Beyond Feared Outcomes: Exploring Sensory Phenomena as a Novel Therapeutic Target for OCD

Dana E. Díaz, Ph.D., Kate D. Fitzgerald, M.D.

Advancing treatment outcomes for obsessive-compulsive disorder (OCD) requires the exploration of novel symptom dimensions and their underlying neural mechanisms. Despite advancements in treatment, 40%–60% of OCD patients achieve only partial recovery, and 10% see no improvement (1–3). For decades, interventions have focused on preventing compulsive responses to obsession-driven, feared outcomes (e.g., repeatedly checking locks to prevent a break-in). However, these approaches may fall short for patients whose compulsions are driven by sensory phenomena (SP)—distressing physical sensations like tingling or pressure, or mental sensations like feelings of incompleteness (i.e., internal tension/discomfort). SP have also been used to describe the premonitory urges that characterize tic disorders, which are commonly comorbid with OCD.

In this issue, Stern and colleagues (4) examine the effects of high-dose ondansetron, a serotonin type 3 ($5\text{-}HT_3$) receptor antagonist, on SP and resting-state functional connectivity (rs-FC) in patients with OCD and/or Tourette's/tic disorder. Results from this placebo-controlled functional MRI (fMRI) clinical trial suggest that ondansetron may enhance the efficacy of serotonin-reuptake inhibitors (SRIs) in treating OCD symptoms (4), possibly through the modulation of interoceptive-sensorimotor circuits implicated in SP (5, 6). We believe this study's strength lies in its experimental therapeutics approach to examine a novel treatment target, SP-related sensorimotor connectivity, for a treatment-resistant dimension of OCD. This work is in line with the National Institute of Mental Health's Research Domain Criteria (RDoC) framework, which emphasizes that examining psychopathology transdiagnostically can uncover shared neural circuits underpinning constructs such as SP, offering insights that may drive the development of targeted and effective treatments across disorders. In this editorial, we aim to underscore the need for RDoC-informed research in experimental medicine and extend the implications of the Stern et al. study for guiding treatment research.

This study contributes to an emerging body of research examining SP as a novel treatment target in OCD (and Tourette's/tic disorder), highlighting the potential for precision medicine to address OCD's heterogeneity. Obsessions and compulsions in OCD vary widely in themes (e.g., contamination/cleaning vs. order/symmetry) and motivations (e.g., fear-based vs. "not-just-right" experiences), and this heterogeneity likely extends to brain function (7). As SP are associated with specific symptom dimensions (e.g., symmetry/ordering, contamination) and comorbidities (e.g., tic disorders) (8), they may reflect a unique subgroup of OCD patients with distinct neurobiological pathways requiring tailored treatment approaches. Future research employing data-driven clustering approaches (7) could help delineate whether neural mechanisms of SP-driven compulsions are distinct from those underlying compulsions designed to prevent feared outcomes (e.g., harm, contamination). Additionally, even within SP, symptoms are heterogeneous, including musculoskeletal sensations; "not-just-right" perceptions triggered by tactile, visual, or auditory input; internal feelings of incompleteness; rising internal tension triggering an urge to repeat (i.e., without preceding obsessions); or physically sensed "urge only" (8). Thus, distinct neurobiological processes occur across different SP subtypes. In either case, data-driven analytic strategies have the potential to reveal brain-behavioral subtypes of OCD to inform the development of targeted interventions.

The Stern et al. study highlights the potential of experimental therapeutics to identify novel treatment targets and mechanisms in OCD, particularly for subgroups with treatment-resistant symptoms such as sensory phenomena.

Stern and colleagues' study of SP is aligned with RDoC's goal of identifying constructs that span traditional diagnostic categories. SP are transdiagnostic, appearing across OCD subtypes and in related conditions such as Tourette's/tic disorders, skin picking, and trichotillomania. Moreover, abnormalities in interoceptive-sensorimotor function have been observed across a variety of other disorders that are commonly comorbid with OCD, including anxiety, mood, and eating disorders, but are not typically directly addressed with standard treatments.

