Treadmill training in Parkinson's disease: possible role of prefrontal modifications in the improved cortical-subcortical network function

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Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by a range of motor symptoms such as bradykinesia, resting tremor, rigidity, and postural instability, as well as non-motor symptoms, such as depression, anxiety, sleep disturbances, and fatigue (Bloem et al., 2021). The underlying pathology involves a progressive loss of dopamine neurons within the substantia nigra, which results in an imbalance between the direct and indirect pathways of the basal ganglia that regulate motor control (Bloem et al., 2021). In addition to pharmacological treatments such as dopamine replacement therapy, non-pharmacological interventions have been investigated in alleviating gait and motor abnormalities in individuals with PD. The use of behavioral interventions in conjunction with pharmacological therapies may offer a more comprehensive approach to managing the motor symptoms of PD. In recent years, neuroimaging techniques have been utilized to explore neural fingerprints of various behavioral interventions (Mak and Wong-Yu, 2019). These techniques have helped elucidate the complex interplay between brain structure and function in PD, offering valuable comprehension of how behavioral approaches could potentially alleviate the motor symptoms of this debilitating disease.

Numerous investigations have analyzed the impact of utilizing a treadmill for walking in PD patients, and the outcomes have been encouraging. The exact mechanism through which treadmill training (TT) benefits individuals with PD is not yet fully established. One possible explanation is that the treadmill belt may serve as an external cue to modulate the pace of walking. This could potentially compensate for the impaired internal rhythm of the basal ganglia, similar to how auditory or visual cues work in PD (Herman et al., 2007). Recent studies evidenced TT as an effective method for improving gait via high-order cognitive pathways in PD patients (Droby et al., 2020). This type of training was shown to bypass the depleted dopamine pathways within the basal ganglia via the recruitment of higher-level cognitive pathways, including the cerebellum and the prefrontal cortex (Maidan et al., 2016; Droby et al., 2020), leading to improved mobility. Moreover, TT can help to increase the intensity and duration of physical activity, promoting overall fitness and reducing the risk of falls (Herman et al., 2009). Since the effects of treadmill training encompass improvements in both cognitive and motor functions, this perspective article will primarily concentrate on the enhancements in motor function and the advantages of utilizing a multimodal approach for analysis.

A recent meta-analysis of magnetic resonance imaging (MRI) studies on the effects of exercise in PD revealed that exercise can enhance intrinsic brain activity in multiple areas including the frontal, parietal, and occipital lobes as well as the cerebellum. This meta-analysis concluded that the efficacy of exercise in PD is not due to changes in the activation of a single brain area, but may result from coordinated changes in multiple brain regions (Li et al., 2022). Numerous studies have explored patterns of neural changes occurring following behavioral interventions in PD using various single-modality imaging techniques (Maidan et al., 2016; Thumm et al., 2018). For example, functional near-infrared spectroscopy (fNIRS) can detect cerebral hemodynamic responses during actual walking tasks. Previous research using fNIRS has shown that individuals with PD have a higher activation of the prefrontal cortex compared to healthy older adults (Maidan et al., 2016). These results suggest that individuals with PD recruit the prefrontal cortex to compensate for insufficient neural activation of the primary motor cortex and impaired motor function. Furthermore, lower prefrontal activation was found during treadmill walking, compared to over-ground walking, suggesting that external pacing of gait reduces the need for compensatory cognitive mechanisms in individuals with PD (Thumm et al., 2018). While these methods are effective in identifying correlates of brain changes, they may not provide a comprehensive understanding of the underlying mechanisms at a whole-brain level.

