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Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder
A Review

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IMPORTANCE Obsessive-compulsive disorder (OCD) is a common and often debilitating psychiatric illness. Recent advances in the understanding of the neuroscience of OCD have provided valuable insights that have begun to transform the way we think about the management of this disorder. This educational review provides an integrated neuroscience perspective on formulation and treatment planning for patients with OCD. The article is organized around key neuroscience themes most relevant for OCD.

OBSERVATIONS An integrated neuroscience formulation of OCD is predicated on a fundamental understanding of phenomenology and symptom dimensions, fear conditioning and extinction, neurochemistry, genetics and animal models, as well as neurocircuitry and neurotherapeutics. Symptom dimensions provide a means to better understand the phenotypic heterogeneity within OCD with an eye toward more personalized treatments. The concept of abnormal fear extinction is central to OCD and to the underlying therapeutic mechanism of exposure and response prevention. A framework for understanding the neurochemistry of OCD focuses on both traditional monoaminergic systems and more recent evidence of glutamatergic and γ-aminobutyric acid–ergic dysfunction. Obsessive-compulsive disorder is highly heritable, and future work is needed to understand the contribution of genes to underlying pathophysiology. A circuit dysregulation framework focuses on cortico-striato-thalamo-cortical circuit dysfunction and the development of neurotherapeutic approaches targeting this circuit. The impact of these concepts on how we think about OCD diagnosis and treatment is discussed. Suggestions for future investigations that have the potential to further enhance the clinical management of OCD are presented.

CONCLUSIONS AND RELEVANCE These key neuroscience themes collectively inform formulation and treatment planning for patients with OCD. The ultimate goal is to increase crosstalk between clinicians and researchers in an effort to facilitate translation of advances in neuroscience research to improved care for patients with OCD.

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"Certain notions are forced into their minds, of which they see the folly and incongruity, and complain that they cannot prevent their intrusion."
-John Haslam, 1798[1]

The Clinical Challenge published in this issue of *JAMA Psychiatry*[2] presents the case of a woman with severe and debilitating contamination obsessions and washing compulsions and the protracted course of treatment required to achieve adequate control of her symptoms. Descriptions of individuals with obsessive-compulsive disorder (OCD) date back to medieval times; the quote above from the English physician John Haslam (1764-1844) is one of the first contemporary sounding accounts of the disorder.[1] While OCD has long been recognized, effective treatment options have only been identified over the last several decades beginning in 1980 with the first randomized clinical trial of clomipramine in OCD.[3] Since then, we have witnessed a period of rapid advancement in the pharmacologic and psychotherapeutic treatment of OCD with the development of the selective serotonin reuptake inhibitors (SSRIs) and exposure and response prevention (ERP) therapy. Alongside these therapeutic discoveries, advances in neuroimaging have characterized the neural circuitry underlying OCD, paving the way for state-of-the-art circuit-based neurotherapeutics. However, while these advances have vastly improved the care of patients with OCD, many patients still experience substantial residual symptoms. We review our current understanding of OCD pathobiology and treatment, while outlining areas where the field still has much to learn.

Theme 1: Phenomenology and Symptom Dimensions

Prior to *DSM-5*,[4] OCD was characterized as an anxiety disorder because anxiety is a common feature of the disorder.[5] However, as anxiety is not requisite for OCD and the condition was deemed by various criteria to be more closely related to other disorders, OCD was moved to its own distinct section of *DSM-5*.[6] This Obsessive-Compulsive and Related Disorders section also contains body dysmorphic disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, and hoarding disorder. By definition, OCD is characterized by obsessions and compulsions. Obsessions are unwanted thoughts and/or images that cause significant distress; compulsions are repetitive behaviors performed in an effort to negate the distress of obsessions. Common compulsions include washing, checking, counting, asking/confessing, and ordering. All patients with OCD have obsessions and/or compulsions, but the individual specifics are highly variable. Although not identical, OCD-related disorders share the feature of repetitive thoughts or behaviors (eg, obsessing about appearance in body dysmorphic disorder and repetitive hair-pulling or skin-picking in trichotillomania and excoriation disorder, respectively).

