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REVIEW

CURRENT ANIMAL MODELS OF OBSESSIVE COMPULSIVE DISORDER: AN UPDATE

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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 review provides the reader with an overview of the currently active animal models of OCD, their strengths and limitations, so that the reader can use the review as a guide for establishing new animal models of OCD, evaluating existing animal models and choosing among them according to one's needs. We review current genetic, pharmacological, neurodevelopmental and behavioral animal models of OCD, and evaluate 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]). On the basis of this evaluation we discuss the usefulness of the different models for screening drugs for anti-compulsive activity, detecting new targets for high frequency stimulation, studying the neural mechanisms of OCD and unraveling the role of gonadal hormones. We then describe potential new treatment strategies that emerge from the convergence of data obtained in different models on the one hand, and how different models can be used to model different subtypes or dimensions of OCD, on the other hand.

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Key words: obsessive compulsive disorder (OCD), behavioral model, genetic model, pharmacological model, mice, rat.

Contents

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Abbreviations: cAMP, cyclic AMP; DCS, D-cycloserine; DHEAS, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; HFS, high frequency stimulation; mCPP, m-chlorophenylpiperazine; NMDA, N-methyl-D-aspartate; OCD, obsessive compulsive disorder; SNRI, selective noradrenalin reuptake inhibitor; S/SRI, selective/serotonin reuptake inhibitor; 5-CSRTT, 5-choice serial reaction time task; 5-HT, serotonin; 8-OHDPAT, 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide.

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During the last 30 years there have been many attempts to develop animal models of obsessive compulsive disorder (OCD, for review see Insel et al., 1994; Joel, 2006a; Korff and Harvey, 2006; Man et al., 2004; Pitman, 1989; Ricciardi and Hurley, 1990; Stein et al., 1994; Wang et al., 2009; Winslow and Insel, 1991). Work in most of these models did not continue beyond the first publication. In the past 5 years, however, there is a change in the field with most papers aiming to study the pharmacology and neural basis of compulsive behaviors using a few established

animal models of OCD, and only a few papers presenting new animal models. In 2006 one of us reviewed the then active animal models of OCD (Joel, 2006a) and in a recent paper we reviewed the work done with established animal models of OCD (Albelda and Joel, in press).

The aim of the present review is to provide the reader with an overview of the currently active animal models of OCD, their strengths and limitations, so that the reader can use the review as a guide for establishing new animal models of OCD, evaluating existing animal models and choosing among them according to one's needs. We will shortly present the established models reviewed in Albelda and Joel (in press; 8-OHDPAT- [8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide] induced decreased alternation, quinpirole-induced compulsive checking, marble burying, signal attenuation and spontaneous stereotypy in deer mice) and summarize only the findings relevant for evaluating their validity, and present in more detail new models of OCD published in the past 5 years (*Sapap3* knockout mice, *Slitrk5* knockout mice, aromatase knockout mice, nest building behavior in house mice following selective breeding, m-chlorophenylpiperazine (mCPP)-induced persistence, and neonatal clomipramine model) as well as an older model that is still in use (schedule induced polydipsia). We will also relate to two tasks in which perseveration has been suggested to model compulsive behavior, namely, 5-choice serial reaction time task (5-CSRTT) and reversal training.

We start by shortly describing some features of OCD (for extensive reviews see Chamberlain et al., 2005; Greist and Jefferson, 2007; Lochner and Stein, 2003) and some issues relevant for the validation of animal models of OCD. Next we describe the three main classes of animal models of OCD, genetic, pharmacological and behavioral, and within each class, review established and new animal models of OCD and evaluate their validity. In the concluding section we discuss the usefulness of the different models for screening drugs for anti-compulsive activity, detecting new targets for high frequency stimulation, studying the neural mechanisms of OCD and unraveling the role of gonadal hormones. We then describe potential new treatment strategies that emerge from the convergence of data obtained in different models on the one hand, and how different models can be used to model different subtypes or dimensions of OCD, on the other hand.

OBSESSIVE-COMPULSIVE DISORDER

OCD is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). The Diagnostic and Statistical Manual of Mental Disorders (4th ed; DSM IV-TR) classifies OCD as an anxiety disorder characterized by obsessive thinking (persistent ideas, thoughts, impulses or images that are experienced as intrusive and inappropriate) and compulsive behavior (repetitive behaviors or mental acts [e.g. hand-washing, checking, praying, counting]) 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, 2006).

Three major neurotransmitter systems have been implicated in the pathophysiology of OCD, the serotonergic, the dopaminergic and the glutamatergic (Goddard et al., 2008; Stein, 2000). The reports that serotonin reuptake inhibitors (selective and non-selective, i.e. clomipramine, S/SRI's) are effective in alleviating obsessions and compulsions in patients led to the hypothesis that dysregulation of the serotonergic (5-HT) system is involved in the pathophysiology of OCD (Zohar and Insel, 1987; Zohar et al., 1992). This hypothesis was later supported by neurobiological, pharmacological and genetic data (for review see Bloch et al., 2008; Murphy et al., 2001; Ozaki et al., 2003; Sasson and Zohar, 1996; Stein, 2000; Westenberg et al., 2007, but see Baumgarten and Grozdanovic, 1998). Yet current data do not converge into a coherent picture regarding the specific dysfunction of the serotonergic system in OCD or the mechanisms by which S/SRIs exert their therapeutic effect. For example, tryptophan depletion does not block the symptom-ameliorating effects of SSRIs, suggesting involvement of additional neurotransmitters (Berney et al., 2006; Külz et al, 2007), and although 5-HT2a and 5-HT2c receptors have been implicated in the pathophysiology of OCD and in the mechanism mediating the therapeutic effect of SSRIs in this disorder, it is currently not clear whether activation or blockade of these receptors would have an anti-compulsive effect (see Flaisher-Grinberg et al., 2008 for discussion and references).

Involvement of the dopaminergic system in the pathophysiology of OCD has been suggested on the basis of the benefits obtained with co-administration of SSRIs and dopamine blockers (McDougle et al., 1990, 1994; Sasson and Zohar, 1996; Westenberg et al., 2007) as well as on clinical observations of obsessions and compulsions in basal ganglia-related disorders, such as Tourette's syndrome and Sydenham's chorea (Asbahr et al., 2005; Frankel et al., 1986; Grad et al., 1987; Pitman et al., 1987). It should be noted that it is difficult to distinguish between the involvement of the dopaminergic and serotonergic systems in OCD because there are complex interactions between these two neurotransmitter systems (for review see Di Giovanni et al., 2008; Marek, 2007; Wood and Wren, 2008) so that drugs that directly affect one system can also have an indirect effect on the other system. For example, 5-HT2c antagonists increase dopamine release (Di Matteo et al., 2001).

Involvement of the glutamatergic system has been recently suggested (for review see Pittenger et al., 2006) on the basis of elevated glutamate levels in the cerebrospinal fluid of drug-naive patients (Chakrabarty et al., 2005); correlations between symptom severity and the level of several glutamatergic metabolites (Starck et al., 2008); improvement of symptoms following treatment with riluzole, a glutamatergic antagonist (Coric et al., 2005; Grant et al., 2007), D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) agonist (Kushner et al., 2007; Wilhelm et al., 2008) and memantine, a non-competitive NMDA antagonist (Aboujaoude et al., 2009); and association of certain polymorphisms in the NMDA receptor gene with susceptibility to OCD (Arnold et al., 2004).

In addition to these three neurotransmitter systems, functional imaging data from patients with idiopathic OCD and evidence from patients with acquired OCD implicate most consistently the orbitofrontal cortex, the cingulate cortex and the basal ganglia in the pathophysiology of obsessions and compulsions (Baxter et al., 1987, 1992; Benkelfat et al., 1990; Berthier et al., 1996; Breiter et al., 1996; Hugo et al., 1999; Rauch et al., 1994; Saxena et al., 1998, 1999; Stein et al., 1999; Swedo et al., 1992, for review see Menzies et al., 2008; Rotge et al., 2009; Stein, 2000). The involvement of these structures in the pathophysiology of OCD is supported by reports that patients refractory to pharmaco- and behavioral therapy (around 30%; Eddy et al., 2004) may be treated by lesion and high frequency stimulation (HFS) to structures and pathways within basal ganglia-thalamo-cortical circuits (Aouizerate et al., 2004, 2005; Greenberg et al., 2006, 2010; Lopes et al., 2004; Mallet et al., 2008; Rauch et al., 2006; Sturm et al., 2003).

In recent years there is a growing recognition that sex hormones play a modulatory role in OCD (Uguz et al., 2007). Specifically, there are sex differences in the age of onset, the presence of additional neurological symptoms and in response to treatment (Brandes et al., 2004; Lochner et al., 2004; Zohar, 1999); life events related to the female hormonal cycle may trigger or exacerbate OCD in women patients (Abramowitz et al., 2003; Labad et al., 2005; Maina et al., 1999); and gonadotropin-releasing hormone (GnRH) agonists were reported to ameliorate OC symptoms in OCD patients (Casas et al., 1986; Eriksson, 2000).

The understanding and treatment of OCD may benefit from appropriate animal models that closely mimic its behavioral and neural manifestations. In light of the accumulating evidence on sex differences in OCD it is highly important that animal models employ both male and female subjects and that animal models in which compulsive-like behavior is modulated by ovarian hormones are used to study the neural mechanisms by which this modulating effect is achieved and to develop new lines of treatment. Unfortunately, to date most studies using animal models of OCD employ only male subjects.

