Multimodal imaging investigation of therapeutic mechanisms of exercise in Parkinson’s disease: Effects on dopamine release, ventral striatal activity and neuroinflammation

by

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Abstract

Objective: Exercise has been shown to be beneficial for people with Parkinson’s disease (PD) however, the underlying mechanisms are unknown. Evidence from animal models has shown exercise-induced changes in the dopaminergic system and decreased neuroinflammation, but these changes have yet to be studied in patient populations. The purpose of this thesis was to study the effects of exercise on dopaminergic function and neuroinflammation using multimodal neuroimaging in subjects with PD.

Methods: Two different comparisons were conducted using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). First, a cross-sectional study compared dopamine release, and ventral striatal activity, between PD habitual exercisers and sedentary PD subjects. Next, a prospective trial was conducted to compare the effects of exercise on ventral striatal activity, dopamine release and neuroinflammation.

Results: The cross-sectional study showed that habitual exercisers have greater dopamine release in the caudate nucleus in response to exercise and greater activation of the ventral striatum in response to monetary reward, compared to sedentary PD subjects. Similarly, the prospective trial showed increased dopamine release in the caudate nucleus in response to repetitive transcranial stimulation after 3 months of aerobic exercise compared to a stretching control group. Moreover, the aerobic group showed increased activity of the ventral striatum in response to monetary reward, compared to the control group. The aerobic group also showed decreased neuroinflammation in the thalamus,
globus pallidus and cerebellum, but those findings were highly dependent on the type of analysis method used and technical limitations of the PET tracer.

Conclusion: The benefits of exercise in PD are likely driven by changes to the dopaminergic system. Aerobic exercise increased dopamine release in the caudate nucleus and increased responsivity in the ventral striatum, suggesting changes to the dorsal striatum and mesolimbic dopaminergic system. The exercise-induced changes in neuroinflammation are limited to the analysis methods and technical constraints of imaging neuroinflammation. Collectively, the findings of this thesis support the use of exercise as an adjunct therapy for PD by showing that the benefits of exercise in PD are the result of neurological changes to the dopaminergic system.
Lay Summary

The benefits of exercise for Parkinson’s disease (PD) have been commonly reported; however, the reasons why exercise is beneficial for PD are unknown. Exercise may increase dopamine and decrease neuroinflammation, but this has yet to be shown in patients. In this study, we used multimodal imaging techniques to show that habitual exercisers with PD have greater dopamine release and greater activity in the ventral striatum (a brain area regulated by dopamine and responsive to reward) compared to sedentary PD subjects. Additionally, this study showed that after 3 months of aerobic exercise dopamine release and activity of the ventral striatum were increased, compared to a stretching control group. There were inconclusive results for the effects of exercise on neuroinflammation, due to technical limitations. Overall, the findings of this thesis show how the brain changes with exercise, and support the use of exercise as an adjunct therapy for PD.
Preface

All of the work presented henceforth was conducted in the Pacific Parkinson’s Research Centre at the University of British Columbia, Point Grey campus. All projects and associated methods were approved by the University of British Columbia’s Research Ethics Board [certificate # H14-02200].

A version of Chapter 2 has been published in Movement Disorders [Sacheli, M. A., Murray, D. K., Vafai, N., Cherkasova, M. V., Dinelle, K., Shahinfard, E., ... Jon Stoessl, A. (2018). Habitual exercisers versus sedentary subjects with Parkinson's Disease: Multimodal PET and fMRI study. Movement Disorders. doi:10.1002/mds.27498]. I was the lead investigator, responsible for conception, organization and execution of the research project, design and execution of the statistical analysis and manuscript composition. Murray DK was involved in the early stages of conception, organization and execution of the research project, review and critique of manuscript. Vafai N, Cherkasova M, Dinelle K and Shahinfard E supported the fMRI and PET data analysis. Neilson N and McKenzie J assisted with patient recruitment, clinical support during scanning, review and critique of manuscript. Appel-Cresswell S, McKeown MJ, Sossi V were involved with the conception and organization of the research project, review and critique of the manuscript. Schulzer M was involved with the design, review and critique of the statistical analysis. Stoessl AJ was the supervisory author on this project and was involved throughout the project in conception, organization and execution of the research project, design of the statistical analysis, review and critique of manuscript.

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Dedication

To people living with Parkinson’s disease,

You continue to inspire and motivate my research.
Chapter I: Introduction

Parkinson’s disease (PD) is a neurodegenerative movement disorder characterized by primary motor manifestations of tremor, rigidity, bradykinesia and postural instability (Jankovic, 2008). The motor manifestations of PD primarily reflect the progressive loss of dopaminergic cells in the substantia nigra pars compacta in the midbrain, resulting in loss of dopamine (DA) throughout the striatum (Albin, Young, & Penney, 1989). Currently, there are no known disease modifying or neuroprotective therapies for PD. Current therapies ameliorate symptoms and include pharmacological and surgical approaches. The mainstay pharmaceutical treatment is DA replacement therapy, most commonly levodopa, and it is very effective for the treatment of motor symptoms, especially early on in the disease. However, as PD progresses, patients are forced to increase the dosage or add supplementary medications to maintain similar therapeutic effects. Further complications that commonly arise include motor fluctuations, where patients may become incapacitated as the effects of the medications wear off between doses (“off” time), or involuntary movements known as dyskinesias. Surgical approaches (e.g. deep brain stimulation, DBS) are effective at treating motor fluctuations and improving quality of life in PD and are becoming increasingly popular. However, not all patients with PD are eligible for surgical interventions, as inclusion criteria are quite rigorous and neurosurgery is inherently invasive. Moreover, up to 90% of patients with PD will suffer from non-motor complications of PD, including but not limited to: mood alterations, depression, speech/swallowing difficulties, cognitive deficits, and autonomic dysfunction (Chaudhuri & Schapira, 2009; Shulman, Taback, Bean, & Weiner, 2001). Unfortunately, many pharmaceutical treatments and surgical approaches are ineffective at
treating non-motor manifestations of disease and in some cases surgery may exacerbate them. In addition to the incomplete coverage of motor and non-motor manifestations, pharmaceutical and surgical treatments have no effect on disease progression. There has yet to be a therapy that provides both symptomatic improvement for the motor and non-motor manifestations of PD, and that beneficially alters disease progression. Thus, alternative adjunct therapies need to be investigated to improve treatment of PD and to provide a comprehensive treatment strategy that addresses motor manifestations, non-motor complications and disease progression in PD. Exercise is an adjunct therapy for which there is both anecdotal and preliminary experimental evidence of improvements in motor manifestations, non-motor complications, and the progression of disease.

