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# Modifying the progression of Parkinson's disease through movement interventions: multimodal quantification of underlying mechanisms

**Manuel Bange, Damian Marc Herz, Dumitru Ciolac, Gabriel Gonzalez-Escamilla, Sergiu Groppa***

**Introduction:** Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The pathological hallmark is the progressive loss of dopaminergic neurons of the substantia nigra pars compacta, which is accompanied by widespread alterations in the structure and function of distributed brain networks. Together, these processes cause a variety of motor symptoms such as bradykinesia, rigidity, tremor, gait disorders, or difficulties in fine motor control (Bange et al., 2022).

While current pharmaceutical and surgical therapies substantially improve most of the parkinsonian symptoms, developing new interventions that delay or halt disease progression, both in regards to neural degeneration as well as progressive symptom worsening, is a key aim for research in PD (Foltynie et al., 2023). Accumulating evidence suggests that exercise and movement interventions, as non-pharmacological complementary strategies, could have the potential to slow down disease progression (Feng et al., 2020). These interventions refer to physical activities and programs designed to improve motor and brain function. The benefits of movement interventions for alleviating motor symptoms are widely accepted. For example, aerobic exercise attenuates general clinical impairment and improves gait and balance (Zhen et al., 2022). While there is no consensus on the optimal intervention, other types like strength training, balance training, gait training, dancing, and Tai Chi seem generally beneficial (Mak et al., 2017). However, the underlying mechanisms involving cerebral structural and functional adaptations linked to exercise and their relationship to molecular responses remain to be fully elucidated. Specifically, it is not clear whether molecular responses to acute exercise can directly slow down degenerative processes, promote neurogenesis, or are connected to neuroplastic processes involving the remodeling of structural or functional connections. The latter can be captured by current or more advanced neuroimaging techniques that have not been fully utilized in movement intervention studies. Furthermore, whether or how exercise modulates pathological oscillatory activity directly related to motor function in PD (e.g., increased beta band power) needs to be established. Integrating results from different lines of research is an important step to link the putative mechanisms underlying exercise-related disease slowing, identify the specific brain systems or networks they affect, and thus ensure the suitability of different interventions.

Here, we provide a perspective on the current state of exercise and movement intervention-induced slowing of disease progression with a focus on the putative mechanisms. We outline the various methods employed to measure structural, functional, and molecular responses related to movement interventions and propose a multimodal and translational framework for the longitudinal and fine-grained assessment of immediate, short-term, and long-term effects, and their interactions with each other. A better understanding of the relevant mechanisms underlying motor improvement and disease slowing should inform the selection of optimal exercises and recommended intensities, tailored to patients' individual needs.

**Modalities to assess the mechanisms of exercise and movement interventions:** ***Structural correlates of movement interventions:*** Structural magnetic resonance imaging (sMRI) of the brain offers several complementary techniques that provide measures of brain morphology and has been used extensively in PD (Lehericy et al., 2017). Recently, sMRI has been applied to study whether aerobic exercise in PD modifies brain structure in the Park-in-Shape trial (Johansson et al., 2021). In this double-blind randomized controlled trial, patients received either an exercise intervention involving cycling on a stationary bike several times per week for 6 months or an active control condition (stretching, flexibility and relaxation exercises). The control group expressed a significant worsening of global brain atrophy over the study period, while the aerobic exercise group did not. Conversely, no differences in focal brain integrity (as reflected by voxel-based morphometry or free water imaging) were detected between groups, suggesting that aerobic exercise might modify brain structure in PD globally, rather than focally. An open question is whether exercise also affects the connections between different brain regions. This could be assessed using diffusion-weighted imaging to visualize white matter tracts via tractography and quantify their microstructural integrity.

***Functional adaptations related to movement interventions:*** The dynamics in neural activity can be studied by functional MRI (fMRI), assessing the blood-oxygenation level dependent-signal. These recordings can be obtained during performing movement-tasks or during rest and can unveil changes in brain activity and functional connectivity in PD (Herz et al., 2021), which has also been applied to study effects of exercise in PD. For example, in the above described Park-in-Shape trial (Johansson et al., 2021), patients performing aerobic exercise expressed increased resting-state fronto-parietal network connectivity after the intervention, which correlated with individual improvement in fitness (as reflected by maximal oxygen consumption). In another recent study resting-state fMRI was obtained before and after PD patients received treadmill training several times per week for 6 weeks (Ding et al., 2022). While motor cortical and cerebellar connectivity was reduced in PD patients compared to controls at baseline, this was normalized by treadmill training in the PD group. Together, these results suggest that fMRI can be used to assess modulatory effects of exercise on functional brain connectivity patterns in PD.

