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Assessing the validity of current mouse genetic models of obsessive–compulsive disorder

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Abstract

Obsessive–compulsive disorder (OCD) is a disorder characterized by unwanted and intrusive thoughts, images, or impulses and/or repetitive behavior. OCD is a major cause of disability; however, the genetic factors and pathophysiological mechanisms underlying this complex, heterogeneous disorder remain largely unknown. During the past decade, a number of putative mouse genetic models of OCD have been developed for the purpose of studying the neural mechanisms underlying this disorder and developing novel treatments. This review presents and evaluates these experimental preparations to date. Models using knockout or transgenic approaches, as well as those examining variation in genetically diverse populations, are evaluated and discussed.

Keywords

anxiety disorder; genetic model; mouse; obsessive–compulsive disorder; validity

Introduction

Obsessive–compulsive disorder (OCD) is a severe mental disorder that has been identified by the World Health Organization as one of the world's ten leading causes of illness-related disability (Murray and Lopez, 1996). Despite the public health burden of OCD, relatively little is known about its neurobiology compared with other major mental disorders. A better understanding of genetic and molecular mechanisms in OCD is immediately required to develop new and more effective treatments. Animal models of OCD provide a critical tool for such investigation, because the consequences of genetic, pharmacological, neuroanatomic, and environmental manipulations can be evaluated directly in animals using approaches that are not feasible in people. This study provides a brief overview of the epidemiology, pathophysiology, treatment, and genetics of OCD, and a comprehensive review of putative mouse genetic models of OCD that have been developed to date.

Obsessive–compulsive disorder

OCD is characterized by recurrent and unwanted intrusive thoughts, impulses or images (obsessions), and/or repetitive behaviors or mental acts that the person feels driven to perform (compulsions). Common themes of obsessions include fear of contamination, fear of harming

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self or others, moral concerns such as scrupulosity, and symmetry. Compulsions can include excessive washing or grooming, counting, checking, telling or confessing, repeating, and hoarding; compulsions are often performed in response to an obsession and are aimed at reducing distress or preventing some feared event.

The lifetime prevalence of OCD is 1–3% in the general population (Robins *et al.*, 1984; Kessler *et al.*, 2005). Although the overall female/male sex ratio has been suggested to be 1–1.5 (Thomsen and Jensen, 1994; Bebbington, 1998; Fireman *et al.*, 2001), this ratio varies with age. The female/male ratio in OCD has been estimated to be 0.53 in patients under 18 years of age, whereas the female/male ratio is 1.47 in adults (Fireman *et al.*, 2001). The onset of OCD has been observed as early as age 4 years (Tobias and Walitza, 2006). Above the age of 65 years, the prevalence of clinically recognized OCD markedly decreases in both sexes (Fireman *et al.*, 2001). OCD patients often present with comorbid psychiatric conditions including tic disorders such as Tourette's syndrome (Leonard *et al.*, 1992; Steingard *et al.*, 1997; Nestadt *et al.*, 2001), anxiety and affective disorders (Nestadt *et al.*, 2001), the impulse control disorder trichotillomania (King *et al.*, 1995; Stewart *et al.*, 2005), somatoform disorders (Nestadt *et al.*, 2001), and eating disorders (Nestadt *et al.*, 2001). Environmental factors including immunologic stress (Dinn *et al.*, 2001; Murphy *et al.*, 2001; Nicholson *et al.*, 2007) have also been implicated in the etiology of OCD. Like many psychiatric disorders, OCD is likely a heterogeneous disorder comprised of several subtypes with distinct genetic and environmental risk factors and pathophysiological mechanisms. This heterogeneity has hindered human genetic studies of OCD and the development of animal models.

Treatment of obsessive–compulsive disorder

Current treatments for OCD are cognitive-behavioral therapy, consisting of exposure and response prevention, and pharmacotherapy with serotonin reuptake inhibitors (SRIs). SRIs, which include the selective SRIs and the tricyclic antidepressant clomipramine, provide the only effective pharmacological monotherapy for OCD (Koran *et al.*, 2007). The delayed onset of therapeutic response to SRIs is substantially longer for OCD patients than for depressed patients. Approximately 2–4 weeks of treatment is required for the initial therapeutic effects of SRIs to emerge in depressed patients (Katz *et al.*, 1996), whereas at least 8–12 weeks of treatment is required in OCD patients (Pallanti *et al.*, 2004). However, 40–60% of OCD patients do not respond to SRI treatment, and those who do often exhibit a partial response (Hollander and Pallanti, 2002). To date, studies have suggested that other tricyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, lithium, antipsychotics, and electroconvulsive therapy are not as effective as monotherapy for OCD (Hollander and Pallanti, 2002; Koran *et al.*, 2007).

Augmentation of SRI treatment with first-generation antipsychotics (Li *et al.*, 2005) and certain second-generation antipsychotics (Erzegovesi *et al.*, 2001; Fineberg and Gale, 2005) has been shown to improve therapeutic response in patients showing poor response to SRI monotherapy (Bloch *et al.*, 2006). For example, haloperidol, risperidone, quetiapine, and olanzapine have all been shown to augment the effects of SRIs in randomized controlled trials (McDougle *et al.*, 1994; McDougle *et al.*, 2000; Bystritsky *et al.*, 2004; Denys *et al.*, 2004). However, negative findings have also been reported from studies of quetiapine (Carey *et al.*, 2005) and olanzapine (Shapira *et al.*, 2004) augmentation, although methodological issues may explain this discrepancy. A systematic review of antipsychotic augmentation (Bloch *et al.*, 2006), which combined nine double-blind, randomized controlled clinical trials involving 278 patients, showed that approximately one-third of OCD patients benefit from antipsychotic augmentation, with strong evidence supporting the efficacy of haloperidol and risperidone. These findings are consistent with the results of pharmacological challenge studies implicating hyperdopaminergic transmission in OCD (Denys *et al.*, 2004).

In summary, SRI is the only effective medication monotherapy for OCD that has led to the speculation that abnormalities in the serotonin system underlie OCD symptoms. However, not all patients respond to SRIs, and some patients benefit from augmentation strategies using dopaminergic agents. The heterogeneity in treatment response presumably reflects heterogeneity in the underlying brain abnormalities. However, the fact that SRIs can alleviate OCD symptoms does not provide evidence that OCD symptoms are caused by serotonergic abnormalities. To develop a better understanding of the mechanisms underlying symptoms in OCD patients, researchers have conducted human genetic and imaging studies, which are reviewed next.

