HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Mov Disord. 2016 January ; 31(1): 23–38. doi:10.1002/mds.26484.

The Therapeutic Potential of Exercise to Improve Mood, Cognition, and Sleep in Parkinson's Disease

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Abstract

In addition to the classic motor symptoms, Parkinson's disease (PD) is associated with a variety of non-motor symptoms that significantly reduce quality of life, even in the early stages of the disease. There is an urgent need to develop evidence-based treatments for these symptoms, which include mood disturbances, cognitive dysfunction, and sleep disruption. We focus here on exercise interventions, which have been used to improve mood, cognition, and sleep in healthy older adults and clinical populations, but to date have primarily targeted motor symptoms in PD. We synthesize the existing literature on the benefits of aerobic exercise and strength training on mood, sleep, and cognition as demonstrated in healthy older adults and adults with PD, and suggest that these types of exercise offer a feasible and promising adjunct treatment for mood, cognition, and sleep difficulties in PD. Across stages of the disease, exercise interventions represent a treatment strategy with the unique ability to improve a range of non-motor symptoms while also alleviating the classic motor symptoms of the disease. Future research in PD should include non-motor outcomes in exercise trials with the goal of developing evidence-based exercise interventions as a safe, broad-spectrum treatment approach to improve mood, cognition, and sleep for individuals with PD.

Keywords

Parkinson's disease; exercise; mood; cognition; sleep

Although traditionally conceptualized as a motor disorder, Parkinson's disease (PD) is also associated with a variety of non-motor symptoms. These symptoms – including disturbances

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Relevant conflicts of interest/financial disclosures: Nothing to report.

Author Roles:
GOR: Design and conceptualization of the manuscript; literature search and review; writing of first draft; review and critique of subsequent drafts.
MWO: Review and critique of manuscript.
TDE: Review and critique of manuscript.
ACG: Review and critique of manuscript.

of mood, cognition, and sleep – substantially reduce quality of life, often to a greater extent than the motor symptoms.[1–4] Also of note, traditional dopaminergic treatments for PD may exacerbate or contribute, at least in part, to mood, cognitive, and especially sleep symptoms in this population.[5] In this article, we present the evidence supporting aerobic exercise and strength training as promising broad-spectrum interventions for these specific non-motor symptoms in PD, beyond the well-established benefits for core motor symptoms. To date, most exercise programs in PD have focused on improving physical function, including gait, mobility, and balance, and on targeting disease-specific physical impairments, such as bradykinesia, rigidity, and strength.[6–8] In general, exercise, including aerobic and resistance training, improves physical function and motor symptoms in PD.[9–19] Given these benefits to core symptoms, exercise has a potential to be one of those rare adjunct interventions to treat principal non-motor symptoms of PD without worsening the primary motor disorder.

In this manuscript, we review the efficacy of aerobic and strengthening exercise interventions in PD relative to more conventional treatments of mood, cognition, and sleep. The following electronic databases were searched: PubMed (1990 to July 6th 2015), Google Scholar (1990 to July 6th 2015), and Cochrane Library (1990 to July 6th 2015); citation tracking was also used to identify relevant references. Specifically, we included studies if they met the following criteria: 1) at least one target population was adults with PD; 2) aerobic exercise and/or resistance exercise was used in at least one of the exercise conditions; 3) at least one outcome measure was included to examine mood (depression or anxiety), cognition, or sleep; 4) the paper was available in English as of July 6, 2015. To inform these findings, we also discuss the relevant literature on aerobic and resistance exercise in healthy older adults, as well as neurologic populations. Although many forms of exercise may be beneficial, we limited our review to studies that included aerobic and/or strengthening exercise, as the evidence in these areas is more developed in healthy older adults and in persons with PD from both a clinical and mechanistic perspective. Also of note, additional non-motor symptoms manifest in PD, including fatigue and autonomic, gastrointestinal, and sensory symptoms,[20] but the literature investigating the effects of exercise on these symptoms remains very limited; accordingly, the present article focuses on the potential benefits of exercise interventions on mood, cognition and sleep only.

Treatment of Mood Symptoms in PD

Mood disturbance (here referring to depression and anxiety) develops in many individuals with PD, even in the early stages of the disease,[21] contributing to poorer quality of life[1,2,22] and caregiver burden.[23] Major depression is estimated to occur in 20–40% of individuals with PD,[24,25] and clinically significant anxiety in approximately 40%[26–28] (prevalence of psychiatric symptoms in PD reviewed in [22]). Depression in PD is associated with poorer emotional well-being, communication, and activities of daily living,[29,30] as well as increased disability, falls, and caregiver distress, with some research indicating that depression may predict 10-year mortality.[31–33] Despite these high prevalence rates and associated distress and disability, clinical management of many non-motor symptoms, including depression and anxiety, remains inadequate.[34]

Anxiety is common but less studied and treated in PD than depression.[34–37] In addition to generalized anxiety disorder, panic disorder, and simple and social phobias, individuals with PD also report recurrent situational anxiety related to their motor symptoms, including fear of falling or fear of crowded places due to freezing of gait.[27,28] Anxiety is associated with reduced quality of life in PD,[38–40] even after controlling for the effects of motor symptoms,[3,41] and to a greater extent than depression.[2]

The high prevalence, early manifestation, and negative impact of anxiety and depression in PD dictate the need to manage and improve these symptoms, which are under-treated and understudied.[42–46] To date, antidepressants have generally yielded non-significant and variable effects for both depression[46,47] and anxiety[46] in PD. Some controlled studies suggest that certain selective serotonin reuptake inhibitors, dual reuptake inhibitors, and dopamine agonists may improve depression in PD, albeit with some risk of treatment-related side effects (e.g. fatigue, dry mouth, orthostatic hypotension, dyskinesia).[48–50] Benzodiazepines are not recommended for the treatment of anxiety in PD due to potential side effects, including autonomic, cognitive, sleep, and psychomotor impairments.[22,51,52] There is emerging evidence for psychosocial alternatives to pharmacologic treatment of mood, with limited but promising data from cognitive behavioral therapy (CBT).[46,53–60]

The Potential of Exercise Interventions for Mood

Exercise interventions have demonstrated robust efficacy in the treatment of mood symptoms in the general population and in older adults, but few exercise trials in PD have included mood as an outcome measure. A meta-analysis of 11 randomized control trials (RCTs) with adults with major depression reported a large combined effect size for exercise, usually aerobic or resistance training, relative to non-active control conditions.[61] More recent meta-analyses confirm a significant acute effect of exercise on depression relative to non-exercising control groups,[62] with benefits generally following programs of at least moderate aerobic activity delivered several times a week, often in a group setting, with session durations of 20 to 45 minutes.[61] Although promising, these meta-analyses are not without limitations, such as restricted power due to the small number of included trials, as well as the selection bias of individuals who volunteer to participate in exercise research.[61,62] Despite this, the benefits of exercise are conferred across a wide range of settings and symptom severities. For example, Mota-Pereira and colleagues[63] found that aerobic exercise (30–45 minute sessions, 5 days/week) offered significant improvement or remission of depression in outpatients who had failed two previous trials of antidepressant medication (see also [64]). Aerobic exercise also has efficacy in combination with antidepressants or CBT.[65,66] Even in healthy adults without clinical depression, exercise interventions, including resistance exercise, have improved depressive symptoms.[67] In sum, exercise has been shown to reduce depression in the general population, suggesting that it may also benefit those with PD and depression, either as a stand-alone or adjunctive intervention to improve mood.

Besides its antidepressant effects, exercise is also anxiolytic.[68,69] Strong effects on self-reported anxiety were documented in a meta-analysis of primarily non-clinical samples[70] with further evidence from clinical trials for panic disorder, generalized anxiety disorder,

and social anxiety.[68] These clinical trials have focused largely on aerobic exercise (usually completed 2–5 times per week, for 5–12 weeks), often in small samples, with unstandardized or unsupervised exercise sessions and/or lacking a non-exercising control group; nevertheless, the results are encouraging and suggest that aerobic exercise, in particular, may effectively treat anxiety disorders, either as a stand-alone intervention or as an adjunct treatment in combination with pharmacotherapy or CBT.[68,71] More controlled studies are needed to determine the optimal exercise dose and modality required to achieve lasting anxiolytic effects.

Exercise has also been shown to improve mood in healthy older adults (e.g. [72]). For example, physical exercise, usually aerobic or resistance training completed 3 times per week for 20–60 minutes for 6–19 weeks, yielded positive short-term outcomes for depressive symptoms;[73,74] and compared to a non-exercising control group, aerobic (but not resistance) exercise was associated with reduced depressive symptoms, regardless of baseline level of depression.[75] Comparing an aerobic exercise program to pharmacological treatment, exercise (three 45-minute sessions/week) was equally effective at reducing depressive symptoms after 16 weeks of treatment, although the study did not control for the social interaction aspect of the exercise group.[76]

There is promising evidence that exercise may improve depression among adults with neurologic disorders,[77] but there remains limited research on the effects of aerobic and resistance exercise on mood in PD specifically. In a large RCT with 231 adults with PD, six months of strengthening exercises (40–60 minutes, 3 times/week) yielded improved positive affect relative to a usual-care control group.[18] In a second controlled trial, individuals with PD were randomized to either an early- or late-start group exercise program (combined cardiovascular and strength training, completed for 60 minutes, 3 days/week, for 24–48 weeks).[78] Participants in the early-start group reported significantly fewer depressive symptoms after 48 weeks, relative to the delayed start group, although there was no control for the potential effects of weekly social interaction on mood. In a comparative trial of three types of exercise (high-intensity treadmill training, lower-intensity treadmill training, and stretching/resistance training), no changes in depression were observed for any group after 3 months of exercise (30–50 minutes, 3 times per week), although participants reported only mild levels of depressive symptoms at baseline.[79] In a smaller study, aerobic exercise, completed twice per week for 12 weeks, improved mood, while maintaining functional ability, among 13 adults with early PD relative to non-exercising PD participants.[80] In a sample of 11 early- to mid-stage participants with PD, 5 participants (mean age=64.0) completed a 4-week general exercise program (60-minute sessions of combined aerobic and resistance training, 4 times/week), and 6 participants (mean age=62.8) completed an exercise-based behavioral treatment focused on increasing amplitude of movement.[81] Although there were no between group differences, the combined group showed improvement in depression and fatigue at all post-intervention assessments (weeks 4, 12, 24), suggesting benefits of both exercise approaches. In an uncontrolled trial, 49 individuals with PD (mean age=65.5) reported reduced depressive symptoms after six months of aerobic walking (3 times/week for 45 minutes per session), although depressive symptoms were very low among this sample.[82] In general, the PD exercise studies that have included mood outcomes have included participants with minimal depressive symptoms, limiting their

generalizability. Even so, these studies provide strong rationale for the targeted use of exercise to improve mood in PD.

