the important advantage of being easy and cheap to run in terms of equipment and time. However, further studies establishing the predictive validity of each of these models are still needed, because to date only the effects of chronic administration of fluoxetine and sub-acute administration of clomipramine and desipramine have been assessed in the 8-OHDPAT model, and only the effects of sub-acute administration of clomipramine have been assessed in the quinpirole model.

5.2. Quinpirole-induced compulsive checking

This model, developed by Szechtman et al. (1998), is produced by chronic treatment of rats with the D2/D3 agonist quinpirole (0.5 mg/kg twice weekly for 5 weeks). Following drug administration, rats are placed individually into a large open field, in which 4 small objects are present at a fixed location, and are videotaped for 55 min. The behavior of quinpirole- and saline-treated rats after the 10th injection is analyzed to obtain the following behavioral measures: frequency of stops in each locale (place or object); mean time interval between two successive visits to a given locale; mean duration of stopping in a given locale; the number of visits to other locales in between returns to a given locale. In addition, the sequence of movements that rats perform during a visit to specific locales is recorded. Quinpirole-treated rats typically exhibit 2 locales in which they stop more frequently (up to 20-fold more) than saline-treated rats. They exhibit much shorter return times to these places and stop at less places between returns, compared to control rats. In addition, quinpirole-treated rats perform a characteristic "ritual-like" set of motor acts at these places (Ben-Pazi et al., 2001; Szechtman et al., 1998, 2001).

On the basis of published descriptions of compulsive behavior in OCD patients as well as their own observations (Eilam and Szechtman, 2005; Szechtman and Eilam, 2005), Szechtman et al. (1998, 2001) argue that the behavior of quinpirole-treated rats is similar in several respects to compulsive checking in OCD patients. First, quinpirole-induced 'compulsive checking' meets formal ethological criteria of OCD compulsive checking, 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 environmental context" (Szechtman et al., 2001, p. 2). Second, it has been shown that compulsive checking in quinpirole-treated rats can be suspended for a period of time, similarly to compulsions in patients (Szechtman et al., 2001). Third, the anti-compulsive drug clomipramine has been found to partially and transiently reduce quinpirole-induced checking (Szechtman et al., 1998). On the basis of this latter finding it has been suggested that quinpirole-induced compulsive checking may provide a model of only a subtype of OCD, namely, of the subgroup of patients that are less responsive to the beneficial effects of SRI treatment (Szechtman et al., 1998).

In summary, the quinpirole model has strong face validity established convincingly using formal ethological criteria. Although it has been shown that quinpirole-induced compulsive checking is partially attenuated by clomipramine, the model's predictive validity would be greatly enhanced by assessment of the effects of SSRIs and, even more critically, of the effects of drugs which are known not to be effective in the treatment of OCD. In addition, although dopaminergic involvement has been suggested in OCD, it is not clear what role dopamine plays in the pathogenesis of OCD, and therefore whether the fact that compulsive checking is induced by a dopaminergic manipulation contributes to the construct validity of this model.

6. Behavioral models

Most early animal models of OCD can be grouped under this heading. These include naturally occurring repetitive or stereotypic behaviors, such as tail chasing, fur chewing and weaving (for review see Insel et al., 1994; Stein et al., 1994; Winslow and Insel, 1991); innate motor behaviors that occur during periods of conflict, frustration or stress (displacement behaviors) such as grooming, cleaning and pecking (for review see Insel et al., 1994; Pitman, 1991; Ricciardi and Hurley, 1990; Winslow and Insel, 1991); and natural behaviors that occur following some behavioral manipulation (adjunctive behaviors, for review see Insel et al., 1994), such as schedule-induced polydipsia (Woods et al., 1993) and food restriction-induced hyperactivity (Altemus et al., 1996). These models are based primarily on behavioral similarity. The effects of SRIs have been tested in only some of the models (Altemus et al., 1996; Nurnberg et al., 1997; Rapoport et al., 1992; Szechtman et al., 1998; Winslow and Insel, 1991; Woods et al., 1993), and in several of these models the effects of drugs known not to be effective in OCD were also tested (Altemus et al., 1996–fluoxetine vs. imipramine; Rapoport et al., 1992–clomipramine, sertraline and fluoxetine vs. desipramine and fenfluramine; Winslow and Insel, 1991–clomipramine vs. desipramine; Woods et al., 1993–fluvoxamine, fluoxetine and clomipramine vs. desipramine, haloperidol and diazepam). Although some of these models have good predictive validity in addition to face validity, many have not been used since the original publications. To date only three behavioral models of OCD are in use, namely, the barbering, marble burying and signal attenuation models. Similarly to earlier behavioral models, barbering and marble burying have been suggested as potential models of OCD on the basis of behavioral similarity. In contrast, the signal attenuation model is a theory-driven model of OCD, in which a 'compulsive'-like