CRITERIA FOR VALIDATING ANIMAL MODELS OF OCD

Previous papers have provided a thorough discussion of criteria for the validation and evaluation of animal models of psychopathology in general (Geyer and Markow, 1995; Matthysse, 1986; McKinney, 1988; McKinney and Bunney, 1969; Willner, 1984, 1986, 1991) and of OCD in particular (Albelda and Joel, in press; Joel, 2006a). In the present paper we treat phenomenological similarity between the behavior in the animal model and the specific symptoms of the human condition as contributing to the face validity of a model; similarity in the mechanism (physiological or psychological) that induces behavioral symptoms and in the neural systems involved as contributing to construct validity; and similarity in response to treatment (pharmacological or other) as contributing to the predictive validity of the model and to its construct validity. Below we detail several important issues related to the assessment of validity of animal models of OCD.

Face validity

In the field of animal models of OCD, a model's face validity is typically based on the induction of behaviors that are similar to compulsions in being repetitive, excessive and inappropriate.

Construct validity

As the physiological and/or psychological causes of OCD are currently unknown, construct validity of animal modes of OCD can be established by demonstrating involvement of the serotonergic, dopaminergic and glutamatergic systems, the orbitofrontal cortex, cingulate cortex and basal ganglia, as well as by demonstrating modulation by ovarian hormones. It is noteworthy that similarity in response to treatment (pharmacological and neurosurgical), which supports the predictive validity of a model (see below) also strengthens its construct validity by demonstrating similarity in the neural systems involved.

Predictive validity

In the field of animal models of OCD, predictive validity can be achieved by demonstrating similarity in response to pharmacological or neurosurgical treatment. Regarding the latter, a model's predictive validity will be enhanced by demonstrating that HFS of the subthalamic nucleus and ventral striatum have an anti-compulsive effect in the model, as the efficacy of HFS of these structures has been convincingly demonstrated in OCD (Aouizerate et al., 2004, 2005; Greenberg et al., 2006, 2010; Mallet et al., 2008; Rauch et al., 2006; Sturm et al., 2003).

The pharmacotherapy of OCD is unique in that to date only S/SRI's have been shown to be effective as a monotherapy. Therefore similarity in response to pharmacotherapy requires a demonstration of both sensitivity to S/SRI's and insensitivity to other classes of drugs, which are not effective in OCD (e.g. non-serotonergic antidepressants such as desipramine, anxiolytic agents such as diazepam, antipsychotics such as haloperidol), but are effective in the other disorders in which S/SRI's are effective (for review see Argyropoulos et al., 2000; Vaswani et al., 2003). It should be noted, however, that insensitivity to S/SRI's does not necessarily undermine a model's relevance to OCD because S/SRI's are not effective in all OCD patients. Therefore, such a model may provide a model of the subgroup of OCD patients that are not responsive to S/SRI's. Yet, also such models should demonstrate insensitivity to other classes of drugs, because although S/SRI's are not effective in all OCD patients, there is currently no other effective monotherapy for this subgroup of OCD patients.

Another issue that should be discussed when considering similarity in pharmacotherapy concerns the regimen of drug administration. In the clinic, SSRIs are

effective only following several weeks of treatment. The question is therefore whether a demonstration of drug effects in a model following acute administration supports that model's predictive validity or undermines it. Following Willner (1991) we have previously argued that because a model's predictive validity is relevant first and foremost for its ability to differentiate between effective and non-effective treatments, this ability is critical for establishing a model's predictive validity, regardless of the regimen of drug administration (Joel, 2006a; Albelda and Joel, in press).

Steps for establishing/evaluating a model's validity

Ideally, an animal model of OCD would show the three types of validity. However, as this is typically not the case we suggest the following method for establishing or evaluating the relevance of a model to OCD. At a first step the behavior in the model should bear some similarity to OCD, that is, the model should have face validity. However, because the behavioral manifestations of OCD are not specific to OCD (e.g. repetitive and perseverative behaviors are common in neurological and psychiatric conditions other than OCD, including Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder; Clark et al., 2007; Cools et al., 2006; Gauggel et al., 2004; Hozumi et al., 2000; Huddy et al., 2009; Itami and Uno, 2002; Waford and Lewine, 2010; Waltz and Gold, 2007), we believe that the relevance of a specific model to OCD cannot be based solely on behavioral similarity (i.e. on face validity).

The second and most important step in establishing/evaluating a model's relevance to OCD is assessing the model's predictive validity. This is because the pharmacological and neurosurgical treatments of OCD are quite specific to this disorder. Thus, selective alleviation by S/SRI's (we reiterate the importance of demonstrating selectivity and not merely efficacy of S/SRI treatment) is specific to OCD, and similarly, beneficial effects of HFS of the subthalamic nucleus were not reported in psychiatric disorders other than OCD (note, however, that HFS of the subthalamic nucleus is a common treatment for Parkinson's disease; HFS of the ventral striatum is not specific to OCD as it is also effective in depression; Bewernick et al., 2010; Malone et al., 2009). Because establishing a model's pharmacological predictive validity is relatively easy, we recommend that this should be the golden standard in establishing animal models of OCD.

The third step in establishing/evaluating a model's relevance to OCD is assessing the model's construct validity, that is, demonstrating involvement of the serotonergic, dopaminergic and glutamatergic systems, the orbitofrontal cortex, cingulate cortex and basal ganglia. Once the etiology of OCD is better understood it would be possible to construct models of OCD on the basis of similar etiology, and evaluate the construct validity of models on the basis of similarity in etiological factors and not only in the neural systems involved.

ANIMAL MODELS OF OCD

Animal models of OCD are typically divided into three classes according to the method used to induce compulsive-like behavior, namely, genetic, pharmacological or behavioral manipulation. Recently a neurodevelopmental model of OCD has been presented, and it represents the first model of a new class, neurodevelopmental models.

Genetic models

Under this heading there are currently seven mice models of OCD in which compulsive-like behavior appears in mice following a known genetic manipulation, and one model in which compulsive-like behavior developed as a result of selective breeding. The first class includes D1CT-7 transgenic mice (Campbell et al., 1999a–c; McGrath et al., 1999a,b; Nordstrom and Burton, 2002), Hoxb8 mutant mice (Greer and Capecchi, 2002), 5-HT2c knockout mice (Chou-Green et al., 2003), dopamine transporter knockdown mice (Berridge et al., 2005), aromatase knockout mice (Hill et al., 2007), *Sapap3*-mutant mice (Welch et al., 2007) and *Slitrk5* knockout mice (Shmelkov et al., 2010). The first four were reviewed in length in Joel (2006a) and a review of the first six can be found in Wang et al. (2009). Here we provide a general description of the strengths and limitations of the four early models, and a more detailed description of the three recent ones, as well as a detailed description of the selective breeding model.

The D1CT-7 transgenic mice, Hoxb8 mutant mice, 5-HT2c knockout mice and dopamine transporter knockdown mice were not created on the basis of a known mutation in humans that was found to be related to OCD, and this is also true for the more recent models. 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. In addition, in some of these models there is some connection between the targeted gene and OCD (e.g. there is evidence implicating 5-HT2c receptors in the pathophysiology or response to treatment in OCD), or between the neural systems affected and OCD (e.g. there are several lines of evidence implicating the dopaminergic system, which is affected in the dopamine transporter knockdown model, in the pathophysiology of OCD). Regretfully, however, none of the earlier models demonstrated the relevance of the behavioral abnormalities to OCD by showing that SSRIs reduce compulsive-like behaviors and that drugs that are known not to be effective in OCD are also not effective in the model (for a detailed review and discussion see Joel, 2006a).

An additional problem relevant to most of the early genetic models is that the genetically modified mice typically exhibit additional behavioral and neural abnormalities, which are not related to OCD (see Joel, 2006a for a detailed discussion). For example, 5-HT2c knockout mice are obese and hyperphagic with impaired satiety mechanisms (Nonogaki et al., 1998; Tecott et al., 1995; Vickers et al., 1999), and exhibit behavioral and neural abnormalities that may be related to cocaine dependence (Rocha et al.,

2002) and Alzheimer's disease (Tecott et al., 1998). Dopamine transporter knockdown mice show behavioral abnormalities and response to treatment that may be relevant to attention deficit hyperactivity disorder, bipolar disorder and drug addiction (Peciña et al., 2003; Ralph-Williams et al., 2003; Zhuang et al., 2001).

On the basis of these shortcomings, Joel (2006a) concluded that it is unlikely that these genetic models are models of OCD, as suggested in the publications cited above, although these models may contribute to our understanding of the role of the modified genes in compulsive (and other) behaviors. Of the three more recent models, the *Sapap3* and the *Slitrk5* knockout models have overcome some of these shortcomings.

Aromatase knockout mice. Aromatase knockout mice were originally developed to study the role of estradiol in the sexual differentiation of the reproductive system (Fisher et al., 1998). Indeed, in a number of studies male knockout mice were found to exhibit abnormal reproductive behaviors (reviewed in Wang et al., 2009). Another study found that male, but not female, knockout mice also showed a decrease in pre-pulse inhibition and an increase in amphetamine-induced activity (Van Den Buuse et al., 2003), deficits, which are typically considered to model schizophrenia (for review see Braff, 2010; Featherstone et al., 2007). A more recent study reported that male, but not female, knockout mice showed increased wheel-running activity and grooming but decreased ambulatory activity. Further analysis revealed a decrease in catechol-O-methyltransferase (one of the major enzymes involved in the metabolic degradation of catecholamines) in the hypothalamus of male knockout mice (Hill et al., 2007), consistent with evidence associating lower catechol-O-methyltransferase activity with higher risk of developing OCD (Karayiorgou et al., 1997).

Summary. Aromatase knockout male 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 it may contribute to our understanding of the role of estradiol in compulsive behaviors. However, pharmacological studies of the effects of drugs that are known to produce beneficial effects in OCD as well as of drugs that are known not to be effective are still needed to determine the relevance of the behavioral abnormalities of aromatase knockout mice to compulsive behaviors in OCD patients.