**Potential mechanisms of benefit from exercise on motor manifestations of PD**

In parkinsonian animal models, aerobic exercise improves motor function, including running velocity (Toy et al., 2014; Vuckovic et al., 2010) and rotarod performance (Petzinger et al., 2007). These improvements in motor performance have been linked to enhanced dopamine (DA) transmission via up-regulation of DA D2 receptors (Petzinger et al., 2007; Vuckovic et al., 2010), increased dendritic spine density, and arborization of medium spiny neurons in the direct and indirect striatal outflow pathways (Toy et al., 2014). Aerobic exercise has also been shown to protect against the effects of neurotoxic agents and to promote behavioural recovery from toxin-induced parkinsonism (Tillerson, Caudle, Reveron, & Miller, 2003). Specifically, when aerobic exercise was administered after a MPTP lesion, it decreased dopamine transporter
immunoreactivity and increased mRNA levels of D2 receptors, demonstrating neuro-restorative properties (Fisher et al., 2004). Exercise following MPTP administration has also been shown to improve dopaminergic transmission through increased dopamine release, reduced reuptake and decreased decay (Petzinger et al., 2007). While acute bouts of aerobic exercise in animal models have resulted in minimal alterations in inflammatory responses, aerobic exercise resulted in activation of the brain-derived neurotrophic factor (BDNF) signalling pathway (Wu et al., 2011). The expression of BDNF induced by exercise may also contribute to the therapeutic benefits of exercise in PD (Speelman et al., 2011; Wu et al., 2011).

In clinical populations of PD, exercise has shown symptomatic benefits for bradykinesia, balance, and improved quality of life (Allen, Sherrington, Paul, & Canning, 2011; Lauhoff, Murphy, Doherty, & Horgan, 2013; Ridgel, Peacock, Fickes, & Kim, 2012; Ridgel, Vitek, & Alberts, 2009; Sage & Almeida, 2009). One theory is that certain types of exercise may increase sensory feedback, which facilitates the function of remaining DA neurons or facilitates cortical reorganization that may bypass the dysfunctional basal ganglia (Sage & Almeida, 2009). Similarly, it has been hypothesized that exercise facilitates brain plasticity and normalizes corticomotor excitability in subjects with PD (Fisher et al., 2008). One untested possibility is that improvements in motor function result from exercise-induced DA release in the dorsal striatum, but these theories all await confirmation.
Potential mechanisms of benefit from exercise on non-motor complications of PD

The mechanisms underlying exercise-induced motor improvements in PD might be similar for non-motor symptoms as well. Exercise has been suggested to improve cognition (da Silva et al., 2018; Murray, Sacheli, Eng, & Stoessl, 2014) and more specifically, executive function (Cruise et al., 2011; Ridgel, Kim, Fickes, Muller, & Alberts, 2011; Tanaka, de Quadros, et al., 2009), processing speed, cognitive flexibility (Picelli et al., 2016), attention and working memory (David et al., 2015). Aerobic exercise has also been shown to improve spatial memory, linked to increased density of cholinergic neurons (Ang, Dawe, Wong, Moochhala, & Ng, 2006). Additionally, emotional reaction, social interaction, and mood in PD also appear to improve with exercise (de Paula, Teixeira-Salmela, Faria, de Brito, & Cardoso, 2006). Voluntary exercise has been shown to prevent depression and learned helplessness in animal models, linked to the normalization of serotonergic neuronal function (Greenwood et al., 2003). Evidence from healthy subjects has shown that regular exercise improves constipation and colonic transit times (De Schryver et al., 2005). This supports the use of exercise as an adjunctive therapy for autonomic dysfunction, a major contributor to impaired quality of life and impaired responsiveness to medication in PD. Exercise is also likely to improve fatigue (Elbers, van Wegen, Verhoef, & Kwakkel, 2012) and sleep (de Paula et al., 2006; Reynolds, Otto, Ellis, & Cronin-Golomb, 2016), but more studies are needed to confirm causal effects. From animal models, improvements in cognition are suggested to be a result of exercise-induced improvements of DA transmission (Fisher et al., 2004), neuroplasticity (Tajiri et al., 2010) and the protection against/reduction of
neuroinflammation in the basal ganglia (Goes et al., 2014; Wu et al., 2011). These mechanisms have yet to be explored in clinical populations, and randomized control trials are needed for further confirmation (Murray et al., 2014).

