Exercise-Induced Neuroplasticity in Human Parkinson’s disease: What is the Evidence Telling Us?

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Abstract

Introduction: While animal models of exercise and PD have pushed the field forward, few studies have addressed exercise-induced neuroplasticity in human PD. **Method:** As a first step toward promoting greater international collaboration on exercise-induced neuroplasticity in human PD, we present data on 8 human PD studies (published between 2008 and 2015) with 144 adults with PD of varying disease severity (Hoehn and Yahr stage 1 to stage 3), using various experimental (e.g., randomized controlled trial) and quasi-experimental designs on the effects of cognitive and physical activity on brain structure or function in PD. We focus on plasticity mechanisms of intervention-induced increases in maximal corticomotor excitability, exercise-induced changes in voxel-based gray matter volume changes and increases in in exercise-induced serum levels of brain derived neurotrophic factor (BDNF). Finally, we provide a future perspective for promoting international, collaborative research on exercise-induced neuroplasticity in human PD. **Conclusion:** An emerging body of evidence suggests exercise triggers several plasticity related events in the human PD brain including corticomotor excitation, increases and decreases in gray matter volume and changes in BDNF levels.
1. **Introduction**

The volume of randomized controlled trials and meta-analytic studies supporting efficacy of physical therapy, exercise or motor training in Parkinson’s disease (PD) is rapidly accumulating [1,2], reflecting a growing interest in health promoting exercise and physical therapy as adjunctive treatment for PD. This prompted the Movement Disorder Society (MDS) Evidence-Based Medicine Panel to review the literature on non-pharmacologic interventions for PD and recommend that physiotherapy and exercise are likely efficacious as adjuncts to levodopa treatment or the control of PD motor symptoms [3]. Citing preclinical work with a rodent model of exercise and PD that had demonstrated effects of physical exercise on dopaminergic neurotransmission [4], the MDS panel further recommended, for the first time, that future studies ought to focus heavily on effect of physical exercise on human PD disease progression [3]. Many safe and efficacious evidence- and experience-based modes of PD physical exercise exist, including: dance, cycling, walking, tai-chi, yoga, treadmill training and resistive exercise.

Internationally, exercise is viewed by movement disorders clinicians as a key medicinal ingredient in patients at all stages of PD who do not display contraindications to becoming more physically active [5-7]. Yet, movement disorders professionals’ voices often invoke a fatalistic attitude toward exercise-induced neuroplasticity in PD. For example, it is widely believed among movement scientists that neuroplasticity-based exercise strategies are still lacking in PD [9].

Since the Movement Disorder Society Evidence-Based Medicine Panel report in 2011, data from animal models of exercise and PD reveal that a physical activity must be self-produced under conditions of heightened arousal to change brain architecture or function. Such activity-dependent structural and functional changes encompass neuroplasticity, neuroprotection and neurorestoration, effects on neurotransmission, neurogenesis, angiogenesis, exercise-induced effects on neuroinflammation, and exercise-induced increased synthesis of endogenous
neurotrophic factors. Specific exercise-induced effects include down regulation of striatal dopamine transporter and vesicular monoamine transporter (DAT & VMAT2; DAT is a primary mechanism for the clearance of dopamine from the extracellular space. Moreover, both DAT and VMAT2 are reliable markers for the integrity of striatal dopaminergic terminals, and amount of DAT correlates with serum BDNF levels in human PD [4, 9-14].

While animal models of exercise and PD have pushed the field forward, few studies have addressed exercise-induced neuroplasticity in human PD. As a first step toward promoting greater international collaboration on exercise-induced neuroplasticity in human PD, we present select studies on physical exercise effects on brain structure or function in human PD. We describe key exercise-induced neuroplasticity mechanisms in PD derived from these studies. Studies on exercise-induced changes in human PD brain are listed in Table 1 and described in the following section.

