Disrupted neural rhythms predict response in deep brain stimulation for OCD

Ventral striatal activity in individuals with OCD has strong circadian periodicity and high predictability in the severely symptomatic state. After deep brain stimulation, these features decrease substantially in clinical responders but remain raised in non-responders, thus providing a measurable predictor of clinical status.

This is a summary of:
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The mission

There is a crucial need to identify and validate neural biomarkers for psychiatric disorders. Although deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) is clinically effective in two-thirds of patients, many patients are still resistant to conventional therapy[1]. At present, parameter selection in DBS for OCD is optimized in a 'guess and check' fashion, a tedious process that is burdensome and time-consuming for both clinicians and patients[2]. A neural biomarker of symptoms and adverse effects could provide insight into the neurobiology of the disorder and ideally even inform therapy delivery. Recent advances in surgical neuromodulation have enabled chronic and continuous on-device intracranial monitoring that has enabled truly naturalistic data collection[3]. By leveraging these new opportunities, we sought to identify neural biomarkers predictive of clinical status in OCD.

The discovery

In an initial cohort of five patients with OCD who received DBS therapy, we leveraged the on-device neurophysiological recording capabilities of the DBS system to collect chronic and continuous neural recordings from the ventral striatum. We tracked low-frequency neural oscillations before and after the initiation of DBS, aiming to identify a signal that distinguished the severe OCD symptom state from the state of clinical response. Given the typical time course (months) required for improvement in OCD symptoms, we focused on biomarkers with a time constant of days to weeks. We validated the discovered biomarker in an additional cohort of seven patients.

Before DBS activation, the symptomatic state of OCD was characterized by high circadian periodicity and predictability of 9 Hz power in the ventral striatum. In the months after DBS initiation, these neural features remained raised in individuals who did not achieve a clinical response. In clinical responders, however, this circadian periodicity and neural predictability was disrupted (Fig. 1). We captured this observation quantitatively by fitting a linear autoregressive model to the time series of 9 Hz power and computing a daily goodness of fit between the true and predicted data. We then trained a classifier using these daily predictability measures and demonstrated accurate classification of clinical status that generalized across patients. Importantly, this classification accuracy held even in individuals with only several days' worth of recordings, which indicates the ability to predict clinical status even with limited data.

The implications

These results represent an important landmark in the search for biomarkers in psychiatric disorders. We provide evidence that neural biomarkers of slowly evolving clinical states might not be episodic variations from baseline, but instead features of variation in the baseline itself. We hope that this work will serve as a launchpad for future ethologically relevant neurobehavioral investigations that seek to relate myriad behavioral variables to observable neural measures. We believe that the approach has the potential to change clinical monitoring strategies in patients undergoing intracranial neuromodulation for a range of psychiatric and neurological disorders.

The sample size of 12 individuals in this study is larger than most studies that use invasive neuromodulation and intracranial recordings but is still small in absolute terms. We hope that three key features of our design improve feasibility over previous methods and thereby enable other groups to attempt replication and rapidly add to the data pool. First, the ability to perform these recordings using a standard, commercially available DBS system. Second, the low burden on patients owing to the passive nature of recordings. Third, the ability to test the accuracy of the model with only a week's worth of data. An important limitation of the study is our rudimentary understanding of the mechanistic changes in neural activity that accompany clinical improvement. The hypotheses we advance regarding the role of the ventral striatum in reward sensitivity and approach behavior need to be tested in future studies.

An immediate goal of ours is to further enhance behavioral and neural quantification outside the clinical setting. This transition towards dense, naturalistic, passively acquired neurobehavioral data would take research into neuropsychiatric disorders such as OCD directly to the lived experiences of affected individuals. Doing so would increase the relevance of the results to patients and also facilitate data acquisition and therapy management, thus enabling more research groups to explore these neurobehavioral relationships further. This feed-forward system would hopefully shed greater light on the neurophysiology of psychiatric disorders, better contextualize them within the cognitive neuroscience framework, and ultimately improve outcomes and access to these therapies for the tremendous number of affected individuals[4,5].