**Potential mechanisms of benefit from exercise on neuroinflammation and disease progression**

Immune responses can be innate, referring to an immediate non-specific reaction to a foreign substance/damage, or adaptive, referring to a cell-mediated and highly focused immune response targeting a specific invader or insult (Blandini, 2013; Stone, Reynolds, Mosley, & Gendelman, 2009). In the central nervous system (CNS) the innate immune response is mediated by cytokines, activation of complementary pathways and activation of microglia, and it is typically designed to repair and protect tissue. However, in response to a persistent stimulus, there is prolonged, chronic activation of microglia, which is commonly referred to as neuroinflammation (W. J. Streit, R. E. Mrak, & W. S. T. Griffin, 2004b). Neuroinflammation is seen in diseased states such as PD, Alzheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis (Streit et al., 2004b) and it is suggested that chronic activation of microglia may be detrimental and increase cell death (Blandini, 2013). It has been theorized that the aggregation of misfolded α-synuclein, which occurs in the parkinsonian brain, also causes activation of microglia (Beraud & Maguire-Zeiss, 2012). Animal models show that activation of microglia is associated with α-synuclein early in PD pathology (Su et al., 2008). Neuroimaging of activated microglia using the first generation translocator protein (TSPO) ligand \[^{11}\text{C}]\text{PK11195}\) has shown elevated binding, suggestive of microglial activation in
idiopathic PD patient populations throughout the brain stem, basal ganglia, striatum and even in the frontal and cortical circuitry (Gerhard et al., 2006). Evidence that the chronic activation of microglia occurs early in disease and persists throughout the disease duration, in conjunction with the interaction of microglial activation with the dysfunctional nigrostriatal pathway, suggests a parallel relationship between neuroinflammation and PD progression (Tansey & Goldberg, 2010). While it is yet to be determined if neuroinflammation is the cause or result of dopaminergic neuronal death in PD, we will, hereby, determine whether exercise results in reduced neuroinflammation and whether this is associated with a lower rate of decline in DA innervation.

**Measuring potential mechanisms of benefit from exercise on Parkinson’s disease**

To investigate the potential mechanisms of benefit from exercise in patients with PD, different types of neuroimaging can be used. While other functional neuroimaging (e.g., electroencephalogram, magnetoencephalography, functional near-infrared spectroscopy) have better temporal resolution, they only provide indirect evidence of dopaminergic function. Positron Emission Tomography (PET) imaging has superior spatial resolution and allows the quantitative determination of molecular data that provide insight into cellular function. The initial pre-clinical evidence links the benefits of exercise to improvements to the dopaminergic system (discussed above). Investigating dopamine release is crucial for the understanding of the mechanisms that underlie the benefits of exercise for PD. DA is released in response to a variety of stimuli, including medications (levodopa, amphetamine), placebo effect (De la Fuente-Fernandez, Lidstone,
& Stoessl, 2006; de la Fuente-Fernandez et al., 2001; Lidstone et al., 2010), and relatively minor physical activity (Ouchi et al., 2001; Ouchi et al., 2002). DA release can be measured using the radiotracer \([^{11}\text{C}]\text{raclopride}\) (RAC), which binds to the D2/3 dopamine receptors. Additionally, PET imaging can be used to study the effects of exercise on dopaminergic terminals (measure of disease progression) using the radio tracer \([^{11}\text{C}]\text{dihydrotetrabenazine}\) (DTBZ), which binds to the vesicular monoamine transporter type 2 (VMAT2), in order to assess the striatal density of DA nerve terminals. Other potential mechanisms such as neuroinflammation can also be investigated using PET using the radiotracer \([^{11}\text{C}]\text{PBR28}\), a marker of microglial activation.

Exercise may also enhance responsivity to reward, which requires neuroimaging with greater temporal resolution. As such, functional magnetic resonance imaging (fMRI) can be used to study the activation of brain areas in response to a task. FMRI is preferred to other types of functional neuroimaging based on relatively high spatial and temporal resolution.

**Rationale and hypothesis**

Preclinical and clinical evidence has shown aerobic exercise to be beneficial for the motor and non-motor manifestations of Parkinson’s disease. Evidence from animal models suggests exercise may have neuroprotective (Tillerson et al., 2003) and neurorestorative properties (Fisher et al., 2004), and may modulate neuroinflammation (Real et al., 2017), all of which may underlie the benefits of exercise for PD and promote behavioural recovery and improve dopamine release (Petzinger et al., 2007). Of particular
interest are changes in the dopaminergic system and potential modulation of neuroinflammation; however, the underlying mechanisms for exercise-derived benefits have yet to be studied in patient populations. The purpose of this dissertation was to examine these possibilities in participants with PD using multimodal neuroimaging techniques.

The **first objective** was to examine differences between habitual exercisers with PD and sedentary PD subjects, using PET and fMRI in a cross-sectional study (Chapter II). We compare differences in acute exercise-evoked dopamine release in the dorsal striatum using $[^{11}\text{C}]$ RAC PET imaging and activation of ventral striatum using a monetary reward task and fMRI imaging.

The **second objective** was to determine the effects of aerobic exercise on dopamine release, ventral striatal activation and neuroinflammation in a prospective, multimodal neuroimaging, randomized control trial. The prospective trial consisted of three sub aims:

1. **Aim I** – We examined the effects of aerobic exercise on reward connectivity using fMRI, and corresponding changes in mood, apathy, and cognition in PD (Chapter III)
2. **Aim II** - In a subset of the cohort, we evaluated the effects of aerobic exercise on repetitive transcranial magnetic stimulation-evoked DA release in the dorsal striatum using $[^{11}\text{C}]$RAC PET, and corresponding changes in motor function in subjects with PD (Chapter III)
iii. Aim III - In a different subset of the cohort, we investigated the effects of exercise on the activation of microglia using PET with a second-generation TSPO ligand $[^{11}C]PBR 28$ (Chapter IV).
Chapter II: Habitual exercisers vs. sedentary subjects with Parkinson’s disease: A multimodal PET and fMRI study

Objective: To examine differences in DA release, reward signalling and clinical features between habitual exercisers and sedentary subjects with Parkinson's disease (PD).

