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Motor-cognitive approach and aerobic training: a synergism for rehabilitative intervention in Parkinson's disease

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Practice points

- Parkinson's disease (PD) is not a mere 'movement disorder,' but rather it is a complex motor behavior disease responsible for a tremendous social and economic impact.
- The optimal management of PD should involve integrated, multidisciplinary approaches combining both pharmacotherapy and non-pharmacological interventions, such as rehabilitation.
- Bottom-up and top-down cognitive coping strategies and adaptive techniques are useful for achieving motor benefits in patients with PD.
- The aerobic exercise may promote neural rearrangements and improve cognition in patients with PD.
- Combining a 'goal-based', motor-cognitive practice with aerobic training seems to provide sustained clinical benefits rather than conventional physical therapy in patients with PD.
- Neuroplastic changes probably drive the clinical rehabilitation-induced benefits in patients with PD.
- Future studies should identify optimal parameters of intensity, frequency and duration of rehabilitation in patients with PD.

Parkinson's disease (PD) results in a complex deterioration of motor behavior. Effective pharmacological or surgical treatments addressing the whole spectrum of both motor and cognitive symptoms are lacking. The cumulative functional impairment may have devastating socio-economic consequences on both patients and caregivers. Comprehensive models of care based on multidisciplinary approaches may succeed in better addressing the overall complexity of PD. Neurorehabilitation is a highly promising non-pharmacological intervention for managing PD. The scientific rationale beyond rehabilitation and its practical applicability remain to be established. In the present perspective, we aim to discuss the current evidence supporting integrated motor-cognitive and aerobic rehabilitation approaches for patients with PD while suggesting a practical framework to optimize this intervention in the next future.

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Parkinson's disease (PD) is the second most common neurodegenerative disorder. In the near future, the prevalence of PD is expected to exceed that of any other known neurological disorder, including Alzheimer's disease. Indeed, according to recent epidemiologic projections, the number of individuals affected by PD is poised for exponential growth [1].

The dopaminergic neuronal loss in the substantia nigra pars compacta is universally regarded as the pathological hallmark of PD [2]. The resulting altered connectivity in cortico–basal ganglia networks is believed to be involved

in the pathophysiology of the cardinal motor symptoms of the disease, including bradykinesia, rigidity and resting tremor [3].

The clinical spectrum of PD, however, encompasses several non-motor features, which are known to be significant determinants of patients' quality of life (QoL) [4]. These include mood changes, anxiety, apathy, fatigue, sleep disturbances, chronic pain, gastrointestinal abnormalities and bladder dysfunction – among others.

Although originally described in terms of motor symptoms, it is generally acknowledged that nowadays PD should no longer be regarded as a mere 'movement disorder,' but rather as a complex motor behavior disease. Consolidated experimental evidence demonstrates how basal ganglia nuclei receive multimodal sensorimotor, cognitive and emotional information from converging cortical pathways and generate a 'compressed' and highly integrated output message to the frontal cortex, where the selection of a proper motor behavior is finally elaborated [5,6]. Notably, this highly integrated computational process encodes for any internally generated motor behavior: from the simplest movement of a single joint, to the most complex motor sequence involving the entire body in order to express emotional contents in a given cognitive setting [7].

This broad physiological complexity should indeed be appreciated by clinical scientists in order to understand the complex phenomenology of PD. Along the disease course, the neurodegenerative process spreads to other, non-dopaminergic neural systems, such as the cholinergic and the noradrenergic pathways [8,9]. At this stage, patients usually develop cognitive, motivational and more complex 'axial' disturbances affecting gait, balance and posture, whose responsiveness to dopamine replacement therapy (DRT) is almost always suboptimal, if not disappointing. Not uncommonly, these conditions may overlap in the same patient, thus exerting an overall detrimental impact on QoL as well as social and emotional well-being [10–12].

Indeed, while in early PD DRT is usually effective in improving self-perceived QoL by addressing the dominant motor features of the disease [13,14], its effectiveness in the medium-advanced stages tends to decrement. Furthermore, the potential onset of DRT-related side effects, such as motor fluctuations, dyskinesia, painful dystonia, dopamine dysregulation syndrome and impulsive–compulsive disorders conspire, over time, to reduce the overall tolerability of pharmacological therapies [15].

