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REVIEW

RODENT MODELS OF OBSESSIVE COMPULSIVE DISORDER: EVALUATING VALIDITY TO INTERPRET EMERGING NEUROBIOLOGY

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Abstract—Obsessive Compulsive Disorder (OCD) is a common neuropsychiatric disorder with unknown molecular underpinnings. Identification of genetic and non-genetic risk factors has largely been elusive, primarily because of a lack of power. In contrast, neuroimaging has consistently implicated the cortico-striatal-thalamo-cortical circuits in OCD. Pharmacological treatment studies also show specificity, with consistent response of OCD symptoms to chronic treatment with serotonin reuptake inhibitors; although most patients are left with residual impairment. In theory, animal models could provide a bridge from the neuroimaging and pharmacology data to an understanding of pathophysiology at the cellular and molecular level. Several mouse models have been proposed using genetic, immunological, pharmacological, and optogenetic tools. These experimental model systems allow testing of hypotheses about the origins of compulsive behavior. Several models have generated behavior that appears compulsive-like, particularly excessive grooming, and some have demonstrated response to chronic serotonin reuptake inhibitors, establishing both face validity and predictive validity. Construct validity is more difficult to establish in the context of a limited understanding of OCD risk factors. Our current models may help us to dissect the circuits and molecular pathways that can elicit OCD-relevant behavior in rodents. We can hope that this growing understanding, coupled with developing technology, will prepare us when robust OCD risk factors are better understood.

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Key words: repetitive behavior, basal ganglia, striatum, optogenetic, autoimmune, autism.

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Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CSTC, cortico-striatal-thalamo-cortical; DBS, deep-brain stimulation; GWAS, genome-wide association studies; MRS, magnetic resonance spectroscopy; OCD, Obsessive Compulsive Disorder; OFC, orbitofrontal cortex; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections; PPI, prepulse inhibition; SRIs, serotonin reuptake inhibitors; VMS, ventral medial striatum.

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INTRODUCTION

Obsessive compulsive disorder (OCD) is a common, chronic condition characterized by persistent, intrusive obsessions, repetitive behavior, and anxiety (Calvocoressi et al., 1998). The disorder affects 1–3% of the population and is among the top ten causes of disability worldwide (Kessler et al., 2005; Koran et al., 2007; Michael and Ritsner, 2007). First-line forms of therapy include serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy; however, only 50–60% of patients show adequate response to available treatments (Koran et al., 2007). For example, a 20–40% decrease in OCD symptoms may result following SRI therapy (Dougherty et al., 2004), which leaves many with clinically significant residual symptoms. In some refractory OCD cases, deep-brain stimulation (DBS) has also been used as a treatment alternative (Sturm et al., 2003; Goodman et al., 2010). Other augmentation therapies, such as antipsychotics and glutamatergic agents, are also being evaluated but have limited evidence for their utility (Arumugham and Reddy, 2013).

Ideally, more effective therapeutics would emerge from an understanding of the etiology of OCD. As with many neuropsychiatric conditions, the underlying causes of OCD are unknown and likely to involve both genetic and environmental factors. Hypotheses based on genetic and neuroimaging data have led researchers to create animal models that recapitulate the hallmarks of the disorder, with the aim of probing the underlying neurobiology. Here, we will discuss the growing number of proposed rodent models of OCD, including pharmacologically induced, genetic, and optogenetic animal models, with a focus on assessment of the validity of the model in relation to knowledge of the human condition. Building upon the initial data on validity, we will describe the emerging understanding of neurobiological mechanisms in each model. Finally, we will discuss the approaches to take growing knowledge from these rodent models and translate it into novel treatments that can be applied in patients with OCD.

Genetic and non-genetic factors likely contribute to OCD risk

To understand the validity of rodent models, we must first understand the risk factors that may contribute to OCD. Abundant evidence for a heritable component of OCD stems from twin and family studies (Grados and Wilcox, 2007; Pauls, 2008). As reviewed elsewhere (Pauls, 2010), OCD symptoms are estimated to be 40–65% heritable in children and 27–47% heritable in adults (van Grootheest et al., 2005). Family studies indicate that OCD is twice as common in first-degree relatives of affected adults and ten times as likely in relatives of affected children (Pauls, 2008). These studies support the premise that OCD risk is derived from a complex combination of genetic and non-genetic factors.

Genetic linkage studies have yet to generate genome-wide significant findings for the core diagnosis of OCD, likely because of lack of statistical power in limited sample sizes (Hanna et al., 2002a; Mathews et al., 2012). The most promising linkage signal is on chromosome 9p24, based upon a suggestive linkage peak in the first genome-wide linkage study that was subsequently directly replicated in a study targeting only this region (Hanna et al., 2002a; Willour et al., 2004a). Another suggestive linkage peak on chromosome 15q14 was identified in two genome-wide linkage studies (Shugart et al., 2006). Genome-wide association studies (GWAS) have been similarly underpowered, to date, in OCD (Stewart et al., 2013b; Mattheisen et al., 2015). A single polymorphism near *BTBD3* reached genome-wide significance in a family-based subset of one GWAS analysis, but was only suggestive in the overall sample (Stewart et al., 2013b).

Candidate genes for OCD have been identified based upon proximity to linkage peaks, biomarker findings, and relationship to pharmacological targets. The strongest candidate gene association findings in OCD focus on *SLC1A1*, which encodes the neuronal glutamate transporter, EAAT3. Multiple studies have reported significant evidence for association OCD with *SLC1A1* polymorphisms, particularly in males with OCD and particularly with polymorphisms in the 3′ region of the gene (Arnold et al., 2006; Dickel et al., 2006; Stewart et al., 2007; Kwon et al., 2009; Shugart et al., 2009; Wendland et al., 2009b; Samuels et al., 2011; Stewart et al., 2013b; Wu et al., 2013); although a recent meta-analysis found only modest associations that were not significant after correcting for multiple testing (Stewart et al., 2013a). Interest in SLC1A1 stemmed from its location under the chromosome 9p24 linkage peak, as well as biomarker studies implicating the glutamate system in OCD. Elevated cerebrospinal fluid glutamate levels in two studies (Chakrabarty et al., 2005a; Bhattacharyya et al., 2009) are matched by increased glutamatergic signal in some magnetic resonance spectroscopy (MRS) studies in OCD (Moore et al., 1998; Rosenberg et al., 2000); although other MRS studies do not find significant differences (Brennan et al., 2013).

Other association studies have generated largely mixed results that are difficult to interpret in the context of a long history of psychiatric candidate genes that have failed to replicate consistently. Additional candidate genes in the glutamate system have also been studied, including *GRIN2B*, which shows evidence of association in some but not all studies (Arnold et al., 2004; Alonso et al., 2012; Cai et al., 2013). The other leading candidate gene is the serotonin transporter, *SLC6A4*, with both common and rare variants exhibiting association in some studies (Ozaki et al., 2003; Dickel et al., 2007; Grados et al., 2007; Saiz et al., 2008; Wendland et al., 2008), but not all (Taylor, 2013). The dopaminergic system (*COMT and DRD4*) has also been implicated via gene association studies; however these findings have yet to be replicated (Billett et al., 1998; Pooley et al., 2007). A lack of clear susceptibility genes contributes to the difficulty of modeling OCD in animals, though this issue is shared by most complex heterogeneous neuropsychiatric disorders.

Apart from genetics, autoimmunity has also received considerable attention as a potential risk factor for