While OCD is a categorical diagnosis, symptomatic heterogeneity suggests that current psychiatric nosology does not adequately capture the underlying pathophysiology on an individual basis. Because this is true for most psychiatric disorders, alternative approaches to studying these disorders are being developed. One such approach is the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health. Research Domain Criteria use a dimensional approach to assess symptom clusters both across and within diagnoses with the ultimate goals being better linkage between clinical/behavioral phenomena and underlying biology, as well as individual-level assessment. Domains in the RDoC framework include cognitive systems, negative-valence and positive-valence systems, arousal and regulatory systems, and systems for social processes. Within each system are constructs and subconstructs. The RDoC approach includes assessment across behavior, circuits, cells, and genes. Some of these constructs and subconstructs appear to be especially pertinent to OCD.

Within negative-valence systems, both acute threat (fear) and potential threat (anxiety) are implicated in OCD. Numerous studies have demonstrated abnormal activation of fear circuitry during exposure to aversive stimuli in patients with OCD.[7] Regarding anxiety, patients with OCD have elevated anxiety sensitivity and overestimation of threat compared with healthy individuals.[8] Other negative-valence abnormalities seen in OCD include attentional bias[9] and intolerance of uncertainty.[10] Another important group of constructs and subconstructs that is likely involved in the pathophysiology of OCD is the positive-valence system, specifically, reward learning and responsiveness to reward. Individuals with OCD are hypervigilant to reward feedback and opt for immediate relief (reduction of anxiety) at the cost of longer-term benefit (quality of life).[11] In other words, patients with OCD seem unable to modulate their future behavior based on immediate feedback. Related to this, habit formation appears to be abnormal in patients with OCD. In a neurocomputational study by Voon et al,[12] the investigators found that patients with OCD made choices based on model-free (ie, habit) vs model-based (ie, executive control) learning. Finally, deficits within the cognitive systems, namely cognitive control[13] and response selection, inhibition, or suppression,[14] have been demonstrated in patients with OCD.

