Non-Invasive Brain Stimulation Combined with Exercise: Synergistic Neuroplasticity in Parkinson's disease: A comprehensive Review

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Abstract:

Motor and non-motor deficits resulting from dopaminergic neuron loss are hallmarks of Parkinson's disease (PD), a progressive neurodegenerative illness. Non-pharmacological therapies that encourage neuroplasticity are becoming more popular since, despite their ability to alleviate symptoms, pharmaceutical treatments are unable to stop the progression of the disease. Among these, non-invasive brain stimulation (NIBS) and exercise have shown promise. Exercise, especially aerobic, resistance, and task-specific training, improves motor and cognitive abilities by increasing cerebral perfusion, synaptic plasticity, and brain-derived neurotrophic factor (BDNF) levels. Similarly, long-term potentiation (LTP)-related mechanisms can be facilitated and cortical excitability modulated by NIBS techniques such as recurrent transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Although their effects are minimal when taken separately, new research indicates that NIBS and exercise may work in concert to improve neuroplastic responses during recovery. The data currently available on the neurobiological processes and therapeutic effects of combined NIBS-exercise therapies in Parkinson's disease is summarized in this review. Along with results from clinical trials showing improved gait, balance, motor performance, and executive function, it talks about their common routes, which include increased BDNF signaling, cortico-striatal connection, and dopaminergic modulation. The necessity of individualized treatment approaches is emphasized by addressing methodological limitations, such as protocol variability and patient responsiveness. Overall, by utilizing synergistic plasticity mechanisms, NIBS and exercise together offer a viable non-invasive method to enhance neurorehabilitation in Parkinson's disease. To comprehend long-term consequences and enhance methods, more research is required.

Key words: Neuroplasticity, Parkinson's Disease, Non-Invasive Brain Stimulation

Introduction:

Parkinson's disease (PD) is a progressive neurodegenerative disorder defined by the loss of dopaminergic neurons in the substantia nigra, leading to signature motor symptoms such as bradykinesia, stiffness, resting tremor, and postural instability(1). In addition to these motor impairments, non-motor symptoms including cognitive decline, fatigue, and mood disturbances significantly affect patients' quality of life(1). While pharmacological interventions such as levodopa provide symptomatic relief, their long-term efficacy is limited by motor fluctuations and dyskinesias, and they do not halt disease progression(2). This has prompted increasing interest in non-pharmacological therapies aimed at promoting neuroplasticity and functional restoration.

Exercise has emerged as a potent modulator of neuroplasticity in PD(3). Regular physical activity, including aerobic, resistance, and task-specific training, is known to upregulate neurotrophic factors such as brain-derived neurotrophic factor (BDNF), improve cerebral perfusion, and enhance synaptic plasticity(3,4). These effects may translate into improved motor learning, cognitive resilience, and delay of disease progression(4).

Similarly, non-invasive brain stimulation (NIBS) methods like transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have demonstrated promise in modifying cortical excitability and producing effects similar to long-term potentiation (LTP) in the prefrontal and motor cortices(5–7). Although NIBS's independent effects on PD symptoms have been limited and inconsistent, mounting data indicates that its real therapeutic potential may be in priming the brain for later rehabilitation, boosting the benefits of exercise through synergistic neuroplastic mechanisms(6).

The purpose of this review is to summarize what is currently known about the independent and interaction effects of NIBS and exercise on neuroplasticity in Parkinson's disease. We examine the theoretical bases for their synergistic benefits, compile data from studies of combination interventions, point out methodological and translational issues, and suggest future lines of inquiry and clinical use.

Exercise and Neuroplasticity in PD

Due to its significant impact on brain health and plasticity, as well as its ability to alleviate motor symptoms, exercise has emerged as a key component of Parkinson's disease (PD) treatment. It has been demonstrated that a variety of exercise regimens, such as strength training, aerobic training, and task-specific motor learning, cause anatomical and functional alterations in the brain that help PD patients with their movement control and cognitive abilities.

Aerobic exercise, in particular, has been associated with increased levels of brain-derived neurotrophic factor (BDNF), a key neurotrophin involved in synaptic plasticity and neuronal survival (8). According to research on animals, treadmill exercise increases the expression of BDNF in the striatum and substantia nigra, which may preserve dopaminergic neurons and alter motor circuitry (9). Long-term aerobic exercise has been shown to improve gait, balance, and executive function in humans, which is correlated with changes in neurochemistry and functional imaging (10).

Resistance training also shows potential for promoting neuroplasticity by enhancing neuromuscular coordination, motor unit recruitment, and cortical excitability. Farley and colleagues observed that amplitude-focused resistance exercises such as LSVT BIG may not only enhance strength but also recalibrate sensorimotor integration and movement scaling through repeated practice and proprioceptive feedback(11).

