BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01422.x
www.brjpharmacol.org

Themed Issue: Translational Neuropharmacology – Using Appropriate Animal Models to Guide Clinical Drug Development

REVIEW

Translational approaches to obsessive-compulsive disorder: from animal models to clinical treatment

NA Fineberg[1,2,3], SR Chamberlain[3,5], E Hollander[6], V Boulougouris[7] and TW Robbins[4,5]

[1]*National OCDs Treatment Service, Hertfordshire Partnership NHS Foundation Trust, Welwyn Garden City,* [2]*University of Hertfordshire, College Lane, Hatfield, Herts.* [3]*Cambridge University School of Clinical Medicine, Addenbrooke's Hospital, Cambridge,* [4]*Department of Experimental Psychology, University of Cambridge, Cambridge,* [5]*Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK,* [6]*Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA, and* [7]*Experimental Psychology Laboratory, Department of Psychiatry, Eginition Hospital, Athens University Medical School, Athens, Greece*

Correspondence
Professor Naomi Fineberg, National OCDs Treatment Service, Hertfordshire Partnership NHS Foundation Trust, Welwyn Garden City AL7 4HQ, UK.
E-mail: srchamb@gmail.com

Keywords
OCD; impulsivity; compulsivity; translational; inhibition; flexibility; serotonin; dopamine

Received
30 October 2010
Revised
20 February 2011
Accepted
28 March 2011

Obsessive-compulsive disorder (OCD) is characterized by obsessions (intrusive thoughts) and compulsions (repetitive ritualistic behaviours) leading to functional impairment. Accumulating evidence links these conditions with underlying dysregulation of fronto-striatal circuitry and monoamine systems. These abnormalities represent key targets for existing and novel treatment interventions. However, the brain bases of these conditions and treatment mechanisms are still not fully elucidated. Animal models simulating the behavioural and clinical manifestations of the disorder show great potential for augmenting our understanding of the pathophysiology and treatment of OCD. This paper provides an overview of what is known about OCD from several perspectives. We begin by describing the clinical features of OCD and the 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) neurobehavioural models. We also discuss their advantages and shortcomings in relation to their capacity to identify potentially efficacious new compounds. It is of interest that there has been rather little evidence of 'false alarms' for therapeutic drug effects in OCD models which actually fail in the clinic. While it is more difficult to model obsessive cognition than compulsive behaviour in experimental animals, it is feasible to infer cognitive inflexibility in certain animal paradigms. Finally, key future neurobiological and treatment research areas are highlighted.

LINKED ARTICLES

This article is part of a themed issue on Translational Neuropharmacology. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2011.164.issue-4

Abbreviations

5CSRTT, 5-choice serial reaction time test; 5-HT, serotonin; APA, American Psychiatric Association; BOLD, blood oxygen level-dependent; CS, conditioned stimulus; DBS, deep brain stimulation; DSM, Diagnostic and Statistical Manual; ELP, excessive lever presses; (f)MRI, (functional) magnetic resonance imaging; ID-ED, intra-dimensional – extra-dimensional; mCPP, meta-chlorophenylpiperazine; NMDA, N methyl-d aspartic acid; O-C, Obsessive-compulsive; OCD, Obsessive-Compulsive Disorder; OCSDs, Obsessive-Compulsive Spectrum Disorders; OFC, Orbitofrontal Cortex; SR, stimulus-response; SSRIs, selective serotonin reuptake inhibitors; SSRT, stop-signal reaction time

Introduction

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder, affecting roughly 2% of the adult population worldwide (Zohar, 1999), and responsible for considerable psychosocial morbidity (Bolton *et al.*, 1995; Hanna, 1995; Hollander *et al.*, 2010). The illness is characterized by obsessions (recurrent unpleasant thoughts) and/or compulsions (repetitive unwanted behaviours that the individual is unable to resist) (APA, 2000). Obsessions and compulsions are experienced as unpleasantly insistent and intrusive. OCD patients usually report a wide range of obsessive-compulsive (O-C) symptoms in a number of overlapping behavioural domains, some of which naturally cluster together, which may also vary over time (Mataix-Cols *et al.*, 2005; Katerberg *et al.*, 2010). The disorder usually emerges in childhood or early adulthood (earlier in males) and runs a lifelong, fluctuating course (Skoog and Skoog, 1999). Existing treatment with drugs and cognitive behavioural forms of psychotherapy are usually only partially effective and roughly one third of cases do not achieve an adequate clinical response (Fineberg and Gale, 2005).

OCD is commonly complicated by the co-occurrence of other 'comorbid' mental disorders, notably depression which supervenes in up to two-thirds of clinical cases (Fineberg *et al.*, 2005a; Peris *et al.*, 2010). Other disorders that are characterized by O-C behaviours, such as O-C personality disorder, body dysmorphic disorder, trichotillomania (repetitive hair-pulling) and Tourette's Syndrome (Hollander, 2008; Hollander *et al.*, 2010; Phillips *et al.*, 2010) also tend to cluster with OCD, occurring either within the same individual or within close family members and implying the possibility of shared pathophysiological mechanisms. Indeed, this so-called 'obsessive-compulsive spectrum disorders (OCSDs)' is characterized by considerable phenotypic heterogeneity and overlap. Moreover, there is evidence of overlap in the treatment-response across some disorders. Thus, the complexity and clinical morbidity associated with OCD is high (Phillips *et al.*, 2010) and new and better treatments are sorely needed.

Multiple layers of evidence link OCD with dysregulation of fronto-striatal neuro-circuitry and associated monoamine systems. However, attribution of cause and effect may easily be confounded by the multiplicity of associated symptom domains that occur within such a complex mental disorder. Translational research investigates underlying mechanisms, and may therefore be more able to pinpoint neural contributions driving *specific aspects* of mental disorders. Convergent evidence from translational studies, largely in human subjects, suggests that a tendency towards behavioural disinhibition (Chamberlain *et al.*, 2005), presumably resulting from failures in 'top–down' cortical control of fronto-striatal neural circuits, or alternatively from over-activity within striatal 'habit' circuitry, may underpin aspects of behavioural compulsivity that are found in OCD and related disorders (Fineberg *et al.*, 2010; Padhi *et al.*, 2010). These abnormalities represent key targets for existing and novel treatment interventions.

As our understanding of the behavioural, cognitive, neural and genetic substrates of OCD and related OCSDs advances, the search and evaluation of appropriate animal models that can be used to test out the efficacy of potential new treatments and their mechanisms of action in early-phase studies becomes increasingly relevant. To date, no universally accepted animal model for OCD exists. However, models of repetitive habits and inhibitory control problems represent possible equivalents of aspects of compulsive behaviour in OCD patients, and may offer potential for enhancing our understanding of the pathophysiology and treatment of OCD and spectrum disorders. Such models need to be validated, in terms of being seen to accurately represent the human condition, and to have the capability to be reliably generated. This review aims critically to evaluate existing animal models of relevance for OCD and related disorders against these criteria. Several studies have provided important information regarding the neural and neurochemical substrates of OCD that could be used to endorse any such model. In addition, the availability of somewhat effective pharmacological treatments, such as clomipramine and the selective serotonin reuptake inhibitors (SSRIs) (Fineberg and Gale, 2005), provides an ancillary criterion for model validation, although their precise mode of action in OCD remains incompletely characterized. In this paper, we focus on (i) ethological models; (ii) genetic and pharmacological models; and (iii) neurobehavioural models. We discuss their advantages and shortcomings with examples of compounds that are of clinical benefit. It is of interest that there has been rather little evidence of 'false alarms' for therapeutic drug effects in OCD models which actually fail in the clinic. Those cases that have arisen may result from an incomplete pharmacological characterization of the model.

Validation criteria for animal models

No single animal model can account for the entire psychiatric syndrome it purports to represent. Therefore, the validation criteria that each model is expected to fulfil in order to demonstrate its validity are, for practical purposes, largely determined by the objective of the model and its intended use (McKinney and Bunney, 1969; Matthysse, 1986; Willner, 1991; Geyer and Markou, 1995; Mckinney, 2000; Geyer and Markou, 2002). According to the well-known classification by Willner 1984), refined by Geyer and Markou (Geyer and Markou, 1995, Geyer and Markou, 2002), the criteria for assessing animal models are grouped into those used to establish *face validity* (phenomenological similarity between inducing conditions and specific symptoms of the human phenomenon), *predictive validity* (the extent to which an animal model allows accurate predictions about the human phenomenon based on the performance of the model, for example, similarity in response to pharmacological or behavioural treatment) and *construct validity* (similarity in underlying physiological or psychological mechanisms). *Reliability*, on the other hand, requires that the behavioural outputs of the model are robust and reproducible between laboratories. Geyer and Markou recommend that the evaluation of animal models in neurobiological research should principally rely on reliability and predictive validity, with face and construct validity, which tend to be, respectively, highly subjective or dependent upon assumptions and inferences, reserved as secondary criteria. Thus, in order to have the capacity to predict the response of a mental disorder such as OCD to a new pharmacological treatment, a proposed animal model needs to produce a specific, measurable behaviour reliably, which is

pharmacologically analogous with the clinical disorder. On the other hand, predictive validity can be unduly restrictive and lead to the generation of 'me-too' compounds (as is the case for antidepressants) as opposed to the enhanced understanding and capacity for innovation which can be attained via construct validity.

Clinical profile of OCD

The hallmark symptoms of OCD involve the unwanted and needless repetition of thoughts and actions. Based on factor analysis, OCD symptoms have been split into four phenotypic categories (Leckman *et al.*, 1997; Summerfeldt *et al.*, 1999; Cavallini *et al.*, 2002): (i) aggressive sexual and religious obsessions with checking compulsions; (ii) symmetry obsessions with compulsions of classification, sorting and repetitiveness; (iii) obsessions of contamination with cleaning compulsions; and (iv) hoarding. Many of these symptoms resemble normal childhood behaviour that disappears during development. Such behaviour appears habit-driven and may be evolutionarily conserved, inasmuch as it is expressed across species (e.g. hoarding, grooming, sorting) and may also fulfil an adaptive role under conditions of privation (Leckman *et al.*, 2010). The maturation of the prefrontal cortex and its subcortical connections may result in the natural suppression of these habitual acts, in favour of more adaptive, goal-directed behaviours (Gillan *et al.*, 2010), and thus, by inference, OCD may arise at least in part as a result of a relative failure of this 'top-down' suppression. There is some evidence that in OCD patients, these symptom clusters differ in terms of constituent temporal and spatial dimensions of the behaviour (Zor *et al.*, 2010), treatment response (Black *et al.*, 1998; Mataix-Cols *et al.*, 1999; Winsberg *et al.*, 1999, Mataix-Cols *et al.*, 2002), co-morbidity with other psychiatric disorders (Samuels *et al.*, 2002), imaging profile (Mataix-Cols *et al.*, 2004; van den Heuvel *et al.*, 2005) and genetic predisposition (Leckman *et al.*, 2003; 2010; Katerberg *et al.*, 2010). Thus, in OCD, the heterogeneity of observed symptomatology may be underpinned by subtly differing pathophysiological mechanisms.

Traditional learning theory applied to OCD proposes that an increase in *anxiety* occurs when an obsessive thought (e.g. of committing an aggressive act) is experienced and that this anxiety subsequently drives the urge to perform a neutralizing ritual (e.g. checking for harm) that has a negatively reinforcing effect, leading to a vicious cycle of obsession and compulsion (Drummond and Fineberg, 2007). In line with this theory, OCD has been categorized as an Anxiety Disorder in the major diagnostic classificatory systems such as the *Diagnostic and Statistical Manual IV* (APA, 2000), implying a key role for anxiety dysregulation in its aetiology. However, the role of anxiety in the pathophysiology of OCD has always been controversial, and its nosological status is currently under review (Hollander, 2008; Hollander *et al.*, 2008; Phillips *et al.*, 2010). Whereas OCD symptoms do generally appear to worsen under psychosocial stress, the expression of psychological and physical anxiety symptoms as part and parcel of the syndrome is unreliable and emotions other than anxiety, such as horror or disgust, may be more prominent (Sprengelmeyer *et al.*, 1997). Depressive symptoms are also common in OCD. The depressive syndrome is associated with relatively increased worry and rumination and less vegetative disturbance compared with major depressive disorder (Fineberg *et al.*, 2005a). Moreover, the depressive symptoms respond to pharmacological treatment in tandem with the OCD (Hoehn-Saric *et al.*, 2000), suggesting that they are integral to this disorder.