Methods: 8 habitual exercisers and 9 sedentary subjects completed $^{11}$C Raclopride (RAC) PET scans before and after stationary cycling to determine exercise-induced release of endogenous DA in the dorsal striatum. Additionally, fMRI assessed ventral striatum activation during reward anticipation. All participants completed motor (UPDRS III; finger tapping; Timed-up-and-go) and non-motor (Beck Depression Inventory; Starkstein Apathy Scale) assessments.

Results: $^{11}$C RAC analysis before and after stationary cycling demonstrated greater DA release in the caudate nuclei of habitual exercisers compared to sedentary subjects (p<0.05). Habitual exercisers revealed greater activation of ventral striatum during the fMRI reward task (p<0.05), and lower apathy (p<0.05) and bradykinesia (p<0.05) scores versus sedentary subjects.

Conclusions: Habitual exercise is associated with preservation of motor and non-motor function, possibly mediated by increased DA release. This study formulates a foundation for prospective randomized controlled studies.
Introduction

Exercise has symptomatic benefits on motor and non-motor manifestations of PD, and may slow disease progression (Ahlskog, 2011). Exercise improves bradykinesia (Ridgel, Muller, Kim, Fickes, & Mera, 2011; Ridgel et al., 2012), balance (Allen et al., 2011; Li et al., 2012), quality of life (Cruise et al., 2011; Lauhoff et al., 2013), cognition (Cruise et al., 2011; David et al., 2015; Murray et al., 2014; Ridgel, Kim, et al., 2011), and mood (Abrantes et al., 2012). However, the mechanisms underlying these benefits are unknown.

Exercise may result in enhanced DA release, contributing to improved motor function (dorsal striatum), enhanced mood, and reduced apathy (ventral striatum, VS). The purpose of this study was to investigate: a) dopamine release in the dorsal striatum using [$^{11}$C]Raclopride (RAC) Positron Emission Tomography (PET) in response to an acute bout of vigorous cycling, b) reward-related activation of the ventral striatum using functional magnetic resonance imaging (fMRI), and c) motor and non-motor behavioural differences in a cross sectional analysis of habitual exercisers and sedentary individuals with PD.

Methods

Seventeen subjects with mild to moderate PD (Hoehn & Yahr stages I-III), according to UK Brain Bank criteria, ages 45-70, were defined as habitual exercisers (HAB; n = 8) or sedentary (SED; n = 9) based on their usual level of exercise (>3 times and >180 minutes/week). Maximal oxygen uptake (VO$_2$ max) was determined in all
subjects to confirm cohort allocation. Each subject participated in two RAC PET scans, one fMRI scan and a battery of motor and non-motor behavioural tests. Exclusion criteria included: (i) atypical Parkinson syndrome (progressive supranuclear palsy, multiple system atrophy, drug-induced etc.), (ii) cognitive impairment (Montreal Cognitive Assessment score, MoCA < 24) or depression (Beck Depression Inventory, BDI score > 18), (iii) significant or unstable cardiovascular or respiratory disease, (iv) significant osteoporosis or arthritis, and (v) other neurological disease. The study was approved by the University of British Columbia (UBC) Clinical Research Ethics Board and carried out in accordance with the Declaration of Helsinki, and the Code of Ethics of the World Medical Association for experiments involving humans. Written informed consent was obtained from all participants prior to the start of the experiment.

**PET imaging**

To investigate DA release in the dorsal striatum, subjects underwent two PET scans (baseline and post exercise) following intravenous bolus administration of RAC (~185 MBq per scan), with a single bout of exercise between scans to elicit DA release. PET scans were conducted on a PET CTI/Siemens High Resolution Research Tomograph (HRRT) with in-plane resolution of 2.4 mm (see supplemental materials for more detail).

RAC PET scans were separated by 2.5 hours (> 7 half-lives for $^{11}$C) to allow decay of injected radioactivity. Prior to the second PET scan, all participants cycled on a bicycle ergometer for 30 minutes at 60% of VO$_2$ reserve (Lammertsma & Hume, 1996). Dopamine release ($\Delta$BP$_{ND} = BP_{ND}$ baseline – BP$_{ND}$ post exercise) was determined by a blinded analyst using the Reference Tissue Model (RTM) with a cerebellar reference
region (Lammertsma & Hume, 1996) for caudate, anterior, middle and posterior putamen, bilaterally. PET scans were performed after overnight withdrawal of dopaminergic medication. One subject from each cohort was excluded for technical reasons.