Motor learning principles that strengthen cortico-striatal circuits and encourage use-dependent plasticity are activated by task-specific training, such as treadmill walking, cycling, and dance-based therapies (12). Combining these workouts with dual-task paradigms, which test cognitive-motor integration and activate larger brain networks, is especially advantageous(13).

Through a number of processes, including increased neurotrophins (particularly BDNF), improved cerebral blood flow and angiogenesis, improved mitochondrial function, decreased oxidative stress, and stimulation of dopaminergic activity, exercise generally seems to serve as a neurobiological modulator in Parkinson's disease (4,14). When combined, these actions may slow the progression of the disease and alleviate both motor and non-motor symptoms.

Importantly, the efficacy of exercise may vary depending on intensity, frequency, and individual characteristics such as disease severity and cognitive status. Therefore, personalizing exercise programs and exploring their combination with adjunctive neurotechnologies, such as non-invasive brain stimulation (NIBS), may offer enhanced therapeutic outcomes via synergistic neuroplastic effects.

Non-Invasive Brain Stimulation (NIBS) in PD

With the goal of improving neuroplasticity and modifying damaged neural circuits, non-invasive brain stimulation (NIBS) has become a possible supplementary treatment for Parkinson's disease (PD). Transcranial direct current stimulation (tDCS) and repeated transcranial magnetic stimulation (rTMS) are the two NIBS modalities most frequently employed in PD research. The potential of both methods to affect cortical excitability and maybe improve motor and cognitive performance in PD has been studied.

In order to create electrical currents in the brain tissue underneath, repetitive TMS applies magnetic pulses to the scalp. rTMS can either raise (high-frequency >5 Hz) or reduce (low-frequency <1 Hz) cortical excitability, depending on the frequency and stimulation pattern (15). It has been demonstrated that bradykinesia, rigidity, gait abnormalities, and mood symptoms can all be alleviated by high-frequency rTMS across the primary motor cortex (M1), dorsolateral prefrontal cortex (DLPFC), or supplementary motor area (SMA) in Parkinson's disease (5,16). M1 stimulation in particular has been shown to provide small but clinically meaningful motor benefits, according to a recent meta-analysis (17).

A portable and affordable substitute is transcranial direct current stimulation (tDCS), which polarizes cortical neurons by passing a weak direct current through scalp electrodes. Excitability is often increased by anodal tDCS and decreased by cathodal stimulation. Anodal tDCS over M1 or DLPFC has been linked to enhanced working memory, dual-task walking, and motor performance in PD(18,19). Crucially, tDCS seems to improve motor learning and memory, especially when paired with behavioural exercises like handwriting practice or gait training(20).

The regulation of cortico-striatal and cortico-cerebellar loops, the encouragement of long-term potentiation (LTP)-like plasticity, and the facilitation of dopamine release are probably the mechanisms via which NIBS works in

Parkinson's disease (20,21). Furthermore, NIBS may restore more healthy patterns of neuronal activity by counteracting the maladaptive plasticity frequently seen in Parkinson's disease.

Notwithstanding encouraging findings, generalizability and practical translation are constrained by the variation in stimulation parameters, target regions, and outcome measures amongst research. Responsiveness to NIBS may also be influenced by patient-specific variables, including genetic variability (e.g., BDNF polymorphisms), drug status, cortical atrophy, and disease severity (22). Therefore, combining NIBS with customized rehabilitation techniques—like exercise—might be a more efficient and complementary way to improve brain plasticity in Parkinson's disease.

Theoretical Framework for Synergistic Effects

A possible method to enhance neuroplasticity and functional recovery in Parkinson's disease (PD) is the combination of physical exercise with non-invasive brain stimulation (NIBS). Exercise has been demonstrated to enhance synaptic plasticity, raise brain-derived neurotrophic factor (BDNF), and enhance motor and cognitive performance in people with Parkinson's disease (3,4). By regulating cortical excitability and promoting learning-related neuroadaptations, NIBS, such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS), can amplify these effects (23).

Due to a priming effect in which NIBS makes neural networks more receptive to activity-dependent plasticity, a number of studies have found that combining NIBS with motor or cognitive activities produces better results than either intervention alone (24). For instance, compared to gait training alone, anodal tDCS over the primary motor cortex (M1) combined with gait training has been linked to improved walking speed, stride length, and balance in PD patients(25). Similarly, tDCS has demonstrated superior improvements in executive function and fine motor abilities when combined with handwriting training or dual-task walking protocols (26,27).