Individuals with OCD also commonly present with movement disorders, most notably tics, that can vary in severity from the relatively rare, explosive actions associated with Tourette's syndrome to commoner mild, barely perceptible facial twitches that are focused around the eyes, nose and mouth and that appear similar to 'neurological soft signs' (Hranov and Fineberg, 2010). The presence of co-morbid tics in children and adolescents with OCD predicts a positive outcome in adulthood, whereas primary hoarding symptoms are associated with persistent OCD (Bloch *et al.*, 2009). Indeed, the OCSDs may, to a greater or lesser extent, represent 'formes-frustes' of OCD. Of these disorders, body dysmorphic disorder (BDD), most closely resembles OCD symptomatically (Phillips *et al.*, 2010). In BDD, an obsessional preoccupation with irregularities of bodily appearance leads to compulsive checking and remediative acts. In contrast, in trichotillomania, rumination is less prominent and the repetitive hair-pulling may produce positively reinforcing, soothing effects (Chamberlain *et al.*, 2007c; 2009).

Neurobiological substrates of OCD

The essential features of OCD and related spectrum disorders most readily captured by animal models are the maladaptive and perseverative behavioural and cognitive outputs (Boulougouris *et al.*, 2009). For example, the repetitive rituals in OCD, or recurrent hair-pulling in trichotillomania. These behaviours are thought to be mediated by dysfunctional nodes within the fronto-striatal circuitry, possibly mediated by glutamate neurotransmission, under modulation by altered dopaminergic or serotoninergic influences. In OCD, neuroimaging studies have implicated in particular the orbitofrontal cortex (OFC) and the caudate nucleus, and cingulotomy has had a limited therapeutic success (Baxter, 1999). Moreover, there may be grounds for considering OCD spectrum disorders as reflecting impaired functioning of several distinct fronto-striatal 'loops' (Graybiel, 1997; Jog *et al.*, 1999; Graybiel and Rauch, 2000; Chamberlain *et al.*, 2005; Nakao *et al.*, 2005; Whiteside *et al.*, 2006; Menzies *et al.*, 2008).

Pharmacological profile of OCD

OCD responds to a characteristically narrow range of pharmacological treatments. According to a considerable body of evidence from randomized controlled clinical trials, drugs with potent inhibitory effects on the synaptic reuptake of serotonin, such as the non-selective tricyclic clomipramine and the more highly selective serotonin reuptake inhibitors (SSRIs), are reasonably effective in approximately two thirds of cases. The treatment effect develops slowly and gradually over weeks and months, and higher SSRI doses, and extended treatment duration appear to produce greater effect sizes (Fineberg and Gale, 2005). Importantly, treatments found to

be effective in other anxiety and affective disorders, such as antidepressants that act via noradrenergic mechanisms, benzodiazepines and mood stabilizers are not effective in OCD. There is very little evidence-based treatment available for SSRI-resistant illness. Positive results from a small number of randomized controlled trials show limited extra benefit from adjunctive first and second generation antipsychotics taken in low or modest doses (Fineberg *et al.*, 2005b; 2006a), and lesser evidence from a randomized trial (Ninan *et al.*, 2006) supports increasing the dose of SSRI above formulary limits (Fineberg *et al.*, 2006b; Pampaloni *et al.*, 2010). Tic-related OCD may respond less well to SSRI monotherapy and preferentially to adjunctive antipsychotic (Fineberg *et al.*, 2006c). Antipsychotics represent first-line treatment for Tourette's Syndrome and it is therefore, interesting that their combination with SSRIs shows greater efficacy in tic-related OCD (Bloch *et al.*, 2006). Compulsions associated with autistic disorders may also respond to low-dose SSRI and to antipsychotics (Kolevzon *et al.*, 2006). Trichotillomania may respond to SRIs and to antipsychotics, though confirmation in well-powered controlled studies is required (Chamberlain *et al.*, 2007c). Trichotillomania has also been shown to respond to treatment with the glutamate modulator N-acetyl cysteine in a randomized placebo-controlled trial (Grant *et al.*, 2009). Promising results from experimental open-label treatment of small numbers of OCD cases with alternative adjunctive glutamatergic compounds, such as riluzole and memantine, remain to be validated in controlled clinical trials.

The pharmacological mechanisms underpinning the anti-obsessional treatment response remain poorly understood. The superior efficacy of SSRI in doses higher than those needed to completely inhibit the serotonin transporter suggest that other receptor mechanisms in addition to increased intrasynaptic serotonin concentrations may be relevant. The extended development of the treatment effect implies the recruitment of adaptive processes such as neurotransmitter receptor modulation, perhaps focussed at neurones within relevant neuro-circuitry such as the OFC and/or caudate nucleus, that may take days or weeks to develop (Blier and de Montigny, 1998). Evidence from pharmacological challenge studies in which the non-selective serotonin receptor agonist m-chlorophenylpiperazine (mCPP) induced OCD symptoms that were blocked by pre-treatment with clomipramine or SSRI (Zohar *et al.*, 1988; Hollander *et al.*, 1991), implicate serotonin receptors in the pathophysiology and the treatment response. There is evidence from ligand-based positron emission tomography studies of striatal and cortical alterations in 5-HT2A receptors and in striatal D2 receptors in OCD (Denys *et al.*, 2004b; Westenberg *et al.*, 2007). Interactions between serotonin and dopamine systems have also been inferred. In rats, co-administration of quetiapine with fluvoxamine, a combination with established efficacy in OCD (Fineberg *et al.*, 2006c), robustly increased dopamine release in the prefrontal cortex (Denys *et al.*, 2004a) and this effect has been suggested to play a possible role in the treatment response.

Lucey *et al.* (1993) suggested the involvement of the cholinergic system in OCD; compared with normal subjects, OCD patients exhibited an increased growth hormone response after pyridostigmine administration, providing evidence of cholinergic hypersensitivity (Lucey *et al.*, 1993). Glutamate has also been implicated in OCD symptomatology; administration of substances that act upon glutaminergic receptors caused exacerbation of compulsive behaviour in a genetic model of OCD and Tourette syndrome (Mcgrath *et al.*, 2000). Moreover, there have been attempts to treat OCD using D-cycloserine, which is active at the glycine site of the NMDA receptor. In addition, during the last years neuropeptides and gene steroids have been implicated in OCD pathophysiology (Lochner *et al.*, 2004a,b). It should nevertheless be noted that, although all these data are limited, they do not contradict the prevailing theory of OCD pathogenesis as resulting from a dysmodulation of orbitofrontal-striatal circuitry via serotoninergic and dopaminergic mechanisms.

Validating animal models for OCD

Animal models of OCD spectrum disorders have generally fulfilled the criteria of face validity, but have sometimes been based on psychological theorizing, thus attempting the deeper level of modelling 'construct validity'. In a seminal experiment, Solomon *et al.* (1953) paired electric shocks with a light to condition dogs to become anxious and escape when the light bulb was switched on (Solomon *et al.*, 1953). This escape behaviour was conceptualized as being close to a compulsive ritual in that it led to immediate relief. By preventing escape ('response prevention') when the light bulb was turned on, Solomon subsequently induced extinction of the conditioned anxiety and of the compulsive urge to escape. In translating aspects of this model to the human condition, early behaviourists such as Meyer (1966) developed exposure and response prevention as an effective form of psychotherapy for OCD (Meyer, 1966). In this approach, Meyer (1966) exposed patients to anxiety-evoking stimuli and constant staff supervision to prevent compulsions. Predictive validity can also be employed to some extent in OCD models, given the known, but largely unexplained, efficacy of the SSRIs and other less widely evaluated candidate treatments such as D1 receptor antagonists and specific 5-HT receptor agents.

Animal models of OCD

Existing animal models for OCD may be grouped into naturally occurring ethological models and laboratory-based genetic, pharmacological and neurobehavioural models.

Ethological models (Table 1)

Ethological models focus on spontaneous persistent behaviours that resemble OCD or more likely trichotillomania. They represent a source of naturalistic stereotypies that may be informative about OCD spectrum disorders (Stein *et al.*, 1994). In general, they have good face validity (in being repetitive and superficially resembling common human compulsions) and some show predictive validity in terms of their response to drug treatment, but low practicality and reliability. Such behaviours are often elicited in veterinary contexts and may be attributed to stressful environments, for example, psychogenic alopecia in cats (Swanepoel *et al.*, 1998), cribbing in horses (Luescher *et al.*, 1998) and repetitive pacing in several species. Other such disorders include tail-chasing

Table 1

Animal models of Obsessive-Compulsive Disorder (OCD)

	Model	Modeled behaviour (Face validity)	Neuroanatomical/neurochemical substrate (construct validity)	Predictive validity
Ethological models	Tail-chasing, acral lick dermatitis in dogs, psychogenic alopecia (hair pulling) in cats, feather picking in birds, cribbing in horses, schedule induced polydipsia, food-restriction-induced hyperactivity	++	?	*The effects of selective serotonin reuptake inhibitors have been tested and compared with the effects of drugs ineffective in OCD e.g. remediating effects of clomipramine on canine lick dermatitis*
Genetic models	Hoxb8 mutant mice	++ (trichotilomania)	++ (gene expression in areas implicated in OCD)	?
	D1CT-7 mice	++ (OCD/TS)	++ (transgene expression in neural systems hyperactive in human OCD)	?
	DAT KD mice	+/– (mimics behaviours relevant to other disorders as well)	+ (dopaminergic involvement) ++ (basal ganglia are implicated in grooming and OCD)	?
	5-HT2c KO mice	+/– (mimics behaviours relevant to other disorders as well)	+ (5-HT2c receptors involvement in OCD) + (functional abnormalities in neural substrates of OCD)	?
	Slitrk5–/– mice	++ (OCD/trichotillomania)	++ (overactivation of brain areas implicated in OCD) + (alterations in glutamate receptor composition)	++ (response to fluoxetine)
	Sapap3 gene mice	++ (trichotillomania and OCD)	++ (gene expression in areas implicated to OCD)	++ (response to fluoxetine)
Pharmacological models	Quinpirole-induced compulsive-checking	+++ (OCD)	+ (dopaminergic involvement in OCD)	+ (response to clomipramine.)
	8-OHDPAT-induced spontaneous alternation	+/– (motor perseveration apparent in other disorders as well)	+ (5-HT1a receptor involvement in OCD)	++ (response to fluoxetine and clomipramine, but not desipramine)
	mCPP-induced directional persistence in Reinforced Spatial Alternation	++ (OCD)	+ (5-HT2c receptor involvement in OCD)	++ (response to fluoxetine, but not to diazepam or desipramine)
Behavioural models	Barbering	+++ (trichotillomania)	++ (spontaneous development)	?
	Marble burying	+ (OCD)	?	+++ (response to SSRIs) – (response to anxiolytics) + (no response to desipramine)
	Signal attenuation	++ (OCD)	+ (deficient psychological process implicated in OCD) ++ (involvement of brain areas implicated in OCD)	+++ (response to fluoxetine, but not diazepam, desipramine or haloperidol)
Other possible behavioural	Reversal learning	+ (OCD)	++ (brain areas implicated in OCD) +++ (5-HT involvement in OCD)	*?*
	Attentional set-shifting	–/+	+ (brain areas implicated in OCD) – (no involvement of 5-HT)	*?*
	Extinction	–/+	?	?
	Habit-learning	–/+	+ (brain areas implicated in OCD)	?
	Stop-signal reaction time task (SSRT)	–/+	++ (brain areas implicated in OCD)	?