Theme 2: Extinction Science

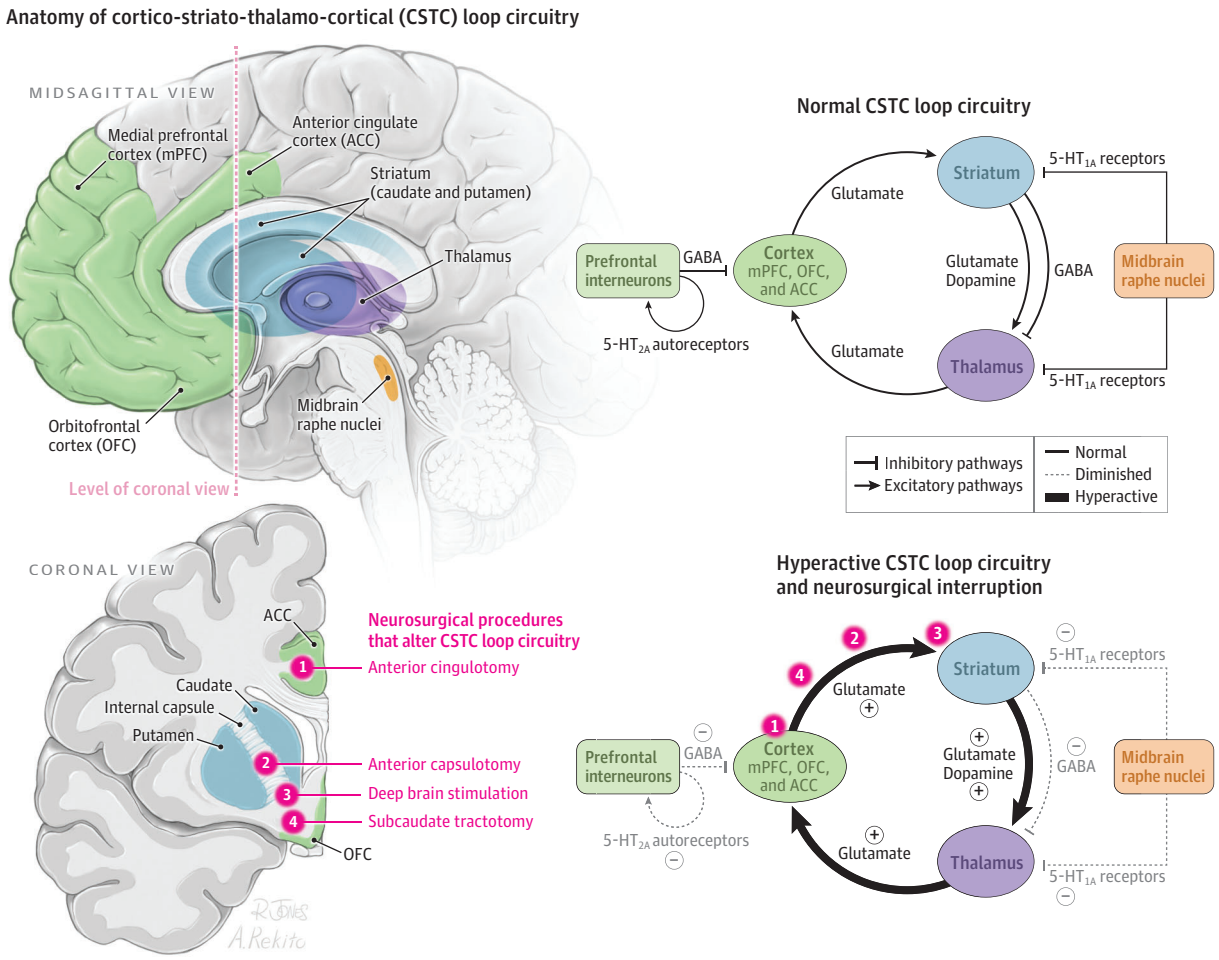
As described earlier, abnormalities in fear processing have been noted in patients with OCD. This dimensional aspect of OCD is particularly important as the first-line treatment for OCD, ERP therapy, is believed to normalize fear processing. Pertinent laboratory studies use fear conditioning and extinction paradigms. In these paradigms, study participants (animals or humans) first learn new fear using a conditioned stimulus coupled with an aversive stimulus (eg, electric shock). Almost all study participants will develop fear conditioning (eg, increased freezing behavior in animals, a rise in skin conductance response in humans) in this type of paradigm. However, group differences begin to appear during fear extinction. During a separate session, following the fear conditioning session, study participants are exposed to the conditioned stimulus without the aversive consequence. Again, almost all individuals will eventually learn that the conditioned stimulus is no longer associated with the aversive stimulus (ie, safety learning) and experience fear extinction (a decline in freezing behavior or skin conductance response). However, patients with OCD display impaired safety learning,[15] and many of the brain regions within the fear circuitry (amygdala, ventromedial prefrontal cortex, dorsal anterior cingulate cortex) have been implicated in the pathophysiology of OCD.[16,17]

Exposure and response prevention therapy is a behavioral therapy technique that involves exposing patients to a triggering stimulus (the exposure) and then preventing their typical response (response prevention) to said stimulus. A classic example is asking a patient with OCD who has contamination fears to touch a surface (eg, doorknob, toilet flusher handle) that they perceive as contaminated. They are then asked, despite their accompanying increasing levels of anxiety, to prevent themselves from responding in the manner they would typically use to lessen their anxiety (eg, washing their hands). For exposure treatments to work, a patient needs to learn that a typical OCD trigger is actually safe. This is usually achieved by asking the patient to repeatedly engage in ERP exercises across different contexts. Exposure and response prevention therapy is fear extinction used therapeutically in the clinical setting and is a first-line treatment for OCD with response rates as high as 70% for patients who are able to complete treatment.[18] A better understanding of the brain regions associated with safety evaluation, such as the ventromedial prefrontal cortex and hippocampus, could have major implications for further enhancing and expediting ERP treatments.