Cognitive Impairment in PD

Like mood symptoms, cognitive impairments are common and heterogeneous in PD,[83–87] even in the early stages of the disease, with widespread implications for quality of life and functional abilities such as driving.[1,88–93] Cognitive disruptions can also co-occur with other non-motor symptoms, tending to be worse in PD with depression, for example.[94,95] Up to 57% of individuals with PD experience some cognitive impairment within the first 3–5 years after diagnosis,[96] including deficits in executive functioning, visuospatial function, and attention/working memory.[97–99] Measures of attention and executive function ("frontal" tests) are often the most sensitive to cognitive compromise.[100] Executive dysfunction often emerges early in the disease course and is thought to be associated with dopaminergic dysfunction in fronto-striatal regions, whereas memory impairment and visuoconstructional difficulties, along with cognitive decline and dementia, may be driven by cortical Lewy body pathology and cholinergic deficiency.[87,88,96,101,102,103] With cognitive impairment beginning in the early stages of PD,[88] there is a corresponding need for early cognitive-enhancement strategies.

The Potential of Exercise Interventions for Cognitive Enhancement

There is reliable evidence for significant benefits conferred upon cognition by exercise programs.[104,105] A meta-analysis of RCTs (29 studies, 2049 participants) has indicated that healthy older adults reliably achieve modest improvements in attention and processing speed, executive function, and memory following aerobic training.[105] The exercise trials ranged in duration from 6 weeks to 18 months, with modal length of 2.5 to 4 months, but with relatively minimal range of exercise intensity or frequency across trials (most often 3 times per week at 70% peak oxygen uptake (VO_2)). Exercise typically comprised brisk walking and/or jogging relative to wait-list control or other comparison conditions (stretching and toning, health education, or relaxation). Greater benefits to attention and processing speed arose from trials that combined aerobic exercise with strength training, relative to aerobic only interventions. Likewise, aerobic training has been reported to improve cognition in healthy older adults, especially for executive-control processes[106] – a finding particularly pertinent to the goal of improving executive dysfunction in PD.[97,100] There remains need for additional research to examine how aerobic exercise may affect various cognitive domains when maintained for extended periods of time (e.g. several years instead of months).[105]

Exercise may also improve general cognitive functioning and balance in older-adult neurological populations, including those with mild cognitive impairment, as well as Alzheimer's disease (AD) and other dementia-causing disorders.[107,108] This research is relevant to PD, given that cognitive impairment, including dementia, often emerges over the course of the disease[109–111] and that an AD-like pattern of brain atrophy in PD may predict cognitive decline.[112] There is preliminary evidence that aerobic exercise may be associated with greater memory improvements among adults with mild cognitive impairment relative to

cognitively intact adults.[105] In a large sample of adults (≥ 50 years) with subjective memory impairment, a six-month exercise program (at least three 50-minute sessions of moderate-intensity aerobic exercise per week) yielded modest improvements on brief cognitive tests of memory, language, and praxis (Alzheimer Disease Assessment Scale – ADAS-Cog) over an 18-month follow-up period; participants in the exercise group also improved on word list delayed recall.[113] It is important to note that the primary outcome measure in this study was a non-specific measure of overall cognitive function, rather than an index of a specific cognitive domain. Relative to a non-active control group, elderly individuals with AD (mean age=78.3) demonstrated improved balance and executive functioning (Clock Drawing Test and Frontal Assessment Battery) following dual-task exercise that paired motor and cognitive tasks (60-minute sessions completed 3 times/week for 4 months).[114] Aerobic training has also been reported to improve visual learning, working memory, and processing speed in psychiatric populations, including depression.[115] In sum, exercise has demonstrated cognitive benefits in healthy older adults and in adults with conditions that may be observed in PD (e.g. depression and dementia), supporting the potential cognition-enhancing role of exercise for PD.

There is initial evidence that these expectations will be realized in PD.[116,117] Aerobic exercise may particularly impact executive function in PD,[118] consistent with the findings in healthy older adults.[106] Twelve weeks of combined aerobic plus anabolic exercise, conducted twice weekly, resulted in selective improvement in frontal-based executive function (spatial working memory and verbal fluency, relative to spatial and pattern recognition memory) in 15 individuals with PD compared to 13 non-exercising PD control participants (all in mild to moderate disease stages and approximately 60 years old).[119] Likewise, in relatively large studies of a long duration, 6 months of moderate-intensity aerobic exercise, conducted three times per week for 45–60 minutes, led to improved executive functioning for individuals with mild to moderate PD (mean age of approximately 65 in both studies), though only one of these studies used a non-exercising PD control group.[82,120] Across these studies, moderate-intensity aerobic exercise, conducted 2–3 times per week, produced promising effects on executive function in the mild to moderate stages of PD, consistent with studies in healthy older adults.[106] In small preliminary case studies, 8 weeks of aerobic exercise, completed 3 times per week for 20–40 minutes, yielded improvements in executive function, verbal fluency, and working memory for three individuals with PD – one with high cognitive performance at baseline (age 66), and two with cognitive impairments (ages 61 and 72).[121,122] Further research is warranted to examine the underlying mechanisms driving these selective improvements, which may relate to increased cerebral perfusion, release of growth factors, or angiogenesis following aerobic exercise, as suggested by Tabak and colleagues.[121] Among healthy older adults, aerobic training, relative to non-aerobic, may even mitigate volume loss in prefrontal regions,[123] which are associated with a variety of executive control processes. Of note, both prefrontal atrophy and executive dysfunction occur in PD, even in the early stages of the disease.[97,124]

At the same time, recent evidence suggests that resistance exercise may also benefit cognition in PD. After 24 months of twice weekly progressive resistance exercise (60–90 minutes per session), adults with PD improved their performance on measures of working memory, inhibition, and attention (Digit Span, Stroop, Brief Test of Attention).[125] The

comparison group completed stretching, balance, and non-progressive strengthening exercises (of the same duration and frequency) and improved on Digit Span and Stroop after 24 months.[125] There were no between-group differences on any of the cognitive measures at 12 or 24 months, and the authors noted that their sample was relatively young, highly educated, and in mild-to moderate disease stages, thereby limiting the generalizability of their findings.[125] Even so, these results provide clear rationale for future research to examine the targeted use of resistance exercise to improve cognition in PD. Taken together, emerging research suggests that aerobic and resistance exercise may improve cognition in PD; however, there remains a need for larger, well-controlled studies on the cognitive effects of exercise interventions among adults with PD.

Sleep Disruption in PD

In the general population, the prevalence of insomnia symptoms ranges from 25% to 48% and insomnia diagnoses from 4.4% to 9.5%.[126–129] Sleep disruptions are common among older adults[130] and are particularly problematic and multifactorial in PD,[40,131,132] with reference to this problem dating back to James Parkinson's observations in his original essay.[133] Fragmented sleep has been reported,[134–139] attributed in part to nighttime motor symptoms,[140,141] with reports of sleep benefits upon control of these symptoms.[142,143] Individuals with PD may present with REM sleep behavior disorder, excessive daytime sleepiness, sleep onset and sleep maintenance insomnia, as well as sleep disordered breathing, restless leg syndrome, and nocturia.[132,144] Furthermore, sleep disturbances in PD are linked to mood and cognitive dysfunction,[145–147] likely related to neurodegenerative changes. The underlying disease pathology in PD is now thought to begin in the brainstem,[148] where damage to specific nuclei (e.g., locus ceruleus, pedunculopontine nucleus) and neurotransmitters (e.g., norepinephrine, serotonin, dopamine, GABA, acetylcholine) likely affects sleep-wake and REM sleep modulation in PD years prior to the manifestation of motor symptoms.[132,140,144,149] Given the magnitude of the impact of sleep disruption on quality of life in PD,[1,150] there is need to address general, age-related, and disease-specific sleep disruptions in those with PD.

The Potential of Exercise Interventions for Sleep Disruption

Meta-analytic review of 25 studies indicates that regular exercise programs help adults achieve moderate-to-large sleep quality benefits, as per the self-reported Pittsburgh Sleep Quality Index (PSQI),[151] which includes subscales of daytime sleepiness as well as sleep disturbance, duration, efficiency, latency, and medication use.[152] The moderate-to-large effects of regular exercise were observed for all PSQI subscales except sleep medication use. Across aerobic, anaerobic, and mixed studies, regular exercise had small effects on total sleep time and sleep efficiency and a small-to-moderate effect on sleep onset latency, predominantly assessed using objective measures (e.g. electroencephalogram or polysomnography).[152] These benefits appear to be uniform across younger and older samples except for weaker effects on sleep-onset latency in older adults, consistent with its general worsening with age.[127] Even individual sessions of exercise, evaluated across 41 studies (predominantly aerobic training), conferred benefit on objective measures of sleep, though with small effect sizes that varied in reliability.[152] Moderate-intensity aerobic

exercise (30- to 40-minute sessions, completed four times per week, for 16 weeks) yielded improvements in self-reported sleep quality (global PSQI score) among healthy older adults (ages 50–76) with sleep complaints, relative to wait-list control participants.[153]

There is some indication that the benefits of exercise for sleep extend to individuals with PD, including improved sleep, quality of life, and daily functioning.[154,155] In an RCT (with stratified randomization), 17 PD participants in mild to moderate stages (mean age=67.8) who completed six months of multimodal exercise (three 60-minute sessions per week of muscular resistance, balance/motor coordination, and aerobic fitness) reported enhanced sleep and functional abilities on standardized questionnaires compared to 17 PD control participants who did not exercise.[155] The sleep questionnaire (Mini-Sleep Questionnaire) included items related to both insomnia and daytime sleepiness. Only the total score was used for data analysis, so it is not possible to determine if exercise more strongly affected insomnia or daytime sleepiness. Likewise, after 36 group sessions of combined aerobic conditioning and muscular strengthening (75 minutes each, 3 times per week, for 3 months), twenty mild- to moderate- stage PD participants (mean age=61.5) reported significant improvements in quality of life, particularly within the domains of emotional reactions, social interactions, and physical ability, as well as reporting a trend toward improved sleep on a self-report questionnaire.[154] A significant limitation of both PD studies was the lack of objective sleep measures. Further research is needed to elucidate potential effects of exercise on daytime and nighttime sleep disturbances, including larger, well-controlled trials that include subjective and objective sleep outcome measures.