behavior is induced by simulating a deficient psychological mechanism hypothesized to underlie compulsive behaviors in OCD.

6.1. Barbering as a mice model of compulsive hair-pulling behavior in trichotillomania and obsessive-compulsive spectrum disorders

Barbering, that is, fur and whisker trimming, is a common behavior in laboratory mice, where barbers (i.e., mice performing the behavior) pluck hair from their companions. Although once considered a normal 'dominance' behavior, Garner et al. (2004a,b) have gathered evidence suggesting that barbering cannot be considered a dominance behavior. Specifically, it is common to observe cages with two barbers where each barber denudes all cagemates (Garner et al., 2004b); females commonly barber male cagemates (Garner et al., 2004b); mice will barber rats when housed together (Hauschka, 1952); and self-barbering mice are as common amongst singly-housed animals as cagemate-barbers are amongst group-housed animals (Garner et al., 2004b). Because barbering is a conspicuous element of the repertoire of a limited subset of individuals, rather than being part of the behavioral repertoire of all mice (Garner et al., 2004b), Garner et al. suggested that barbering is a form of abnormal behavior. Moreover, there are several phenomenological, demographical, and etiological similarities between barbering and compulsive hair plucking in humans (trichotillomania). Thus, similar to trichotillomania, barbers predominately pluck hair from the scalp and around the eyes and the genitals; barbering is female biased, has its onset during puberty and is more prevalent in breeding mice than in colony mice; and there is evidence for a role of genetic background in barbering (Garner et al., 2004b).

Although barbering seems to have strong face validity as a model of trichotillomania, it currently lacks predictive and construct validity. Barbering has an important advantage over other models, in that it develops spontaneously, and thus may provide insight into a range of genetic and environmental etiologic factors in trichotillomania. However, the fact that barbering is not experimentally induced has its down side, because breeding mice to yield a sufficient number of barbers is likely to involve production of excess asymptomatic mice (the percent of barbers in different mice strains was reported to be between 1.3% and 13.5%; Garner et al., 2004b).

6.2. Marble burying in mice

Rodents use bedding material to bury noxious as well as harmless objects. Inhibition of object burying was originally suggested as a screening test for anxiolytic activity, because the duration and extent of burying of both noxious and harmless objects were reduced by a variety of anxiolytic drugs, at doses that did not reduce behavioral output in general (Broekkamp et al., 1986; Treit, 1985; Treit et al., 1981). Although later studies have provided further support for the sensitivity of marble burying to anxiolytic drugs, the finding that burying was reduced by serotonin reuptake inhibitors raised the possibility that this behavior may be related to OCD (Broekkamp et al., 1986; Broekkamp and Jenck, 1989). Indeed, careful analysis of marble burying behavior has later led to the conclusion that it does not model anxiety, but may rather be related to compulsive behaviors (Gyertyan, 1995; Londei et al., 1998; Njung'e and Handley, 1991). Thus, mice did not avoid the marbles when given the opportunity to do so, suggesting that the marbles have no aversive or fear-provoking properties (Njung'e and Handley, 1991), and repeated exposure to marbles did not lead to habituation of marble burying, suggesting that this behavior is not related to novelty or fear (Londei et al., 1998; Njung'e and Handley, 1991). Londei et al. (1998) suggested that marble burying may begin as an appropriate investigative activity. However, because the marbles are non-reactive, they cannot provide the animal with the necessary stimuli to a natural ending of the investigation, and this "frustrated" investigation leads to compulsive burying. This suggestion is in line with the view that compulsive behaviors result from an inability to achieve a sense of task completion (for a recent review see Szechtman and Woody, 2004). Interestingly, this view has served as the basis of the signal attenuation model of OCD, reviewed next.