If identified, shared neurobiological substrates for SP could be targeted to inform cross-diagnostic interventions. In this study, neural substrates for SP were examined across OCD and Tourette's/tic disorders. However, the small

sample size for Tourette's/tic disorder limited the study's statistical power to detect common or distinct treatment effects relative to OCD. Future research should prioritize larger, more diverse samples, including patients with Tourette's/tic disorder and other comorbid conditions characterized by interoceptive and/or sensorimotor disturbances. Combining these broader perspectives with targeted clustering approaches will be essential to developing precision medicine strategies that address SP-related symptoms and improve outcomes for OCD and other disorders characterized by SP.

The study's application leverages the RDoC framework by focusing on neural circuits underpinning SP. Interestingly, changes in rs-FC that were associated with ondansetron treatment were not the same as those that were associated with change in SP. Across ondansetron and placebo groups, reductions in SP correlated with decreased global connectivity or "hubness" in the right sensorimotor cortex, a region thought to drive the premonitory urges and sensations characteristic of SP. By contrast, for patients treated with ondansetron compared to those who received placebo, reductions in SP correlated with decreased local connectivity or "near neighbor coherence" within the brainstem. However, neither of these changes in brain connectivity was found to be associated with pre- to post-treatment change in OCD symptoms. It is worth noting that previous work demonstrating changes in brain connectivity following treatment has also failed to show correlations with OCD symptom improvement (9). These findings underscore the complexity of linking neural changes to clinical outcomes in neuroimaging clinical trials.

Although ondansetron did not outperform placebo in reducing SP or OCD symptoms in the full sample, OCD patients taking a concomitant SRI exhibited greater OCD symptom reduction and decreased global sensorimotor cortex connectivity ("hubness") following treatment with ondansetron compared to placebo. Interestingly, these participants did not experience reductions in SP. Below, we discuss the potential mechanisms underlying these findings and suggestions for future research.

Across all participants, ondansetron uniquely reduced brainstem local coherence (akin to measures of regional homogeneity) compared to placebo. Ondansetron's proposed mechanism involves blocking 5-HT_3 receptors, which are densely located in brainstem, modulating neurotransmitter release and ultimately influencing interoceptive and somatosensory signals to higher-order cortical regions. SRIs also influence subcortical-cortical connectivity, which may interact with changes induced by ondansetron. For instance, a pilot study by Bernstein et al. (10) found that treatment with sertraline led to increased rs-FC between the putamen and the frontal cortex, insula, and operculum in youths with OCD compared with healthy control subjects, and that this change in connectivity correlated with greater symptom improvement. Notably, these regions are involved in sensorimotor integration (putamen) and interoception (insula), mechanisms hypothesized to underlie SP and be modulated by ondansetron. Continued research should examine changes in the function and connectivity of these subcortical-cortical sensorimotor circuits following combined therapy with ondansetron and SRIs. Interestingly, exposure and response prevention therapy has also been shown to modulate subcortical-cortical connectivity (11). Future studies should test whether ondansetron enhances the efficacy of cognitive-behavioral therapy, or whether its effects are specific to treatment with SRIs.

Notably, and contrary to the authors' predictions, ondansetron reduced OCD symptoms without effects on SP in patients taking SRIs, raising important mechanistic questions for future research. It is possible that undetected changes in SP underlie OCD symptom improvement, for instance, by altering interoceptive awareness, salience, or tolerance of SP rather than frequency or type. More sensitive measures of SP and/or longer treatment durations may help clarify whether changes in SP moderate effects of ondansetron on OCD symptoms. Alternatively, ondansetron may alleviate symptoms through broader modulation of interoceptive-sensorimotor circuits, independent of SP. These findings underscore the need for iterative hypothesis refinement in experimental medicine.

