The perils of Deep Brain Stimulation in Psychiatry: Big claims, on the backs of small sample sizes.

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Title: The perils of Deep Brain Stimulation in Psychiatry: Big claims, on the backs of small sample sizes. Reply to Widge et al. - Inconsistent CFC Changes from VC/VS DBS Ventral Capsule/Ventral Striatum Deep Brain Stimulation Does Not Consistently Diminish Occipital Cross-Frequency Coupling

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Response to Reviewers: We've done the minor changes.

The perils of Deep Brain Stimulation in Psychiatry: Big claims, on the backs of small sample sizes

Reply to Widge et al. – Inconsistent CFC Changes from VC/VS DBS

Ventral Capsule/Ventral Striatum Deep Brain Stimulation Does Not Consistently Diminish Occipital Cross-Frequency Coupling

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While there is overall consensus on how DBS of the basal ganglia of Parkinson's patients leads to symptom reduction benefits, precise therapeutic mechanism of such stimulation in psychiatric disorders is still a matter of investigation. We recently proposed that the high frequency stimulation of the internal capsule of patients with obsessive compulsive disorder (OCD), could disrupt the degree of rhythmicity (i.e. Phase preservation) of ongoing oscillations generated at the cortex which would subsequently reduce the connectivity of the cortex with sub-cortical areas [1].

Supporting this view was our observation that the DBS of the ventral internal capsule capsule attenuated cross-frequency interactions of the phase of ongoing beta (13–30 Hz), and power of low gamma (30–50 Hz), over the occipital cortex of 7 OCD patients [2]. Our study was published on the heels of another study which observed DBS-induced changes in motor cortex beta-gamma coupling during DBS for Parkinson's disease [3].

However, the current study by Widge et al. [4] did not replicate our finding of DBS modulation of the cross-frequency interaction in their sample of 4 depressed and 1 OCD patients which underwent DBS near the internal capsule. We believe Widge et al. provide an important contribution to the field of DBS in psychiatry, by clearly demonstrating that more work needs to be done to understand how DBS of subcortical areas changes activity across the cortex, and ultimately influences cognition. Currently, the field of DBS in psychiatry contains many studies which make significant claims, based on observations on very low number of subjects. These big claims based on small sample sizes make the therapeutic efficacy of DBS in alleviating psychiatric symptoms still a matter of debate. However, we do disagree with Widge et al.'s account of a factor which could NOT be causing the discrepancy in between our observations.

We are in agreement that the most significant difference between our two studies was the duration that DBS was turned off: 1 week in our study, and 2 hours in theirs. While the authors do acknowledge this difference as a possible factor, they underestimate it (we believe incorrectly) based on evidence from a previous animal study [5]. The Ewing and Grace study found that stopping DBS of the nucleus accumbens (Nacc) shell in freely moving rats resulted in a rebound of oscillatory power in the Nacc, as well as coherence between limbic sites. Widge et al's rationale here is if DBS in human patients attenuated any cross-frequency coupling, based on the Ewing and Grace study, there should be an immediate rebound in cross-frequency coupling after the halting of the stimulation. However, we need to point out here that the focus of Ewing and Grace's study was on change in the power of oscillatory activity in the NAcc, and coherence within limbic sites. These findings have little direct relevance to cross-frequency interactions at the cortical layer. Moreover, we would be quite interested to see if Widge et al. were able to replicate the oscillatory power rebounds observed by Ewing and Grace at the level of the cortex.

Additional differences between our studies were that the patients had different psychiatric symptoms, as well as frequency of stimulation. These things could indeed play a factor. However, Widge et al. propose that our opposing findings would likely be due to “un-modeled characteristics of the two samples“ such as pre-operative clinical or electrophysiologic phenotypes, slight variation in electrode placement as well as the location of the active DBS contact, and subtle differences in the testing environment. Here we fully agree with the authors that each of these factors could contribute to difference in findings between centres. One point though that we feel the need to raise is that although Widge et al. cite a recent study by Samaha et al. [6] as evidence that cognitive factors influence the phase and peak frequency property of oscillations, our work (published a few months earlier than Samaha et al.) suggests quite the contrary. We found that in healthy participants the peak frequency and phase property of oscillatory activity factors were not influenced by top-down cognitive factors [7].

Finally, the current discussion inevitably raises a rather important question. Is the attenuation on cross-frequency coupling we observed in our study subtle and dependent on finely tuned environmental and participant characteristics or something more robust and generalizable across patients? At this stage we are fully willing to concede that we currently do not have the answer to this question. We are also in full agreement with Widge et al., that in order to identify the clinical significance of DBS in psychiatry, far more coordination among centres across the world doing such research is needed. This coordination would entail the sharing of critical information such as stimulation settings, the exact location of electrodes superimposed on individual structural scans, patient characteristics, and finally analysis scripts, all of which would allow for testing for the replicability of findings. Admittingly there are likely hurdles to such open access of data, such as patient privacy issues as well as resistance from some principle investigators. However, this is a crucial period for the field of DBS in psychiatry where recent studies are questioning its efficacy [8]. In order to make big claims using small sample sizes, the books have to open.

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