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Review article

Cross-species models of OCD spectrum disorders

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ABSTRACT

Several axis-I neuropsychiatric disorders are characterised by repetitive motor habits suggestive of underlying inhibitory dyscontrol, and may constitute members of a putative obsessive–compulsive (OC) spectrum. Notable examples include obsessive–compulsive disorder (OCD) and trichotillomania (repetitive hair-pulling). Multiple tiers of evidence link these conditions with underlying dysregulation of fronto-striatal circuitry and monoamine systems. These abnormalities represent key targets for existing and novel treatment interventions. Nonetheless, the brain bases of these conditions, and treatment mechanisms, remain poorly characterised. Animal models of repetitive habits and inhibitory control problems show great potential for augmenting our understanding of the pathophysiology and treatment of OC spectrum conditions. Here, we begin by describing clinical features of OC spectrum disorders, and criteria used to assess the validity of animal models of symptomatology. Namely, face validity (phenomenological similarity between inducing conditions and specific symptoms of the human phenomenon), predictive validity (similarity in response to treatment) and construct validity (similarity in underlying physiological or psychological mechanisms). We then survey animal models of OC spectrum conditions within this framework, focusing on (i) ethological models; (ii) genetic and pharmacological models; and (iii) behavioral models. Key future research directions are highlighted.

Contents

1. Introduction

Advances in our understanding of the genetic and neural substrates of obsessive–compulsive disorder (OCD) and related spectrum disorders such as trichotillomania, as well as their characteristic behavioral and cognitive symptoms, render the search and evaluation of appropriate animal models especially timely. Such modelling in neurology and neuropsychiatry generally occurs on at least two levels; the etiological, in terms of genetics and molecular pathology, and the symptomatic, in terms of identifying suitable neurocognitive endophenotypes that encompass the range of behavioral and psychiatric manifestations of particular disorders in the context of altered brain circuitry. The former is generally difficult in psychiatry as distinct from

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

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

2. Assessing animal models

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

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

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

3. Clinical profile and neurobiological substrate of OCD

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

The essential features of OCD and related spectrum disorders capable of being captured by animal models are the maladaptive and perseverative behavioral or cognitive output, mediated by dysfunctional nodes within the fronto-striatal circuitry, probably modulated by altered dopaminergic or serotoninergic influences: for example, the repetitive rituals in OCD, or hair-pulling in trichotillomania. Human neuroimaging studies have implicated in particular the orbitofrontal cortex and the caudate nucleus in OCD, and cingulotomy has had a limited therapeutic success (see Baxter, 1999). However, there may be grounds for considering OCD-spectrum disorders as reflecting impaired functioning of several distinct fronto-striatal 'loops' (Graybiel and Rauch, 2000; Chamberlain et al., 2005; Nakao et al., 2005; Whiteside et al., 2006; Chamberlain et al., 2007a; Choi et al., 2007; Menzies et al., 2008). Animal models of OCD spectrum disorders have generally fulfilled the criteria of 'face validity', but have sometimes been based on psychological theorising about the nature of OCD, thus attempting the deeper level of modelling, 'construct validity'. 'Predictive validity' can therefore be employed to a limited extent in OCD, given the known, but largely unexplained, efficacy of the SSRIs (beginning with fluoxetine) and other less widely evaluated candidate treatments such as dopamine D1 receptor antagonists and specific 5-HT receptor agents.

4. Current ethological and laboratory animal models of OCD

4.1. Ethological animal models of OCD (Table 1)

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

Table 1
Animal models of obsessive–compulsive disorder (OCD).

