Towards a convergent biomarker and treatment for obsessive-compulsive disorder

Lancet Psychiatry 2026
Published Online
October 7, 2026
https://doi.org/10.1016/S2215-0366(26)00277-4

The search for clinically actionable biomarkers for obsessive-compulsive disorder (OCD) has focused on corticostriatal circuits of the brain, but a reliable candidate remains to be found. We argue that a promising biomarker is high-frequency rhythms in the orbitofrontal cortex, spanning the high-beta rhythm (>20 Hz) to low-gamma rhythm (<55 Hz) range, which converge across treatment designs, invasive and non-invasive measurements, clinical and subclinical populations, and invasive and non-invasive interventions, making these rhythms both observable and actionable.

The orbitofrontal cortex is a crucial node in OCD. Neuroimaging studies show metabolic alterations in the orbitofrontal cortex in individuals with OCD,[1] and animal studies find that optogenetic manipulation of orbitofrontal cortex neurons alters compulsive behaviours.[2] Such evidence establishes the orbitofrontal cortex as the spatial locus of interest, but its dynamics, particularly how orbitofrontal cortex oscillations contribute to impaired function, remain underexplored.

Electroencephalography (EEG) studies in humans offer some evidence, pointing to beta oscillations (13–30 Hz) as a relevant process. Individuals with OCD show impaired connectivity in the beta-band, which correlates with the severity of symptoms.[3] Source estimation procedures identify orbital regions as one source of these beta-band rhythms.[3] In students with obsessive-compulsive symptoms, beta oscillations in frontocentral sensors were associated with the severity of reactive obsessions, specifically those arising in response to external distressing situations.[4] Thus, beta rhythmic activity that is measured noninvasively is a possible signature associated with OCD.

The potential involvement of beta rhythms in OCD is supported by surgical treatment studies showing beta-band changes in EEG. Deep brain stimulation of the anterior limb of the internal capsule produces transient scalp beta oscillations around approximately 31 Hz, with the strength of these oscillations larger in individuals with symptoms that responded to treatment than in those whose symptoms did not respond. The strength of the beta oscillations further correlates with the connectivity of the stimulated region with the orbitofrontal cortex.[5] Deep brain stimulation of the nucleus accumbens also modulates beta activity (16–25 Hz) and its cross-frequency coordination, source-localised to orbitofrontal cortex and adjacent regions such as ventromedial prefrontal cortex.[6] Bilateral capsulotomy modulates high-beta activity (20–35 Hz) in magnetoencephalography (MEG) for at least 6 months, alongside improvements in anxiety and depression.[7] Thus, across targets and modalities, effective interventions converge on modulating frontal high-beta activity, suggesting its putative relevance to OCD.

This evidence links beta oscillations to the orbitofrontal cortex only indirectly, via scalp or MEG source estimation, and to symptoms only via trait-level severity or post-treatment change. A genuine biomarker requires additional evidence: presence during active symptom expression, within-individual symptom tracking, and causal manipulability. Two studies have addressed this gap.[8,9]