Sapap3 knockout mice. Welch and colleagues (2007) found that at the age of 4–6 months *Sapap3* knockout mice (males and females; Feng, personal communication) show excessive self-grooming with no sign of peripheral cutaneous defects, as well as increased anxiety-like behaviors in several tests, with no change in activity level. Excessive grooming and increased anxiety-like behaviors were reduced following repeated injections (for 6 days), but not a single injection, of the SSRI fluoxetine, supporting the relevance of these abnormal behaviors to OCD.

Sapap3 is expressed mainly in the striatum, and *Sapap3* knockout mice had specific defects in the structure of the postsynaptic complex of cortico-striatal synapses. Specifically, these mice exhibited reduced cortico-striatal synaptic transmission and defects in the functioning of NMDA and AMPA glutamate receptors (Welch et al., 2007). As the striatum and the glutamatergic system are implicated in the pathophysiology of OCD (see Introduction), these findings contribute to the construct validity of this model. Another experiment found that *Sapap3* knockout mice that received intrastriatal injection of lentiviruses expressing SAPAP3 showed less grooming and anxiety-like behaviors compared with non-treated *Sapap3* knockout mice, demonstrating that loss of SAPAP3 in the striatum was critical for the development of these behaviors, and suggesting that the altered functioning of the glutamatergic striatal system is involved in producing excessive grooming and anxiety-like behaviors (Welch et al., 2007).

Summary. Compared to previous genetic models of OCD, the *Sapap3* knockout model has two advantages. First, *Sapap3* knockout mice show a more restricted profile of behavioral and neural abnormalities, all of which are relevant to OCD (in contrast to previous models, which showed abnormalities not typical of OCD, for example, obesity, see above). Thus, *Sapap3* knockout mice showed increased grooming and anxiety-like behaviors, and abnormalities in the striatum and the glutamatergic system. It is possible, however, that future studies assessing additional behaviors and neural systems will reveal a wider range of behavioral and neural abnormalities, and that some of these abnormalities will be more relevant to disorders other than OCD, as found for previous genetic models. The second advantage of the *Sapap3* model is that it is the first to support the relevance of the behavioral abnormalities to OCD by demonstrating that an SSRI produces a beneficial effect in the model. In order to further establish the relevance of the *Sapap3* model to OCD it is important that drugs that are known not to be effective in OCD will also be tested and shown not to be effective in the model.

Slitrk5 knockout mice. Shmelkov et al. (2010) found that starting at the age of 3 months, *Slitrk5* knockout mice develop excessive self-grooming, increased marble burying and increased anxiety-like behaviors (as manifested in the open field test and the elevated plus maze), with no gross motor deficits. (The data presented in this paper were from male mice. The phenotype was also present in females, although a careful analysis of sex differences was not performed; Lee, personal communication). Excessive grooming was ameliorated by repeated administration (for 21 days) of fluoxetine, supporting the relevance of this behavior to OCD.

Slitrk5 knockout mice showed increased expression of FosB, which was restricted to the orbitofrontal cortex, as well as anatomical abnormalities in the striatum, including decreased volume, decreased dendritic complexity of striatal neurons and a reduced number of glutamate receptors. These findings support the construct validity of this model.

Summary. As was the case with *Sapap3* mice, *Slitrk5* knockout mice exhibit a restricted profile of behavioral and neural abnormalities, which are relevant to OCD (but, as was the case with the *Sapap3* model, it is possible that future studies assessing additional behaviors and neural systems will reveal a wider range of behavioral and neural abnormalities). Thus, *Slitrk5* knockout mice showed increased compulsive- and anxiety-like behaviors, and the relevance of these behavioral abnormalities to OCD was supported by successfully demonstrating that an SSRI decreases these behaviors. Here too it is important that drugs which are known not to be effective in OCD will be tested and shown not to be effective in the model. The construct validity of this model derives from the existence of neural abnormalities in the striatum, the glutamatergic system and the orbitofrontal cortex of *Slitrk5* knockout mice. We recommend that future studies study the role of sex in this model.

Nest building behavior in house mice following selective breeding. Selective breeding of house mice (*Mus musculus*) over 55 generations resulted in a 40-fold difference between BIG and SMALL mice in the amount of cotton used for nest building (Bult and Lynch, 1996, 1997, 2000). Because nest building behavior is a naturally occurring repetitive and stereotypic behavior, Greene-Schloesser et al. (2011) suggested that the excessive nest building in BIG mice may provide an animal model of OCD, and tested this hypothesis in male mice. Indeed, nest-building behavior in BIG male mice was reduced by repeated administration of the SSRI fluoxetine (administered orally for 4 weeks) and of the SRI clomipramine (administered orally for 12 weeks) but not by repeated administration of the selective noradrenalin reuptake inhibitor (SNRI) desipramine (administered orally for 4 weeks; Greene-Schloesser et al., 2011), supporting the relevance of nest building in BIG mice to OCD, and lending the model predictive validity.

Interestingly, the increased compulsivity of BIG mice was not restricted to nest building, as BIG male mice were found to burry more marbles in the marble-burying test compared to SMALL male mice. Fluoxetine significantly decreased marble burying in BIG mice without affecting locomotor activity (as measured in a running wheel). Moreover, BIG male mice were found to be significantly lower in measures of anxiety-like behaviors in comparison to SMALL mice both in the open field and in the elevated plus maze, suggesting that increased marble burying in BIG mice reflects increased compulsivity rather than increased anxiety (Greene-Schloesser et al., 2011).

Summary. BIG male mice may serve as a mouse model of OCD with good face validity, derived from increased nest building and marble burying, and good predictive validity, derived from their selective response to drugs that are effective in treating OCD patients. Of the genetic models, the BIG mice model has the most restricted behavioral profile, affecting only compulsive-like behaviors, and the best predictive validity, as this is the only model in which a drug that is not effective in OCD has been tested and shown not to be effective. Its predictive validity will be further supported by demonstrating that it is not responsive to additional classes of drugs, which are not effective in OCD. Further studies elucidating the genetic and neural differences between BIG and SMALL mice may provide insight into genetic factors in OCD and the neural systems involved. The main shortcoming of this model, which it shares with some of the other genetic models (i.e. 5-HT2c knockout mice and dopamine transporter knockdown mice), is that only male subjects were tested, and we highly recommend that future studies test both male and female subjects.

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. The most studied pharmacological models of OCD are 8-OHDPAT-induced decreased alternation and quinpirole-induced compulsive checking, which have recently been reviewed (Albelda and Joel, in press). Here we shortly present these models and summarize the main findings relevant to evaluating their validity, and present in more detail a newer pharmacological model of OCD presented by Tsaltas and colleagues (2005).

Quinpirole-induced compulsive checking. In this model, developed by Szechtman and colleagues (1998), rats are repeatedly injected with quinpirole, a D2/D3 agonist (twice a week at a dose of 0.5 mg/kg, over a 5-week period) and allowed to explore a large open field containing four small objects. Following the 10th injection, the behavior of quinpirole- and saline-treated rats is coded for a duration of 55 min according to the following behavioral measures: frequency of stops in each location (place or object); mean duration between two consecutive visits to a given location; mean duration of stopping in a given location; the number of visits to other locations in between returns to a given location. Compared with saline-treated rats, quinpirole-treated rats typically exhibit two favorite locations (i.e. locations in which they stop up to 20 fold more compared to other locations). In addition, their return times to these locations are much shorter and they stop at fewer places between returns, compared with control rats (Szechtman et al., 1998, 2001).

The relevance of quinpirole-induced compulsive checking to OCD is based primarily on behavioral similarity, which derives from an ethological analysis of quinpirole-induced compulsive checking, on the one hand, and compulsions in OCD patients, on the other hand (Eilam and Szechtman, 2005; Szechtman and Eilam, 2005; Zadicario et al., 2007). This analysis led Szechtman and colleagues to claim that quinpirole-induced compulsive checking meets formal ethological criteria of compulsive checking in OCD, including: (a) a preoccupation with and an exaggerated hesitancy to leave the item(s) of interest, (b) a ritual-like motor activity pattern, and (c) dependence of checking behavior on environmental context (Szechtman et al., 2001, p. 2). Although it has been shown that

quinpirole-induced compulsive checking is partially attenuated by the SRI clomipramine (Szechtman et al., 1998), the model currently lacks pharmacological predictive validity, as drugs that are known not to be effective in the treatment of OCD have not been tested.

In contrast to its lack of pharmacological predictive validity, the quinpirole model has good predictive validity with regard to HFS. Specifically, HFS of the subthalamic nucleus and of the shell and core subregions of the nucleus accumbens have been shown to decrease quinpirole-induced compulsive checking without affecting locomotion (Mundt et al., 2009; Winter et al., 2008b), in line with reports in OCD patients on the beneficial effects of HFS of the subthalamic nucleus and nucleus accumbens.

The findings with HFS also contribute to the construct validity of the quinpirole model by demonstrating similarity in the neural systems involved. Yet the results of other studies are less supportive, as lesions to the orbitofrontal cortex had no effect on quinpirole-induced compulsive checking (Dvorkin et al., 2010).

Summary. Quinpirole-induced compulsive checking provides an animal model of OCD with excellent face validity and predictive validity with regard to HFS, but not with regard to pharmacotherapy. Findings implicating the subthalamic nucleus and nucleus accumbens in the model supports the latter's construct validity, yet the finding that lesions to the orbitofrontal cortex do not affect compulsive checking detracts from its construct validity. 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.

8-OHDPAT-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, perseveration and indecision. The most common version of this model uses acute administration of the 5-HT1a agonist 8-OHDPAT to decrease spontaneous alternation. Specifically, food deprived rats are run in a T-maze in which the two goal boxes (one black and the other white) are always baited with food reward. Each rat is given several trials a day (seven, in Yadin et al., 1991), during which it is placed in the start box and allowed to choose one of the goal arms. The critical measure is the number of choices made until an alternation occurs (a score of 1 represents perfect alternation). Acute administration of 8-OHDPAT leads to a reduction in spontaneous alternation (e.g. 8-OHDPAT-treated animals obtained a score of ~2.5 compared with ~1.5 in control animals, Yadin et al., 1991).