Potential Mechanisms of Action of Exercise on Mood, Cognition, and Sleep

Dopaminergic dysfunction in the hypothalamus and limbic regions may be associated with disturbances of mood, cognition, and sleep in PD.[156–159] It is plausible then that exercise may improve these non-motor symptoms at least partially via dopaminergic mechanisms. More specifically, exercise may modulate dopaminergic and glutamatergic neurotransmission, and thereby attenuate basal ganglia hyperexcitability in PD.[160,161] Among exercising rats (n=10) relative to sedentary counterparts (n=9), aerobic exercise (6 weeks of wheel running) has been associated with increased dopamine synthesis and reduced inhibition of dopamine neurons in the substantia nigra pars compacta.[162] Preliminary evidence in humans suggests that aerobic exercise (three 60-minute treadmill sessions/week for 8 weeks) may lead to increased dopaminergic signaling (per imaging with positron emission tomography) and improved postural control in the early stages of PD.[163] Although non-motor outcomes were not included in this pilot study, the reported improvements in postural control are potentially relevant for non-motor symptoms given that common neural substrates may modulate balance control and anxiety (e.g. parabrachial nucleus network and associated connections to limbic regions).[156,164,165]

Besides its dopaminergic effects, regular exercise also has a wide variety of effects on non-dopaminergic neurotransmitter systems, including serotonergic, noradrenergic, and GABA-ergic systems, which is relevant for depression, anxiety, and sleep.[166,167] In rats that swam (n=18) 5 days a week for 10 weeks (typically 30 minutes per day), exercise was associated with increased hippocampal levels of serotonin and norepinephrine[168] – two

neurotransmitters that have been implicated in modulation of anxiety, depression, and sleep.[156,169–171] In regard to the potential for improved cognition,[172] animal work indicates that serotonin is necessary in order to achieve exercise-induced neurogenesis in the hippocampus (n=30 per group).[173] In human research, aerobic exercise (three 30-minute cycling sessions per week, for 7 weeks) has been associated with reduced depression and reduced blood serotonin, relative to a stretching-control group.[174] This effect is similar to effects of selective serotonin reuptake inhibitors, although the sample consisted of healthy undergraduate students who were not pre-screened for anxiety or depression, which limits its generalizability. These findings suggest that aerobic exercise may increase levels of serotonin and norepinephrine in the brain, which may positively affect mood, cognition, and sleep. For example, cognitive dysfunction and sleep disturbances (e.g. insomnia, vivid dreaming, and sleep-disordered breathing) in PD are generally unresponsive to dopamine therapy,[175] suggesting that these symptoms may develop, at least in part, through non-dopaminergic mechanisms. Likewise, anxiety in PD is associated with dysfunction in a variety of neurotransmitter systems, including noradrenergic and serotonergic, which may precede dopaminergic depletion.[156] Aerobic exercise, then, could act upon these non-dopaminergic systems to improve non-motor symptoms, particularly in the early stages of PD.

The mechanisms by which exercise may affect non-motor symptoms, especially cognition, in PD may be similar to structural and functional brain changes and proliferation of growth factors seen in exercising healthy adults. Higher aerobic fitness in healthy older adults (mean age=66.6) has been associated with greater gray matter volume in dorsolateral prefrontal cortex and improved executive function (Stroop test of inhibition) and spatial working memory.[176] The association with prefrontal volume is relevant to PD as affected individuals may show prefrontal and hippocampal atrophy even in early stages of the disease.[124] Imaging with positron emission tomography has also revealed that prefrontal dysfunction in PD (hypometabolism) contributes to difficulties with set-shifting.[177] Following a one-year walking intervention (three 40-minute sessions per week), aerobic fitness in older adults was associated with white matter changes in frontal and temporal regions, as well as improved short-term memory relative to an active control group (flexibility, toning, and balance).[178] Also following one year of aerobic exercise, increased functional connectivity in the temporal lobe among healthy older adults (mean age=66.4) was associated with increased levels of growth factors, including brain-derived neurotrophic factor (BDNF), as well as insulin-like growth factor type 1, and vascular endothelial growth factor.[179] Consistent with these findings, regular aerobic exercise in healthy older adults is thought to promote neuroplasticity and facilitate learning and memory through the release of neurotrophins, including BDNF, glia-derived neurotrophin (GDNF), nerve growth factor (NGF), and galanin.[106,180] In PD, aerobic exercise may increase the production of growth factors and promote gray and white matter changes, especially in prefrontal regions, both of which may contribute to improved cognitive function.

Animal and cellular studies further highlight the important effects of BDNF on neurogenesis, dendritic growth, and long-term potentiation.[181–184] Meta-analytic review of 29 human studies (1111 participants) indicates that single sessions of exercise induce BDNF activity and that there is a significant increase in this activity with regular exercise.[185] These

effects appear reliable enough that Szuhany and colleagues[185] suggested that exercise can be considered as an intervention to induce BDNF for subsequent therapeutic benefit, although they note that future research is needed to examine the effects of exercise type (e.g. aerobic versus resistance training) on BDNF. Rodent and human studies indicate that BDNF may mediate both the mood and cognitive effects of exercise,[186–189] with a particular effect on executive function in older adults,[190] which is known to be compromised in PD.[97]

These mechanisms may relate to potential cognitive benefits of exercise in PD, given the known executive dysfunction and reduced BDNF expression in this population. Postmortem human studies and rodent studies indicate significantly reduced expression of BDNF in the substantia nigra in PD,[191–194] and surviving dopaminergic neurons in the substantia nigra express reduced BDNF compared to control cases.[192] In a 6-hydroxydopamine (6-OHDA) rat model of PD, exercise (4 weeks of treadmill running, 30 minutes/day, 5 days/week) has been found to increase levels of BDNF in the striatum.[195] In a recent human study of early-stage PD, 28 days of intensive aerobic exercise increased BDNF levels, improved motor symptoms (balance and gait),[196] and potentially slowed motor symptom progression after a two-year follow-up.[197] Indeed, drawing largely from animal studies, Fumagalli and colleagues[198] posited that BDNF may function as a neuroprotective molecule and also a neuromodulator in PD, such that it is associated with the loss of dopaminergic neurons when inhibited, and with improved cognition when expressed. Exercise may improve hippocampal function via BDNF expression,[199] and in non-PD rats (n=7 per group), BDNF expression has been associated with exercise-induced enhancement on learning and recall on the Morris water maze after one week of voluntary wheel running.[189] Though there are limitations related to translating results in animal models of PD to humans with PD,[200] animal work as well as emerging human research suggest that aerobic exercise may lead to improvements in cognition that may be mediated, at least in part, by increased production of BDNF.[201] In sum, the potential effects of exercise-induced BDNF on cognition in PD are particularly promising.

These findings suggest that exercise has potential neuroprotective and neurorestorative effects in PD, which may be associated with subsequent improvements in overall brain health, mood, and especially cognition,[118] though the majority of this evidence in PD comes from animal studies and small pilot studies. Other mechanisms may be active for the effects of exercise on sleep, and potentially include body temperature elevation (to promote slow wave sleep), increased cytokine levels, heart rate variability (and associated improvements in vagal modulation and parasympathetic control), as well as increased BDNF activity and associated changes in mood.[152,202,203] As sleep disruption is a core symptom of depression, and aerobic exercise improves depression, it is plausible that exercise may benefit sleep as a function of improved mood, or *vice versa*.[202,204] It may also be important to consider the potential effects of aerobic exercise on cholinergic function, as demonstrated in non-PD animal studies.[205] It is unknown whether these positive effects translate to persons with PD, but it warrants examination, given the association between cholinergic dysfunction and disturbances of sleep, mood, and cognition in PD.[132,149] Ultimately, sleep benefits from exercise may result from some of the same or alternative mechanisms as those that positively affect mood and cognition.

It is also important to consider potential mechanisms specific to resistance exercise in PD. Progressive resistance training in PD has yielded improvements in strength and motor symptoms, as well as cognition.[19,125] Future research should more closely examine the effects of resistance training on non-motor symptoms in PD, especially cognition, which may relate to reduced levels of homocysteine and/or increased levels of insulin-like growth factor I.[206] At the same time, resistance training may facilitate motor improvements via increased neural drive and central neural changes, such as cross-education and reduced agonist-antagonist coactivation.[207] These mechanisms may be relevant for PD given the reduced muscle activation observed in the disorder, which largely contributes to bradykinesia and muscle weakness.[206] Drawing from functional neuroimaging studies, resistance training may also promote functional neuroplasticity in the cortex and basal ganglia, although all of these potential mechanisms require further study in PD.[206] For a review of potential mechanisms of resistance exercise in PD, please see [206].

Exercise Dose and Adherence in PD

Public health guidelines recommend a minimum of 150 minutes of moderate-intensity aerobic exercise plus 2–3 sessions of strengthening exercises per week for adults aged 18–65,[208] but it is unknown whether this recommendation is also appropriate for individuals with PD. Optimal dosing of exercise in PD has not been determined. Current research efforts are beginning to examine this question, including an ongoing multi-site, randomized, controlled study designed to compare moderate-intensity to high-intensity aerobic training in PD.[209] Intensive rehabilitation strategies (three daily exercise sessions, 60 minutes each, 5 days per week, for 4 weeks) that include aerobic exercise (heart rate reserve ≤60%; maximum speed of treadmill scrolling=3.5 km/hour) revealed increased BDNF levels and improved motor symptoms in the early stages of PD, suggesting the benefits of higher intensity exercise[196] as well as potential benefits in cognition via BDNF. Other exercise trials in PD, however, reveal equivalent benefits related to physical function for both low (50 minutes at 40%-50% of heart rate reserve) and high (30 minutes at 70%-80% of heart rate reserve) intensity of aerobic exercise conducted 3 times a week for 3 months.[79] In studies examining the benefits of strength training, high-intensity resistance programs have been shown to be safe and efficacious and associated with greater improvements in quality of life relative to active control groups.[8,210,211] A progressive resistance training program (at least 5% increase in resistance as participants were able) was found to be more effective in improving motor symptoms than a strengthening program that was not progressive (no systematic increase in load), suggesting greater benefits of a high dosing,[8] although both programs produced improvements in cognition after 24 months.[125] The only other non-motor outcome included in these studies was quality of life, which may capture secondary effects on mood, but otherwise, the effects of exercise intensity on mood and sleep in PD remain largely unknown and warrant further study.[212]

Generally speaking, adherence to exercise programs among adults with PD is relatively high (often >80%) in the context of research where there is typically a great deal of emphasis on promoting adherence.[213] Likewise, across exercise trials in PD, retention rates are largely above 80%, with studies typically conducted in clinic and lasting 8 weeks on average, though some studies have reported similar retention rates for trials of a longer duration (up

to two years).[8,79,213] Persons with PD tolerate exercise programs quite well with relatively low dropout rates (~10–20%) and minimal adverse effects.[8,18,78,79,82,213,214] The majority of adverse events tend to consist of relatively mild musculoskeletal issues that resolve relatively quickly and do not require medical attention or restrict activities.[18,82,214] This minimal-risk profile compares favorably to medications for non-motor symptoms in PD,[215] and provides further support for the use of exercise to simultaneously improve multiple motor and non-motor symptoms. At the same time, it should be noted that the largely supervised, in-clinic nature of current exercise studies in PD may limit generalizability of these findings to motivated research participants who have access to a highly structured research setting. Further research is warranted to better examine the longevity of effects and to effectively tailor the content, dose, and delivery of exercise programs to individuals at various stages of PD.