With regard to the predictive validity of the marble burying model, although there are several reports that burying is decreased by SSRIs at doses that do not affect locomotor activity (Hirano et al., 2005; Ichimaru et al., 1995; Njung'e and Handley, 1991; Takeuchi et al., 2002), and that such a suppressive effect is not exerted by desipramine (Ichimaru et al., 1995), the well documented finding that burying is also reduced by drugs that do not have anti-compulsive activity, such as diazepam (e.g., Broekkamp et al., 1986; Broekkamp and Jenck, 1989; Ichimaru et al., 1995; Njung'e and Handley, 1991) undermines the predictive validity of the marble burying model. The report of Ichimaru et al. (1995) that the effects of diazepam completely disappear with repeated administration, whereas this is not the case with the SSRI fluvoxamine, raises the promising possibility that marble burying may show selective response to SSRIs if repeated rather than acute administration is used. This possibility, however, still awaits additional supportive evidence.

6.3. The signal attenuation model

The signal attenuation model, developed by Joel et al. (Joel and Avisar, 2001; Joel and Doljansky, 2003; Joel et al., 2001, 2004, 2005a,b), is best described as a theory-driven model. This model has been developed on the basis of the theoretical proposition that compulsive behaviors result from a deficit in the feedback associated with the performance of normal goal-directed responses (Baxter, 1999; Gray, 1982; Malloy, 1987; Pitman, 1987, 1991; Reed, 1977; Szechtman and Woody, 2004, for review see Otto, 1992). In the model, the goal-directed behavior is lever-pressing for food. The feedback associated with making a response is manipulated using the following strategy: Rats are first trained to lever-press for food, whose delivery is accompanied by a stimulus which had been previously paired with food. In this manner the stimulus is

established as a feedback cue which signals that the lever-press response was effective in producing food. The "signaling" property of the stimulus is then attenuated by repeatedly presenting the stimulus without food (without the rat emitting the lever-press response). Finally, the effects of *Signal Attenuation* on lever-press responding are assessed under extinction conditions (i.e., pressing the lever results in the presentation of the stimulus but no food is delivered).

Because the test is carried out under extinction conditions and an encounter of non-reward produces an increase in operant responding (i.e., an extinction burst), the behavior of rats undergoing an extinction test preceded by a signal attenuation stage is compared to that of rats in an extinction session that is not preceded by signal attenuation (a procedure referred to as 'regular extinction'). The effects of non-reward are clearly seen in the 'regular extinction' procedure in the form of a high number of excessive lever-presses that are followed by magazine entry (excessive lever-presses in completed trials, ELP-C). Such a behavior is also exhibited by rats that undergo signal attenuation prior to the extinction test, but these rats show in addition an equally high number of lever-presses that are *not* followed by magazine entry (i.e., excessive lever-presses in uncompleted trials, ELP-U, Joel and Doljansky, 2003; Joel et al., 2004, 2005a). Because this behavior is seen to a much lesser extent in rats undergoing 'regular extinction', it was suggested to reflect rats' response to the encounter of an attenuated signal, and therefore to provide the behavioral measure of 'compulsive' behavior in the model. Signal attenuation-induced ELP-U bears some face similarity to compulsive behaviors in OCD, because the cessation of the attempts to collect a reward, which indicates that the rat detected the change in response consequences, combined with the increased emission of the lever-press response, makes the operant behavior both excessive and "inappropriate" or "unreasonable", thus fulfilling two important criteria of compulsive behavior (DSM-IV; Rapoport, 1989; Reed, 1985).