Human genetic studies of obsessive–compulsive disorder

Current approaches to gene discovery in complex disorders such as OCD include twin studies, family studies, segregation analysis, and association analysis. Recently, much attention has been given to the potential role of gene copy number variations in the etiology of complex disorders (Ji *et al.*, 2000; Beckmann *et al.*, 2007). Although some copy number variations have been linked to autistic and obsessive–compulsive traits (Nakamine *et al.*, 2008), none have so far been associated with OCD. Family studies suggest that OCD is familial; a recent meta-analysis of five OCD family studies indicated that there was a significantly increased risk of OCD among relatives of probands (Hettema *et al.*, 2001). Twin studies also suggest that OCD is heritable (Wolff *et al.*, 2000; Van Grootheest *et al.*, 2005; Mathews *et al.*, 2007; Hur and Jeong, 2008; Pauls, 2008), with some estimating the heritability of OCD to be between 45 and 65% in children and 27–47% in adults (Van Grootheest *et al.*, 2005; Pauls, 2008). Thus, genetic factors play an important role in at least some forms of OCD. Segregation analysis studies examining the patterns of transmission of OCD in families have yielded inconsistent findings regarding the model of inheritance in OCD (Di Bella *et al.*, 2000; Khanna *et al.*, 2001; Nestadt *et al.*, 2001). Overall, findings suggest that there are some genes of major effect that contribute to the development of OCD, and that OCD is a multigenic disorder.

Over 60 candidate gene studies for OCD have been reported (Hemmings and Stein, 2006; Pauls, 2008). Numerous genes coding for elements of neurotransmitter systems implicated in OCD have been examined for association with OCD. These include genes for the serotonergic system such as the 5-HT1B (Pirola *et al.*, 2002) and 5-HT2A receptors (Camarena *et al.*, 2004), the serotonin transporter (Hu *et al.*, 2006; Wendland *et al.*, 2007), and monoamine oxidase A (Camarena *et al.*, 2004). The dopaminergic receptor genes DRD2, DRD3, and DRD4 (Billett *et al.*, 1998; Di Bella *et al.*, 2000; Camarena *et al.*, 2004; Delorme *et al.*, 2005), and catechol-O-methyltransferase (COMT) gene (Alsobrook *et al.*, 2002) have also been studied. Other candidate genes examined include those involved in the glutamatergic (Delorme *et al.*, 2005; Hu *et al.*, 2006) and opioid (Urraca *et al.*, 2004) systems and neurotrophic factors including brain-derived neurotrophic factor (Hall *et al.*, 2003; Hemmings *et al.*, 2007; Wendland *et al.*, 2007; Alonso *et al.*, 2008).

Overall, the results of candidate gene studies have been mixed, with some studies suggesting a genetic association, and others failing to replicate findings. Furthermore, none have achieved genome-wide significance. The only candidate gene for which positive findings have been consistently replicated is the glutamate transporter gene *SLC1A1* (Nestadt *et al.*, 2001; Dickel *et al.*, 2006; Hu *et al.*, 2006; Stewart *et al.*, 2007). Furthermore, two genome-wide linkage studies (Khanna *et al.*, 2001; Willour *et al.*, 2004) identified a linkage peak spanning the entire 9p24 region which contains the glutamate transporter, although genome-wide significance was not achieved in either study. The polymorphism responsible for this linkage peak and the functional consequences of this variant on the glutamate transporter are currently unknown.

Neuroanatomy and neurochemistry of obsessive–compulsive disorder

There are no postmortem studies of the brains of OCD patients to provide insight into the pathophysiology of the disorder. Therefore, prevailing views regarding which neural circuits might be malfunctioning in OCD patients come primarily from neuroimaging studies, and case reports of OCD onset after traumatic brain lesion (Baxter *et al.*, 1995; Saxena and Rauch, 2000; Zuccato *et al.*, 2001; Husted *et al.*, 2006; Menzies *et al.*, 2008a). Briefly, abnormalities in fronto-subcortical brain regions and circuits have been consistently identified in OCD. Imaging studies have identified increased activity in the orbitofrontal cortex, caudate nucleus, and thalamus, which are connected to form circuits or functional ‘loops’. Increased activity in these structures has been found in the untreated state (Swedo *et al.*, 1989; Sawle *et al.*, 1991; Rubin *et al.*, 1992; Baxter *et al.*, 1995; Lucey *et al.*, 1995; Perani *et al.*, 1995) and during symptom provocation (McGuire *et al.*, 1994; Breiter *et al.*, 1996; Stein *et al.*, 2000). Successful treatment with SRIs or cognitive behavioral therapy attenuates hyperactivity in these structures (Benkelfat *et al.*, 1990; Swedo *et al.*, 1992; Azmitia *et al.*, 1995; Schwartz *et al.*, 1996; Saxena *et al.*, 1999; Saxena *et al.*, 2002) and abolishes the correlations in brain activity between these structures that are observed during illness (Schwartz *et al.*, 1996).

The structural organization of fronto-subcortical circuits consists of numerous parallel connections, each linking different subcompartments of the prefrontal cortex, basal ganglia, and thalamus in discrete loops (Saxena and Rauch, 2000). Each compartment contains two different functional loops termed as the ‘direct’ and the ‘indirect’ pathways, which facilitate and inhibit complex behavioral routines, respectively. The direct pathway consists of excitatory inputs from frontal cortex to the caudate, which inhibits the internal globus pallidus and substantia nigra reticulata, resulting in disinhibition of the thalamus, which forms reciprocal excitatory connections with frontal cortex. In contrast, the indirect pathway inhibits or interrupts these ongoing cortico-thalamo processing routines by inhibiting the thalamus through the indirect basal ganglia control system (Baxter *et al.*, 1995; Saxena and Rauch, 2000). Hyperactivity of the direct pathways has been implicated in OCD. Experimental evidence in humans, primates, rodents, and lizards suggests that activity within these circuits is involved in mediating behavioral responses towards socioterritorial concerns such as dominance displays, hygiene, order, and harm (MacLean, 1978; Baxter *et al.*, 1995; Saxena and Rauch, 2000).

Recent work has reported differential patterns of brain activity in different symptom dimensions of OCD (Mataix-Cols *et al.*, 2004; Saxena *et al.*, 2004). For example, OCD patients showed greater activation than controls in the putamen/globus pallidus, thalamus, and dorsal cortical areas while imagining checking during symptom provocation, and greater activation than controls in left precentral gyrus and right orbitofrontal cortex while imagining hoarding (Mataix-Cols *et al.*, 2004). However, it has also been proposed that the fronto-striatal model of OCD may be incomplete, at least for some subtypes of OCD. For example, the fronto-striatal model does not incorporate the potential role of paralimbic regions in the pathophysiology of OCD (Saxena *et al.*, 2004; Mataix-Cols and van den Heuvel, 2006).