Given the multi-layered complexity of PD, it is generally acknowledged that its optimal management should involve multidisciplinary approaches combining both pharmacotherapy and non-pharmacological interventions [16,17]. Among the latter, growing evidence supports neurorehabilitation as an effective complementary treatment for the management of PD [18–26]. Neurorehabilitation could be defined as the set of clinical and carer interventions aimed at recovery from nervous system damage (due to acquired injuries or to degenerative diseases) by reducing or compensating for the functional disturbances by using the patients' individual neuroplastic resources.

In the past years, the complex interplay between basal ganglia and cortical–cerebellar networks in the modulation of both cognitive-motivational (non-motor) and motor aspects of action [5,27–31] has been increasingly considered in the development of novel integrated rehabilitative approaches (see [Figure 1](#)). Furthermore, emerging evidence from basic science and clinical studies suggested the potential for add-on aerobic exercise to boost brain plasticity mainly through long-term potentiation (LTP) phenomena [32].

In the current perspective, we aim to discuss the potential for integrated motor-cognitive rehabilitation practices and aerobic exercise to harness greater and more sustained clinical benefits than any uni-dimensional rehabilitative approach alone. Potential ways to combine these two methodologies within routine rehabilitation protocols will be finally discussed.

Motor-cognitive intervention in PD: scientific rationale & clinical evidence

A number of different rehabilitative protocols designed for PD were previously reported in the clinical literature [20,21]. The vast majority of them focused on improving basic motor aspects of PD [33–36]. Overall, results from these interventions were mixed and somewhat conflicting. Further, these protocols did not expressly investigate the influence of cognitive processes in modulating patients' final motor behavior [5,27–31].

However, mounting evidence suggests that the broad degenerative process underlying PD may manifest with a complex clinical phenomenology involving not only primary motor aspects of action, but also cognitive, emotional and motivational drivers [5,26,29,30,37]. This huge neural networks disruption could explain why PD motor signs and symptoms may be preceded or accompanied by a wide range of neuropsychiatric features (such as anxiety, apathy, depression, fatigue and psychosis) [38], whose potential impact on functional outcomes has been described in the rehabilitation field [39,40]. In the last years, the importance of engaging subject's cognition in order to achieve greater motor benefits began to be increasingly considered [37]. More specifically, the impairment of basal

Figure 1. The role of the basal ganglia–cortico–cerebellar networks in motor behavior: implications for rehabilitation.

Schematically, the striatum can be divided into three principal nuclei with different functions: the nucleus accumbens plays a crucial role in decision-making and in reward-based learning; the nucleus caudatum is fundamental for motor learning and for action planning; finally, the putamen has a pivotal role for scheduling and executing habitual-automatic motor skills. These nuclei are strictly interconnected with limbic, associative and sensorimotor cortical areas, respectively. From a functional point of view, these corticostriatal structures are central to learn and express each single motor behavior: the motivation to move for reaching a goal is driven by the accumbens–OFC network; the network linking the caudatum with PFC, parietal cortex and SMA represents the neural system for action planning; motor execution is finally provided by the putamen–SMA–PMC–MC network. The cerebellum monitors the motor performance, contributes to error correction of the ‘ongoing’ action and generates a continuous signal for maintaining the congruency of the motor behavior. Considering this functional complexity, in a rehabilitative perspective, the treatment of a neurological disorder leading to the disruption of motor behavior (such as Parkinson’s disease) has to be designed considering all the motor, motivational and cognitive aspects underlying the dysfunction. OFC: Orbitofrontal cortex; PFC: Prefrontal cortex; PMC: Premotor cortex; MC: Motor cortex; SMA: Supplementary motor area.

ganglia–cortical–cerebellar networks in PD has been involved in: i) an aberrant expression of habitual-automatic, goal-based actions [41–44], ii) the dysregulation of reward-based [45–47] and error-based learning processes [48,49], and iii) an impaired switching from automatic to voluntary and goal-based actions [50–53]. The aforementioned mechanisms are believed to underline the pathophysiology of bradykinesia [54], walking problems – including freezing of gait [55], postural abnormalities and balance disturbances with falls [56–58], writing and manual dexterity problems [59], speech [60] and swallowing deficits [61] in these patients.

