Clinical Neurophysiology 130 (2019) 548–549

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

# Linking invasive and noninvasive neuromodulation techniques to study network properties of the brain

See Article, pages 558–567

In the present issue of *Clinical Neurophysiology*, Ni et al. comprehensively review the transcranial magnetic stimulation (TMS) literature to find mechanistic links that shed light on how deep brain stimulation (DBS) modulates the primary motor cortex (M1) (Ni et al., 2019).

This is a very comprehensive review that aims to bridge findings from invasive and non-invasive brain stimulation to enhance our understanding of the mechanisms of DBS with respect to the pathophysiology of the underlying movement disorder.

Both methods modulate brain networks (instead of specific isolated brain regions) and it comes as a natural thought that they might both be used to target the same disease- or symptom-specific network to alter a pathological brain state. TMS also allows to measure output parameters of motor cortical excitability. Here, the most common metrics are (a change in) amplitude of the motor evoked potentials (MEP) and motor cortical excitability. In the present context, changes in MEP amplitude are used to study effects of TMS or DBS on distant brain structures such as M1.

Ni et al. review the literature in which TMS is applied to patients also treated by DBS in the subthalamic nucleus (STN), the internal pallidum (GPi) or the ventral intermediate nucleus of the thalamus (VIM). The review is rich in specific information and represents a great resource to answer questions of how DBS would change different TMS parameters in different diseases when stimulating at different targets. Given the many details reported in the review, it is impossible to summarize all findings in this editorial. Still, we aim at reflecting some aspects in the following. The main body of the review is divided into three parts. First, they review effects of therapeutic (high-frequency) DBS on M1. Second, effects of single pulse DBS are studied. Finally, plastic effects of DBS are reviewed.

A well described "network treatment" is DBS to the VIM for treatment of Essential Tremor (ET). It is a network target due to the fact that modulating the cerebellothalamic pathway (and specifically the decussating dentatorubrothalamic tract) is crucial for beneficial therapeutic outcome (Calabrese et al., 2015). This is widely accepted and the tract has even been used for surgical targeting (Coenen et al., 2014). A TMS-derived correlate to study this pathway is paired-pulse cerebellar inhibition. TMS pulses delivered to the cerebellum inhibit the MEP produced by a motor cortical TMS pulse 4–7 ms later – which shows that the cerebello-thalamo-cortical pathway can be excited by TMS (Hallett, 2007). Concluding from the review article, this inhibition was preserved in mild ET patients but absent in ET DBS patients in the off stimulation state. Crucially, the inhibition was restored in the on state. Authors conclude that thalamic DBS functionally changes the excitability of inhibitory neurons and normalizes the activity along the cerebello-thalamo-cortical pathway.

Moving on to single-pulse DBS, authors mention that these evoke negative cortically evoked potentials (EP) at 3–4 ms intervals (likely due to antidromic activation of the hyperdirect pathway) and positive EPs at 18–25 ms (likely via activation of the indirect pathway). Consistently, paired pulse paradigms (where the TMS pulse follows the DBS pulse with short latency) facilitated MEPs when latencies fell into either the 3–4 or 18–25 ms range. This is a very advanced stimulation technique that allows studying a direct interaction of cortical and subcortical stimulation. In the GPi (studies in cervical dystonia patients), single DBS pulses again produced two EPs (negative at ~10 ms and positive at ~25 ms). Here, MEPs were facilitated by GPi DBS delivered ~10 ms before motor cortical TMS and inhibited when delivered ~25 ms before. Authors speculate that the two EPs following both STN- and GPi-DBS may in fact stem from the same sources (i.e. hyperdirect and indirect pathways) and the longer latency of the first in GPi DBS could be explained by synaptic relay between GPi and STN (which are structurally connected via Edinger's comb system).

Specifically, in dystonia, it is crucial to investigate long-term effects of neuromodulation that are mediated by plasticity. Here, TMS represents an outstanding method to investigate plasticity using paired associative stimulation. Several groups have shown exaggerated cortical plasticity in dystonia and its modulation by DBS. Interestingly, plasticity could gradually be restored to the level of healthy controls by GPi DBS over the course of several months and the degree of plasticity is related to how long the DBS effects outlast stimulation when switched off.