Neurochemical imaging studies of OCD have also been conducted, including imaging of serotonergic, dopaminergic, and glutamatergic neurochemical systems. Overall, these studies are limited by small samples and inconsistent findings in the few cases where replication has been attempted. However, these studies offer some evidence for serotonergic, dopaminergic, and/or glutamatergic abnormalities in OCD and in the frontal-striatal circuits previously implicated in OCD. Owing to the specific efficacy of SRIs for the treatment for OCD, most neurochemical studies in OCD have focused on the serotonergic system. Single-photon emission computed tomography studies of 5-HTT binding have reported disparate results, with some reporting increased, decreased, or no difference in midbrain 5-HTT binding (Pogarell *et*

et al., 2003; Simpson *et al.*, 2003; Stengler-Wenzke *et al.*, 2004; Van der Wee *et al.*, 2004). Others have found increased 5-HT_{2A} binding in OCD patients in the caudate (Adams *et al.*, 2005); however, given the low density of 5-HT_{2A} receptors in the caudate, the reliability of this finding is questionable. Single-photon emission computed tomography studies investigating the dopaminergic system have led to inconsistent or unreplicated findings in small samples (Denys *et al.*, 2004). Proton magnetic resonance spectroscopic studies conducted by Rosenberg *et al.* (2000) showed increased glutamate in the caudate nucleus of SRI-naïve children with OCD, which were normalized by selective SRI treatment (Rosenberg *et al.*, 2000). This led to the speculation that OCD patients have abnormalities in glutamatergic-serotonergic neurotransmission and to the development of hyperglutamatergic models of OCD. This finding has led to the hypothesis that the orbitofrontal hyperactivity observed in OCD is because of hyperglutamatergic output to the striatum (Carlsson, 2000; Rosenberg *et al.*, 2001; Pittenger *et al.*, 2006). In summary, although much has been learned regarding patterns of brain activation that correlate with OCD symptoms, much about the brain mechanism of OCD remains obscure. This has led to increasing interest in developing animal models that could help dissect the neural circuits implicated in OCD and clarify the role of serotonergic, dopaminergic, and glutamatergic neurochemical systems.

Developing and validating animal models

Animal models are experimental preparations that permit phenomena of interest in one species to be studied in another species. Owing to the heterogeneity and evolving nature of psychiatric diagnostic categories, current approaches to the development of animal models focus on mimicking only specific aspects of disorders, rather than the entire syndrome. Although few such aspects are specific to any one neuropsychiatric disorder, this approach remains more feasible and powerful than attempting to model a neuropsychiatric disorder in its entirety (Geyer and Markou, 1995). In an ideal approach, a well-established endophenotype for the disorder of interest can be modeled in animals. Endophenotypes refer to phenotypes that are invisible to the naked eye and are associated with the disorder. They include neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological measures, and provide more straightforward measures for study than symptoms. To be considered an endophenotype, a measure must be (i) associated with illness in the population, (ii) heritable, (iii) primarily state-independent, (iv) co-segregate with illness in families, and (v) found in nonaffected family members at a higher rate than in the general population (Bailey *et al.*, 1995). Although recent efforts have made progress towards identifying endophenotypes in OCD, these findings will require further study and replication (Swerdlow *et al.*, 1993; Hoenig *et al.*, 2005; Chamberlain *et al.*, 2007; Menzies *et al.*, 2008b). In the absence of a well-established endophenotype for study, an alternative approach is to model an aspect or core feature of the disorder of interest (Geyer and Markou, 1995). This approach has been used most often to model aspects of OCD in animals. For example, many animal models of OCD have utilized repetitive or stereotyped behaviors as the primary dependent measure.

Criteria for the validation of animal models for neuropsychiatric disorders have been proposed and refined over the past several decades (McKinney and Bunney, 1969; Matthysse, 1986; Markou *et al.*, 1993; Willner, 1997). However, various types of validation criteria have been defined somewhat inconsistently by different groups within this field. In this review, we apply the terminology and basic approaches used by Geyer and Markou (1995), which are taken directly from the literatures of philosophy, psychology, and measurement (Boring, 1945; Bridgman, 1945; Mosier, 1947; Cronbach and Meehl, 1955; Campbell and Fiske, 1959). They suggest that the only necessary and sufficient criterion for the initial use of any type of animal model is predictive validity, which refers to the ability of a model to make accurate predictions about the human phenomenon of interest (Geyer and Markou, 1995). Importantly, predictive

validity refers not only to the ability of the model to predict drug effects, but also its ability to make accurate predictions about the effects of any variable on the human condition of interest, including environmental or epidemiological variables. Another type of predictive validity is reliability, which refers to the consistency and stability of results obtained from the same experimental preparation within and between laboratories. Simply, an unreliable model cannot make accurate predictions. Furthermore, the predictive validity of any animal model can only be as sound as the information available in the clinical literature regarding the disorder being modeled (Geyer and Markou, 1995).

There are other types of criteria, including construct and face validity. Neither is required for the use or validation of an animal model (Geyer and Markou, 1995). Briefly, face validity refers to the phenomenological similarity between the dependent measure and the symptom being modeled. Face validity is often misleading because the same biological process can produce dissimilar symptoms across species, and seemingly identical symptoms can be produced by different underlying biological processes. Furthermore, arguments for face validity are subjective and cannot be rigorously defended. Thus, although face validity can provide a heuristic starting point for developing a model, it cannot be used to validate a model. Construct validity refers to whether or not a test or procedure measures or correlates with a theoretical construct it is intended to measure (Campbell and Fiske, 1959). However, construct validity can only rarely be established firmly because conceptions about what a test is supposed to measure are constantly evolving as theories and theoretical constructs are being modified. Therefore, the validity of a model cannot be determined by its degree of construct validation (Geyer and Markou, 1995).