It therefore follows that, from a cognitive and motor learning perspective, rehabilitation in PD should aim to foster the re-acquisition of lost habitual, goal-based motor behavior [37]. To achieve this result, clinicians may take advantage of multidisciplinary approaches [26] including physiotherapy, occupational therapy [62], speech and swallowing therapies [63].

Although both the implicit learning and executive control may be affected in PD [64–68], it has been shown that PD patients remain capable to apply bottom-up and top-down cognitive coping strategies and benefit from adaptive techniques. These include explicit cues, such as verbal instructions, and implicit cues, such as environmental sounds or visual signals [37,69–75].

It is believed that cues allow patients for engaging the volitional-executive control of movements, thus bypassing dysfunctional sensorimotor-habitual networks, while reinforcing the cortical mechanisms involved in motor drive [76–78]. While the explicit cues likely exploit executive functions mediated by the caudatum–prefrontal cortex network, implicit cues are thought to act through entrainment and attention focusing via the cerebellum–prefrontal cortex network [37,79,80].

An additional rehabilitative strategy involves the use of feedback-based learning. The underlying neural pathway seems to be found in the striatum–prefrontal cortex network [81]. Feedback-based motor learning involves the volitional, constant modulation of the ongoing motor behaviors based on internal and/or external signals that are strictly action-specific [82,83].

The overall effects of adaptive techniques (external cues, internal cues and feedback-based motor learning) may translate into clinical improvements on mobility, balance, gait, posture – among others [70–72,75,84].

The fact that PD patients may effectively apply to cognitive strategies in order to cope with their motor disability suggests that rehabilitative interventions engaging cognition may indeed harness motor learning schemata leading to broad clinical, motor and functional benefits [32]. As a case in point, many robotic-mechanical devices adopted in the field of neurological rehabilitation engage cognition to achieve motor benefits. Treadmill training represents the prototype among the tools used in this motor-cognitive perspective. The main goals of treadmill training are improving gait and enhancing patients' physiological reserve. Training parameters such as speed and workload can be individualized for each subject, while the intensity and challenge of the training can be dynamically adjusted overtime. While using this device, kinetic signals provided by the sliding belt allow patients for focusing their attention to the active control of gait. As such, treadmill training may exert a normalizing effect on spatiotemporal gait parameters, thus improving gait rhythmicity and reducing gait variability in patients with PD, especially when associated with cues, feedback and music cueing [85–87]. Worthy of interest in this field is the use of virtual reality (VR), a computerized simulation that allows patients to interact with a virtual environment through multiple sensorial modalities [88,89], thus stimulating both motor and cognitive processes, simultaneously [90]. VR provides augmented feedback about performance and may enable individualized repetitive practice of motor function. The use of VR provides patients with benefits in the short and long-term period [91,92].

Another effective cognitive rehabilitative technique is motor imagery (MI). This is based on a conscious access with the intention to move. A large body of evidence suggests that imagined and executed actions share the same neural structures, recruiting overlapping regions [90,93,94]. Consistently, it has been demonstrated that MI may improve both motor performance and motor learning processes [94]. In the same way, Action Observation Therapy (AOT) represents a further, interesting and effective cognitive instrument for motor rehabilitation in PD [94]. AOT is based on the observation and imitation of specific motor actions for facilitating the motor learning processes, probably through the activation of the so-called 'mirror neurons' system [95,96]. A recent study demonstrated that this technique is effective in treating freezing of gait and that benefits may be sustained over a 4-weeks follow-up period [96]. The cognitively-mediated effects of this modality of rehabilitation were recently supported by imaging studies reporting an increased recruitment of frontoparietal areas in patients undergoing AOT [97]. Over the past years, motor-cognitive training showed a great efficacy in ameliorating a lot of goal-based, automatic motor behaviors, thus corroborating the valuable role of these strategies for the management of parkinsonian patients [37].

In this scenario, dual task training is a prime example of motor-cognitive interplay and a highly appealing technique to be implemented in the management of PD [98].