	Model	Modeled behavior (face validity)	Neuroanatomical/neurochemical substrate (construct validity)	Predictive validity
Ethological models	Tail-chasing (Brown et al., 1987), acral lick dermatitis (ALD — paw licking) in dogs (Rapoport et al., 1992), psychogenic alopecia (hair pulling) in cats (Swanepoel et al., 1998), feather picking in birds (Grindlinger and Ramsay, 1991), cribbing in horses (Luescher et al., 1998), schedule-induced polydipsia (Woods et al., 1993), food-restriction-induced hyperactivity (Altemus et al., 1996)	Spontaneous persistent behaviors with genetic components reminiscent of OCD	Although these models offer good face similarity and predictive validity, construct validity is difficult to be tested mainly due to the fact that they focus on spontaneous persistent behaviors	The effects of SSRIs have been tested and compared to the effects of drugs ineffective in OCD e.g. remediating effects of clomipramine on canine lick dermatitis
Genetic models	Hoxb8 mutant mice (Greer and Cappechi, 2002)	Excessive grooming similar to that seen in trichotillomania and OCD	Hoxb8 gene is expressed in OFC, the anterior cingulate, the striatum and the limbic system, all of which are implicated in OCD	There are no reports on the isomorphic response of these models with clinical compulsive behavior
	D1CT-7 mice (Campbell et al., 1999a,b; McGrath et al., 1999)	Perseveration and repetitive leaping TS-like behaviors	Transgene expression in neural systems hyperactive in human OCD, e.g. amygdala, somatosensory/insular and orbitofrontal cortical regions	
	DAT KD mice (Berridge et al., 2005)	Sequential super-stereotypy apparent in OCD/TS patients in the form of rigid patterns of actions, language or thought	Dopaminergic involvement in OCD. Basal ganglia are implicated in grooming and OCD	
	5-HT2c KO mice (Chou-Green et al., 2003)	Perseverative 'head-dipping' and excessively orderly chewing of screen material similar to human OC symptoms such as ordering, washing etc.	5-HT2c receptors involvement in OCD pathophysiology	
Pharmacological models	Quinpirole-induced compulsive checking (Szechtman et al., 1998)	Compulsive checking in OCD patients (e.g. ritual-like motor activities)	Dopaminergic involvement in OCD pathophysiology	Quinpirole-induced compulsive checking is reduced following treatment with clomipramine.
	8-OHDPAT-induced spontaneous alternation (Yadin et al., 1992)		5-HT1a receptors involvement in OCD pathophysiology	Administration of fluoxetine (chronic) and clomipramine (sub-acute), but not desipramine, offers protection from the 8-OHDPAT-induced decrease in spontaneous alternation
	mCPP-induced directional persistence in Reinforced Spatial Alternation (Tsaltas et al., 2005)		5-HT2c receptor involvement in OCD pathophysiology	Chronic treatment with fluoxetine, but not with diazepam or desipramine, blocks the mCPP-induced directional persistence.
Behavioral models	Barbering (Garner et al., 2004)	Compulsive hair plucking in humans (trichotillomania)	Spontaneous development	No reports
	Marble burying (Ichimaru et al., 1995)	Inability to achieve a sense of task completion	No reports	Marble burying is sensitive to SSRIs and diazepam. However, the effects of diazepam disappear following repeated administration which is not the case with SSRIs, e.g. fluvoxamine. No response to desipramine
	Signal attenuation (Joel and Avisar, 2001; Joel et al., 2004)	Compulsive lever-pressing is both excessive and unreasonable, as are compulsions in OCD patients.	1. Similarities in the compulsivity-inducing mechanism (i.e. attenuation of an external feedback and a deficient response feedback mechanism, respectively) 2. Orbital, but not medial prefrontal or amygdala, lesions induce compulsive lever-pressing	Acute administration of fluoxetine, but not diazepam, desipramine or haloperidol, reduces compulsive lever-pressing
Other possible behavioral models	Reversal learning (Boulougouris et al., 2007; Chudasama and Robbins 2003; Clarke et al., 2004)	Inability to withhold, modify or sustain adaptive behavior in response to changing situational demands	Lesions to the orbitofrontal cortex (OFC) as well as 5-HT depletion in this brain region heavily implicated in OCD disrupt reversal learning, manifested as increased perseverative responding to the prepotent stimulus.	The isomorphic response of these models with clinical compulsive behaviour needs to be tested.
	Attentional set-shifting (Extra-dimensional shift) (Birrell and Brown, 2000; Clarke et al, 2007)		Sensitive to: lateral frontal lesions and catecholamine but not 5-HT depletion in monkeys and medial prefrontal cortical lesions in rats.	
	Extinction		No reports but see signal attenuation model	
	Habit-learning (Killcross and Coutureau, 2003; Yin and Knowlton, 2006)	This behavior is controlled by stimulus–response links with a generally weakened influence of the ultimate goal	Habit-learning is mediated by specific sectors of the striatum and can be influenced by prefrontal cortical mechanisms.	

(continued on next page)

Table 1 (*continued*)

	Model	Modeled behavior (face validity)	Neuroanatomical/neurochemical substrate (construct validity)	Predictive validity
Other possible behavioral	Stop-signal reaction time task (SSRT) (Eagle and Robbins, 2003; Eagle et al., 2008; Aron et al, 2003a,b,c)	'Impulsive' responding particularly as it is impaired in ADHD	Studies in human patients with frontal lobe damage have localised the critical zone for SSRT to the right inferior gyrus while others to the striatum.	The SSRT is insensitive to serotoninergic manipulations both in rats and humans.

5-HT: serotonin; 5-HT2c KO mice: 5-HT2c receptor knockout (KO) mice; 8-OHDPAT: 8-hydroxy-2-(di-*n*i-popylamino)-tetralin hydrobromide, 5-HT1A agonist; ADHD: Attention deficit/hyperactivity disorder; ALD: Acral lick dermatitis; D1CT mice: transgenic mice expressing a neuropotentiating protein (cholera toxin A1 subunit) within a cortical-limbic subset of dopamine D1-receptor expressing (D1+) neurons; DAT KD mice: dopamine transporter (DAT) knockout (KD) mice, expressing 10% of wild-type DAT levels and exhibit elevated extracellular dopamine concentration; mCPP: meta-chlorophenylpiperazine, non-selective serotonin agonist; OFC: orbitofrontal cortex; SSRIs: selective serotonin reuptake inhibitors; SSRT: Stop-signal reaction time task; TS: Tourette's syndrome.