Current genetic mouse models of obsessive–compulsive disorder

The intended purpose of an animal model determines the criteria it should satisfy in order to establish its validity (Geyer and Markou, 1995). The putative animal genetic models of OCD reviewed here were developed for the purpose of studying the pathophysiological mechanisms underlying a core feature of OCD. Therefore, the present review will summarize and critique these models in terms of their usefulness for this purpose. Ideally, such models should show strong predictive validity for the most well-characterized aspects of OCD, which include therapeutic drug response and the time course of action. Other characteristics of OCD including epidemiological factors and abnormalities in fronto-subcortical neural circuits can also contribute to the predictive validity of a genetic model of OCD. However, less well-established findings in OCD provide weaker tools for establishing predictive validity. For example, the details of how fronto-cortical circuits are malfunctioning in OCD remain unknown, and whether abnormalities in these circuits cause OCD symptoms or are the result of OCD symptoms is not clear. Thus, a mouse genetic model that directly leads to abnormalities in fronto-cortical circuits may or may not replicate the pathophysiology of OCD.

Current genetic mouse models of OCD utilize two major strategies: forward or reverse genetic approaches. The vast majority of these are reverse genetic models in which a candidate gene was directly manipulated using knockout or transgenic approaches and the behavioral effects were characterized. Furthermore, reverse genetic approaches have utilized different strategies; some have targeted the serotonergic or dopaminergic systems, and others have targeted fronto-subcortical neural circuits or were serendipitous. Two forward genetic, or spontaneous, models are also reviewed that examine variation in OCD-like behavior in genetically diverse populations. Although ‘gene finding’ approaches such as quantitative trait loci (QTL) mapping have not yet been applied to these spontaneous models, the results of these studies provide the groundwork for such work.

Reverse genetic models

D1CT-7 mutant mice

D1CT-7 transgenic mice were generated by Burton and colleagues (Smicun *et al.*, 1999) and express an intracellular form of cholera toxin (CT), a neuromodulating enzyme that chronically activates stimulatory G-protein signal transduction and cAMP synthesis. D1CT-7 mutant mice express CT under the control of the D1 promoter in a subset of D1 receptor-containing neurons within the amygdalar intercalated nucleus and in cortical areas that project to orbitofrontal cortex and striatum (Cryan *et al.*, 1999; Smicun *et al.*, 1999). D1CT-7 mice were found to exhibit a constellation of compulsive behaviors including episodes of repetition of normal behaviors, repetitive nonaggressive biting of siblings during grooming, and repetitive leaping (Smicun *et al.*, 1999). D1CT-7 mice also exhibited increased anxiety-related behavior in the open field and light–dark tests compared with littermates (Cryan *et al.*, 1999). Moreover, D1CT-7 mice were reported to exhibit Tourette’s syndrome-like behaviors including juvenile-onset tics, increased tic number, complexity, flurries, and voluntary tic suppression (Nordstrom and Burton, 2002). The apparent similarity between compulsive and tic-related behaviors in D1CT-7 mice and the symptoms of OCD and Tourette’s syndrome contribute to the face validity of this model. However, D1CT-7 mice also exhibit additional phenotypes that have not been linked to OCD, including limbic seizures (Campbell *et al.*, 2000).

The brain regions in which the CT transgene is expressed in D1CT-7 mutant mice overlap with the neural circuitry implicated in OCD. Furthermore, the chronic potentiation of cortical and limbic D1+ neurons, which was shown by increased cAMP tissue content, is thought to result in increased glutamatergic output to the striatum, although this was not measured directly in these mice. As hyperactivity of cortico-striatal circuits has been implicated in OCD (Breiter and Rauch, 1996; Breiter *et al.*, 1996; Stewart *et al.*, 2005) (Smicun *et al.*, 1999), the D1CT-7 mutant mouse model might be argued to show some predictive validity.

The effects of some drug treatments on behavior have been reported in D1CT-7 mutant mice. For example, a noncataleptic dose of clonidine was shown to reduce tics in these mice (Nordstrom and Burton, 2002). However, some but not all double-blind placebo-controlled studies have shown efficacy for clonidine in Tourette’s syndrome (Goetz *et al.*, 1987; Leckman *et al.*, 1991; Singer *et al.*, 1995), and no efficacy for clonidine has been shown in OCD (Gaffney *et al.*, 2002). Whether the repetitive behavior and tics exhibited by D1CT-7 mice can be reduced by chronic SRI treatment remains to be examined.

Dopamine transporter knockdown mice

Dopamine transporter knockdown (DAT KD) mice express only 10% of normal DAT levels, have slower dopamine clearance, and exhibit 70% increases in extracellular dopamine levels (Zhuang *et al.*, 2001). DAT KD mice also exhibit hyperactivity, which can be blocked by the administration of amphetamine (Zhuang *et al.*, 2001) or valproic acid (Ralph-Williams *et al.*, 2003), which provide treatment for attention-deficit hyperactivity disorder and mania, respectively. DAT KD mice have also been reported to show reduced habituation to novelty (Zhuang *et al.*, 2001), and increased motivation to work for food reward (Pecina *et al.*, 2003; Cagniard *et al.*, 2006).

Berridge *et al.* (2004) characterized syntactic grooming chain patterns in DAT KD mice. Syntactic grooming chain patterns are defined as a fixed action pattern that serially links up to 25 grooming movements in four predictable phases that follow one syntactic rule. DAT KD mice were found to show stronger and more rigid syntactic grooming chain patterns that were more resistant to interruption. The more rigid syntactic grooming chain patterns identified in DAT KD mice were proposed to resemble sequential super-stereotypy in Tourette’s syndrome

and OCD (Sheppard *et al.*, 1999). Sequential super-stereotypy refers to the overly rigid sequential patterns of action, language, or thought that are observed in these disorders. The rigid grooming chain patterns in DAT KD mice seem to have face validity for sequential super-stereotypy in OCD.

Dysfunction of basal ganglia circuits has been implicated in both Tourette's syndrome and OCD. In addition, the basal ganglia have been implicated in organizing sequential patterns of movement and thought, including syntactic grooming chain patterns. For example, neurons in the dorsolateral neostriatum increase firing by 116% during syntactic grooming chains in the rat (Berridge *et al.*, 2005), and neuronal activity during spatial planning in primates suggests that the caudate nucleus is instrumental in running sequences of movements (Kermadi and Joseph, 1995). Furthermore, lesions of the neostriatum disrupts the serial pattern of syntactic grooming chains, but does not impair constituent grooming movements in rats (Cromwell and Berridge, 1996; Berridge *et al.*, 2005). Therefore, Berridge *et al.* (2004) suggest that the more stereotyped syntactic grooming chains observed in DAT KD mice are likely to involve dysfunction of the neostriatum, although this was not proven directly. However, one human genetic study found enhanced, rather than reduced, dopamine transporter binding in psychotropic-naïve patients with OCD (Van der Wee *et al.*, 2004), suggesting that DAT KD mice might not provide a strategy for modeling OCD. At the same time, this human genetic finding will require replication. In summary, more work will be required to establish predictive validity of the DAT KD model for aspects of OCD.

