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Non-invasive brain stimulation to treat cognitive symptoms of Parkinson's disease

Transcranial non-invasive brain stimulation (NIBS) techniques include particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), although other non-invasive stimulation techniques have also been employed. The rTMS uses a rapidly changing magnetic field to induce currents and action potentials in underlying brain tissue. The tDCS involves the application of weak (1–2mA) electrical currents to modulate neuronal membrane potential. Although the precise mechanisms of NIBS aftereffects have not been fully elucidated, rTMS has been shown to modulate several neurotransmitter systems, increase neurotrophic factors, and induce changes on neuronal synapses by long-term potentiation (LTP) and long-term depression (LTD)-like mechanisms (for review, see Rektorova and Anderkova 2017) [1]. LTD-like mechanisms also apply for the underpinnings of tDCS [2]. The aftereffects of NIBS depend on the stimulation protocols and on the precise coil/electrode placement as well as on the current "state" of the brain [3,4]. Both rTMS and tDCS can be used to excite (high-frequency rTMS, anodal tDCS) or inhibit (low-frequency rTMS, cathodal tDCS) the underlying cortical tissue; the evidence pertains to NIBS applied over the motor cortex, but it may vary when the NIBS is targeted to sites other than motor cortices (e.g. L. Brabenec et al., 2015) [5].

The behavioral aftereffects of rTMS and tDCS may outlast the duration of multiple sessions of stimulation by weeks or months and thus may have therapeutic potential [6]. In general, both techniques may modulate the abnormal brain reorganization caused by distinct brain pathology and/or they may interact with the normal processes of brain plasticity such that they may enhance compensatory mechanisms and lead to an increased brain reserve, thus potentiating brain resilience [7]. However, the aftereffects vary broadly across subjects [8] and so far, rTMS has been FDA approved only for the treatment of pharmaco-resistant depression [9]. As for the treatment of cognitive impairment in PD, there is no universal agreement on efficacy, on which stimulation protocols should be utilized, and for how long they should be applied. Only a few studies are available with preliminary results, and most concern depressed PD subjects [1].

Jessica Trung and collaborators (2019) [10] in their work published in this issue of *Parkinsonism and Related Disorders*, used a theta burst stimulation (TBS) protocol that can modulate cognitive functions [11] and impact the functional connectivity of major cognitive control networks [12,13]. Compared to classical rTMS protocols, TBS is short, with good participant compliance [14]. In this single-blinded, sham-controlled, parallel group randomized study, 28 PD patients with mild cognitive impairment (PD-MCI) received altogether 6 sessions of intermittent theta burst stimulation (iTBS); i.e. an excitatory stimulation protocol when applied over the motor cortex [14]. The iTBS (active, n = 14 or sham, n = 14) was applied over the left dorsolateral prefrontal cortex (DLPFC). The stimulation site was based on the results of Nagano-Saito and collaborators [15] who showed decreased activity in this region during a set-shifting task in PD-MCI patients. Neuropsychological testing was performed pre-, post-1 day, post-10 days, and post-30 days after the iTBS intervention. Repeated measures ANCOVA did not show significant time × group interaction effects; in other words, the results showed an increase in overall cognition up to one month in both groups, without any significant differences between them. Improvements were seen in the attention domain for both groups and in the visuospatial domain only in the active group. The authors concluded that results of this preliminary study indicate a potential therapeutic effect of multiple-session iTBS on cognitive improvement in PD-MCI that is likely mediated by improved visuospatial functions.

While the study is well designed and the methods used are sound, the results do not show clear NIBS effects of ultrashort repeated sessions of active iTBS on cognitive functions in PD-MCI as compared to sham stimulation. Various reasons might explain these results. Some are technical factors related to NIBS techniques (such as potential placebo effects of iTBS, effects of residual electromagnetic field induction even by the sham coil, interindividual variability in response [16,17], too few stimulation sessions, or non-optimal stimulation protocol). Some are pertaining cognitive tools, such as potential practice effects in both groups that surpass the effects of active iTBS (despite the fact that the authors introduced parallel versions of some cognitive tests). Stimulating PD-MCI subjects multimodally (here by NIBS and cognitive training) might provide cognitive improvement in PD-MCI and this definitely warrants further research. The effects of combined cognitive training and rTMS have been shown in Alzheimer's disease patients [18] and in PD-MCI subjects in whom tDCS was combined with cognitive training [19]. Neuroimaging and neurophysiological methods may be additionally applied to inform about where, when, and how to stimulate the brain and whom to choose for treatment [4,17].