By utilizing a multimodal approach that integrates data from various sources such as clinical assessments, behavioral measures, and imaging techniques, we can gain a deeper and more intricate understanding of the interplay between brain function and behavior, both in healthy as well as neurological patient populations (Zhang et al., 2020). One of the key features of multimodal analysis is the integration of multiple imaging techniques. For instance, fNIRS can be employed to measure cortical activity in PD patients during specific tasks like walking. However, it has limited spatial resolution and cannot accurately capture activity in deep brain structures. To overcome this limitation, functional MRI (fMRI) can be used to assess deep brain structures with a resolution of a few square millimeters, allowing for an evaluation of subcortical brain activity. Although fMRI is often measured during the resting state, analyzing the relationship between fNIRS and fMRI can uncover the associated changes in intrinsic brain activity during task conditions.

In a recent study, we examined the impact of TT on the prefrontal cortex activity and the brain cortical-subcortical network (Ding et al., 2022). This study combined fNIRS and resting-state fMRI (rs-fMRI) techniques to examine how TT affects prefrontal activity during walking tasks and the underlying pattern of brain connectivity in PD patients. Corroborating previous findings, we demonstrated that before TT, PD patients exhibited higher levels of prefrontal activity while walking compared to healthy older adults. After undergoing 6 weeks of TT, this prefrontal activity decreased and was accompanied by improvement in gait performance. This could be attributed to either neuroplastic changes in brain functions or improved walking ability, resulting in a reduced need for compensation via prefrontal cortex activation. However, higher levels of prefrontal activity were still observed in the PD group during a dual-walking task (walking while subtracting 3-digit numbers) compared to usual walking tasks. Despite PD patients exhibiting markedly higher levels of prefrontal activity during a dual-walking task in comparison to usual walking, a prior study incorporating a virtual reality component to TT to enhance cognitive engagement, and attentional demands demonstrated the possibility to decrease the prefrontal activation during dual-walking task following the training (Maidan et al., 2018). This reduced prefrontal activity following TT might indicate enhanced cognitive capacity, enabling the allocation of greater cognitive resources towards concurrent task processing, thereby leading to improvements in motor performance.

The novelty of Ding et al. (2022) study was the use of brain connectivity and machine learning techniques to identify modifications in brain networks that are associated with changes in prefrontal activity during walking after TT. This approach provides supplementary information for a better understanding of the relationship between prefrontal activity and the underlying neural mechanisms that support this connection. Specifically, effective connectivity (EC) estimates, which provide directionality and reveal key insights into the influence one brain region has over another, were derived from rs-fMRI and used as predictors of prefrontal activity in support vector regression models. The optimal model trained on specific ECs can be represented as a network configuration and has been demonstrated to explain a substantial proportion of prefrontal activity during usual walking (before TT: R^2 = 0.63 ± 0.1; after TT: R^2 = 0.71 ± 0.03). The study utilized the SHapley Additive exPlanations (SHAP) method to assess the contributions of the EC as predictors to the predicted outcome in the model (Lundberg and Lee, 2017), aiming to enhance the comprehension and interpretation of the machine learning results. This is achieved to measure the marginal contribution of each EC in the model to the prediction outcome, taking into account the interactions between ECs and enabling to identify the most informative ECs and the assessment of their impact on the prediction outcome, providing a more informed understanding of the results (**Figure 1A**). Prior to TT, the brain network associated with the observed elevated prefrontal activity primarily involved subcortical and cerebellar modulations, which are responsible for both motor and cognitive functions. Notably, the most informative EC predictor within this network was the unidirectional connectivity from the cerebellum to the prefrontal cortex, indicating the critical role of the cerebellum. It is widely recognized that the cerebellum plays a significant role in promoting motor learning and movement variability, and may guide the prefrontal cortex in regulating movement and programming cognition during walking (Takakusaki and Okumura, 2008). Following TT, a notable increase in the number of brain regions involved in the associated network (**Figure 1A**). The connections from both the brainstem and subcortical regions to the prefrontal cortex are important components within the executive system and exhibited to be the most informative predictors within the network. These findings suggest that TT could potentially enhance resilience to executive impairment. Such outcomes underscore the efficacy of TT in restoring optimal brain function, akin to the harmonious functioning of an orchestra.

