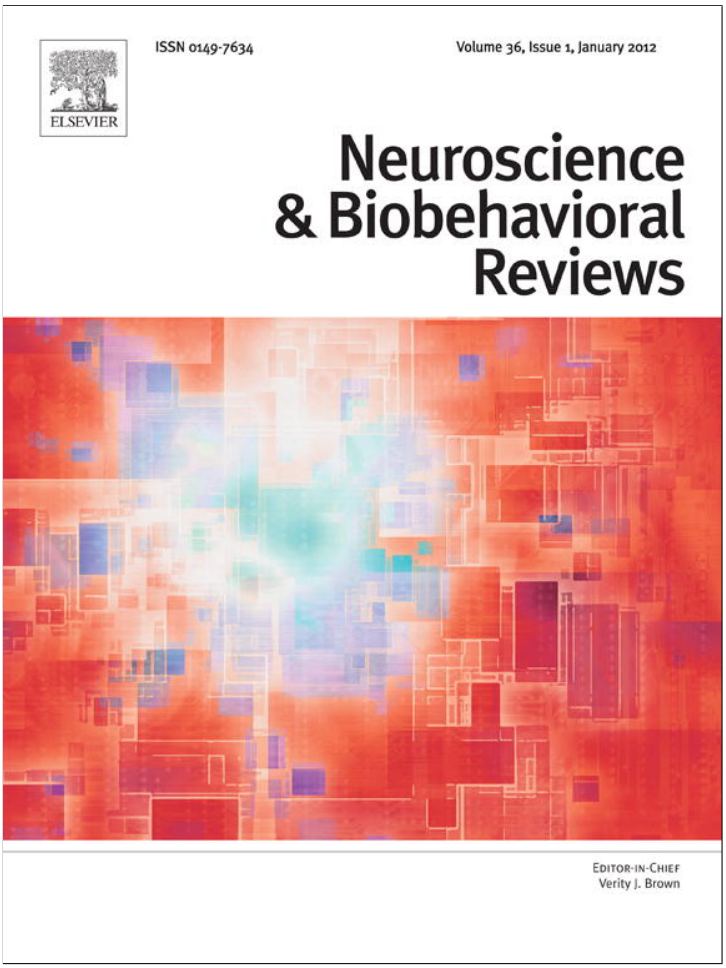

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Review

Animal models of obsessive-compulsive disorder: Exploring pharmacology and neural substrates

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ABSTRACT

During the last 30 years there have been many attempts to develop animal models of obsessive-compulsive disorder (OCD). Most models have not been studied further following the original publication, and in the past few years, most papers present studies employing a few established animal models, exploring the neural basis of compulsive behavior and developing new treatment strategies. Here we summarize findings from the five most studied animal models of OCD: 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. We evaluate each model's face validity, derived from similarity between the behavior in the model and the specific symptoms of the human condition, predictive validity, derived from similarity in response to treatment (pharmacological or other), and construct validity, derived from similarity in the mechanism (physiological or psychological) that induces behavioral symptoms and in the neural systems involved. We present ideas regarding future clinical research based on each model's findings, and on this basis, also emphasize possible new approaches for the treatment of OCD.

Contents

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1. Introduction

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). Yet most of these models have not been studied further following the original publication. The past few years have seen a change in the field. Although new models have been presented (Andersen et al., 2010; Hill et al., 2007; Korff et al., 2008, 2009; Shmelkov et al., 2010; Tsaltas et al., 2005; Welch et al., 2007), most papers reported studies aiming to develop new treatment strategies and to study the neural basis of compulsive behavior using a few established animal models of OCD. The primary aim of the present review is to review the most studied animal models of OCD and evaluate their validity, and the secondary aim is to provide some ideas regarding future clinical research based on current findings.

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 criteria for the validation and evaluation of animal models of psychiatric disorders in general and of OCD in particular. Next we review the five most studied animal models of OCD, namely, 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. For each model we shortly describe the manipulation used to induce compulsive behavior and estimate the model's pharmacological predictive validity. We next summarize new data on the model's pharmacology and neural substrates, and on the basis of these data assess the model's validity and summarize possible implications for clinical research. The final section of the review summarizes the findings obtained in the different models, with special emphasis on possible new approaches for the treatment of OCD.

1.1. Obsessive-compulsive disorder

OCD is a psychiatric affliction with a lifetime prevalence of 1–3% (Rasmussen and Eisen, 1992; Sasson et al., 1997). According to the Diagnostic and Statistical Manual of Mental Disorders (4th ed; DSM IV), the essential features of OCD are recurrent obsessions and/or compulsions (e.g., doubting, checking, washing) that are time consuming (i.e., they take more than 1 h a day) or cause marked distress or significant impairment. To date, the most effective treatments for OCD are pharmacological treatment, using serotonin reuptake inhibitors (SRIs, e.g., Masand and Gupta, 1999; Piccinelli et al., 1995; Pigott and Seay, 1999; Stein et al., 1995; Zohar et al., 1992), and behavioral treatment, using the response exposure and prevention technique (e.g., Simpson et al., 2004). Yet, around 30% of the patients are refractory to pharmaco- and behavioral therapy (Eddy et al., 2004). Some of these treatment-resistant patients are treated by lesions to structures and pathways within basal ganglia-thalamo-cortical circuits (for review see, Lopes et al., 2004) as well as by high frequency stimulation (HFS) of the ventral striatum region (Aouizerate et al., 2004, 2005; Greenberg et al., 2006, 2008; Rauch et al., 2006; Sturm et al., 2003) the subthalamic nucleus (Mallet et al., 2008), and the thalamic reticular nucleus and the inferior thalamic peduncles (Jimenez et al., 2007; Jimenez-Ponce et al., 2009).

Several neural systems have been implicated in the pathophysiology of OCD: The results of neuroimaging studies in OCD patients have implicated most consistently the *orbitofrontal cortex, the cingulate cortex and the basal ganglia*, and more recently also regions within the *parietal lobe*, in the pathophysiology of obsessions and compulsions (for review see Menzies et al., 2008; Rotge et al., 2009; Saxena et al., 1998; Stein, 2000). Dysregulation of the *serotonergic (5-HT) system* has been suggested primarily on the basis of the effectiveness of SRI's and selective serotonin reuptake inhibitors (SSRI's) in alleviating obsessions and compulsions in patients (Zohar and Insel, 1987; Zohar et al., 1992), and has received further support from neurobiological, pharmacological and more recently genetic data (for review see Murphy et al., 2001; Ozaki et al., 2003; Sasson and Zohar, 1996; Stein, 2000, but see Baumgarten and Grozdanovic, 1998). Abnormalities of the *dopaminergic system* have also been implicated in the pathophysiology of OCD, based on surplus therapeutic benefits obtained with co-administration of SSRI's and dopamine blockers (McDougle et al., 1990, 1994; Sasson and Zohar, 1996) as well as on clinical observations of obsessions and compulsions in basal ganglia-related disorders, such as Tourette's syndrome (Frankel et al., 1986; Grad et al., 1987; Pitman et al., 1987). More recently, an increasing body of evidence points also to the involvement of the *glutamatergic system* in OCD (for review, see Pittenger et al., 2006), including association of certain polymorphisms in the NMDA receptor gene with susceptibility to OCD

(Arnold et al., 2004); elevated glutamate levels in the cerebro-spinal fluid of drug-naïve 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 D-cycloserine (DCS), a partial NMDA agonist (blinded controlled trials, Kushner et al., 2007; Wilhelm et al., 2008), riluzole, a glutamatergic antagonist (open-label trials, Coric et al., 2005; Grant et al., 2007), and memantine, a non-competitive NMDA antagonist (an open-label trial, Aboujaoude et al., 2009). There is also some evidence suggesting the involvement of *nitric oxide* (NO) in OCD. Atmaca et al. (2005) found that OCD patients have higher NO levels in their plasma compared to healthy subjects and that these levels are positively correlated with the severity of OC symptoms. The possibility that high NO levels are related to OC symptoms is supported by the fact that SSRI's, anti-dopaminergic drugs and the NMDA antagonist memantine, all used to treat OCD patients, inhibit the synthesis of NO (Almeida et al., 2006; Park and West, 2009; Zhang et al., 2010). Reports that 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) suggest that *ovarian hormones* play a modulatory role in OCD (Uguz et al., 2007). Indeed, gonadotropine-releasing hormone (GnRH) agonists were reported to ameliorate OC symptoms in OCD patients (Casas et al., 1986; Eriksson, 2000).