The hypothesis, derived at the behavioral level, that excessive lever-presses that are *not* followed by magazine entry (ELP-U) are the critical behavioral measure in the signal attenuation model, whereas excessive lever-presses that are followed by magazine entry (ELP-C) merely reflect the encounter of non-reward in the test, was further supported by the different patterns of drug effects on ELP-C and on ELP-U in the post-training signal attenuation and regular extinction procedures. In short, an anti-compulsive effect is demonstrated in the model by a reduction in ELP-U in the post-training signal attenuation procedure but not in the regular extinction procedure; an effect on extinction is evident in a decrease in ELP-C in the two procedures; and a general effect on motor output is manifested in a decrease in ELP-C and in ELP-U in the two procedures (for further exposition see Joel and Doljansky, 2003; Joel et al., 2004, 2005a).

Thus far it has been shown that acute administration of two SSRIs (paroxetine and fluvoxamine) had an 'anti-compulsive' effect in the model, whereas acute administration of a tricyclic antidepressant (desipramine), an anxiolytic (diazepam) and an antipsychotic (haloperidol) drug, did not, supporting the predictive validity of the model. Specifically, paroxetine and fluvoxamine reduced the number of ELP-U in post-training signal attenuation but not in regular extinction; desipramine did not affect ELP-U in both procedures; haloperidol decreased the number of ELP-U in both procedures; and diazepam had no effect on signal attenuation-induced ELP-U at doses that markedly reduced ELP-U in regular extinction (Joel and Doljansky, 2003; Joel et al., 2004).

It has also been shown that dopaminergic manipulations affect compulsive lever-pressing (Joel et al., 2001; Joel and Doljansky, 2003). Interestingly, administration of the D1 antagonist, SCH 23390, was found to have an 'anti-compulsive' effect (Joel and Doljansky, 2003), suggesting that blockade of D1 receptors may provide a new approach to the treatment of OCD (see Saxena et al., 1998, for a similar suggestion made on the basis of a theoretical model of OCD).

In a series of lesion studies (Joel et al., 2005a, 2005b) if has been shown that lesions to the rat orbital cortex (which may be analog to the primate orbitofrontal cortex, e.g., Groenewegen and Uylings, 2000; Ongur and Price, 2000; Schoenbaum and Setlow, 2001; Uylings et al., 2003), enhanced selectively 'compulsive' lever-pressing, whereas lesions to the rat medial prefrontal cortex (which may correspond to regions in the dorsal and lateral subdivisions of the primate prefrontal cortex, e.g., Groenewegen and Uylings, 2000; Kesner, 2000; Ongur and Price, 2000; Uylings et al., 2003) and to the basolateral nucleus of the amygdala did not affect 'compulsive' lever-pressing. Given that in humans, lesion to the orbitofrontal cortex may result in compulsive behavior which is similar to that of idiopathic OCD (Berthier et al., 1996; Hugo et al., 1999), and that functional imaging findings in OCD patients consistently implicate the orbitofrontal cortex in this disorder (see Introduction), but rarely report evidence for an involvement of the dorsal and lateral prefrontal cortex (but see, Kwon et al., 2003a for evidence implicating these regions in OCD) or of the amygdala (but see, Breiter et al., 1996; Horwitz et al., 1991; Kwon et al., 2003b for evidence implicating the amygdala in OCD), the finding that compulsive lever-pressing is enhanced following lesions to the orbital cortex but not to the medial prefrontal cortex or to the basolateral nucleus of the amygdala, further supports the hypothesis that compulsive lever-pressing may serve to model compulsive behavior in OCD, and lends the signal attenuation model construct validity.