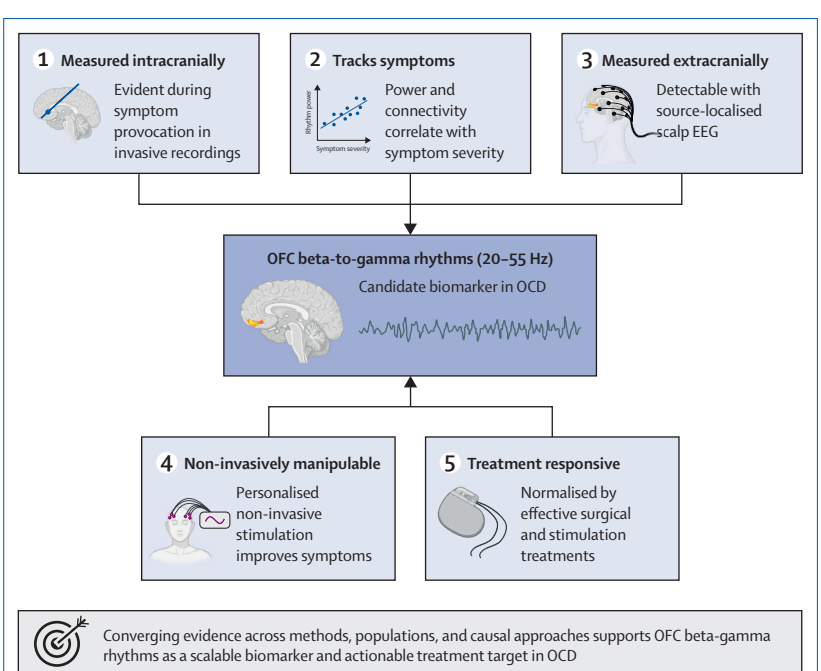

Figure: **A rhythmic biomarker in the orbitofrontal cortex in obsessive-compulsive disorder**
Multiple converging lines of evidence support high-beta and low-gamma orbitofrontal cortex rhythm (20–55 Hz) as a candidate biomarker for OCD. EEG= electroencephalography. OFC=orbitofrontal cortex. OCD=obsessive-compulsive disorder.

Downloaded for Anonymous User (n/a) at Boston University from ClinicalKey.com by Elsevier on October 20, 2026.
For personal use only. No other uses without permission. Copyright ©2026. Elsevier Inc. All rights reserved.

Nho and colleagues recorded orbitofrontal cortex activity invasively during direct electrical stimulation of the ventral basal ganglia in three patients with treatment-resistant OCD, during individualised symptom provocation associated with each patient's obsessional content.[8] A consistent high-frequency rhythm (30–55 Hz) emerged in the anteromedial orbitofrontal cortex during high-symptom states and tracked symptom intensity over 5-min intervals as individuals transitioned between symptom-provoking and neutral contexts.[8] The rhythm's range overlapped with previous high-beta signatures but extended into low-gamma frequencies. Because recordings were invasive, this response could be directly localised to the orbitofrontal cortex, rather than inferred through source estimation. When deep brain stimulation of the basal ganglia relieved symptoms, this orbitofrontal cortex rhythm decreased concurrently, anchoring the signature both in the orbitofrontal cortex and in rapid, within-session symptom change.[8]

A separate study using high-definition transcranial alternating current stimulation, a technique for manipulating brain rhythms non-invasively, in individuals with subclinical obsessive-compulsive symptoms also supports a causal role.[9] Non-invasive stimulation was directed to the orbitofrontal cortex, guided by computational models of current flow to optimise targeted stimulation, and personalised by matching current frequency to each individual's peak high-beta or low-gamma frequency (20–35 Hz) during motivated decision making. 30-min sessions daily for 5 days reduced obsessive-compulsive symptoms relative to control group, with effects persisting for 3 months and scaling with baseline severity.[9] Thus, non-invasive manipulation of beta or gamma frequencies in the orbitofrontal cortex reduced subclinical obsessive-compulsive symptoms.

Together, these studies show that high-frequency orbitofrontal cortex rhythms in the beta (and extending to gamma) range are active during obsessive-compulsive symptom expression, track symptom fluctuation, are responsive to existing invasive treatments, and are directly manipulable via non-invasive orbitofrontal cortex stimulation to improve symptoms, with evidence across both clinical and subclinical populations. Accordingly, we argue that beta-to-gamma rhythms in the orbitofrontal cortex merit serious consideration as a biomarker and treatment target in OCD (figure).

Future research should explore the precise functional relevance of these rhythms to OCD symptomatic experience. One possibility is that these rhythms regulate behavioural flexibility by shaping the balance between exploration and exploitation during decision making.[10] Whether these rhythms reflect a neuronal unitary process or involve multiple interacting component rhythms, how they depend on context and how far they generalise to other disorders of compulsivity remain open questions. Importantly, given that parts of this rhythmic signature are accessible via non-invasive methods, such as scalp EEG, and manipulable via non-invasive stimulation approaches, such as transcranial alternating current stimulation, there is potential for scalable diagnostic and therapeutic applications that should be explored.