Only few studies have focused on predicting outcomes following non-pharmacological treatment [20]. Knowledge of such predictors may allow clinicians to elucidate the sources of inter-individual variability in NIBS responses and to provide more tailored therapeutic intervention. Among potential interacting factors, the role of Aβ-pathology on non-pharmacological treatments should be explored as supporting evidence corroborates its detrimental effect on cognitive performance in PD since the early stage [21].

Neuroimaging and neurophysiology can also be utilized as readouts of neural changes induced by NIBS [22]. Online monitoring of the state of the brain has been suggested by several authors [4]. The objective is to optimally tailor the NIBS treatment to meet the specific needs of individual patients. Stimulating multiple targets [23], combining invasive and noninvasive stimulation techniques [24], combining NIBS with cognitive training [25] and other pharmacological and non-pharmacological interventions [26] should be further explored in future

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studies.

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References

[1] I. Rektorová, Ľ. Anderková, Noninvasive brain stimulation and implications for nonmotor symptoms in Parkinson's disease, Int. Rev. Neurobiol. 134 (2017) 1091–1110.
[2] A. Flöel, tDCS-enhanced motor and cognitive function in neurological diseases, Neuroimage 85 (2014) 934–947.
[3] L. Anderkova, I. Eliasova, R. Marecek, E. Janousova, I. Rektorova, Distinct pattern of gray matter atrophy in mild Alzheimer's disease impacts on cognitive outcomes of noninvasive brain stimulation, J. Alzheimer's Dis. 48 (2015) 251–260.
[4] T.O. Bergmann, A. Karabanov, G. Hartwigsen, A. Thielscher, H.R. Siebner, Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives, NeuroImage 140 (2016) 4–19.
[5] L. Brabenec, P. Klobusiakova, M. Barton, J. Mekyska, Z. Galaz, V. Zvoncak, T. Kiska, J. Mucha, Z. Smekal, M. Kostalova, I. Rektorova, Non-invasive stimulation of the auditory feedback area for improved articulation in Parkinson's disease, Park. Relat. Disord. 61 (2019) 187–192.
[6] R. Biundo, E. Fiorenzato, A. Antonini, Nonmotor symptoms and natural history of Parkinson's disease: evidence from cognitive dysfunction and role of noninvasive interventions, Int. Rev. Neurobiol. 133 (2017) 389–415.
[7] A. Priori, M. Hallett, J.C. Rothwell, Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain Stimulat. 2 (2009) 241–245.
[8] A. Latorre, L. Rocchi, A. Berardelli, K.P. Bhatia, J.C. Rothwell, The interindividual variability of transcranial magnetic stimulation effects: implications for diagnostic use in movement disorders, Mov. Disord. 34 (2019) 936–949.
[9] M.S. George, S.H. Lisanby, D. Avery, W.M. McDonald, V. Durkalski, M. Pavlicova, B. Anderson, Z. Nahas, P. Bulow, P. Zarkowski, P.E. 3rd Holtzheimer, T. Schwartz, H.A. Sackeim, Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial, Arch. Gen. Psychiatr. 67 (2010) 507–516.
[10] J. Trung, A. Hanganu, S. Jobert, C. Degroot, B. Mejia-Constain, M. Kibreab, M.A. Bruneau, A.L. Lafontaine, A. Strafella, O. Monchi, Transcranial magnetic stimulation improves cognition over time in Parkinson's disease, Parkinsonism Relat. Disord (2019), https://doi.org/10.1016/j.parkreldis.2019.07.006 Epub ahead of print, Jul 8.
[11] J.H. Ko, O. Monchi, A. Ptito, P. Bloomfield, S. Houle, A.P. Strafella, Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task—a TMS–[11C] raclopride PET study, Eur. J. Neurosci. 28 (2010) 2147–2155.