ineffective in OCD (Winslow and Insel, 1991; Rapoport et al., 1992; Woods et al., 1993; Altemus et al., 1996; Nurnberg et al., 1997). It is worth noting that the reported efficacy of clomipramine in OCD and trichotillomania was predicated by observations of its remediating effects on canine lick dermatitis (Swedo et al., 1989; Rapoport et al., 1992) and similar abnormal behavior elicited in veterinary contexts, for example, psychogenic alopecia in cats (Swanepoel et al., 1998), cribbing in horses (Luescher et al., 1998) and repetitive pacing in several species, often elicited by stressful environments, continue to be a valid source of naturalistic stereotypies that may be informative about OCD spectrum disorders (Stein et al., 1994). Both stereotypies and schedule-induced polydipsia have been considered as 'coping responses' that hypothetically reduce stress. This hypothesis, however, has proved difficult to test experimentally and may well not apply to all forms of stereotypy (Table 1).

4.2. Genetic and pharmacological models of OCD (Table 1)

In terms of *genetic models*, these have largely been based on face validity, and include the *hoxb8* mutant (Greer and Cappechi, 2002) as well as genetic manipulations of both dopamine (DA) and 5-HT functioning leading to similar behavior. Greer and Cappechi (2002) reported that mice with mutations of the Hoxb8 gene (expressed in the orbital cortex, the striatum and the limbic system, all of which are implicated in OCD pathophysiology) groomed excessively to the point of hair removal and skin lesions compared with their control counterparts. In terms of genetic manipulations of DA and 5-HT, boosting D1 receptor function by a neuropotentiating cholera toxin expressed in the pyriform cortex and amygdala produces perseveration and repetitive jumping behavior in mice, named D1CT-7 mice, probably mediated ultimately via striatal mechanisms (Campbell et al., 1999a,b,c). It should also be noted that this repetitive jumping behavior was exacerbated by the administration of yohimbine, an anxiogenic drug (McGrath et al., 1999). Knock-down of the dopamine transporter (DAT) produces 'sequential super-stereotypy' in mice, named DAT KD mice, with the perseverative performance of quite complex chains of grooming behavior (Berridge et al., 2005). A knock-down of the 5-HT2C receptor similarly leads to perseverative 'head-dipping' or the excessively orderly chewing of screen material (Chou-Green et al., 2003), a compulsive behavior (accompanied by other like responses such as stereotypic locomotion and excessive self-aggressive grooming), which has also been shown in rats: following chronic lesions of median raphé nucleus (Hoshino et al., 2004). Some of these responses obviously have clear superficial parallels to some of the elaborative rituals in OCD, possibly related to hygiene and checking. However, it is of course essentially impossible to know in fact how closely related they are. It seems likely that these examples of stereotyped behavior are mediated by striatal structures, given the known role of the caudate–putamen in stereotyped behavior produced by psychomotor stimulant drugs (Creese and Iversen, 1975) and in normal grooming sequences (Aldridge and Berridge, 1998).

It is tempting to utilise *pharmacological models* based on the stereotypy produced by stimulants such as amphetamine at high doses (Lyon and Robbins, 1975). Although stereotypies in rodents typically consist of gnawing and licking with repetitive sideways movements of the head which may represent vestiges of orienting behavior, they can be elaborated in many ways, for example, to include grooming (including allogrooming, Sahakian and Robbins, 1975) and perseverative operant behavior in which rats may continue to work for food they do not eat (Robbins and Sahakian, 1983). These responses are dopamine-mediated, but it may be a mistake to consider them as being directly related to OCD spectrum disorder as, for example, treatment of mice receiving the D1 receptor potentiation treatment actually exhibit reduced stereotypy after treatment with cocaine, showing that drug-induced stereotypy and the behavior produced by enhanced D1 receptor over-expression do not necessarily lie on the same continuum (Campbell et al., 1999a). This may also be reflected in clinical experience. For example, D-amphetamine has actually been shown to ameliorate OCD symptoms in certain circumstances (Insel et al., 1983). Nevertheless, Szechtman et al. (1998) have shown that the D2/D3 agonist quinpirole leads to behavior that can be analysed as a form of repetitive 'checking' behavior in rats. Specifically, following drug administration (0.5 mg/kg twice weekly for 5 weeks), rats were placed individually into an open field with four objects at fixed locations and their activity was recorded for 55 min. Analysis of quinpirole and saline treated rats revealed that quinpirole-treated rats stopped at two locales more frequently than controls and exhibited a "ritual-like" set of motor activities at these places (Szechtman et al., 1998). This behavior is reduced by treatment with clomipramine.