Theme 3: Neurochemistry

Obsessive-compulsive disorder has long been conceived as a disorder of serotonergic dysfunction based on the established efficacy of serotonin (5-HT) reuptake inhibitors, such as the SSRIs and clomipramine.[19] Neuroimaging studies using positron emission tomography and single-photon emission computed tomography to examine 5-HT transporter and receptor density have yielded equivocal results but collectively provide some evidence of regional 5-HT abnormalities in OCD, most notably, decreased 5-HT transporter availability within thalamus and midbrain regions, increased 5-HT_{2A} receptor availability within caudate, and decreased 5-HT_{2A} receptor availability in prefrontal regions.[20] These findings have been hypothesized to reflect lower synaptic serotonin within the cortico-striato-thalamo-cortical (CSTC) circuit implicated in OCD (**Figure**). However, given the inconsistent findings from these studies and the fact that roughly half of patients with OCD treated with an SSRI do

Figure. Anatomy and Neurochemical Models of CSTC Loop Circuitry Implicated in Obsessive-Compulsive Disorder With Associated Neurotherapeutic Interventions



Normal excitatory and inhibitory connections contributing to CSTC circuitry are shown in simplified form. The hyperactive CSTC circuit implicated in obsessive-compulsive disorder (OCD) exhibits diminished serotonergic and GABAergic inhibitory tone from both mPFC interneurons and midbrain raphe nuclei, resulting in striatal dopaminergic and glutamatergic hyperactivity driving unrestrained CSTC activity. Neurosurgical procedures that alter the hyperactive CSTC circuitry may relieve severe, treatment-refractory OCD. Surgical lesions include anterior cingulotomy, subcaudate tractotomy, and anterior capsulotomy, which may be performed through an open or gamma knife approach. Deep brain stimulation is performed in the ventral capsule and ventral striatum, just posterior to the capsulotomy lesion target. 5-HT indicates 5 hydroxytryptamine; GABA, γ-aminobutyric acid.

not respond,[21] neurotransmitter systems beyond 5-HT likely play a role in the pathophysiology of OCD.

Positron emission tomography and single-photon emission computed tomography studies have also demonstrated increased striatal dopamine transporter density and decreased striatal D_2/D_3 and D_1 receptor binding in patients with OCD, suggestive of dopaminergic hyperactivity in this region (Figure).[20] Accordingly, meta-analyses support the use of antipsychotic medications, particularly the high-affinity D_2 receptor antagonist risperidone, as SSRI augmentation treatments for OCD.[22,23] However, only about one-third of patients with treatment-refractory OCD respond to antipsychotic augmentation,[22] often leaving clinicians in search of other augmentation strategies.

Several lines of evidence support a role for abnormal glutamatergic neurotransmission in the pathophysiology of OCD. Early studies using magnetic resonance spectroscopy demonstrated elevations in glutamate and its related metabolite glutamine (a combined measure termed *Glx*) in the caudate nucleus of pediatric patients with OCD (Figure) that appeared to normalize with paroxetine treatment.[24,25] However, subsequent efforts to replicate these findings have been largely unsuccessful.[26] Several glutamate-related genes have been associated with OCD and have spawned the development of transgenic animal models of OCD (see section Theme 4, Genetics and Animal Models). A number of small preliminary clinical trials have investigated glutamate-modulating interventions, such as memantine, riluzole, and *N*-acetylcysteine, as potential SSRI augmentation treatments for OCD. These showed promising results at least in a subset of patients with OCD.[27] Additionally, ketamine rapidly reduced OCD symptoms after a single intravenous infusion in a small placebo-controlled crossover trial,[28] although an open-label trial in patients with more severe and treatment-resistant OCD showed no benefit.[29] All in all, more investigation is needed to determine whether

glutamatergic medications have utility as OCD treatments, and if so, in which patient populations.

The role of γ-aminobutyric acid (GABA) dysfunction in OCD has been relatively understudied. However, abnormalities in prefrontal inhibitory neurotransmission posited to result from deficient GABAergic activity[30] and reduced medial prefrontal and orbitofrontal cortical GABA levels have been identified in patients with OCD (Figure).[31,32] Moreover, an acute increase in medial prefrontal levels of GABA after ketamine infusion was significantly associated with rapid OCD symptom reduction.[33] These findings underscore the need for further exploration of a potential role for GABAergic abnormalities in OCD.