CHH has patents related to sensing and brain stimulation for the treatment of neuropsychiatric disorders in general (United States Patent and Trademark Office [USPTO] serial number 63/170,404 and 63/220,432; international publication number WO 2022/212891 A1) as well as use of tractography for circuit-based brain stimulation (USPTO serial number 63/210,472; international publication number WO 2022/266000). CHH is a consultant for Boston Scientific, Abbott, Medtronic, and Insightec and receives honoraria for educational lectures. KWS is a consultant for Johnson & Johnson. CHH, KWS, and LQ declare their roles as inventors on a provisional patent application (application number PCT/US2024/052096) focused on substance use disorders and related electrophysiology. All other authors declare no competing interests.

We gratefully acknowledge the support of NIH R01-MH114877, R01-AG063775, R01-AG082645, R01-AG090379, R01-AG097619, 1DP1OD040905, R01-MH124760, the Brain & Behavior Research Foundation, the International Obsessive-Compulsive Disorder Foundation, the Foundation for OCD Research, the Rodan Family Foundation, the Valinhos Foundation, and the AE Research Foundation. Any opinions, findings, conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the funders. We thank Bruce Freundlich (University of Pennsylvania) for connecting the authors and for highlighting the potential synergy between our respective lines of work, which helped catalyse this Comment.

*Shrey Grover, Liming Qiu, Katherine W Scangos, Casey H Halpern, *Robert M G Reinhart*
rmgr@bu.edu

Department of Psychological & Brain Sciences, Boston University, Boston, MA 02215, USA (SG, RMGR); Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (LQ, KWS, CHH); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (KWS); Center for Systems Neuroscience, Boston University, Boston, MA, USA (RMGR); Cognitive Neuroimaging Center, Boston University, Boston, MA, USA (RMGR); Center for Research in Sensory Communications and Neural Technology, Boston University, Boston, MA, USA (RMGR)

1 Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev* 2008; **32:** 525–49.

2 Burguière E, Monteiro P, Feng G, Graybiel AM. Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. *Science* 2013; **340:** 1243–6.

3 Chen K, Xiao Y, Zhu S, et al. Electroencephalography source-space functional connectivity reveals frequency-specific brain network dysfunctions in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2025; **143:** 111561.

Downloaded for Anonymous User (n/a) at Boston University from ClinicalKey.com by Elsevier on October 20, 2026.
For personal use only. No other uses without permission. Copyright ©2026. Elsevier Inc. All rights reserved.

4 Gemelli ZT, Ayazi M, Lee H-J. Characterizing autogenous and reactive obsessions using theta and beta oscillations under inhibitory demands. *J Psychiatr Res* 2025; **181:** 579–85.

5 Van Bogaert T, Figee M, Kopell BH, et al. Electrophysiological biomarkers reflect target engagement and response using deep brain stimulation for obsessive-compulsive disorder. *Biol Psychiatry Glob Open Sci* 2026; **6:** 100609.

6 Treu S, Gonzalez-Rosa JJ, Soto-Leon V, et al. A ventromedial prefrontal dysrhythmia in obsessive-compulsive disorder is attenuated by nucleus accumbens deep brain stimulation. *Brain Stimul* 2021; **14:** 761–70.

7 Chang JG, Kim D-W, Jung HH, et al. Evaluation of changes in neural oscillation after bilateral capsulotomy in treatment refractory obsessive-compulsive disorder using magnetoencephalogram. *Asian J Psychiatr* 2023; **82:** 103473.

8 Nho Y-H, Qiu L, Seilheimer RL, et al. Human orbitofrontal neural activity is linked to obsessive-compulsive behavioral dynamics. *Cell* 2026; **189:** 739–47.

9 Grover S, Nguyen JA, Viswanathan V, Reinhart RMG. High-frequency neuromodulation improves obsessive-compulsive behavior. *Nat Med* 2021; **27**: 232–8.

10 Domenech P, Rheims S, Koechlin E. Neural mechanisms resolving exploitation-exploration dilemmas in the medial prefrontal cortex. *Science* 2020; **369:** eabb0184.

Downloaded for Anonymous User (n/a) at Boston University from ClinicalKey.com by Elsevier on October 20, 2026.
For personal use only. No other uses without permission. Copyright ©2026. Elsevier Inc. All rights reserved.