The understanding and treatment of diseases such as OCD must rely heavily on appropriate animal models that closely mimic their behavioral and if possible their neural manifestations. This is especially true for OCD as its neuropathological mechanisms are still largely unknown, and many patients are either treatment-resistant or experience only partial alleviation of symptoms. Before reviewing animal models of OCD that are currently in use, we discuss the criteria for the validation and evaluation of animal models.

1.2. Evaluating the validity of animal models

Animal models are "experimental preparations developed in one species for the purpose of studying phenomena occurring in another species" (McKinney, 1988, p. 20). Although there has been an expansion in the development and use of animal models in psychiatry, and several papers aiming at providing a conceptual framework for guiding the development of this field have been published (Geyer and Markou, 1995; Matthysse, 1986; McKinney, 1988; McKinney and Bunney, 1969; Willner, 1984, 1986, 1991), there is still a lack of clarity regarding the terminology and classification of animal models and their validation criteria (for review see 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 (for a comprehensive discussion of the criteria for the validation and evaluation of animal models of psychopathology see Joel, 2006a).

1.2.1. Criteria for validating animal models of OCD

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, that is, that are repetitive, excessive and inappropriate. There are also a few animal models that mimic other aspects typical of OCD, such as perseveration. Most notable of these is the 8-OHDPAT model reviewed below, but perseveration in additional tasks has also been suggested to provide a model of OCD (e.g., the stop-signal reaction time task, Boulougouris et al., 2009; the 5-choice serial reaction time task, Chudasama et al., 2003; reversal learning, Boulougouris et al., 2007; Clarke et al., 2007). Of these, only 8-OHDPAT-induced perseveration has been shown to have pharmacological similarity to OCD (see below). Because perseveration is common in neurological and psychiatric conditions other than OCD (e.g., Parkinson's disease, schizophrenia, depression and bipolar disorder, ADHD, Hozumi et al., 2000; Waford and Lewine, 2010), we chose not to discuss tasks in which the predictive validity of perseveration has not been demonstrated. Finally, we would like to note that animal models of OCD can model only abnormal behaviors typical of OCD patients, but cannot model one of the main symptoms of OCD, namely, obsessional ideation.

A model's *predictive validity* should be established by a demonstration of selective alleviation of symptoms by SRI's and SSRI's, as well as by demonstrating the efficacy of HFS of the subthalamic nucleus and ventral striatum in the model. We would like to emphasize three points with respect to the establishment of predictive validity on the basis of pharmacological similarity. First, it is critical to demonstrate both sensitivity to S/SRI's and insensitivity to other classes of drugs (e.g., non-serotonergic antidepressants such as desipramine, anxiolytic agents such as diazepam), which are not effective in OCD but are effective in other conditions which are responsive to S/SRI treatment, such as depression, generalized anxiety disorder, panic disorder and social phobia (for reviews see Argyropoulos et al., 2000; Vaswani et al., 2003). Second, because S/SRI's are not effective in all OCD patients, a lack of effect of S/SRI's in a model may suggest that it is a model of compulsive behavior in the subgroup of OCD patients that do not respond to S/SRI treatment, rather than demonstrate that it is not a model of OCD. Yet, such a model should still demonstrate insensitivity to other types of pharmacological treatment, because there is currently no other effective monotherapy for this subgroup of OCD patients. The third point concerns the issue of acute versus chronic drug administration. In OCD patients S/SRI's are effective only after several weeks of repeated administration. Although several authors pointed to some difficulties with the notion of delayed drug effects in psychiatric disorders (e.g., Agid et al., 2003; Matthysse, 1986), this notion raises a question regarding the predictive validity of animal models that show beneficial effects after acute drug administration. As a model's predictive validity is relevant first and foremost for its ability to differentiate between effective and non-effective treatments, we view this ability as critical for establishing a model's predictive validity, regardless of the regimen of drug administration (for a similar view see Willner, 1991). In practice, although this issue is relevant for animal models of many psychiatric disorders (in which response to pharmacological treatment is evident only after several weeks of treatment), whether emphasis is placed on treatment regime greatly depends on the psychopathology that is being modeled. In the field of animal models of OCD some models used chronic (3–5 weeks of daily injections) or sub-chronic (3 injections over 24 h) regimen of drug administration to establish predictive validity (e.g., the 8-OHDPAT and quinpirole models), whereas others have mainly used acute administration (e.g., marble burying and signal attenuation).

As the physiological and/or psychological causes of OCD are currently unknown, *construct validity* can be established by demonstrating involvement of the orbitofrontal cortex, cingulate cortex and basal ganglia, as well as of ovarian hormones and the serotonergic, dopaminergic and glutamatergic systems. As discussed above, evidence supporting the predictive validity of a model (e.g., a similar response to treatment) also strengthens its construct validity by demonstrating similarity in the neural systems involved. A more indirect way to strengthen a model's construct validity is to demonstrate in the model cognitive deficits typical of OCD using equivalent tasks for humans and animals. Possible candidates for such an assessment could be the stop-signal reaction time and

the intradimensional–extradimensional shift tasks, in which OCD patients are impaired (Chamberlain et al., 2006; Menzies et al., 2008). Unfortunately, performance in these tasks was not assessed in any of the models reviewed here.

In the sections below we first present for each animal model the evidence relevant to establishing its pharmacological predictive validity, on the basis of only response to S/SRI's and prescription drugs known not to be effective in OCD. We then review data acquired using the model, and on the basis of these data evaluate the model's face, construct and predictive validity and describe possible implications for clinical research. Regarding the latter we would like to emphasize that findings obtained in animals are not easily translated into clinical practice. At best, such findings suggest the possible value of certain directions for clinical research in humans. The likelihood that data obtained in animal models may be translated into clinical practice is greater when several models point in the same direction. In the last section of the paper we summarize the results obtained in the different models and discuss areas of convergence.

2. Leading animal models of OCD

2.1. 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-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OHDPAT) to decrease spontaneous alternation.

2.1.1. Pharmacological predictive validity

8-OHDPAT-induced decreased alternation is prevented by both sub-chronic and chronic administration of the SSRI fluoxetine (ranging from 3 injections over 24 h to 48 injections over 21 days, Fernandez-Guasti et al., 2006; Umathe et al., 2009b; Yadin et al., 1991) and by sub-chronic administration of the SRI clomipramine (3 injections over 24 h, Andrade et al., 2009; Fernandez-Guasti et al., 2003), but not by sub-chronic administration of the tricyclic antidepressant desipramine (Fernandez-Guasti et al., 2003), supporting the predictive validity of this model.

2.1.2. The role of ovarian hormones

Having shown that 8-OHDPAT-induced decreased alternation is more robust in pre-pubertal male than in pre-pubertal female rats (Ulloa et al., 2004, reviewed in Joel, 2006a), this group went on to explore the influence of sex and hormonal status on spontaneous alternation in mature rats (Agrati et al., 2005). As opposed to pre-pubertal rats, mature male and female rats did not differ in sensitivity to 8-OHDPAT. However, 8-OHDPAT-induced decreased alternation varied in mature females along the estrous cycle, being non-significant during estrous and highest during proestrous. In addition, 8-OHDPAT-induced decreased alternation was high during gestation day 17, low on gestation day 21 and non-existent during lactation (Agrati et al., 2005). These findings clearly reflect the modulation of 8-OHDPAT-induced decreased alternation by the fluctuating levels of endogenous ovarian hormones, and thus contribute to the construct validity of the model.

In order to further explore the role of ovarian hormones in 8-OHDPAT-induced decreased alternation of female rats and their possible interaction with the serotonergic system, Fernandez-Guasti et al. (2006) studied the effects of the SSRI fluoxetine on 8-OHDPAT-induced decreased alternation in intact female rats on different stages of the estrous cycle and in ovariectomized rats treated with progesterone and/or estradiol. In intact rats, sub-chronic administration (3 injections) of fluoxetine was effective in reducing 8-OHDPAT-induced perseveration during diestrous and proestrous which are characterized by high perseveration, but not during estrous, which is characterized by low 8-OHDPAT-induced perseveration. In ovariectomized rats, acute administration of progesterone as well as of progesterone and estradiol abolished the perseverative effect of a low (1 mg/kg), but not a high (2 mg/kg), dose of 8-OHDPAT, whereas acute administration of estradiol had no effect. Interestingly, fluoxetine blocked the 8-OHDPAT (2 mg/kg)-induced perseveration in ovariectomized rats but not in ovariectomized rats treated with progesterone and estradiol.