Sapap3-mutant mice

SAP90/PSD95-associated protein 3 (Sapap 3) is a postsynaptic scaffolding protein at excitatory synapses that is highly expressed in the striatum. Welch *et al.* (2007) showed that knockout of Sapap3 in mice leads to compulsive overgrooming that emerges by 4–6 months of age. Specifically, 100% of Sapap3 KO mice developed lesions on their head, neck, and snout, which were the results of substantial increases in self-grooming. No obvious peripheral defects such as abnormal sensory innervation were found. Sapap 3 KO mice also showed increased anxiety-related behaviors in the open field, light–dark test, and elevated zero maze; overall locomotor activity was not altered. Six days of treatment with 5λmg/kg fluoxetine (once per day, intraperitoneally), dramatically reduced overgrooming in Sapap 3 KO mice, but did not alter grooming behavior in wild-type (WT) mice. A single injection of 5λ(mg/kg fluoxetine had no effect; thus, 2–6 days of 5λmg/kg fluoxetine treatment are required to reduce overgrooming in these mice. The same subchronic fluoxetine treatment regimen also reduced the latency for Sapap3 KO mice to enter the light chamber in the light–dark test, although a similar trend was apparent in WT mice.

The overgrooming phenotype of Sapap 3 KO mice could be argued to exhibit face validity for OCD. Although the reduction of overgrooming behavior by fluoxetine in Sapap 3 KO mice is intriguing, several points should be noted. One, the time response to subchronic treatment is inconsistent with the therapeutic response in OCD patients, which typically requires 8–12 weeks, and is twice as long as the therapeutic delay for treating depression. Although the time course for the onset of behavioral effects of SRIs may not be identical in humans and mice, other behavioral models showing antidepressant and anxiolytic effects of chronic SRIs in mice have found that at least 12–14 days of treatment are required (Willner, 1997; Dulawa *et al.*, 2004; Shanahan *et al.*, 2008). Two, the dose of fluoxetine used (5λmg/kg/day) is substantially lower than doses typically found to reduce anxiety and depression-related behavior in mice in chronic models (Dulawa *et al.*, 2004; Shanahan *et al.*, 2008; Yalcin *et al.*, 2008) (10–20λmg/kg/day), and higher doses of SRIs are typically required to treat OCD compared with depression and other anxiety disorders.

Welch *et al.* (2007) also showed that Sapap 3 KO mice have cortico-striatal synaptic defects. Cortico-striatal synapses of Sapap 3 KO mice revealed structural defects in the postsynaptic complex, increased expression of the NR1 subunit of the NMDA receptor, and reduced total field potentials. Thus, Sapap 3 KO mice show reduced cortico-striatal synaptic transmission. Importantly, lentiviral-mediated selective expression of Sapap 3 in the striatum reversed the synaptic and behavioral defects, suggesting that the absence of Sapap 3 in the striatum causes the synaptic and behavioral phenotypes. The involvement of cortico-striatal synapses in the phenotype of Sapap 3 KO mice contributes to predictive validity of the model. However, the ability of short-term fluoxetine treatment to reduce overgrooming suggests that Sapap 3 KO mice lack predictive validity as an animal model of OCD. To our knowledge, no human genetic studies to date have examined the Sapap3 gene in OCD patients.

5-HT2C knockout mice

Since their initial generation, 5-HT2C KO mice have been extensively characterized (Tecott *et al.*, 1995). These mice exhibit numerous physiological and behavioral phenotypes, many of which involve changes in ingestive behavior and energy balance. 5-HT2C KO mice develop mid-life obesity as a consequence of hyperphagia and impaired satiety mechanisms, and die from spontaneous seizures beginning at 5 weeks of age (Tecott *et al.*, 1995; Brennan *et al.*, 1997; Applegate and Tecott, 1998; Tecott and Abdallah, 2003). 5-HT2C KO mice also show increased motor activity in young adulthood, (Nonogaki *et al.*, 2003) and show altered sleep homeostasis (Waterston *et al.*, 2002).

In addition to exhibiting hyperphagia, 5-HT2C knockout mice also show increased chewing of non-nutritive objects. Chou-Green *et al.* (2003) characterized object chewing in 5-HT2C knockout mice and suggested that the increased 'neat' and highly organized patterns of chewing observed could provide a promising model of compulsive behavior in OCD. 5-HT2C KO mice were found to chew more clay than WT mice, and to chew plastic screens in a more regular pattern than WT mice. Finally, 5-HT2C KO mice were reported to exhibit more head-dipping behavior than WT mice, which was suggested to reflect a form of nonoral compulsive behavior. Mice were tested at approximately 6 months of age in all experiments (Chou-Green *et al.*, 2003).

The increases in behaviors defined as 'compulsive' by Chou-Green *et al.* (2003) can be argued to have face validity for OCD. However, head-dipping behavior has been well validated as a measure of exploration/anxiety, rather than compulsive behavior. For example, head-dipping behavior is altered by anxiolytic drugs such as benzodiazepines (File, 1981; Shimada *et al.*, 1995), whereas core features of OCD including compulsive behaviors are not (Lelliott and Monteiro, 1986; Hollander and Pallanti, 2002; Hollander *et al.*, 2003). In addition, 5-HT2C KO mice have been reported to show less anxiety-related behavior than WT mice, which appears inconsistent with anxiety symptoms in OCD (Heisler *et al.*, 2007). Further experiments will be required to establish whether compulsive chewing in 5-HT2C KO mice exhibits any predictive validity for OCD.

There is some evidence to suggest that 5-HT2C receptors play a role in the etiology of OCD. Many (Zohar *et al.*, 1987; Hollander *et al.*, 1992; Erzegovesi *et al.*, 2001; Gross-Isseroff *et al.*, 2004) but not all human pharmacological challenge studies have shown that the 5-HT2B/C agonist 1-(3-chlorophenyl)piperazine (m-CPP) exacerbates symptoms in OCD patients (McDougle *et al.*, 1995; Khanna *et al.*, 2001; de Leeuw and Westenberg, 2008). However, m-CPP is not a highly selective 5-HT2C agonist, and shows similar IC₅₀ values for 5-HT₂, 5-HT_{1A}, 5-HT_{1B}, and α -adrenergic receptors (values ranging from 360–1300 nmol/l) (Hamik and Peroutka, 1989; Blalock *et al.*, 2003). If the stimulation of 5-HT2C receptors does in fact

exacerbate OCD symptoms in at least some patients, then 5-HT_{2C} KO mice might provide a model of resistance to OCD, at least with respect to 5-HT_{2C} mediated effects.