Treatment Stage and Exercise Intervention

Exercise has been shown to be beneficial to individuals with PD across Hoehn & Yahr stages I-IV, with most trials focusing on stages II and III.[6,12,216–218] At the same time, the potential neuroprotective and neurorestorative effects of exercise[118] underscore its importance early in the course of the disease.[219] Non-motor symptoms of PD, including disturbances in sleep and mood, can emerge years before the motor symptoms.[136,220,221] In particular, individuals in the early stages may present with depression or anxiety that may be more distressing or interfering than the motor symptoms.[222] Accordingly, exercise programs are particularly well suited to early implementation in PD with the potential for diffuse non-motor benefits (e.g. mood, sleep, cognition) and few side effects or adverse events. By implementing exercise interventions to improve depression, for example, in the early stages of PD, we can hope to also affect associated comorbidities, such as anxiety, memory difficulties, and sleep disruption[223] and subsequently improve daily functioning and quality of life (e.g. [224]). Of note, sufficient dopamine replenishment, most often with carbidopa/levodopa, may be necessary to facilitate adherence and motivation for regular exercise and to avoid the formation of sedentary habits among individuals with PD.[201,225] The majority of exercise trials in PD have been conducted with participants on appropriate dosages of dopaminergic medication, and the combined effect of dopaminergic medication plus exercise in PD has yielded greater physical benefits relative to medication or exercise alone.[226] These findings highlight the importance of dopamine replenishment to enhance motor functioning and allow adults with PD to exercise at sufficient doses and intensities. In sum, for as long as individuals with PD are able to safely engage in physical activity, exercise should be seriously considered as an intervention strategy with the potential for widespread benefits for both non-motor and motor symptoms.

Conclusion

The conceptualization of PD has shifted from that of a pure motor disorder, with a burgeoning research effort in the domain of non-motor symptoms.[4,36] There is as yet limited research on the management of mood, cognitive, and sleep symptoms in PD,[34] with these symptoms often being comorbid.[227] As we expand our understanding of the etiology and manifestation of the non-motor symptoms, a shift in attention to identifying and prescribing

effective treatment is warranted. If these symptoms do share underlying pathologies, it is possible that a single treatment may yield multi-faceted symptom improvement.

Aerobic and resistance exercise, in particular, offer especially promising treatment strategies for alleviating a spectrum of PD symptoms, including motor function, mood, cognition, and sleep. It is important to emphasize that exercise programs have generally been well tolerated in PD with few adverse events,[12,216,228,229] attenuating concerns about the ability of individuals with PD to successfully complete prescribed exercise due to motor limitations.

In conclusion, exercise presents a particularly feasible treatment approach in PD with minimal side effects and the potential to yield broad-spectrum benefits related to mood, cognition, and sleep, particularly if implemented in the early stages of the disease. The known benefits of exercise in healthy older adults may very well translate to this population, driven by potentially overlapping mechanisms. As with the majority of PD studies, exercise research in PD has focused primarily on the motor symptoms and largely failed to consider its potential to improve non-motor symptoms. Future studies should include a variety of non-motor outcome measures to systematically examine the effects of exercise on these symptoms. With greater research and clinical attention devoted to the potential utility of exercise interventions in PD, we may meet the goal of simultaneously treating motor and non-motor symptoms, and ultimately optimize quality of life for persons living with this disorder.

Acknowledgements

None.

Financial disclosure/COI: This work was supported by the National Institute of Mental Health (F31MH102961 to G.O.R).

Full Financial Disclosures of all Authors for the Past Year:

Gretchen O. Reynolds:

F31MH102961 Reynolds (PI) 09/30/13-09/29/16 NIMH, “A Cognitive-Behavioral Intervention for Anxiety in Parkinson’s Disease”

Michael W. Otto:

“Enhancing Panic and Smoking Reduction Treatment with d-cycloserine” (R34 DA034658) Role: Co-PI

“Improving Therapeutic Learning in Depression: Proof of Concept” (R21MH102646) Role: PI

Terry D. Ellis:

RSS Industries Ellis (PI) April 2014 – March 2015 “Feasibility and Usability of the Theracycle in People with Parkinson disease: A Pilot Study”.

VA Health Services & Development IIR 11-342 Sparrow (PI) April 2013 – April 2017 “Telemedicine Intervention to Improve Physical Function in Persons with Parkinson Disease” Role: Co-Investigator

American Parkinson Disease Association Ellis (PI) 09/01/2013 – 08/31/2015 “Promoting Physical Activity in Persons with Parkinson Disease” Role: PI

Alice Cronin-Golomb:

American Parkinson's Disease Association 09/01/15-08/31/16 "Attentional and Exercise Interventions to Improve Non-Motor and Motor Symptoms of Parkinson's Disease" Role: PI

1I01RX001696 Sparrow (PI) 10/1/14-09/30/18 Veterans Administration "A Telemedicine Intervention to Improve Cognitive Function in Patients with Parkinson's Disease" Role: Investigator

References

1. Duncan GW, Khoo TK, Yarnall AJ, et al. Health-related quality of life in early Parkinson's disease: The impact of nonmotor symptoms. Mov Disord. 2014; 29:195–202. [PubMed: 24123307]
2. Hanna KK, Cronin-Golomb A. Impact of anxiety on quality of life in Parkinson's disease. Parkinsons Dis. 2012; 2012:640707. [PubMed: 22191074]
3. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Parkinsonism Relat Disord. 2008; 14:37–42. [PubMed: 17627863]
4. Cronin-Golomb A. Emergence of nonmotor symptoms as the focus of research and treatment of Parkinson's disease: introduction to the special section on nonmotor dysfunctions in Parkinson's disease. Behav Neurosci. 2013; 127:135–138. [PubMed: 23565933]
5. Park A, Stacy M. Non-motor symptoms in Parkinson's disease. J Neurol. 2009; 256(Suppl 3):293–298. [PubMed: 19711119]
6. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2008; 23:631–640. [PubMed: 18181210]
7. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. Cochrane Database Syst Rev. 2012; 7:CD002817. [PubMed: 22786482]
8. Corcos DM, Robichaud JA, David FJ, et al. A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. Mov Disord. 2013; 28:1230–1240. [PubMed: 23536417]
9. Allen NE, Sherrington C, Paul SS, Canning CG. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. Mov Disord. 2011; 26:1605–1615. [PubMed: 21674624]
10. Allen NE, Canning CG, Sherrington C, et al. The effects of an exercise program on fall risk factors in people with Parkinson's disease: a randomized controlled trial. Mov Disord. 2010; 25:1217–1225. [PubMed: 20629134]
11. Gobbi LT, Oliveira-Ferreira MD, Caetano MJ, et al. Exercise programs improve mobility and balance in people with Parkinson's disease. Parkinsonism Relat Disord. 2009; 15(Suppl 3):S49–S52. [PubMed: 20083007]
12. Li F, Harmer P, Fitzgerald K, et al. Tai chi and postural stability in patients with Parkinson's disease. N Engl J Med. 2012; 366:511–519. [PubMed: 22316445]
13. Goodwin VA, Richards SH, Henley W, Ewings P, Taylor AH, Campbell JL. An exercise intervention to prevent falls in people with Parkinson's disease: a pragmatic randomised controlled trial. J Neurol Neurosurg Psychiatry. 2011; 82:1232–1238. [PubMed: 21856692]
14. Mehrholz J, Friis R, Kugler J, Twork S, Storch A, Pohl M. Treadmill training for patients with Parkinson's disease. Cochrane Database Syst Rev. 2010; 1:CD007830. [PubMed: 20091652]
15. Grazina R, Massano J. Physical exercise and Parkinson's disease: influence on symptoms, disease course and prevention. Rev Neurosci. 2013; 24:139–152. [PubMed: 23492553]
16. Earhart GM, Falvo MJ. Parkinson disease and exercise. Compr Physiol. 2013; 3:833–848. [PubMed: 23720332]
17. van der Kolk NM, King LA. Effects of exercise on mobility in people with Parkinson's disease. Mov Disord. 2013; 28:1587–1596. [PubMed: 24132847]
18. Canning CG, Sherrington C, Lord SR, et al. Exercise for falls prevention in Parkinson disease: a randomized controlled trial. Neurology. 2015; 84:304–312. [PubMed: 25552576]