These results are not easily interpreted because in intact rats high levels of progesterone and estradiol augment the effect of 8-OHDPAT (i.e., increase 8-OHDPAT-induced perseveration), whereas in ovariectomized rats they antagonize the effect of 8-OHDPAT. Moreover, whereas in intact rats fluoxetine blocked 8-OHDPAT-induced perseveration under conditions of high progesterone and estradiol, in ovariectomized rats it had no effect under such conditions, but could block 8-OHDPAT-induced perseveration in non-treated ovariectomized rats. We would like to note that these discrepancies between findings in intact and ovariectomized rats *undermine the validity of ovariectomized rats as a model system for studying the role of ovarian hormones in females.*

2.1.3. The role of neurosteroid hormones

Several studies have reported a dysregulation of neurosteroids in OCD patients, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS, Bigos et al., 2009) and cortisol (as well as of corticotrophin releasing factor, Altemus et al., 1992; Catapano et al., 1990). Based on these findings, Umathe et al. (2009b) tested the effects of several neurosteroids on 8-OHDPAT-induced decreased alternation in male rats (as well as on marble burying in male mice, see below).

Rats were acutely injected with DHEAS (i.p.) or with the neurosteroid 5α-pregnan-3α-ol-20-one (allopregnanolone, a metabolite of progesterone, intra-cerebro-ventricularly, i.c.v.) and then received an injection of 8-OHDPAT. Allopregnanolone counteracted 8-OHDPAT-induced decrease in spontaneous alternation, whereas DHEAS augmented 8-OHDPAT's effect, that is, further decreased spontaneous alternation. The same effects were obtained when allopregnanolone and DHEAS were administered once daily for 21 days and 8-OHDPAT was administered on the 22nd day. These results show that these neurosteroids can modulate 8-OHDPAT-induced decrease in spontaneous alternation. However, because this study did not include control groups that received only the neurosteroids, it is impossible to determine whether these results are not reflecting additive effects of the neurosteroids and of 8-OHDPAT on spontaneous alternation. In other words, a demonstration that administration of neurosteroids alone does not affect spontaneous alternation is needed to support the authors' suggestion that the neurosteroids are modulating the effect of 8-OHDPAT on spontaneous alternation.

2.1.4. Lesions and deep brain stimulation

Andrade et al. (2009) studied the effects of a lesion to the thalamic reticular nucleus and to the orbitofrontal cortex on 8-OHDPAT-induced decreased alternation in male rats. Lesion to the thalamic reticular nucleus was as effective as the SRI clomipramine in attenuating the effects of 8-OHDPAT, whereas lesion to the orbitofrontal cortex had no effect. The two lesions had no effect on spontaneous alternation. In another study, low, but not high, frequency stimulation of the thalamic reticular nucleus was effective in reducing 8-OHDPAT-induced perseveration, again without affecting spontaneous alternation (Andrade et al., 2010). This is in contrast to reports that HFS of this nucleus has a therapeutic effect

in OCD patients (Jimenez et al., 2007; Jimenez-Ponce et al., 2009), and therefore detracts from the predictive and construct validity of the model.

2.1.5. Evaluating validity

8-OHDPAT-induced decreased alternation provides an animal model of OCD with some predictive validity re pharmacotherapy, but not re HFS. As such, 8-OHDPAT-induced decreased alternation may be a useful tool for screening anti-compulsive drugs. The findings demonstrating that 8-OHDPAT-induced decreased alternation is modulated by ovarian and related hormones suggest that this model 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, we would like to reiterate that at least in this model, ovariectomized rats cannot be used as a model system for studying the role of ovarian hormones in females.

The face validity of the model is questionable, 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, GABA, 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) (for a detailed discussion see Joel, 2006a). Yet, the fact that decreased alternation is induced by a serotonergic manipulation supports the construct validity of the model, because the serotonergic system has been implicated in the pathophysiology of OCD. Further support to the model's construct validity is derived from the evidence for involvement of ovarian hormones and from the similar pharmacological profile of 8-OHDPAT-induced decreased alternation and compulsions in OCD. Yet the findings that HFS of the thalamic reticular nucleus and lesion to the orbitofrontal cortex had no effect on 8-OHDPAT-induced decreased alternation detract from its construct validity, and question its ability to help unravel the neurobiological mechanisms of compulsive behaviors.

2.1.6. Possible implications for clinical research

The results obtained in the 8-OHDPAT-induced decreased alternation model suggest that symptom severity and the efficacy of SSRIs in female OCD patients may change according to circulating levels of estradiol and progesterone. These results stress the need to take into account the level of endogenous ovarian hormones when treating female patients, as has previously been suggested (Nestadt, 2008). Results obtained in the 8-OHDPAT model also point to the possible use of the neurosteroid allopregnanolone (a metabolite of progesterone) as a putative treatment for OCD, a possibility that is strengthened by the finding that allopregnanolone reduces compulsive-like behavior also in the marble-burying model (see below).

2.2. Quinpirole-induced compulsive checking

In this model, developed by Szechtman et al. (1998), compulsive behavior is induced by chronic treatment of rats with the D2/D3 agonist quinpirole (0.5 mg/kg twice weekly for 5 weeks). Following drug administration, rats are placed individually into a large open field, in which 4 small objects are present at a fixed location, and are videotaped for 55 min. The behavior of quinpirole- and saline-treated rats is analyzed to obtain the following behavioral measures: frequency of stops in each locale (place or object); mean time interval between two successive visits to a given locale; mean duration of stopping in a given locale; the number of visits to other locales in between returns to a given locale. Quinpirole-treated rats gradually develop preference to 2 locales in which they stop more frequently (up to 20-fold more) than saline-treated rats. They exhibit much shorter return times to these places and stop at fewer places between returns, compared to control rats (Szechtman et al., 1998, 2001). In addition, quinpirole-treated rats perform a characteristic "ritual-like' set of motor acts at these places (Ben-Pazi et al., 2001). On the basis of published descriptions of compulsive behavior in OCD patients as well as their own observations (Eilam and Szechtman, 2005; Szechtman and Eilam, 2005), Szechtman et al. (1998, 2001) argued 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). These similarities establish the face validity of this model.

2.2.1. Pharmacological predictive validity

Quinpirole-induced compulsive checking has been shown to be partially attenuated by chronic administration (daily injections over 5 weeks) of the SRI clomipramine (Szechtman et al., 1998). Studies testing the effects of SSRIs and, even more critically, of drugs which are known not to be effective in the treatment of OCD, are crucial for establishing the predictive validity of this model.

2.2.2. The effects of high frequency stimulation, temporary inactivation and lesion

Winter and colleagues (Mundt et al., 2009; Winter et al., 2008b) tested the effects of HFS of the shell and core subregions of the nucleus accumbens (NAC) as well as the effects of HFS and of muscimol-induced temporary inactivation of the subthalamic nucleus on quinpirole-induced compulsive checking in male rats. Following 10 injections of quinpirole (or saline for the control group), followed each by behavioral testing in the open field, rats underwent stereotaxic surgery for the bilateral implantation of either electrodes (HFS) or guide cannulae (temporary inactivation). Next, rats received additional injections of quinpirole (or saline) and their behavior was again assessed under HFS or inactivation. Finally, a last behavioral assessment was carried out without HFS or temporary inactivation, in order to assess the reversibility of the treatment.

HFS of the subthalamic nucleus did not have any influence on checking behavior of saline-treated rats or on their locomotor activity. In contrast, in quinpirole-treated rats HFS of the subthalamic nucleus reduced compulsive behavior without affecting locomotion, and this effect was transient. Temporary inactivation of the subthalamic nucleus dose-dependently decreased locomotion, but not checking, in saline-treated rats. In quinpirole-treated rats, the lowest dose of muscimol had no effect, the intermediate dose decreased compulsive checking without affecting locomotion, and the highest dose decreased both checking and locomotion. Similar to HFS, the effects of temporary inactivation were transient (Winter et al., 2008b).

HFS of the NAC shell and core did not have any influence on checking behavior of saline-treated rats but increased their locomotor activity. In contrast, in quinpirole-treated rats, HFS of the shell and core reduced compulsive behavior without affecting locomotion, and this effect was transient (Mundt et al., 2009). The results obtained with HFS of the subthalamic nucleus and NAC strongly support the predictive validity of the model.