8-OHDPAT-induced decreased alternation is prevented in males and females by repeated administration of the SSRI fluoxetine (Fernández-Guasti et al, 2006; Umathe et al., 2009b; Yadin et al., 1991) and the SRI clomipramine (Andrade et al., 2009; Fernandez-Guasti et al., 2003), but not by the tricyclic antidepressant desipramine (Fernandez-Guasti et al., 2003). These findings lend the model predictive validity, and suggest that it may be a useful tool for screening anti-compulsive drugs.

Current data do not support, however, the predictive validity of the model with regard to HFS. Specifically, 8-OHDPAT-induced decreased alteration was reduced by low, but not high, frequency stimulation of the thalamic reticular nucleus (Andrade et al., 2009). Because in OCD patients HFS of this nucleus has a therapeutic effect (Jiménez et al, 2007; Jiménez-Ponce et al., 2009), the findings in the model undermine its predictive validity.

The finding that stimulation and lesion of the thalamic reticular nucleus decrease 8-OHDPAT-induced decreased alteration (Andrade et al., 2009) contributes, however, to the model's construct validity by demonstrating similarity in the neural systems involved. In contrast, the finding that lesion to the orbitofrontal cortex does not affect 8-OHDPAT-induced decreased alteration (Andrade et al., 2009) detracts from the model's construct validity.

Further support for the construct validity of the 8-OHDPAT-induced decreased alternation model comes from findings on the role of ovarian hormones (reviewed in Albelda and Joel, in press). Specifically, there are sex differences in responsiveness to 8-OHDPAT (earlier for males; Ulloa et al., 2004, reviewed in Joel, 2006a), and symptom severity and response to treatment are modulated by ovarian hormones in females (Agrati et al., 2005; Fernández-Guasti et al, 2006, reviewed in Albelda and Joel, in press). These observations suggest that the 8-OHDPAT-induced decreased alternation model may serve to study the role of ovarian hormones in OCD. It is important to note, however, that the results obtained in intact female rats were different from those obtained in ovariectomized rats, suggesting that the latter is not a valid model system for studying the role of ovarian hormones in females (see Albelda and Joel, in press, for a detailed review and discussion).

8-OHDPAT-induced decreased alteration was counteracted and augmented, respectively, by administration of the neurosteroids allopregnanolone (5α-Pregnan-3α-ol-20-one, a metabolite of progesterone, i.c.v.) and dehydroepiandrosterone sulfate (DHEAS, i.p.) (Umathe et al., 2009b), in line with studies reporting dysregulation of neurosteroids in OCD patients (dehydroepiandrosterone, and DHEAS, Bigos et al., 2009; cortisol, Catapano et al., 1990). Regretfully, because the effects of these neurosteroids on spontaneous alternation were not assessed it is impossible to determine whether these results are not reflecting the additive effects of the neurosteroids and of 8-OHDPAT on spontaneous alternation, rather than a true modulation of the effects of 8-OHDPAT.

Summary. 8-OHDPAT-induced decreased alternation provides an animal model of OCD with good predictive validity with regard to pharmacotherapy but not with regard to HFS. Yet its pharmacological predictive validity will be strengthened by testing additional drugs that are known not to be effective in OCD, because to date only desipra-

mine has been tested. The finding that 8-OHDPAT-induced decreased alternation is modulated by ovarian and related hormones contributes to the construct validity of the model and suggests that it can be used to further study the role of these hormones in compulsive behaviors and to develop new lines of treatment on the basis of this knowledge. However, as a model of OCD, 8-OHDPAT-induced decreased alternation may not be very useful for understanding the neurobiological mechanisms of compulsive behaviors. This is because decreased alternation is common in neurological and psychiatric conditions other than OCD (e.g. Parkinson's disease, schizophrenia), and has been shown to result from interference with many neurotransmitter systems (including glutamate, gamma aminobutyric acid, acetylcholine, norepinephrine, serotonin and dopamine; Myhrer, 2003) as well as with many different psychological processes (including sensory, attentional, emotional and motor; Richman et al., 1986). In addition, although serotonergic involvement has been suggested in OCD, it is not clear what role serotonin plays in the pathogenesis of OCD, and therefore whether the fact that perseveration is induced by a serotonergic manipulation contributes to the construct validity of this model (for a detailed discussion see Joel, 2006a). The concern regarding the usefulness of this model for understanding the neurobiological mechanisms of compulsive behaviors is reinforced by reports that HFS of the thalamic reticular nucleus and lesion to the orbitofrontal cortex had no effect on 8-OHDPAT-induced perseveration. Therefore the 8-OHDPAT model, which is easy and cheap to run, is recommended as a screening test for anti-compulsive drug activity in males and females, but not as a model system to study the neural mechanisms of OCD.

mCPP-induced persistence. This model builds on the tendency of normal rats to show a side bias (termed "directional persistence" in Tsaltas et al., 2005) in the initial stages of training in a non-match to sample task in a T-maze (termed "rewarded alternation" in Tsaltas et al., 2005), and of the 5-HT agonist mCPP to lead to the re-emergence of this bias, even after extended training (Tsaltas et al., 2005). In this procedure, after 1 week of habituation to the T-maze, rats are trained in a non-match to sample task (receiving initially two, then four and finally eight trials per day) until all animals reach performance criterion. After this baseline stage (which lasts around 350 trials), administration of drugs begins. Rat's preference to one of the arms in the T-maze is estimated using a Persistence Index. After excluding the 25% of the rats which had the lowest Persistence Index scores, Tsaltas and colleagues (2005) found that 4 days of administration of mCPP resulted in an increase in Persistence Index score. Pre-treatment for 20 days with fluoxetine, but not with desipramine or diazepam, prevented mCPP-induced increased persistence. Taken together, these results suggest that mCPP-induced increased persistence in a non-match to sample task may be a model of OCD with good predictive validity.

Summary. The mCPP-induced persistence model is similar to the 8-OHDPAT-induced decrease in spontaneous alternation in that in both models activation of the serotonergic system results in increased perseveration. As such, the mCPP-induced persistence model has the same shortcomings as the 8-OHDPAT model in terms of its suitability for studying the neurobiology of compulsive behaviors (see above). The mCPP-induced persistence model has another disadvantage, not shared with the 8-OHDPAT model, in that it is highly time consuming to run, as only the baseline phase requires hundreds of trials. Therefore although this model has good predictive validity, it is not recommended as a screening test for anti-compulsive drugs.

Neurodevelopmental models

The neonatal clomipramine model (Andersen et al., 2010) is the first neurodevelopmental model of OCD. Under this class we suggest to group models in which a manipulation early in development leads to the emergence of symptoms at a later stage. We would like to note that although in the present review we grouped genetic models under a separate class, they can also be grouped under the class of neurodevelopmental models, as in their case the early manipulation is genetic. In contrast, we suggest not to include in the neurodevelopmental class models in which compulsive-like behaviors develop spontaneously, such as barbering (the plucking of cage mate's hair and whiskers by mice, Garner et al., 2004; for review see Joel, 2006a) and spontaneous stereotypy in deer mice (see below), which historically are grouped under behavioral models, because in the case of these latter models there is no explicit inducing manipulation.

Neonatal clomipramine model. In Andersen and colleagues' (2010) model, neonatal rats are exposed to repeated injections of the SRI clomipramine (15 mg/kg, twice daily between postnatal days 9–16) and their behavior is assessed at adulthood. Regretfully, although there are plenty of data showing that male and female rats respond differently to neonatal manipulations (Fumagalli et al., 2009; McCormick et al., 1995; Richardson et al., 2006; Suárez et al., 2009; Viveros et al., 2009; Wilber et al., 2007; Zuena et al., 2008), only the behavior of male rats was assessed in this study. Clomipramine-treated adult male rats showed elevated anxiety, as measured in the plus-maze, less spontaneous alternation in a T-maze, and increased hoarding, assessed by counting the number of accumulated food pellets on the bottom of the cage. In addition, these rats buried more marbles, which may reflect increased anxiety or increased compulsivity. Finally, clomipramine-treated rats were impaired in acquiring a win-shift task in an eight-arm radial maze and a visual discrimination task and its reversal in a T-maze. Yet, these rats did not exhibit increased perseveration. Interestingly, clomipramine-treated rats showed increased latency to choose arms and were reported to typically sit in front of an arm for a long time (Andersen et al., 2010), a behavior

reminiscent of that of 8-OHDPAT-treated rats in the T-maze (Seibell et al., 2003).

Andersen et al. (2010) also assessed the level of mRNA for 5-HT1a, 5-HT1d, 5-HT2c and D2 receptors in the striatum, orbitofrontal cortex and medial prefrontal cortex, and found only increased mRNA for 5-HT2c in the orbitofrontal cortex and for D2 in the striatum of clomipramine-treated rats compared with vehicle-treated rats. In addition, there was a strong correlation (r=0.76) between these two measures.

Summary. The neonatal clomipramine model is promising in that some of the behaviors exhibited by the treated rats bear similarities to behaviors of OCD patients, and there is overlap between regions that may be involved in producing abnormal behaviors in the model and in OCD. Yet, the demonstration of a similar pharmacological profile is critical for strengthening the model's relevance to OCD, especially because none of the behavioral alterations is specific to OCD. This notwithstanding, as the first neurodevelopmental model of OCD the neonatal clomipramine model paves the way to a new group of models in which compulsive-like behaviors are induced by a neonatal manipulation. Although the causes of OCD are not known, early life events have been implicated in its etiology (Mathews et al., 2008). We would like to reiterate that it is highly important that in this and similar models both females and males are tested, as there is evidence for sex differences in both the course of OCD and response to perinatal manipulations.