As mentioned above, perseveration is a term that can be applied to a variety of behavioral outputs ranging from relatively simple to complex. The 'complex' category is where it is not a motor output that is performed repetitively, but approach to a particular goal, or the persistence in complex sequences of behavior. We also include in the 'complex' category trained operant behavior (in which rats keep on working for food they do not eat) and also both spontaneous (Yadin et al., 1992) and reinforced delayed alternation behavior (Tsaltas et al., 2005), which can become perseverative if the animal continues to make the previous choice, following treatment for example, with dopaminergic or serotoninergic agents. At yet higher levels of organisation, we can consider impairments of object reversal behavior to reflect a 'higher order' form of perseveration as the animal may perseverate in responding to a formerly reinforced stimulus, even though its spatial position is shifted across trials. Such behavior occurs when 5-HT depletion is effected in the orbitofrontal cortex (Clarke et al., 2004, 2005, 2007) in marmoset monkeys. Moreover, this behavior is truly perseverative in the sense that reversal learning is normal if the previously rewarded stimulus is substituted by a novel one (Clarke et al., 2007). However, this form of perseverative responding is probably not the same as that produced by perseveration of a learned rule in the Wisconsin Card Sort Test following, for example, frontal lobe damage (or OCD), which involves a so-called 'extra-dimensional shift' (EDS). This form of attentional shifting is impaired by lateral frontal lesions in the marmoset and by catecholamine, but not 5-HT, depletion (Clarke et al., 2005, 2007; for a review, see also Robbins, 2005.

4.3. Signal attenuation and extinction: behavioral models of OCD (Table 1)

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

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

4.4. Putative behavioral animal models of OCD (Table 1)

It would be parsimonious to describe all of these examples of perseverative responding from the level of single response elements to complicated sequences of behavior, to a perseverative attentional focus, as resulting from failures of 'behavioral inhibition'. However, the fact that they are mediated by both striatal and different prefrontal cortical sectors suggests that these are not the same forms of inhibition and that a generic explanation in terms of behavioral inhibition may lack explanatory power. However, it is possible that particular forms of behavioral inhibition are impaired in OCD spectrum disorders. There are several other theoretical positions that may be especially useful in explaining certain forms of OCD, while capturing some of the clinical observations of patients exhibiting these disorders. Thus, one set of theoretical constructs suggests that anxiety (e.g. Mowrer, 1960) is the prime trigger of OCD, as posited, for example, by Rachman and Hodgson (1980). Active avoidance behavior in animals is well known to be very persistent as it so rarely has the opportunity for extinction — and drugs such as D-amphetamine exacerbate this perseverative tendency. Thus behavior that initially has some adaptive value, for example, in avoiding shocks, apparently loses its rationale after thousands of trials in which shock is never presented. We have previously alluded to the possibility that stereotyped behavior acts as a coping response to reduce stress, and this is essentially the same contingency. A more recent formulation is that by Szechtman and Woody (2004) that OCD-like behavior arises as an aberrant excess of behavior motivated by the need for security. These theories are of obvious clinical interest and will ultimately depend on their validation by the importance assigned to anxiety in producing the persistent symptoms of OCD. A related concept is that of exaggerated habit-learning, where behavior is controlled by stimulus–response (S–R) links with a generally weakened influence of the ultimate goal. Recent evidence (e.g. Yin and Knowlton, 2006) strongly supports the hypothesis that habit-learning in the rat is mediated by specific sectors of the rat striatum (those probably homologous to the putamen). However, we have to consider what types of mechanism are brought into play to turn habits into compulsions (for a discussion of compulsive drug-taking, which may be governed by similar mechanisms, see Everitt and Robbins, 2005). Evidence also indicates that habit-learning in the striatum can be influenced by prefrontal cortical mechanisms (e.g. Killcross and Coutureau, 2003).

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

4.4.1. The stop-signal reaction time task (SSRT)

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

In terms of neural substrates, studies of human patients with frontal lobe damage have localised the critical zone for SSRT to the right inferior frontal gyrus (Aron et al., 2003a) and other data implicate the striatum in this inhibitory process (Aron et al., 2003c). It is intriguing that precisely the same structure is implicated in the EDS, according to a recent fMRI study (Hampshire and Owen, 2006). A method of measuring SSRT in rats has been developed which is dependent on possibly homologous structures in the lateral orbitofrontal cortex and medial striatum (Eagle and Robbins, 2003; Eagle et al., 2008).

Intriguingly, however, the SSRT is insensitive to serotoninergic manipulations in both rats (Eagle et al., unpublished data) and humans (Clark et al., 2005; Chamberlain et al., 2006b, 2007b).

5. Conclusions

We are thus intriguingly close to providing useful theoretically motivated models of OCD spectrum disorders, particularly with regard to repetitive motoric habits and inhibitory failures. Nonetheless, significant puzzles still remain (Table 1). For example, two of the most sensitive of the human tests used to highlight deficits in OCD (the stop-signal and ID/ED tests) appear to be more dependent on the integrity of the inferior frontal cortex rather than the orbitofrontal cortex (OFC). Moreover, OCD patients are not markedly impaired on simple reversal learning, which has been associated in animal studies with damage to the OFC (Boulougouris et al., 2007), and which is sensitive to 5-HT manipulations (Boulougouris et al., 2008). Neuroimaging versions of these tasks may yet identify subtle brain dysfunction in patients and unaffected relatives at risk of OC spectrum conditions, in the absence of overt behavioral deficits. OCD has received the most research attention to date; it would be of considerable interest to determine whether the more obvious motor manifestations of other conditions such as trichotillomania are associated with structural and/or functional impairments of similar cortico-striatal loops, possibly more at striatal than cortical nodes, or whether, as seems likely, these are associated with impairments in other fronto-striatal pathways, for example, related to the putamen and its role in the control of motor output.