Furthermore, it has been shown that the increase in compulsive lever-pressing following orbital lesion is prevented by the SSRI paroxetine, and is paralleled by an increase in the density of the striatal serotonin transporter, suggesting that orbital lesion-induced compulsivity is mediated by alterations of the serotonergic system, possibly of the striatal serotonergic system (Joel et al., 2005a). These findings are of particular importance given that in OCD the orbitofrontal cortex and the striatum function abnormally, and that drugs that block the serotonin transporter act in OCD patients to reduce symptoms as well as to reduce the increased metabolism of the orbitofrontal cortex and the striatum (Baxter et al., 1992; Benkelfat et al., 1990; Cottraux et al., 1996; McGuire et al., 1994; Rauch et al., 1994; Saxena et al., 1999; Swedo et al.,

Table 1
Assessment of the models against validating criteria

		Face validity		Predictive validity		Construct validity	
		Symptom similarity	Demographic similarity	Response to SRI's	No response to drugs not effective in OCD	Similarity of inducing mechanism	Similar neural substrates
Genetic models	D1CT-7 mice	++ (OCD+TS)				?	+(transgene expression in areas implicated in OCD)
	Hoxb8 mutant mice	++ (trichotillomania)				?	++(gene expression in areas implicated in OCD)
	5-HT2c KO mice	+/− (also mimics behavioral abnormalities that may be relevant to other disorders)				+ (there is evidence for involvement of 5-HT2c receptors in OCD)	+(functional abnormalities in neural systems implicated in OCD)
	DAT KD mice	+/− (also mimics behavioral abnormalities that may be relevant to other disorders)				+ (there is evidence for dopaminergic involvement in OCD)	++ (neural systems implicated in grooming also implicated in OCD)
Pharmacological models	8-OHDPAT-induced decrease in spontaneous alternation	+/− (motor perseveration is common in many disorders)	+ Gender differences in young rats	++	+(no response to desipramine)	+ (there is evidence for involvement of 5-HT1a receptors in OCD)	
	Quinpirole-induced decrease in spontaneous alternation	+/− (motor perseveration is common in many disorders)		+		+ (there is evidence for dopaminergic involvement in OCD)	
	Quinpirole-induced compulsive checking	+++		(+)		+ (there is evidence for dopaminergic involvement in OCD)	
Behavioral models	Barbering	+++ (trichotillomania)	Gender differences Effects of reproductive status			++Spontaneous	
	Marble burying	+		+++	− (response to anxiolytics) + (no response to desipramine)	?	
	Signal attenuation	++		+++	+++ (no response to diazepam, desipramine, haloperidol)	+ (simulates a deficient psychological process implicated in OCD)	++ (involvement of orbital cortex)

The models are listed (under abbreviated titles) in the order in which they appear in the text. Each column estimates the extent to which a model meets each criterion (+, ++ or +++, model does well; −,−− or −−−, model does badly; blank, there are no relevant data).

1992). Although the extrapolation from an animal model to the clinical condition is problematic, these findings raise the possibility that in some OCD patients a primary orbitofrontal dysfunction leads to striatal serotonergic malfunction and to compulsive behavior, and that anti-obsessional/anti-compulsive drugs act by normalizing the dysfunctional striatal serotonergic system (for a comprehensive discussion see Joel et al., 2005a). Interestingly, several imaging studies have reported that patients with lower pretreatment orbitofrontal cortex metabolism responded better to SRI treatment (Brody et al., 1998; Rauch et al., 2002; Saxena et al., 1999; Swedo et al., 1989), and there is some evidence that orbitofrontal cortex volume is reduced in OCD patients (Szeszko et al., 1999).

In summary, signal attenuation may provide an animal model of OCD with: construct validity, which derives from similarities in the compulsivity-inducing mechanism (i.e., attenuation of an external feedback and a deficient response feedback mechanism, respectively) and in the neural systems involved (the orbital cortex and the serotonergic and dopaminergic systems); face validity, that is, 'compulsive' lever-pressing is both excessive and unreasonable, as are compulsions; and predictive validity, that is, selectivity for anti-obsessional/anti-compulsive drugs.

