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REVIEW

USING MICE TO MODEL OBSESSIVE COMPULSIVE DISORDER: FROM GENES TO CIRCUITS

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Abstract—Obsessive Compulsive Disorder (OCD) is a severe, chronic, and highly prevalent psychiatric disorder that affects between 1.5% and 3% of people worldwide. Despite its severity, high prevalence, and clear societal cost, current OCD therapies are only partially effective. In order to ultimately develop improved treatments for this severe mental illness, we need further research to gain an improved understanding of the pathophysiology that underlies obsessions and compulsions. Though studies in OCD patients can provide some insight into the disease process, studies in humans are inherently limited in their ability to dissect pathologic processes because of their non-invasive nature. The recent development of strategies for genetic and circuit-specific manipulation in rodent models finally allows us to identify the molecular, cellular, and circuit events that lead to abnormal repetitive behaviors and affect dysregulation relevant to OCD. This review will highlight recent studies in mouse model systems that have used transgenic and optogenetic tools in combination with classic pharmacology and behavioral techniques to advance our understanding of these pathologic processes.

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Key words: Obsessive Compulsive Disorder (OCD), orbitofrontal cortex (OFC), basal ganglia, animal models, anxiety, optogenetic.

Contents

INTRODUCTION

Obsessive Compulsive Disorder (OCD) is a severe, chronic, and highly prevalent psychiatric disorder that affects between 1.5% and 3% of people worldwide,

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Abbreviations: 5-HT1B, Serotonin-1B receptor; ACC, anterior cingulate cortex; ChR2, channelrhodopsin; CSTC, cortico-striato-thalamo-cortical; D1, dopamine 1 receptor; DBS, deep-brain stimulation; DREADDs, Designer Receptors Exclusively Activated by Designer Drugs; DSM-5, Diagnostic and Statistical Manual-5; GPCRs, G-protein coupled receptors; GWAS, genome-wide association studies; KO, knockout; lOFC, lateral orbitofrontal cortex; mOFC, medial OFC; PPI, prepulse inhibition; OCD, Obsessive Compulsive Disorder; OFC, orbitofrontal cortex; SRI, serotonin reuptake inhibitor; VMS, ventromedial striatum.

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independent of ethnicity and cultural group studied (Koran, 2000). According to the 1996 report by the World Health Organization, it was listed as the world's 10th leading cause of illness-related disability (Murray and Lopez, 1996). In the US alone, the costs associated with treatment of OCD and work loss due to symptoms are estimated at up to 10 billion dollars annually (Eaton et al., 2008). Yet despite its severity, high prevalence, and clear societal cost, current OCD therapies are only partially effective. This is in part because OCD remains underdiagnosed, under-treated, and understudied due to lack of recognition by health care providers, stigma associated with symptoms by patients, and lack of understanding of the seriousness of the illness by the general public and research organizations. In order to ultimately develop improved treatments for this severe mental illness, we need further research to gain an improved understanding of the pathophysiology that underlies obsessions and compulsions.

Though studies in OCD patients can provide some insight into the disease process, studies in humans are inherently limited in their ability to dissect pathologic processes because of their non-invasive nature. The recent development of strategies for genetic and circuit-specific manipulation in rodent models finally allows us to identify the molecular, cellular, and circuit events that lead to abnormal repetitive behaviors and affect dysregulation relevant to OCD. This review will highlight recent studies in mouse model systems that have used transgenic and optogenetic tools in combination with classic pharmacology and behavioral techniques to advance our understanding of these pathologic processes.

Clinical features of OCD

Despite recent changes to the Diagnostic and Statistical Manual-5 (DSM-5), the core clinical features of OCD remain the same (Leckman et al., 2010a; Goodman et al., 2014). OCD consists of obsessions, which are recurrent, persistent, intrusive thoughts, impulses, or images; or compulsions, which are repetitive behaviors or mental acts that patients typically engage in to reduce the severe anxiety or dread that is associated with the obsessions (Monzani et al., 2014; Van Ameringen et al., 2014; Stein et al., 2014). Though both obsessions and compulsions are not required to meet diagnostic criteria for OCD, both are typically present (Williams et al., 2011) and tend to be linked together, such that a compulsion is performed in response to a particular obsessive thought. Notably, although OCD is no longer classified as an anxiety disorder according to DSM-5, anxiety symptoms are a prominent feature in many OCD patients (Diniz et al., 2012; Bienvenu et al., 2012). Specifically, obsessions are often associated with significant distress, and compulsions are typically performed in a conscious attempt to reduce this severe distress. For example, an intrusive thought about one's hands being contaminated would typically be accompanied by a spike in anxiety followed by a compulsive hand-washing ritual, and completion of the ritual would lead to a temporary decrease in anxiety. Although performing compulsions can provide immediate relief, it is typically fleeting. In fact, execution of these rituals is actually believed to strengthen dysfunctional neural circuits that underlie OCD, leading ultimately to increased anxiety and symptom persistence. These illness features are important to consider when developing neurobiological models of the disorder.

It is clear that OCD is a heterogeneous disorder (Mataix-Cols et al., 2005), but it is less clear how the illness should be divided into subgroups. This is an active area of investigation, and therefore many metrics currently exist for 'carving the joints'. First, there is strong evidence that tic-related OCD is neurobiologically distinct, with different neurochemical features, distinct striatal pathophysiology, and higher prevalence in males (Baxter et al., 1988). There have also been suggestions that early-onset OCD (mean age of onset between 7.5 and 12.5 years (Geller, 2006) may correspond to a distinct subtype with different genetic and environmental underpinnings (Eichstedt and Arnold, 2001). Variations in level of insight into OCD symptoms may also represent biologically meaningful differences (Leckman et al., 2010b), and are now delineated by specifiers in DSM-5. Finally, differences in specific content of obsessions and compulsions may potentially correspond to distinct neurobiological substrates (Mataix-Cols et al., 2004), as most clearly demonstrated for hoarding (now a separate disorder in DSM-5) (Saxena, 2007; Mataix-Cols et al., 2010).

Neural circuit abnormalities associated with OCD

Over the past 20 years, functional and structural neuroimaging studies have led to the discovery of aberrant neural circuits in OCD patients. A remarkable convergence of findings from neuroanatomical and functional studies collectively implicates cortico-striato-thalamo-cortical (CSTC) circuits in OCD pathophysiology (Rauch et al., 1997; Saxena et al., 2001; Maia et al., 2008; Rotge et al., 2010). Though discrepancies are found in the directionality of findings, this is typically attributed to either heterogeneity of illness, or differences in stage of development or illness course. These findings are described in detail below.

Structural neuroimaging. Although exact findings have varied across studies, structural abnormalities in CSTC circuits involving orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum have been repeatedly demonstrated in OCD (Pittenger et al., 2011; Rodman et al., 2012; de Wit et al., 2014). The largest structural MRI study to date reported reduced medial OFC gray matter and increased gray matter in the highly-connected (Haber, 2003; Di Martino et al., 2008) ventral striatum (i.e. ventral putamen, nucleus accumbens, and olfactory tubercle) (Pujol et al., 2004). In addition, a recent meta-analysis reported reduced volumes of left ACC and bilateral OFC, and increased thalamic volumes bilaterally, but no differences in basal ganglia volumes relative to control samples (Rotge et al., 2009). However, another meta-analysis demonstrated changes in basal ganglia (i.e. increased bilateral caudate gray matter volume) as well as decreased bilateral ACC volume, in OCD patients (Radua and Mataix-Cols, 2009), while a recent mega-analysis demonstrated a reduction in ACC,

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