Another way to non-invasively assess neural activity is to record the electrical signals produced by large populations of neurons using electroencephalography (EEG). This method offers a high temporal resolution, operating within the millisecond range. Exercise and movement intervention studies investigating electrical brain activity in PD patients are still scarce. One study showed that aerobic training, strength training, and physical therapy increase the mean frequency in patients with PD (Carvalho et al., 2015). Furthermore, combined resistance and body-weight interval training has the potential to improve sleep-spindle density in patients with PD, leading to better performance in the memory domain (Memon et al., 2022). Further, EEG has proven valuable in capturing alterations in oscillatory brain activity both during and following exercise in healthy participants (Gramkow et al., 2020). For instance, acute physical effort leads to an immediate increase in alpha and beta power in the frontal, central, and parietal areas. Rest recordings after exercise often show an increase in delta, alpha and beta power in the frontal and central regions, although occasional reductions are also reported (Gramkow et al., 2020). While higher exercise intensity amplifies these effects, potential differences related to the specific exercise modality at hand remain unclear. Long-term alterations after regular exercise are studied to a lesser degree. In that regard, first evidence suggests an increase in alpha and a decrease in low beta power in people with mild cognitive impairment (Amjad et al., 2019). If similar effects are present in patients with PD, specifically reductions in the low beta band could be relevant due to the presence of pathologically enhanced oscillations in this frequency range. Overall, our understanding of the impact of exercise on electrophysiological brain activity in patients with PD is still in its early stages. Moving forward, it is advisable to use EEG in long-term study designs and leverage cutting-edge analytical methods. For example, applying source-reconstruction allows estimating the neural origins of the measured signals, thereby increasing the spatial precision of EEG. Especially when combined with connectivity measures, this approach would be particularly valuable for exploring the effects of exercise and movement interventions on inter-regional communication within widespread brain networks.

***Possible underlying molecular processes related to movement interventions:*** Addressing the molecular basis of physical exercise-induced slowing of disease progression is essential to disclose the mechanistic links to neuroprotection and advance therapeutic solutions for PD patients. Because studying molecular processes usually involves invasive procedures that are not possible in humans, a critical step involves employing animal models with subsequent translation to human studies and ideally to clinical settings. Importantly, the translation is possible because physical exercise improves motor performance both in patients and parkinsonian animals (Ahlskog, 2018; Palasz et al., 2020). Emerging evidence suggests that physical training elicits neuroprotective effects both in healthy and models of brain pathology (Ahlskog, 2018), which may potentially interfere with disease progression. It has been postulated that these effects are mediated by specific neurotrophic, cellular, transcriptional, metabolic, and mitochondrial factors. Particularly, animal studies show increased expression of brain-derived neurotrophic factor (BDNF) following physical activity in several brain regions, including midbrain, substantia nigra, hippocampus, and the cortex (Palasz et al., 2020). As the spatial distribution of BDNF can only be assessed postmortem, this method is not feasible for application in living humans.

Data from animal models of PD further show an increase in number of tyrosine hydroxylase neurons, elevated dopamine levels in the substantia nigra, elevated expression of tropomyosin receptor kinase B and anti-inflammatory cytokines, and enhanced mitochondrial proteostasis following physical exercises (Palasz et al., 2020). Similarly, long-term exercise increases the release of dopamine immediately after exercise in PD patients. It is important to mention that increases in BDNF levels and other molecular factors following exercise constitute acute effects. How sustained and extended regiments of physical training may prompt long-term beneficial effects via molecular mechanisms in PD remains to be elucidated. Furthermore, translating the findings from animal to human studies is challenging due to several constraints involving the differences in the anatomical and physiological organization of the brain, particularly the motor system, the extent of possible experimental manipulations, the applicability of investigational and research tools, and pathophysiological and temporal heterogeneities of animal disease models and humans. Lastly, exploring movement interventions other than aerobic exercise seems challenging in animals due to the complex behavior involved, which is neither accessible in animals nor comparable to that of humans.

