Commentary

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When, How, and Where: Combining Psychotherapy and Neuromodulation for Obsessive-Compulsive Disorder

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Despite being among the 10 most personally debilitating disorders and the fourth most common psychiatric disorder, obsessive-compulsive disorder (OCD) remains difficult to treat. Pharmaco- and psychotherapy, including exposure and response prevention (ERP) therapy, are first-line interventions to treat OCD, and yet only 50% of patients with OCD achieve a clinically meaningful improvement in symptoms after monotherapy or combination therapy (1). Repetitive transcranial magnetic stimulation (rTMS)—as either monotherapy or an adjunctive agent to psychotherapy or medication—potentially offers an effective alternative for patients who do not respond adequately to first-line treatments. However, investigations into rTMS for OCD differ substantially in treatment design, including stimulation site and individual targeting approaches, as well as how and when to combine this intervention with psychotherapy.

The companion articles by Fitzsimmons *et al.* (2) and Postma *et al.* (3) in the current issue of *Biological Psychiatry* provide valuable mechanistic and clinical insights into two potential rTMS stimulation sites in combination with ERP therapy. Patients enrolled in the study received 16 sessions of neuronavigated 10-Hz rTMS immediately before a session of ERP. rTMS was randomized to two candidate stimulation sites with documented treatment efficacy in OCD, the left dorsolateral prefrontal cortex (DLPFC) or presupplementary motor area (preSMA), or a control site, the vertex. Functional magnetic resonance imaging (fMRI) was acquired in all participants before and after treatment, which included tasks designed to engage circuits recruiting stimulation sites of interest, including during the Tower of London (TOL) task and the stop signal task (SST). Crucially, baseline neural activity during these tasks was used to identify participant-specific DLPFC or preSMA targets, with task-based activation during the TOL task and SST used to identify the individual DLPFC and preSMA stimulation sites, respectively.

Intriguingly, while both the DLPFC and preSMA targets have evidence suggesting that rTMS targeting these regions alleviates the symptoms of OCD, participants randomized to either active rTMS and ERP arms responded as well as those who received vertex stimulation with ERP. This null finding underscores several important investigative leads that could expand our understanding of the interplay of rTMS and psychotherapy. First, participants received 16 twice-weekly sessions of rTMS immediately followed by ERP. While the sufficient number of rTMS treatments needed to treat OCD is unclear, conventional rTMS monotherapies involve up to 30 once daily sessions. It could be that active rTMS on non-ERP days or multiple rTMS sessions per day—perhaps before and after ERP—could clarify whether additional rTMS sessions are required to evaluate this combination therapy. Similarly, participants received rTMS and ERP at each session, and it is unclear whether having participants initiate rTMS or ERP simultaneously, staggered, or sequentially could bolster clinical efficacy. One possible option could include an initial accelerated rTMS course to initiate neuronal plasticity or metaplasticity (2), followed by integrated rTMS-ERP sessions to further modulate this effect. Future studies will be required to clarify when and how many rTMS and ERP sessions are necessary to maximize the clinical benefit in OCD.

Another outstanding area of investigation is targeting approaches to individualize rTMS for patients diagnosed with OCD. Innovatively, patients enrolled in these studies received personalized rTMS over the preSMA or DLPFC, and targeting was performed using task-based fMRI. This task-based approach could address potential limitations of using resting-state fMRI to guide stimulation. More specifically, resting-state connectivity-based rTMS targeting in major depressive disorder has conflicting evidence on whether it improves clinical efficacy over scalp heuristics (4), and this modality may be sensitive to modeling choices (5). Task-based fMRI may address some of these hurdles as it tends to better explain interindividual differences in behavior and psychopathology over resting-state fMRI (6). However, while every participant randomized to the DLPFC rTMS arm received an individualized stimulation target using the TOL task, 74% of those randomized to the preSMA rTMS arm did not have an identifiable preSMA hotspot during the SST and were stimulated over a literature-derived target.