19. Lamotte G, Skender E, Rafferty MR, David FJ, Sadowsky S, Corcos DM. Effects of progressive resistance exercise training on the motor and nonmotor features of Parkinson's disease: a review. Kinesiol Rev. 2015; 4:11–27.
20. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006; 5:235–245. [PubMed: 16488379]
21. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand. 2006; 113:211–220. [PubMed: 16542159]
22. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. Neurobiol Dis. 2012; 46:581–589. [PubMed: 22245219]
23. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. 2006; 12:35–41. [PubMed: 16271496]
24. Lieberman A. Depression in Parkinson's disease -- a review. Acta Neurol Scand. 2006; 113:1–8. [PubMed: 16367891]
25. Veazey C, Aki SO, Cook KF, Lai EC, Kunik ME. Prevalence and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2005; 17:310–323. [PubMed: 16179652]
26. Walsh K, Bennett G. Parkinson's disease and anxiety. Postgrad Med J. 2001; 77:89–93. [PubMed: 11161073]
27. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord. 2009; 24:2175–2186. [PubMed: 19768724]
28. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Mov Disord. 2009; 24:1333–1338. [PubMed: 19425086]
29. Oguru M, Tachibana H, Toda K, Okuda B, Oka N. Apathy and depression in Parkinson disease. J Geriatr Psychiatry Neurol. 2010; 23:35–41. [PubMed: 20015839]
30. Holroyd S, Currie LJ, Wooten GF. Depression is associated with impairment of ADL, not motor function in Parkinson disease. Neurology. 2005; 64:2134–2135. [PubMed: 15985588]
31. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am Geriatr Soc. 2004; 52:784–788. [PubMed: 15086662]
32. Hughes TA, Ross HF, Mindham RH, Spokes EG. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand. 2004; 110:118–123. [PubMed: 15242420]
33. Bryant MS, Rintala DH, Hou JG, et al. The relation of falls to fatigue, depression and daytime sleepiness in Parkinson's disease. Eur Neurol. 2012; 67:326–330. [PubMed: 22555623]
34. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011; 26(Suppl 3):S42–S80. [PubMed: 22021174]
35. Chen JJ, Marsh L. Anxiety in Parkinson's disease: identification and management. Ther Adv Neurol Disord. 2014; 7:52–59. [PubMed: 24409202]
36. Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. Mov Disord. 2011; 26:1022–1031. [PubMed: 21626547]
37. Dissanayaka NN, White E, O'Sullivan JD, Marsh R, Pachana NA, Byrne GJ. The clinical spectrum of anxiety in Parkinson's disease. Mov Disord. 2014; 29:967–975. [PubMed: 25043800]
38. Carod-Artal FJ, Ziomkowski S, Mourao Mesquita H, Martinez-Martin P. Anxiety and depression: main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. Parkinsonism Relat Disord. 2008; 14:102–108. [PubMed: 17719828]
39. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. Mov Disord. 2010; 25:838–845. [PubMed: 20461800]
40. Havlikova E, van Dijk JP, Nagyova I, et al. The impact of sleep and mood disorders on quality of life in Parkinson's disease patients. J Neurol. 2011; 258:2222–2229. [PubMed: 21614432]
41. Bonnet AM, Czernecki V. Non-motor symptoms in Parkinson's disease: cognition and behavior. Geriatr Psychol Neuropsychiatr Vieil. 2013; 11:295–304. [PubMed: 24026132]

42. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol. 2003; 16:178–183. [PubMed: 12967062]
43. Frisina PG, Borod JC, Foldi NS, Tenenbaum HR. Depression in Parkinson's disease: health risks, etiology, and treatment options. Neuropsychiatr Dis Treat. 2008; 4:81–91. [PubMed: 18728814]
44. Palanci J, Marsh L, Pontone GM. Gaps in treatment for anxiety in Parkinson disease. Am J Geriatr Psychiatry. 2011; 19:907–908. [PubMed: 21795961]
45. Pontone GM, Williams JR, Anderson KE, et al. Pharmacologic treatment of anxiety disorders in Parkinson disease. Am J Geriatr Psychiatry. 2013; 21:520–528. [PubMed: 23567419]
46. Troeung L, Egan SJ, Gasson N. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. PLoS One. 2013; 8:e79510. [PubMed: 24236141]
47. Rocha FL, Murad MG, Stumpf BP, Hara C, Fuzikawa C. Antidepressants for depression in Parkinson's disease: systematic review and meta-analysis. J Psychopharmacol. 2013; 27:417–423. [PubMed: 23427193]
48. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. 2012; 78:1229–1236. [PubMed: 22496199]
49. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010; 9:573–580. [PubMed: 20452823]
50. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009; 72:886–892. [PubMed: 19092112]
51. Connolly BS, Fox SH. Drug treatments for the neuropsychiatric complications of Parkinson's disease. Expert Rev Neurother. 2012; 12:1439–1449. [PubMed: 23237351]
52. Weintraub, D.; Hoops, S. Anxiety Syndromes and Panic Attacks. In: Olanow, CW.; Stocchi, F.; Lang, AE., editors. Parkinson's Disease: Non-Motor and Non-Dopaminergic Features. 2011. p. 193-202.
53. Charidimou A, Seamons J, Selai C, Schrag A. The role of cognitive-behavioural therapy for patients with depression in Parkinson's disease. Parkinsons Dis. 2011; 2011:737523. [PubMed: 21766001]
54. Armento ME, Stanley MA, Marsh L, et al. Cognitive behavioral therapy for depression and anxiety in Parkinson's disease: a clinical review. J Parkinsons Dis. 2012; 2:135–151. [PubMed: 23939438]
55. Dobkin RD, Menza M, Bienfait KL. CBT for the treatment of depression in Parkinson's disease: a promising nonpharmacological approach. Expert Rev Neurother. 2008; 8:27–35. [PubMed: 18088199]
56. Farabaugh A, Locascio JJ, Yap L, et al. Cognitive-behavioral therapy for patients with Parkinson's disease and comorbid major depressive disorder. Psychosomatics. 2010; 51:124–129. [PubMed: 20332287]
57. Troeung L, Egan SJ, Gasson N. A waitlist-controlled trial of group cognitive behavioural therapy for depression and anxiety in Parkinson's disease. BMC Psychiatry. 2014; 14:19. [PubMed: 24467781]
58. Veazey C, Cook KF, Stanley M, Lai EC, Kunik ME. Telephone-administered cognitive behavioral therapy: a case study of anxiety and depression in Parkinson's disease. J Clin Psychol Med Settings. 2009; 16:243–253. [PubMed: 19404724]
59. Yang S, Sajatovic M, Walter BL. Psychosocial interventions for depression and anxiety in Parkinson's disease. J Geriatr Psychiatry Neurol. 2012; 25:113–121. [PubMed: 22689704]
60. Heinrichs N, Hoffman EC, Hofmann SG. Cognitive-behavioral treatment for social phobia in Parkinson's disease: a single-case study. Cogn Behav Pract. 2001; 8:328–335. [PubMed: 16770438]
61. Stathopoulou G, Powers MB, Berry AC, Smits JA, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review. Clin Psychol Sci Prac. 2006; 13:179–193.
62. Krogh J, Nordentoft M, Sterne JA, Lawlor DA. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry. 2011; 72:529–538. [PubMed: 21034688]

63. Mota-Pereira J, Carvalho S, Silverio J, et al. Moderate physical exercise and quality of life in patients with treatment-resistant major depressive disorder. J Psychiatr Res. 2011; 45:1657–1659. [PubMed: 21908006]
64. Salehi I, Hosseini SM, Haghighi M, et al. Electroconvulsive therapy and aerobic exercise training increased BDNF and ameliorated depressive symptoms in patients suffering from treatment-resistant major depressive disorder. J Psychiatr Res. 2014; 57:117–124. [PubMed: 25073431]
65. Mura G, Moro MF, Patten SB, Carta MG. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. CNS Spectr. 2014; 19:496–508. [PubMed: 24589012]
66. Merom D, Phongsavan P, Wagner R, et al. Promoting walking as an adjunct intervention to group cognitive behavioral therapy for anxiety disorders--a pilot group randomized trial. J Anxiety Disord. 2008; 22:959–968. [PubMed: 17988832]
67. Conn VS. Depressive symptom outcomes of physical activity interventions: meta-analysis findings. Ann Behav Med. 2010; 39:128–138. [PubMed: 20422333]
68. Asmundson GJ, Fetzner MG, Deboer LB, Powers MB, Otto MW, Smits JA. Let's get physical: a contemporary review of the anxiolytic effects of exercise for anxiety and its disorders. Depress Anxiety. 2013; 30:362–373. [PubMed: 23300122]
69. Petruzzello SJ, Landers DM, Hatfield BD, Kubitz KA, Salazar W. A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Outcomes and mechanisms. Sports Med. 1991; 11:143–182. [PubMed: 1828608]
70. Wipfli BM, Rethorst CD, Landers DM. The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis. J Sport Exerc Psychol. 2008; 30:392–410. [PubMed: 18723899]
71. Gaudlitz K, Plag J, Dimeo F, Strohle A. Aerobic exercise training facilitates the effectiveness of cognitive behavioral therapy in panic disorder. Depress Anxiety. 2015; 32:221–228. [PubMed: 25515221]
72. Bridle C, Spanjers K, Patel S, Atherton NM, Lamb SE. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2012; 201:180–185. [PubMed: 22945926]
73. Blake H, Mo P, Malik S, Thomas S. How effective are physical activity interventions for alleviating depressive symptoms in older people? A systematic review. Clin Rehabil. 2009; 23:873–887. [PubMed: 19675114]
74. Brenes GA, Williamson JD, Messier SP, et al. Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. Aging Ment Health. 2007; 11:61–68. [PubMed: 17164159]
75. Penninx BW, Rejeski WJ, Pandya J, et al. Exercise and depressive symptoms: a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. J Gerontol B Psychol Sci Soc Sci. 2002; 57:P124–P132. [PubMed: 11867660]
76. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. Arch Intern Med. 1999; 159:2349–2356. [PubMed: 10547175]
77. Adamson BC, Ensari I, Motl RW. Effect of exercise on depressive symptoms in adults with neurologic disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2015; 96:1329–1338. [PubMed: 25596001]
78. Park A, Zid D, Russell J, et al. Effects of a formal exercise program on Parkinson's disease: a pilot study using a delayed start design. Parkinsonism Relat Disord. 2014; 20:106–111. [PubMed: 24209458]
79. Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. JAMA Neurol. 2013; 70:183–190. [PubMed: 23128427]
80. Bridgewater KJ, Sharpe MH. Aerobic exercise and early Parkinson's disease. Neurorehabil Neural Repair. 1996; 10:233–241.
81. Dashtipour K, Johnson E, Kani C, et al. Effect of exercise on motor and nonmotor symptoms of Parkinson's disease. Parkinsons Dis. 2015; 2015:586378. [PubMed: 25722915]
82. Uc EY, Doerschug KC, Magnotta V, et al. Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. Neurology. 2014; 83:413–425. [PubMed: 24991037]