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References

Abbruzzese, M., Bellodi, L., Ferri, S., Scarone, S., 1995. Frontal lobe dysfunction in schizophrenia and obsessive–compulsive disorder: a neuropsychological study. Brain and Cognition 27, 202–212.

Aldridge, J.W., Berridge, K.C., 1998. Coding of serial order by neostriatal neurons: a "natural action" approach to movement sequence. The Journal of Neuroscience 18, 2777–2787.

Altemus, M., Glowa, J.R., Galliven, E., Leong, Y.M., Murphy, D.L., 1996. Effects of serotonergic agents on food-restriction-induced hyperactivity. Pharmacology, Biochemistry and Behavior 53, 123–131.

Aron, A.R., Dowson, J.H., Sahakian, B.J., Robbins, T.W., 2003a. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 54, 1465–1468.

Aron, A.R., Fletcher, P.C., Bullmore, E.T., Sahakian, B.J., Robbins, T.W., 2003b. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nature Neuroscience 6, 115–116.

Aron, A.R., Watkins, L., Sahakian, B.J., Monsell, S., Barker, R.A., Robbins, T.W., 2003c. Task-set switching deficits in early-stage Huntington's disease: implications for basal ganglia function. Journal of Cognitive Neuroscience 15, 629–642.

Bannon, S., Gonsalvez, C.J., Croft, R.J., Boyce, P.M., 2002. Response inhibition deficits in obsessive–compulsive disorder. Psychiatry Research 110, 165–174.

Baxter, L., 1999. Functional imaging of brain systems mediating obsessive–compulsive disorder. In: Charney, D.S., Nestler, E.J., Bunney, B.S. (Eds.), Neurobiology of Mental Illness. Oxford University Press, USA, pp. 534–547.

Berridge, K.C., Aldridge, J.W., Houchard, K.R., Zhuang, X., 2005. Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. BMC Biology 3, 4.

Birrell, J.M., Brown, V.J., 2000. Medial frontal cortex mediates perceptual attentional set-shifting in the rat. Journal of Neuroscience 20, 4320–4324.

Black, D.W., Monahan, P., Gable, J., Blum, N., Clancy, G., Baker, P., 1998. Hoarding and treatment response in 38 non-depressed subjects with obsessive–compulsive disorder. Journal of Clinical Psychiatry 59, 420–425.

Boulougouris, V., Dalley, J.W., Robbins, T.W., 2007. Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. Behavioural Brain Research 179, 219–228.

Boulougouris, V., Glennon, J.C., Robbins, T.W., 2008. Dissociable effects of selective 5-HT (2A) and 5-HT(2C) receptor antagonists on serial spatial reversal learning in rats. Neuropsychopharmacology 33, 2007–2019.

Brown, S.A., Crowell-Davis, S., Malcolm, T., Edwards, P., 1987. Naloxone-responsive compulsive tail chasing in a dog. Journal of the American Veterinary Medical Association 190, 884–886.

Campbell, K.M., McGrath, M.J., Burton, F.H., 1999a. Behavioral effects of cocaine on a transgenic mouse model of cortical-limbic compulsion. Brain Research 833, 216–224.

Campbell, K.M., McGrath, M.J., Burton, F.H., 1999b. Differential response of cortical-limbic neuropotentiated compulsive mice to dopamine D1 and D2 receptor antagonists. European Journal of Pharmacolology 371, 103–111.

Campbell, K.M., de Lecea, L., Severynse, D.M., Caron, M.G., McGrath, M.J., Sparber, S.B., Sun, L.Y., Burton, F.H., 1999c. OCD-Like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1+ neurons. The Journal of Neuroscience 19, 5044–5053.

Cavallini, M.C., Di Bella, D., Siliprandi, F., Malchiodi, F., Bellodi, L., 2002. Exploratory factor analysis of obsessive–compulsive patients and association with 5-HTTLPR polymorphism. American Journal of Medical Genetics 114, 347-335.

Cavedini, P., Ferri, S., Scarone, S., Bellodi, L., 1998. Frontal lobe dysfunction in obsessive–compulsive disorder and major depression: a clinical–neuropsychological study. Psychiatry Research 78, 21–28.

Chamberlain, S.R., Blackwell, A.D., Fineberg, N.A., Robbins, T.W., Sahakian, B.J., 2005. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neuroscience and Biobehavioral Reviews 29, 399–419.

Chamberlain, S.R., Fineberg, N.A., Blackwell, A.D., Robbins, T.W., Sahakian, B.J., 2006a. Motor inhibition and cognitive flexibility in obsessive–compulsive disorder and trichotillomania. The American Journal of Psychiatry 163, 1282–1284.