2. Physical exercise induced corticomotor and volumetric changes

In 2008, Beth Fisher at the University of Southern California demonstrated effects of high-intensity treadmill training on corticomotor excitability (low excitability is a marker for PD severity) [15]. They found increased corticomotor excitability and improvements in self-selected walking speed and several standardized gait parameters with high-intensity treadmill training [15]. In 2013, Fisher and colleagues conducted a small pilot randomized controlled trial to examine dopaminergic D2 receptor binding potential among four adults with early stage PD using continuous treadmill walking [16]. Using PET imaging, they reported an increase in dopamine D2 receptor density within the regional boundaries of the dorsal striatum (putamen) among the experimental group and no change or decrease (23%) in dopamine D2 receptor density in the PD controls. This may be important, as D2 receptors are inhibitory and their activation is associated with medium spiny neurons in the striatum, and, D2 receptors are an important source of corticostriatal glutaminergic input modulation.
Interestingly, Fisher demonstrated walking on a motorized treadmill transferred to improved kinematics on a secondary, untrained postural task [16]. During this task the PD participants improved their performance of walking at a self-selected pace, turning 90 degrees, and walking in a new direction (a mobility marker for PD axial rigidity) [16]. This is clinically relevant new information as prior studies reported a cardinal feature of PD is lack of carry-over from one learned task (e.g., treadmill walking) to another context (e.g., turning). It is conceivable that higher exercise intensities, which are untypical for physical therapy interventions with older deconditioned adults with PD, is necessary to trigger D2 changes before practiced tasks generalize to new environments.

Training confers rapid changes in brain grey matter volume in PD. In 2014 Berhard Sehm at Leipzig University, Germany, found time dependent changes in gray matter (GM) volume within six 45 minute balance training sessions in structurally connected lateralized parietal-basal ganglia circuitry networks including an increase in left inferior parietal cortex (IPC) after 2 training sessions, and a decrease in IPC GM volume after 4 training sessions, and a GM increase in right lingual gyrus after 4 training session [17]. Additionally, training activated the right cerebellum and there were no significant changes in GM volume during follow-up. Among the PD participants, these data associated with training-induced changes in the right anterior precuneus, left ventral pre-motor cortex, bilateral anterior cingulate cortex, left middle temporal gyrus, and the left inferior parietal cortex. For the healthy controls the only area that correlated with training-induced changes was the left hippocampus [17]. These training-induced changes are clinically relevant to PD because deficits in parietal-basal ganglia circuitry are associated with performance problems during dual-task interference and set-shifting behaviors beginning at PD diagnosis. Additionally, volumetric changes in PD brain and a 5.5 point decrease in the UPDRS motor score were shown with an 8 week mindfulness meditation based intervention conducted by Barbara Pickut and colleagues, University of Antwerp [26]. Therefore it is
encouraging that these brain areas remain changeable in early to mid stage PD with relatively few training bouts.

3. Neurotrophins

Serum levels of neurotrophins such as glia cell line-derived neurotrophic factor (GDNF), and brain derived neurotrophic factors (BDNFs) regulate survival and activity of dopaminergic neurons. They are “powerful inhibitors of apoptosis-mediated neuronal death and neurotoxin-induced degeneration of dopaminergic neurons”, suggesting their potential use in neuroprotective physical exercise interventions in PD [18].

In animal models of exercise and PD, continuous treadmill running upregulates messenger ribonucleic acid (mRNA), striatal glia cell line-derived neurotrophic factor (GDNF) and production of GDNF producing cells (via glia); increases BDNF in the substantia nigra pars compacta and caudate putamen and prevents down regulation of the BDNF signaling pathway in the substantia nigra and striatum [10, 12, 13].

In human PD, two cross sectional studies of neurotrophic levels found reduced levels of GDNF. Serum levels of BDNF correlate with PD disease duration (r=0.52, P<0.0001, disease duration=7.6 years [19, 20]. This discovery led Jerzy Zoladz and colleagues of the Physiology and Biochemistry workgroup, Cracow University, Poland, to conduct an 8 week intermittent aerobic bicycle training study to evaluate whether cycling could increase serum BDNF levels [21]. The twelve participants with PD (Hoehn and Yahr stage 1 to 3, 2-16 years disease duration) cycled in 5 minute bouts for 40 minutes at a cadence that was set at 30% faster than their self-selected pedaling rate. Thus, the researchers employed a design that is clinically highly relevant to PD rehabilitation – the forced-limb use paradigm, and examined whether forced use increases BDNF levels. In their experiment, Zoladz and colleagues assessed serum BDNF levels, serum tumor necrosis factor-α levels and basal serum soluble vascular adhesion molecule 1 (TNF-α & VCAMs, are valid immunological markers for severity of non-motor
features in PD and critical for microglia and astroglia activation). They found exercise-induced basal serum BDNF levels were increased post exercise (34%, \( P=0.03 \)), and decreased post-exercise basal sVCAM1 and TNF-\( \alpha \) (\( P=0.001 \), and \( P=0.03 \) respectively) [21]. In addition, exercise decreased the total score on the Unified Parkinson’s Disease Rating Scale (UPDRS pre training=48.9±4.3, UPDRS post training=38.1±3.9, \( P=0.01 \)). Thus, an intermittent exercise regime, typically administered by physical therapists to treat deconditioning, resulted in increased BDNF, improved inflammatory marker expression and less overall functional impairment.