Corroborating evidence that this difference in individualized targeting for the DLPFC and preSMA could impact target engagement can be found in treatment arm–specific changes in task-based activity during these tasks (2). More specifically, widespread reductions in planning-related activity during the TOL task were found in individuals randomized to the DLPFC arm compared with those either in the vertex or preSMA arms. This pre- to posttreatment reduction correlated with symptom improvement and provides strong mechanistic evidence to support the study's individualized DLPFC targeting approach. In contrast, the relationship between preSMA-rTMS and SST activity change is less robust, with no significant group differences and a weaker association between reductions of task activity during error processing and preSMA-rTMS symptom

SEE CORRESPONDING ARTICLES ON PAGES 678 AND 688

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improvement. This discrepancy could signal one of two possibilities. First, it could be that DLPFC-rTMS with ERP may better engage theorized circuits and may be the better of the two stimulation sites to combine with this psychotherapy. Second, target engagement may be more robust for those who received rTMS using their individualized preSMA hotspot.

While atypical DLPFC or preSMA activity during both tasks is well documented in patients with OCD relative to control individuals, several alternative targeting approaches also come to mind in light of the findings presented by Fitzsimmons *et al.* (2) and Postma *et al.* (3). First, the authors used task-related local activity to identify the rTMS hotspot, whereas resting-state approaches typically use functional connectivity. Functional connectivity assesses the extent to which neural activation fluctuations between a pair of brain regions covary over time. It could be that the ideal task-based hotspot involves functional connectivity, especially given that rTMS can modulate downstream monosynaptic connections of the stimulation site, which could be further examined using a psychophysiological interaction.

Another possibility is that an alternative task paradigm—perhaps one with task conditions with similar content to ERP therapy—could more reliably yield individualized rTMS targets intended to augment this psychotherapy beyond the DLPFC. Interestingly, the authors also acquired task-related activity during symptom provocation in this trial, and the baseline biomarkers of rTMS response during this task are reported in a secondary article by Houben *et al.* (7). In their article, Houben *et al.* found preliminary evidence that preSMA activity during the task predicted response to rTMS targeting the preSMA but not the vertex arm (see Table S3 in Houben *et al.*). The authors' rich data could provide valuable evidence to resolve the utility of symptom provocation over the SST in preSMA-rTMS targeting. One secondary analysis to understand the relationship between symptom provocation and preSMA targeting could determine whether the distance from the symptom provocation–localized and the SST-localized preSMA hotspots predicts subsequent response.

Baseline task-based fMRI predictors of symptom improvement (3) also reveal interesting mechanistic insights. Reassuringly, baseline task-related activity predicted improvement only to the two active rTMS arms both immediately post-treatment and at 3 months' follow-up. The predictive task corresponded to the treatment arm; for example, DLPFC-rTMS response was associated with baseline TOL task activity. This indicates that baseline biological characteristics could also help guide rTMS targeting. Furthermore, OCD is a highly heterogeneous disorder, with symptom dimensions distinguished by brain-based measures and symptom response to first-line interventions. It could be that baseline characteristics predicting treatment response to specific stimulation sites are related to specific symptom dimensions. For example, earlier work by van den Heuvel *et al.* (8) found that severity in specific symptom domains was correlated with regional gray and white matter volume. Symmetry/ordering symptoms were associated with insula volume, which topographically overlaps with baseline biomarkers (3) and pre- to posttreatment changes in brain activity (4) during the SST for preSMA-rTMS. Comorbidities also may play a role in rTMS target selection, with evidence suggesting that SMA-rTMS may be better suited for individuals with both OCD and a comorbid tic disorder (9). Given these findings, and evidence that symmetry symptoms are particularly associated with a comorbid tic disorder diagnosis (10), it could be that there is a subset of individuals whose baseline brain and/or clinical characteristics indicate that preSMA-rTMS is an ideal stimulation target.

In conclusion, the studies by Fitzsimmons *et al.* (2) and Postma *et al.* (3) provide important insights into the potential for rTMS as an adjunctive therapy for OCD, especially when combined with ERP. Although the null findings regarding the efficacy of rTMS as well as preSMA-rTMS targeting suggest that further optimization is necessary, they highlight critical areas for future investigation. These include refining the number and timing of rTMS sessions, exploring connectivity-based individualized targeting approaches, and considering alternative task paradigms to improve the precision and effectiveness of rTMS-ERP combinations. The use of task-based fMRI to guide rTMS targeting is a promising step forward, although the variability in individual response underscores the complexity of OCD and the need for more tailored treatment strategies. As research continues, further exploration of baseline biomarkers and symptom-specific predictors will be essential for advancing the clinical application of rTMS in OCD, offering hope for more effective, personalized interventions for those who struggle with this debilitating disorder.

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