Chamberlain, S.R., Muller, U., Blackwell, A.D., Clark, L., Robbins, T.W., Sahakian, B.J., 2006b. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 311, 861–863.

Chamberlain, S.R., Fineberg, N.A., Menzies, L.A., Blackwell, A.D., Bullmore, E.T., Robbins, T.W., Sahakian, B.J., 2007a. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive–compulsive disorder. The American Journal of Psychiatry 164, 335–338.

Chamberlain, S.R., Müller, U., Deakin, J.B., Corlett, P.R., Dowson, J., Cardinal, R.N., Aitken, M.R., Robbins, T.W., Sahakian, B.J., 2007b. Lack of deleterious effects of buspirone on cognition in healthy male volunteers. Journal of Psychopharmacology 21, 210–215.

Choi, J.S., Kim, S.H., Yoo, S.Y., Kang, D.H., Kim, C.W., Lee, J.M., Kim, I.Y., Kim, S.I., Kim, Y.Y., Kwon, J.S., 2007. Shape deformity of the corpus striatum in obsessive–compulsive disorder. Psychiatry Research: Neuroimaging 155, 257–264.

Chou-Green, J.M., Holscher, T.D., Dallman, M.F., Akana, S.F., 2003. Compulsive behavior in the 5-HT2C receptor knockout mouse. Physiology & Behavior 785, 641–649.

Chudasama, Y., Robbins, T.W., 2003. Dissociable contribution of the orbitofrontal and infralimbic cortex to pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. Journal of Neuroscience 23, 8771–8780.

Chudasama, Y., Passetti, F., Rhodes, S.E., Lopian, D., Desai, A., Robbins, T.W., 2003. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. Behavioural Brain Research 146, 105–119.

Clark, L., Roiser, J.P., Cools, R., Rubinsztein, D.C., Sahakian, B.J., Robbins, T.W., 2005. Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology 182, 570–578.

Clarke, H.F., Dalley, J.W., Crofts, H.S., Robbins, T.W., Roberts, A.C., 2004. Cognitive inflexibility after prefrontal serotonin depletion. Science 304, 878–880.

Clarke, H.F., Walker, S.C., Crofts, H.S., Dalley, J.W., Robbins, T.W., Roberts, A.C., 2005. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. The Journal of Neuroscience 25, 532–538.

Clarke, H.F., Walker, S.C., Dalley, J.W., Robbins, T.W., Roberts, A.C., 2007. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cerebral Cortex 17, 18–27.

Creese, I., Iversen, S.D., 1975. The pharmacological and anatomical substrates of the amphetamine response in the rat. Brain Research 83, 419–436.

Eagle, D.M., Robbins, T.W., 2003. Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and D-amphetamine. Behavioral Neuroscience 117, 1302–1317.

Eagle, D.M., Baunez, C., Hutcheson, D.M., Lehmann, O., Shah, A.P., Robbins, T.W., 2008. Stop-signal reaction time task performance: role of prefrontal cortex and subthalamic nucleus. Cerebral Cortex 18, 178–188.

Enright, S.J., Beech, A.R., 1993. Reduced cognitive inhibition in obsessive–compulsive disorder. British Journal of Clinical Psychology 32, 67–74.

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience 8, 1481–1489.

Fineberg, N.A., Gale, T.M., 2005. Evidence-based pharmacotherapy of obsessive–compulsive disorder. The International Journal of Neuropsychopharmacology 8, 107–129.

Garner, J.P., Dufour, B., Gregg, L.E., Weisker, S.M., Mench, J.A., 2004. Social and husbandry factors affecting the prevalence and severity of barbering ('whisker trimming') by laboratory mice. Applied Animal Behaviour Science 89, 263–282.

Geyer, M.A., Markou, A., 1995. Animal models of psychiatric disorders. In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: the Fourth Generation of Progress. Raven Press, Ltd, New York, pp. 787–798.

Geyer, M.A., Markou, A., 2002. The role of preclinical models in the development of psychotropic drugs. In: Davis, K.L., Coyle, J.T., Nemeroff, C. (Eds.), Psychopharmacology: the Fifth Generation of Progress. Lippincott Williams & Wilkins, Philadelphia, pp. 445–455.

Gray, J.A., 2000. The Neuropsychology of Anxiety. Oxford University Press, New York.

Graybiel, A.M., Rauch, S.L., 2000. Toward a neurobiology of obsessive–compulsive disorder. Neuron 28, 343–347.

Greer, J.M., Cappechi, M.R., 2002. Hoxb8 is required for normal grooming behaviour in mice. Neuron 33, 23–34.

Grindlinger, H.M., Ramsay, E., 1991. Compulsive feather picking in birds. Archives of General Psychiatry 48, 857.

Hampshire, A., Owen, A.M., 2006. Fractionating attentional control using event-related fMRI. Cerebral Cortex 16, 1679–1689.

Hollander, E., Rosen, J., 2000. Impulsivity. Journal of Psychopharmacology 14, S39–S44.

Hoshino, K., Uga, D.A., de Paula, H.M., 2004. The compulsive-like aspect of the head dipping emission in rats with chronic electrolytic lesion in the area of the medial raphé nucleus. Brazilian Journal of Medical and Biological Research 37, 245–250.