Collectively, the above findings suggest that an array of neurochemical abnormalities may underlie OCD. At its core, OCD seems to involve overactive CSTC circuits evidenced by striatal dopaminergic and glutamatergic hyperactivity (Figure). The etiology of this hyperactive state remains unclear but may result from primary abnormalities in glutamate-related genes expressed within CSTC brain regions and/or may be secondary to diminished midbrain and prefrontal serotonergic activity. Serotonergic projections from the raphe nuclei inhibit dopaminergic activity in the striatum[34] and thalamic activity via stimulation of 5-HT_{1A} receptors,[35] while stimulatory 5-HT_{2A} autoreceptors on prefrontal GABA interneurons inhibit striatal glutamatergic activity (Figure).[36] Thus, SSRIs may reduce OCD symptoms by dampening striatal dopaminergic and glutamatergic hyperactivity through enhanced serotonergic inhibition. In addition to serotonergic deficits, reduced prefrontal GABAergic inhibitory tone may also increase striatal activity either through direct projections to striatum or indirectly via projections to orbitofrontal cortex (Figure).[31] While this model is an oversimplification, it provides a foundation for further investigation into the pathophysiology of OCD and the development of novel treatment approaches.

Theme 4: Genetics and Animal Models

Obsessive-compulsive disorder is familial, with a 4-fold increased risk among first-degree relatives of those with OCD compared with those without the illness.[37] Obsessive-compulsive disorder is a complex genetic disorder that likely involves many genes, with less predictable inheritance patterns than those found in single-gene mendelian dominant and recessive illnesses such as Huntington disease and cystic fibrosis. While the identified familiality of OCD reflects a combination of environmental and inherited genetic influences, the specific role of genetics was supported by a large twin study of obsessions and compulsions, reporting estimated heritability rates of 27% to 47% in adult and 45% to 65% in childhood-onset presentation.[38]

With advances in molecular genetic technology, a search for specific OCD risk genes became possible. Mirroring research efforts in other psychiatric disorders, a plethora of hypothesis-driven candidate gene studies of OCD were conducted over the last decade focusing largely on serotonergic and glutamatergic neurotransmitter systems.[39] Unfortunately, these studies were frequently underpowered and yielded false-positive findings that failed to replicate in subsequent studies. Even the most replicated genetic finding in OCD involving the gene *SLC1A1*, which encodes the neuronal glutamate transporter, failed to show a significant association in a meta-analysis of 3 positive independent studies.[40]

Driven by the above suboptimal results for candidate gene studies and by evolving technological capacity and efficiency, hypothesis-free searches across the full genome for disease risk genes emerged. Genome-wide association studies (GWAS) were conducted with strictly defined thresholds for significance, requiring *P* values less than 5×10^{-8}. Genome-wide association studies projects conducted by the International OCD Foundation Genetics Collaborative[41] and by the OCD Collaborative Genetics Association Study[42] and their subsequent meta-analysis[43] comprised more than 2800 OCD cases, 400 complete trios, and 7000 controls. While no significantly associated single-nucleotide polymorphisms or haplotype blocks were identified, top hits included those near or within genes coding for *DLGAP1* and *PTPRD*, proteins critical for glutamatergic synapse development and differentiation, respectively. Notably, the mouse homologue of *DLGAP1*, *SAPAP3*, has been knocked out in mice resulting in animals that groom excessively and act anxiously in laboratory assays.[44-46]

Secondary use of GWAS data has helped to clarify many aspects of OCD genetics. First, in keeping with twin-study–derived estimates, GWAS-data–derived heritability estimates for OCD range between 28% and 43%.[43,47] Second, OCD heritability appears to be conferred more frequently through very common single-nucleotide polymorphisms (eg, most contributing single-nucleotide polymorphisms have minor allele frequencies greater than 40%)[43] rather than via rare mutations (eg, 0% is captured by variants with minor allele frequencies <5%).[48] Third, with respect to rare copy number variants, deletions in 16p13.11 have been implicated, although de novo mutations were found in only 1.4% of cases.[48] Fourth, GWAS data further confirmed the polygenic nature of OCD,[49] providing some explanation for historic challenges in identifying single genes of large effect. Fifth, SSRI treatment response in the OCD Collaborative Genetics Association Study cohort further supported a role for genes involved in glutamatergic and serotonergic neurotransmission.[50]