This synergy is believed to be mechanized by convergent neuroplasticity pathways. While NIBS may enhance the expression of receptors and intracellular signaling involved in long-term potentiation (LTP)-like plasticity, exercise raises systemic levels of neurotrophic substances such as BDNF and insulin-like growth factor 1 (IGF-1) (28,29). As a result, the brain has a "plasticity window" during which functional remodeling is more likely to occur.

Heterogeneity in study methods continues to be a significant drawback in spite of these positive results. It is still unclear when, how hard, and in what order to perform NIBS and exercise. According to some research, NIBS may activate the motor cortex for future learning, therefore it may be more advantageous to use it before or during exercise than after (30). Moreover, treatment responsiveness may be impacted by individual differences in BDNF gene polymorphisms, baseline fitness, and illness development, underscoring the necessity of tailored strategies (31).

In summary, the integration of NIBS and exercise represents a frontier in PD rehabilitation, leveraging the principles of activity-dependent plasticity and neuromodulation to enhance outcomes. Future research should focus on identifying the most effective NIBS-exercise pairings, optimizing dosage and protocols, and elucidating the underlying biological mechanisms.

Current Evidence: Combined Interventions in PD

An increasingly popular approach to Parkinson's disease (PD) rehabilitation is the combination of physical activity with non-invasive brain stimulation (NIBS). Randomized controlled trials (RCTs), pilot studies, and feasibility studies are among the few but growing studies that have examined the potential additive or synergistic effects of combining particular NIBS protocols with particular exercise modalities.

Types of Interventions:

Up until now, the majority of research has used transcranial direct current stimulation (tDCS) that targets the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), or primary motor cortex (M1) in combination with functional or aerobic exercise like cycling, treadmill training, or task-oriented gait activities. In a randomized pilot trial, for instance, Manor et al. (2018) found that anodal tDCS over M1 in conjunction with aerobic cycling improved bradykinesia and motor reaction time in PD patients when compared to sham stimulation with exercise alone(32).

In a different study, Dagan et al. (2018) used multitarget tDCS (M1 + prefrontal regions) in conjunction with a gait-training procedure, which improved dual-task walking ability and decreased freezing of gait episodes(25). In a case series involving PD patients, Kaski et al. (2014) also showed improved improvements in motor function and postural stability when anodal tDCS was used during tango dancing(27).

Outcome Measures:

Numerous outcome measures have been used in studies to evaluate the efficacy of combined therapies. These consist of:

- Motor Function: Timed up and go (TUG), gait speed evaluations, and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III).
- Cognitive: dual-task performance measures, executive function tasks (such the Stroop test), and the Montreal Cognitive Assessment (MoCA).
- Neuroimaging and Biomarkers for Neurophysiology: A few exploratory investigations have used functional MRI, cortical excitability indices via transcranial magnetic stimulation (TMS), and functional near-infrared spectroscopy (fNIRS) (33,34).

The general trend across trials is an enhancement in motor outcomes—particularly gait, postural control, and fine motor skills—when exercise is paired with NIBS, compared to either intervention in isolation. Improvements in executive function and attention have also been reported, though cognitive findings remain less consistent (35).

Limitations and Gaps

Notwithstanding encouraging outcomes, the existing body of research is distinguished by a number of significant limitations:

- Small Sample Sizes: The majority of research had fewer than thirty participants, which restricts the generalizability and statistical power.
- Heterogeneous Protocols: Cross-study comparisons are challenging because to the significant variation in exercise type, intervention timing, outcome measures, and stimulation parameters (intensity, duration, and site).
- Short-Term Follow-Up: Seldom are long-term impacts and benefit retention after an intervention documented.
- Underrepresentation of Neurobiological Correlates: Research on how combination treatment affects neurotrophic factors, connectivity, or structural brain changes is lacking.

These limitations underline the need for more comprehensive, multicenter studies with standardized protocols and long-term follow-up to validate the mechanisms and efficacy of NIBS-exercise regimens in Parkinson's disease.

Challenges and Considerations

Research and clinical application are complicated by a number of methodological, biological, and ethical issues, despite the growing interest in using exercise and non-invasive brain stimulation (NIBS) as a rehabilitative therapy for Parkinson's disease (PD).

Methodological Considerations:

The ideal timing of NIBS in relation to exercise is a significant methodological difficulty. With varying theoretical explanations, studies have administered stimulation in different ways prior to, during, or following exercise sessions. For example, whereas concurrent application may promote task-related neuronal activation, pre-exercise stimulation may prime neural circuits to improve plasticity(36,37). There is a dearth of comparable evidence, yet, and there is disagreement over which timing produces the strongest or most enduring benefits.