In a follow-up study, Jaroslaw Marusiak and colleagues examined the effect of interval exercise on a stationary cycle ergometer on BDNF levels and rigidity among 11 adults with mild to moderate severity PD and 11 healthy controls [22]. They found exercise increased the level of BDNF (\( p=0.035 \)), and decrease in rigidity (UPDRS, \( P=0.048 \)), myometric muscle stiffness (biceps brachii, \( P=0.030 \)) and tremor frequency (\( P=0.006 \)). Increased BDNF levels correlated with improvements in PD rigidity, muscle stiffness and frequency (\( P\leq0.05 \)) [22].

Giuseppe Frazzitta from the Moriggia-Pelascini Hospital, Italy, employed a pragmatic randomized controlled single blind parallel group design to assess effects of a multi-modal rehabilitation intervention among 10 inpatients with early stage PD who were all being treated with rasagiline monotherapy for the duration of the trial [23]. This study is clinically relevant to PD because the intervention was conducted on a clinical ward and not in an isolated laboratory and consisted of physical therapy exercises that most patients with early stage PD would likely receive during inpatient hospital physical therapy. The primary outcomes were serum BDNF concentration and UPDRS-III score. A particular strength of this study was the use of a masked assessor, who administered the UPDRS and the secondary outcomes, previously validated for use in PD: the berg balance scale and a timed performance based outcome measure of physical fitness in PD, the 6-minute walk test. The study found a 14% (\( P=0.017 \)) increase in BDNF serum levels among the intervention group after 10 days of treatment, and BDNF levels
remained elevated until discharge [23]. There was no change in BDNF levels in the control group. All secondary outcomes improved in the intervention but not the control group (P≤0.01). There was no statistical relation between the balance or physical fitness measures and BDNF serum levels [23].

Finally, studies have only just begun to examine whether BDNF levels change with cognitive interventions in PD. Recently an Italian study led by Francesco Angelucci employed a parallel group, double-blind randomized design to evaluate effects of cognitive training on executive functioning and BDNF levels among 15 adults with mild cognitive impairment secondary to PD [24]. Post-tests of serum BDNF levels and scores on the Zoo Map Test of the Behavioral Assessment of the Dysexecutive Syndrome battery, a valid measure of planning ability as part of executive function, revealed increased BDNF serum levels in the experimental group (P=<0.05) but not in the controls [24]. Similar to the results of the study by Frazzitta [23], there was no association between BDNF level change scores and change scores on the standardized cognitive tests [24].

Taken together, the studies highlighted in table 1 suggest that physiologic use of exercise can be an important component of neuroplastic changes in human PD brain and supports our hypothesis that self-produced activity is important in slowing, halting or reversing human PD. The studies have several limitations, including, selection bias, modest sample sizes, use of quasi-experimental designs, and enrollment of participants in the early PD stage. Enrolling participants early in the disease is logical as younger PD age has been associated with greater physiologic reserve, enhanced tolerability for high intensity exercise, and lower risk for adverse events. Possibly failure to detect correlations among BDNF levels and the PD functional outcome measures in several studies could indicate limitations in the data itself or may indicate a very minimal relation among those with early PD. Research with larger sample sizes and at all stages of the disease is warranted.
4. Future Directions

Neurotrophins such as BDNF could prove to become useful markers for PD-related neuroplasticity or exercise-induced health outcomes. However, much work remains until this promise comes true.

Another issue is to determine the association between BDNF and physical activity levels as well as relationships with pharmacologic interventions or de novo patients. Parkinson’s disease is characterized by low levels of physical activity (PA), however, neuroplasticity studies have not addressed PA levels. Perhaps this is because few studies have reported on PA levels in PD and even fewer have investigated increasing the weekly amount of PA in PD. Therefore, it remains unclear whether neurotrophin levels are a function of physical activity or physical inactivity in PD.