Animal models of OCD have also helped to elucidate potential genetic contributors to its pathophysiology. Knockout mouse models of note include *SAPAP3* (as previously discussed),[46] *HOXB8*,[51] and *SLITRK5*,[52] which cause impaired synaptic activity, corticostriatal dysfunction, and pathologic grooming. Targeted sequencing found enrichment of potentially causative variants in 4 genes, including *NRXN1* and *HTR2A*, which alter postsynaptic binding domains, *CTTNBP2*, involved in synapse maintenance, and *REEP3*, involved in vesicle trafficking.[53]

In summary, GWAS and animal studies of OCD have provided convergent evidence implicating genes involved in glutamatergic neurotransmission and synaptic function. Future work examining epigenetic effects, pharmacogenetics, and the putative role of autoimmunity[54] is warranted to further elucidate the genetics of OCD with a long-term goal of improving treatment options.

Theme 5: Neurocircuitry and Neurotherapeutics

Among psychiatric disorders, OCD has arguably the most well-accepted brain circuit model, grounded in the notion of compulsions as habitual, nearly automatic actions. Habits depend on recurrent circuits that connect cerebral cortex to the basal ganglia, termed *CSTC loops*. In the CSTC model of OCD, these loops become hyperactive or hyperconnected, self-exciting in a runaway positive feedback loop.[17,55] This leads to the urge to perform compulsions, which in turn consolidates/strengthens the habit of performing compulsions, increasing the urge. Exposure and response prevention therapy might then break the chain by patients instead practicing the habit of not enacting their compulsions. There remains substantial debate over whether obsessions or compulsions arise first.[45,56]

The conceptualization of CSTC circuit(s) has evolved. From early on, models focused on a direct vs indirect pathway with OCD being an imbalance in their relative drive.[44,45] However, whereas initial models conceptualized multiple parallel CSTC loops (Figure), each connecting different aspects of cortex and basal ganglia, recent advances have established cascading spiral connections across the CSTC loops.[17,57] Regardless, all the model variants predict that CSTC structures should be hyperactive and hyperconnected in OCD.

Human and animal studies provide evidence for the CSTC model. Structures involved in these loops, particularly the caudate nucleus, dorsal anterior cingulate cortex, and orbitofrontal cortex, are abnormally active in patients with OCD at rest and with symptom provocation, and this hyperactivity attenuates with pharmacologic and behavioral treatment.[16] Newer studies have extended this to functional connectivity as measured by functional magnetic resonance imaging and again have found abnormalities in multiple connections within the CSTC circuits.[44,58-60] Patients with OCD show abnormalities on executive function tasks that directly depend on CSTC circuits.[44,56,61,62] Finally, as noted earlier, a key glutamate gene needed for CSTC loop development, *SAPAP3*, has been knocked out in mice. Those mice show abnormal (compulsive) grooming and also have abnormal corticostriatal synaptic properties.[44] When the CSTC abnormality is reversed, the grooming stops[63]; when it is induced by nongenetic means, abnormal grooming develops.[64] Compulsive grooming in mice is a weak model for OCD in humans, but collectively, these results give credence to CSTC abnormalities as important in OCD.