Studies differ greatly in terms of stimulation parameters, such as electrode montage, current intensity, and session length. Although the majority of tDCS procedures use intensities ranging from 1 to 2 mA for 15 to 30 minutes, it is yet unknown if stronger or longer-lasting results can be obtained with higher intensities or repeated doses (38). Protocol standardization is further complicated by the fact that the site of stimulation (e.g., M1 vs. DLPFC) probably affects the specificity of results (motor vs. cognitive)(39).

Biological Considerations:

The effectiveness of an intervention is also impacted by the biological diversity across PD patients. For instance, responsiveness to NIBS may be changed by individual variations in cortical excitability, which can be impacted by age, comorbidities, or past exercise experience (40). Furthermore, the severity of the disease and its stage of progression are rarely controlled in studies, although they probably affect the potential for neuroplastic change. Because their neurological substrates are retained, early-stage patients may benefit more from such therapies (41).

Medication status, especially dopaminergic therapy, which interacts with neuroplasticity pathways, is another confounding factor. In experimental designs, it is crucial to control or report medication timing since there is evidence that dopamine replacement may affect the effects of NIBS, either amplifying or masking stimulation-induced changes (42).

Ethical and Practical Challenges:

Practically speaking, there are issues with cost and accessibility when delivering integrated NIBS and exercise regimens in healthcare settings. Although tDCS devices are portable and reasonably priced, patient education and physician training are necessary for their safe and efficient administration (43). Additionally, adherence may be problematic, particularly for older persons who have cognitive loss, mobility impairments, or little support from caregivers (44). Additionally, there are ethical issues to take into account, especially when using innovative neurostimulation techniques on susceptible groups. As the field shifts toward home-based or self-administered models of tDCS, it is imperative to ensure informed consent, monitor for adverse effects, and establish equitable access in order to ensure ethical deployment (45).

All things considered, overcoming these obstacles is essential to improving the therapeutic usefulness of combined therapies and producing trustworthy, repeatable data.

Future Directions and Recommendations

A promising yet unexplored area of treatment for Parkinson's disease (PD) is the combination of exercise and non-invasive brain stimulation (NIBS). A number of future directions should be given priority in order to improve its scientific knowledge and therapeutic usefulness.

1. Standardization of Protocols

Standardizing stimulation and exercise parameters, such as electrode location, session frequency, exercise type (e.g., resistance, aerobic, or dual-task), and stimulation timing (pre-, during, and post-exercise), must be the goal of future research. Current study designs are heterogeneous, which restricts the comparison of results and makes meta-analytic synthesis difficult (39,46).

2. Personalized Interventions

According to new research, tailored treatment plans that take into account the patient's cognitive state, cortical excitability, and illness stage may improve results (16,40). To customize combined therapies based on baseline biomarkers, motor scores, and neuroimaging profiles, machine learning techniques and predictive models may be investigated (47).

3. Mechanistic Studies

How combined NIBS-exercise therapies influence motor and non-motor circuits requires more mechanistic investigation employing neuroimaging (fMRI, PET) and electrophysiological methods (TMS, EEG). Understanding dopaminergic and non-dopaminergic networks and their interactions with therapies that induce plasticity should receive particular attention (48,49).

4. Longitudinal and Real-World Studies

To date, the majority of research have been brief and carried out in carefully monitored lab settings. Real-world studies that look at cost-effectiveness, adherence, and practicality in community or home-based settings are needed, as are longitudinal trials that evaluate benefit retention (50,51).

5. Ethical Frameworks and Policy Integration

To maintain safe and fair access, it will be essential to develop ethical guidelines, training protocols, and health policy integration as NIBS devices become more commercially available and portable. To scale these technologies responsibly, doctors, ethicists, and politicians must work across disciplines (52).

Conclusion

The emerging convergence of non-invasive brain stimulation (NIBS) and exercise-based therapies in Parkinson's disease (PD) underscores a promising multimodal strategy to address both motor and cognitive impairments. Each intervention independently contributes to neuroplastic changes; however, when combined, they may act synergistically to enhance rehabilitation outcomes by simultaneously targeting cortical excitability, motor learning, and cognitive engagement.

Current evidence, though limited, supports the feasibility and preliminary efficacy of these combined interventions. Still, methodological heterogeneity, small sample sizes, and limited mechanistic insight have constrained broader clinical application. Addressing these gaps requires well-designed **interdisciplinary clinical trials**, integrating neurophysiological, imaging, and behavioural outcome measures to better understand and optimize this therapeutic synergy.

The field is now poised for a **translational leap**—from isolated interventions to **integrated, personalized rehabilitation paradigms**. This will demand close collaboration among neurologists, physiotherapists, neuroscientists, biomedical engineers, and ethicists to refine protocols, ensure patient safety, and facilitate access. With a concerted research agenda, combined NIBS-exercise approaches could redefine the rehabilitation landscape for individuals living with PD.

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