To the Editor:

Deep brain stimulation (DBS) entails electrode implantation and high-frequency electrical stimulation of a specific brain target. DBS targeted at the nucleus accumbens (NAc) is a promising treatment option for otherwise treatment-refractory obsessive-compulsive disorder (OCD) (1). Recently, our group demonstrated that NAc DBS in OCD not only results in local activity changes but also in reduction of pathological overconnectivity throughout the frontostriatal network (2). This reduction in overconnectivity correlates with symptom improvements, empirically supporting the hypothesis that DBS overwrites pathologic network activity (3). The goal of our current endeavor was to determine mechanistically how DBS could modulate connectivity within the frontostriatal network.

The electroencephalogram (EEG) is a noninvasive neuroimaging technique that provides a time window into the network activity of millions of neurons. Neuronal interactions in the EEG can be observed as the synchronization (i.e., phase locking) of oscillatory activity between sending and receiving regions (4) (Figure 1A). A key intrinsic prerequisite of synchronization between oscillations is the phase stability of the oscillations; otherwise synchronization cannot occur for an extended period of time (Figure 1A). Thus, even subtle changes in phase stability could have a profound influence on interactions between brain areas. We hypothesized that DBS interferes with the ability of brain areas to communicate effectively by interfering with the phase stability of oscillations.

To measure DBS effects on phase stability, we recorded the resting-state EEG of 8 OCD patients (mean age 44.8, SD = 11.03, 5 women) twice, first with DBS on and 1 week later with DBS off. We focused on how DBS affected the phase stability of the frontal theta (3–8 Hz) oscillation. Theta oscillations (Figure 1B) are important for coordinating brain regions (5) and memory (6) and are also associated with other frontostriatal functions such as cognitive control and goal-directed behaviors (7,8). To quantify phase stability, we used the Phase-Preservation Index (PPI) (9).

The PPI yields a number between 0 and 1 and quantifies the consistency of phase stability over time, with higher values...
indicating greater phase stability. We computed the PPI for each subject and session at 25-msec intervals from an arbitrary reference to have an adequate estimate of phase stability over time for their dominant peak theta frequency (3–8 Hz; Figure 1C). Statistical significance was determined using a parametric cluster-corrected bootstrap procedure using 1000 bootstraps, which is valid for nonparametric data such as the PPI (10).

One-week DBS OFF resulted in a significant average increase in symptom severity of 30% as measured with the Yale Brown Obsessive Compulsive Scale ($t_{17} = -2.74, p < .05$). DBS ON reduced the phase stability of frontal theta oscillations (all $p$s < .05), without affecting theta power ($t_{17} = .251, p = \text{not significant}$, Figure 1C).

This reduction of phase stability has the potential to significantly reduce the likelihood of neural communication between brain areas of the network being stimulated. This is consistent with previous findings, which found DBS to result in less low-frequency coupling without disturbing the local neural activity giving rise to oscillations. Combined, these results suggest that although stimulated neurons are still producing oscillations, these oscillations fail to synchronize (11). Similar to our findings in OCD, Parkinson’s disease patients also show excessive network connectivity, but here between the subthalamic nucleus and the motor cortex. This connectivity correlates with PD symptoms and is reduced after treatment (12,13).

Our study is the first to show that the synchroniza-

dynamics within the frontostriatal network could play a role in OCD pathology and treatment. Our results may serve as a first step in optimizing DBS treatment strategies by fine-tuning the stimulation parameters that show the desired rate of network disconnection. This is even more relevant in psychiatric indications where there is an absence of directly observable outcome measures such as those available in PD. Furthermore, intervention to reduce pathological connectivity could have implications for research into a number of other disorders treated by DBS, such as PD (14), depression (15), and addiction (16,17).

Ruud Smolders$^{a,b}$
Ali Mazaheri$^{a,b}$
Guido van Wingena,b
Martijn Figeea,b
Pelle P. de Koningsb
Damiaan Denys$^{a,c}$

$^a$Department of Psychiatry and $^b$Brain Imaging Center, Academic Medical Center;
and $^c$The Netherlands Institute for Neuroscience, an Institute of the Royal
Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands.

*Corresponding author E-mail: ali.mazah@gmail.com.

Authors RS and AM authors contributed equally to this work.

This study was supported by Grant No. 916.66.095 from The Netherlands Organization for Scientific Research ZON-MW VENI program awarded to DD. AM

was supported by a VENI Grant (No. 016.115.196) from the Netherlands Organization for Scientific Research.

DD receives occasional consultant fees from Medtronic for educational purposes. AM, RS, GW, MF, and PK reported no biomedical financial interests or potential conflicts of interest.


http://dx.doi.org/10.1016/j.biopsych.2013.03.012