Animal models of Obsessive-Compulsive Disorder (OCD). Each column estimates the extent to which a model meets each criterion (+, ++ or +++, model does well; –, model does badly; ?, there are no relevant data). 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+) neurones; 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.

(Brown *et al.*, 1987), fur-chewing and acral lick dermatitis (paw licking) in dogs (Rapoport *et al.*, 1992); feather-picking in birds (Grindlinger and Ramsay, 1991); wheel-running and allogrooming (or 'barbering', akin to trichotillomania) in mice (Garner *et al.*, 2004a,b). For behaviours that represent natural responses under stress, some degree of construct validity for compulsions is also inferred inasmuch as the compulsive behaviours are performed in states assumed to correspond to anxiety. These include marble-burying in mice (the use of bedding material to bury noxious/harmless objects), which may be induced by basic fear avoidance mechanisms (Ichimaru *et al.*, 1995), displacement behaviour in the face of the thwarting of goal-directed activities including 'schedule induced polydipsia' (Robbins and Koob, 1980; Woods *et al.*, 1993) and food-restriction-induced hyperactivity (Altemus *et al.*, 1996). Both stereotypies and schedule-induced polydipsia have been considered as 'coping responses' that hypothetically reduce stress, akin to compulsions. This hypothesis, however, has proven difficult to test experimentally and may well not apply to all forms of stereotypy.

Some of these models have tested the effects of SSRIs in comparison to drugs ineffective in OCD (Winslow and Insel, 1991; Rapoport *et al.*, 1992; Woods *et al.*, 1993; Altemus *et al.*, 1996; Nurnberg *et al.*, 1997). For example, the 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). In addition, the SSRIs, fluvoxamine and citalopram, clomipramine and a selective, non-peptidergic NK(1) receptor antagonist (RP67580) were all observed to block marble-burying in mice (Millan *et al.*, 2002; Wolinsky *et al.*, 2006). Although the biological bases of this behaviour remain unclear, these observations hint that NK(1) receptors may be implicated in compulsive disorders. However, it is possible that these models relate more to anxiety and the behavioural response to stress than to OCD *per se*. Agomelatine, a mixed melatonin agonist and 5-HT_{2C} antagonist with established antidepressant and anxiolytic effects in clinical populations, has also been shown to reduce stress-induced marble burying in mice (Hamon *et al.*, 2005), suggesting potential efficacy in OCD that is in need of validation in a clinical population.

Genetic models of OCD (Table 1)

Several studies indicate that the pathogenesis of OCD has a genetic component. Three genome-wide linkage studies of OCD have so far been published (Hanna *et al.*, 2002; 2007; Shugart *et al.*, 2006).

So far, only single-nucleotide polymorphisms in the glutamate transporter gene *SLC1A1*, on chromosome 9p24, have been found to be associated with OCD. This transporter is widely expressed in neurones and also involved in cysteine transport. Moreoever, sequence variations in SLC1A1 are also associated with susceptibility to atypical antipsychotic-induced O-C symptoms (Kwon *et al.*, 2009). According to other association studies, several candidate genes have been found as possible risk factors for OCD, including those that involve the serotonergic (e.g. serotonin transporter 5-HTTLPR, 5-HT_{2A} receptor, 5-HT_{1D} receptor (Zohar *et al.*, 2004), TPH2 (Mossner *et al.*, 2006), dopaminergic (e.g. DRD4, COMT) (Pooley *et al.*, 2007) and glutamatergic system (e.g. SLC1A1) (Wendland *et al.*, 2009). One murine model of autism, in which a genetically engineered 6.3 Mb duplication of the human 15q11-13 chromosome leads to increased anxiety and impaired reversal learning associated with increased transmission at 5-HT_{2C} receptors, appears to have some relevance to compulsive behaviour (Nakatani *et al.*, 2009).

Animal models for OCD were not created on the basis of a known mutation in humans that was found to be related to OCD. These models rely on genetic manipulations on mice and are largely based on face validity and behavioural similarity, that is, the behaviour of genetically modified mice resembles in some specific respects that of OCD patients. Some of these responses show clear superficial parallels to the compulsive grooming that characterizes trichotillomania, and perhaps more obliquely to the more elaborate rituals of OCD, including those related to cleaning and checking. It seems likely that these examples of stereotyped behaviour are mediated by basal ganglia, given the known role of the caudate-putamen in stereotyped behaviour produced by psychomotor stimulant drugs such as amphetamine (Creese and Iversen, 1975) and in normal grooming sequences (Aldridge and Berridge, 1998).

Greer and Capecchi (2002) reported that mice with mutations of the *Hoxb8 gene* (expressed in the OFC, 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 (Greer and Capecchi, 2002). These mutant mice also excessively groom their wild-type cage mates, suggesting that the excessive grooming behaviour is centrally generated. Evidence suggests that in the mouse brain, the only detectable cells derived from Hoxb8 cell lineage are microglia (Chen *et al.*, 2010), and the far-reaching role of such microglia in the regulation of the brain's immune activity is becoming increasingly apparent. Normal bone marrow transplantation into lethally irradiated Hoxb8 mutant mice rescues the excessive grooming behaviour. Thus, pathological grooming behaviour observed in Hoxb8 mutant mice may originate from defective microglia within OCD-relevant neurocircuitry, and the HoxB8 model offers a paradigm for exploration – at the molecular genetic and cellular levels – of the mechanism by which perturbation of immune function may lead to O-C symptomatology. The HoxB8 model is promising in that excessive grooming has superficial similarity to the symptomatology of OC spectrum disorders and may involve neural systems similar to the ones implicated in OCD, yet, it lacks predictive validity in terms of drug treatment. Immunological dysfunctions such as these are becoming widely linked to many psychiatric disorders including OCD and autism (Leonard and Swedo, 2001; Ashwood *et al.*, 2010).

In the *D1CT-7 mouse model*, genetic manipulation of dopamine (D1) receptor function using a neuro-potentiating cholera toxin, expressed in the pyriform cortex and amygdala, produces perseveration and repetitive jumping. These effects are probably ultimately mediated via striatal mechanisms (Campbell *et al.*, 1999a,b,c). The repetitive jumping behaviour may be exacerbated by the administration of yohimbine, an anxiogenic drug with antagonist actions at alpha-2 adrenergic receptors inter alia (Mcgrath *et al.*, 1999). Although the D1CT-7 model is promising in the

sense that some of the behaviours exhibited by the mice bear similarities to those observed in OCD, and again implicates common neural systems as in OCD, the pharmacological isomorphism of the model with OCD is necessary for strengthening the model's relevance to OCD. To date, only the effects of dopaminergic (i.e. cocaine, and D1 and D2 antagonists) and noradrenergic (clonidine) agents have been assessed (Campbell *et al.*, 1999b; Nordstrom and Burton, 2002), and thus again, predictive validity is absent.

Knock-down of the dopamine transporter in mice *(DAT KD mice)* produces 'sequential super-stereotypy' with the perseverative performance of complex chains of grooming behaviour (Berridge *et al.*, 2005). Likewise, a *knock-down of the 5-HT$_{2C}$ receptor* leads to perseverative 'head-dipping' or the excessively orderly chewing of screen material (Chou-green *et al.*, 2003), a compulsive behaviour which – together with stereotypic locomotion and excessive self-aggressive grooming – has also been shown in rats following chronic lesions of the median raphé nucleus (Hoshino *et al.*, 2004). However, the data obtained from this genetic preparation do not match with other data investigating the same receptor, possibly because of unspecified compensatory processes that may develop in the transgenic preparation, as recent pharmacological data indicate the opposite finding that 5-HT$_{2C}$ receptor activation is associated with increased compulsivity (Tsaltas *et al.*, 2005; Boulougouris *et al.*, 2008).

The Slitrk family of transmembrane proteins are highly expressed in the nervous system (Zuchner *et al.*, 2006). The function of Slitrks during development of the nervous system has yet to be clearly defined, though they are thought to regulate axon outgrowth during development. A recent study in *Slitrk5*$^{-/-}$ mice demonstrated that loss of the neurone-specific transmembrane protein, SLIT and NTRK-like protein-5 (Slitrk5), leads to OCD-like behaviours, which manifests as excessive self-grooming and increased anxiety-like behaviour, and is alleviated by the SSRI, fluoxetine. The knockout mice also show selective over-activation of the OFC, abnormalities in striatal anatomy and cell morphology and alterations in glutamate receptor composition, which contribute to deficient corticostriatal neurotransmission. Slitrk5 may be an essential molecule for normally functioning corticostriatal synapses and its knock-down may provide a new mouse model of OCD-like behaviours with a degree of predictive, as well as construct and face validity (Shmelkov *et al.*, 2010).

The *Sapap 3* gene is responsible for synaptic scaffolding and migration of glutamate nerve cells from the caudate to the orbitofrontal cortex. A recent study (Welch *et al.*, 2007) found that mice with a deletion of the Sapap3 gene groomed themselves excessively, exhibited increased anxiety-like behaviour, and had corticostriatal synaptic defects, all of which were preventable with lentiviral-mediated expression of Sapap3 in the striatum. The behavioural abnormalities were also reversible with fluoxetine. Further experimentation showed that variation within the human Sapap3 gene was associated with grooming disorders (pathologic nail biting, pathologic skin picking and/or trichotillomania), suggesting that Sapap3 is a promising functional candidate gene for human grooming disorders (Bienvenu *et al.*, 2009).

In summary, although the genetic models of OCD offer good face validity and behavioural similarities with human OCD, there is often a lack of evidence on the pharmacological isomorphism of these models with OCD. However, if these models were to fulfil the criterion of predictive validity, they may provide great insight for our understanding of the neurochemical mechanisms of OCD.

Pharmacological animal models of OCD

Pharmacological models tend to be based on dopamine-induced stereotypy produced by high doses of stimulant drugs such as d-amphetamine and cocaine (Lyon and Robbins, 1975) and appear superficially appealing as models for OCD. Stereotypies in rodents typically consist of gnawing and licking with repetitive sideways movements of the head, which may represent vestiges of orienting behaviour. They can be elaborated in such models to include grooming (including allogrooming) (Sahakian and Robbins, 1975) and perseverative operant behaviour in which rats may continue to work for food they do not eat (Robbins and Sahakian, 1983). However, there is sufficient evidence to question whether stimulant induced stereotypies represent a true correlate of compulsive behaviour. For example, DICT-7 mice that experience D1 receptor potentiation exhibit reduced stereotypy after treatment with cocaine, suggesting that drug-induced stereotypy and the stereotypies produced by enhanced D1 receptor over-expression do not lie on the same continuum (Campbell *et al.*, 1999b). Furthermore, in clinical studies, single doses of d-amphetamine have been shown to ameliorate OCD symptoms (Insel *et al.*, 1983; Joffe *et al.*, 1991). Notwithstanding, Szechtman *et al.* (1998) have shown that the D2/D3 DA receptor agonist quinpirole leads to behaviour that can be analysed as a form of repetitive 'checking' in rats (Szechtman *et al.*, 1998). Specifically, following drug administration (quinpirole 0.5 mg·kg^{-1} or saline, 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. Compared with saline, quinpirole-treated rats visited two locations more frequently than controls and at these sites exhibited a 'ritual-like' set of motor activities. Moreover, this behaviour is reduced by treatment with clomipramine, consistent with it being a plausible model for OCD.