Ichimaru, Y., Egawa, T., Sawa, A., 1995. 5-HT1A-receptor subtype mediates the effect of fluvoxamine, a selective serotonin reuptake inhibitor, on marble-burying behavior in mice. Journal of Pharmacology 68, 65–70.

Insel, T.R., Hamilton, J.A., Guttmacher, L.B., Murphy, D.L., 1983. D-amphetamine in obsessive–compulsive disorder. Psychopharmacology 80, 231–235.

Joel, D., Avisar, A., 2001. Excessive lever pressing following post-training signal attenuation in rats: a possible animal model of obsessive compulsive disorder? Behavioural Brain Research 123, 77–87.

Joel, D., Ben-Amir, E., Doljansky, J., Flaisher, S., 2004. 'Compulsive' lever-pressing in rats is attenuated by the serotonin re-uptake inhibitors paroxetine and fluvoxamine but not by the tricyclic antidepressant desipramine or the anxiolytic diazepam. Behavioural Pharmacology 15, 241–252.

Killcross, S., Coutureau, E., 2003. Coordination of actions and habits in the medial prefrontal cortex of rats. Cerebral Cortex 13, 400–408.

Leckman, J.F., Grice, D.E., Boardman, J., Zhang, H., Vitale, A., Bondi, C., Alsobrook, J., Peterson, B.S., Cohen, D.J., Rasmussen, S.A., Goodman, W.K., McDougle, C.J., Pauls, D.L., 1997. Symptoms of obsessive–compulsive disorder. American Journal of Psychiatry 154, 911–917.

Leckman, J.F., Pauls, D.L., Zhang, H., Rosario-Campos, M.C., Katsovich, L., Kidd, K.K., Pakstis, A.J., Alsobrook, J.P., Robertson, M.M., McMahon, W.M., Walkup, J.T., van de Wetering, B.J., King, R.A., Cohen, D.J., and the Tourette Syndrome Association International Consortium for Genetics, 2003. Obsessive–compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. American Journal of Medical Genetics 116B, 60–68.

Logan, G., Cowan, W., 1984. On the ability to inhibit thought, and action: a theory of an act of control. Psychological Review 91, 295–327.

Luescher, U.A., McKeown, D.B., Dean, H., 1998. A cross-sectional study on compulsive behaviour (stable vices) in horses. Equine Veterinary Journal Supplement 27, 14–18.

Lyon, M., Robbins, T.W., 1975. The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In: Essman, W., Valzelli, L. (Eds.), Current Developments in Psychopharmacology, vol. 4. Spectrum, New York, pp. 79–163.

Mataix-Cols, D., Rauch, S.L., Manzo, P.A., Jenike, M.A., Baer, L., 1999. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive–compulsive disorder. American Journal of Psychiatry 156, 1409–1416.

Mataix-Cols, D., Marks, I.M., Greist, J.H., Kobak, K.A., Baer, L., 2002. Obsessive–compulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: results from a controlled trial. Psychotherapy and Psychosomatics 71, 255–262.

Matthysse, S., 1986. Animal models in psychiatric research. Progress in Brain Research 65, 259–270.

McGrath, M.J., Campbell, K.M., Veldman, M.B., Burton, F.H., 1999. Anxiety in transgenic mouse model of cortical-limbic neuro-potentiated compulsive behaviour. Behavioural Pharmacology 10, 435–443.

McKinney, W.T., Bunney, W.E., 1969. Animal model of depression: a review of evidence: implications for research. Archives of General Psychiatry 21, 240–248.

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., Bullmore, E.T., 2008. Integrating evidence from neuroimaging and neuropsychological studies of Obsessive–compulsive disorder: the orbitofronto-striatal model revisited. Neuroscience and Biobehavioral Reviews 32, 525–549.

Mowrer, O.H., 1960. Learning Theory and Behavior. Wiley, New York.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., Kawamoto, M., 2005. A functional MRI comparison of patients with obsessive–compulsive disorder and normal controls during a Chinese character Stroop task. Psychiatry Research 139, 101–114.

Nurnberg, H.G., Keith, S.J., Paxton, D.M., 1997. Consideration of the relevance of ethological animal models for human repetitive behavioral spectrum disorders. Biological Psychiatry 411, 226–229.

Rachman, S.J., Hodgson, R.J., 1980. Obsessions and Compulsions. Prentice-Hall, Englewood Cliffs, NJ.

Rapoport, J.L., Ryland, D.H., Kriete, M., 1992. Drug treatment of canine acral lick. An animal model of obsessive–compulsive disorder. Archives of General Psychiatry 49, 517–521.

Rescorla, R.A., 2001. Experimental extinction. In: Mowrer, R.R., Klein, S. (Eds.), Handbook of Contemporary Learning Theories. Hillsdale, Erlbaum, NJ, pp. 119–154.

Robbins, T.W., 2005. Chemistry of the mind: neurochemical modulation of prefrontal cortical function. The Journal of Comparative Neurology 493, 140–146.