**MRI/fMRI imaging**

In order to assess the impact of habitual exercise on the mesolimbic dopamine reward system, we used functional MRI. fMRI has both spatial and temporal resolution superior to PET, both of which are important for the assessment of the reward pathways, especially as activity may be different during anticipatory and consummatory phases of reward delivery (Jordan, Zahodne, Okun, & Bowers, 2013). Activation of the ventral striatum is thought to correlate with dopamine release (Knutson & Gibbs, 2007; Schott et al., 2008) and the use of fMRI avoided the need for additional radioactivity. MRI scans were conducted on a Philips Achieva 3.0 Tesla scanner at the UBC MRI Research Centre. T1 scans were registered to the subject’s fMRI scans; scans were aligned to the Montreal Neurological Institute (MNI) space, and a region of interest (ROI) mask of the VS was created. The inverse registration matrix of the T1 scan to MNI space was applied to the ROI masks using FMRIB Software Library v5.0 (FSL) linear and non-linear registration tools (FLIRT, FNIRT) to bring the VS ROI data back into the patient’s native space. Subjects were scanned during a monetary reward task that required randomly selecting 1 of 4 cards. The probability of winning varied between blocks (20 consecutive trials/probability): 0%, 50%, 75% and 100% (van der Vegt et al., 2013). Subjects were explicitly informed about the probability of obtaining a monetary reward ($0.50) for selecting a winning card during each block. For each selected card, subjects were
provided visual (happy or sad face) and auditory (cheers or sighs) feedback. Each trial lasted 22-25 seconds and comprised an anticipatory phase (10 seconds immediately prior to feedback), a reward period (10 seconds immediately after feedback) and a 2-5 second inter-trial jitter period. For each patient, the voxel intensity of the VS ROI was calculated for each block and the difference between voxel intensity at baseline (average of the 2-second jitter period between all trials, 40 seconds per block) and the activity period of the anticipation period was calculated. Percent signal change (PSC) of blood oxygen level dependent (BOLD) signal of the ventral striatum (VS) during the anticipatory phase was the measure of interest as an indicator of dopaminergic function (Berridge, 2007). The monetary task was selected based on previous evidence showing activation of the nucleus accumbens (Knutson, Fong, Adams, Varner, & Hommer, 2001). Other reward tasks such as a natural hedonic stimuli (e.g., offering juice to a fasting subject) were considered, but unpublished data from our lab have suggested limited effectiveness in eliciting activation of the ventral striatum. All subjects were scanned off medication. Two subjects from the HAB group were excluded due to ferromagnetic metal implants.

Clinical assessments

Motor (Unified Parkinson’s Disease Rating Scale motor section, UPDRS III; Purdue pegboard; finger tapping; Timed-up-and-go, TUG and simple reaction time, RT) and non-motor (MoCA, BDI; and Starkstein Apathy Scale, SAS) functions were assessed. Clinical data were collected in both OFF and ON medication states.
**Statistical analysis**

The PET imaging data - dopamine release (i.e. change in RAC BP$_{ND}$) were compared using a 2 x 2 (group x side, better/worse hemisphere) ANCOVA with baseline RAC BP$_{ND}$ as a covariate. Age was not included in the model as there was no significant correlation between age and DA release ($p>0.05$) despite a difference of age between the groups.

The fMRI data were analyzed by a 2-way repeated measures analysis of covariance (RM ANCOVA) (group x probability with age and UPDRS III OFF as covariates) at the time point immediately prior to feedback, as that was likely to show maximal activity of the VS (Berridge, 2007).

Student’s $t$-tests were used to compare the motor and non-motor clinical data. A P value of $<0.05$ was used to determine significance across all statistical tests. Significant interactions were investigated using a Fisher’s LSD post hoc analysis.

**Results**

**PET imaging**

Habitual exercisers were approximately 6 years younger than the sedentary group ($t(16)=-2.40$, $p<0.05$). Baseline caudate RAC BP$_{ND}$ was higher in the HABs in both worse (contralateral to the more affected body side) ($t(14)=2.48$, $p<0.05$) and better hemispheres ($t(14)=2.51$, $p<0.05$) (Figure 1–A). There was no group difference in BP$_{ND}$ in any of the three regions of the putamen, nor was there any effect of age on BP$_{ND}$ amongst the participants. After 30 minutes of cycling there was a group by hemisphere
interaction ($F_{(1, 12)} = 5.6804, p<.05$) for $\Delta B P_{ND}$ in the caudate. The same trend was seen if age was added (in addition to baseline $B P_{ND}$) as a covariate ($p=0.055$). Post hoc analysis with Fisher’s LSD revealed greater caudate dopamine release in HAB compared to SED ($p<0.05$) in the worse hemisphere, and a similar pattern ($p=0.053$) in the better hemisphere.

fMRI imaging

Habitual exercisers had greater PSC in the VS of the worse hemisphere compared to sedentary subjects ($F_{(1, 12)} = 13.88, p<0.01$, main effect of group, Figure 1–E). The main effect of probability and group by probability interaction terms were not significant, but examination of the means suggests that the main effect of group is likely driven by the 75% and 100% probabilities.

Clinical assessments

As expected, HAB were more active on baseline exercise screening tool ($t(16)=5.03, p<0.01$) and time spent exercising ($t(16)=4.23, p<0.01$), and had a greater VO$_2$ max ($t(15)=8.63, p<0.01$) (Table 1). HAB had lower apathy scores ($S A S \ t(13)=-3.04, p<0.05$) (Figure 1-D) and were faster on finger tapping (right hand ($t(16)=2.93, p<0.01$), left hand ($t(14)=2.91, p<0.05$)) (Figure 1-C) and TUG ($t(12)=-2.38, p<0.05$) (Figure 1-B) (see Table 1 for a full list of clinical assessments).

Discussion

Amongst other factors, the symptomatic benefits of exercise may arise from increased activity in DA pathways (increased release, receptor density or both) leading to
changes in synaptic strength, and increased dendritic spine formation (Petzinger et al., 2013; Petzinger et al., 2015). Exercise may also improve neuronal survival and increase neurogenesis, increase neurotrophic factors, modulate immune responses, and improve mitochondrial function (Petzinger et al., 2013). We provide direct evidence for increased activity-evoked DA release in the caudate of habitual exercisers and indirect evidence for a similar effect in the mesolimbic pathway, where there was increased activation during performance of a monetary reward task. Habitual exercisers had less bradykinesia and better functional gait (TUG), which may result from greater striatal DA release. Increased DA release within the caudate may also contribute to the improvement of cognition reported in longitudinal exercise trials (Cruise et al., 2011; David et al., 2015; Petzinger et al., 2013; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009).