Perseveration is a term that can be applied to a variety of behavioural outputs ranging from relatively simple to complex. In 'simple' cases, a motor output is performed repetitively, whereas 'complex' perseveration includes activities such as repetitive approach towards a specific, perhaps moving, goal or persistence in complex sequences of operant behaviour, for example in which rats persist in lever-pressing for food they do not eat. In this type of model, administration of a 5-HT$_{2A}$ receptor antagonist had only weak effects on compulsive lever pressing (Flaisher-Grinberg *et al.*, 2008). In addition, both spontaneous (Yadin *et al.*, 1991) and reinforced delayed alternation behaviour (Tsaltas *et al.*, 2005) can become perseverative if the animal continues to make the previous choice. In the rewarded T-maze alternation rat model, Tsaltas *et al.* (2005) found that administration of mCPP, a mixed serotonin agonist with potent 5-HT$_{2C}$ agonist effects, increased persistence or compulsivity of responding, whereas chronic pre-treatment with an SSRI (fluoxetine), but not a benzodiazepine or desipramine, abolished the effects of mCPP. These results mirror those seen in OCD patients, where acute pharmacological challenge with mCPP exacer-

bated OCD symptomatology, and this effect was attenuated by pretreatment with fluoxetine (Hollander *et al.*, 1991) and clomipramine (Zohar *et al.*, 1988). These factors suggest the rewarded T-maze alternation rat model may represent a plausible proxy for OCD. Challenge with the 5-HT_{1B} receptor agonist naratriptan had no effect on compulsivity within this model (Tsaltas *et al.*, 2005), suggesting a specific function for the 5-HT_{2C} receptor in OCD, which may be down-regulated by chronic SSRI treatment. Activation of the 5-HT_{2C} receptor has also been shown to induce self-grooming in rats, further supporting the hypothesis that selective stimulation of central 5-HT_{2C} receptors exacerbates OCD symptoms (Graf, 2006). Consistent with these findings, Boulougouris *et al.* (2008) found that a 5-HT_{2C} receptor antagonist improved perseverative responding in rats during reversal learning (see below) (Boulougouris *et al.*, 2008). The same effect was observed in a spatial alternation model of OCD: 5-HT_{2C}, but not 5-HT_{2A}, receptor antagonism blocked the mCPP-induced directional persistence. The novel antidepressant agomelatine, which shows a degree of selectivity for 5-HT_{2C}receptor antagonism, suppressed stress-induced glutamate release in the prefrontal cortex of stressed rats, in addition to reduced stress-induced marble burying (see above) suggesting a possible role in anxiety and OCD (Tardito *et al.*, 2010). Blockade of stress-induced increase of glutamate release in the rat prefrontal/frontal cortex by agomelatine involves synergy between melatonergic and 5-HT_{2C} receptor-dependent pathways.

Neurobehavioural models of OCD

Various aspects of human behaviour can be successfully modelled in animals. Neuropsychological and brain imaging studies in OCD patients and their unaffected first-degree relatives revealed performance and/or neural processing deficits in several forms of cognitive or behavioural flexibility and in inhibitory response control: *(i) reversal learning, (ii) extra-dimensional attentional set-shifting and (iii) motor impulsivity*; these different forms of behaviour are normally modulated in humans and other animals including rats and monkeys by (i) serotonin, (ii) catecholamine (i.e. dopamine and noradrenaline) and (iii) noradrenaline respectively. These impairments are thought to contribute towards the development of 'cognitive inflexibility' and 'motor impulsivity' as endophenotypic traits within OCD families (Chamberlain *et al.*, 2005; 2007b; Chamberlain and Menzies, 2009).

Reversal learning. *Reversal learning* refers to the reversal of reinforcement contingencies in a two-choice discrimination paradigm, such that the response to a previously rewarded stimulus is now punished and *vice versa*. Impairments of such reversal learning may reflect perseveration in responding to a formerly reinforced stimulus, even though its spatial position is shifted over trials. OCD patients and their unaffected relatives have both been shown to exhibit a reduced blood oxygen level-dependent response in the OFC during visual reversal learning, suggesting a possible neuroendophenotype for OCD (Chamberlain *et al.*, 2008). In marmoset monkeys, impaired visual (object) reversal learning is induced not only by orbitofrontal lesions (Dias *et al.*, 1996), but also by 5-HT depletion, specifically within the prefrontal cortex (Clarke *et al.*, 2004) and in later studies when restricted to the OFC (Clarke *et al.*, 2005; 2007). This behaviour appears to be selectively perseverative (rather than resulting from excessive avoidance of the previously non-reinforced stimulus) in nature, insofar as the reversal learning returns to normal if the previously rewarded stimulus is substituted by a novel one (Clarke *et al.*, 2007). It is important to realize that this perseverative behaviour does not simply represent enhanced resistance to extinction; in fact, OFC 5-HT loss does not enhance responding in the extinction of a visual discrimination, although such animals are biased in their responding to the formerly reinforced stimulus. By contrast, selective dopamine depletion from the OFC causes no such bias, but leads to great persistence in responding in extinction (Walker *et al.*, 2009). It is important for this model that involvement of the striatum is also confirmed. The OFC projects to the medial striatum and nucleus accumbens in marmosets (Roberts *et al.*, 2007). Moreover, excitotoxic lesions of the medial striatum also lead to enhanced perseverative behaviour during reversal (Clarke *et al.*, 2008). Thus, specific orbitofrontal-striatal loops are implicated in this form of cognitive rigidity.

Overall, although there is evident translation from rodent to monkey and humans, including OCD patients for the neural substrates of reversal learning deficits, there has been little attempt thus far to remediate reversal learning deficits in these studies of non-human primates, although reversal learning (though of the spatial rather than visual object reversal type) has been used to assess 5-HT agents in rats (Boulougouris *et al.*, 2008). Hence, predictive validation of the reversal learning model has been limited. However, a recent study has shown an obvious relationship among reversal, 5-HT and effects of stress in rats, with elevated stress being associated with impaired reversal learning (Lapiz-Bluhm *et al.*, 2009). This may demonstrate an important relationship between rigidity induced by a cortical lesion in conjunction with effects of stress (presumably leading to anxiety), mediated by the ascending 5-HT system.

Extra-dimensional (ED) set shifting. In clinical studies, another common form of perseverative responding involves derangement of *attentional set-shifting*, exemplified by perseveration of a learned rule or stimulus category/dimension (such as 'sort by the perceptual category shape') in the Wisconsin Card Sort Test. Such impairment may occur as a result of frontal lobe damage (see below). In work by Chamberlain and colleagues, patients with OCD and their unaffected first-degree relatives showed impaired extra-dimensional set-shifting on the CANTAB intra-dimensional – ED task (where subjects are impaired in shifting attention from one perceptual dimension (or aspect) of a complex stimulus to another (Chamberlain *et al.*, 2006; 2007b). OCD patients with concurrent OCPD were significantly more affected (Fineberg *et al.*, 2007) and groups of patients with BDD (Jefferies *et al.*, 2010), and schizophrenia with OCD (Patel *et al.*, 2010), as well as schizophrenia without OCD (Pantelis *et al.*, 1999), have also shown ED impairment compared with a suitably matched control group. Thus, impaired ED-shifting may represent a hallmark of compulsive responding associated with cognitive inflexibility. As opposed to reversal learning, this form of attentional set-shifting modelled in the marmoset is

impaired by lateral frontal – but not orbitofrontal – cortex lesions and by catecholamine – but not 5-HT – depletion (see Robbins, 2005 for review). It is also of importance that, whereas the impaired ED-shifting in OCD patients is also seen in their unaffected first-degree relatives (Chamberlain *et al.*, 2007a), this is not the case for schizophrenia (Ceaser *et al.*, 2008), suggesting that this form of cognitive inflexibility may be an endophenotype for OCD but not for schizophrenia.

Signal attenuation. Another neurobehavioural model with confirmed predictive validity invokes *'signal attenuation'* as a mechanism for compulsive responding. According to this model, OCD results from deficient feedback associated with the completion of goal-directed responses. Normal functioning of such feedback prevents pointless repetitions of responses once their goal has been attained. The goal-directed behaviour of this model is instrumental lever-pressing for food. The feedback for a successful response is a compound stimulus of light and tone. The 'feedback deficit', assumed to underlie compulsive behaviour is induced in the model by means of attenuation of the 'signalling property' of this compound stimulus (repeated presentation without food in the absence of lever-pressing opportunity). The behavioural control condition for this attenuation process is termed 'regular extinction', and is identical in training and testing sequence, apart from the omission of the 'stimulus devaluation' (assumed to be equivalent to 'signal attenuation') stage. The effects of 'signal attenuation' on lever-press responding are assessed under extinction conditions through comparisons to the effects of 'regular extinction'. Regular extinction and, to a lesser extent, extinction after signal attenuation, both produce excessive lever-presses (ELP) followed by magazine entry (ELP-Completed, ELP-C). Extinction after signal attenuation additionally produces excessive lever-presses not followed by magazine entry (ELP-Uncompleted, ELP-U). According to the authors, ELP-C reflects rats' response to non-reward while ELP-U reflects response to the encounter of an attenuated signal and constitutes the model's focal behaviour (surplus lever pressing). Arguably, Joel and Avisar (2001; Joel *et al.*, 2004) have developed this model more comprehensively than any other model of OCD (Joel and Avisar, 2001; Joel *et al.*, 2004). The instrumental lever-pressing 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 behaviour is also enhanced by lesions of the rat OFC and sensitive to manipulations of the medial striatum, to which the OFC projects. Joel and colleagues have thus established many of the validating criteria for a successful model of OCD, although the exact theoretical explanation in terms of signal attenuation may perhaps be queried.

Signal attenuation appears to resemble a special form of extinction in which Pavlovian associations of a conditioned stimulus are extinguished differentially with respect to instrumental responding. The perseveration in instrumental behaviour arises because the terminal links in the response chain leading to food are extinguished. Extinction itself also depends on an inhibitory process which 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, namely the five-choice serial reaction time task (5CSRTT). The 5CSRTT (Robbins, 2002) is conducted in operant chambers equipped with an arc of nine holes, four of which are occluded and five exposed. Animals are required to initiate the trial by nose-poking in the food magazine, detect a target visual stimulus presented for 0.5 s randomly in one of the five exposed holes, and then make a nose-poke response to the hole where the light appeared (rewarded response). Perseverative nose-poking possibly caused by a failure to detect response feedback cues can arise from lesions to the OFC in rats (Chudasama and Robbins, 2003).

Exaggerated habit-learning. A related concept is that of *exaggerated habit-learning*, where compulsive behaviour is driven by relatively heightened stimulus-response (S-R) associations coupled with a generally weakened influence of the ultimate goal. Compulsivity, in the context of OCD, may depend upon a propensity towards excessive, stereotyped behaviour which is carried out to reduce the likelihood of adverse consequences (APA, 2000; Chamberlain *et al.*, 2009). OCD patients acknowledge that their behaviours are excessive and typically ineffective, yet they are unable to exert adequate control over the drive to perform these compulsive acts. This observation has led to the hypothesis that OCD compulsions may not be under goal-directed control and instead are driven by maladaptive habit learning (Graybiel and Rauch, 2000; Boulougouris *et al.*, 2009). A study on humans with OCD provides the first experimental evidence for a selective impairment in OCD patients in flexible, goal-directed control over behaviour, forcing them to rely instead on S-R habits (Gillan *et al.*, 2010).

Recent neuroscientific investigations implicate a circuit linking ventromedial prefrontal cortex (vmPFC) and caudate in goal-directed action control. Thus, persistent dominant habitual control can be induced in animals by lesioning specific brain areas (see Balleine and O'Doherty, 2010 for review). Animals with lesions to the dorsomedial striatum (DMS) and the prelimbic cortex persist in habitually responding towards food outcomes that are no longer desirable as a consequence of pairing with lithium chloride-induced nausea or specific satiety (Corbit and Balleine, 2003; Killcross and Coutureau, 2003; Yin *et al.*, 2005). More recently, human functional magnetic resonance imaging (fMRI) studies have provided convergent support for this dissociation in homologous brain regions. Studies using instrumental learning tasks have implicated the vmPFC (Valentin *et al.*, 2007; De Wit *et al.*, 2009) and anterior caudate nucleus (DMS in rodents) (Tricomi *et al.*, 2004; Tanaka *et al.*, 2008) in goal-directed response selection. Importantly, habitual control is supported by different neural structures, including specific sectors of the striatum (dorsolateral striatum, probably homologous to the putamen) (e.g. Yin and Knowlton, 2006) and infralimbic cortex in animals (Coutureau and Killcross, 2003; Yin *et al.*, 2004) and the putamen in humans (Tricomi *et al.*, 2009). Thus, in OCD, disrupted goal-directed control may force OCD patients to rely strongly on inflexible, S-R habits which are supported by a parallel corticostriatal pathway, including the putamen and possibly the sensorimotor cortex (Tricomi *et al.*, 2009; Balleine and O'Doherty, 2010). A major unanswered question is how habitual responding is converted into compulsive

behaviour, relevant to OCD. One clue may come from the observation that amphetamine sensitization has been shown to enhance habit learning (Nelson and Killcross, 2006). Sensitization is a form of neural plasticity that leads to heightened behavioural responses to the drug, probably mediated by elevated striatal dopamine function, and so this suggests again that dopamine contributes to compulsive behaviour. Additionally, recent observations have shown how stress may also enhance habit learning in rats (Dias-Ferreira *et al.*, 2009), suggesting once again a link between anxiety states in OCD and compulsive behaviour.