Dvorkin et al. (2010) tested the effects of neurotoxic lesions to the NAC core, the orbitofrontal cortex and the basolateral amygdala on quinpirole-induced compulsive checking. After receiving 8 injections of quinpirole or vehicle over a period of 4 weeks, male rats underwent lesion or sham operation, and following a recovery period received 2 additional injections of quinpirole or vehicle (according to their original treatment before the lesion). Lesions to the NAC core, orbitofrontal cortex and basolateral amygdala

had no effect on quinpirole-induced compulsive checking. Interestingly, in vehicle-treated rats, lesions to the orbitofrontal cortex decreased, whereas lesions to the NAC core increased checking behavior. The fact that checking behavior in NAC lesioned rats was almost as intensive as that of sham-operated quinpirole-treated rats, led the authors to suggest that in the intact brain quinpirole acts to inhibit the NAC core, and this inhibition leads to excessive checking (Dvorkin et al., 2010).

2.2.3. The role of kappa-opioid receptors

Perreault et al. (2007a) demonstrated that repeated administration of the kappa opioid agonist (+)-(5a, 7a, 8β)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspirol[4.5]dec-8-yl]-benzeneacetamide) (U69593) facilitated quinpirole-induced locomotor sensitization (i.e., enhanced locomotor activity as measured by distance traveled in activity chambers). In order to strengthen the claim that quinpirole-induced compulsive checking is dependent on a drug-induced sensitized state (Eilam and Szechtman, 2005; Szechtman et al., 1999; Szechtman et al., 1998), the same group went on to check whether U69593 will also facilitate quinpirole-induced compulsive checking (Perreault et al., 2007b).

Male rats received 10 injections of either quinpirole, U69593, a combination of quinpirole and U69593, or vehicle. Indeed, activation of kappa receptors facilitated the development of quinpirole-induced compulsive checking, that is, this behavior was evident after fewer injections relative to rats treated with quinpirole alone. Treatment with the kappa agonist on its own had no effect. Perreault et al. (2007b) also found that treatment with either quinpirole, the kappa agonist or both increased the number of D2 and D3 receptors in their high affinity state in the NAC as well as the number of high affinity D2 receptors in the caudate-putamen, supporting the role of these receptors and of the striatum in compulsive checking.

2.2.4. The role of pituitary hormones

Following several reports of a correlation between the level of pituitary hormones such as vasopressin, oxytocin and adrenocorticotropine, and the severity of OC symptom in patients (for review see McDougle et al., 1999), Dvorkin et al. (2008) tested the effects of hypophysectomy (removal of the anterior and posterior pituitary) on quinpirole-induced compulsive checking in male rats. Hypophysectomized and intact rats received repeated injections of quinpirole or vehicle. The effects of hypophysectomy on compulsive checking were limited to a decrease in the number of stops before returning to a rat's favorite locale, suggesting that quinpirole-induced compulsive checking is not dependant on the presence of pituitary hormones (Dvorkin et al., 2008).

2.2.5. Evaluating validity

Quinpirole-induced compulsive checking provides an animal model of OCD with good face validity and strong predictive validity re HFS. Yet, its predictive validity re pharmacotherapy would be greatly enhanced by assessment of the effects of SSRIs and, even more critically, of drugs which are known not to be effective in the treatment of OCD. This is because although SRI/SSRI's are not effective in all OCD patients, there is currently no other effective monotherapy for this subgroup of patients. The role of the striatum and of D2 receptors in the model as well as the findings that HFS of the subthalamic nucleus and NAC exerts an anti-compulsive effect supports the model's construct validity, yet the finding that lesions to the orbitofrontal cortex do not affect compulsive checking detracts from its construct validity.

2.2.6. Possible implications for clinical research

The results obtained in the quinpirole-induced compulsive checking model suggest that blockade of kappa opioid receptors may be beneficial in OCD.

2.3. 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). Thus, mice did not avoid the marbles when given the opportunity to do so, suggesting that the marbles have no aversive or fear-provoking properties (Njung'e and Handley, 1991), and repeated exposure to marbles did not lead to habituation of marble burying, suggesting that this behavior is not related to novelty or fear (Londei et al., 1998; Njung'e and Handley, 1991). Londei et al. (1998) suggested that marble burying may begin as an appropriate, investigative, activity. However, because the marbles are non-reactive, they cannot provide the animal with the necessary stimuli to a natural ending of the investigation, and this "frustrated" investigation leads to compulsive burying. This suggestion is in line with the view that compulsive behaviors result from an inability to achieve a sense of task completion (for a recent review see Szechtman and Woody, 2004), a view which served as the basis of the signal attenuation model of OCD, reviewed next. Although earlier studies used mice, marble burying has recently also been tested in rats (Schneider and Popik, 2007; Llaneza and Frye, 2009).

2.3.1. Pharmacological predictive validity

There are many reports that burying in male mice and rats is decreased by SSRIs at doses that do not affect locomotor activity (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 one report that such a suppressive effect is not exerted by desipramine (Ichimaru et al., 1995). However, the well documented finding that burying is also reduced by anxiolytic drugs that do not have anti-compulsive activity, such as diazepam and clonazepam (e.g., 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) undermines the predictive validity of marble burying.

In females, drug effects on marble burying were assessed only in rats displaying cycle-dependant changes in marble-burying (see below). Acute administration of 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).

These results, together with the results reported in males, highlight two important points re the predictive validity of marble burying. First, marble burying does not differentiate between anti-compulsive and anxiolytic activity, and may also be sensitive to some non-serotonergic anti-depressive drugs (i.e., 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]). On the up side, marble burying was found not to be sensitive to a neuroleptic drug. Second, it is critical to assess the effects of drugs also on locomotion, in order to differentiate between an anti-compulsive/anxiety effect and a general decrease in behavioral output.

2.3.2. The role of ovarian and related hormones

Schneider and Popik (2007) found that a subgroup (about 30%) of normally cycling female rats displayed changes in marble-burying behavior along the estrous cycle, burying more marbles during dietestrous compared to proestrous. In rats displaying cycle-dependant changes in marble burying, acute administration of the ovarian hormone progesterone attenuated the increase in marble-burying behavior at dietestrous, without concomitantly decreasing locomotion.

Llaneza and Frye (2009) found that in cycling rats, the time rats spent in marble burying was decreased in proestrous compared to diestrous, although there were no differences between the number of marbles buried. In addition, acute administration of progesterone alone or in combination with estradiol decreased the time ovariectomized rats spent in marble-burying compared to ovariectomized rats treated with vehicle, while estradiol on its own failed to exert such an effect. Again, there were no differences between the groups in the number of marbles buried. It should be noted that although Llaneza and Frye's (2009) results with cycling rats are similar to those of Schneider and Popik (2007), the validity of the time spent actively burying marbles as a behavioral measure of compulsivity has not been previously demonstrated. In addition, Llaneza and Frye (2009) did not assess the influence of the different manipulations on locomotor activity, therefore it is not clear whether the observed effects are specific to marble burying or are a result of non-specific changes in activity level.

Acute administration of the neurosteroid allopregnanolone (i.c.v.) or its precursor, progesterone, decreased marble burying in male mice, but administration of the 5-α reductase inhibitor finasteride, an allopregnanolone indirect antagonist, did not affect marble burying. In contrast, acute administration of the neurosteroid DHEAS (i.p.) increased marble burying. None of these compounds had any effect on locomotor activity (Umathe et al., 2009b).

Exposure of mice to 3 h of restrain (acute stress) or to 6 weeks of social isolation (chronic stress), decreased and increased, respectively, the number of marbles buried, in line with studies reporting increased and decreased allopregnanolone levels following acute (Purdy et al., 1991) and social isolation stress (Guidotti et al., 2001), respectively. The possibility that the decrease in marble burying following restrain stress was mediated by an increase in neurosteroid levels was supported by the finding that the allopregnanolone indirect antagonist finasteride reduced the effect of restrain stress on marble burying. None of these manipulations affected locomotion (Umathe et al., 2009b).

