Biological Psychiatry

Deep Brain Stimulation Diminishes Cross-Frequency Coupling in Obsessive-Compulsive Disorder

To the Editor:

Deep brain stimulation (DBS) has been shown to be an effective treatment for neurologic disorders such as Parkinson's disease (PD) (1) and psychiatric disorders such as obsessive-compulsive disorder (OCD) (2). However, the mechanisms underlying the therapeutic benefits of DBS are still unclear. A recent groundbreaking study reported that DBS of the basal ganglia in patients with PD is able to suppress cross-frequency coupling (CFC) between beta phase and broadband gamma amplitude over the motor cortex (3). The authors have speculated that this disruption in cross-frequency interactions in the motor cortex is a mechanism by which DBS of the basal ganglia serves to reduce movement disturbances in PD. Here, we extend the findings of this study and provide new evidence that the modulatory influence of basal ganglia DBS on cross-frequency neuronal interactions is not limited to the motor cortex of patients with PD but can also be found in the visual cortex of patients with OCD.

Attentional biases to threatening stimuli have often been reported in anxiety disorders including OCD (4). Previous work showed that activity in the basal ganglia can modulate visual attentional switches through frontoposterior connections (5). Through the same pathway, we hypothesized that alterations in striatal activity through DBS in the ventral internal capsule in patients with OCD serves to reduce the bottom-up attentional