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EXPERT OPINION

"This manuscript describes the preliminary findings of a study examining potential biomarkers associated with response to ventral striatum deep brain stimulation for intractable OCD. Data were collected using a commercially available device so that a potential biomarker could be actionable in clinical practice without the need for research devices." **Darin Dougherty, Massachusetts General Hospital, Boston, MA, USA.**

FIGURE

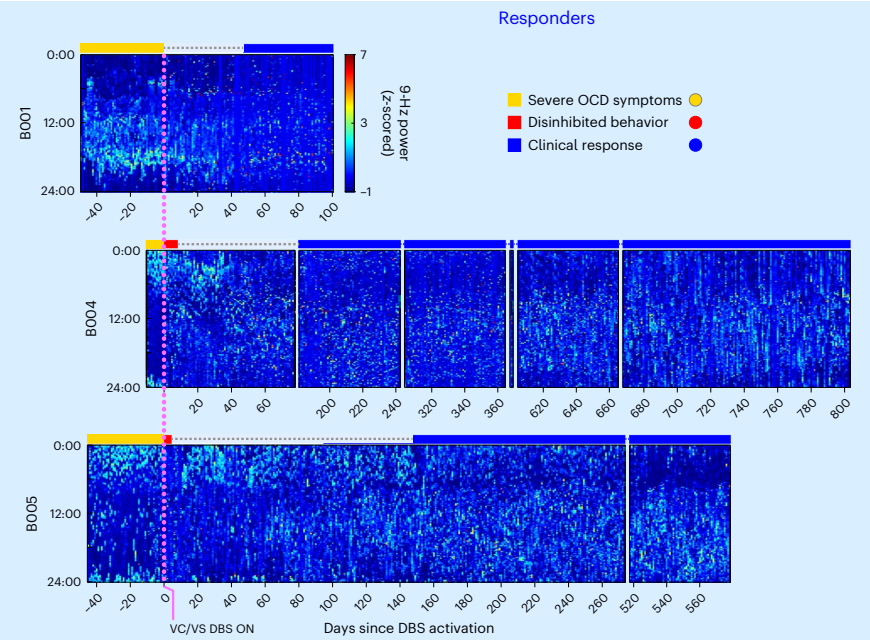

Fig. 1 | Disrupted neural predictability indicates clinical response to DBS. The heat maps show variations in 9 Hz ventral striatal power (color axis) throughout the day (*y* axis) over time relative to DBS initiation (*x* axis) in three clinical responders. In the symptomatic state (yellow bars), neural activity before DBS initiation (vertical purple dotted line) was highly predictable, with consistent peaks and trough across a 24-h period. After clinical response (blue bars), this predictability reduced significantly and durably. This pattern was maintained across the larger cohort, such that the degree of neural predictability accurately indicated clinical status.

BEHIND THE PAPER

Our biggest surprise came early in the project and was the motivation for continuing to do these neural recordings at all. We were wrapping up a previous trial on DBS for OCD using a research device (Medtronic RC+S) that was designed for scientific research. In comparison, we had low expectations for its commercially available replacement (Medtronic Percept), which had less capability for high-resolution recordings. We thus set up the relatively low-resolution chronic recordings in the 9 Hz band as described but did not expect them to reveal much. In the following months, we were surprised to see this prominent neural pattern of circadian periodicity so consistently, and even more so to see it change with clinical response. It turned out that the low-resolution recordings were perfectly suited for the chronicity required to perform these at-home, long-term recordings. **N.R.P. & S.A.S.**

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FROM THE EDITOR

"This study uses a new approach for conducting long-term intracranial recordings during the everyday lives of individuals with OCD, which enables researchers to identify neural signatures that are predictive of future changes in symptom state and responses to DBS therapy. This neural biomarker could alert clinicians of impending symptom onsets or even trigger an automatic stimulation parameter change on a future closed-loop enabled DBS system." **Editorial Team, *Nature Medicine*.**