Motor response inhibition. In addition to a possible shift in control to habit-based representations, OCD patients also exhibit decreased behavioural and cognitive inhibition in a variety of tasks (Tien *et al.*, 1992; Enright and Beech, 1993; Rosenberg *et al.*, 1997; Bannon *et al.*, 2002; see Chamberlain *et al.*, 2005 for review), in addition to the increased errors they show on the alternation learning task (Abbruzzese *et al.*, 1997; Cavedini *et al.*, 1998). However, motor response inhibition is perhaps most readily investigated using the *stop-signal reaction time task*, in which it is necessary to stop an already-initiated response on presentation of a stop-signal. The stop-signal reaction time (SSRT) may be calculated in humans by measuring the response latency required to successfully cancel a response in a choice-reaction time procedure (Logan *et al.*, 1984). A recent comparative study of OCD and trichotillomania (Chamberlain *et al.*, 2006) 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 ED-shift test, whereas trichotillomania patients were not. These data suggest that whereas OCD is accompanied by a general problem in cognitive flexibility, trichotillomania is associated more specifically with a failure to inhibit pre-planned motor activity. Moreover, recent studies of OCD patients and their first-degree relatives (Chamberlain *et al.*, 2007b; Menzies *et al.*, 2007) identified behavioural deficits on these tasks in 'at risk' individuals, linked with structural abnormalities of fronto-striatal circuitry.

Studies of human patients with frontal lobe damage have localized one critical zone for SSRT to the right inferior frontal gyrus (Aron *et al.*, 2003) and other data implicate the striatum and subthalamic nucleus in this inhibitory process (Aron *et al.*, 2007, but see also Hampshire *et al.*, 2010). A similar neural network may be implicated in the ED-shift, according to a recent fMRI study (Hampshire and Owen, 2006) and other evidence of common noradrenergic mediation (Lapiz and Morilak, 2006; Robinson *et al.*, 2008b). A method of measuring SSRT in rats has been developed, which is dependent on possibly homologous structures in the lateral OFC and medial striatum (Eagle and Robbins, 2003; Eagle *et al.*, 2007). Intriguingly, however, the SSRT is insensitive to serotoninergic manipulations in both rats and humans (Chamberlain and Sahakian, 2007), but may be amenable to noradrenergic remediation, for example, with methylphenidate or atomoxetine in patients with attention deficit hyperactivity disorder (Chamberlain *et al.*, 2007a; Devito *et al.*, 2009).

Lengthened SSRTs can be interpreted as enhanced impulsivity, supporting the view of functional relationships between impulsivity and compulsivity postulated clinically (Hollander and Rosen, 2000) in animal models of stimulant drug addiction (Everitt and Robbins, 2005; Berlin *et al.*, 2008). In view of these possible links between the two constructs, an intriguing dissociation between premature responding in the 5CSRTT and reversal learning (i.e. impulsivity and compulsivity) has been reported. Specifically, studies utilizing the 5CSRTT have shown that systemic administration of a 5-HT_{2C} antagonist (SB 242084) exacerbated the enhanced impulsivity normally observed following global 5-HT depletion produced by intra-cerebroventricular administration of 5,7-dihydroxytryptamine; a similar SB242084-related enhancement in impulsivity was seen in sham-operated rats (Winstanley *et al.*, 2004). In contrast, systemic administration of a selective 5-HT_{2A} receptor antagonist (M100907) had opposite actions, remediating impulsivity in both sham-operated and 5-HT-depleted rats. These contrasting influences of the 5-HT_{2A} and 5-HT_{2C} receptor antagonists were mimicked by infusions of the drugs into the nucleus accumbens, but not the medial prefrontal cortex, in intact animals (Robinson *et al.*, 2008a). On the contrary, studies utilizing a simple serial spatial reversal task, shown to be sensitive to orbitofrontal lesions (Boulougouris *et al.*, 2007), showed that systemic administration of the 5-HT_{2C} receptor antagonist promoted reversal learning, while M100907 had the opposite effect of impairing it. Note that in terms of remediation, this is opposite to what was found for measures of impulsivity. Similar enhancements of reversal learning after treatment with the 5-HT_{2C} antagonist were also found after infusion into the OFC (Boulougouris and Robbins, 2010).

Regardless of the precise elucidation of mechanism, these data pharmacologically dissociate impulsivity and compulsivity, suggesting that they cannot arise simply from a common process of behavioural disinhibition. This dissociation must be task-dependent as both tasks require response inhibition for efficient performance, suggesting that there is some other aspect of the processes engaged by the task, which differentiates them. These results also imply that impulsivity and compulsivity are functionally separate and reciprocally yoked, lending support to the impulsive–compulsive diathesis model (Hollander and Wong, 1995). They also suggest that impulsivity and compulsivity are neuroanatomically and neurochemically dissociated by selective 5-HT2 receptor agents and may lead to new clinical applications. However, further experimental evidence is required to resolve how these data fit with the consistent finding that OFC 5-HT depleted marmosets show impairments on visual object reversal learning (Clarke *et al.*, 2004; 2005). In addition, it would seem likely that these seemingly opposed effects are mediated through separate neural pathways: in the case of impulsivity, through projections from the infralimbic vmPFC (area 25), an area richly innervated by 5-HT_{2A} receptors and strongly implicated in affective regulation, towards the shell of the nucleus accumbens (Vertes, 2004) and, in the case of compulsivity, in connections between the OFC and the caudate nucleus (or the dorsomedial striatum in the rat) (Schilman *et al.*, 2008).

Anxiety models

Several other theoretical positions may be especially useful in explaining certain forms of OCD. For example, the theoretical construct that anxiety is the prime trigger of OCD, as posited for example by Rachman and Hodgson (1980), should not be underestimated (Rachman and Hodgson, 1980). Active avoidance behaviour 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 (Lyon and Robbins, 1975). Thus, behaviour that initially has some adaptive value, for example, that results in avoiding shocks, apparently loses its rationale after thousands of trials in which shock is never presented. A more recent formulation by Szechtman and Woody (2004) suggests that OCD-like activity arises as an aberrant excess of behaviour motivated by the need for security (Szechtman and Woody, 2004). 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.

These findings may provide interesting new insights into the clinical understanding of compulsivity in OCD that link habit and goal-directed learning and affective state. Consider this common example. Seeing, or being reminded of a potential contaminant triggers anxiety relating to a potentially catastrophic outcome, and activates the compulsive response of washing one's hands. Although the individual clearly recognizes that this act has little or no bearing on contracting illness, performing the compulsion causes a momentary reduction in anxiety which is experienced as relief. In other words, the act of washing one's hands may not be driven by its direct consequences, but rather by external triggers of compulsive habits that are reinforced by the experience of relief within the general aversive motivational state of anxiety. Although compulsivity, in the context of OCD, is avoidant and not appetitive, it is likely that the same fundamental mechanisms may give rise to reliance on S-R habit reinforcement. In line with this hypothesis, Kim *et al*. (2006) showed that the OFC is engaged not only when people gain rewarding events, but also when aversive events are successfully avoided (Kim *et al*., 2006).

Deep Brain Stimulation (DBS)

In patients with severe, treatment refractory OCD, psychosurgery is sometimes considered as a means of alleviating the symptoms (for review see Greenberg *et al*., 2010). In one such approach – DBS – small electrodes are implanted into the brain guided by imaging techniques, and are subsequentially used to stimulate particular neural nodes. Several pilot patient studies have reported beneficial reductions in OCD symptoms when electrodes have been implanted into such neural regions as the ventral striatum (Greenberg *et al*., 2008), caudate (Aouizerate *et al*., 2004), subthalamic nucleus (Mallet *et al*., 2008) and the nucleus accumbens (Denys *et al*., 2010). As described previously, most of these regions have been implicated in the neurobiology of OCD *per se*; however, it should be noted that choice of electrode site has also been guided by what is known of the neurobiology. Several translational studies have explored effects of DBS in animal models of the disorder.

Low- but not high-frequency stimulation of the thalamic nucleus was effective in reducing 8-OHDPAT-induced perseveration in rats (Andrade *et al*., 2009). In the rat, quinpirole-induced repetitive checking model, high frequency stimulation of the subthalamic nucleus reduced compulsive behaviours transiently, as did stimulation of the nucleus accumbens shell and core (Klavir *et al*., 2009; Mundt *et al*., 2009; Djodari-Irani *et al*., 2011). Similar benefits have been reported in the signal attenuation model of Joel and colleagues, with post-training high-frequency stimulation of the subthalamic nucleus, and globus pallidus, leading to anti-compulsive effects (Klavir *et al*., 2009). Collectively, the available animal studies involving stimulation of specific neural regions show remarkable parallels with findings in human OCD patients, and also suggest potential novel therapeutic anatomical targets.

Conclusions

We are thus intriguingly close to providing useful theoretically motivated models of OCD, particularly with regard to repetitive motoric habits and inhibitory failure. The animal models reviewed above constitute an important vehicle for the investigation of several aspects of OCD. However, every model has its strengths and weaknesses (Table 1) which should be taken into consideration for determining the needs it can serve. An important feature of a model for anti-compulsive activity screening is its predictive validity. Regarding predictive validity, it should be noted that around 40–60% of OCD patients are resistant to SSRI monotherapy (Fineberg *et al*., 2006b). Therefore, the establishment of a model's predictive validity lies not only on the effectiveness of SSRIs but, more importantly, on the ineffectiveness of drugs known not to be efficacious in OCD as well. Additionally, chronic drug administration might be a good candidate for such a differentiation. The signal attenuation and reinforced spatial alternation models of OCD have good predictive validity, as they have shown pharmacological isomorphism with the treatment of OCD and the lack of effect on the models' focal behaviours of drugs not effective to OCD treatment. However, the signal attenuation model is not suitable for examining the effects of chronic pharmacological treatment, as prolonged drug administration may contaminate the early stages of the procedure. Yet, the genetic and neurobehavioural models previously discussed lack predictive validity, although they look more convincing in terms of construct validity and may have promise for the development and screening of anti-compulsive drugs.

Elucidation of the neurobiological substrates of OCD is amply represented in many animal models, contributing to their construct validity. Additionally, behavioural models such as those based on signal attenuation or reversal learning have already been shown to be sensitive to serotoninergic/dopaminergic systems and orbitofrontal dysfunction, both heavily implicated in OCD. On the other hand, genetic models of OCD involving single gene alterations might be extremely useful for the understanding of certain forms of

OCD pathophysiology. It would be of considerable interest to determine whether the more obvious motor manifestations of the 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.

Although none of the animal models reviewed in this paper can account for simulating OCD in its entirety, as presupposed by an 'ideal' model, some could potentially be enhanced by further investigation. None of the animal models provide a good model for obsessions, as opposed to compulsive behaviours. Given the heterogeneity and aetiological complexity of OCD, the findings emerging from the combined use of different models may provide insight to the various aspects and aetiology of the disorder and lead to new treatments. Direct comparison of these findings might also elucidate genuine anti-compulsive effects rather than effects limited to a specific model that is not necessarily related to OCD.

