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Neuroscience. Illuminating the neural circuitry of compulsive behaviors

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Sentence Summary:

In this issue, two ground-breaking reports describe the use of optogenetics to control a brain circuit that drives repetitive behavior, opening up new possibilities for the treatment of compulsive disorders.

Rational development of biodiagnostics and therapeutics has been slow for neuropsychiatric disorders, in part because of difficulties in establishing validated models of pathophysiology. Successful translational medical science benefits from robust animal models and homology with humans at multiple levels, including genes, cells, circuits, systems, and behavior. This stands in contrast to a historical tendency to tautologically identify new treatments based on their ability to achieve effects similar to those of existing (but inadequate) medications. In this issue, a tandem of reports[1,2] describe seminal experiments that use the transformative technique of optogenetics[3] to produce and relieve compulsive-like behaviors in animal models. Their pioneering work highlights promising opportunities and persistent obstacles in the field.

Obsessive compulsive disorder (OCD) is characterized by unwanted intrusive thoughts (obsessions) and ritualized repetitive behaviors (compulsions)[4]. Compulsions are conceptualized as responses to urges or anxiety associated with obsessions. Classic examples include obsessions about contamination, which are associated with anxiety and lead to washing compulsions. Obsessions and compulsions are often unpleasant and time-consuming; those afflicted feel tormented and can be functionally disabled. The complexity of OCD is emblematic of challenges in developing animal models of psychiatric disorders, in that the compulsive element (repetitive behavior) is readily measured, whereas the obsessional element (intrusive thoughts) is exceedingly difficult to quantify. Compulsive behaviors are not unique to OCD, but rather are a feature of numerous neuropsychiatric disorders, including autism, substance use disorders, and Tourette's disorder[4]. In the context of such limitations of the Diagnostic and Statistical Manual (DSM), the NIMH has developed the Research Domain Criteria (RDoC)[5] to advance models that link genetics, neuroanatomy, physiology, and behavior in ways that may cut across disorders as currently defined. Compulsions are a prevalent example of such a cross-cutting behavioral phenomenon.

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There are essentially no biomarkers or assays that can serve as diagnostic tests in psychiatry[6]. Findings from humans with OCD support a circuitry model focused on a network of brain regions comprising orbitofrontal and anterior cingulate cortex, striatum, and thalamus[7]. Decades of functional brain imaging data indicate that, in OCD, the nodes of this network exhibit hyperactivity at rest that is exacerbated during symptom induction and attenuated by successful treatment[8]. These conclusions rely on correlations between diagnosis and functional imaging measures; we lack the ability to induce the signs and symptoms of the disorder by manipulating activity within specific circuits. Moreover, the imaging data were obtained at modest spatial resolution, making it impossible to test hypotheses regarding the specific microcircuitry intertwined within pathways and macrostructures of interest.

There are corresponding limitations in OCD therapeutics. Although treatments including pharmacotherapy with selective serotonergic reuptake inhibitors (SSRIs) have modest efficacy, many patients are refractory, and responders are often left with residual symptoms[9]. OCD is a prime example where advances in circuitry models have fueled interest in regional neurostimulation, such as by deep brain stimulation (DBS)[10] and transcranial magnetic stimulation (TMS)[11]. Recently, DBS of a ventral striatal target for OCD earned a (controversial) humanitarian device exemption with the FDA. However, these methods of gross regional stimulation as a means of modulating circuits parallel the crude spatial knowledge from human neuroimaging, lacking specified targets at cellular levels. Although efforts have been made to enable differential modulation of cells and fibers by scale/size, orientation/direction, and mylenation status[12], these advances pale in comparison with the neuroanatomic and cellular specificity possible with optogenetics[1–3].

By identifying the specific circuits involved in regulating repetitive behaviors (Fig. 1), these new reports[1,2] have broad implications for understanding the neural basis of OCD and other disorders that include compulsivity as a clinical feature. For example, repetitive behavior is a core feature of autism spectrum disorders, and in fact many researchers engaged in autism research in rodents utilize some of the same basic models described in these reports[13]. The striatal regions under study have also been implicated in the development of the types of repetitive behaviors seen with addiction that, via drug-induced neuroplasticity, become habits[14]. Consistent with RDoC principles, these “trans-diagnostic” behaviors may have common brain substrates, and novel therapeutics that target them may have broad indications that cut across conditions previously conceptualized as being unrelated. It is exciting to envision the prospect of highly selective methods of stimulating brain circuits, both to improve neural-network-based disease models and to leverage new knowledge with more refined neurostimulation or pharmacologic therapies. Optogenetics provides a glimpse of a paradigm shift in this direction.