In PD, gait function tends to shift from a healthy, semi-automatic pattern to a maladaptive profile where attention-based strategies are inappropriately used to maintain locomotion. These compensatory strategies are not optimized for natural walking and when a second cognitive task is applied, the resulting attention shift may decrease walking speed and smoothness, ultimately leading to gait disruption and falls [99,100].

While in PD the abrupt administration of dual tasks can exert disruptive effects on walking, compelling evidence also suggests that motor strategies based on repetitive dual task training and dual task reinforcement may improve the cognitive reserve of these patients, thus ameliorating their gait function in clinical and ecological settings [101,102].

Based on previous reports from stroke literature [103], Yang and colleagues investigated the effects from cognitive dual task training on gait function in patients with PD. A decreased double support time was found following a 12 sessions program (30 min each session, three sessions per week for 4 weeks); furthermore, motor dual task gait training led to decreased gait variability in motor dual task walking conditions [101].

Finally, the application of noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), may maximize clinical benefits through mechanisms involving cortical plasticity [104,105]. The underlying molecular basis is not fully known, but it seems to involve synaptic remodeling through LTP and long-term depression (LTD) phenomena [106].

Manenti *et al.*, [107] investigated the effects of anodal transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in combination with physical therapy in PD patients. Patients were either assigned to anodal tDCS plus physical therapy (2 weeks of treatment consisting of daily direct current stimulation application for 25 min during physical therapy), or to sham neuromodulation plus physical therapy. While significant improvements in motor skills and depressive symptoms were observed in both groups, performances on PD Cognitive Rating Scale and verbal fluency tests improved only following add-on neuromodulation. These benefits were sustained

over time (3 months). A number of studies emphasized the potential of tDCS and rTMS to modulate both motor and cognitive functions [108–111] and to improve neuroplasticity [104,105].

Interestingly, add-on tDCS in conjunction with dual task gait training may positively influence cognitive performances while walking under certain experimental conditions [112]. The effect of tDCS and rTMS on prefrontal cortex [108,113,114] could be related to modulation of functional connectivity on corticostriatal level, thus somehow replicating what is observed with rehabilitative interventions based on motor-cognitive training. This provides further evidence for motor benefits that are mediated, at least partially, by neuroplastic phenomena.

Using different behavioral tasks probing reaction time (RTs), Ortelli *et al.*, [115] investigated the relationship between asymmetric dopaminergic degeneration and attentional resources in PD patients undergoing motor-cognitive rehabilitation. Attention-mediated performances did not significantly differ between right-side (RPD) and left-side (LPD) predominantly affected patients. However, only LPD patients showed significant improvements on attentional tasks following motor-cognitive rehabilitation. The authors hypothesized that these different profiles of cognitive modifiability in PD patients may be related to a lateralized susceptibility of the nigrostriatal system to neuronal degeneration and brain plasticity [115]. Importantly, these findings were in agreement with a previous randomized controlled trial describing the effects of 24 weeks of structured exercise interventions in PD [116]. The study provided Class IV level evidence for Progressive Resistance Exercise or Modified Fitness Counts in improving attention and working memory in non-demented PD patients with mild-to-moderate disease severity.

Aerobic exercise in PD: scientific rationale & clinical evidence

Solid experimental evidence suggests that physical exercise may promote brain plasticity through the activation of neurotrophin signaling pathways [117], synaptogenesis [118], angiogenesis and neurogenesis [119,120]. Furthermore, beneficial effects from aerobic exercises may be mediated by reduced neuroinflammation [121] oxidative stress [122], and by improved intracellular calcium homeostasis [123].

In PD models, aerobic exercise may induce compensatory rearrangements of dopamine neurotransmissions by virtue of neuroplastic changes involving the striatal–thalamic–cortical motor circuits [32,124–127]. In neurotoxin-based models of PD, such as MPTP and 6-OHDA, physical exercise facilitates dopamine release (DA) through the modulation of DA receptors [124,128,129]. Using western immunoblotting analysis of synaptoneurosome and *in vivo* positron emission tomography imaging with DA-D2R specific ligand [¹⁸F]fallypride, Vučković *et al.*, [130] observed an increase in striatal DA-D2R expression within dorsal striatum in MPTP mice following treadmill training. Notably, the increase expression of DA-D2R in the dorsal striatum has been linked to the potential restoration of automatic motor patterns in PD models [32].