[12] C. Gratton, T.G. Lee, E.M. Nomura, M. D'Esposito, The effect of theta-burst TMS on cognitive control networks measured with resting state fMRI, Front. Syst. Neurosci. 7 (2013) 124.
[13] L. Anderkova, D. Pizem, P. Klobusiakova, M. Gajdos, E. Koritakova, I. Rektorova, Theta burst stimulation enhances connectivity of the dorsal attention network in young healthy subjects: an exploratory study, Neural Plast. 13 (2018) 3106918.
[14] Y.Z. Huang, M.J. Edwards, E. Rounis, K.P. Bhatia, J.C. Rothwell, Theta burst stimulation of the human motor cortex, Neuron 45 (2005) 201–206.
[15] A. Nagano-Saito, C. Habak, B. Mejía-Constaín, C. Degroot, L. Monetta, T. Jubault, C. Bedetti, A.L. Lafontaine, S. Chouinard, V. Soland, Effect of mild cognitive impairment on the patterns of neural activity in early Parkinson's disease, Neurobiol. Aging 35 (2014) 223–231.
[16] A. Guerra, V. López-Alonso, B. Cheeran, A. Suppa, Solutions for managing variability in non-invasive brain stimulation studies, Neurosci. Lett. 30 (2017) 133332.
[17] A. Jannati, P.J. Fried, G. Block, L.M. Oberman, A. Rotenberg, A. Pascual-Leone, Test-retest reliability of the effects of continuous theta-burst stimulation, Front. Neurosci. 13 (2018) 447.
[18] J.P. Nguyen, A. Suarez, E. Le Saout, M. Meignier, J. Nizard, J.P. Lefaucheur, Combining cognitive training and multi-site rTMS to improve cognitive functions in Alzheimer's disease, Brain Stimul 11 (2018) 651–652.
[19] R. Biundo, L. Weis, E. Fiorenzato, G. Gentile, M. Giglio, R. Schifano, M.C. Campo, V. Marcon, P. Martinez-Martin, P. Bisiacchi, A. Antonini, Double blind randomized trial of tDCS versus sham in Parkinson patients with mild cognitive impairment receiving cognitive training, Brain Stimul 8 (2015) 1223–1225.
[20] N.W. Baileya, K.E. Hoya, N.C. Rogaschb, R.H. Thomsona, S. McQueena, D. Elliota, C.M. Sullivana, B.D. Fulcherb, Z.J. Daskalakisc, P.B. Fitzgeralda, Differentiating responders and non-responders to rTMS treatment for depression after one week using resting EEG connectivity measures, J. Affect. Disord. 242 (2019) 68–79.
[21] E. Fiorenzato, R. Biundo, D. Cecchin, A.C. Frigo, J. Kim, L. Weis, A.P. Strafella, A. Antonini, Brain amyloid contribution to cognitive dysfunction in early-stage Parkinson's disease: the PPMI dataset, J. Alzheimer's Dis. 66 (2018) 229–237.
[22] T. Sverak, L. Albrechtova, M. Lamos, I. Rektorova, L. Ustohal, Intensive repetitive transcranial magnetic stimulation changes EEG microstates in schizophrenia: a pilot study, Schizophr. Res. 193 (2018) 451–452.
[23] M. Brys, M.D. Fox, S. Agarwal, M. Biagioni, G. Dacpano, P. Kumar, E. Pirraglia, R. Chen, A. Wu, H. Fernandez, A. Wagle Shukla, J.S. Lou, Z. Gray, D.K. Simon, A. Di Rocco, A. Pascual-Leone, Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease: a randomized trial, Neurology 87 (2016) 1907–1915.
[24] K. Udupa, N. Bahl, Z. Ni, C. Gunraj, F. Mazzella, E. Moro, M. Hodaie, A.M. Lozano, A.E. Lang, R. Chen, Cortical plasticity induction by pairing subthalamic nucleus deep-brain stimulation and primary motor cortical transcranial magnetic stimulation in Parkinson's disease, J. Neurosci. 36 (2016) 396–404.
[25] B.J. Lawrence, N. Gasson, R.S. Bucks, L. Troeung, A.M. Loftus, Cognitive training and noninvasive brain stimulation for cognition in Parkinson's disease: a meta-analysis, Neurorehabilitation Neural Repair 31 (2017) 597–608.
[26] R. Manenti, M. Brambilla, A. Benussi, S. Rosini, C. Cobelli, C. Ferrari, M. Petesi, I. Orizio, A. Padovani, B. Borroni, M. Cotelli, Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy, Mov. Disord. 31 (2016) 715–724.

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