**Discussion:** While the positive impact of exercise on motor performance and mobility, as well as the potential to slow down the progression in people with PD is becoming widely acknowledged, the focus of this perspective has been to highlight various tools that proved useful in exploring the underlying mechanisms. Deciphering the mechanisms underlying exercise-related modulation of movement and disease progression may help health professionals and patients in the development and selection of adequate exercise programs. It is essential to ascertain which interventions are most suitable, determine their appropriate intensity and time frame, as well as to identify the specific brain systems or networks that are targeted. In this regard, neuroimaging techniques like sMRI have proven utility in providing insights into structural exercise-related adaptations in the brain, whereas fMRI and EEG can quantify functional characteristics related to neural activity. Especially when considering that the brain works in sets of communicating regions, interregional structural and functional connectivity effects have been investigated rarely and should come into focus in future studies. Because exercise and movement interventions immediately modulate molecular mechanisms related to neurotrophic, cellular, transcriptional, metabolic, and mitochondrial factors, the relationship between such biochemical compounds to structural and functional adaptations are also of particular interest. To investigate these unresolved aspects, we propose that the cross-modal integration of neuroimaging, electrophysiology, and molecular research, in conjunction with clinical and biomechanical evaluation, could provide a comprehensive picture of the effects of exercise across various levels of brain organization (**Figure 1**). In this regard, it was recently shown that microstructural and vascular brain alterations after one week of strength and endurance training occurred even when serum BDNF was not affected in healthy people (Steventon et al., 2021). However, it is unclear if these results can be translated to people affected by PD, where processes of structural and functional adaptation might be altered. Furthermore, it is highly probable that interactions between different processes span multiple timescales, where various levels affect each other with a temporal delay. Thus, a one-week intervention might not be sufficient to identify possible interactions that occur with a temporal delay. Furthermore, due to the gradual progression of PD, potentially disease-modifying effects may only become apparent after a significant period of time has elapsed. Therefore, exercise studies must provide close-meshed monitoring of the multiple organizational levels over prolonged timescales to quantify acute, short-, and long-term effects, as well as their interactions and interdependencies across time. Such an approach might aid uncovering the complex mechanisms underlying the benefits of exercise and movement interventions in PD. This holistic understanding will enable a more comprehensive evaluation of the beneficial effects of exercise and movement interventions across multiple timescales, shedding light on the intricate connections between the different aspects that could lead to a slowing of disease progression. Ultimately, this knowledge will contribute to the development of more effective exercise-based interventions and personalized treatment strategies for people with PD.

**Conclusions:** Although the positive effects of exercise and movement interventions to improve motor function are well-established, the processes related to a potential slowing of disease progression in PD remain to be fully elucidated. The integration of complementary modalities to quantify the influence of exercise on different time scales and on different levels of brain tissue in PD is necessary to link cerebral structural and functional adaptations to molecular responses. This is an important step to ensure the suitability of different interventions, pinpoint the specific brain systems or networks they affect, and thus optimize their selection and programming.

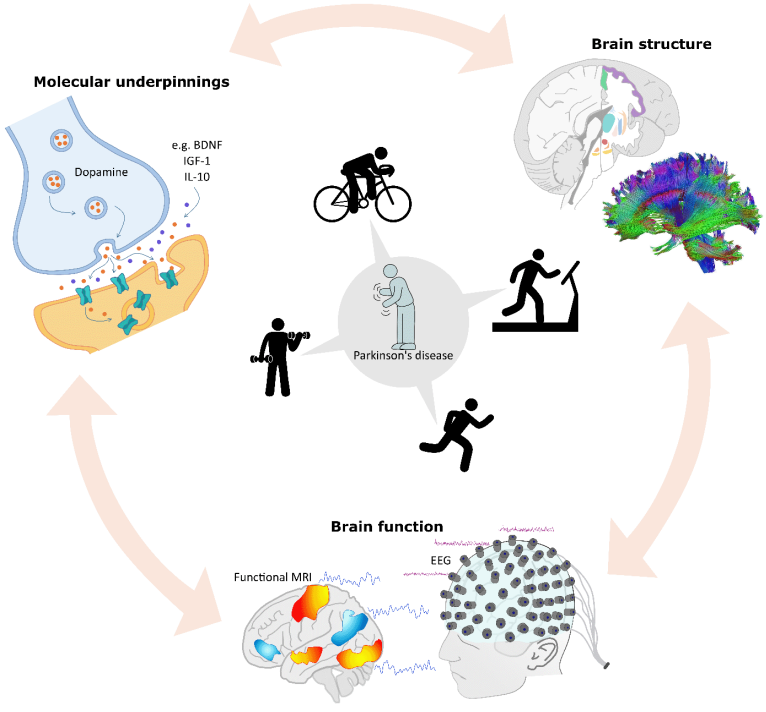


**Figure 1** | **Exercise and movement interventions potentially slow down disease progression via alterations across different levels of structural and functional organization of the brain.**
Interactions in between brain structure (e.g., grey matter density or white matter connectivity; top right), brain function (e.g., intra- and inter-regional communication; bottom), and molecular processes (e.g., increasing brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and dopamine expression, or regulating anti-inflammatory cytokines like interleukin 10 (IL-10); top left) are not fully elucidated. A better understanding of the relevant mechanisms should aid clinicians and therapists in the selection of optimal intervention schemes and the recommended intensities, ultimately helping them to provide patients with informed prescriptions that are tailored to a patient's individual needs. Created with DSI-Studio (https://dsi-studio.labsolver.org/) and Inkscape (https://inkscape.org). EEG: Electroencephalography.

