Lather, Rinse, Repeat? Breaking Repetitive Behaviors With Repetitive Stimulation

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Compulsive behaviors are a common human experience, manifesting, for example, as hard-to-break habits. Compulsive behaviors can, however, become pathological in a range of psychiatric disorders, including obsessive-compulsive disorder (OCD), trichotillomania, and excoriation disorder, among others. Despite a patient's strong conscious desire to stop compulsive behaviors, these problematic repetitive behaviors are often highly inflexible to change, resulting in substantial negative effects on quality of life. Across disorders, compulsive behaviors might be interpreted as a problem of "stopping" (1, 2), that is, a reduced ability to apply the brakes on a deeply entrenched, overlearned behavior. Given a preponderance of partial or nonresponse to conventional treatments in compulsive behavior disorders, there is an urgent need to understand which regions in the brain perpetuate compulsions, and how we can effectively target these regions in treatment.

Deep brain stimulation (DBS) targeting distinct subcortical regions is a treatment option approved by the U.S. Food and Drug Administration (FDA) for certain cases of intractable compulsive symptoms, and while some patients receive substantial benefit from this invasive therapy, others do not improve after subcortical stimulation (3). Noninvasive neuromodulation is approved by the FDA for treatment-resistant OCD (4), and these noninvasive therapies have greater potential to scale for a much larger proportion of the patient population. In particular, theta burst stimulation (TBS) is a promising noninvasive treatment strategy utilizing a very efficient stimulation methodology, and it has the potential to affect a number of psychiatric disorders. Interestingly, three DBS targets in OCD (ventral striatum, subthalamic nucleus, and anterior limb of the internal capsule) have been shown to influence the orbitofrontal cortex (OFC) (5), which can be targeted using TBS. There is convergent evidence of OFC hyperactivity in disorders like OCD. In rodents, for instance, the induction of hyperactivity in the OFC can cause persistent compulsive behaviors (6). In patients with OCD, correlational evidence from MRI and positron emission tomography has identified abnormally elevated activity in the OFC (7, 8). Despite this, the causal relationship between OFC functioning and compulsive behaviors in humans has remained elusive.

In this issue of the *Journal*, Price et al. (9) report on the application of an innovative, transdiagnostic approach to tackling the precise role of the OFC in driving human compulsions. Price et al. recruited patients with prominent compulsive symptoms who were diagnosed with a range of obsessive-compulsive spectrum disorders, including OCD, trichotillomania, excoriation disorder, and body dysmorphic disorder. To manipulate OFC function, the authors leveraged the differential effects of intermittent and continuous TBS (iTBS and cTBS) on cortical activity; on average, iTBS facilitates and cTBS inhibits the excitability of a stimulated cortical region for up to an hour (10). Patients were randomized to receive a single session of iTBS or cTBS of the OFC, which was followed immediately by practice in applying effortful control over habitual behaviors. Price et al. demonstrated that direct modulation of OFC function by cTBS both decreased OFC activity and improved individual compulsive behaviors. Critically, these effects were selective to cTBS; iTBS-induced increases in OFC activity did not lead to improvements in the ability to control compulsive behaviors.

An exciting implication of these findings is that TBS treatment aimed at reducing OFC activity may improve compulsive behaviors in a range of compulsive behavior disorders.

By investigating compulsive symptoms across several compulsive behavior disorders, Price et al. advanced a dimensional rather than diagnostic understanding of the neural basis of compulsive behaviors. A more dimensional approach to the investigation of obsessive-compulsive spectrum disorders will likely prove to be fruitful in the coming years, given the heterogeneity of symptoms that occur within disorders like OCD. In further support for a dimensional approach, Price and colleagues' findings are highly concordant with recent evidence that OFC electrical stimulation can reduce compulsive behaviors in adults without a clinical diagnosis (11). Thus, the OFC may play a causal role in perpetuating compulsive behaviors across health and disease.

An exciting implication of these findings is that TBS treatment aimed at reducing OFC activity may improve compulsive behaviors in a range of compulsive behavior disorders. Additionally, in line with recent reports (11), Price et al. found that worse compulsive symptoms at baseline were related to greater improvements after cTBS, hinting that OFC stimulation may be especially effective for patients with

severe compulsive symptoms. Large randomized clinical trials of OFC cTBS will be instrumental in translating these novel findings to the clinic. So far, preliminary evidence in OCD suggests that repeated sessions of similar forms of inhibitory brain stimulation (12, 13), or cTBS in particular (14), targeting the OFC may be effective for treating compulsive symptoms in some treatment-refractory patients.

Studies in humans have always been limited when it comes to inferring causality, but as demonstrated by Price et al., the direct, noninvasive modulation of cortical regions with TBS offers a powerful method to selectively heighten or dampen regional activity. It is important to keep in mind, however, that while studies in rodents can enact fine-tuned control or inactivation of a brain region, the effects of the form of cTBS used in this study on brain function and behavior remain somewhat variable. Price et al. examined that variability, and found that greater reductions in OFC activity in response to cTBS were associated with greater reductions in compulsive behaviors. This relationship raises the question: Can TBS be optimized to more effectively and consistently dampen OFC activity, thereby maximizing therapeutic benefits? For example, individual differences in brain state at baseline (e.g., functional connectivity, cortical reactivity to acute stimulation) might be useful for predicting subsequent TBS effects. By addressing sources of variability in future work, perhaps cTBS could be refined as a treatment for compulsive behavior disorders through the selection of optimal cTBS candidates and/or personalization of cTBS based on individual differences prior to treatment.

