PERSPECTIVE

Evaluating rehabilitation interventions in Parkinson's disease with functional MRI: a promising neuroprotective strategy

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 10 million people worldwide (Planetta et al., 2014; Zigmond and Smeyne, 2014). The principal clinical features of PD are bradykinesia, rigidity, tremor at rest and postural instability (Planetta et al., 2014). It is known that both PD itself and the use of anti-parkinson drugs are associated with several non-motor symptoms such as cognitive impairment, neuropsychiatric disturbances and sleep, autonomic, and sensory disorders (Park and Stacy, 2009; Foster et al., 2014). The histopathological hallmark of PD is the reduction of dopaminergic cells in the substantia nigra pars compacta, causing dopamine deficiency in specific nuclei of the basal ganglia such as the dorsal striatum (Fearnley and Lees, 1991; Planetta et al., 2014). The disruption of the dopaminergic system has long been regarded as the major cause of PD; however, it has been shown that a widespread involvement of several non-dopaminergic pathways also contribute to the clinical manifestations of PD (Park et al., 2014).

Despite dopamine replacement therapy can improve some of the motor symptoms in most of PD patients for up to a decade, this therapy is poorly effective on cognitive function (Schapira et al., 2009; Zigmond and Smeyne, 2014). Currently, there are no treatment options able to significantly slow the progression of PD or reverse its neurodegenerative processes (Zigmond and Smeyne, 2014).

Implementation of rehabilitation strategies might change the course of the disease; however, measures of brain changes after treatment should be used to quantify the effects and compare different protocols or approaches in clinical trials.

Rehabilitation: The rehabilitation strategies in PD have been classified into three categories (Foster et al., 2014): (1) exercise or physical activity, (2) environmental cues, stimuli, and objects, and (3) self-management and cognitive-behavioral strategies.

Exercise is emerging as an effective rehabilitation therapy in PD, especially for the motor symptoms (*i.e.*, gait and balance) that are known to be associated with severe complications such as reduced mobility and increased risk of falls (Goodwin et al., 2008). Indeed, it has been shown that exercise might improve motor performance through a facilitation of both the cognitive and automatic control of movement and it might ameliorate cognition and emotional status (Petzinger et al., 2013; Zigmond and Smeyne, 2014). In recent years, several clinical trials have been launched to demonstrate the role of physical activity on reducing the risk of falls or improving UPDRS (Unified Parkinson's Disease Rating Scale) motor scores, balance or gait performance (Petzinger et al., 2013; Foster et al., 2014). For example, it has been shown in mild to moderate PD that aerobic walking exercise can improve motor function and fatigue together with mood, executive control and quality of life (Uc et al., 2014). Moreover, the practice of dance has been reported to be a short-term effective intervention that significantly improves the motor performance as compared with no intervention (Sharp and Hewitt, 2014). Clinical evidence has also shown that tai chi program performed consistently better than the resistance-training and stretching in maximum excursion of movements and in directional control in PD (Li et al., 2012).

Physical exercise demonstrated its benefits not only in PD patients but also in other conditions involving CNS damage such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, spinal cord injury and stroke (Goodwin et al., 2008; Zigmond and Smeyne, 2014).

There is a strong rationale behind the impact of physical exercise on neuroprotection in PD: it increases mitochondrial energy, stimulates antioxidant activity, reduces inflammation, causes angiogenesis and produces synaptogenesis (Zigmond and Smeyne, 2014). Recently published data suggest that exercise paradigms, including both goal-based practice and aerobic training, might work synergistically to promote neuroplasticity processes and improve the effects of aberrant circuitry within the basal ganglia in PD (Petzinger et al., 2013). Neuroplasticity is defined as the reorganization of neural networks in response to new experiences and changes in behaviour or environment, caused by brain encoding and learning (Kleim and Jones, 2008). Neuroplasticity is based on structural and physiological cellular mechanisms including synaptogenesis, neurogenesis, neuronal sprouting, and potentiation of synaptic strength (Südhof and Malenka, 2008). The above mentioned exercise-induced changes on brain physiology might help to create a favorable environment for neuroplasticity in PD (Petzinger et al., 2013).