Mesolimbic DA release signals anticipation of reward (Berridge, 2007; Knutson et al., 2001; van der Vegt et al., 2013). Our fMRI paradigm showed greater activation of the ventral striatum in anticipation of monetary reward in habitual exercisers compared to sedentary PD subjects. Our findings suggest that exercise may also be associated with enhanced function in the mesolimbic pathway, resulting in increased capacity to anticipate reward. This was associated with clinical differences in mood, i.e. habitual exercisers were less apathetic compared to sedentary subjects (Figure 1D). These differences in ventral striatal activation may extend beyond PD and perhaps contribute to anecdotal evidence that habitual exercisers, both with and without PD, experience a feeling of wellbeing or reward as a result of exercise.
Limitations

The interpretations of our results are limited by the cross-sectional design of this study and the relatively limited sample size. The most important potential confound is reverse causation – i.e., that patients with less severe PD, less apathy and better mood are more likely to exercise and accordingly perform better on clinical assessments; they will also release more dopamine in response to both physical and motivational stimuli. Thus, differences in motor and non-motor function and DA release could conceivably reflect milder disease in the HAB group. Exercise may also be associated with a healthier lifestyle including better diet, more active social life, and fewer comorbidities. These possibilities are best addressed by a prospective randomized trial, currently underway.

Similarly, the interpretation could potentially be limited by the significant difference in age between the two groups. Age can affect the amount of dopamine released at the synapse, however, as previously noted, there was no significant correlation between age and dopamine release in our subjects and the results from the PET data did not change when age was added as a covariate.

The higher baseline caudate $BD_{ND}$ in the HABs is another limitation and may reflect a lower cumulative dose of dopaminergic medication in this group. However, differences in binding potential at baseline may also arise from increased D2 receptors in response to exercise, as has been previously suggested (Fisher et al., 2013). More research is needed to determine the effects of exercise on post-synaptic receptor density and neurogenesis.
The perception of exercise intensity may also have differed between the two cohorts. By controlling the relative intensity at 60% VO$_2$ reserve, the absolute workloads of exercise were different between groups. It could be argued that the differences in DA release result from the difference in absolute workloads. However, DA release may occur at even low levels of exertion (i.e. lower limb movement while in the scanner) (Ouchi et al., 2002). Additionally, group differences in DA release were also observed in VS during anticipation of monetary reward rather than during exercise.

The fMRI results were limited to the VS as a pre-planned comparison was preferred to a whole brain analysis. Given previous findings, showing activation of the nucleus accumbens (Knutson et al., 2001) it was hypothesized that differences between the groups would likely be in the VS as opposed to other areas. Additionally, the study was not powered for multiple comparisons given the low sample size and multiple probabilities. Future studies should conduct full brain maps to determine the global changes of exercise on reward processing.

While it appears that exercise plays a role in the clinical outcome of subjects with PD, future randomized control trials are needed to determine the cause-effect relationship between exercise and enhanced DA release, response to anticipation of reward and clinical outcomes. Future studies should also investigate other potential mechanisms of benefit from exercise.
Acknowledgements

This work was funded by the Pacific Parkinson’s Research Institute. Matthew Sacheli was supported by Parkinson Canada; A Jon Stoessl is supported by Canada Research Chairs. The authors would also like to thank TRIUMF for their contributions to the PET scans.

Supplemental

PET image acquisition

Each PET scan was preceded by a 10-minute transmission scan conducted with $^{137}$Cs rods for attenuation correction. Emission scans were obtained in dynamic mode (16 frames of increasing time) over 60 minutes following intravenous bolus infusion of $[^{11}C]$Raclopride and captured 206 planes (thickness of 1.2 mm).

Subjects were positioned using external lasers such that the scanner gantry was parallel to the inferior orbital-external medial line. Once the subject was positioned, a thermoplastic mask was moulded to the subject to minimize head movement during the scan and to assist with repositioning for the second scan. A Polaris Vicra motion capture system (©Northern Digital Inc., Waterloo, ON, Canada) was used to track head motion during the scan.

PET image analysis

Each PET scan was realigned using the motion tracking data and then the second half of the scan was realigned to the first. For each subject, the post exercise scan was
then realigned to the baseline scan.

Regions of interest (ROIs) with a standard ellipse size and shape were placed on the caudate ($74.3 \text{ mm}^2$), anterior and middle putamen ($47.5 \text{ mm}^2$), and the posterior putamen ($50.5 \text{ mm}^2$) of the baseline and post exercise scans. Binding potential (BP) was determined using tissue-input Logan analysis with a cerebellar reference region (size = $2520.85 \text{ mm}^2$) (Logan et al., 1996). The difference in BP between the baseline and post exercise scans was used to calculate dopamine release ($\Delta \text{BP}_{ND} = \text{BP}_{ND \text{ baseline}} - \text{BP}_{ND \text{ post exercise}}$). PET scans were performed after overnight withdrawal of dopaminergic medication.

**fMRI task**

The MRI scan consisted of a T1 weighted structural scan, 6 minute resting state-fMRI, and four blocks of fMRI scans during a monetary reward task to measure the blood oxygen level dependent (BOLD) signal of the ventral striatum (VS) in response to reward. The structural MRI used a T1-weighted Turbo Field Echo sequence (repetition time, TR 7724ms) with a field of view of $256\times200\times170$ and a voxel size of $1.0 \text{ mm}^3$. The fMRI (resting state and task) had a TR of 2000ms, an echo time (TE) of 30ms, field of view $240\times240\times143$ and voxel size of $3.0\text{mm}^3$.

Similar to the PET imaging, external lasers were used to position the subjects so the scanner gantry was parallel to the inferior orbital-external line. Subjects held a 4-button pad in their preferred hand and were instructed to select one of four cards by
pushing a button to move a cursor across the screen. A headset was also positioned on the subject’s ears for auditory feedback on the outcome.