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## References

Ahlskog JE (2018) Aerobic exercise: evidence for a direct brain effect to slow Parkinson disease progression. Mayo Clin Proc 93:360-372.
Amjad I, Toor H, Niazi IK, Afzal H, Jochumsen M, Shafique M, Allen K, Haavik H, Ahmed T (2019) Therapeutic effects of aerobic exercise on EEG parameters and higher cognitive functions in mild cognitive impairment patients. Int J Neurosci 129:551-562.
Bange M, Gonzalez-Escamilla G, Lang NSC, Ding H, Radetz A, Herz DM, Schöllhorn WI, Muthuraman M, Groppa S (2022) Gait abnormalities in Parkinson's disease are associated with extracellular free-water characteristics in the substantia nigra. J Parkinsons Dis 12:1575-1590.
Carvalho A, Barbirato D, Araujo N, Martins JV, Cavalcanti JL, Santos TM, Coutinho ES, Laks J, Deslandes AC (2015) Comparison of strength training, aerobic training, and additional physical therapy as supplementary treatments for Parkinson's disease: pilot study. Clin Interv Aging 10:183-191.
Ding H, Droby A, Anwar AR, Bange M, Hausdorff JM, Nasseroleslami B, Mirelman A, Maidan I, Groppa S, Muthuraman M (2022) Treadmill training in Parkinson's disease is underpinned by the interregional connectivity in cortical-subcortical network. NPJ Parkinsons Dis 8:153.
Feng YS, Yang SD, Tan ZX, Wang MM, Xing Y, Dong F, Zhang F (2020) The benefits and mechanisms of exercise training for Parkinson's disease. Life Sci 245:117345.
Foltynie T, Gandhi S, Gonzalez-Robles C, Zeissler ML, Mills G, Barker R, Carpenter J, Schrag A, Schapira A, Bandmann O, Mullin S, Duffen J, McFarthing K, Chataway J, Parmar M, Carroll C; EJS ACT-PD Consortium (2023) Towards a multi-arm multi-stage platform trial of disease modifying approaches in Parkinson's disease. Brain 146:2717-2722.
Gramkow MH, Hasselbalch SG, Waldemar G, Frederiksen KS (2020) Resting state EEG in exercise intervention studies: a systematic review of effects and methods. Front Hum Neurosci 14:155.
Herz DM, Meder D, Camilleri JA, Eickhoff SB, Siebner HR (2021) Brain motor network changes in Parkinson's disease: evidence from meta-analytic modeling. Mov Disord 36:1180-1190.
Johansson ME, Cameron IGM, Van der Kolk NM, de Vries NM, Klimars E, Toni I, Bloem BR, Helmich RC (2021) Aerobic exercise alters brain function and structure in Parkinson's disease: a randomized controlled trial. Ann Neurol 91:203-216.
Lehericy S, Vaillancourt DE, Seppi K, Monchi O, Rektorova I, Antonini A, McKeown MJ, Masellis M, Berg D, Rowe JB, Lewis SJG, Williams-Gray CH, Tessitore A, Siebner HR (2017) The role of high-field magnetic resonance imaging in parkinsonian disorders: Pushing the boundaries forward. Mov Disord 32:510-525.
Mak MK, Wong-Yu IS, Shen X, Chung CL (2017) Long-term effects of exercise and physical therapy in people with Parkinson disease. Nat Rev Neurol 13:689-703.
Memon AA, Catiul C, Irwin Z, Pilkington J, Memon RA, Joop A, Wood KH, Cutter G, Bamman M, Miocinovic S, Amara AW (2022) Effects of exercise on sleep spindles in Parkinson's disease. Front Rehabil Sci 3:952289.
Palasz E, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G (2020) BDNF as a promising therapeutic agent in Parkinson's disease. Int J Mol Sci 21:1170.
Steventon JJ, Chandler HL, Foster C, Dingsdale H, Germuska M, Massey T, Parker G, Wise RG, Murphy K (2021) Changes in white matter microstructure and MRI-derived cerebral blood flow after 1-week of exercise training. Sci Rep 11:22061.
Zhen K, Zhang S, Tao X, Li G, Lv Y, Yu L (2022) A systematic review and meta-analysis on effects of aerobic exercise in people with Parkinson's disease. NPJ Parkinsons Dis 8:146.

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