Acute administration of the GnRH agonist leuprolide and of the SSRI fluoxetine attenuated marble-burying in male mice without any effect on locomotion, both when given separately and when co-administered at sub-effective doses. Pre-treatment with the serotonin depleting agent PCPA significantly attenuated the effect of leuprolide and completely abolished the effect of fluoxetine on marble-burying, without influencing locomotion. Similarly, pre-treatment with a GnRH antagonist (pGlu-D-Phe-Trp-Ser-Tyr-DAla-Leu-Arg-Pro-Gly-NH2) attenuated the effects of leuprolide and of fluoxetine on marble-burying with no effect on locomotion. When administered on their own, both PCPA and the GnRH antagonist had no effect on marble-burying and locomotion (Uday et al., 2007). In addition, acute administration of the 5-HT2a/2c antagonist ritanserin abolished the leuprolide-induced decrease in marble-burying of male mice without having any effect on locomotion. Ritanserin treatment on its own had no effect on marble-burying or on locomotion (Gaikwad et al., 2010). These results suggest that the anti-compulsive effects of GnRH may depend upon serotonergic activity, and specifically, that the effects of leuprolide in the marble-burying model are mediated through 5-HT2A/2C receptors (Gaikwad et al., 2010).

These findings point to the involvement of ovarian and related hormones in compulsive behavior in both males and females, in line with evidence implicating this system in OCD patients (see Section 1). However, in order to use marble burying to detect compounds with a potential anti-compulsive activity, this test must be combined with an additional animal model of OCD, because marble burying does not differentiate between anti-compulsive drugs and anxiolytic drugs.

2.3.3. The role of serotonin and dopamine receptors

Hedlund and Sutcliffe (2007) tested the involvement of the 5-HT7 receptor in marble-burying using 5-HT7 KO mice (5-HT7$^{-/-}$). They found that 5-HT7$^{-/-}$ mice buried less marbles compared to their wild-type siblings (5-HT7$^{+/+}$). In addition, an acute administration of the 5-HT7 receptor antagonist (R)-3-(2-(2-(4-methylpiperidin-1-yl)-ethyl)pyrrolidine-1-sulfonyl)phenol) (SB-269970) to 5-HT7$^{+/+}$ mice was sufficient to produce a similar reduction in marble-burying to that observed in untreated 5-HT7$^{-/-}$ mice. While Hedlund and Sutcliffe did not assess locomotion in their study, based on previous studies using the 5-HT7$^{-/-}$ mice and SB-269970 they claimed that effects on locomotion were unlikely.

Egashira et al. (2008c) tested the effects of various atypical antipsychotics and dopaminergic and serotonergic agents on marble burying in male mice and tried to discern their mechanism of action. The atypical antipsychotics olanzapine, quietapine and aripiprazole reduced marble-burying, but aripiprazole was the only drug to do so without reducing locomotion and impairing motor coordination (as assessed in the Rota-rod test). This finding is of special interest as there is one blinded controlled study (Masi et al., 2010) and a few open-label trials and case reports (Muscatello et al., 2011; Sarkar et al., 2008) demonstrating augmentation of S/SRI treatment with aripiprazole in treatment-resistant OCD patients. As aripiprazole is a partial agonist at D2 receptors, a 5-HT1A receptor agonist and a 5-HT2A receptor antagonist (Potkin et al., 2003), Egashira et al. (2008c) conducted additional experiments attempting to identify which action contributes to aripiprazole's effect on marble burying. Administration of the 5-HT1A agonist 8-OHDPAT decreased marble burying, and this effect was blocked by administration of the selective 5-HT1A receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexane carboxamide (WAY100635). Administration of the 5-HT2A receptor antagonist ketanserin did not affect marble-burying, and administration of the D2 receptor agonist quinpirole as well as of the selective D2 receptor antagonist L-741,626 reduced marble-burying, but only L-741,626 did so without impairing locomotion. Although these findings suggest that aripiprazole may exert its therapeutic effect via either activation of 5-HT1A receptors or blockade of D2 receptors, administration of the 5-HT1A antagonist WAY100635 did not block the effect of aripiprazole on marble burying.

2.3.4. The role of the NMDA receptor and other calcium channels

Egashira et al. (2008b) found that acute administration of the NMDA antagonists MK-801, memantine and amantadine to male mice decreased marble burying without concomitantly decreasing locomotion (MK-801 actually increased locomotion). In contrast, administration of the AMPA receptor antagonist NBQX or the glutamate release inhibitor riluzole had no effect on marble burying. These results are compatible with human studies pointing to the

involvement of the NMDA receptor in OCD (Arnold et al., 2004) and demonstrating a therapeutic effect for memantine on 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).

Because NMDA receptor activation leads to an increase in intracellular Ca^{2+} levels, Egashira et al. (2008a) tested whether blockade of voltage-gated calcium channels which are not coupled to the NMDA receptor would lead to the same result as NMDA blockade. Indeed, administration of the calcium-channel antagonists amlodipine, clinidipine, nilvadipine and flunarizine was found to attenuate marble-burying without any effect on locomotion, suggesting that intracellular Ca^{2+} plays an important role in marble-burying behavior.

2.3.5. The role of nitric oxide (NO)

Umathe et al. (2009a) tested the effects of NO agonists and antagonists on marble-burying and on the ability of SSRI's to attenuate this behavior. Administration of the NO agonists L-arginine (NO precursor), sodium nitroprusside (NO donor) or sildenafil (a phosphodiesterase 5 inhibitor which prevents degradation of NO-induced cGMP) to male mice significantly increased marble-burying and brain levels of nitrites (end products of NO) compared to vehicle-treated rats. In contrast, administration of the NO antagonist 7-nitroindazole (a specific neuronal NO synthase inhibitor) decreased marble burying and brain nitrite levels. The same effect was also obtained following administration of the SSRI paroxetine. Co-administration of each of the NO agonists with either 7-nitroindazole or paroxetine prevented 7-nitroindazole- and paroxetine-induced decrease of marble-burying and reduction in brain nitrite levels. Importantly, none of the drugs had any effect on locomotion (Umathe et al., 2009a).

The results of Umathe et al. (2009a) were partly replicated and extended by Krass et al. (2010). Krass et al. (2010) also found that 7-nitroindazole decreased marble burying, but in this study 7-nitroindazole also decreased locomotion. Two other NO-related compounds, the neuronal NO synthase inhibitor TRIM and the L-arginine metabolite agmatine, decreased marble-burying without affecting locomotion. However, the mechanism by which agmatine decreased marble-burying is not clear, as administration of this drug did not affect brain NO levels. L-arginine, which was found to increase marble-burying in Umathe et al's study, had no effect on this behavior in Krass et al's study, a difference that may be attributed to the lower dose used in the latter study (500 mg/kg versus 800 mg/kg in Umathe et al., 2009a). Nevertheless, congruent with Umathe et al., Krass et al. found that pre-treatment with L-arginine counteracted the effect of paroxetine and of another SSRI, citalopram, on marble-burying.

The findings of the two studies suggest a possible role for NO in marble burying, maybe through its interaction with the serotonergic system. As there are reports of high NO levels in OCD patients, these findings contribute to the construct validity of the marble-burying model. Further studies assessing the effects of NO on compulsive behavior in other animal models of OCD are warranted.

2.3.6. The role of sigma 1 and sigma 2 receptors and their interaction with SSRI's

Sigma receptors are intracellular receptors consisting of two sub-types: sigma 1 and sigma 2 (Narita et al., 1996), with sigma 1 expressed in the brain and the CNS (for review, see Hayashi and Su, 2004). SSRI's have a moderate to high affinity for sigma 1 but not for sigma 2 receptors, with fluvoxamine demonstrating the highest affinity (Hashimoto et al., 2007; Narita et al., 1996). Activation of sigma 1 receptors has beneficial effects on memory and on depressive- and anxiety-like behaviors in mice (for review see Hayashi and Su, 2004). Based on these findings, Egashira et al. (2007) tested the effects of sigma 1 receptor agonists and antagonists on marble-burying in male mice and their interaction with fluvoxamine and paroxetine.

Administration of the sigma 1 receptor agonists (+)-SKF 10047 or PRE-084 decreased marble-burying without any effect on locomotion. Administration of the sigma 1 receptor antagonists BD 1047 and BD 1063 counteracted the decrease in marble-burying induced by the administration of fluvoxamine but not of paroxetine. Neither antagonist had any effect on marble-burying or on locomotor activity on its own (except for BD 1063 at a dose of 3 mg/kg, which was therefore not used further in the study). Administration of the sigma 2 receptor antagonist SM-21 on marble burying in fluvoxamine-treated mice failed to counteract fluvoxamine's effect on marble burying.