Behavioral models

Most animal models of OCD fall under this category, which can be further divided into 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), or following some behavioral manipulation (adjunctive behaviors), such as schedule-induced polydipsia (Woods et al., 1993) and food restriction-induced hyperactivity (Altemus et al., 1996). More recently, repetitive or perseverative emission of a learned behavior that occurs spontaneously or following a behavioral manipulation has been suggested as a model of OCD. The best example of this class is the signal attenuation model.

The most studied behavioral models of OCD are the signal attenuation and marble burying. Here we shortly present these models as well as a new behavioral model of OCD, spontaneous stereotypy in deer mice, which were reviewed in Albelda and Joel (in press), and summarize the main findings relevant for evaluating their validity. We then describe in more detail the schedule-induced polydipsia model, presented first in 1993 by Woods and colleagues and still in use. We start, however, by considering two behavioral paradigms in which perseveration has been suggested to model compulsive behavior, namely, the 5-choice serial reaction time task and reversal training.

Behavioral models of OCD based on perseveration. As detailed above, perseveration induced by 8-OHDPAT is one of the leading pharmacological models of OCD. More recently perseveration occurring spontaneously in the 5-choice serial reaction time task (Chudasama et al., 2003) or following a change in task contingencies in reversal training (Boulougouris et al., 2007a,b; Clarke et al., 2007) has been suggested to provide models of OCD, on the basis of studies reporting perseverative behavior during neurocognitive tasks in OCD patients (Abbruzzese et al., 1995; Moritz et al., 2009).

Perseveration in the 5-choice serial reaction time task (5-CSRTT). In this task, carried out with rats or mice, the animal is tested in an apparatus containing five food magazines. In each given trial a certain magazine is cued by a light stimulus in a random order and the animal learns to collect a food reward from the cued magazine. Perseveration in this task is defined as repeated responses to a specific magazine after it has been rewarded (Bari et al., 2008; Chudasama et al., 2003; for review see Robbins, 2002).

There are no reports on the effects of S/SRIs on perseveration in the 5-CSRTT. The finding that administration of the SNRI atomoxetine to male rats did not affect perseveration in this task (Robinson et al., 2008), is encouraging, yet further studies assessing the effects of S/SRIs as well as of additional drugs that are inefficient in OCD are crucial for establishing the predictive validity of this model.

In male rats, lesions to the orbitofrontal cortex increased perseverative responses in the 5-CSRTT (Chudasama et al., 2003), supporting the construct validity of the model. Lesions to the medial striatum also increased perseverative responses, but in addition disrupted task accuracy and increased premature responses (Rogers et al., 2001).

Summary. Perseverative responding in the 5-CSRTT has face validity and some construct validity. However, because perseveration is common in additional psychiatric and neurological disorders it is crucial to demonstrate that perseveration in 5-CSRTT is relevant to OCD by establishing its pharmacological predictive validity.

Reversal training. In a typical reversal learning task, once a rat learns to press one of two levers for a food reward, the reinforcement contingency is reversed, and the formerly non-reinforced lever becomes the reinforced lever and vice versa. Perseveration in this task is measured as the number of responses on the previously reinforced lever made before the animal reaches chance-level performance (Boulougouris et al., 2007a,b). Reversal learning has also been assessed in primates, typically using visual discrimination rather than position discrimination. Once the animal learns to respond to one of two different visual stimuli presented on a screen in order to obtain a reward, the reinforcement contingency is reversed and the formerly non-reinforced stimulus becomes reinforced. The measure

of perseveration is identical to that described for rats (Clarke et al., 2007).

Reversal learning is improved by administration of the SSRI citalopram (male rats, Bari et al., 2010; note that the authors did not present data on the effects of citalopram on perseverative responding so the mechanism by which citalopram improved reversal learning is not clear) but also of the SNRI's atomoxetine (male rats and primates; Seu et al., 2009) and desipramine (male rats; Seu and Jentsch, 2009; Seu et al., 2009). Importantly, in the study by Seu et al. (2009) the improvement in reversal performance after administration of desipramine and atomoxetine was mainly due to a decrease in perseverative responding, a finding that further questions the predictive validity of this behavior as compulsive-like.

Perseveration in reversal training is increased after selective depletion of 5-HT from the orbitofrontal cortex and lateral prefrontal cortex in male and female primates (Clarke et al., 2007) and after orbitofrontal cortex lesions in male rats (Boulougouris et al., 2007a). Perseveration is also increased in male rats following systemic administration of the 5-HT2a antagonist M100907 and decreased following systemic administration of the 5-HT2c antagonist SB 242084 (Boulougouris et al., 2007b). The evidence for involvement of the serotonergic system and of the orbitofrontal cortex in perseveration in reversal learning supports the construct validity of the model.

Summary. Although perseverative responding during reversal training has face and construct validity, its pharmacological profile undermines the suggestion that this behavior may serve as a model of OCD.

Marble burying in mice and rats. 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, but 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 led to the conclusion that it does not model anxiety, but may rather be related to compulsive behaviors (Gyertyán, 1995; Londei et al., 1998; Njung'e and Handley, 1991; Thomas et al., 2009). Although earlier studies used mice, marble burying has recently also been tested in rats (Schneider and Popik, 2007). In a typical experiment, the animal is placed in a clear cage bedded with 5 cm of sawdust, upon which glass marbles are arranged (nine for rats or 20–25 for mice). The animal is allowed 10 (rats) or 30 (mice) min in the cage, after which it is removed and the number of marbles buried (covered two-thirds of the way or more) is recorded. A greater number of buried marbles represents a higher degree of compulsivity (Witkin, 2008). When assessing the effects of drugs on marble burying it is critical to also assess drugs' effects on activity level, to refute the possibility that a reduction in marble burying reflects a non-specific decrease in behavioral output.

In males, marble burying is decreased by SSRIs at doses that do not affect locomotion (Egashira et al., 2007; Hirano et al., 2005; Ichimaru et al., 1995; Krass et al., 2010; Njung'e and Handley, 1991; Schneider and Popik, 2007; Takeuchi et al., 2002; Uday et al., 2007; Umathe et al., 2008, 2009a,b), and this suppressive effect is not exerted by desipramine (Ichimaru et al., 1995). However, the well documented finding that burying is also reduced by drugs that do not have an anti-compulsive activity, such as diazepam (Broekkamp et al., 1986; Broekkamp and Jenck, 1989; Ichimaru et al., 1995; Njung'e and Handley, 1991; Schneider and Popik, 2007; Treit, 1985; Treit et al., 1981) detracts from the predictive validity of marble burying. 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.

In a sub-group (about 30%) of normally cycling female rats, marble burying was found to fluctuate along the estrous cycle, being higher during dietestrous compared with proestrous (Schneider and Popik, 2007). In these rats acute administration of progesterone, the SSRI fluoxetine, the non-serotonergic antidepressant nomifensine, and the anxiolytic diazepam attenuated the increase in marble-burying behavior at dietestrous, without concomitantly decreasing locomotion. In contrast, the neuroleptic chlorpromazine did not affect the behavior of these rats, and the non-serotonergic antidepressant desipramine decreased both marble burying and locomotion (Schneider and Popik, 2007). The finding that marble burying fluctuates along the estrous cycle and is affected by the administration of progesterone contributes to the construct validity of the model.

There is also evidence that sex hormones modulate marble burying in males. Specifically, acute administration of the neurosteroid allopregnanolone (i.c.v.) or its precursor, progesterone (Umathe et al., 2009b), as well as of the GnRH agonist leuprolide (Uday et al., 2007) decreased marble burying but not locomotion. Acute administration of the neurosteroid DHEAS (i.p.) increased marble burying but not locomotion (Umathe et al., 2009b). As there is some evidence for dysregulation of neurosteroids, including DHEAS, in OCD patients (Bigos et al., 2009), these results strengthen the relevance of marble burying to OCD.

Additional neurotransmitter systems that have been shown to play a role in marble burying in males and have been implicated in the pathophysiology of OCD are the serotonergic (5-HT1a and 5-HT7 receptors; Egashira et al., 2008b; Hedlund and Sutcliffe, 2007), dopaminergic (D2 receptors; Egashira et al., 2008b) and glutamatergic (NMDA receptors; Egashira et al., 2008a). The latter is of particular interest as some of the compounds used by Egashira et al. (2008a) are also used to treat OCD patients. Egashira et al. (2008a) found that the NMDA antagonists MK-801, memantine and amantadine decreased marble burying without concomitantly decreasing locomotion, whereas the AMPA receptor antagonist NBQX or the glutamate release inhibitor riluzole had no effect (Egashira

et al., 2008a). These results are compatible with human studies pointing to the involvement of the NMDA receptor in OCD (see Introduction) and demonstrating a therapeutic effect for memantine in OCD patients (Aboujaoude et al., 2009). However they are incongruent with studies demonstrating a therapeutic effect of riluzole on OCD patients (Coric et al., 2005; Grant et al., 2007).

There is also evidence for the involvement of the nitric oxide system in marble burying in males. Specifically, nitric oxide agonists and antagonists have been shown to increase and decrease marble burying, respectively, with no effect on locomotion (Krass et al., 2010; Umathe et al., 2009a). As there is some evidence for high nitric oxide levels in OCD patients (Atmaca et al., 2005), these findings contribute to the construct validity of the marble burying model.