Another key consideration for brain stimulation treatments is the duration of beneficial effects. Remarkably, Price et al. found that a *single* session of cTBS reduced individual compulsive behaviors for up to 1 week. This finding is consistent with recent evidence in a nonclinical population that 5 days of noninvasive OFC stimulation can improve compulsive behaviors for up to 3 months (11). Longer-term follow-up assessments will therefore be important in future work to establish the durability of cTBS effects on compulsive symptoms, as well as the dose of OFC stimulation needed to optimize that durability.

In order to effectively translate Price and colleagues' findings into treatment, the comparative efficacy of OFC stimulation and stimulation of other putative targets for disorders like OCD will also need to be evaluated. For example, the supplementary motor area (15) and dorsomedial prefrontal cortex (16) are effective stimulation targets for some patients with OCD. Therefore, the elegant mechanistic investigation presented by Price et al. should be extended to cortical regions beyond the OFC. Given the heterogeneous symptom profiles and frequent comorbidities in compulsive behavior disorders, large clinical trials comparing the efficacy of OFC and other cortical targets would also have an opportunity to evaluate whether there are subtypes of patients who respond best to one target compared with another.

Similarly, whereas Price et al. appropriately investigated the effects of OFC modulation on fMRI measures of OFC activity, the mechanistic understanding of OFC involvement in compulsive behaviors would benefit greatly from the investigation of different aspects of cortical functioning, such as OFC functional connectivity with downstream subcortical regions. The OFC is an important node within cortico-striato-thalamo-cortical circuitry. In addition to OFC hyperactivity, OFC hyperconnectivity within this circuitry has been implicated in compulsive behavior disorders (17). Therefore, by investigating the engagement of OFC networks, a more complete picture of OFC cTBS effects might arise.

Now that the OFC has been clearly delineated as a candidate brain stimulation target, determining the ideal stimulation approach will require a collaborative effort. The authors were diligent to narrow the effects of OFC modulation by combining TBS with habit override training. Nevertheless, a remaining open question is how the stimulation of functionally heterogeneous subregions around the frontal pole might more or less effectively treat compulsive behaviors. Although Price et al. found that subtle variations in coil positioning near their Brodmann area 10 target did not systematically influence compulsive behaviors, it has been shown in depression that individual functional connectivity–based targeting may lead to better treatment outcomes (18). Extending this principle to compulsive behavior disorders, varied OFC targets and their functional connectivity profiles will need to be explored. Another important question raised by this work is whether brain stimulation treatments for compulsive behavior disorders require state-dependent stimulation, or whether cTBS on its own, directed to optimized targets, would be effective.

In sum, patients suffering from chronic compulsive behaviors rarely achieve remission with current treatments. A better understanding of the brain regions causally linked to compulsive behaviors stands to open up treatment avenues for many disorders characterized by compulsive behaviors. The thoughtful and creative work by Price et al. has therefore built a mechanistic foundation for future translational science to build upon. It will be exciting to see how noninvasive repetitive cortical stimulation is developed in the coming years to benefit patients who suffer from compulsive symptoms.

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REFERENCES

1. Hinds AL, Woody EZ, Van Ameringen M, et al: When too much is not enough: obsessive-compulsive disorder as a pathology of stopping, rather than starting. PLoS One 2012; 7:e30586

2. Gillan CM, Kosinski M, Whelan R, et al: Characterizing a psychiatric symptom dimension related to deficits in goal-directed control. eLife 2016; 5:e11305
3. Greenberg B, McLaughlin N, Rasmussen S: Neurosurgeries for intractable OCD: deep brain stimulation and gamma ventral capsulotomy compared. Brain Stimul 2019; 12:461
4. Carmi L, Tendler A, Bystritsky A, et al: Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatry 2019; 176:931–938
5. Bourne SK, Eckhardt CA, Sheth SA, et al: Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. Front Integr Neurosci 2012; 6:29
6. Ahmari SE, Spellman T, Douglass NL, et al: Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 2013; 340:1234–1239
7. Menzies L, Chamberlain SR, Laird AR, et al: Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 2008; 32:525–549
8. Rotge J-Y, Guehl D, Dilharreguy B, et al: Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. J Psychiatry Neurosci 2008; 33:405–412
9. Price RB, Gillan CM, Hanlon C, et al: Effect of experimental manipulation of the orbitofrontal cortex on short-term markers of compulsive behavior: a theta burst stimulation study. Am J Psychiatry 2021; 178:459–468
10. Huang Y-Z, Edwards MJ, Rounis E, et al: Theta burst stimulation of the human motor cortex. Neuron 2005; 45:201–206
11. Grover S, Nguyen JA, Viswanathan V, et al: High-frequency neuromodulation improves obsessive-compulsive behavior. Nat Med 2021; 27:232–238
12. Ruffini C, Locatelli M, Lucca A, et al: Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry 2009; 11:226–230
13. Nauczyciel C, Le Jeune F, Naudet F, et al: Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transl Psychiatry 2014; 4:e436
14. Williams NR, Sudheimer KD, Cole EJ, et al: Accelerated neuromodulation therapy for obsessive-compulsive disorder. Brain Stimul 2021; 14:435–437
15. Berlim MT, Neufeld NH, Van den Eynde F: Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 2013; 47:999–1006
16. Dunlop K, Woodside B, Olmsted M, et al: Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Neuropsychopharmacology 2016; 41:1395–1403
17. Harrison BJ, Soriano-Mas C, Pujol J, et al: Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch Gen Psychiatry 2009; 66:1189–1200
18. Cash RFH, Weigand A, Zalesky A, et al: Using brain imaging to improve spatial targeting of transcranial magnetic stimulation for depression. Biol Psychiatry (Online ahead of print, June 7, 2020)