The fMRI task was specifically designed to investigate the anticipation to monetary reward. The task was a chance-based card task designed to manipulate the expectation of reward with 4 different probabilities of winning (0%, 50%, 75% and 100%). Subjects had 20 trials at each probability, where success at each trial was worth $0.50. There were no losses and no requirement for skills to be learned during the task. Multiple probabilities were tested to allow for greatest response at maximal reward value (100% probability) or maximal uncertainty of reward (50% probability) (Fiorillo, Tobler, & Schultz, 2003), but also to account for a maximal response in PD subjects at an intermediate probability of 75% (Lidstone et al., 2010). Regardless of performance all subjects were paid $30 for participation, but this was unknown to the subject until after the completion of the study.
Authors’ Roles

Matthew A. Sacheli – conception, organization and execution of the research project, design and execution of the statistical analysis and writing of the manuscript.

Danielle K. Murray - conception, organization and execution of the research project, review and critique of manuscript.

Nasim Vafai – data analysis support (fMRI)

Mariya Cherkasova – data analysis (fMRI)

Katie Dinelle – data analysis support (PET)

Elham Shahinfard – data analysis (fMRI)

Nicole Neilson – patient recruitment, clinical support during scanning, review and critique of manuscript.

Jess McKenzie - patient recruitment, clinical support during scanning

Silke Appel-Cresswell – conception and organization of the research project, review and critique of the manuscript

Martin J McKeown - conception and organization of the research project, design of the fMRI data analysis

Michael Schulzer – design, review and critique of the statistical analysis

Vesna Sossi - conception, organization and execution of the research project, design of the PET analysis, review and critique of the manuscript.

A. Jon Stoessl - conception, organization and execution of the research project, design of the statistical analysis, review and critique of manuscript.
## Table 1. Participant demographics and clinical assessments

<table>
<thead>
<tr>
<th></th>
<th>Habitual Mean (SD)</th>
<th>Sedentary Mean (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since Dx</td>
<td>6.29 (4.50)</td>
<td>5.14 (2.04)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.78 (6.16)</td>
<td>68.89 (4.78)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td>8M</td>
<td>5M, 4F</td>
<td>-</td>
</tr>
<tr>
<td>UPDRS III (OFF)</td>
<td>21.42 (8.62)</td>
<td>26.00 (15.67)</td>
<td>ns</td>
</tr>
<tr>
<td>UPDRS III (ON)</td>
<td>18.00 (10.46)</td>
<td>23.33 (13.73)</td>
<td>ns</td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>36.62 (6.40)</td>
<td>16.83 (3.24)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Amount of exercise (# of times/ week)</td>
<td>16.21 (6.70)</td>
<td>3.07 (3.72)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Amount of exercise (minutes/ week)</td>
<td>476.31 (63.17)</td>
<td>104.26 (63.17)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Pegboard ON total (# of pegs)</td>
<td>39.25 (9.04)</td>
<td>37.00 (9.76)</td>
<td>ns</td>
</tr>
<tr>
<td>Finger tapping ON RH (# of taps)</td>
<td>76.38 (10.91)</td>
<td>64.78 (6.83)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Finger tapping ON LH (# of taps)</td>
<td>75.75 (18.00)</td>
<td>58.11 (4.91)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Finger tapping OFF RH (# of taps)</td>
<td>68.67 (8.16)</td>
<td>63.88 (7.28)</td>
<td>ns</td>
</tr>
<tr>
<td>Finger tapping OFF LH (# of taps)</td>
<td>50.63 (32.58)</td>
<td>53.78 (20.66)</td>
<td>ns</td>
</tr>
<tr>
<td>Timed-up-and-go OFF (s)</td>
<td>7.55 (0.85)</td>
<td>11.34 (4.09)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>BDI</td>
<td>4.00 (3.94)</td>
<td>11.06 (6.92)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>MoCA</td>
<td>28.17 (1.17)</td>
<td>29.00 (1.41)</td>
<td>ns</td>
</tr>
<tr>
<td>SAS positive questions</td>
<td>3.33 (1.51)</td>
<td>8.88 (4.85)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>SAS negative questions</td>
<td>4.50 (2.59)</td>
<td>6.63 (2.56)</td>
<td>ns</td>
</tr>
<tr>
<td>SAS Total score</td>
<td>7.83 (2.93)</td>
<td>15.50 (7.15)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>WH Caudate - RAC1</td>
<td>3.34 (0.57)</td>
<td>2.71 (0.54)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>BH Caudate - RAC1</td>
<td>3.31 (0.58)</td>
<td>2.71 (0.51)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>WH Anterior Putamen - RAC1</td>
<td>3.87 (0.51)</td>
<td>3.66 (0.72)</td>
<td>ns</td>
</tr>
<tr>
<td>BH Anterior Putamen- RAC1</td>
<td>4.02 (0.56)</td>
<td>3.40 (0.66)</td>
<td>ns</td>
</tr>
<tr>
<td>WH Middle Putamen - RAC1</td>
<td>4.63 (1.15)</td>
<td>4.30 (1.01)</td>
<td>ns</td>
</tr>
<tr>
<td>BH Middle Putamen - RAC1</td>
<td>4.93 (1.15)</td>
<td>4.08 (0.98)</td>
<td>ns</td>
</tr>
<tr>
<td>WH Posterior Putamen - RAC1</td>
<td>4.30 (1.26)</td>
<td>3.73 (0.06)</td>
<td>ns</td>
</tr>
<tr>
<td>BH Posterior Putamen - RAC1</td>
<td>4.49 (1.19)</td>
<td>3.16 (0.77)</td>
<td>ns</td>
</tr>
<tr>
<td>Daily dose PD medications (levodopa equivalents)</td>
<td>793.43 (450.16)</td>
<td>516.67 (291.82)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Years since Dx, years since diagnosis by a neurologist; UPDRS III, Unified Parkinson’s Disease Rating Scale motor section OFF (after 12 hour withdrawal from dopaminergic medication), ON (peak dose); VO2 max, maximal oxygen consumption during cycling;
Baseline exercise participation counts/week, the average amount of exercises done for more than 20 minutes multiplied by intensity, x1 for mild, x2 for moderate and x3 for vigorous exercise; Baseline exercise participation minutes/week, duration of exercise activities recorded in minutes multiplied by the counts per week; Pegboard, Purdue Pegboard – number of pegs placed in 60 seconds; TMT A & B, Trail Making Test version A (numbers only) and B (numbers and letters); Finger tapping, number of taps in 60 seconds; Timed-up-and-go, the time it takes to get up from a chair, walk 3m, turn around, walk 3m and sit down, average of 3 trials at normal walking pace (only collected in OFF state); Reaction time, simple reaction time, average of 5 trials; BDI, Beck Depression Inventory, MoCA, Montreal Cognitive Assessments; SAS, Starkstein Apathy Scale, positive questions (q1-8), negative questions (q9-14), total, sum score; RAC1, baseline Raclopride binding potential; WH, worse hemisphere contralateral to the more affected side of the body; BH, better hemisphere; Daily dose PD medications (levodopa equivalents), all subjects were on Sinemet IR or CR except for 2 subjects in the SED group were only on DA agonists (both in SED group), 2 subjects were on DA agonists + Sinemet (1 SED and one HAB) and 1 subject was treatment naïve (HAB group); and ns, not statistically significant.
Figure 1. PET, clinical, and fMRI results.
PET (A) ∆ Binding potential, baseline binding potential – Post 30 minutes of exercise, greater ∆ BP represents greater dopamine release. WH, worse hemisphere contralateral to the more affected side of the body; BH, better hemisphere. Clinical (B-D), B) Timed-up-and-go: Average time it takes to get up from a chair, walk 3m, turn around, walk 3m and sit down, lower time indicated better functional movement. C) Finger tapping: total number of taps over 30 seconds for the right and left hands for HAB and SED at peak dose. D) Starkstein Apathy Scale: Total apathy scores for habitual and sedentary PD.
subjects, higher scores denote greater apathy. fMRI (E) Anticipation of reward in habitual exercisers and sedentary PD subjects, Percent signal change differences at all probabilities (0%, 50%, 75%, 100%) in the worse hemisphere. *p<0.05, **p<0.01, #p=0.053, error bars denote SEM.
Chapter III: Exercise increases caudate dopamine release and ventral striatal activation in Parkinson’s disease

