Coherence: A Unifying Mechanism of Deep Brain Stimulation

NeuroForum on:

Wang DD, de Hemptinne C, Miocinovic S, Ostrem JL, Galifianakis NB, San Luciano M, Starr PA (2018) Pallidal Deep-Brain Stimulation Disrupts Pallidal Beta Oscillations and Coherence with Primary Motor Cortex in Parkinson's Disease. J Neurosci 38:4556–4568.

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Running Title: DBS Mechanism Unifying Model

Acknowledgments: I thank my supervisor Prof. Dr. med. Andrea Kühn for her helpful support during mansuscript writing.

Funding: The author is supported by a Doctoral Research Grant from the German Academic Exchange Service-DAAD.

Abstract

Deep brain stimulation is a powerful neurostimulation technique that proved its efficacy in treating a group of neurological diseases. Several scientific works tried to understand the mechanism of action of deep brain stimulation. Wang *et al.* (*J Neurosci* 38:4556–4568, 2018) demonstrated a new evidence on the role of inter-regional neuro-oscillatory coherence as a promising model to explain mechanism the of deep brain stimulation.

Since its advent, deep brain stimulation (DBS) has been viewed as an effective, therapeutic approach to movement disorders like Parkinson's disease (PD), tremor and dystonia to name a few. The efficacy of DBS treatment tempted many scientists to investigate the mechanism of action by which DBS could have influenced different pathological processes. Compared to its preceding surgical procedures (like thalamotomy and pallidotomy), DBS was first supposed to inhibit the targeted area, which then was explained by the classical 'rate-model' (Udupa and Chen, 2015). However, following studies revealed controversial results indicating excitation instead of inhibition of the target structures. The rate-model has partially explained DBS mechanism of action. This particular issue pushed the researchers to adopt the notion of bursting-pattern as an alternative explanation (Montgomery and Gale, 2008). Others expanded the interpretation of local effect of DBS to remote area changes (De Hemptinne et al., 2015; Ni et al., 2018). This concept lent the probability that remote effects could be responsible for therapeutic efficacy by perturbing pathological oscillations which dominate the neuronal network connected to the DBS target. Nevertheless, the number of possible explanatory mechanisms are still expanding. Animal and human studies showed important contribution of neuroplasticity as a mechanism to explain the latent effect of DBS (as in dystonia). Additionally, new studies indicated the possibility of electrotaxis and neurogenesis surrounding the DBS electrode which should involve some molecular mechanism and mediators release. Other studies claimed the involvement of glial cells in part of the mechanisms mediating DBS effects (Ashkan et al., 2017).

Based on this diversity, the current scientific opinion is that a possible multifactorial neuromodulatory mechanism underlies the DBS effect instead of simple electrical perturbation of deep brain structures (Ashkan et al., 2017). To this end, scientists are still trying to find a grand unification to the dilemmatic concepts of DBS mechanism. Movement disorders have been the first to be treated with DBS as an alternative approach to surgical lesioning. In particular, PD has been extensively studied as a prototypic example in clinical and scientific literature. DBS was thought as a superior method to surgical lesioning as it offers adjustable settings according to the patient needs. Another important issue is the reversibility of side effects induced by high frequency electrical stimulation. In order to achieve a good outcome from DBS implantation, it is important to understand both the mechanism of action as well as the pathophysiology of the disease state to be treated. Since the mechanisms of action are diverse, DBS mechanisms have been approached with different research tools such as local field potentials (LFPs) and electroencephalographic recordings, neuroimaging and a multitude of other neurophysiological means. Intuitively, it is confusing how DBS can treat hypo- as well as hyper-kinetic movement disorders targeting the same or different brain areas with high frequency (around 130Hz) electrical stimulation (Nambu, 2008).

Recently in the Journal of Neuroscience, Wang et al. (2018) showed further evidence that shed light on the importance of oscillatory coherence between neuronal populations residing in DBS target area and cortical areas connected to it. These authors provided new insightful view of the possible DBS mechanism in different brain targets and disorders.