7. Conclusions

Each of the models surveyed above has strengths and limitations (Table 1) which are important for choosing the aim(s) it can serve. In the context of *screening for anti-compulsive activity*, the most critical features of a model are its predictive validity and its cost-effectiveness. With regard to predictive validity, it is important to reiterate that about half of OCD patients do not respond to an SSRI monotherapy, yet, there is currently no other monotherapy that is effective in these patients. Therefore a demonstration of lack of effect of drugs that are known *not* to be effective in the treatment of OCD is more critical than a demonstration of effect of SSRIs for establishing a model's predictive validity. Of the models reviewed above, the most easy and cheap procedures are the marble burying test, which requires no behavioral training and no pharmacological manipulation, and the 8-OHDPAT-induced decreased alternation, which requires limited behavioral training and an acute administration of 8-OHDPAT. These two models currently lack, however, sufficient predictive validity. In the 8-OHDPAT model, a demonstration of lack of effect of drugs that are known not to be effective in the treatment of OCD is particularly important, because spontaneous alternation is known to be highly sensitive to pharmacological manipulations of all of the major neurotransmitter systems. For the marble burying model, it is critical to establish conditions that would enable the differentiation between the action of anxiolytic and anti-compulsive drugs, because acute administration of both classes of drugs reduces burying. Although the use of chronic drug administration may provide a means for such a differentiation, this possibility awaits additional supportive evidence. The signal attenuation model has good predictive validity, as it can differentiate between the effects of SSRIs and of drugs not effective in the treatment of OCD. It requires, however, special equipment (operant boxes) and about 2 weeks of behavioral training. In addition, the post-training signal attenuation procedure is not well suited for chronic drug administration studies, because repeated drug administration may affect behavior in the early stages of the procedure (e.g., lever-press training, signal attenuation). The genetic models carry promise for the development and screening of anti-compulsive drugs, yet they currently lack predictive validity.

An additional use of animal models is the *elucidation of the neurobiological mechanisms of the modeled condition*. In this context, similarity in the inducing mechanism seems to be the critical feature, although it cannot be evaluated directly, as the etiology of OCD is currently unknown. Given that the etiology of OCD most likely involves the interaction of multiple genetic and environmental factors (Murphy et al., 2001), animal models in which the compulsive behavior develops spontaneously may be particularly useful, because they may mimic more fully the range of genetic and environmental etiologic factors in the modeled condition. Barbering in mice may provide such a model, provided that similarity in response to treatment and in the underlying neural substrates is demonstrated. In contrast, genetic models of OCD involving single gene alterations (i.e., the *Hoxb8* mutant, the 5-HT2c receptor knockout and the DAT knockdown mouse models) are less likely to mimic the etiology of OCD. However, if these models provide further evidence for their relevance to OCD, they may contribute greatly to the identification of candidate genes and neural systems that may be involved in this disorder. The signal attenuation model uses a different approach, namely, a simulation of the psychological process that is assumed to underlie compulsive behaviors. Although there are clear differences between a deficient internal response feedback mechanism and an attenuated external feedback, the finding that compulsive behavior in the model has similarities to compulsive behaviors in patients in terms of response to treatment and neural systems involved suggests that this model may by useful in the study of the neurobiological mechanisms of compulsive behaviors. This model has already yielded findings which may shed light on the observed association between a dysfunction of the orbitofrontal cortex and of the serotonergic system in OCD.

Although none of the models reviewed provides an ideal animal model of OCD, several look promising and may be enhanced through further experimentation. Because OCD is most probably a heterogeneous and an etiologically complex disorder, the use of different models may allow investigation of the various aspects and subtypes of OCD. In addition, when attempting to develop and/or test new treatments for OCD, combining results obtained using different models may help uncover genuine anti-compulsive effects (rather than an effect specific to some parameter of a particular model that is not necessarily related to OCD). Finally, animal models of OCD may be used to test specific etiological theories of OCD.

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