Acknowledgements and conflicts of interest

This work was partly funded via a Wellcome Trust Programme Grant (089589/Z/09/Z) awarded to Dr TW Robbins. Dr SR Chamberlain has consulted for Cambridge Cognition, Shire and P1Vital. Dr V Boulougouris is funded by the Bodossaki Foundation Postdoctoral Scholarship. Dr Fineberg has consulted for Lundbeck, Glaxo-Smith Kline, Servier and Bristol Myers Squibb; has received research support from Lundbeck, Glaxo-SmithKline, Astra Zeneca, Wellcome, Cephalon, ECNP and Servier; has received honoraria for lectures at scientific meetings from Janssen, Jazz, Lundbeck, Servier, Astra Zeneca and Wyeth; and has received financial support to attend scientific meetings from Janssen, Bristol Myers Squibb, Jazz, Lundbeck, Servier, Astra Zeneca, Wyeth, Cephalon and the International College of OC Spectrum Disorders. Dr TW Robbins has consulted for Cambridge Cognition, Pfizer, Lilly, GlaxoSmithKline and Lundbeck; and has received research grants from Lilly, GlaxoSmithKline and Lundbeck. Dr Hollander has consulted for Transcept, Neuropharm, Nastech and Cypress; has received research support from Forest, Transcept, NARSAD and the Orphan Products Division of FDA; has received honoraria for lectures at scientific meetings from Lundbeck; and has received financial support to attend scientific meetings from Lundbeck, and the International College of OC Spectrum Disorders. The Behavioural and Clinical Neuroscience Institute is co-funded by the MRC and the Wellcome Trust.

References

Abbruzzese M, Ferri S, Scarone S (1997). The selective breakdown of frontal functions in patients with obsessive-compulsive disorder and in patients with schizophrenia: a double dissociation experimental finding. Neuropsychologia 35: 907–912.

Aldridge JW, Berridge KC (1998). Coding of serial order by neostriatal neurons: a 'natural action' approach to movement sequence. J Neurosci 18: 2777–2787.

Altemus M, Glowa JR, Galliven E, Leong YM, Murphy DL (1996). Effects of serotonergic agents on food-restriction-induced hyperactivity. Pharmacol Biochem Behav 53: 123–131.

Andrade P, Fernandez-Guasti A, Carrillo-Ruiz JD, Ulloa RE, Ramirez Y, Reyes R *et al*. (2009). Effects of bilateral lesions in thalamic reticular nucleus and orbitofrontal cortex in a T-maze perseverative model produced by 8-OH-DPAT in rats. Behav Brain Res 203: 108–112.

Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A *et al*. (2004). Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. J Neurosurg 101: 682–686.

APA (2000). Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association: Washington, DC.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 6: 115–116.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27: 3743–3752.

Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, Van De Water J (2010). Altered T cell responses in children with autism. Brain Behav Immun [Epub ahead of print].

Balleine BW, O'doherty JP (2010). Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology 35: 48–69.

Bannon S, Gonsalvez CJ, Croft RJ, Boyce PM (2002). Response inhibition deficits in obsessive-compulsive disorder. Psychiatry Res 110: 165–174.

Baxter L (1999). Functional imaging of brain systems mediating obsessive-compulsive disorder. In: Charney DS, Nestler EJ, Bunney BS (eds). Neurobiology of Mental Illness. Oxford University Press: Oxford, pp. 534–547.

Berlin HA, Hamilton H, Hollander E (2008). Neurocognition and temperament in pathological gambling. *American Psychiatric Association, conference poster.* Washington, DC.

Berridge KC, Aldridge JW, Houchard KR, 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 Biol 3: 4.

Bienvenu OJ, Wang Y, Shugart YY, Welch JM, Grados MA, Fyer AJ *et al*. (2009). Sapap3 and pathological grooming in humans: Results from the OCD collaborative genetics study. Am J Med Genet B Neuropsychiatr Genet 150B: 710–720.

Black DW, Monahan P, Gable J, Blum N, Clancy G, Baker P (1998). Hoarding and treatment response in 38 nondepressed subjects with Obsessive-Compulsive Disorder. J Clin Psychiatry 59: 420–425.

Blier P, De Montigny C (1998). Possible serotonergic mechanisms underlying the antidepressant and anti-obsessive-compulsive disorder responses. Biol Psychiatry 44: 313–323.

Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF (2006). A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry 11: 622–632.

Bloch MH, Craiglow BG, Landeros-Weisenberger A, Dombrowski PA, Panza KE, Peterson BS *et al.* (2009). Predictors of early adult outcomes in pediatric-onset obsessive-compulsive disorder. Pediatrics 124: 1085–1093.

Bolton D, Luckie M, Steinberg D (1995). Long-term course of obsessive-compulsive disorder treated in adolescence. J Am Acad Child Adolesc Psychiatry 34: 1441–1450.

Boulougouris V, Robbins TW (2010). Enhancement of spatial reversal learning by 5-HT2C receptor antagonism is neuroanatomically specific. J Neurosci 30: 930–938.

Boulougouris V, Dalley JW, Robbins TW (2007). Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. Behav Brain Res 179: 219–228.

Boulougouris V, Glennon JC, Robbins TW (2008). Dissociable effects of selective 5-HT2A and 5-HT2C receptor antagonists on serial spatial reversal learning in rats. Neuropsychopharmacology 33: 2007–2019.

Boulougouris V, Chamberlain SR, Robbins TW (2009). Cross-species models of OCD spectrum disorders. Psychiatry Res 170: 15–21.

Brown SA, Crowell-Davis S, Malcolm T, Edwards P (1987). Naloxone-responsive compulsive tail chasing in a dog. J Am Vet Med Assoc 190: 884–886.

Campbell KM, De Lecea L, Severynse DM, Caron MG, Mcgrath MJ, Sparber SB *et al.* (1999a). OCD-Like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1+ neurons. J Neurosci 19: 5044–5053.

Campbell KM, Mcgrath MJ, Burton FH (1999b). Behavioral effects of cocaine on a transgenic mouse model of cortical-limbic compulsion. Brain Res 833: 216–224.

Campbell KM, Mcgrath MJ, Burton FH (1999c). Differential response of cortical-limbic neuropotentiated compulsive mice to dopamine D1 and D2 receptor antagonists. Eur J Pharmacol 371: 103–111.

Cavallini MC, Di Bella D, Siliprandi F, Malchiodi F, Bellodi L (2002). Exploratory factor analysis of obsessive-compulsive patients and association with 5-HTTLPR polymorphism. Am J Med Genet 114: 347–353.

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

Ceaser AE, Goldberg TE, Egan MF, Mcmahon RP, Weinberger DR, Gold JM (2008). Set-shifting ability and schizophrenia: a marker of clinical illness or an intermediate phenotype? Biol Psychiatry 64: 782–788.

Chamberlain SR, Menzies L (2009). Endophenotypes of obsessive-compulsive disorder: rationale, evidence and future potential. Expert Rev Neurother 9: 1133–1146.

Chamberlain SR, Sahakian BJ (2007). The neuropsychiatry of impulsivity. Curr Opin Psychiatry 20: 255–261.

Chamberlain SR, Blackwell AD, Fineberg N, Robbins TW, Sahakian BJ (2005). The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev 29: 399–419.

Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. Am J Psychiatry 163: 1282–1284.

Chamberlain SR, Del Campo N, Dowson J, Müller U, Clark L, Robbins TW *et al.* (2007a). Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biol Psychiatry 62: 977–984.

Chamberlain SR, Fineberg NA, Menzies LA, Blackwell AD, Bullmore ET, Robbins TW *et al.* (2007b). Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. Am J Psychiatry 164: 335–338.

Chamberlain SR, Menzies L, Sahakian BJ, Fineberg NA (2007c). Lifting the veil on Trichotillomania. Am J Psychiatry 164: 568–574.

Chamberlain SR, Menzies L, Hampshire A, Suckling J, Fineberg NA, Del Campo N *et al.* (2008). Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science 321: 421–422.

Chamberlain SR, Odlaug BL, Boulougouris V, Fineberg NA, Grant JE (2009). Trichotillomania: neurobiology and treatment. Neurosci Biobehav Rev 33: 831–842.

Chen SK, Tvrdik P, Peden E, Cho S, Wu S, Spangrude G *et al.* (2010). Hematopoietic origin of pathological grooming in Hoxb8 mutant mice. Cell 141: 775–785.

Chou-Green JM, Holscher TD, Dallman MF, Akana SF (2003). Compulsive behavior in the 5-HT2C receptor knockout mouse. Physiol Behav 78: 641–649.

Chudasama Y, Robbins TW (2003). Dissociable contributions of the orbitofrontal and infralimbic cortex to pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. J Neurosci 23: 8771–8780.

Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC (2004). Cognitive inflexibility after prefrontal serotonin depletion. Science 304: 878–880.

Clarke HF, Walker SC, Crofts HS, Dalley JW, Robbins TW, Roberts AC (2005). Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. J Neurosci 25: 532–538.

Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC (2007). Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb Cortex 17: 18–27.

Clarke HF, Robbins TW, Roberts AC (2008). Lesions of the medial striatum in monkeys produce perseverative impairments during reversal learning similar to those produced by lesions of the orbitofrontal cortex. J Neurosci 28: 10972–10982.

Corbit LH, Balleine BW (2003). The role of prelimbic cortex in instrumental conditioning. Behav Brain Res 146: 145–157.

Coutureau E, Killcross S (2003). Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. Behav Brain Res 146: 167–174.

Creese I, Iversen SD (1975). The pharmacological and anatomical substrates of the amphetamine response in the rat. Brain Res 83: 419–436.

De Wit S, Corlett PR, Aitken MR, Dickinson A, Fletcher PC (2009). Differential engagement of the ventromedial prefrontal cortex by goal-directed and habitual behavior toward food pictures in humans. J Neurosci 29: 11330–11338.

Denys D, Klompmakers AA, Westenberg HG (2004a). Synergistic dopamine increase in the rat prefrontal cortex with the combination of quetiapine and fluvoxamine. Psychopharmacology (Berl) 176: 195–203.

Denys D, Van Der Wee N, Janssen J, De Geus F, Westenberg HG (2004b). Low level of dopaminergic D(2) receptor binding in obsessive-compulsive disorder. Biol Psychiatry 55: 1041–1045.

Denys D, Mantione M, Figee M, Van Den Munckhof P, Koerselman F, Westenberg H *et al*. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 67: 1061–1068.

Devito EE, Blackwell AD, Clark L, Kent L, Dezsery AM, Turner DC *et al*. (2009). Methylphenidate improves response inhibition but not reflection-impulsivity in children with attention deficit hyperactivity disorder (ADHD). Psychopharmacology (Berl) 202: 531–539.

Dias R, Robbins TW, Roberts AC (1996). Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380: 69–72.

Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ *et al*. (2009). Chronic stress causes frontostriatal reorganization and affects decision-making. Science 325: 621–625.

Djodari-Irani A, Klein J, Banzhaf J, Joel D, Heinz A, Harnack D *et al*. (2011). Activity modulation of the globus pallidus and the nucleus entopeduncularis affects compulsive checking in rats. Behav Brain Res 219: 149–158.

Drummond LM, Fineberg NA (2007). Obsessive-compulsive disorders. In: Stein G (ed.). College Seminars in Adult Psychiatry. Gaskell: London, pp. 270–286.

Eagle DM, Robbins TW (2003). Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. Behav Neurosci 117: 1302–1317.

Eagle DM, Tufft MR, Goodchild HL, Robbins TW (2007). Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. Psychopharmacology (Berl) 192: 193–206.

Enright SJ, Beech AR (1993). Reduced cognitive inhibition in obsessive-compulsive disorder. Br J Clin Psychol 32 (Pt 1): 67–74.

Everitt BJ, Robbins TW (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8: 1481–1489.

Fineberg NA, Gale TM (2005). Evidence-based pharmacotherapy of obsessivecompulsive disorder. Int J Neuropsychopharmacol 8: 107–129.