Summary. Marble burying provides a model of OCD with good face validity and some construct validity. Its predictive validity should be regarded with caution for several reasons. First, marble burying cannot differentiate between anti-compulsive and anxiolytic activity. Second, although marble burying detected the anti-compulsive activity of the atypical antipsychotic aripiprazole (Egashira et al., 2008b), it failed to detect the anti-compulsive activity of riluzole (Egashira et al., 2008a), suggesting that it may not be sensitive to all classes of anti-compulsive drugs. Last, although marble burying is not sensitive to desipramine, it may be sensitive to other non-serotonergic anti-depressants such as nomifensine (however, it is possible that sensitivity to this drug is related to its anxiolytic effects, as there are a few reports that nomifensine has an anxiolytic activity in addition to its anti-depressive effect [Forrest et al., 1977; Habermann, 1977]). The finding that marble burying is sensitive to both anti-compulsive and anxiolytic drugs raises the question of whether marble burying is relevant to OCD or to anxiety. This question is not resolved by other findings, because although some of the results obtained in marble burying support its relevance to OCD, they may also be related to other anxiety disorders. Specifically, the findings that marble burying is related to high levels of nitric oxide, is decreased by administration of the NMDA blocker memantine and the atypical antipsychotic aripiprazole, and is modulated by ovarian and related hormones, are in line with what is known on the involvement of these systems in OCD (Aboujaoude et al., 2009; Abramowitz et al., 2003; Arnold et al., 2004; Atmaca et al., 2005; Brandes et al., 2004; Casas et al., 1986; Eriksson, 2000; Labad et al., 2005; Lochner et al., 2004; Maina et al., 1999; Masi et al., 2010; Muscatello et al., 2011; Sarkar et al., 2008; Uguz et al., 2007; Zohar, 1999). Yet, these three systems have also been implicated in anxiety disorders (Biojone et al., 2010; Minkeviciene et al., 2008; Volke et al., 1997; Walf and Frye, 2006; Worthington et al., 2005; Zhang et al., 2010; for a detailed discussion see Albelda and Joel, in press).

We would like to note that although marble burying cannot differentiate between anti-compulsive and anxiolytic drugs it is the most straightforward and cost-effective procedure of all current animal models of OCD. As such it is well suited for initial screening for anti-compulsive activity, which should be followed by drug screening using other animal models that can differentiate between anti-compulsive and anxiolytic activity.

The signal attenuation model. The signal attenuation model has been developed by Joel and colleagues (for review see Joel, 2006b) 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, rats are first trained to press a lever for a food reward whose delivery is accompanied by the presentation of the magazine light and a tone. In this manner the light and tone stimulus is established as a feedback cue which signals that the lever-press response was effective in producing food. The ability of the stimulus to signal reward is then attenuated by repeatedly presenting the stimulus without food (note that the levers are not present at this stage of training). 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). In order to differentiate between the effects of signal attenuation and of extinction per se, the behavior of rats undergoing an extinction test preceded by a signal attenuation stage is compared with that of rats in an extinction session that is not preceded by signal attenuation (a procedure referred to as “regular extinction”). An anti-compulsive effect in the model is evidenced in a decrease in the number of “compulsive” lever-pressing, that is, excessive lever-presses that are not followed by magazine entry, in rats that underwent signal attenuation, with no effect on the number of excessive lever-presses that are not followed by magazine entry in rats that underwent regular extinction (for further exposition see Joel, 2006b).

In male rats, acute administration of the SSRIs paroxetine and fluvoxamine exerted an anti-compulsive effect, whereas acute administration of the tricyclic antidepressant desipramine, the anxiolytic diazepam and the antipsychotic haloperidol, did not, supporting the predictive validity of the model (Joel and Doljansky, 2003; Joel et al., 2004). The signal attenuation model also has good predictive validity with regard to HFS as HFS of the subthalamic nucleus was found to exert an anti-compulsive effect (Klavir et al., 2009).

The findings with HFS also contribute to the construct validity of the signal attenuation model by demonstrating similarity in the neural systems involved. Other regions that have been shown to play a role in compulsive lever-pressing are the orbtiofrontal cortex, entopeduncular nucleus and globus pallidus (Joel et al., 2005a,b; Joel and Klavir, 2006; Klavir et al., 2011). HFS of the entopeduncular nucleus and globus pallidus (the rat’s equivalents of the primate’s internal and external segments of the globus pallidus, respectively) has been shown to exert an anti-compulsive effect in the model (Klavir et al., 2011). Lesions

to the orbtiofrontal cortex and to the subthalamic nucleus were found to increase compulsive lever-pressing and decrease the content of dopamine and serotonin in the striatum (Joel et al., 2005a,b; Schilman et al., 2010; Winter et al., 2008a), suggesting that dysregulation of striatal serotonin and/or dopamine is a final common pathway by which different brain pathologies may lead to compulsive behaviors (Winter et al., 2008a). This hypothesis was supported by a recent demonstration that intrastriatal administration of paroxetine abolishes orbitofrontal lesion-induced compulsivity (Schilman et al., 2010).

Other studies provided additional evidence for the involvement of the serotonergic (5-HT2c receptors; Flaisher-Grinberg et al., 2008) and dopaminergic (D1 receptors; Joel and Doljansky, 2003) systems in compulsive lever-pressing, as well as for the involvement of the glutamatergic system (NMDA receptors; Albelda et al., 2010), further supporting the construct validity of the signal attenuation model. The finding that D-cycloserine, a partial NMDA agonist, decreased compulsive lever-pressing (Albelda et al., 2010), is of interest also in the context of predictive validity, because this drug was reported to successfully augment cognitive-behavior therapy in OCD patients (Kushner et al., 2007; Wilhelm et al., 2008).

There is also evidence for the involvement of ovarian hormones in compulsive lever-pressing. Thus, compulsive lever-pressing in females was found to fluctuate along the estrous cycle; acute administration of estradiol to pre-pubertal female rats attenuated compulsive lever-pressing; and withdrawal from chronic administration of estradiol increased compulsive lever-pressing in pre-pubertal female rats (Flaisher-Grinberg et al., 2009).

Summary. Signal attenuation provides an animal model of OCD with face validity, that is, "compulsive" lever-pressing is both excessive and unreasonable, as are compulsions, very good predictive validity with regard to pharmacotherapy and HFS and very good construct validity. The latter 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 orbitofrontal cortex, nuclei of the basal ganglia [striatum, subthalamic nucleus, entopeduncular nucleus, globus pallidus] the serotonergic, dopaminergic and glutamatergic systems and ovarian hormones). As such, this model may serve to study the neural substrates of OCD and to screen for anti-compulsive therapies. However, the signal attenuation model is not well-suited for assessing the mechanism of action of SSRI's and other drugs that require repeated administration to achieve a beneficial effect, because repeated drug administration may affect behavior in the early stages of the procedure (e.g. lever-press training, signal attenuation). Other shortcomings of this model are that it requires special equipment (operant boxes), it has not been tested in additional laboratories and most of the work done in this model used only male rats. We hope future studies will also include female rats.

Spontaneous stereotypy in deer mice. This model belongs to the group of naturally occurring repetitive or stereotypic behaviors, and as most of the other models in this group it is also based primarily on behavioral similarity. Deer mice (*Peromyscus maniculatus bairdii*) spontaneously develop stereotypic behaviors consisting of vertical jumping, backward somersaulting and patterned running (Powell et al., 1999). Mice (male and female) are divided into high, low and non-stereotypic on the basis of a stereotypic score given to each rat following observation for several hours (Korff et al., 2008). It is not clear, however, whether high stereotypic mice or both high and low stereotypic mice are considered to model OCD. This is because some of the studies of the pharmacology and neural substrates of stereotypy were done on both high and low stereotypic mice, others only on high stereotypic mice, and yet others compared high with low stereotypic mice, or high and low stereotypic mice with non-stereotypic mice.

While stereotypic behaviors occur in additional neuropsychiatric disorders (e.g. autism, schizophrenia), the relevance of stereotypic behaviors in deer mice to OCD is strengthened by the demonstration that they are decreased by repeated administration (for 21 days) of fluoxetine but not of desipramine (Korff et al., 2008). Other results, however, are less consistent with the known pharmacology of OCD. Thus, stereotypic behaviors in both high and low stereotypic mice were decreased by repeated (4 days) systemic administration of the 5-HT2a/2c agonist mCPP and of the D2/D3 agonist quinpirole (Korff et al., 2008). Although these results implicate the serotonergic and dopaminergic systems in stereotypic behaviors in deer mice, and in this sense contribute to the construct validity of this model as a model of OCD, in the clinic acute administration of mCPP typically exacerbates symptoms (Broocks et al., 1998; Gross-Isseroff et al., 2004; Hollander et al., 1991; Murphy et al., 1989; Pigott et al., 1993; Stern et al., 1998; Zohar and Insel, 1987; but see Charney et al., 1988; Goodman et al., 1995; Ho Pian et al., 1998; Khanna et al., 2001, who failed to obtain this effect, and Pigott et al., 1992 who found that chronic administration of mCPP ameliorated symptoms after the initial exacerbation), and D2 antagonists, rather than agonists, are used to augment SSRI treatment (McDougle et al., 1990, 1994; Sasson and Zohar, 1996; Saxena et al., 1996).

The construct validity of the model is supported by an additional line of studies. High stereotypic mice showed decreased enkephalin content and increased dynorphin/enkephalin ratio in the striatum, compared with low stereotypic mice (Presti and Lewis, 2005). These results suggest that high stereotypy may be mediated by increased activity in the direct basal ganglia-thalamo-cortical pathway and decreased activity in the indirect pathway (Presti and Lewis, 2005). In line with this hypothesis, blockade of striatal D1 receptors (which abandon on neurons of the direct pathway) as well as blockade of NMDA glutamate receptors, was found to decrease stereotypies in these mice, without affecting motor activity in general (Presti et al., 2003). The findings suggesting that imbalance in the direct and indirect pathways of the basal ganglia-thalamo-

cortical circuits may mediate spontaneous stereotypy in deer mice lend the model construct validity. Moreover, imbalance between the direct and indirect pathways has been suggested to underlie compulsions in OCD, and D1 antagonists have been suggested to ameliorate compulsions (Saxena et al., 1998).