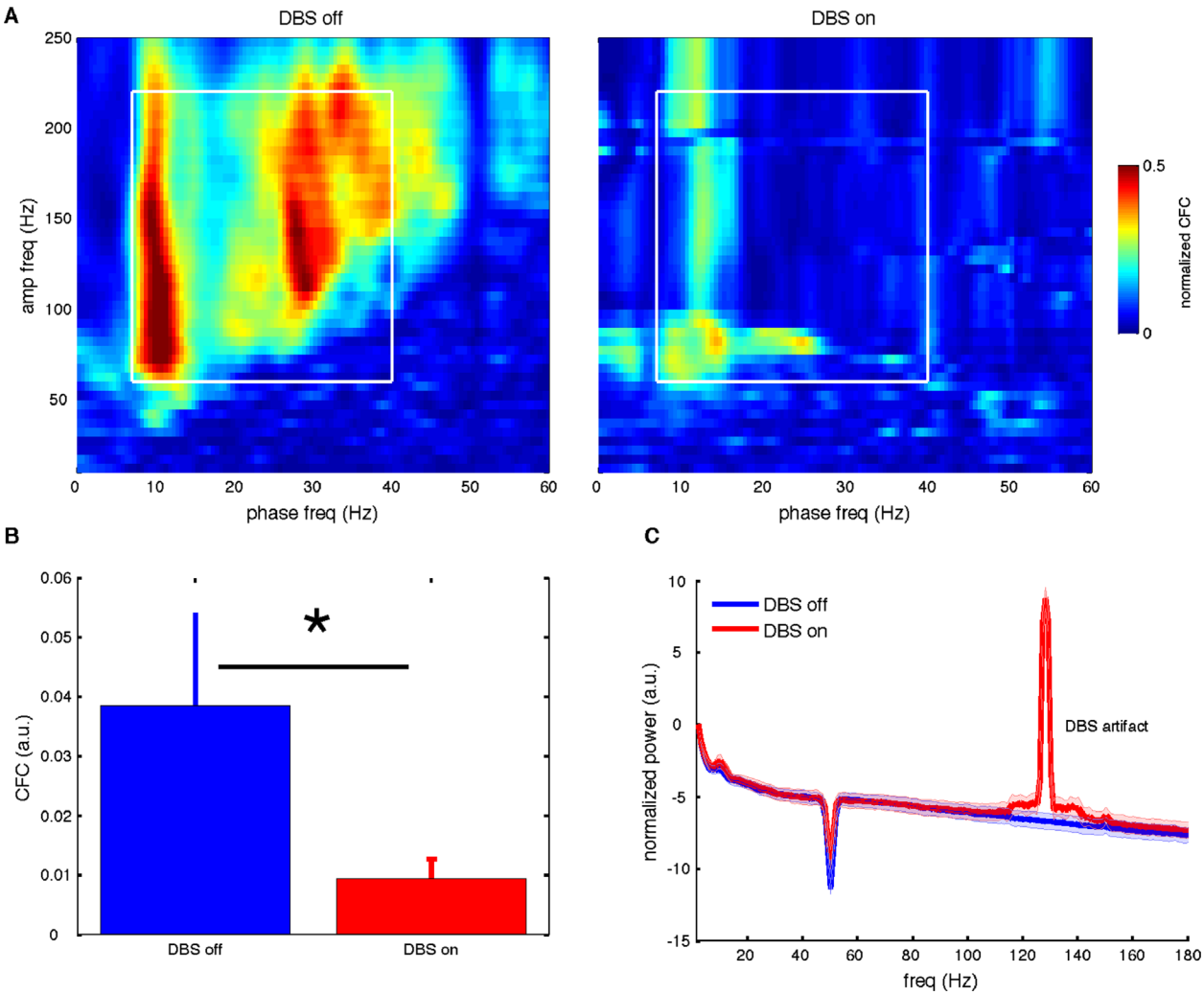

Figure 1. Cross-frequency coupling (CFC) as measured in the mid-occipital cortex is significantly suppressed when deep brain stimulation (DBS) is "on." **(A)** Average CFC values over all patients when DBS is "off" versus "on." The CFC values were normalized by the maximum of the window before averaging over patients. The white box shows the window over which the CFC values were averaged to compare the two conditions. **(B)** Average CFC values over the selected window in **(A)** with SEM over all patients. Significant comparison corresponds to $p = .0275$. **(C)** Mean together with SE of the power spectra over all patients. a.u., arbitrary unit.

http://dx.doi.org/10.1016/j.biopsych.2015.05.021
ISSN: 0006-3223

capacity of the visual cortex such that the amount of information reaching the prefrontal cortex is reduced. To assess this hypothesis, we examined electroencephalography data of patients with OCD undergoing DBS of the ventral internal capsule. We focused our analyses on the mid-occipital cortex, which has been shown to demonstrate resting-state CFC in healthy subjects (6). This study included 7 patients with OCD who all received the same bilateral stimulation frequency of 130 Hz using the Medtronic Activa PC system (Medtronic, Minneapolis, Minnesota). All patients responded positively to the treatment. Electroencephalography resting-state data (eyes open) were collected over 2 minutes for each patient using an ANT amplifier (ANT neuro, Enschede, the Netherlands), with a sampling frequency of 512 Hz, once with DBS "on" and once with DBS "off." The DBS "on" was followed by 1 week DBS "off." Data were read and preprocessed using FieldTrip software toolbox (7). To remove line noise, a band-stop Butterworth fourth-order filter with the frequency bandwidth of 4 Hz was used. Filtered data were re-referenced to the common average across all channels to obtain a better signal-to-noise ratio and to remove any common activity across all channels. Power spectra were extracted using the Welch method by dividing the 2 minutes into windows of 1 second with a 50% overlap. The CFC was assessed based on the coherence between low-frequency oscillations and the amplitude envelope of the high-frequency oscillations (6). Six cycles were used for extracting the high-frequency amplitude. The phase frequency resolution of .5 Hz was obtained using the fast Fourier transform with 1024 time points.

We found that CFC was much stronger over the mid-occipital cortex when DBS was "off" compared with when DBS was "on" (Figure 1A). To compare the CFC values across the two conditions, we averaged the CFC values over a selected window shown in Figure 1A, which is phase frequency between 7 Hz and 40 Hz and amplitude frequency between 60 Hz and 220 Hz for each subject. We used the Kolmogorov-Smirnov test to compare the two values across the two groups. Group analysis confirmed CFC between phase of low-frequency oscillations, and amplitude of high-frequency oscillations was significantly suppressed when DBS was "on" compared with when DBS was "off" ($p = .0275$). As Figure 1A indicates the presence of multiple couplings, we repeated the group analysis with phase frequency in the alpha (8–12 Hz), beta (13–30 Hz), low gamma (30–50 Hz), and high gamma (50–100 Hz) bands. The result showed that only the couplings between the broadband gamma amplitude and phase of beta and low gamma bands were significantly reduced when DBS was "on" ($p = .0275$ and $p = .0042$, respectively). Furthermore, the CFC effect cannot be explained by power because there is no significant difference across the two conditions, as can be seen in Figure 1C.

Previous work in our laboratory has demonstrated that DBS in patients with OCD normalizes the overconnectivity between the nucleus accumbens and prefrontal cortex (8), which we hypothesized to be the result of disruptions of phase stability of slow rhythms over the prefrontal cortex (9). Phase synchrony has been shown to reflect communication across brain regions (10). In light of these new findings, we propose that DBS improves brain function by dampening neuronal interactions between over-connected cognitive control networks. The disruption of overall phase synchronization by DBS not only reduces top-down communication from the cortex to the basal ganglia, but also reduces the bottom-up attentional capacity of the visual cortex. These disruptions serve to reduce the disease-specific maladaptive connectivity within the brain.

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Acknowledgments and Disclosures

We thank Ole Jensen for discussions on cross-frequency coupling and Ruud Smolders for helping with collecting data sets.

NL, PRS, MF, and DD contributed equally to this work. PRS received an unrestricted research grant from Medtronic and acts as independent consultant for Medtronic on educational matters. AB, AM, NL, MF, and DD report no biomedical financial interests or potential conflicts of interest.

Article Information

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