It is hypothesized that exercise-induced effects on brain plasticity may also involve other non-dopaminergic circuitries. Consolidated evidence from *in vitro* and animal models shows that following dopamine depletion, a glutamate overdrive within corticostriatal connections tends to emerge. This phenomenon has been linked to aberrant learning and memory processes [131]. In neurotoxin-based rodent models of PD, exercise seems able to reverse this aberrant hyperactive glutamatergic state by reducing the presynaptic release of glutamate. Interestingly, these changes are accompanied by changes in the firing pattern of nigral dopamine neurons, suggesting a strong correlation between these two neurochemical systems in PD [123,132].

In addition to changes in neurotransmitters, modulation of neurotrophic factors may play an important role in the exercise-induced neuroplastic changes. These proteins are pivotal in key neurobiological processes including neuronal survival, growth and synaptogenesis [133,134]. Specifically, the action of BDNF is a candidate mechanism underlying exercise-induced benefits. Literature data suggest that BDNF release can help to optimize brain plasticity outcomes via exercise interventions, which could be properly relevant in the context of multimodal training (i.e., exercise and cognitive stimulation) [135]. Interestingly, in the context of exercise, the candidate tissues for the addition of BDNF to circulation is not only the brain, but also skeletal muscle, peripheral blood mononuclear cells, vascular endothelial cells and platelets via the spleen [135]. In particular, endothelial cells rapidly secrete BDNF in proportion to the magnitude of exercise-like stimuli, including shear stress [136] and reductions in PO₂ [137]. Consistently with the upregulation of central BDNF expression in rodents, physical activity was found to increase circulating BDNF levels in both healthy humans and PD patients [138–140]. Fontanesi *et al.*, [140] tested the hypothesis that a 4-week rehabilitation program, including aerobic exercise and functional and goal-directed training, could enhance BDNF-TrkB signaling in lymphocytes in patients with PD (Hoehn & Yahr stage 2–3). Following the intervention, a significant improvement in motor and non-motor symptoms along with an up-regulation of BDNF-TrkB signaling [140] was observed. Moreover, changes in the Unified Parkinson's Disease

Rating Scale significantly correlated with the increase in TrkB signaling, thus suggesting that clinical benefits in this population may be mediated by enhanced BDNF-TrkB signaling in lymphocyte. Two randomized controlled trials tested the rehabilitation effects on functional outcomes in PD and whether the treatment increases the BDNF serum levels [141]. Frazzitta *et al.*, [142] enrolled 30 participants in early stages of PD who were assigned to intensive rehabilitation or to a control group (no rehabilitation). The intervention lasted 28 days and included aerobic exercise. The authors found that the intervention increased the BDNF levels and improved PD signs [142]. Sajatovic *et al.*, [143] aimed to compare changes in depression in people with PD with comorbid depression between individual versus group exercise plus chronic disease self-management. The authors selected some biomarkers of inflammation and neuronal integrity, including BDNF, as outcome measures possibly related to mechanisms involved in depression. They found a significant increase in plasma BDNF level that corresponded to the initial 12-week 'intensive' portion of the interventions [143].

Similarly to what observed in animal models, Fisher and colleagues [144] reported an increased in DA-D2R binding potential within the dorsal striatum of individuals with early stage PD following an 8 weeks training program. Interestingly, these findings specifically correlated with improved postural control, suggesting that benefits from exercise may also be task-specific. Other studies seem to indicate dose-dependent effects from physical activity. However, the specific role played by motor tasks and dose in influencing the final clinical outcomes remains a matter of investigation. Finally, mounting evidence from different neurophysiologic studies suggest that high-intensity exercise may normalize corticomotor excitability in early PD [145]. These findings are consistent with the well-known relationship between exercise intensity and BDNF levels, with higher exercise intensities inducing larger BDNF increases [146]: noteworthy, low to moderate intensity exercise is less effective than high-intensity exercise at increasing BDNF concentrations in healthy adults [147,148].