The Authors included two sets of patients, 20 with rigid-akinetic PD and 14 with isolated dystonia, implanted with DBS electrode in the globus pallidus internus (Gpi). In order to tackle the issue of coherence as a potential DBS mechanism, Wang et al. recorded intraoperative microelectrode LFPs simultaneously with sensorimotor cortex electrocorticography ECoG. The latter offers a higher resolution spatial accuracy than conventional scalp electroencephalography and helped in understanding the remote effect of DBS stimulation. Wang et al. also recorded signals during different behavioral tasks (rest, movement execution and finger tapping). This part was meant more to explain and compare disease-specific pathophysiological changes. The authors also investigated neuronal oscillation characteristics during DBS stimulation period. This is important because it addresses the core concepts of local and remote DBS effects and clarifies how neuronal oscillations interact between the targeted area and connected-hubs. Wang et al. introduced different signal analysis metrics in order to achieve their goals, namely spectral power, beta burst, coherence and phase-amplitude coupling (PAC). These metrics allowed in-depth exploration of how neuronal oscillation could reflect disease-specific pathophysiological biomarkers and examination of DBS related effects.

In summary, the authors showed increased resting-state pallidal low beta band power in PD and theta band power in dystonia. This finding corroborated previous ~~work~~ results and emphasized the concept of disease-specific oscillatory profile (Neumann et al., 2017). Cortically (M1) recorded oscillation was not different between PD and dystonia. Additionally, more movement-induced alpha and beta desynchronization in the GPi was observed in PD than in dystonia group. During DBS ON, pallidal beta power was decreased as clinical symptoms disappeared. The authors investigated different beta burst characteristics of the GPi LFP recordings and found significantly increased mean amplitude of beta burst in PD group while the duration, distribution and frequency of such bursts didn't differ. Linked to the aforementioned finding of spectral power, the authors inferred a conclusion that enhanced pallidal beta power is a result of increased amplitude in the beta burst.

Coherence, a measure of synchrony and strength of information transmission between two oscillators, has been shown by the authors to be increased in beta band of PD group between GPi and M1. This enhanced interregional coherence is assumed to be a pathological signature of PD. Strikingly, the authors also found reduction in this pathological coherence during DBS ON period. Coherence suppression was associated with clinically evident disappearance of PD symptoms. This finding highlights the importance of such metric in the mechanism underpinning DBS effect. The pallido-M1 coherence changes have been illustrated by reduction of beta phase synchrony and beta amplitude coupling. Together with previous data supporting the reduction of GPi-M1 theta coherence in dystonia (Barow et al., 2014), the authors draw a conclusion about the importance of DBS-targeted coherence modulation among the most prevailing (pathological) frequency in disease-specific manner. This finding underscores the commonality of DBS modulatory mechanism in different diseases and introduces a new hypothesis of DBS mechanism, the "**coherence-model**". Although Wang et al. argued against the presence of direct

GPi-cortical connection, a growing body of evidence favors the presence of such pathway (paralleling that of the STN-M1 hyperdirect pathway) (Neumann et al., 2015). The presence of such pathway could secure fast and faithful neural transmission in a way that pallidocortical coherence can be timely achieved. M1 PAC didn't significantly differ between DBS ON and OFF state in PD although there was a propensity toward reduction. This could be attributed to the low number of patients (only 4 recorded during DBS ON).

The concept of inter-regional coherence has a great impact on the scientific understanding of the mechanistic dynamic driving DBS therapeutic effects. As it has been evidenced by previous works, PD is characterized by strong beta phase coherence between subthalamic nucleus and M1 which has been modulated by subthalamic DBS (Malekmohammadi et al., 2018). Another clue has been provided by Barow et al. (2014) showing GPi DBS reduction of pathological theta coherence between GPi and cortex. Nonetheless, the finding of Wang et al. (2018) paved the way to support the model of interference with basal ganglial-cortical pathological coherence as a grand theory to explain DBS effects. One can view this model as a promising guide to boost a powerful future DBS therapy. The question of how the coherence-model could fit to all types of movement disorders, like tremor, still deserves further exploration.

The new coherence-model provides rationale for further research. Future studies would try to explore the applicability of this model to other disease states and different DBS targets. As DBS is not restricted to treatment of movement disorders, previous evidence has already shown encouraging results of frequency-specific network based coherence changes in an animal model of obsessive compulsive disorder targeting the nucleus accumbens (McCracken and Grace, 2009). Furthermore, different non-invasive brain stimulation techniques have been shown to alter inter-regional coherence in health and disease . The utility of the current findings in unifying invasive and non-invasive brain stimulation mechanisms in different neurological diseases requires further investigation. That being said, we have just started to catch a glimpse on the integrated mechanism underlying DBS neuromodulatory power.

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