PERSPECTIVE

Non-pharmacological interventions for Parkinson's disease mild cognitive impairment: future directions for research

Parkinson's disease-mild cognitive impairment (PD-MCI) currently represents a valid diagnostic clinical entity with potential interest for therapeutic purpose. MCI is present in approximately 25–30% of non-demented patients with PD (Weintraub et al., 2018). Several risk factors are associated with Parkinson's disease dementia (PDD) occurrence, such as old age at onset, long disease duration, motor impairment and MCI (Nicoletti et al., 2019). Specifically, PD-MCI patients with a higher risk for conversion into PDD report specific neurocognitive deficits in semantic language, figure drawing/copying and visuospatial tasks (Vasconcellos et al., 2019). Thus, the implementation of strategies counteracting a more severe cognitive deterioration of PD-MCI patients is urgently required.

Currently, some kinds of non-pharmacological interventions have been experimented in PD-MCI but there is lack of synthesis summarizing their potential effects. Our perspective aims at addressing this issue. On the basis of the available findings to date, we suggest that combined interventions of transcranial direct current stimulation (tDCS) of the frontal cortex along with cognitive training seem to be the most effective in ameliorating cognitive status and even reducing motor disability of PD-MCI patients. Indeed, tDCS may help in reorganizing neural activation patterns and in facilitating neural plasticity of targeted brain regions, potentially modulating functional connectivity among cortico-striatal and thalamo-cortical circuits, with positive implications for cognitive and motor rehabilitation. Newly, it has been demonstrated that tDCS of the dorsolateral prefrontal cortex (DLPFC) enhances attention and executive control due to an increased release of dopamine neurotransmitter in brain circuits (Fukai et al., 2019). We would also stress that moderate-intensity aerobic exercise (i.e., 150 minutes performed 3 times per week) - reported in the Global Recommendations on Physical Activity for Health (WHO, 2010) - should be routinely contemplated as rehabilitation adjunctive strategy to cognitive stimulation of PD-MCI patients, by focusing on the core areas of motor impairment, such as difficulty in movement initiation, balance and gait control, falls prevention and rhythmic movement of walking. Physical activity in PD may influence brain plasticity, according to aerobic exercise types demonstrating greater benefit for biochemical and physiological processes of the brain, particularly in relation to the prefrontal cortex (Cusso et al., 2016). Moreover, physical activity has been found to influence brain neurochemistry and plasticity through the brain-derived neurothrophic factor that provides a neuroprotective role for nigral dopamine neurons and regulates branching and remodelling of axons and dendrites whose length is reduced in PD (Zaia-Milatovic et al., 2005).

Comprehensively, in a wider holistic perspective, promoting patients' engagement in social activities (e.g., citizens' associations/sport clubs) may also play a pivotal role in reducing apathy and depression and in improving social cognition, thanks to the amelioration of patients' cognitive vitality and emotional wellbeing beyond education and IQ for which studies have deserved consideration as cognitive reserve markers. Large randomized controlled trials with follow-ups contemplating integrated interventions of tDCS and cognitive/physical training are welcome in the next future.

PD is associated with non-motor deficits including cognitive disturbances and emotional impairment, autonomic dysfunction and sleep disorders, neuropsychiatric features and sensory deficits. Cognitive disturbances are mainly characterized by executive, attention and visuospatial deficits, reflecting a dysfunction of frontostriatal and parietal networks activity (Cammisuli and Crowe, 2018).

Manenti et al. (2016) investigated the effects of tDCS applied over the DLPFC starting at the beginning of physical intervention in PD-MCI patients (i.e., 5 sessions of 25 minutes at 2 mA), demonstrating that it can improve motor abilities, reduce depressive symptoms and enhance global cognition and verbal fluency. They further showed that a bi-dimensional 2-week program of computerized cognitive training in association with tDCS over the DLPFC at 2 mA for 25 minutes represents a useful approach in the management of mood and cognitive dysfunction of language, attentional and executive abilities of PD-MCI patients (Manenti et al., 2018). In a recent outstanding study, Lawrence et al. (2018) randomized 42 participants with PD-MCI in a 4-week program, including (1) standard cognitive training, (2) tailored cognitive training, (3) tDCS, (4) standard cognitive training plus tDCS, (5) tailored cognitive training plus tDCS, and (6) a control group, by documenting that those receiving cognitive training (standard or tailored one) or tDCS demonstrated significant improvement of cognitive and functional outcomes, and that combining these interventions resulted in a greater therapeutic effect.

More recently, a systematic review of randomized controlled trials of the last ten years (da Silva et al., 2018) documented that adapted tango and treadmill training or combined cognitive (i.e., Wii Fit™) and motor training (i.e., stretching, strengthening, and axial mobility exercise) promote significant effects on global cognition, processing speed, sustained attention and mental flexibility in patients with a 6-year diagnosis of PD. In particular, a treadmill training performed 3 times a week for a period of 2 months, produced larger improvement (da Silva et al., 2018).

Besides to cognitive and physical enhancements, some studies addressed the issue of social cognition in PD pa-

tients, too, given that they show difficulties in attributing mental states to others, and in predicting and explaining behaviour according to these mental states (i.e., Theory of Mind, ToM). In a randomized, double-blind, sham-controlled study, Adenzato et al. (2019) applied active tDCS over the medial frontal cortex to improve ToM performance in 20 patients with PD-MCI while a same number of healthy matched controls were asked to perform the ToM task without tDCS. Individual and social ToM abilities were evaluated by the Reading the mind in the Eyes and the Attribution of Intention tasks, respectively. Each patient randomly received both active tDCS (i.e., 1.5 mA for 6 minutes) and sham (i.e., placebo) stimulation over the medial frontal cortex in 2 different sessions, separated by at least 48-hour washout period. They found that PD-MCI patients performed worse than controls on ToM tasks that, in turn, correlated with executive efficiency and could be enhanced by active tDCS.

Finally, cognitive reserve-explaining someway how individual differences in neural pathways and cognitive processes may affect an individual's ability to compensate for brain pathological processes - has been explored, too. Researchers pointed out that higher levels of education and IQ are associated with decreased odds of PD-MCI in a cohort of 119 non-demented PD patients (Amstrong et al., 2012).

Findings from forthcoming investigations replicating and implementing previous findings will advance our understanding of brain plasticity mechanisms in PD, by designing more effective rehabilitative strategies for people with MCI.

Davide Maria Cammisuli*, Roberto Ceravolo, Ubaldo Bonuccelli
Neurology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy (Cammisuli DM, Ceravolo R, Bonuccelli U)
Clinical Psychology, Psychophysiology and Clinical Neuropsychology Laboratory, Department of Medicine and Surgery, University of Parma, Parma, Italy (Cammisuli DM)
***Correspondence to:** Davide Maria Cammisuli, PhD, d.cammisuli@med.unipi.it.*
***orcid:** 0000-0002-8340-1867 (Davide Maria Cammisuli)*
***Received:** November 25, 2019*
***Peer review started:** November 28, 2019*
***Accepted:** December 13, 2019*
***Published online:** February 28, 2020*

***doi:** 10.4103/1673-5374.276329*
***Copyright license agreement:** The Copyright License Agreement has been signed by all authors before publication.*
***Plagiarism check:** Checked twice by iThenticate.*
***Peer review:** Externally peer reviewed.*

***Open peer reviewer:** Cristina Agliardi, IRCCS Fondazione Don Carlo Gnocchi, Italy.*

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P-Reviewer: Agliardi C; C-Editors: Zhao M, Li JY; T-Editor: Jia Y