Fineberg NA, Fourie H, Gale TM, Sivakumaran T (2005a). Comorbid depression in obsessive compulsive disorder (OCD): symptomatic differences to major depressive disorder. J Affect Disord 87: 327–330.

Fineberg NA, Sivakumaran T, Roberts A, Gale T (2005b). Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. Int Clin Psychopharmacol 20: 223–226.

Fineberg NA, Gale TM, Sivakumaran T (2006a). A review of antipsychotics in the treatment of obsessive compulsive disorder. J Psychopharmacol 20: 97–103.

Fineberg NA, Nigam A, Silvakumaran T (2006b). Pharmacological strategies for treatment-resistant obsessive compulsive disorder. Psychiatr Ann 36: 464–474.

Fineberg NA, Stein DJ, Premkumar P, Carey P, Sivakumaran T, Vythilingum B *et al*. (2006c). Adjunctive quetiapine for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: a meta-analysis of randomized controlled treatment trials. Int Clin Psychopharmacol 21: 337–343.

Fineberg NA, Sharma P, Sivakumaran T, Sahakian B, Chamberlain SR (2007). Does obsessive-compulsive personality disorder belong within the obsessive-compulsive spectrum? CNS Spectr 12: 467–482.

Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A *et al*. (2010). Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacology 35: 591–604.

Flaisher-Grinberg S, Klavir O, Joel D (2008). The role of 5-HT2A and 5-HT2C receptors in the signal attenuation rat model of obsessive-compulsive disorder. Int J Neuropsychopharmacol 11: 811–825.

Garner JP, Dufour B, Gregg LE, Weisker SM, Mench JA (2004a). Social and husbandry factors affecting the prevalence and severity of barbering ('whisker trimming') by laboratory mice. Appl Anim Behav Sci 89: 263–282.

Garner JP, Weisker SM, Dufour B, Mench JA (2004b). Barbering (fur and whisker trimming) by laboratory mice as a model of human trichotillomania and obsessive-compulsive spectrum disorders. Comp Med 54: 216–224.

Geyer MA, Markou A (1995). Animal models of psychiatric disorders. In: Bloom FE, Kupfer DJ (eds). Psychopharmacology: The Fourth Generation of Progress. Raven Press: New York, pp. 787–798.

Geyer MA, Markou A (2002). The role of preclinical models in the development of psychotropic drugs. In: Davis KL, Coyle JT, Nemeroff C (eds). Psychopharmacology: the Fifth Generation of Progress. LWW: Hagerstown, MD, USA, pp. 445–455.

Gillan CM, Butt M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW *et al*. (2010). Disrupted balance between goal-directed behavior versus habit learning in obsessive-compulsive disorder. Am J Psychiatry (in press).

Graf M (2006). 5-HT2c receptor activation induces grooming behaviour in rats: possible correlations with obsessive-compulsive disorder. Neuropsychopharmacol Hung 8: 23–28.

Grant JE, Odlaug BL, Kim SW (2009). N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Arch Gen Psychiatry 66: 756–763.

Graybiel AM (1997). The basal ganglia and cognitive pattern generators. Schizophr Bull 23: 459–469.

Graybiel AM, Rauch SL (2000). Toward a neurobiology of obsessive-compulsive disorder. Neuron 28: 343–347.

Greenberg BD, Gabriels LA, Malone DA, Jr, Rezai AR, Friehs GM, Okun MS *et al*. (2008). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 15: 64–79.

Greenberg BD, Rauch SL, Haber SN (2010). Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology 35: 317–336.

Greer JM, Capecchi MR (2002). Hoxb8 is required for normal grooming behavior in mice. Neuron 33: 23–34.

Grindlinger HM, Ramsay E (1991). Compulsive feather picking in birds. Arch Gen Psychiatry 48: 857.

Hamon M, Boer PA, Mocaer E (2005). New perspectives in the pathophysiology and treatment of affective disorders: the role of melatonin and serotonin. Medicographia 27: 228–235.

Hampshire A, Owen AM (2006). Fractionating attentional control using event-related fMRI. Cereb Cortex 16: 1679–1689.

Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50: 1313–1319.

Hanna GL (1995). Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry 34: 19–27.

Hanna GL, Veenstra-Vanderweele J, Cox NJ, Boehnke M, Himle JA, Curtis GC *et al*. (2002). Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. Am J Med Genet 114: 541–552.

Hanna GL, Veenstra-Vanderweele J, Cox NJ, Van Etten M, Fischer DJ, Himle JA *et al*. (2007). Evidence for a susceptibility locus on chromosome 10p15 in early-onset obsessive-compulsive disorder. Biol Psychiatry 62: 856–862.

Hoehn-Saric R, Ninan P, Black DW, Stahl S, Greist JH, Lydiard B *et al*. (2000). Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. Arch Gen Psychiatry 57: 76–82.

Hollander E (2008). Obsessive-compulsive spectrum phenomena and the DSM-V developmental process. CNS Spectr 13: 107–108.

Hollander E, Rosen J (2000). Impulsivity. J Psychopharmacol 14: S39–S44.

Hollander E, Wong CM (1995). Obsessive-compulsive spectrum disorders. J Clin Psychiatry 56 (Suppl 4): 3–6; discussion 53–5.

Hollander E, Decaria C, Gully R, Nitescu A, Suckow RF, Gorman JM *et al*. (1991). Effects of chronic fluoxetine treatment on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine in obsessive-compulsive disorder. Psychiatry Res 36: 1–17.

Hollander E, Braun A, Simeon D (2008). Should OCD leave the anxiety disorders in DSM-V? The case for obsessive compulsive-related disorders. Depress Anxiety 25: 317–329.

Hollander E, Stein DJ, Fineberg NA, Marteau F, Legault M (2010). Quality of life outcomes in patients with obsessive-compulsive disorder: relationship to treatment response and symptom relapse. J Clin Psychiatry 71: 784–792.

Hoshino K, Uga DA, De Paula HM (2004). The compulsive-like aspect of the head dipping emission in rats with chronic electrolytic lesion in the area of the median raphe nucleus. Braz J Med Biol Res 37: 245–250.

Hranov G, Fineberg NA (2010). Are tics an essential symptom of the obsessive compulsive syndrome? Eur Neuropsychopharmacol 20: s521.

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. Jpn J Pharmacol 68: 65–70.

Insel TR, Hamilton JA, Guttmacher LB, Murphy DL (1983). d-amphetamine in obsessive-compulsive disorder. Psychopharmacology (Berl) 80: 231–235.

Jefferies K, Laws K, Fineberg NA (2010). Cognitive and perceptual processing in body dysmorphic disorder. Eur Neuropsychopharmacol 20: s309.

Joel D, Avisar A (2001). Excessive lever pressing following post-training signal attenuation in rats: a possible animal model of obsessive compulsive disorder? Behav Brain Res 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. Behav Pharmacol 15: 241–252.

Joffe RT, Swinson RP, Levitt AJ (1991). Acute psychostimulant challenge in primary obsessive-compulsive disorder. J Clin Psychopharmacol 11: 237–241.

Jog MS, Kubota Y, Connolly CI, Hillegaart V, Graybiel AM (1999). Building neural representations of habits. Science 286: 1745–1749.

Katerberg H, Delucchi KL, Stewart SE, Lochner C, Denys DA, Stack DE *et al*. (2010). Symptom dimensions in OCD: item-level factor analysis and heritability estimates. Behav Genet 40: 505–517.

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

Kim H, Shimojo S, O'doherty JP (2006). Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. PLoS Biol 4: e233.

Klavir O, Flash S, Winter C, Joel D (2009). High frequency stimulation and pharmacological inactivation of the subthalamic nucleus reduces 'compulsive' lever-pressing in rats. Exp Neurol 215: 101–109.

Kolevzon A, Mathewson KA, Hollander E (2006). Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. J Clin Psychiatry 67: 407–414.

Kwon JS, Joo YH, Nam HJ, Lim M, Cho EY, Jung MH *et al*. (2009). Association of the glutamate transporter gene SLC1A1 with atypical antipsychotics-induced obsessive-compulsive symptoms. Arch Gen Psychiatry 66: 1233–1241.

Lapiz MD, Morilak DA (2006). Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137: 1039–1049.

Lapiz-Bluhm MD, Soto-Pina AE, Hensler JG, Morilak DA (2009). Chronic intermittent cold stress and serotonin depletion induce deficits of reversal learning in an attentional set-shifting test in rats. Psychopharmacology (Berl) 202: 329–341.

Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C *et al*. (1997). Symptoms of obsessive-compulsive disorder. Am J Psychiatry 154: 911–917.

Leckman JF, Pauls DL, Zhang H, Rosario-Campos MC, Katsovich L, Kidd KK *et al*. (2003). Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. Am J Med Genet B Neuropsychiatr Genet 116B: 60–68.

Leckman JF, Denys D, Simpson HB, Mataix-Cols D, Hollander E, Saxena S *et al*. (2010). Obsessive-compulsive disorder: a review of the diagnostic criteria and possible subtypes and dimensional specifiers for DSM-V. Depress Anxiety 27: 507–527.

Leonard HL, Swedo SE (2001). Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Int J Neuropsychopharmacol 4: 191–198.

Lochner C, Hemmings SM, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA *et al*. (2004a). Corrigendum to 'gender in obsessive-compulsive disorder: clinical and genetic findings' [Eur. Neuropsychopharmacol. 14 (2004) 105–113]. Eur Neuropsychopharmacol 14: 437–445.

Lochner C, Hemmings SM, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA *et al*. (2004b). Gender in obsessive-compulsive disorder: clinical and genetic findings. Eur Neuropsychopharmacol 14: 105–113.

Logan GD, Cowan WB, Davis KA (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform 10: 276–291.

Lucey JV, Butcher G, Clare AW, Dinan TG (1993). Elevated growth hormone responses to pyridostigmine in obsessive-compulsive disorder: evidence of cholinergic supersensitivity. Am J Psychiatry 150: 961–962.

Luescher UA, Mckeown DB, Dean H (1998). A cross-sectional study on compulsive behaviour (stable vices) in horses. Equine Vet J Suppl 27: 14–18.

Lyon M, Robbins TW (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. Spectrum: New York, pp. 80–163.

Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D *et al.* (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med 359: 2121–2134.

Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, 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. Am J Psychiatry 156: 1409–1416.

Mataix-Cols D, Marks IM, Greist JH, Kobak KA, Baer L (2002). Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: results from a controlled trial. Psychother Psychosom 71: 255–262.

Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML (2004). Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry 61: 564–576.

Mataix-Cols D, Rosario-Campos MC, Leckman JF (2005). A multidimensional model of obsessive-compulsive disorder. Am J Psychiatry 162: 228–238.

Matthysse S (1986). Animal models in psychiatric research. Prog Brain Res 65: 259–270.

Mcgrath MJ, Campbell KM, Veldman MB, Burton FH (1999). Anxiety in a transgenic mouse model of cortical-limbic neuro-potentiated compulsive behavior. Behav Pharmacol 10: 435–443.

Mcgrath MJ, Campbell KM, Parks CR, Burton FH (2000). Glutamatergic drugs exacerbate symptomatic behavior in a transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder. Brain Res 877: 23–30.

Mckinney WT (2000). Animal research and its relevance to psychiatry. In: Sadock BJ, Sadock VA (eds). Kaplan & Sadock's Comprehensive Textbook of Psychiatry. LWW: Baltimore, MD, USA, pp. 545–563.

Mckinney WT Jr, Bunney WE Jr (1969). Animal model of depression. I. Review of evidence: implications for research. Arch Gen Psychiatry 21: 240–248.

Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, Del Campo N *et al.* (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. Brain 130: 3223–3236.

Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 32: 525–549.

Meyer V (1966). Modification of expectations in cases with obsessional rituals. Behav Res Ther 4: 273–280.