The Stern et al. study highlights the potential of experimental therapeutics to identify novel treatment targets and mechanisms in OCD, particularly for subgroups with treatment-resistant symptoms such as SP. As discussed above, the study findings open several avenues for future research, including the investigation of SP as a subtype of OCD and as a transdiagnostic symptom dimension, as well as ondansetron's ability to augment effects of cognitive-behavioral interventions. Longer studies leveraging longitudinal and multimodal approaches could further illuminate the relation of SP-related neural substrates to OCD symptom expression. Additionally, examining structural correlates of SP (e.g., regional gray matter volumes, white matter integrity) and incorporating task-based imaging in studies of ondansetron could clarify underlying neural pathways of SP and specific functional processes elicited by treatment, offering more precise insights into treatment mechanisms. Data-driven statistical approaches that measure person- or subgroup-specific trajectories may also help to resolve the association between change in transdiagnostic constructs (e.g., SP), related neural substrates, and OCD symptoms in fMRI clinical trials. For instance, a study comparing therapy with exposure and response prevention to a control therapy leveraged Group Iterative Multiple Model Estimation, which incorporates individual heterogeneity into group analyses of brain connectivity, revealing changes in functional connectivity specific to exposure and response prevention that were not observable with standard group-averaging methods (9). Data-driven clustering approaches have also proven valuable for identifying pretreatment neural biomarkers that predict symptom reduction. For instance, machine learning has identified distinct OCD subgroups based on rs-FC abnormalities in the default mode network, with one subgroup

displaying poorer responses to SRIs and cognitive-behavioral therapy (12). Similarly, independent components analysis of pretreatment rs-FC in OCD patients identified a subgroup of participants with alterations in functional connectivity that predicted response to exposure and response prevention (13). These approaches highlight the potential of personalized and precision medicine in tailoring treatments to the unique neurobiological profiles of individuals or subgroups, ultimately advancing our ability to address treatment-resistant symptoms and optimize outcomes for OCD patients.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, Columbia University Irving Medical Center (Díaz, Fitzgerald), and New York State Psychiatric Institute (Fitzgerald), New York.

Send correspondence to Dr. Fitzgerald (kf2688@cumc.columbia.edu).

The authors report no financial relationships with commercial interests.

Accepted January 6, 2025.

Am J Psychiatry 2025; 182:234–236; doi: 10.1176/appi.ajp.20241213

REFERENCES

1. Denys D: Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am 2006; 29:553–584
2. Eddy KT, Dutra L, Bradley R, et al: A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. Clin Psychol Rev 2004; 24:1011–1030
3. Fineberg NA, Reghunandanan S, Brown A, et al: Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond. Aust N Z J Psychiatry 2013; 47:121–141
4. Stern ER, Collins KA, Bragdon LB, et al: Randomized controlled trial of the effects of high-dose ondansetron on clinical symptoms and brain connectivity in obsessive-compulsive and tic disorders. Am J Psychiatry 2025; 182:285–296
5. Brown C, Shahab R, Collins K, et al: Functional neural mechanisms of sensory phenomena in obsessive-compulsive disorder. J Psychiatr Res 2019; 109:68–75
6. Caseras X, Murphy K, Mataix-Cols D, et al: Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. Hum Brain Mapp 2013; 34:1220–1229
7. De Nadai AS, Fitzgerald KD, Norman LJ, et al: Defining brain-based OCD patient profiles using task-based fMRI and unsupervised machine learning. Neuropsychopharmacology 2023; 48: 402–409
8. Ferrão YA, Shavitt RG, Prado H, et al: Sensory phenomena associated with repetitive behaviors in obsessive-compulsive disorder: an exploratory study of 1001 patients. Psychiatry Res 2012; 197:253–258
9. Becker HC, Beltz AM, Himle JA, et al: Changes in brain network connections after exposure and response prevention therapy for obsessive-compulsive disorder in adolescents and adults. Biol Psychiatry Cogn Neurosci Neuroimaging 2024; 9:70–79
10. Bernstein GA, Cullen KR, Harris EC, et al: Sertraline effects on striatal resting-state functional connectivity in youth with obsessive-compulsive disorder: a pilot study. J Am Acad Child Adolesc Psychiatry 2019; 58:486–495
11. Russman Block S, Norman LJ, Zhang X, et al: Resting-state connectivity and response to psychotherapy treatment in adolescents and adults with OCD: a randomized clinical trial. Am J Psychiatry 2023; 180:89–99
12. Kwak S, Kim M, Kim T, et al: Defining data-driven subgroups of obsessive-compulsive disorder with different treatment responses based on resting-state functional connectivity. Transl Psychiatry 2020; 10:359
13. Shi TC, Pagliaccio D, Cyr M, et al: Network-based functional connectivity predicts response to exposure therapy in unmedicated adults with obsessive-compulsive disorder. Neuropsychopharmacology 2021; 46:1035–1044