BDNF levels may vary with air quality. This presents a further challenge, as a recent study in healthy adults demonstrated that serum BDNF levels were lower during traffic related cycling than in controlled indoor environments (e.g., air filtered room) [27]. Bicycling confers promising neuroplasticity benefits in PD. Air quality varies significantly regionally and within and between countries and continents (http://aqicn.org/map/world/). In countries with unusually high atmospheric air pollutants (e.g., China, with one of the largest PD populations in the world) increased risk of adverse health conditions during outdoor exercise would include lack of BDNF enhancing effects on PD brain plasticity.

Finally, recent evidence indicates a possible role for exercise-training induced modifications in human DNA methylation among genes and molecular pathways associated with human PD brain, including exercise-induced positive regulation of neurogenesis, and exercise-induced reprogrammed synaptic neurotransmission [28]. While modifications in human DNA methylation via aerobic exercise training have been found in healthy young adult humans [28], the hypothesis that exercise modifies genes and molecular pathways in PD offers an interesting opportunity for future research in the field of exercise-induced neuroplasticity in human PD.
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References


increases BDNF serum levels in parkinsonian patients: A randomized study.


Table 1. Intervention-induced neuroplasticity in human PD

<table>
<thead>
<tr>
<th>Plasticity marker</th>
<th>PD n</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in maximal corticomotor excitability and improved gait parameters\textsuperscript{a}</td>
<td>30</td>
<td>15</td>
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<tr>
<td>Weakening of the overactive indirect striatal pathway DA-D2R expression\textsuperscript{b}</td>
<td>4</td>
<td>16</td>
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<tr>
<td>Change in gray matter volume\textsuperscript{c}</td>
<td>47</td>
<td>17, 26</td>
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<tr>
<td>Increase in BDNF level\textsuperscript{d}</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Increase in BDNF level and decreased rigidity\textsuperscript{e}</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Increase in BDNF level\textsuperscript{f}</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Increase in BDNF level\textsuperscript{g}</td>
<td>15</td>
<td>24</td>
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Table note: PD, Parkinson’s disease; DA, dopamine; D2R, Dopamine class 2; receptor; BDNF, serum brain derived neurotrophic factor; n=number of PD participants enrolled.

\textsuperscript{a} – 24 training sessions of continuous walking on a motorized treadmill with or without use of a partial body weight support harness, with an exercise prescription goal of reaching 3.0 metabolic equivalent of task (MET) and/or 75% of the age adjusted maximum heart rate for each training session lasting up to 45 minutes in duration.

\textsuperscript{b} - 24 training sessions of progressive treadmill running starting at 75% of age–adjusted maximum heart rate for up to 45 minutes duration over 2 months. Intervention was via motorized treadmill training with 2 PD participants harnessed without body unweighing. Harness was worn for safety. Participants with PD were ambulatory without assistive devices, within 1 year of diagnosis, verbally encouraged by physical therapists exercise leader to run at a pace faster than they self-selected.

\textsuperscript{c} – 6 training sessions of balance exercises over 6 consecutive weeks (1 session per week with each session lasting 45 minutes). Participants were tested before the intervention (pre-test) and after 2 and 4 weeks (post-test). In addition, follow-up tests were conducted 1 week and 5 months after administering the post-test to 20 participants with PD and 16 healthy controls matched for age and gender [17]. Eight weeks of mindfulness meditation based intervention [26].

\textsuperscript{d} - 24 training sessions of intermittent cycling on a stationary ergometer at 60-75% of age-adjusted maximum heart rate for 60 minutes per session over 2 months.

\textsuperscript{e} – 24 training sessions of intermittent cycling. 60 minute long training session, 3 times per week for 8 weeks. Eleven PD participants with mild to moderate PD (Hoehn and Yahr scale=2.3±0.72).

\textsuperscript{f} – 80 physiotherapy and exercise training sessions as follows: 3 times 60 minute physical-and occupational therapy sessions per day on 5 days per week for 4 weeks duration including: aerobic exercise, stretching, balance training, and gait training using a computerized platform. Thirty minutes of treadmill walking at ≤60% heart rate reserve at a maximum treadmill speed of 3.5 km/h, 20 treadmill walking sessions over 4 weeks.

\textsuperscript{g} -12 cognitive treatment sessions in 4 weeks (3 per week) with each session lasting 45 minutes with a focus on shifting ability [25].
Conflicts of interest: None