83. Mamikonyan E, Moberg PJ, Siderowf A, et al. Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores. Parkinsonism Relat Disord. 2009; 15:226–231. [PubMed: 18595765]
84. Dalrymple-Alford JC, Livingston L, MacAskill MR, et al. Characterizing mild cognitive impairment in Parkinson's disease. Mov Disord. 2011; 26:629–636. [PubMed: 21287603]
85. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012; 27:349–356. [PubMed: 22275317]
86. Litvan I, Aarsland D, Adler CH, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord. 2011; 26:1814–1824. [PubMed: 21661055]
87. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol. 2010; 9:1200–1213. [PubMed: 20880750]
88. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012; 11:697–707. [PubMed: 22814541]
89. Devos H, Vandenberghe W, Tant M, et al. Driving and off-road impairments underlying failure on road testing in Parkinson's disease. Mov Disord. 2013; 28:1949–1956. [PubMed: 24166984]
90. Kurtis MM, Rodriguez-Blazquez C, Martinez-Martin P. Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2013; 19:1152–1155. [PubMed: 23953775]
91. Schiehser DM, Han SD, Lessig S, Song DD, Zizak V, Filoteo JV. Predictors of health status in nondepressed and nondemented individuals with Parkinson's disease. Arch Clin Neuropsychol. 2009; 24:699–709. [PubMed: 19767296]
92. Uc EY, Rizzo M, Johnson AM, Dastrup E, Anderson SW, Dawson JD. Road safety in drivers with Parkinson disease. Neurology. 2009; 73:2112–2119. [PubMed: 20018639]
93. Amick MM, Grace J, Ott BR. Visual and cognitive predictors of driving safety in Parkinson's disease patients. Arch Clin Neuropsychol. 2007; 22:957–967. [PubMed: 17851032]
94. Fernandez HH, See RH, Gary MF, et al. Depressive symptoms in Parkinson disease correlate with impaired global and specific cognitive performance. J Geriatr Psychiatry Neurol. 2009; 22:223–227. [PubMed: 19429848]
95. Santangelo G, Vitale C, Trojano L, et al. Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol. 2009; 256:632–638. [PubMed: 19370301]
96. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007; 130:1787–1798. [PubMed: 17535834]
97. Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. J Neuropsychol. 2013; 7:193–224. [PubMed: 24007368]
98. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005; 65:1239–1245. [PubMed: 16247051]
99. Pfeiffer HC, Lokkegaard A, Zoetmulder M, Friberg L, Werdelin L. Cognitive impairment in early-stage non-demented Parkinson's disease patients. Acta Neurol Scand. 2014; 129:307–318. [PubMed: 24117192]
100. Miller IN, Neargarder S, Risi MM, Cronin-Golomb A. Frontal and posterior subtypes of neuropsychological deficit in Parkinson's disease. Behav Neurosci. 2013; 127:175–183. [PubMed: 23398433]
101. Levy G, Jacobs DM, Tang MX, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord. 2002; 17:1221–1226. [PubMed: 12465060]
102. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009; 132:2958–2969. [PubMed: 19812213]

103. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. Neurodegener Dis. 2013; 11:79–92. [PubMed: 23038420]
104. Etnier JL, Nowell PM, Landers DM, Sibley BA. A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res Rev. 2006; 52:119–130. [PubMed: 16490256]
105. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med. 2010; 72:239–252. [PubMed: 20223924]
106. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003; 14:125–130. [PubMed: 12661673]
107. Hernandez SS, Coelho FG, Gobbi S, Stella F. Effects of physical activity on cognitive functions, balance and risk of falls in elderly patients with Alzheimer's dementia. Rev Bras Fisioter. 2010; 14:68–74. [PubMed: 20414564]
108. Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2013; 12:CD006489. [PubMed: 24302466]
109. Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. Arch Neurol. 2002; 59:102–112. [PubMed: 11790237]
110. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain. 2011; 134:1493–1505. [PubMed: 21596773]
111. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. Front Neurol. 2012; 3:88. [PubMed: 22654785]
112. Weintraub D, Dietz N, Duda JE, et al. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain. 2012; 135:170–180. [PubMed: 22108576]
113. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008; 300:1027–1037. [PubMed: 18768414]
114. Pedroso RV, Coelho FG, Santos-Galduroz RF, Costa JL, Gobbi S, Stella F. Balance, executive functions and falls in elderly with Alzheimer's disease (AD): a longitudinal study. Arch Gerontol Geriatr. 2012; 54:348–351. [PubMed: 21774999]
115. Oertel-Knochel V, Mehler P, Thiel C, et al. Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. Eur Arch Psychiatry Clin Neurosci. 2014; 264:589–604. [PubMed: 24487666]
116. Hindle JV, Petrelli A, Clare L, Kalbe E. Nonpharmacological enhancement of cognitive function in Parkinson's disease: a systematic review. Mov Disord. 2013; 28:1034–1049. [PubMed: 23426759]
117. Murray DK, Sacheli MA, Eng JJ, Stoessl AJ. The effects of exercise on cognition in Parkinson's disease: a systematic review. Transl Neurodegener. 2014; 3:5. [PubMed: 24559472]
118. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol. 2013; 12:716–726. [PubMed: 23769598]
119. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. Acta Neurol Scand. 2011; 123:13–19. [PubMed: 20199518]
120. Tanaka K, Quadros AC Jr, Santos RF, Stella F, Gobbi LT, Gobbi S. Benefits of physical exercise on executive functions in older people with Parkinson's disease. Brain Cogn. 2009; 69:435–441. [PubMed: 19006643]
121. Tabak R, Aquije G, Fisher BE. Aerobic exercise to improve executive function in Parkinson disease: a case series. J Neurol Phys Ther. 2013; 37:58–64. [PubMed: 23632453]
122. Nocera JR, Altmann LJ, Sapienza C, Okun MS, Hass CJ. Can exercise improve language and cognition in Parkinson's disease? A case report. Neurocase. 2010; 16:301–306. [PubMed: 20391181]

123. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006; 61:1166–1170. [PubMed: 17167157]

124. Bruck A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry. 2004; 75:1467–1469. [PubMed: 15377698]

125. David FJ, Robichaud JA, Leurgans SE, et al. Exercise Improves Cognition in Parkinson's Disease: The PRET-PD Randomized, Clinical Trial. Mov Disord. 2015 Epub ahead of print.

126. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev. 2002; 6:97–111. [PubMed: 12531146]

127. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004; 27:1255–1273. [PubMed: 15586779]

128. Mallon L, Broman JE, Hetta J. Relationship between insomnia, depression, and mortality: a 12-year follow-up of older adults in the community. Int Psychogeriatr. 2000; 12:295–306. [PubMed: 11081951]

129. Morin CM, LeBlanc M, Daley M, Gregoire JP, Merette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. Sleep Med. 2006; 7:123–130. [PubMed: 16459140]

130. Crowley K. Sleep and sleep disorders in older adults. Neuropsychol Rev. 2011; 21:41–53. [PubMed: 21225347]

131. Barber A, Dashtipour K. Sleep disturbances in Parkinson's disease with emphasis on rapid eye movement sleep behavior disorder. Int J Neurosci. 2012; 122:407–412. [PubMed: 22463496]

132. Diederich NJ, McIntyre DJ. Sleep disorders in Parkinson's disease: many causes, few therapeutic options. J Neurol Sci. 2012; 314:12–19. [PubMed: 22118862]

133. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002; 14:223–236. discussion 222. Originally published as a monograph by Sherwood, Neely, and Jones (London, 1817). [PubMed: 11983801]

134. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. Mov Disord. 1990; 5:280–285. [PubMed: 2259351]

135. Pappert EJ, Goetz CG, Niederman FG, Raman R, Leurgans S. Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. Mov Disord. 1999; 14:117–121. [PubMed: 9918353]

136. Claassen DO, Kutscher SJ. Sleep disturbances in Parkinson's disease patients and management options. Nat Sci Sleep. 2011; 3:125–133. [PubMed: 23616723]

137. Comella CL. Sleep disorders in Parkinson's disease: an overview. Mov Disord. 2007; 22(Suppl 17):S367–S373. [PubMed: 18175398]

138. Stavitsky K, Saurman JL, McNamara P, Cronin-Golomb A. Sleep in Parkinson's disease: a comparison of actigraphy and subjective measures. Parkinsonism Relat Disord. 2010; 16:280–283. [PubMed: 20202887]

139. Stavitsky K, Cronin-Golomb A. Sleep quality in Parkinson's disease: an examination of clinical variables. Cogn Behav Neurol. 2011; 24:43–49. [PubMed: 21537164]

140. Grinberg LT, Rueb U, Alho AT, Heinsen H. Brainstem pathology and non-motor symptoms in PD. J Neurol Sci. 2010; 289:81–88. [PubMed: 19758601]

141. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008; 15(Suppl 1):14–20. [PubMed: 18353132]

142. Trenkwalder C, Kies B, Rudzinska M, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord. 2011; 26:90–99. [PubMed: 21322021]

143. Wood LD. Clinical review and treatment of select adverse effects of dopamine receptor agonists in Parkinson's disease. Drugs Aging. 2010; 27:295–310. [PubMed: 20359261]

144. Menza M, Dobkin RD, Marin H, Bienfait K. Sleep disturbances in Parkinson's disease. Mov Disord. 2010; 25(Suppl 1):S117–S122. [PubMed: 20187236]