These findings point to the involvement of sigma 1 receptors in marble burying and in the therapeutic effects of fluvoxamine, but not of paroxetine, and imply a different mechanism of action for these two drugs. As in the case of NO and hypothalamic hormones, further studies employing additional animal models of OCD are needed in order to better understand the involvement of sigma receptors in compulsive behavior.

2.3.7. Evaluating validity

Marble burying has good face validity as an animal model of OCD. However, it lacks in predictive validity as it cannot differentiate between anti-compulsive and anxiolytic activity. Moreover, marble burying failed to detect the anti-compulsive activity of riluzole, suggesting that it may not be sensitive to all classes of anti-compulsive drugs. We would like to note that although anxiety is a major source of suffering in OCD, anxiolytic drugs are not effective in alleviating obsessions and compulsions. Therefore the fact that marble burying cannot differentiate between anti-compulsive and anxiolytic drugs seriously detracts from the usefulness of marble burying as a screening test for anti-compulsive drugs. The question whether marble burying provides a model of OCD or of anxiety is also not resolved by other findings. Specifically, although some of the results obtained in marble burying support its relevance to OCD, they may also be related to other anxiety disorders. Thus, the findings that marble burying is modulated by ovarian and related hormones, is related to high levels of NO, and is decreased by administration of the NMDA blocker memantine and the atypical antipsychotic aripiprazole, are in line with what is known on the involvement of these systems in OCD. Yet, modulation by ovarian hormones is also true for other anxiety disorders (for review, see Walf and Frye, 2006), NO was found to play a role in animal models of anxiety (Volke et al., 1997; Zhang et al., 2010), memantine was found to decrease anxiety in animal models of anxiety (Minkeviciene et al., 2008) and aripiprazole was reported to be effective as an augmentation therapy for anxiety disorders in humans and to decrease anxiety-like behaviors in animal models of anxiety (Biojone et al., 2010; Worthington et al., 2005).

2.3.8. Possible implications for clinical research

The results reviewed point to two classes of drugs that may be beneficial in OCD. The first are drugs with agonistic activity at sigma 1 receptors. The second is aripiprazole, an atypical antipsychotic. For the latter the results also suggest that its anti-compulsive effects may be independent of its action at 5-HT1A or 5-HT2A receptors and may be mediated through its antagonistic effects at D2 receptors. This possibility is in line with the fact that D2 blockers are used to augment SSRI treatment in OCD patients. However, as explained above, these hypotheses should be tested in another animal model of OCD. Finally, as in the 8-OHDPAT model (see above), the marble-burying model also suggests the neurosteroid allopregnanolone as a possible treatment for OCD.

2.4. The signal attenuation model

The signal attenuation model was 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, the goal-directed behavior is lever-pressing for food, and the feedback associated with making a response is manipulated using the following strategy: rats are first trained to lever-press for food, whose delivery is accompanied by a stimulus which had been previously paired with food. In this manner the stimulus is established as a feedback cue which signals that the lever-press response was effective in producing food. The "signaling" property of the stimulus is then attenuated by repeatedly presenting the stimulus without food (without the rat emitting the lever-press response). Finally, the effects of *signal attenuation* on lever-press responding are assessed under extinction conditions (i.e., pressing the lever results in the presentation of the stimulus but no food is delivered). 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 to 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 excessive lever-presses that are not followed by magazine entry in rats that underwent signal attenuation but not in rats that underwent regular extinction (for further exposition see Joel, 2006b).

2.4.1. Pharmacological predictive validity

Acute administration of two SSRIs (paroxetine and fluvoxamine) was found to exert an anti-compulsive effect in the model, whereas acute administration of a tricyclic antidepressant (desipramine), an anxiolytic (diazepam) and an antipsychotic (haloperidol) drug, did not, supporting the predictive validity of the model (Joel and Doljansky, 2003; Joel et al., 2004).

2.4.2. The role of ovarian hormones

Although there were no differences in compulsive lever-pressing between pre-pubertal and adult male and female rats, compulsive responding was found to fluctuate along the estrous cycle, being highest during late diestrous and lowest during estrous. In addition, acute administration of estradiol to pre-pubertal female rats was found to attenuate compulsive behavior, suggesting that estradiol exerts an anti-compulsive effect. Withdrawal from chronic administration of estradiol was shown to increase compulsive lever-pressing in pre-pubertal female rats (Flaisher-Grinberg et al., 2009), supporting the hypothesis that the increased risk of onset and exacerbation of OCD in women post-partum may be a result of the decrease in the level of estradiol, which was elevated during pregnancy (Hill et al., 2007). Taken together, these findings demonstrate that compulsive lever-pressing is modulated by ovarian hormones, and thus contribute to the construct validity of the model.

2.4.3. The role of serotonin, dopamine and glutamate receptors

In a series of experiments testing the effects of 5-HT2A and 5-HT2C agonists and antagonists, acute administration of the 5-HT2C antagonist RS 102221 exerted an anti-compulsive effect, whereas administration of the 5-HT2A antagonist MDL 11,939 and of the 5-HT2A/2C agonist DOI did not (Flaisher-Grinberg et al., 2008). Administration of RS 102221 directly into the orbitofrontal cortex also decreased compulsive lever pressing, suggesting that the critical site of anti-compulsive effect of this drug is 5-HT2C receptors within the orbitofrontal cortex (Flaisher-Grinberg et al., 2008).

Another series of experiments tested the involvement of dopamine receptors in compulsive lever-pressing. Withdrawal from repeated administration of the D1 antagonist SCH 23390 or the D2 agonist quinpirole (but not of the D1 agonist SKF 38393 or the D2 antagonist haloperidol) led to an increase in compulsive lever pressing (Joel et al., 2001). These results were interpreted as suggesting that stimulation of D1 receptors is involved in compulsive lever-pressing (Joel et al., 2001), a hypothesis that was later supported by the demonstration that acute administration of a D1 antagonist (SCH 23390), but not of a D2 antagonist (haloperidol), exerts an anti-compulsive effect in the signal attenuation model (Joel and Doljansky, 2003).

Acute administration of the partial NMDA agonist D-cycloserine selectively decreased compulsive lever-pressing, whereas acute administration of the NMDA antagonist MK 801 had a non-selective effect on lever-press responding (Albelda et al., 2010).

2.4.4. The effects of lesion and deep brain stimulation

The neural substrates of compulsive lever-pressing were studied in several experiments. In line with data implicating dysfunction of the orbitofrontal cortex in OCD (see Section 1), manipulations of the rat orbitofrontal cortex were shown to affect compulsive lever-pressing (Flaisher-Grinberg et al., 2008; Joel et al., 2005a,b; Joel and Klavir, 2006). Interestingly, the increase in compulsive lever-pressing following lesions to the orbtiofrontal cortex was paralleled by an increase in the density of the striatal serotonin transporter, suggesting that orbitofrontal lesion-induced compulsivity is mediated by alterations of the striatal serotonergic system (Joel et al., 2005a). This hypothesis was supported by the results of a recent study, which found that orbitofrontal lesions decrease the content of dopamine and serotonine in the striatum, and that intra-striatal administration of paroxetine abolishes orbitofrontal lesion-induced increased compulsivity (Schilman et al., 2010).

In another study, lesions to the subthalamic nucleus were found to also increase compulsive behavior and decrease dopamine and serotonin content in the striatum, leading to the hypothesis 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).

In contrast to the effects of pre-training lesions to the subthalamic nucleus, post-training temporary inactivation (using muscimol) as well as HFS of the subthalamic nucleus exerted an anti-compulsive effect in the model (Klavir et al., 2009), further strengthening the model's predictive validity.

Finally, HFS, but not low frequency stimulation, of the entopeduncular nucleus and of the globus pallidus (the rat's equivalents of the primate's internal and external segments of the globus pallidus, respectively) were found to exert an anti-compulsive effect (Klavir et al., 2011).

2.4.5. Evaluating validity

Signal attenuation provides an animal model of OCD with good face, predictive and construct validity. The model's construct validity is derived from similarities to OCD 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). The model's predictive validity is based on selectivity for anti-obsessional/anti-compulsive drugs and on the effectiveness of HFS of the subthalamic nucleus. The model can thus be used to screen for anti-compulsive therapies. It should be noted, however, that the 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). Finally, the signal attenuation model can be used to test the involvement of ovarian hormones in OCD as it is sensitive to spontaneous and externally induced fluctuations in the level of these hormones.