Overall, these findings in humans seem to recapitulate prior evidence from both *in vitro* and animal models, suggesting that neuroplastic re-arrangements following intensive exercise may be mediated through different, potentially interconnected molecular mechanisms [124,129].

For the scopes of the present perspective, it is noteworthy that exercise paradigms incorporating aerobic training in PD may improve cognition and motor learning in addition to their known effects on motor function [32,149].

Indeed, the dopaminergic neuronal loss in the basal ganglia may directly affect cognitive functions with specific respect to executive domains [150,151]. Different studies with functional magnetic resonance imaging suggest that aerobic exercise may increase connectivity between brain regions specifically involved in affect, reward, learning, memory, attention and executive control [152]. In this setting, Duchesne *et al.*, [153] described a functional re-organization of brain activity in cerebral regions concerned with motor learning (hippocampus, striatum and cerebellum) in 19 early stage PD patients following a 12-week progressive aerobic training. These functional changes were accompanied by improvements on behavioral outcomes observed in PD patients. Together with additional data showing improved executive functions following aerobic exercise [154], current evidence suggests that cognitive benefits following physical activity could be mediated by enhanced activation in frontal brain regions.

Silveira *et al.*, [155] compared the effects of aerobic and goal-based exercise on five cognitive domains (attention and working memory, executive functions, memory, language and visuospatial function) in cognitively normal and impaired individuals with PD who were randomly allocated into three intervention groups: aerobic, goal-based and control. The authors found that aerobic exercise was more effective than goal-based exercise in improving executive functions (i.e., inhibitory control) in both cognitively normal and impaired individuals with PD.

These findings are extremely relevant in light of the role played by frontal brain regions in modulating attentive processes putatively used to compensate for impaired motor automaticity in PD [37].

Integrating motor-cognitive rehabilitation with aerobic exercise: open questions

Mounting evidence from clinical, behavioral, brain imaging, animal models and *in vitro* studies, supports the combined use of intensive, 'goal-based', motor-cognitive practices with aerobic training to achieve greater and more sustained clinical benefits in patients with PD (Figure 2) [32,37,134]. In the attempt to optimize complementary models of care for PD, we believe that future rehabilitative approaches should integrate both motor-cognitive and aerobic interventions. While cognitive engagement seems critical to achieve motor-behavioral benefits, aerobic training may act synergistically by maximizing brain plasticity. Indeed, this perspective of care encompasses all the main strategies historically adopted in PD rehabilitation: cueing techniques [156], use of feedback [157], verbal instructions [158] external focus [75], MI [159,160], biofeedback [161], AOT [96,160], mechanical devices [85,86], VR [92,92], non-invasive brain stimulation techniques [104,105], front-to-front physical therapy [25], aquatic therapy [162,163],

Figure 2. The theories on which rehabilitation in Parkinson disease should be based.

Combining an intensive and 'goal-based', motor-cognitive practice with aerobic training promotes neuroplasticity at the corticostriatal level, stimulates the executive resources and promotes the learning processes, thus probably representing the best way to obtain sustained improvements in Parkinson's disease (see both of the paragraphs about motor-cognitive intervention and aerobic exercise in Parkinson's disease).

speech and swallowing therapies [61] and occupational therapy [62]. Cognitive engagement may play an equally important role in other complementary activities designed for patients with PD, including dance therapy [164,165], art therapy and music therapy [166].

Future personalized protocols aiming to integrate these modalities of rehabilitation should also identify optimal parameters of intensity, frequency, duration and task-specific exercises to improve effectiveness and tolerability. This element introduces the question regarding the actual level of standardization and reproducibility of complementary interventions in PD. Although the current methodological heterogeneity of published studies prevents from pooling the available evidence to generate conclusive recommendations, growing evidence seems to confirm and converge on the use of multidisciplinary models of care [25,26,167–171] involving different health professionals including neurologists, psychiatrists, physical therapists, occupational therapists, speech therapists, psychologists, nurses, social workers – among others. This approach may succeed in shifting the pendulum from the current construct of 'one disease – one disability' to more comprehensive and integrated strategies focusing on patient's individual complexity; and functional, familiar and social needs as a whole. Hopefully, different clinical, demographical and medical aspects (including comorbidities) should be weighted to adapt the intervention to the needing and personal motor and cognitive resources of each patient. For example, 'moving' the intervention toward the goal-based cognitive side, rather than to the aerobic side, could be useful for frail, advanced-stages patients. Conversely, the aerobic exercise,