Estrogen-deficient mice

Aromatase cytochrome P450, the product of the *cyp19* gene, is present in mouse brain, gonads, adipose tissue, and bone, and catalyzes the final step of biosynthesis of estrogen from androgens. Aromatase knockout (ArKO) mice are estrogen deficient (Fisher *et al.*, 1998). Male ArKO mice show changes in reproductive behavior including reductions in breeding, increased aggression towards estrous females, and infanticide (Miyata and Honda, 1994; Matsumoto *et al.*, 2003). They also exhibit numerous physiological abnormalities including impaired spermatogenesis (Robertson, 1979), ovarian abnormalities, deficient bone growth and density (Oz *et al.*, 2001), and increased adiposity (Cunningham and Jones, 2000; Heine *et al.*, 2000). With respect to emotional behavior, ArKO male mice show a substantial reduction in aggressive behavior in the resident intruder paradigm (Toda *et al.*, 2001); however, anxiety and depression-related behavior was found to be unaltered in ArKO mice (Dalla *et al.*, 2005). Many of the phenotypes observed in ArKO mice can be reversed with exogenous estrogen treatment (Hill *et al.*, 2007).

Male, but not female, ArKO mice exhibit compulsive behavior beginning at 6 months of age, including increased wheel running, grooming, and barbering. Compulsive wheel running in these mice is not because of generalized hyperactivity, but because they also show reduced locomotion in a home cage environment. By 1 year of age, male, but not female, ArKO mice show apoptosis in the medial preoptic area, which is involved in grooming behavior in mice. Furthermore, decreases in total and membrane-bound COMT protein levels were observed in the hypothalamus, but not frontal cortex, of male ArKO mice. These changes in COMT expression appear concomitantly with compulsive behavior. Three weeks of estrogen replacement was shown to reverse the wheel running and compulsive grooming phenotypes, and the reductions in hypothalamic COMT. Finally, ArKO male, but not female, mice show reductions in inhibition from 1 to 18 months of age (van den Buuse *et al.*, 2003), a form of startle plasticity that has been found to be reduced in OCD (Swerdlow *et al.*, 1993; Hoenig *et al.*, 2005).

The sex ratio and the age of onset of compulsive behavior in ArKO mice do not correspond to those observed in OCD, which might suggest lack of predictive validity in this regard. For example, 6 months of age in a mouse represents mid-to-late adulthood, while the onset of OCD occurs substantially earlier in the lifespan. However, OCD is likely a heterogeneous disorder with multiple subtypes. Therefore, if the ArKO model was found to exhibit strong predictive validity in other respects, the model could theoretically provide a useful tool for studying a subtype of OCD that is specific to males. Increased compulsive wheel running, grooming, and barbering observed in ArKO male mice contribute to the face validity of the model. Reduced function of COMT resulting from genetic microdeletion or lower functioning alleles has been associated with OCD, particularly in males (Gogos *et al.*, 1998; Pooley *et al.*, 2007; Schindler and Anghelescu, 2007), although not all studies have replicated this finding (Ohara *et al.*, 1998; Erdal *et al.*, 2003; Meira-Lima *et al.*, 2004; Walitza *et al.*, 2008). It remains to be determined whether the reductions in COMT expression in ArKO mice are responsible for the compulsive behaviors exhibited by these mice. However, COMT KO mice have not been reported to exhibit compulsive behaviors, although these measures may not have been investigated. Currently, ArKO mice exhibit face validity for OCD, but more studies will be required to assess whether this model exhibits predictive validity for OCD.

Hoxb8 mutant mice

Greer and Capecchi (2002) generated and characterized Hoxb8 knockout (KO) mice. The *Hoxb8* gene is a member of the mammalian Hox (Homeo-box containing) complex, which is a group of 39 transcription factors well known for their role in providing positional information along the anteroposterior axis during early development (Capecchi, 1997), and are also expressed in the CNS during adulthood. Hundred percent of Hoxb8 KO mice showed excessive grooming leading to hair removal and deep skin lesions during induced grooming assays and also spontaneously in the home cage. No skin or peripheral nervous system abnormalities were observed (Frank *et al.*, 2002).

The overgrooming phenotype in these mice was suggested to be similar to the excessive grooming seen in trichotillomania and in some types of OCD (Frank *et al.*, 2002). The authors also showed that Hoxb8 mRNA is expressed in brain regions known as the ‘OCD-circuit’. However, Hoxb8 mRNA was also localized to the entire cortex, olfactory bulb, hippocampus, cerebellum, and brain stem, suggesting that Hoxb8 expression is widespread, and not specific to brain regions implicated in OCD. Although the overgrooming phenotype in Hoxb8 KO mice contributes to the face validity of the model, the expression pattern of Hoxb8 is perhaps too broad to contribute predictive validity to the model. The effects of chronic SRI treatment on the overgrooming phenotype of Hoxb8 mice have not been reported.

More recently, Holstege *et al.* (2008) reported spinal dorsal laminae dysfunction in Hoxb8 KO mice. As Hoxb8 is also expressed at high levels in the dorsal spinal cord throughout embryogenesis and after birth, Hoxb8 KO mice were evaluated for spinal sensory system anatomy and function. Holstege *et al.* (2008) showed that the overgrooming phenotype in Hoxb8 KO mice was alleviated by applying local anesthetic underneath bald patches of skin, indicating that overgrooming of these areas depends on peripheral nerve activity. Hoxb8 KO mice also showed attenuated avoidance reactions to heat and capsaicin. Consistent with these sensory deficits, a lower neural count and neuronal disorganization was found in the dorsal-most laminae at lumbar levels, leading to a smaller dorsal horn and narrowed projection field of nociceptive and thermoceptive afferents. Thus, these more recent findings suggest that sensory abnormalities are responsible for the overgrooming phenotype of Hoxb8 KO mice. These findings illustrate that face validity can provide a starting point for developing a model, but can be misleading, and cannot be used to validate a model.