Additional studies found evidence for the involvement of the frontal cortex in stereotypic behaviors. Specifically, high stereotypic mice exhibited deficient glutathione system in the frontal cortex, but not striatum, compared with low stereotypic and non-stereotypic mice (Güldenpfennig et al., 2011). High and low stereotypic mice exhibited elevated levels of cyclic AMP (cAMP) in the frontal cortex, but not striatum, compared with non-stereotypic mice, and repeated administration (for 21 days) of fluoxetine to high stereotypic mice decreased both stereotypic behaviors and cAMP levels in the frontal cortex, but not striatum (Korff et al., 2009).

Summary. Spontaneous stereotypy in deer mice may be an example of an animal model of an endophenotype, for example, vulnerability to developing repetitive behavior or compulsive behavior, rather than a model of OCD (Joel et al., 2008). As such behaviors predominate in OCD, studying the neural mechanisms of spontaneous stereotypy in deer mice may advance our knowledge of neural circuits relevant to OCD. In addition, because in this model stereotypy develops spontaneously it may provide insight into a range of genetic and environmental etiologic factors in OCD. Future studies should further establish the relevance of spontaneous stereotypy in deer mice to compulsive behaviors by testing additional drugs that are known not to be effective in OCD as to date only desipramine has been tested. An advantage of this model is that both male and female mice are tested. Unfortunately, the authors do not report whether there were sex differences.

Schedule-induced polydipsia. In this procedure, first suggested as an animal model of OCD by Woods et al. (1993), food deprived rats are trained to collect a food reward on a fixed-interval schedule (usually one to two food rewards every 60 s), while having free access to drinking water. Typically within 3–5 weeks of training in this reinforcement schedule rats begin to consume excessive amounts of water during training, that is, 5–10 times more than control rats that receive the same amount of food all at once. Polydipsic behavior has been suggested to be analogous to the excessive and purposeless behaviors seen in OCD (Platt et al., 2001; Woods et al., 1993). When assessing the effects of a manipulation on schedule-induced polydipsia it is critical to also assess its effects on the amount of drinking in the control group, to refute the possibility that a reduction in polydipsic behavior reflects a non-specific decrease in drinking.

In male rats, schedule-induced polydipsia (but not drinking in the control group) is reduced by chronic administration of the S/SRIs clomipramine, fluoxetine and fluvoxamine and is unaffected by chronic administration of the tricyclic antidepressant desipramine, the typical antipsychotic haloperidol or the anxiolytic diazepam (Woods et al., 1993). These findings lend the model predictive validity, and suggest that it may be a useful tool for screening anti-compulsive drugs.

van Kuyck et al. (2008) found that high (100 Hz), but not low (2 Hz), frequency stimulation of the nucleus accumbens shell, the mediodorsal thalamic nucleus and the bed nucleus of the stria terminalis reduced polydipsic behavior in male rats. Regretfully the study did not test the effects of stimulation on drinking in control rats, so it is impossible to determine whether the reduction in water intake is specific to polydipsic drinking. If the decrease in drinking is shown to be specific to schedule-induced polydipsia, then these results would greatly support the predictive and construct validity of the model, as the nucleus accumbens and the mediodorsal thalamic nucleus are part of the basal ganglia-thalamo-cortical circuits implicated in the pathophysiology of OCD (see Introduction) and HFS of the nucleus accumbens has proved effective against OC symptoms in OCD patients (Huff et al., 2010; Sturm et al., 2003; Tass et al., 2003).

Support for the model's construct validity is provided by studies demonstrating the involvement of the serotonergic system in schedule-induced polydipsia. Acute administration of 5-HT2c agonists (Ro 60-0175/ORG 35030, Ro 60-0332/ORG 35035 and WAY 163909) decreased polydipsic behavior in both male and female rats without any effect on the amount of water consumed in control rats (Martin et al., 1998; Rosenzweig-Lipson et al., 2007). Co-administration of fluoxetine and either the 5-HT1a antagonist WAY 100635 or the 5-HT1b partial agonist GR 127935 accelerated the ability of fluoxetine to reduce polydipsic behavior in male rats, whereas the administration of either WAY 100635 or GR 127935 alone had no effect (Hogg and Dalvi, 2004). The various treatments did not affect water consumption in the home cage, suggesting that the effect was specific for polydipsic behavior (Hogg and Dalvi, 2004).

Summary. Schedule-induced polydipsia provides an animal model of OCD with excellent predictive validity regarding psychopharmacology and possibly neurosurgery, provided additional studies demonstrate that HFS has a selective effect on polydipsic behavior. Such a demonstration would also contribute to the construct validity of the model, which is also strengthened by evidence for the involvement of the serotonergic system. We hope that future studies will also include female rats as subjects.

CONCLUSIONS

Table 1 summarizes our evaluation of the face, predictive and construct validity of each of the models reviewed. On the basis of this evaluation we discuss the usefulness of the different models for screening drugs for anti-compulsive activity, detecting new targets for high frequency stimulation, studying the neural mechanisms of OCD and unraveling the role of gonadal hormones. We then describe potential new treatment strategies that emerge from the convergence of data obtained in different models on the one hand, and how different models can be used to model

Table 1. Assessment of the models against validating criteria

	Face validity (symptom similarity)	Predictive validity			Construct validity	
		Pharmacological		HFS		
		Response to S/SRI's and other treatments effective in OCD	No response to drugs not effective in OCD	Response to HFS	Similarity of inducing mechanism	Similar neural substrates
Genetic models						
Aromatase knockout mice	+/− (also mimics behavioral abnormalities that may be relevant to other disorders)	Not tested	Not tested	Not tested	+ (there is evidence for involvement of estradiol in OCD)	+ (decrease in catechol-O-methyltransferase)
Sapap3 knockout mice	++ (increased self-grooming and anxiety-like behaviors)	+ (SSRI)	Not tested	Not tested	?	++ (gene expression in areas implicated in OCD; abnormal cortico-striatal synapses)
Slitrk5 knockout mice	++ (increased self-grooming, marble burying and anxiety-like behaviors)	+ (SSRI)	Not tested	Not tested	?	++ (increased FosB expression in orbitofrontal cortex; anatomical abnormalities in striatum)
Nest building in house mice	+++ (increased nest building and marble burying; decreased anxiety-like behaviors)	++ (SRIs; SSRIs)	+ (no response to desipramine)	Not tested	++ (spontaneous)	Not tested
Pharmacological models						
Quinpirole-induced compulsive checking	+++	+/− (partial alleviation by SRI)	Not tested	+++ (HFS of subthalamic nucleus and nucleus accumbens)	+ (there is evidence for dopaminergic involvement in OCD)	+ (HFS of subthalamic nucleus and nucleus accumbens decrease symptoms) − (lesion to orbitofrontal cortex had no effect)
8-OHDPAT-induced decrease in spontaneous alternation	+/− (motor perseveration is common in many disorders)	++ (SRI and SSRI)	+ (no response to desipramine)	− (HFS of thalamic reticular nucleus not effective)	+ (there is evidence for involvement of 5-HT1a receptors in OCD)	++ (modulation by sex hormones; lesion of thalamic reticular nucleus decrease symptoms) − (lesion to orbitofrontal cortex had no effect)
mCPP-induced persistence	+/− (motor perseveration is common in many disorders)	+ (SSRI)	++ (no response to desipramine and diazepam)	Not tested	+ (mCPP exacerbates symptoms in some OCD patients)	Not tested
Neurodevelopmental models						
Neonatal clomipramine model	++ (increased perseveration, marble burying, hoarding and anxiety-like behaviors) − (impaired learning)	Not tested	Not tested	Not tested	?	++ (increased mRNA for 5-HT2c in orbitofrontal cortex and for D2 in striatum)

Table 1. Continued

	Face validity (symptom similarity)	Predictive validity			Construct validity	
		Pharmacological		HFS		
		Response to S/SRI's and other treatments effective in OCD	No response to drugs not effective in OCD	Response to HFS	Similarity of inducing mechanism	Similar neural substrates
Behavioral models						
Perseveration in the 5-CSRTT	+/− (motor perseveration is common in many disorders)	Not tested	+ (no response to atomoxetine)	Not tested	?	+ (increased after lesions to orbitofrontal cortex)
Perseveration in reversal training	+/− (motor perseveration is common in many disorders)	+ (SSRI)	−−− (response to atomoxetine and desipramine)	Not tested	?	+++ (increased after selective depletion of 5-HT from orbitofrontal cortex and lateral prefrontal cortex, after lesions to orbitofrontal cortex and after administration of a 5-HT2a antagonist; decreased after administration of a 5-HT2c antagonist)
Marble burying	+	+++ (SSRIs, memantine, aripiprazole) − (no response to riluzole)	+ (no response to desipramine) −−− (response to anxiolytics)	Not tested	?	++ (modulation by sex hormones; involvement of NMDA receptors, nitric oxide)
Signal attenuation	++	++ (SSRIs, DCS)	+++ (no response to diazepam, desipramine, haloperidol)	++ HFS of subthalamic nucleus)	+ (simulates a deficient psychological process implicated in OCD)	+++ (modulation by sex hormones, involvement of orbitofrontal cortex, striatum, serotonin, dopamine, glutamate)
Spontaneous stereotypy in deer mice	+/− (stereotypy is common in many disorders)	+ (SSRIs)	+ (no response to desipramine) − (decreased by mCPP and quinpirole)	Not tested	++ Spontaneous	++ (decreased enkephalin and increased dynorphin/enkephalin ratio in striatum; elevated cAMP in frontal cortex)
Schedule-induced polydipsia	+	++ (SRI and SSRI)	+++ (no response to desipramine, haloperidol diazepam)	+/− (HFS of nucleus accumbens, mediodorsal thalamic nucleus, bed nucleus of the stria terminalis, but the specificity to polydipsia needs to be demonstrated)	?	+ (decreased after administration of a 5-HT2c agonist; HFS of nucleus accumbens, mediodorsal thalamic nucleus, bed nucleus of the stria terminalis decrease symptoms)

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; ? or Not tested, there are no relevant data).

different subtypes or dimensions of OCD, on the other hand.