Millan MJ, Girardon S, Mullot J, Brocco M, Dekeyne A (2002). Stereospecific blockade of marble-burying behaviour in mice by selective, non-peptidergic neurokinin1 (NK1) receptor antagonists. Neuropharmacology 42: 677–684.

Mossner R, Walitza S, Geller F, Scherag A, Gutknecht L, Jacob C *et al.* (2006). Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol 9: 437–442.

Mundt A, Klein J, Joel D, Heinz A, Djodari-Irani A, Harnack D *et al.* (2009). High-frequency stimulation of the nucleus accumbens core and shell reduces quinpirole-induced compulsive checking in rats. Eur J Neurosci 29: 2401–2412.

Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C *et al.* (2005). A functional MRI comparison of patients with obsessive-compulsive disorder and normal controls during a Chinese character Stroop task. Psychiatry Res 139: 101–114.

Nakatani J, Tamada K, Hatanaka F, Ise S, Ohta H, Inoue K *et al.* (2009). Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism. Cell 137: 1235–1246.

Nelson A, Killcross S (2006). Amphetamine exposure enhances habit formation. J Neurosci 26: 3805–3812.

Ninan PT, Koran LM, Kiev A, Davidson JR, Rasmussen SA, Zajecka JM *et al.* (2006). High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. J Clin Psychiatry 67: 15–22.

Nordstrom EJ, Burton FH (2002). A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry. Mol Psychiatry 7: 617–625, 524.

Nurnberg HG, Keith SJ, Paxton DM (1997). Consideration of the relevance of ethological animal models for human repetitive behavioral spectrum disorders. Biol Psychiatry 41: 226–229.

Padhi A, Mehdi AM, Craig K, Fineberg NA (2010). Current classification of impulse control disorders: cognitive versus behavioural impulsivity and the role of personality. In: Potenza MN, Grant JE (eds). Oxford Handbook of Impulse Control Disorders. Oxford University Press: Oxford (in press).

Pampaloni I, Sivakumaran T, Hawley CJ, Al Allaq A, Farrow J, Nelson S *et al.* (2010). High-dose selective serotonin reuptake inhibitors in OCD: a systematic retrospective case notes survey. J Psychopharmacol 24: 1439–1445.

Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW (1999). Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. Schizophr Res 37: 251–270.

Patel DD, Laws KR, Padhi A, Farrow JM, Mukhopadhaya K, Krishnaiah R *et al.* (2010). The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. Psychol Med 40: 921–933.

Peris TS, Bergman RL, Asarnow JR, Langley A, Mccracken JT, Piacentini J (2010). Clinical and cognitive correlates of depressive symptoms among youth with obsessive compulsive disorder. J Clin Child Adolesc Psychol 39: 616–626.

Phillips KA, Stein DJ, Rauch SL, Hollander E, Fallon BA, Barsky A *et al.* (2010). Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? Depress Anxiety 27: 528–555.

Pooley EC, Fineberg N, Harrison PJ (2007). The met(158) allele of catechol-O-methyltransferase (COMT) is associated with obsessive-compulsive disorder in men: case-control study and meta-analysis. Mol Psychiatry 12: 556–561.

Rachman S, Hodgson R (1980). Obsessions and Compulsions. Prentice Hall: New York.

Rapoport JL, Ryland DH, Kriete M (1992). Drug treatment of canine acral lick. An animal model of obsessive-compulsive disorder. Arch Gen Psychiatry 49: 517–521.

Rescorla RA (2001). Retraining of extinguished Pavlovian stimuli. J Exp Psychol Anim Behav Process 27: 115–124.

Robbins TW (2002). The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl) 163: 362–380.

Robbins TW (2005). Chemistry of the mind: neurochemical modulation of prefrontal cortical function. J Comp Neurol 493: 140–146.

Robbins TW, Koob GF (1980). Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285: 409–412.

Robbins TW, Sahakian BJ (1983). Behavioural effects of psychomotor stimulant drugs: clinical and neuropsychological implications. In: CREESE I (ed.). Stimulants, Neurochemical, Behavioural and Clinical Perspectives. Raven Press: New York, pp. 301–338.

Roberts AC, Tomic DL, Parkinson CH, Roeling TA, Cutter DJ, Robbins TW *et al.* (2007). Forebrain connectivity of the prefrontal cortex in the marmoset monkey (Callithrix jacchus): an anterograde and retrograde tract-tracing study. J Comp Neurol 502: 86–112.

Robinson ES, Dalley JW, Theobald DE, Glennon JC, Pezze MA, Murphy ER *et al.* (2008a). Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. Neuropsychopharmacology 33: 2398–2406.

Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X *et al.* (2008b). Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 33: 1028–1037.

Rosenberg DR, Dick EL, O'hearn KM, Sweeney JA (1997). Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. J Psychiatry Neurosci 22: 29–38.

Sahakian BJ, Robbins TW (1975). The effects of test environment and rearing condition on amphetamine-induced stereotypy in the guinea-pig. Psychopharmacologia 45: s115–s117.

Samuels J, Bienvenu OJ, Riddle MA, Cullen BA, Grados MA, Liang KY *et al.* (2002). Hoarding in obsessive compulsive disorder: results from a case-control study. Behav Res Ther 40: 517–528.

Schilman EA, Uylings HB, Galis-De Graaf Y, Joel D, Groenewegen HJ (2008). The orbital cortex in rats topographically projects to central parts of the caudate-putamen complex. Neurosci Lett 432: 40–45.

Shmelkov SV, Hormigo A, Jing D, Proenca CC, Bath KG, Milde T *et al.* (2010). Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice. Nat Med 16: 598–602, 1p following 602.

Shugart YY, Samuels J, Willour VL, Grados MA, Greenberg BD, Knowles JA *et al.* (2006). Genomewide linkage scan for obsessive-compulsive disorder: evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. Mol Psychiatry 11: 763–770.

Skoog G, Skoog I (1999). A 40-year follow-up of patients with obsessive-compulsive disorder [see comments]. Arch Gen Psychiatry 56: 121–127.

Solomon RL, Kamin LJ, Wynne LC (1953). Traumatic avoidance learning: the outcomes of several extinction procedures with dogs. J Abnorm Psychol 48: 291–302.

Sprengelmeyer R, Young AW, Pundt I, Sprengelmeyer A, Calder AJ, Berrios G *et al.* (1997). Disgust implicated in obsessive-compulsive disorder. Proc R Soc Lond B Biol Sci 264: 1767–1773.

Stein DJ, Dodman NH, Borchelt P, Hollander E (1994). Behavioral disorders in veterinary practice: relevance to psychiatry. Compr Psychiatry 35: 275–285.

Summerfeldt LJ, Richter MA, Antony MM, Swinson RP (1999). Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analytic study. Behav Res Ther 37: 297–311.

Swanepoel N, Lee E, Stein DJ (1998). Psychogenic alopecia in a cat: response to clomipramine. J S Afr Vet Assoc 69: 22.

Swedo SE, Leonard HL, Rapoport JL, Lenane MC, Goldberger EL, Cheslow DL (1989). A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). N Engl J Med 321: 497–501.

Szechtman H, Woody E (2004). Obsessive-compulsive disorder as a disturbance of security motivation. Psychol Rev 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). Behav Neurosci 112: 1475–1485.

Tanaka SC, Balleine BW, O'doherty JP (2008). Calculating consequences: brain systems that encode the causal effects of actions. J Neurosci 28: 6750–6755.

Tardito D, Milanese M, Bonifacino T, Musazzi L, Grilli M, Mallei A *et al.* (2010). Blockade of stress-induced increase of glutamate release in the rat prefrontal/frontal cortex by agomelatine involves synergy between melatonergic and 5-HT2C receptor-dependent pathways. BMC Neurosci 11: 68.

Tien AY, Pearlson GD, Machlin SR, Bylsma FW, Hoehn-Saric R (1992). Oculomotor performance in obsessive-compulsive disorder. Am J Psychiatry 149: 641–646.

Tricomi E, Balleine BW, O'doherty JP (2009). A specific role for posterior dorsolateral striatum in human habit learning. Eur J Neurosci 29: 2225–2232.

Tricomi EM, Delgado MR, Fiez JA (2004). Modulation of caudate activity by action contingency. Neuron 41: 281–292.

Tsaltas E, Kontis D, Chrysikakou S, Giannou H, Biba A, Pallidi S *et al.* (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. Biol Psychiatry 57: 1176–1185.

Valentin VV, Dickinson A, O'doherty JP (2007). Determining the neural substrates of goal-directed learning in the human brain. J Neurosci 27: 4019–4026.

Van Den Heuvel OA, Veltman DJ, Groenewegen HJ, Witter MP, Merkelbach J, Cath DC *et al.* (2005). Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Arch Gen Psychiatry 62: 922–933.

Vertes RP (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51: 32–58.

Walker SC, Robbins TW, Roberts AC (2009). Differential contributions of dopamine and serotonin to orbitofrontal cortex function in the marmoset. Cereb Cortex 19: 889–898.

Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD *et al*. (2007). Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature 448: 894–900.

Wendland JR, Moya PR, Timpano KR, Anavitarte AP, Kruse MR, Wheaton MG *et al*. (2009). A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder. Arch Gen Psychiatry 66: 408–416.

Westenberg HG, Fineberg NA, Denys D (2007). Neurobiology of obsessive-compulsive disorder: serotonin and beyond. CNS Spectr 12: 14–27.

Whiteside SP, Port JD, Deacon BJ, Abramowitz JS (2006). A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. Psychiatry Res 146: 137–147.

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

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 ME, Cassic KS, Koran LM (1999). Hoarding in obsessive-compulsive disorder: a report of 20 cases. J Clin Psychiatry 60: 591–597.

Winslow JT, Insel TR (1991). Neuroethological models of obsessive-compulsive disorder. In: Zohar J, Insel TR, Rasmussen S (eds). The Psychobiology of Obsessive-Compulsive Disorder. Springer: New York, pp. 179–182.

Winstanley CA, Theobald DE, Dalley JW, Glennon JC, Robbins TW (2004). 5-HT2A and 5-HT2C receptor antagonists have opposing effects on a measure of impulsivity: interactions with global 5-HT depletion. Psychopharmacology (Berl) 176: 376–385.

Wolinsky TD, Smith DG, Nugent B, Antonijevic I, Moore N (2006). Potentiation of SSRI efficacy by neurokinin 1 receptor antagonism. Int J Neuropsychopharmacol 9: s114.

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

Yadin E, Friedman E, Bridger WH (1991). Spontaneous alternation behavior: an animal model for obsessive-compulsive disorder? Pharmacol Biochem Behav 40: 311–315.

Yin HH, Knowlton BJ (2006). The role of the basal ganglia in habit formation. Nat Rev Neurosci 7: 464–476.

Yin HH, Knowlton BJ, Balleine BW (2004). Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci 19: 181–189.

Yin HH, Ostlund SB, Knowlton BJ, Balleine BW (2005). The role of the dorsomedial striatum in instrumental conditioning. Eur J Neurosci 22: 513–523.

Zohar AH (1999). The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am 8: 445–460.

Zohar J, Insel TR, Zohar-Kadouch RC, Hill JL, Murphy DL (1988). Serotonergic responsivity in obsessive-compulsive disorder. Effects of chronic clomipramine treatment. Arch Gen Psychiatry 45: 167–172.

Zohar J, Kennedy JL, Hollander E, Koran LM (2004). Serotonin-1D hypothesis of obsessive-compulsive disorder: an update. J Clin Psychiatry 65 (Suppl. 14): 18–21.

Zor R, Fineberg NA, Hermesh H, Eilam D (2010). A video telemetry documentation of OCD behavior: Studying cultural impact on OC behavior and the validity of OCD sub-typing. *Poster presented at the Annual Meeting of the International College of Obsessive-Compulsive Spectrum Disorders, Amsterdam, ND. September 2nd, 2010*.

Zuchner S, Cuccaro ML, Tran-Viet KN, Cope H, Krishnan RR, Pericak-Vance MA *et al*. (2006). SLITRK1 mutations in trichotillomania. Mol Psychiatry 11: 887.