promoting plasticity, can be advantageously adopted in cognitively impaired patients for whom the cognitive, goal-based approach is hampered. Moreover, when the cognitive, goal-based approach is exploitable, it is crucial to evaluate which are the problems the patient presents in performing actions in a multi-dimension perspective (including the motor, motivational and cognitive aspects): how much the patient is motivated to perform the specific action (i.e., walking, or talking or writing)? Is it possible to increase his/her motivation? Does the patient know the correct strategies to manage the difficulties in action performing? Is it possible to modify his/her adopted strategies for ameliorating the motor performance? Which motor aspects are impaired? Finally, the time to spend in the different activities (occupational therapy, speech therapy, balance training, gait training, psychological therapy etc.) should be framed on the basis of what any single patient really needs. Therefore, algorithms to stratify the interventions and make them even more person-centered could be designed in the upcoming future. As a matter of fact, the multidisciplinary approach has been preliminarily reported to be effective in improving clinical conditions and QoL in PD [25,26,167–171], although further appropriately designed, well-powered studies are needed to corroborate these findings.

Results from these studies raise the question regarding the cost–benefit ratio and the practical applicability of these integrated interventions. Given the current demographic trend, the prevalence of PD is expected to exponentially increase in the next years, thus reaching a pandemic dimension [1]. The enormous social and economic impact for patients and their caregivers [172,173] is aggravated by the aggregate burden of pharmacological therapies in terms of direct costs, adverse reactions and side effects [174,175]. Therefore, the cost saving effect of multifaceted comprehensive non-pharmacological approaches preserving long-term functionality and improving QoL may be outstanding, especially if compared with the aggregate cost deriving from addressing every patient's comorbidity separately. This favorable aspect is also partially suggested by prior studies reporting a reduced or controlled amount of dopaminergic medications administered to PD patients receiving dedicated rehabilitation programs [25,26]. These considerations should be included in economic models evaluating the cost–effectiveness of rehabilitation.

Further questions related to the optimal outcomes chosen to measure the aggregate effect of comprehensive and integrated neurorehabilitative approaches should also be addressed. Intuitively, the simple use of clinical tools biased toward appendicular motor function may not capture clinically significant improvements occurring in multiple, interdependent functional domains. Broader, comprehensive measures should be incorporated into both clinical practice and clinical trials, including kinematic, cognitive, psychological, emotional, behavioral and social outcomes. Moreover, only few studies evaluated cost–consequences analysis of rehabilitation in PD and many limitations stand [176]. Converging literature indicates that dedicated rehabilitative interventions are associated with fewer complications and lower costs in real world settings [177].

Finally, the optimal setting in which motor-cognitive rehabilitation and aerobic interventions may be administered remains to be defined. While an inpatient setting may be optimal to ensure treatments requiring higher intensity of care, home-based activities (possibly tele-monitored by electronic devices or smartphone applications) as well as outpatient programs, should be implemented to favor the maintenance of benefits over time. The coordination of different health professionals within dedicated networks and constant interactions with patients' communities through outreach programs may successfully serve to this purpose and should therefore be encouraged [178].

Conclusion & future perspective

A large amount of data suggest that effective rehabilitative interventions for PD should incorporate motor-cognitive training with aerobic activities and be designed accordingly. The specification of the chosen rehabilitative parameters, such as intensity, specificity and complexity, should always be formally disclosed in order to promote standardization and comparability of different protocols across dedicated centers. Future studies should address these methodological considerations in order to generate high quality experimental evidence (e.g., by comparing different protocols embracing the motor-cognitive interplay in randomized controlled trials) and lead to the identification of optimal models of care in PD. The development of comprehensive, patient-centered modalities of rehabilitation may succeed in harnessing long-lived clinical benefits and improvements in QoL in patients affected by this destructive disease.

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