2.4.6. Possible implications for clinical research

The results obtained in the signal attenuation model point to 3 receptors whose targeting may be beneficial in OCD, namely, the 5-HT2C, D1 and NMDA receptors. Specifically, blockade of 5-HT2C receptors may have an anti-compulsive effect in OCD patients, possibly by acting on 5-HT2C receptors within the orbitofrontal cortex. Blockade of D1 receptors may also be beneficial, as has been suggested on the basis of theoretical considerations (Saxena et al., 1998, see below). Partial agonism, rather than blockade, of the NMDA receptor by DCS may exert a direct anti-compulsive effect, in addition to augmentation of cognitive-behavior therapy, as has been reported for OCD patients (Kushner et al., 2007; Wilhelm et al., 2008). Last, results in the signal attenuation model suggest that HFS of either segment of the globus pallidus may provide an additional therapeutic strategy for OCD.

2.5. Spontaneous stereotypy in deer mice

This model is based primarily on behavioral similarity. Deer mice (*Peromyscus maniculatus bairdii*) have been shown to spontaneously develop stereotypic behaviors consisting of vertical jumping, backward somersaulting and patterned running (Powell et al., 1999). In this model, the behavior of each mouse during a period of several hours is analyzed, and each mouse is given a stereotypic score, according to which the mice are divided into high, low and non-stereotypic (e.g., 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 to low stereotypic mice, or high and low stereotypic mice to non-stereotypic mice.

In contrast to most other models of OCD, in this model male and female mice were used in all studies, in line with the recent emphasis on the importance of studying the two sexes (e.g., a recent Editorial in Nature titled "Putting gender on the agenda", Nature, 2010). The authors do not report, however, whether the data were analyzed with sex as a main factor, and what were the results of such an analysis.

2.5.1. Pharmacological predictive validity

Stereotypic behaviors in deer mice were decreased by repeated administration (for 21 days) of fluoxetine but not of desipramine (Korff et al., 2008), supporting the predictive validity of this model.

2.5.2. The role of serotonin, dopamine and glutamate receptors

Stereotypic behaviors in both high and low stereotypic mice were decreased by systemic administration of the 5-HT2A/2C agonist mCPP and of the D2 agonist quinpirole (Korff et al., 2008). Blockade of striatal D1 receptors as well as blockade of striatal NMDA glutamate receptors, was found to decrease stereotypies in high stereotypic mice, without affecting motor activity in general (Presti et al., 2003). Other findings from the same group found that activating or blocking other dopamine receptors does not affect spontaneous stereotypic behavior. Specifically, intra-striatal administration of the D1/D2 agonist apomorphine, the D1 agonist SKF81297, the D2 agonist quinpirole and the D2 antagonist raclopride failed to affect spontaneous stereotypic behavior in high stereotypic mice (Presti et al., 2004).

2.5.3. Neural substrates

Presti and Lewis (2005) found that compared to low stereotypic mice, high stereotypic mice show decreased enkephalin content and increased dynorphin/enkephalin ratio in the striatum, suggesting that high stereotypy may be mediated by an imbalance in the functioning of the direct and indirect basal ganglia-thalamo-cortical pathways, with the former showing increased functioning and the latter decreased functioning.

Another study found evidence for the involvement of the frontal cortex in stereotypic behaviors. Specifically, Korff et al. (2009) found elevated levels of cyclic adenosine monophosphate (cAMP) in the frontal cortex, but not striatum, of high and low stereotypic mice compared to non-stereotypic mice. 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).

2.5.4. Evaluating validity

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 fluoxetine but not by desipramine. Other results, however, are less consistent with the known pharmacology of OCD, as in the clinic the 5-HT2A/2C agonist mCPP (which decreased stereotypy in deer mice) has been reported to also exacerbate 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 et al., 1987), 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). Therefore the predictive validity of spontaneous stereotypy in deer mice is questionable.

The model, however, has good construct validity which derives from demonstration of the involvement of the striatum, frontal cortex and the serotonergic, dopaminergic and glutamatergic systems. The construct validity of the model is also supported by the findings of decreased enkephalin content and increased dynorphin/enkephalin ratio in the striatum of high stereotypic mice, which suggest that high stereotypy may be mediated by an imbalance in the functioning of the direct and indirect basal ganglia-thalamo-cortical pathways, as has previously been hypothesized (Saxena et al., 1998). Indeed, as predicted by Saxena et al. (1998) on the basis of the hypothesis that the direct pathway is hyperactive relative to the indirect pathway, blockade of striatal D1 receptors (which abandon on neurons of the direct pathway) decreased stereotypies in high stereotypic mice.

It would be of interest to test whether high stereotypic mice show additional forms of compulsive-like behaviors, such as increased grooming, increased marble burying, etc. Such an assessment may help decide whether spontaneous stereotypy in deer mice is a model of OCD or a model of an endophenotype, i.e., vulnerability to developing repetitive behaviors, which may be relevant for additional disorders (Joel et al., 2008). As detailed above, the pharmacology of spontaneous stereotypy only partially supports the specificity of this behavior to OCD. Yet, regardless of whether spontaneous stereotypy in deer mice is an animal model of OCD or of vulnerability to developing repetitive behavior, studying the neural mechanisms of spontaneous stereotypy in deer mice may advance our knowledge of neural circuits relevant to such behaviors in OCD.

Table 1
Summary of findings obtained in the different models.

	8-OHDPAT	Marble burying	Signal attenuation	Quinpirole model	Deer mice (males and females)
Serotonin					
Serotonin reuptake inhibitors	SSRI (fluoxetine males[1,3] and females[2] in diestrous and proestrous) ↓	SSRI (fluoxetine[1] males and females in diestrous) ↓			SSRI (fluoxetine[3]) ↓
			SSRI (fluvoxamine[1]) ↓		
		SSRI (paroxetine[1]) ↓	SSRI (paroxetine[1]) ↓		
		SSRI (citalopram[1]) ↓			
	SRI (clomipramine[2]) ↓			SRI (clomipramine[3]) ↓↔	
Serotonin depletion (PCPA)		↔			
5-HT1A	5-HT1A agonist (8-OHDPAT[1]) ↑	5-HT1A agonist (8-OHDPAT[1]) ↓			
		5-HT1A agonist, 5-HT2A antagonist, D2 partial agonist (aripiprazole[1]) ↓			
5-HT2A		5-HT1A agonist, 5-HT2A antagonist, D2 partial agonist (aripiprazole[1]) ↓			
		5-HT2A antagonist (ketanserin[1]) ↔	5-HT2A antagonist (MDL 11,939[1]) ↔		
			5-HT2A/2C agonist (DOI[1]) ↔		5-HT2A/2C agonist (mCPP[2]) ↓
5-HT2C			5-HT2A/2C agonist (DOI[1]) ↔		5-HT2A/2C agonist (mCPP[2]) ↓
			5-HT2C antagonist (RS 102221[1]) ↓		
5-HT7		5-HT7 antagonist (SB-269970[1]) ↓			
		Knock-out of 5-HT7 receptors ↓			
Dopamine					
D1			D1 antagonist (SCH 23390[1]) ↓		D1 antagonist (SCH 23390[1], intra-striatal) ↓
					D1 agonist (SKF81297[1], intra-striatal) ↔
					D1/D2 agonist (apomorphine[1], intra-striatal) ↔
D2		5-HT1A agonist, 5-HT2A antagonist, D2 partial agonist (aripiprazole[1]) ↓			
				D2/D3 agonist (quinpirole[3]) ↑	D2/D3 agonist (quinpirole[2]) ↓
					D2/D3 agonist (quinpirole[1], intra-striatal) ↔
					D1/D2 agonist (apomorphine[1], intra-striatal) ↔
		D2 antagonist (L-741,626[1]) ↓	D2/D3/D4 antagonist (haloperidol[1]) ↔		D2 antagonist (raclopride[1], intra-striatal) ↔
Glutamate					
NMDA		NMDA antagonist (MK-801[1]) ↓	NMDA antagonist (MK-801[1]) ↔		NMDA antagonist (MK-801[1], intra-striatal) ↓
		NMDA antagonist (memantine[1]) ↓	NMDA agonist (D-cycloserine[1]) ↓		
		NMDA antagonist (amantadine[1])↓			
AMPA		AMPA receptor antagonist (NBQX[1]) ↔			
Glutamate release inhibitor		Glutamate release inhibitor (riluzole[1]) ↔			

Table 1 (*Continued*)