The prevailing neurocircuit hypothesis has influenced neurotherapeutic approaches: attempts to manage OCD by directly interfering with CSTC loop function. These comprise ablative surgeries and brain stimulation, with the latter further divided into noninvasive (transcranial magnetic stimulation) and invasive (deep brain stimulation [DBS]). The surgical approaches include anterior capsulotomy, subcaudate tractotomy, anterior cingulotomy, and limbic leucotomy (a combination of the cingulotomy and subcaudate tractotomy). All are supported by open-label data, with response rates (defined as a 35% or greater improvement on the Yale-Brown Obsessive Compulsive Scale) in the 35% to 75% range and overall favorable adverse effect profiles, in terms of mortality or long-term morbidity.[65] The variability in response rate is higher among studies of the same procedure than between procedures. Unique among these, capsulotomy has been developed into a gamma knife surgical procedure, which enabled a true sham-controlled trial.[66] That trial did not reach significance in its primary analysis, but long-term follow-up showed improvements comparable to open capsulotomy.

Brain stimulation offers the circuit-disrupting advantages of lesions but with the possibility of adjusting stimulation dose in response to patient (non)improvement. Transcranial magnetic stimulation, which has seen rapid adoption for major depression, has received much interest. The left dorsolateral prefrontal cortex target used for depression shows no benefit for OCD.[67] A target more closely linked to the CSTC loops, the supplementary motor area, had modest positive effects in 2 sham-controlled transcranial magnetic stimulation trials and a meta-analysis.[68] Supplementary motor area transcranial magnetic stimulation might therefore be indicated as an adjunct to ERP therapy and evidence-based medications, although it is often considered experimental by insurers. Deep brain stimulation, the therapy elected by the patient presented in the Clinical Challenge in this issue of *JAMA Psychiatry*,[2] is a more invasive approach that implants electrodes directly into CSTC loop structures, where they then deliver continuous high-frequency stimulation. European trials demonstrated limbic regions of the subthalamic nucleus as an effective DBS site.[69] However, more teams have focused on the ventral internal capsule/ventral striatum. This site, a white matter hub containing multiple CSTC loops, has open-label and randomized clinical trial data supporting its efficacy in OCD, with response rates also in the 33% to 75% range.[70,71] Ventral internal capsule/ventral striatum DBS is approved by the US Food and Drug Administration under a Humanitarian Device Exemption for OCD on the basis of those data. A major advantage of DBS over ablative procedures is that it is reversible and adjustable. This allows brain measurements with and without stimulation, which have confirmed that DBS changes the activity of multiple CSTC structures.[44,71,72] On the other hand, those same properties allow patient relapse from device failures and potential stimulation overdoses leading to hypomania.[73,74] Closed loop systems that self-adjust stimulation in response to CSTC loop activity might resolve such problems but remain largely theoretical.[73,75]

An important caveat for both genetic and circuit studies is that historically, they have often treated OCD as a single disorder. Psychological factor analyses have repeatedly suggested multiple phenotypic subtypes of OCD, each with a different biology; the same extends to the presence/absence of comorbid tics.[45,61] As noted earlier, clinical and experimental psychiatry are moving toward a dimensional concept of illness, characterizing patients' impairments in specific domains of functioning. Obsessive-compulsive disorder may be particularly amenable to that concept because different CSTC loops are believed to contribute to unique aspects of the syndrome.[17] If a reliable, quantifiable dimensional framework can be developed, it may increase the targeting precision and thus the efficacy, of OCD neurotherapeutics.[75]

Conclusions

Advances in understanding the genetic, molecular, and neural underpinnings of OCD have rivaled that of any other psychiatric disorder over the last 30 years. Moving forward, we expect several key areas of OCD research to be the focus of accelerated growth and development. First, the substantial phenotypic heterogeneity within the OCD diagnosis merits further exploration into the biological differences between OCD symptom subtypes using deep phenotyping, an RDoC approach, and advanced neuroimaging techniques. Second, based on the ever growing evidence supporting a role for glutamatergic dysfunction in OCD, investigation of novel glutamate-modulating interventions in OCD is warranted. Third, given evidence of extinction learning deficits in OCD, continued investigation into potential pharmacologic, neuromodulatory, or behavioral approaches to augment ERP therapy is a priority. Lastly, continued improvement and refinement of neurotherapeutic/neurostimulation approaches for OCD is an area of immense potential. Ultimately, advancement in these areas holds promise for treatment interventions that can be prescribed in a neuroscientifically informed manner using a precision medicine approach for patients with OCD on an individualized basis to enhance outcomes.

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