Furthermore, in Ding et al. (2022) we confirmed the validity of EC estimation based on large-scale brain regions using classification models, achieving a mean accuracy of 91.05%, as shown in **Figure 1B**. Each EC feature in the pattern holds predictive information, helping to distinguish between PD patients and healthy old adults. The EC from the subcortical region to the motor cortex was a strong indicator of PD. In line with the literature, these findings demonstrate that increased tonic inhibition in the internal segment of the globus pallidus leads to decreased excitation of the motor cortex's thalamus in PD, causing movement

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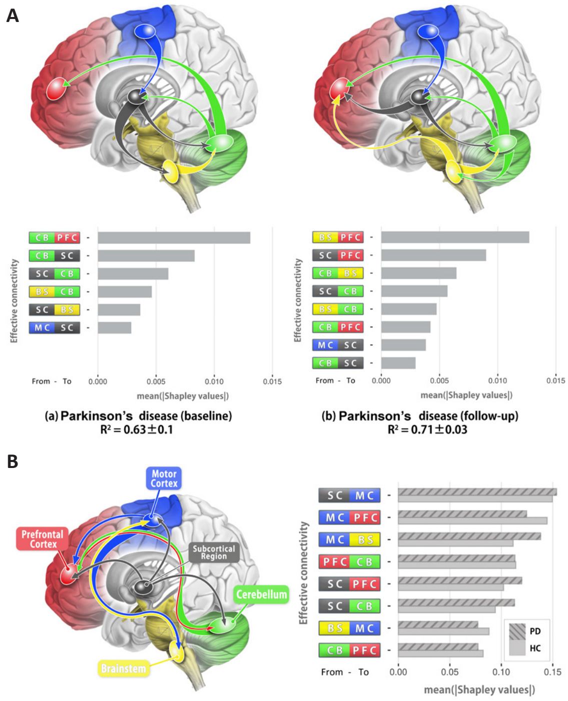

Figure 1 | Optimal support vector machine (SVM) models for regression and classification with feature contribution.
(A) SVM regression model for prefrontal activity during walking trained on resting-state EC connectivity for PD patients before (a) and after (b) treadmill training, with feature contribution based on Shapley values. (B) SVM classification based on resting-state EC features, achieving a 91.05% mean accuracy, 93.68% mean sensitivity ±3.9, and 88.42% mean specificity ±7 in classifying patients at baseline and HC. The corresponding feature contributions (gray bars) are listed below each model, with Shapley values ranked in descending order by the average of both groups. Created using Adobe Creative Cloud and Tableau software. BS: Brainstem; CB: cerebellum; EC: effective connectivity; HC: healthy controls; MC: motor cortex; PD: Parkinson's disease patients at baseline; PFC: prefrontal cortex; SC: subcortical region.

problems and dysfunction (Purves et al., 2018). These results indicate that the major EC predictors are linked to the cerebral cortex and subcortical regions that play a part in the cortico-basal ganglia pathway. The EC features that effectively differentiate the two groups suggest the presence of disparities between them. The reciprocal connections between the brainstem and the motor cortex, as well as the cerebellum and prefrontal cortex, suggest bidirectional impairments in these pathways in PD. Since the fronto-cerebellar association in PD is not yet clear, these results provide a new perspective regarding its potential role in compensatory processes following motor training in PD.

To develop a more comprehensive understanding of the neural fingerprints as a result of the various physiotherapy interventions in patients with PD, future studies should combine multimodal imaging techniques such as electroencephalography, fMRI, and other modalities should be incorporated into further research. Additionally, meta-analyses studies can potentially facilitate identifying/assessing the effectiveness of the different interventions in PD patients. The multidisciplinary approach, as discussed in this article, can provide valuable insights into changes in large-scale brain regions involved in motor and cognitive function and the underlying neural mechanisms. Ultimately, these insights can help in the development of more personalized and effective treatments for PD.

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