	8-OHDPAT	Marble burying	Signal attenuation	Quinpirole model	Deer mice (males and females)
Sigma 1		Sigma 1 receptor agonist ((+)-SKF 10047[1]) ↓ Sigma 1 receptor agonist (PRE-084[1]) ↓			
NO		NO agonist (L-arginine[1]) ↑ NO agonist (sodium nitroprusside[1]) ↑ NO agonist (sildenafil[1]) ↑ NO antagonist (7-nitroindazole[1]) ↓ NO antagonist (TRIM[1]) ↓ NO antagonist (agmatine[1]) ↓			
Ovarian and related hormones					
Spontaneous fluctuations (females)	Estrous – low		Estrous – low		
	Proestrous – high	Proestrous – low Diestrous – high	Diestrous – high		
Ovariectomized rats (females)	P[1], P+E[1] ↓ E[1] ↔	P[1], P+E[1] ↓ E[1] ↔			
Estradiol (females)			E[1] ↓		
DHEA	↑	↑			
Allopregnanolone	↓	↓			
Progesterone		↓ (Males[1] and females[1])			
GnRH		GnRH agonist (leuprolide[1]) ↓			
Opoids				Kappa opioid agonist (U69593[3]) ↑	
DBS					
Subthalamic nucleus			HFS ↓	HFS ↓	
Nucleus accumbens				HFS ↓	
Globus pallidus			HFS ↓		
Entopeduncular nucleus			HFS ↓		
Thalamic reticular nucleus	LFS ↓ HFS ↔				

Unless otherwise stated, the findings relate to male mice or rats.
Abbreviations: P: progesterone; E: estradiol; DBS: deep brain stimulation; HFS: high frequency stimulation; LFS: low frequency stimulation.
↑ denotes an increase in compulsive-like behavior. ↓ denotes a decrease in compulsive-like behavior. ↔ denotes no effect on compulsive-like behavior.
[1]denotes an acute administration regimen. [2]denotes a sub-chronic administration regimen (3–5 injections). [3]denotes a chronic administration regimen (>5 injections).

2.5.5. Possible implications for clinical research

Spontaneous stereotypy in deer mice has an important advantage in that it develops spontaneously, and thus may provide insight into a range of genetic and environmental etiologic factors in OCD. In addition, because male and female mice are regularly tested in this model, it may serve to further study the interaction between ovarian hormones and compulsive behaviors and develop new strategies of treatment for females.

3. Conclusions

Each of the models surveyed above has strengths and limitations, which dictate the aim(s) it can serve. In the context of screening for anti-compulsive activity, the most critical features of a model are its predictive validity and its cost-effectiveness. With regard to predictive validity, it is important to reiterate that about half of OCD patients do not respond to an SSRI monotherapy, yet, there is currently no other monotherapy that is effective in these patients. Therefore a demonstration of lack of effect of drugs that are known not to be effective in the treatment of OCD is more critical than a demonstration of effect of SSRIs for establishing a model's predictive validity. All of the models reviewed above, except quinpirole-induced compulsive checking, have demonstrated lack of effect for at least one class of drugs known not to be effective in OCD.

Regarding cost-effectiveness, the most straightforward and cost-effective procedures are the marble-burying test, which requires no behavioral training and no pharmacological manipulation, and the 8-OHDPAT-induced decreased alternation, which requires limited behavioral training and an acute administration of 8-OHDPAT. Indeed, these two models are the most studied models of OCD. Their predictive validity, however, is currently lacking and should be improved before they can serve for drug screening. In the 8-OHDPAT model, a demonstration of a lack of effect of drugs that are known not to be effective in the treatment of OCD is particularly important (to date only desipramine has been tested), because spontaneous alternation is known to be highly sensitive to pharmacological manipulations of all of the major neurotransmitter systems (see above). For the marble-burying model, it is critical to establish conditions that would enable the differentiation between the action of anxiolytic and anti-compulsive drugs, because acute administration of both classes of drugs reduces burying. Of the other three models, the signal attenuation model has the best predictive validity, as it can differentiate between the effects of SSRI's and of several classes of drugs not effective in the treatment of OCD. It requires, however, special equipment (operant boxes) and about 2 weeks of behavioral training. In addition, the post-training signal attenuation procedure is not well suited for chronic drug administration studies, because repeated drug administration may affect behavior in the early stages of the procedure (e.g., lever-press training, signal attenuation).

Combining several animal models of OCD in order to detect anti-compulsive activity is 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. Table 1 summarizes the findings obtained using the different models. As can be seen, the data from two or more models converge only in a few domains. The area of research where the convergence is greatest involves the role of ovarian and related hormones in compulsive behavior. This has been studied in the marble burying, 8-OHDPAT and signal attenuation models. In the latter two models, females in estrous show less compulsivity than females in proestrous, whereas in the former model the reversed pattern has been found. Interestingly, although the fluctuations of compulsive behavior along the estrous cycle show the opposite pattern in the marble burying and 8-OHDPAT models, exogenous sex hormones exerted similar effects in the two models in ovariectomized females and in intact males. Specifically, in the two models, progesterone, with or without estradiol, decreased compulsive behavior in ovariectomized females, whereas estradiol had no effect, and DHEAS and allopregnanolone increased and decreased, respectively, compulsive behavior in males. The results obtained in the three animal models of OCD strongly suggest that new treatment strategies may be developed on the basis of the involvement of sex hormones in compulsive behavior in both males and females. *We would like to reiterate the importance of using both male and female subjects in the study of the pharmacology of OCD.*

Unfortunately, although most animal models were used to study the main neurotransmitter systems implicated in OCD (serotonergic, dopaminergic and glutamatergic), there is relatively little overlap between the specific types of receptors studied in each model, and in most areas of convergence the results are not consistent between models (e.g., the effects of D2 agonists, 5-HT1A agonist, 5-HT2A antagonist). However, current data do suggest that blockade of D1 and NMDA receptors may have beneficial effects in OCD. It is also noteworthy that the quinpirole and signal attenuation models have good predictive validity re HFS, and they may be used for detecting brain regions whose electrical stimulation may produce an anti-compulsive effect.

An additional use of animal models is the elucidation of the neurobiological mechanisms of the modeled condition. In this context, similarity in the inducing mechanism seems to be the critical feature, although in the case of OCD it cannot be evaluated directly, as the etiology of this disorder is currently unknown. Of the models reviewed here, the signal attenuation model has the best construct validity, derived both from the manipulation used to induce compulsive behavior and the findings demonstrating the involvement of the major neural systems implicated in OCD in compulsive behavior in the model. The signal attenuation model has already yielded a hypothesis accounting for the observed association between a dysfunction of the orbitofrontal cortex and of the serotonergic system in OCD, namely, that pathology of the former leads to dysregulation of the striatal serotonergic system which leads to compulsive behavior (Joel et al., 2005a). This hypothesis was later supported by demonstrating that intra-striatal administration of an SSRI blocked orbitofrontal-lesion-induced compulsivity (Schilman et al., 2010). Another hypothesis derived from work in the signal attenuation model relates to the heterogeneity of OCD. Specifically, Joel and colleagues suggested that dysfunction of the striatal serotonergic and/or dopaminergic systems is the final common pathway in producing compulsive behavior following different brain pathologies (Schilman et al., 2010; Winter et al., 2008a).

Involvement of the striatum, nucleus accumbens and subthalamic nucleus in compulsive behavior has also been found in the quinpirole model, and of the striatum and frontal cortex in the deer mouse model. Findings in the deer mouse model further suggest that imbalance in the direct and indirect pathways of the basal ganglia-thalamo-cortical circuits may mediate spontaneous stereotypy. This latter finding is of interest given that compulsive behavior develops spontaneously in the deer mouse model, a characteristic which may make the model particularly useful in elucidating the neural substrates of compulsive behavior.

We hope future studies will study the role of the parietal cortex in animal models of OCD, as parietal regions have recently been implicated in the pathophysiology of OCD (Menzies et al., 2008; Rotge et al., 2009). We also encourage assessment of neurocognitive deficits in suitable animal models (i.e., models in which compulsive behavior is induced by a pharmacological or a genetic manipulation, or emerges spontaneously) as another means to strengthen the construct validity of such models. Most appealing are tasks that can be used in both humans and rats, such as the stop-signal reac-

tion time and the intradimensional–extradimensional shift tasks, in which OCD patients have been shown to be impaired (see above).

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