In light of the multifaceted, heterogeneous and chronic nature of PD, patients would benefit from strategies that are adequately suited for the stage of disease and from interventions focused on physical performance skills and occupational performance through physical activity (Foster et al., 2014).

fMRI: The role of structural imaging in PD is limited to support clinical findings in differentiating idiopathic PD from atypical or secondary parkinsonisms (Stoessl et al., 2014). MRI is the most commonly used method for non-invasively investigating the brain structure and function *in vivo* (Planetta et al., 2014; Stoessl et al., 2014).

The contrast measured by means of functional MRI (fMRI) depends on blood oxygenation level-dependent (BOLD) signal that measures changes in relative amount of oxy/deoxyhaemoglobin under local hemodynamics changes induced by metabolic demands of neuronal activity (Planetta et al., 2014; Stoessl et al., 2014). BOLD changes can be used not only to measure task-dependent activity but also to assess temporal coherence of spatially segregated brain areas. Particularly brain activity can be assessed with fMRI data by calculating the temporal correlations of low-frequency spontaneous BOLD signal fluctuations between spatially distant regions in a rest condition (Stoessl et al., 2014). Abnormal resting state functional connectivity in PD has been recently demonstrated in brain networks studies (Stoessl et al., 2014). For instance, patients with PD showed decreased coupling in the cortico-striatal sensorimotor network and between the striatum and the brainstem and increased coupling in the associative network, possibly reflecting compensatory mechanisms (Helmich et al., 2010; Hacker et al., 2012). Moreover, in patients with tremor, an increased functional connectivity was reported between the internal globus pallidus, putamen and the cerebello-thalamic circuit, consistent

with increased oscillatory electromyography (EMG) activity in these pathways (Helmich et al., 2011). Most importantly, the authors were also able to correlate MRI functional connectivity changes with EMG tremor activities leading them to conclude that resting tremor may be a consequence of pathological interactions between the basal ganglia and the cerebello-thalamic circuit (Helmich et al., 2011).

The resting-state functional connectivity of motor circuits has been recently investigated using autoradiography in parkinsonian rats after long-term aerobic exercise, providing an interesting framework to explore the exercise-induced brain changes in PD (Wang et al., 2015). The authors showed that the effects of 4 weeks forced running wheel exercise in parkinsonian rodents included reintegration of the dorsolateral striatum into the motor network, emergence of the ventrolateral striatum as a network hub and increased resting-state functional connectivity among the motor cortex, motor thalamus, basal ganglia, and cerebellum (Wang et al., 2015).

To date, the effects of rehabilitation and exercise have been poorly explored with fMRI in patients with PD. In particular, there is lack of knowledge about the neural correlates of the effects of either rehabilitation strategies or physical exercise alone or in combination, and their relationship with motor and non-motor symptoms in PD. Exploring the rehabilitation-induced brain functional connectivity changes and the effects on the clinical management of PD patients will lead to a better understanding of the undergoing neuroplasticity processes and potentially to the identification of novel disease-modifying interventions in PD. On this perspective, fMRI can be an extremely important tool, potentially able to explore the training-induced functional brain plasticity mechanisms and related neural networks in patients with PD as it has been already performed in healthy subjects (Taubert et al., 2011). It will be crucial to take into account the clinical eterogeneity of PD, ranging from akinetic-rigid to tremor dominant phenotypes (Zhang et al., 2015), the effect of disease compensatory mechanisms, medication, life style, diet or other confounding factors to avoid imaging analysis type II errors (Planetta et al., 2014; Stoessl et al., 2014).

To sum up, the development of patient-tailored rehabilitation strategies for PD, taking into account motor and non-motor symptoms as well as psycho-physical and social environment will be a target of great interest in the following years.

Quantitative functional MR imaging will play a crucial role to measure effectiveness of rehabilitation therapies in clinical trials and their effect on the dopaminergic pathological stream and its compensatory mechanisms.

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***Accepted:** 2015-03-11*
***doi:**10.4103/1673-5374.156957* ***http**://www.nrronline.org/*
Mallio CA, Zobel BB, Quattrocchi CC (2015) Evaluating rehabilitation interventions in Parkinson's disease with functional MRI: a promising neuroprotective strategy. Neural Regen Res 10(5):702-703.

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