Screening drugs for anti-compulsive activity

The most important aspect of a model for screening drugs is the model's pharmacological predictive validity. An additional, practical aspect is the cost-effectiveness of a model. The models which are best validated pharmacologically are schedule-induced polydipsia and signal attenuation. In both, several drugs that are effective in OCD were found to be effective in the model, and several classes of drugs that are known not to be effective in OCD were shown not to be effective in the model. In terms of cost-effectiveness, the signal attenuation model requires special equipment (operant boxes), whereas the schedule-induced polydipsia model requires only feeders that can be programmed for scheduled delivery of food. An additional advantage of the schedule-induced polydipsia model is that it is suited for testing the effects of chronic drug administration whereas the signal attenuation model is not.

Another model that should be considered when one needs a screening test for detecting drugs with anti-compulsive activity is marble burying, because of its low requirements in terms of equipment and time. This model has been shown to be responsive to several classes of drugs that are effective in OCD, and although it cannot differentiate between anti-compulsive and anxiolytic activity it can be used for initial screening, to be followed by screening in better validated models, such as schedule-induced polydipsia and signal attenuation.

If one wishes to detect drugs that may have beneficial effects in the group of patients that are non responsive to S/SRI's, one can use the quinpirole model, as to date it is the only model in which an SRI has been tested and found not to exert a clear therapeutic effect. It must be noted, however, that there are currently no data demonstrating that the quinpirole model does not respond to drugs that are not effective in OCD. Such data are needed before this model can serve to detect drugs with an anti-compulsive potential for the subgroup of non-responders OCD patients.

Last, the only models to date that can be used to screen drugs for anti-compulsive activity in females are 8-OHDPAT-induced decreased alternation and spontaneous stereotypy in deer mice, as these are the only models in which predictive validity was established in females. Yet the predictive validity of both models will be enhanced by testing additional drugs that are not effective in OCD as up to date only desipramine has been tested. It is also possible to use the marble burying model for screening for anti-compulsive activity in females, but one needs to first select the sub-group of females in which marble burying fluctuates along the estrous cycle (about 30% of normally cycling females; Schneider and Popik, 2007), as predictive validity was tested and demonstrated only for this subgroup. We hope that additional models will soon establish their predictive validity in female subjects.

Detecting new targets for high frequency stimulation

Of the models reviewed here only two models have predictive validity with regard to HFS, namely, the quinpirole model and the signal attenuation model. The schedule-induced polydipsia model could also serve this purpose if it is shown that HFS has a selective effect on polydipsic behavior. It should be noted that although the effects of HFS of relevant structures have not been tested in most animal models of OCD, the effects of HFS of the reticular thalamic nucleus have been tested in the 8-OHDPAT-induced decreased alternation model, but produced no effect. Because HFS of this nucleus has a therapeutic effect in OCD patients, this result suggests that the 8-OHDPAT model may not be suitable for detecting targets for HFS in OCD.

Studying the neural mechanisms of OCD

The most important aspect of a model for studying neural mechanisms is the model's construct validity. To date the signal attenuation model is the best validated in this respect as all of the major neural systems implicated in the pathophysiology of OCD have been shown to play a role in the model. Additional models that may be useful in elucidating the neural mechanisms of OCD are the neonatal clomipramine model, *Sapap3* and *Slitrk5* models and the spontaneous stereotypy in deer mice model, because in these four models there is evidence for abnormalities in neural systems implicated in OCD. Of these models the deer mice model is of special interest as in this model the abnormal behavior develops spontaneously.

We would like to note that although perseveration in the 5-choice serial reaction time task and reversal training involves neural systems that have been implicated in OCD, the relevance of perseveration in these tasks to OCD still awaits confirmation. This is because the face validity of these models rests only on perseveration, which is common in many psychiatric and neurological conditions, and they currently lack predictive validity.

The other models of OCD reviewed here are either with little (marble burying, aromatase knockout mice) or no (nest building in house mice, mCPP-induced persistence) data supporting similarity between the model and OCD in the neural systems involved (except for demonstrating similarity in response to pharmacological treatment), or have conflicting data with regard to such similarity (quinpirole and 8-OHDPAT models). Of these models, the nest building model seems to be of most interest for further studies of its neural substrates. This is because the abnormal behavior in the nest building model occurs following selective breeding and not following a specific genetic or pharmacological manipulation. Therefore the neural alteration in this model may more closely resemble the neural abnormalities in OCD, as currently there is no single mutation associated with this disorder, nor is there a drug that is known to induce compulsive behaviors in healthy subjects.

Unraveling the role of gonadal hormones

To date there is evidence for modulation of compulsive behavior by ovarian hormones in three models: 8-OHDPAT-induced decreased alternation, marble burying and signal attenuation. Of these, the first two models have also demonstrated modulation of compulsive behavior by gonadal hormones in male rats. The 8-OHDPAT-induced decreased alternation model is also suitable for studying the interplay between gonadal hormones and response to treatment, as the effects of an SSRI were found to depend on the hormonal status of the animal. We would like to remind the reader that the effects of ovarian hormones on compulsive behavior were different in intact and ovariectomized rats, suggesting that the latter may not be a valid model system for studying the role of ovarian hormones in females.

Potential new targets for treatment

Combining several animal models of OCD in order to detect anti-compulsive activity of specific drugs or manipulations may be beneficial because it may help differentiate between a genuine anti-compulsive effect and an effect specific to some parameter of a particular model that is not necessarily related to OCD. There are several areas of convergence in the data reviewed here. There is currently evidence from the 8-OHDPAT and marble burying models that progesterone (with or without estradiol) and allopregnanolone decrease compulsive-like behavior in ovariectomized females and in intact males. Another area of convergence relates to a potential therapeutic effect of drugs that block D1 receptors. Thus, in the signal attenuation model systemic administration of a D1 antagonist decreased compulsive-like behavior, and in the deer mice model a similar effect was obtained following intrastriatal administration of the same drug. Current data also point to a possible anti-compulsive effect of blockade of 5-HT2c receptors in the orbitofrontal cortex. Specifically, in the neonatal clomipramine model, mRNA for 5-HT2c receptors was increased in the orbitofrontal cortex (Andersen et al., 2010), and in the signal attenuation model, intra-orbital (as well as systemic) administration of a 5-HT2c antagonist reduced compulsive lever-pressing (Flaisher-Grinberg et al., 2008). Other data, however, suggest that activation of 5-HT2c receptors may have a beneficial effect in OCD. Thus, in the deer mice model a 5-HT2a/c agonist (mCPP) decreased symptoms, and 5-HT2c receptor knockout (KO) mice show compulsive-like behaviors. As detailed in the Introduction, current data in OCD patients are controversial, and do not allow a clear prediction regarding whether activation or blockade of these receptors would have an anti-compulsive effect, and it is possible that different patients would show different responses to such drugs (for example, although some patients experience exacerbation of OC symptoms following activation of 5-HT2c receptors (Broocks et al., 1998; Gross-Isseroff et al., 2004; Hollander et al., 1991; Murphy et al., 1989; Pigott et al., 1993; Stern et al., 1998; Zohar and Insel, 1987), others do not (Charney et al., 1988; Goodman et al., 1995; Ho Pian et al., 1998; Khanna et al., 2001)). We deal further with the latter possibility in the next section.

Modeling different subtypes or dimensions of OCD

OCD is a heterogeneous disorder and there have been several attempts to describe subtypes or dimensions of OCD according to different criteria including symptomatology (e.g. washers, checkers, hoarders), response to treatment (e.g. responders versus non-responders) and co-morbid diagnosis (for review see Mataix-Cols et al., 2005). Clearly it would be an immense contribution to our understanding and treatment of OCD if different animal models could be linked to specific subtypes or dimensions of OCD. It should be noted that this approach is opposite to the one detailed above in which the convergence of evidence from different models is taken to support its relevance to OCD. Here, in contrast, differences between models are viewed as reflecting different aspects of OCD rather than arbitrary aspects of a model, which are not related to OCD.

The data reviewed here provide only hints in this direction. Specifically, as detailed above, quinpirole-induced checking has the potential to become a model of non-responders OCD patients. The neonatal clomipramine, the mCPP-induced persistence and the signal attenuation models may be relevant to OCD patients in which over-activation or hypersensitivity of 5-HT2c receptors plays a role in compulsive behaviors, whereas the deer mice and the 5-HT2c knockout mice models may be relevant to OCD patients in which under-activation or hyposensitivity of 5-HT2c receptors plays a role in compulsive behaviors. In terms of symptomatology, the neonatal clomipramine model may be more relevant to studying the mechanisms of hoarding, as it is the first model to demonstrate increased hoarding in treated animals (as the assessment of hoarding as done in Andersen et al. (2010) is extremely easy, it is highly recommended that such an assessment is included in additional models). 5-HT2c receptor KO mice may be more relevant to OCD patients obsessed with symmetry (Chou-Green et al., 2003), whereas D1CT-7 and Hoxb8 mutant mice may be more relevant to cleaners, as they show excessive grooming (for review see Joel, 2006a). D1CT-7 may also provide a model of OCD patients with co-morbid tic disorder whereas the 5-HT2c receptor knockout mice may provide a model of OCD with co-morbid eating disorders (for review see Joel, 2006a).

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