Spontaneous models

Spontaneous barbering

Behavior-associated hair loss has been described in many species including nonhuman primates, sheep, dogs, cats, rabbits, guinea pigs, and laboratory rats and mice (Bresnahan *et al.*, 1983; Honess *et al.*, 2005; Reinhardt, 2005). This behavior has been considered abnormal because it is observed almost exclusively in confined animals. In laboratory mice, this behavior has frequently been termed barbering, and consists of plucking or trimming of fur or whiskers of oneself or cage mates. Substantial differences in barbering have been reported between various inbred mouse strains, suggesting that barbering behavior has a strong genetic component (Kalueff *et al.*, 2007). Barbering is also affected by environmental factors including confinement and husbandry factors such as diet, age of weaning, and enrichment (Kalueff *et al.*, 2006). The construct that barbering represents remains unclear, although it has been suggested to reflect a form of dominance behavior (Long, 1972; Strozik and Festing, 1981; Sarna *et al.*, 2000), or a stress-evoked behavioral response to confinement (Kalueff *et al.*, 2006).

Garner *et al.* (2004) proposed that barbering in laboratory rodents might provide an animal model of human trichotillomania, an impulse control disorder characterized by compulsive hair pulling. Trichotillomania patients report an overwhelming urge to pull hair, a build up of tension, and a subsequent sense of relief after hair pulling. Trichotillomania exhibits comorbidity with OCD (Stewart *et al.*, 2005), and has also been proposed to be an obsessive-compulsive spectrum disorder, although the appropriate classification for trichotillomania remains controversial (Azmitia *et al.*, 1995; Lochner *et al.*, 2005; Arzeno Ferrao *et al.*, 2006). Garner *et al.* (2004) performed a large-scale study of the phenomenology and epidemiology of barbering in multiple inbred and outbred mouse strains. They suggested that spontaneous barbering shows good face validity for trichotillomania, in that both barbers and trichotillomania patients pluck hair from the orbital areas, dorsal head region, and genitals (Garner *et al.*, 2004). Although barbering could be argued to exhibit more face validity for trichotillomania than for OCD, barbering shows more predictive validity as a model for OCD with respect to epidemiological factors. For example, female mice were reported to be one and a half times more likely to barber than males, which is consistent with the 1–1.5 female/male sex ratio reported in OCD (Thomsen and Jensen, 1994; Bebbington, 1998; Fireman *et al.*, 2001), whereas the female/male sex ratio in trichotillomania is 2.55 (Oranje *et al.*, 1986; Christenson *et al.*, 1991a). The prevalence of barbering by age in mice also more closely resembled the prevalence of OCD across the lifespan than that for trichotillomania. For example, the mean age of onset is significantly earlier for trichotillomania than for OCD (12 vs. 19 years) (Christenson *et al.*, 1991b; Graber and Arndt, 1993; Lochner *et al.*, 2005; Sah *et al.*, 2008), although no prepubescent mice showed barbering behavior. In addition, breeder mice were five times more likely to barber than nonbreeders. Pregnancy and childbirth have been reported to trigger the onset of OCD (Albert *et al.*, 2002; Uguz *et al.*, 2007), and the postpartum period is associated with a worsening of OCD symptoms (Williams and Koran, 1997). However, reproductive events have not been associated with worsening of symptoms in trichotillomania (Keuthen *et al.*, 1997; Lochner *et al.*, 2005; Uguz *et al.*, 2007).

More experiments will be required to determine whether spontaneous barbering exhibits predictive validity as a model for OCD. Further, testing the predictive validity of barbering as a model of trichotillomania will be complicated by the lack of conclusive data on the efficacy of pharmacological treatments for the disorder (Streichenwein and Thornby, 1995; Ninan *et al.*, 2000; Dougherty *et al.*, 2006).

Stereotypic behavior in Deer mice

Peromyscus maniculatus bairdii (deer mice) develop high rates of spontaneous stereotypy when housed under standard laboratory conditions (Powell *et al.*, 1999). Typical forms of stereotypy performed by deer mice are somersaulting or flipping, repetitive jumping, and pattern running. These behaviors emerge between 20 and 30 days of age, and several factors including environmental enrichment, litter, and genetic diversity within the population contribute to variability of the phenotype (Powell *et al.*, 1999; Powell *et al.*, 2000; Turner *et al.*, 2002). Both male and female deer mice develop spontaneous stereotypy at similar rates (Powell *et al.*, 1999). Recently, Korff *et al.* (2008) studied population diversity in the expression of stereotypic behavior in deer mice housed under standard laboratory conditions. The effects of chronic treatment with effective (fluoxetine) but not ineffective (desipramine) treatments for OCD were also evaluated.

Eight-week-old deer mice showed substantial variability in spontaneous stereotypy. Approximately 15% of mice showed virtually no stereotypic behavior, similar to C57BL/6 inbred mice. Forty-three percent of deer mice showed high levels of stereotypy, and the remaining showed intermediate levels. Twenty-one days of daily injection with 10 or 20 mg/kg/day fluoxetine, but not desipramine, robustly attenuated spontaneous stereotypy in both

the high and intermediate stereotypy groups. Thus, this represents the only model to date showing reduction in OCD-related behavior after chronic SRI, but not other antidepressant, treatment.

Although these results are very promising, it will be important to demonstrate that acute and short-term treatment with fluoxetine does not produce the same effects. Korff *et al.* (2008) also examined the effects of subchronic treatment with the nonselective 5-HT_{2B/C} agonist mCPP and the dopamine D₂ agonist quinpirole on spontaneous stereotypy in deer mice. However, the effects of these drugs are much less informative regarding the predictive validity of the model, because the effects of subchronic treatment with these drugs in OCD are not well established. Other studies in deer mice examining the effects of striatal manipulations on spontaneous stereotypy have implicated the striatum in these behaviors (Presti *et al.*, 2003). Thus, the deer mouse model of spontaneous stereotypy shows face and some predictive validity as an animal model of OCD.

Discussion

Animal genetic models of OCD are currently in the early stages of development and validation. The models reviewed here evaluated the effects of genetic manipulation or genetic diversity on behavioral measures with face validity for an aspect of OCD. These behavioral measures consist of various forms of compulsive or stereotypic behavior that provided a heuristic starting point for developing a model of OCD. Some of these models have also established some degree of predictive validity for OCD with respect to epidemiological factors, neural circuitry, or drug treatment effects. Future work further examining the predictive validity of these models will be critical for establishing their usefulness as models for studying mechanistic aspects of OCD.