Robbins, T.W., Koob, G.F., 1980. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285, 409–412.

Robbins, T.W., Sahakian, B.J., 1983. Behavioural effects of psychomotor stimulant drugs: clinical and neuropsychological implications. In: Creese, I. (Ed.), Stimulants, Neurochemical, Behavioral and Clinical Perspectives. Raven Press, New York, pp. 301–338.

Rosenberg, D.R., Dick, E.L., O'Hearn, K.M., Sweeney, J.A., 1997. Response-inhibition deficits in obsessive–compulsive disorder: an indicator of dysfunction in frontostriatal circuits. Journal of Psychiatry and Neuroscience 22, 29–38.

Sahakian, B.J., Robbins, T.W., 1975. The effects of test environment and rearing condition on amphetamine-induced stereotypy in the guinea-pig. Psychopharmacologia 45, S115–S117.

Samuels, J., Bienvenu, O.J., Riddle, M.A., Cullen, B.A., Grados, M.A., Liang, K.Y., Hoehn-Saric, K., Nestadt, G., 2002. Hoarding in obsessive–compulsive disorder: results from a case–control study. Behaviour Research and Therapy 40, 517–528.

Segal, D.S., Geyer, M.A., 1985. Animal models of psychopathology. In: Judd, L.L., Groves, P.M. (Eds.), Psychobiological Foundations of Clinical Psychiatry. J.B. Lippincott, Philadelphia. Chap.45.

Stein, D.J., Hollander, E., 1995. Obsessive–compulsive spectrum disorders. The Journal of Clinical Psychiatry 56, 265–266.

Stein, D.J., Dodman, N.H., Borchelt, P., Hollander, E., 1994. Behavioral disorders in veterinary practice: relevance to psychiatry. Comprehensive Psychiatry 35, 275–285.

Summerfeldt, L.J., Richter, M.A., Antony, M.M., Swinson, R.P., 1999. Symptom structure in obsessive–compulsive disorder: a confirmatory factor-analytic study. Behaviour Research and Therapy 37, 297–311.

Swanepoel, N., Lee, E., Stein, D.J., 1998. Psychogenic alopecia in a cat: response to clomipramine. Journal of the South African Veterinary Association 69, 22.

Swedo, S.E., Leonard, H.L., Rapoport, J.L., Lenane, M.C., Goldberger, E.L., Cheslow, D.L., 1989. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). The New England Journal of Medicine 321, 497–501.

Szechtman, H., Woody, E., 2004. Obsessive–compulsive disorder as a disturbance of security motivation. Psychological Review 111, 111–127.

Szechtman, H., Sulis, W., Eilam, D., 1998. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive–compulsive disorder (OCD). Behavioral Neuroscience 112, 1475–1485.

Tien, A.Y., Pearlson, G.D., Machlin, S.R., Bylsma, F.W., Hoehn-Saric, R., 1992. Oculomotor performance in obsessive–compulsive disorder. American Journal of Psychiatry 149, 641–646.

Tsaltas, E., Kontis, D., Chrysikakou, S., Giannou, H., Biba, A., Pallidi, S., Christodoulou, A., Maillis, A., Rabavilas, A., 2005. Reinforced spatial alternation as an animal model of obsessive–compulsive disorder (OCD): investigation of 5-HT2C and 5-HT1D receptor involvement in OCD pathophysiology. Biological Psychiatry 57, 1176–1185.

Whiteside, S.P., Port, J.D., Deacon, B.J., Abramowitz, J.S., 2006. A magnetic resonance spectroscopy investigation of obsessive–compulsive disorder and anxiety. Psychiatry Research 146, 137–147.

Willner, P., 1984. The validity of animal models of depression. Psychopharmacology 83, 1–16 (Berl).

Willner, P., 1991. Behavioural models in psychopharmacology. In: Willner, P. (Ed.), Behavioural Models in Psychopharmacology: Theoretical, Industrial and Clinical Perspectives. Cambridge University Press, Cambridge, pp. 3–18.

Winsberg, M.E., Cassic, K.S., Koran, L.M., 1999. Hoarding in obsessive–compulsive disorder: a report of 20 cases. Journal of Clinical Psychiatry 60, 591–597.

Winslow, J.T., Insel, T.R., 1991. Neuroethological models of obsessive–compulsive disorder. In: Zohar, J., Insel, T., Rasmussen, S. (Eds.), The Psychobiology of Obsessive–Compulsive Disorder. Springer Publishing Company, New York, pp. 208–226.

Woods, A., Smith, C., Szewczak, M., Dunn, R.W., Cornfeldt, M., Corbett, R., 1993. Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. Psychopharmacology 112, 195–198.

Yadin, E., Friedman, E., Bridger, W.H., 1992. Spontaneous alternation behavior: an animal model for obsessive–compulsive disorder? Pharmacology Biochemistry and Behavior 40, 311–315.

Yin, H.H., Knowlton, B.J., 2006. The role of the basal ganglia in habit formation. Nature Reviews Neuroscience 7, 464–476.