Some obstacles to using optogenetics in non-human primates or clinical settings remain[15]. Challenges include logistical issues (an optical fiber that tethers the subject to the stimulator), ethical and pragmatic concerns (use of viral vectors to express receptors that create neural sensitivity to light stimulation), and considering that these disorders often arise in childhood and adolescence[4], the largely unaddressed question about how this type of intervention affects the developing brain. A lesson of the Ahmari report[1] is that acute

stimulation does not produce repetitive behaviors; the fact repeated stimulation is essential for the phenotype to develop suggests that signs of compulsive disorders can be acquired via neuroplasticity. More work is needed to examine how optogenetic manipulation of key circuits early in life affects developmental trajectories to ensure no unintended effects. These current limitations notwithstanding, this cutting-edge and insightful research[1,2] elucidates the neurocircuitry of compulsive behavior with unprecedented clarity. While there is still far to go, these discoveries represent a major leap forward toward methods for one day "flipping the off-switch" on pathological compulsive behaviors.

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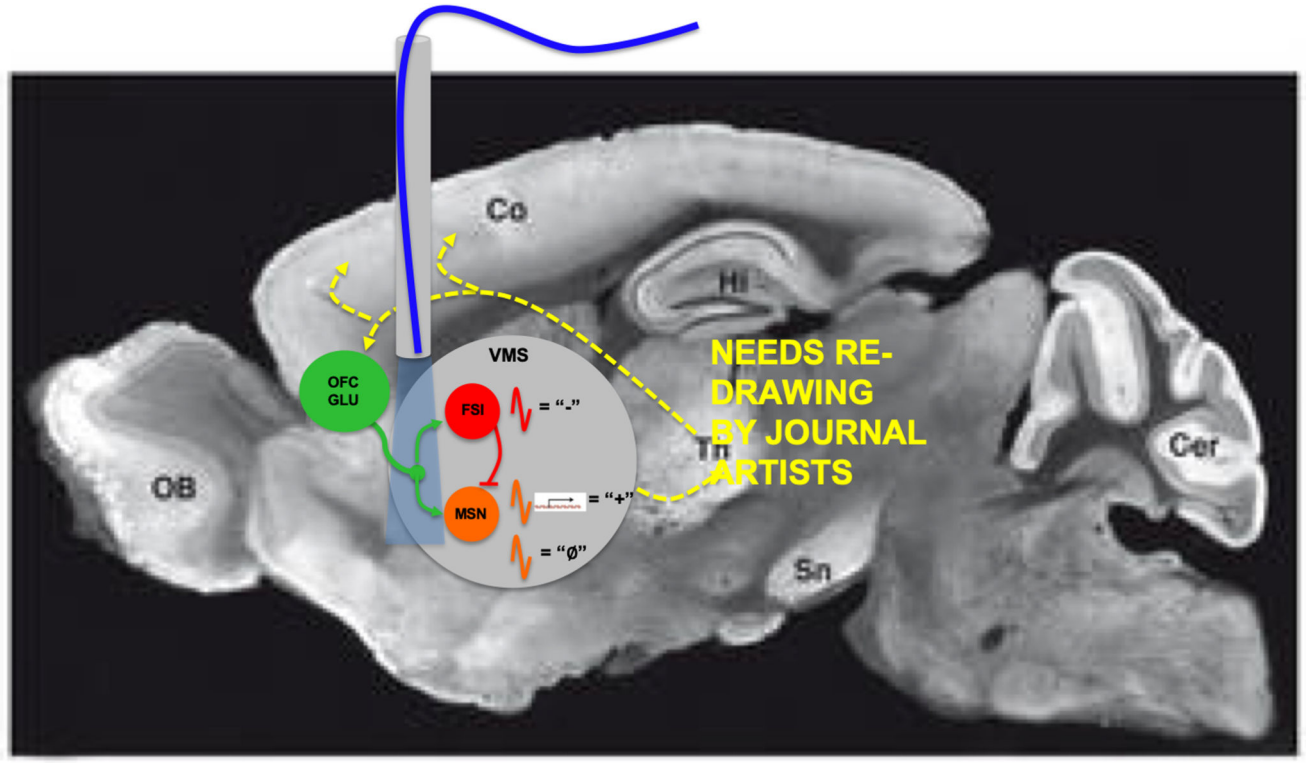

Fig. 1:

Putative roles of orbital frontal cortex (OFC) and ventral medial striatum (VMS) circuits in regulation of repetitive behaviors. Repeated optogenetic stimulation that activates the OFC-VMS pathway (Green) can produce repetitive behaviors ("+") in wild-type mice, presumably by elevating activity of medium spiny neurons (MSNs; Orange) and triggering neuroadaptations[1]. *Sapap3*-mutant mice have high levels of repetitive behavior and deficits in repression of MSN activity, both of which are normalized ("−") by optogenetic stimulation that activates fast-spiking interneurons (FSIs; Red)[2]. Dashed lines depict downstream elements of circuits implicated in OCD.