Although face validity can provide a heuristic starting point for developing a novel animal model for a disorder, face validity based on subjective arguments, is often disagreed upon, and cannot be used to validate a model. Animals' behavior in the models reviewed presently could be argued to show face validity for compulsive behaviors in OCD. For example, barbering, overgrooming, self-mutilation, chewing non-nutritive objects, somersaulting or flipping, repetitive jumping, pattern running, rigid syntactic grooming chains, and compulsive wheel running have been suggested by some to resemble certain OCD symptoms such as compulsive washing and ritualistic behaviors. Although these mouse behaviors may have phenomenological similarities with compulsions in OCD, only experiments testing the effects of variables with known effects in OCD (i.e. SRIs) in the model can determine which of these behaviors share similar fundamental underlying mechanisms with compulsions in OCD. For example, chronic SRI treatment has been shown to reduce spontaneous stereotypy in deer mice (Korff *et al.*, 2008) drug-induced perseveration in the T-maze (Yadin *et al.*, 1991) and opiate-induced oral stereotypy (Wennemer and Kornetsky, 1999); however, chronic SRI treatment does not prevent other types of repetitive behaviors such as apomorphine-induced stereotypy (Rurak and Melzacka, 1985), baseline grooming behavior (Yalcin *et al.*, 2008), and quinperole-induced compulsive checking (Szechtman *et al.*, 1998). In summary, only empirical testing can determine which forms of repetitive behavior show predictive validity for OCD.

Some of the models reviewed here show some predictive validity for OCD with respect to epidemiological factors, neural circuitry, or drug treatment. For example, spontaneous barbering shows several epidemiological commonalities with OCD including sex ratio, prevalence by age, and increased incidence associated with reproductive events (Garner *et al.*, 2004). Abnormal compulsive and stereotyped behaviors in Sapap 3 KO mice (Welch *et al.*, 2007), DICT-7 (Smicun *et al.*, 1999; Nordstrom and Burton, 2002), DAT KD (Berridge *et al.*, 2005), and deer mice (Korff *et al.*, 2008) were directly or indirectly linked with altered functioning of fronto-subcortical circuitry which has been implicated in OCD. However,

knowledge regarding the specific abnormalities in fronto-subcortical circuitry in OCD remains limited. Abnormal activity within these circuits detected in human imaging studies could result from primary pathology elsewhere in the brain, and recent data suggest that different subtypes of OCD may have different types of brain abnormalities (Mataix-Cols *et al.*, 2004). Thus, demonstrating involvement of fronto-subcortical circuitry in putative animal model of OCD does not necessarily contribute to the predictive validity of the model. Undoubtedly, such findings still provide valuable insights into the control of compulsive behavior, and could generate testable hypotheses for studies of OCD patients.

Some of the models reviewed here showed sensitivity to drug treatments that are effective in OCD. For example, stereotyped behavior of deer mice housed in laboratory conditions was substantially reduced by chronic (3 week) SRI treatment. Furthermore, chronic treatment with the tricyclic antidepressant desipramine, which is ineffective in OCD, did not alter stereotypic behaviors in deer mice (Korff *et al.*, 2008). If future studies show that short-term treatment with SRIs does not reduce stereotypic behavior in deer mice, this model will demonstrate strong predictive validity as a model of OCD that is sensitive to effective therapeutics as well as their time course of action. Testing the behavioral effects and the time course of action of SRIs and other antidepressants provides one of the most straightforward means to test the predictive validity of a novel model of OCD, because the effects of these drugs have been so well characterized by numerous double-blind, placebo-controlled studies (Hollander and Pallanti, 2002). However, one weakness of this approach is that approximately half of OCD patients do not respond to SRI treatment (Hollander and Pallanti, 2002). A putative animal model of OCD that does not show sensitivity to chronic SRI treatment would then require validation based on other factors, such as epidemiological factors or neural circuitry. However, different subtypes of OCD may exhibit epidemiological characteristics that vary substantially from the population as a whole, and the precise neural circuitry involved in OCD is unknown. Thus, animal models of 'treatment resistant' OCD will be far more difficult to validate. Identification of endophenotypes for OCD will be critical for the development of current and novel animal models of OCD.

Genetic models of neuropsychiatric disorders using forward or reverse genetic approaches offer unique advantages and disadvantages. Forward genetic approaches begin with a phenotype of interest and attempt to identify the genetic variants that underlie the observed phenotypic variability. These studies focus on a genetically diverse population, such as a second-generation intercross (F2 cross) between two inbred strains, an outbred strain, or a wild population. QTL mapping strategies can then be applied to identify regions and ultimately specific genes that harbor variants that affect the trait of interest. Gene expression studies can also be used alone or in combination with QTL approaches to identify novel genes for the behavior of interest (Noctor *et al.*, 2001; Flint *et al.*, 2005; Palmer *et al.*, 2006). As forward genetic strategies do not make assumptions about which genes will influence the trait, they have the potential to identify completely novel genes. Major drawbacks include the substantial animal numbers, time, cost, and effort required, as well as difficulties associated with ultimately pinpointing a gene. Such approaches could be applied to the spontaneous barbering phenotype characterized by Garner *et al.* (2004) or the stereotypic behavior characterized in deer mice by Korff *et al.* (2008). Reverse genetic approaches examine the effect of genetic manipulation (i.e. knockout or transgenic approaches) of a specific gene of interest. Reverse genetic approaches offer the advantage of better feasibility, relatively lower cost, and increased practicality; however, this approach does not allow for the identification of novel genes. Furthermore, attempting to model genetically complex neuropsychiatric disorders by altering the function of a single gene has been criticized. However, modeling only a specific aspect of a disorder increases the likelihood of a single gene playing a significant role in the phenotype. Furthermore, some human genetic studies of OCD suggest that single genes might contribute substantially to the risk for certain subtypes of OCD. In the end, forward and reverse genetic approaches should be seen as

complimentary rather than mutually exclusive approaches, because genes initially identified by forward genetics can be specifically tested using the tools of reverse genetics. For example, the first mammalian circadian rhythm gene, 'clock', was discovered using forward genetic screens in mice (Vitaterna *et al.*, 1994) and was confirmed using a transgenic replacement strategy (Antoch *et al.*, 1997). Subsequent reverse genetic studies in mice have shown that clock modulates phenotypes relevant to bipolar disorder, which has been associated with abnormalities in the circadian system (Jones, 2001; Roybal *et al.*, 2007).

In summary, a number of current genetic models of OCD show face and some predictive validity for OCD. Future work examining the effects of interventions with known consequences in OCD patients, such as chronic SRI treatment, in these mouse genetic models will be critical for their further development and validation. Furthermore, the identification of endophenotypes, or novel genes, treatments, or pathophysiological findings in OCD would greatly benefit the development of animal models for this disorder.

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