Moving beyond the current review by Ni and colleagues – and beyond the diagnostic capability of TMS toward its potential to *modulate* brain regions, a unifying concept holds the hypothesis that DBS and TMS would target the same network at different nodes: DBS modulates a subcortical node of the network while TMS would alter its properties at cortical level. First evidence that this concept may hold true indeed has been published in recent

https://doi.org/10.1016/j.clinph.2018.12.006

years (Fox et al., 2014; Weigand et al., 2018; Horn et al., 2017b). In a perspective article, Fox and colleagues demonstrated for a total of 14 brain disorders that subcortical (invasive) and cortical (noninvasive) stimulation sites used to treat the same symptom are linked by distributed functional networks. For instance, the most common DBS target used to treat Major Depressive Disorder, the subgenual cortex at Brodmann area 25 (Mayberg et al., 2005) is anti-correlated to the left dorsolateral prefrontal cortex usually stimulated by TMS. Based on the initial perspective article that both treatments could modulate the same network (Fox et al., 2012), Weigand and colleagues prospectively validated this concept: The more functionally anti-correlated the TMS site was to the subgenual cortex, the better the antidepressive treatment effect was (Weigand et al., 2018). Fox further hypothesized that DBS sites in Parkinson's disease should be positively correlated to SMA (a region that has been used to treat PD with inhibitory TMS) and negatively correlated to M1 (used with excitatory TMS) (Shirota et al., 2013; Fox et al., 2014). Complementing this strand of observations in the TMS field, a DBS study showed that the optimal electrode to treat PD in the STN has a fitting connectivity profile: One that is positively correlated to SMA and inversely correlated to M1 (Horn et al., 2017a, 2017b). In fact, such connectivity profiles of "effective" STN-DBS electrodes could be used to predict therapeutic outcome across DBS centers and surgeons (Horn et al., 2017b). This accumulating evidence suggests that one may invasively and noninvasively modulate distributed brain networks that could then ameliorate specific symptoms. Such networks could be termed "therapeutic networks" and the underlying pathology a "circuitopathy". In other words, circuits that show aberrant activity and dynamics may be treated by retuning those networks toward the healthy domain. Finally, it is likely that such circuitopathies code for specific symptoms, rather than for the whole symptom spectrum of a disease (Kühn and Volkmann, 2017).

Concluding, it is of uttermost importance to characterize symptom-specific networks that may overlap in different brain disorders to identify the optimal target for intervention. In this way, one could picture a personalized treatment strategy in the future: Based on the patient-specific constellation of symptoms, a specific "therapeutic network" could be outlined based on network databases. Specific network nodes should be defined for intervention, while retuning this network may include invasive and noninvasive neuromodulation strategies. The review article by Ni and colleagues in the present issue of *Clinical Neurophysiology* represents a valuable resource to get an overview of the current state of combined DBS and TMS studies. It concludes with promising perspectives such as combined (therapeutic) applications of DBS and TMS, using TMS-derived measures to guide DBS programming and even adaptive DBS or future functional studies with DBS and TMS. Further work that was not the prime focus of their article is to combine DBS and TMS for maximal synergistic results of neuromodulation.

## Conflict of interest statement

None.

## References


Calabrese E, Hickey P, Hulette C, Zhang J, Parente B, Lad SP, et al. Postmortem diffusion MRI of the human brainstem and thalamus for deep brain stimulator electrode localization. Hum Brain Mapp 2015;36:3167–78.

Coenen VA, Allert N, Paus S, Kronenbürger M, Urbach H, Mädler B. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor. Neurosurgery 2014;75:657–69. discussion 669-70.

Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc Natl Acad Sci U S A 2014;111:E4367–75.

Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012;72:595–603.

Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55:187–99.

Horn A, Kühn AA, Merkl A, Shih L, Alterman R, Fox M. Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space. NeuroImage 2017a;150:395–404.

Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol 2017b;82:67–78.

Kühn AA, Volkmann J. Innovations in deep brain stimulation methodology. Movement Disord 2017;32:11–9.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651–60.

Ni Z, Udupa K, Hallett M, Chen R. Effects of deep brain stimulation on the primary motor cortex: Insights from transcranial magnetic stimulation studies. Clin Neurophysiol 2019;130(4):558–67.

Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y. Research committee on rTMS treatment of Parkinson's Disease. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. Neurology 2013;80:1400–5.

Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective validation that subgenual connectivity predicts antidepressant efficacy of transcranial magnetic stimulation sites. Biol Psychiatry 2018;84:28–37.



Andreas Horn
Andrea A. Kühn *
*Movement Disorder and Neuromodulation Unit, Dept. of Neurology, Charité Universitaetsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany*
* *Corresponding author.*
*E-mail address:* andrea.kuehn@charite.de (A.A. Kühn)


Accepted 21 December 2018

Available online 18 January 2019