145. Neikrug AB, Maglione JE, Liu L, et al. Effects of sleep disorders on the non-motor symptoms of Parkinson disease. J Clin Sleep Med. 2013; 9:1119–1129. [PubMed: 24235892]
146. Borek LL, Kohn R, Friedman JH. Mood and sleep in Parkinson's disease. J Clin Psychiatry. 2006; 67:958–963. [PubMed: 16848656]
147. Stavitsky K, Neargarder S, Bogdanova Y, McNamara P, Cronin-Golomb A. The impact of sleep quality on cognitive functioning in Parkinson's disease. J Int Neuropsychol Soc. 2012; 18:108–117. [PubMed: 22152279]
148. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318:121–134. [PubMed: 15338272]
149. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. Behav Brain Res. 2011; 221:564–573. [PubMed: 20060022]
150. Stocchi F, Barbato L, Nordera G, Berardelli A, Ruggieri S. Sleep disorders in Parkinson's disease. J Neurol. 1998; 245(Suppl 1):S15–S18. [PubMed: 9617717]
151. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28:193–213. [PubMed: 2748771]
152. Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. J Behav Med. 2015; 38:427–449. [PubMed: 25596964]
153. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. JAMA. 1997; 277:32–37. [PubMed: 8980207]
154. Rodrigues de Paula F, Teixeira-Salmela LF, Coelho de Morais Faria CD, Rocha de Brito P, Cardoso F. Impact of an exercise program on physical, emotional, and social aspects of quality of life of individuals with Parkinson's disease. Mov Disord. 2006; 21:1073–1077. [PubMed: 16637049]
155. Nascimento CM, Ayan C, Cancela JM, Gobbi LT, Gobbi S, Stella F. Effect of a multimodal exercise program on sleep disturbances and instrumental activities of daily living performance on Parkinson's and Alzheimer's disease patients. Geriatr Gerontol Int. 2014; 14:259–266. [PubMed: 23647635]
156. Prediger RD, Matheus FC, Schwarzbold ML, Lima MM, Vital MA. Anxiety in Parkinson's disease: a critical review of experimental and clinical studies. Neuropharmacology. 2012; 62:115–124. [PubMed: 21903105]
157. Chaudhuri KR, Odin P. The challenge of non-motor symptoms in Parkinson's disease. Prog Brain Res. 2010; 184:325–341. [PubMed: 20887883]
158. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009; 8:464–474. [PubMed: 19375664]
159. Chaudhuri KR. The dopaminergic basis of sleep dysfunction and non motor symptoms of Parkinson's disease: evidence from functional imaging. Exp Neurol. 2009; 216:247–248. [PubMed: 19146855]
160. Petzinger GM, Fisher BE, Van Leeuwen JE, et al. Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. Mov Disord. 2010; 25(Suppl 1):S141–S145. [PubMed: 20187247]
161. Fisher BE, Wu AD, Salem GJ, et al. The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. Arch Phys Med Rehabil. 2008; 89:1221–1229. [PubMed: 18534554]
162. Foley TE, Fleshner M. Neuroplasticity of dopamine circuits after exercise: implications for central fatigue. Neuromolecular Med. 2008; 10:67–80. [PubMed: 18274707]
163. Fisher BE, Li Q, Nacca A, et al. Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. Neuroreport. 2013; 24:509–514. [PubMed: 23636255]
164. Balaban CD, Thayer JF. Neurological bases for balance-anxiety links. J Anxiety Disord. 2001; 15:53–79. [PubMed: 11388358]

165. Balaban CD. Neural substrates linking balance control and anxiety. Physiol Behav. 2002; 77:469–475. [PubMed: 12526985]
166. DeBoer LB, Powers MB, Utschig AC, Otto MW, Smits JA. Exploring exercise as an avenue for the treatment of anxiety disorders. Expert Rev Neurother. 2012; 12:1011–1022. [PubMed: 23002943]
167. Melancon MO, Lorrain D, Dionne IJ. Exercise and sleep in aging: emphasis on serotonin. Pathol Biol (Paris). 2014; 62:276–283. [PubMed: 25104243]
168. He SB, Tang WG, Tang WJ, Kao XL, Zhang CG, Wong XT. Exercise intervention may prevent depression. Int J Sports Med. 2012; 33:525–530. [PubMed: 22504906]
169. Millan MJ. The neurobiology and control of anxious states. Prog Neurobiol. 2003; 70:83–244. [PubMed: 12927745]
170. Palazidou E. The neurobiology of depression. Br Med Bull. 2012; 101:127–145. [PubMed: 22334281]
171. Monti JM. Serotonin control of sleep-wake behavior. Sleep Med Rev. 2011; 15:269–281. [PubMed: 21459634]
172. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011; 108:3017–3022. [PubMed: 21282661]
173. Klempin F, Beis D, Mosienko V, Kempermann G, Bader M, Alenina N. Serotonin is required for exercise-induced adult hippocampal neurogenesis. J Neurosci. 2013; 33:8270–8275. [PubMed: 23658167]
174. Wipfli B, Landers D, Nagoshi C, Ringenbach S. An examination of serotonin and psychological variables in the relationship between exercise and mental health. Scand J Med Sci Sports. 2011; 21:474–481. [PubMed: 20030777]
175. Lee HM, Koh SB. Many faces of Parkinson's disease: non-motor symptoms of Parkinson's disease. J Mov Disord. 2015; 8:92–97. [PubMed: 26090081]
176. Weinstein AM, Voss MW, Prakash RS, et al. The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. Brain Behav Immun. 2012; 26:811–819. [PubMed: 22172477]
177. Sawada Y, Nishio Y, Suzuki K, et al. Attentional set-shifting deficit in Parkinson's disease is associated with prefrontal dysfunction: an FDG-PET study. PLoS One. 2012; 7:e38498. [PubMed: 22685575]
178. Voss MW, Heo S, Prakash RS, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp. 2013; 34:2972–2985. [PubMed: 22674729]
179. Voss MW, Erickson KI, Prakash RS, et al. Neurobiological markers of exercise-related brain plasticity in older adults. Brain Behav Immun. 2013; 28:90–99. [PubMed: 23123199]
180. Hirsch MA, Farley BG. Exercise and neuroplasticity in persons living with Parkinson's disease. Eur J Phys Rehabil Med. 2009; 45:215–229. [PubMed: 19532109]
181. Altar CA. Neurotrophins and depression. Trends Pharmacol Sci. 1999; 20:59–61. [PubMed: 10101965]
182. Gorski JA, Zeiler SR, Tamowski S, Jones KR. Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J Neurosci. 2003; 23:6856–6865. [PubMed: 12890780]
183. Huang ZJ, Kirkwood A, Pizzorusso T, et al. BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. Cell. 1999; 98:739–755. [PubMed: 10499792]
184. Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci. 2005; 6:603–614. [PubMed: 16062169]
185. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J Psychiatr Res. 2015; 60:56–64. [PubMed: 25455510]
186. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. Neuroscientist. 2012; 18:82–97. [PubMed: 21531985]
187. Heyman E, Gamelin FX, Goekint M, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression. Psychoneuroendocrinology. 2012; 37:844–851. [PubMed: 22029953]

188. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci. 2005; 25:8680–8685. [PubMed: 16177036]

189. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci. 2004; 20:2580–2590. [PubMed: 15548201]

190. Leckie RL, Oberlin LE, Voss MW, et al. BDNF mediates improvements in executive function following a 1-year exercise intervention. Front Hum Neurosci. 2014; 8:985. [PubMed: 25566019]

191. Parain K, Murer MG, Yan Q, et al. Reduced expression of brain-derived neurotrophic factor protein in Parkinson's disease substantia nigra. Neuroreport. 1999; 10:557–561. [PubMed: 10208589]

192. Howells DW, Porritt MJ, Wong JY, et al. Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol. 2000; 166:127–135. [PubMed: 11031089]

193. Mogi M, Togari A, Kondo T, et al. Brain-derived growth factor and nerve growth factor concentrations are decreased in the substantia nigra in Parkinson's disease. Neurosci Lett. 1999; 270:45–48. [PubMed: 10454142]

194. Porritt MJ, Batchelor PE, Howells DW. Inhibiting BDNF expression by antisense oligonucleotide infusion causes loss of nigral dopaminergic neurons. Exp Neurol. 2005; 192:226–234. [PubMed: 15698637]

195. Tajiri N, Yasuhara T, Shingo T, et al. Exercise exerts neuroprotective effects on Parkinson's disease model of rats. Brain Res. 2010; 1310:200–207. [PubMed: 19900418]

196. Frazzitta G, Maestri R, Ghilardi MF, et al. Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. Neurorehabil Neural Repair. 2014; 28:163–168. [PubMed: 24213955]

197. Frazzitta G, Maestri R, Bertotti G, et al. Intensive rehabilitation treatment in early Parkinson's disease: a randomized pilot study with a 2-year follow-up. Neurorehabil Neural Repair. 2015; 29:123–131. [PubMed: 25038064]

198. Fumagalli F, Racagni G, Riva MA. Shedding light into the role of BDNF in the pharmacotherapy of Parkinson's disease. Pharmacogenomics J. 2006; 6:95–104. [PubMed: 16402079]

199. Intlekofer KA, Cotman CW. Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. Neurobiol Dis. 2013; 57:47–55. [PubMed: 22750524]

200. Potashkin JA, Blume SR, Runkle NK. Limitations of animal models of Parkinson's disease. Parkinsons Dis. 2010; 2011:658083. [PubMed: 21209719]

201. Ahlskog JE. Does vigorous exercise have a neuroprotective effect in Parkinson disease? Neurology. 2011; 77:288–294. [PubMed: 21768599]

202. Uchida S, Shioda K, Morita Y, Kubota C, Ganeko M, Takeda N. Exercise effects on sleep physiology. Front Neurol. 2012; 3:48. [PubMed: 22485106]

203. Buman MP, King AC. Exercise as a treatment to enhance sleep. Am J Lifestyle Med. 2010; 4:500–514.

204. Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: efficacy and dose response. Am J Prev Med. 2005; 28:1–8. [PubMed: 15626549]

205. Ang ET, Gomez-Pinilla F. Potential therapeutic effects of exercise to the brain. Curr Med Chem. 2007; 14:2564–2571. [PubMed: 17979709]

206. David FJ, Rafferty MR, Robichaud JA, et al. Progressive resistance exercise and Parkinson's disease: a review of potential mechanisms. Parkinsons Dis. 2012; 2012:124527. [PubMed: 22191068]

207. Falvo MJ, Schilling BK, Earhart GM. Parkinson's disease and resistive exercise: rationale, review, and recommendations. Mov Disord. 2008; 23:1–11. [PubMed: 17894327]

208. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007; 116:1081–1093. [PubMed: 17671237]

209. Moore CG, Schenkman M, Kohrt WM, Delitto A, Hall DA, Corcos D. Study in Parkinson disease of exercise (SPARX): translating high-intensity exercise from animals to humans. Contemp Clin Trials. 2013; 36:90–98. [PubMed: 23770108]

210. Dibble LE, Hale TF, Marcus RL, Droge J, Gerber JP, LaStayo PC. High-intensity resistance training amplifies muscle hypertrophy and functional gains in persons with Parkinson's disease. Mov Disord. 2006; 21:1444–1452. [PubMed: 16773643]
211. Dibble LE, Hale TF, Marcus RL, Gerber JP, LaStayo PC. High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with Parkinson's disease: a preliminary study. Parkinsonism Relat Disord. 2009; 15:752–757. [PubMed: 19497777]
212. Lamotte G, Rafferty MR, Prodoehl J, et al. Effects of endurance exercise training on the motor and non-motor features of Parkinson's disease: a review. J Parkinsons Dis. 2015; 5:21–41. [PubMed: 25374272]
213. Allen NE, Sherrington C, Suriyarachchi GD, Paul SS, Song J, Canning CG. Exercise and motor training in people with Parkinson's disease: a systematic review of participant characteristics, intervention delivery, retention rates, adherence, and adverse events in clinical trials. Parkinsons Dis. 2012; 2012:854328. [PubMed: 22191077]
214. Schenkman M, Hall DA, Baron AE, Schwartz RS, Mettler P, Kohrt WM. Exercise for people in early- or mid-stage Parkinson disease: a 16-month randomized controlled trial. Phys Ther. 2012; 92:1395–1410. [PubMed: 22822237]
215. Liu J, Dong J, Wang L, Su Y, Yan P, Sun S. Comparative efficacy and acceptability of antidepressants in Parkinson's disease: a network meta-analysis. PLoS One. 2013; 8:e76651. [PubMed: 24098546]
216. van Eijkeren FJ, Reijmers RS, Kleinveld MJ, Minten A, Bruggen JP, Bloem BR. Nordic walking improves mobility in Parkinson's disease. Mov Disord. 2008; 23:2239–2243. [PubMed: 18816697]
217. Ellis T, Katz DI, White DK, DePiero TJ, Hohler AD, Saint-Hilaire M. Effectiveness of an inpatient multidisciplinary rehabilitation program for people with Parkinson disease. Phys Ther. 2008; 88:812–819. [PubMed: 18436568]
218. Monticone M, Ambrosini E, Laurini A, Rocca B, Foti C. In-patient multidisciplinary rehabilitation for Parkinson's disease: a randomized controlled trial. Mov Disord. 2015; 30:1050–1058. [PubMed: 26095443]
219. Ellis T, Motl RW. Physical activity behavior change in persons with neurologic disorders: overview and examples from Parkinson disease and multiple sclerosis. J Neurol Phys Ther. 2013; 37:85–90. [PubMed: 23632452]
220. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology. 2010; 75:494–499. [PubMed: 20668263]
221. Jacob EL, Gatto NM, Thompson A, Bordelon Y, Ritz B. Occurrence of depression and anxiety prior to Parkinson's disease. Parkinsonism Relat Disord. 2010; 16:576–581. [PubMed: 20674460]
222. Bhidayasiri R, Truong DD. Therapeutic strategies for nonmotor symptoms in early Parkinson's disease: the case for a higher priority and stronger evidence. Parkinsonism Relat Disord. 2012; 18(Suppl 1):S110–S113. [PubMed: 22166405]
223. Dissanayaka NN, Sellbach A, Silburn PA, O'Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson's disease. J Affect Disord. 2011; 132:82–88. [PubMed: 21356559]
224. Lin EH, Katon W, Von Korff M, et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. JAMA. 2003; 290:2428–2429. [PubMed: 14612479]
225. Ahlskog JE. Cheaper, simpler, and better: tips for treating seniors with Parkinson disease. Mayo Clin Proc. 2011; 86:1211–1216. [PubMed: 22134940]
226. Dibble LE, Foreman KB, Addison O, Marcus RL, LaStayo PC. Exercise and medication effects on persons with Parkinson disease across the domains of disability: a randomized clinical trial. J Neurol Phys Ther. 2015; 39:85–92. [PubMed: 25742370]
227. Aarsland D, Taylor JP, Weintraub D. Psychiatric issues in cognitive impairment. Mov Disord. 2014; 29:651–662. [PubMed: 24757113]

228. States RA, Spierer DK, Salem Y. Long-term group exercise for people with Parkinson's disease: a feasibility study. J Neurol Phys Ther. 2011; 35:122–128. [PubMed: 21934373]

229. Ellis T, Latham NK, DeAngelis TR, Thomas CA, Saint-Hilaire M, Bickmore TW. Feasibility of a virtual exercise coach to promote walking in community-dwelling persons with Parkinson disease. Am J Phys Med Rehabil. 2013; 92:472–481. [PubMed: 23552335]

Table 1

Exercise interventions for mood in PD.

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Mood Outcome Measures	Main Results	Limitations
Canning et al., 2015[18]	RCT	71.0	40-60 minutes of strengthening	231	3X/wk for 6 months (in clinic + at home)	Usual-care	PANAS	Improved affect in exercise group compared to usual care	No attention control; Mood measures included as secondary outcomes
Park et al., 2014[78]	RCT (delayed-start)	59.9	60 minutes of combined aerobic and resistance	31	3X/wk for 48 weeks (in clinic)	Delayed-start at 24 weeks	BDI	Greater reduction in depression in early-start group compared to late-start group at 48 weeks	Greater social interaction in early-start group relative to late-start group
Shulman et al., 2013[79]	RCT	65.8	3 exercise groups: 1) 30 minutes of high-intensity treadmill exercise; 2) 50 minutes of low-intensity treadmill exercise; 3) stretching and resistance training	67	3X/wk for 3 months (in clinic)	Stretching and resistance exercise (comparative trial)	BDI	No change in depression within any group	No non-exercising comparison condition
Bridgewater & Sharpe, 1996[80]	Pilot RCT	67.3 (EX); 66.5 (CON)	20-30 minutes of aerobic exercise (+ warm-up calisthenics and cool-down stretching)	26	2X/wk for 3 months (in clinic)	Usual care + attendance at “interest talks” once every 3 wks	LPDQ	Improved mood in exercise group	Small sample size; Less social interaction in control group
Dashtipour et al., 2015[81]	Prospective, double-blinded randomized trial	63.4	60 minutes of combined aerobic and resistance	11	4X/wk for 4 weeks (in clinic)	Exercise based behavioral treatment (LSVT BIG)	BAI, BDI	Reduced depression in combined group	Small sample size; Combined data analysis across both groups

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Mood Outcome Measures	Main Results	Limitations
Uc et al., 2014[82]	Uncontrolled phase I/II trial	65.5	45 minutes of aerobic walking	49	3X/wk for 6 months (at home)	None	GDS	Reduced depression across all completers	Lack of a control group

BAI=Beck Anxiety Inventory. BDI=Beck Depression Inventory. CON=control group. EX=exercise group. GDS=Geriatric Depression Scale; LPDQ=Levine-Pilowsky Depression Questionnaire. LSVT BIG=Lee Silverman Voice Therapy. PANAS=Positive affect subscale of the Positive and Negative Affect Schedule. PD=Parkinson's disease. RCT=randomized controlled trial.

Table 2

Exercise interventions for cognition in PD.

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Cognitive Outcome Measures	Main Results	Limitations
Cruise et al., 2011[119]	Controlled trial	59.5 (EX); 60.6 (CON)	60 minutes of progressive aerobic and anabolic exercise	28	2X/wk for 3 months (in clinic)	Usual lifestyle	COWAT, MMSE, PRM and SRM, SOC, SWM	EX group improved on specific measures of executive function (SWM, COWAT)	No attention control; No random allocation to groups
Uc et al., 2014[82]	Uncontrolled phase I/II trial	65.5	45 minutes of aerobic walking	49	3X/wk for 6 months (at home)	None	Complex Figure Copy and Recall, COWAT, Eriksen flanker task, JLO, MoCA, RAVLT, Stroop, TMT B-A, WCST	Improved performance on flanker task after exercise program	Lack of a control group
Tanaka et al., 2009[120]	Quasi-experimental design	65.4	60 minutes of multimodal exercise (aerobics, flexibility, muscular resistance, motor coordination, balance)	20	3X/wk for 6 months (in clinic)	Usual lifestyle	Symbol Search, WCST	Improved executive function (WCST categories completed and perseverative errors) in the exercise group	Small sample size; Non-randomized control group; No attention control
Tabak et al., 2013[121]	Case series	61, 72	60 minutes of aerobic exercise	2	3X/wk for 2 months (in clinic)	None	CTT, MoCA, PDCRS	Both participants improved on all measures of executive function after exercise	Case series design; Selection bias; No attention control
Nocera et al., 2010[122]	Case study	66	20 minutes of aerobic exercise	1	3X/week for 2 months (in clinic)	None	COWAT, Digit Span Forward and Backward, MMSE, Picture Description, Stroop	Improved performance on Stroop, COWAT (especially animal fluency), Digit Span Backward, and Picture	Case study design; Limited generalizability

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Cognitive Outcome Measures	Main Results	Limitations
								Description after exercise program	
David et al., 2015[125]	RCT	59.0 (EX); 58.6 (CON)	60-90 minutes of progressive resistance exercise (PRET)	51	2X/wk for 24 months (in clinic)	Stretching, balance, and non-progressive strengthening (mFC)	BTA, Digit Span, Stroop	At 24 months: PRET improved on BTA, Digit Span, and Stroop; and mFC improved on Digit Span and Stroop; No between-group differences at 12 or 24 months	No non-exercising comparison condition; Limited Generalizability (due to high education and younger age of participants)

BTA=Brief Test of Attention. CON=control group. COWAT=Controlled Oral Word Association Test. CTT=Color Trails Test 1 and 2. EX=exercise group. JLO=Judgment of Line Orientation Test. mFC=modified Fitness Counts. MMSE=Mini-Mental Status Examination. MOCA=Montreal Cognitive Assessment. PD=Parkinson's disease. PDCRS=Parkinson's Disease Cognitive Rating Scale. PRET=Progressive Resistance Exercise Training. PRM and SRM=Pattern and Spatial Recognition Memory (computerized versions) from the Cambridge Neuropsychological Test Automated Battery. RAVLT=Rey Auditory Verbal Learning Test. SOC=Stockings of Cambridge. SWM=Spatial Working Memory. TMT=Trail Making Test. WCST=Wisconsin Card Sorting Test.

Table 3

Exercise interventions for sleep in PD.

Authors	Study design	Mean Age	Intervention	Sample Size	Exercise Frequency/Duration/ Setting	Control Group	Sleep Outcome Measures	Main Results	Limitations
Nascimento et al., 2014[155]	RCT with stratified randomization	66.3 (PD, CON) 67.8 (PD, EX)	60 minutes of muscular resistance, balance/motor coordination, and aerobic fitness	34	3X/week for 6 months (in clinic)	Usual care	MSQ	Improvements in sleep disturbance (insomnia + daytime sleepiness) in exercise group	No objective measures of sleep; No attention control
Rodrigues de Paula et al., 2006[154]	Uncontrolled trial	61.5	75 minutes of combined aerobic conditioning and muscular strengthening	20	3X/week for 3 months (in clinic)	None	NHP-S	Trend for improved sleep after exercise program	Lack of a control group; Small sample size; Non-specific and subjective measure of sleep

CON=control group. EX=exercise group. MSQ=Mini-Sleep Questionnaire (MSQ). NHP-S=Nottingham Health Profile (sleep domain). PD=Parkinson's disease.