Objective: To examine the effects of aerobic exercise on evoked dopamine release and activity of the ventral striatum using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in Parkinson’s disease (PD).

Methods: Thirty-five participants were randomly allocated to a 36-session aerobic exercise or control intervention. Participants underwent an fMRI scan while playing a reward task before and after the intervention to determine the effect of exercise on the activity of the ventral striatum in anticipation of reward. A subset of participants (n=25) completed [11C]Raclopride PET scans to determine the effect of aerobic exercise on repetitive transcranial magnetic stimulation (rTMS)-evoked release of endogenous dopamine in the dorsal striatum. All participants completed motor (MDS-UPDRS III; finger tapping; Timed-up-and-go) and non-motor assessments (Starkstein Apathy scale, Beck Depression Inventory, reaction time, Positive and Negative Affect Schedule, Trail Making Test (A and B), and Montreal Cognitive Assessment) before and after the interventions.

Results: The aerobic group exhibited increased activity in the ventral striatum during fMRI in anticipation of 75% probability of reward (p=0.01). The aerobic group also demonstrated increased rTMS-evoked dopamine release in the caudate nucleus (p=0.044) and increased baseline non-displaceable binding potential in the posterior putamen of the less affected rTMS stimulated hemisphere measured by PET (p=0.03).
Conclusions: Aerobic exercise alters responsivity of the ventral striatum, likely related to changes to the mesolimbic dopaminergic pathway, and increases evoked dopamine release in the caudate nucleus. This suggests that the therapeutic benefits of exercise are in part related to corticostriatal plasticity and enhanced dopamine release.
Introduction

Exercise results in improvements in motor and non-motor manifestations of Parkinson’s disease (PD). People with PD who exercise regularly show improved clinical outcomes and better quality of life (Baatile, Langbein, Weaver, Maloney, & Jost, 2000; Bollinger, Cowan, & LaFontaine, 2012; de Paula et al., 2006). Additionally, exercise improves cognitive function, particularly executive function (David et al., 2015; Murray et al., 2014; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009), and reduces apathy and depression (Abrantes et al., 2012).

The beneficial effects of exercise may be related to changes in the dopaminergic system. One possible mechanism is upregulation of dopamine (DA) D2 receptors (Fisher et al., 2013; Petzinger et al., 2007; Vuckovic et al., 2010), which would be commensurate with both motor and non-motor improvements (Cruise et al., 2011; David et al., 2015; Murray et al., 2014; Ridgel, Kim, et al., 2011; Ridgel, Muller, et al., 2011; Ridgel et al., 2012).

Aerobic exercise also changes the vasculature in the brain, increases neurotrophic signalling and promotes neurogenesis (Petzinger et al., 2013). Neuroimaging evidence in older adults suggests that aerobic fitness is associated with improved white matter integrity in prefrontal and temporal brain regions (Voss et al., 2013). In addition to these biological changes, participation in exercise is commonly linked to enhanced social interaction, which also leads to improved well-being and quality of life (de Paula et al., 2006). Multiple mechanisms likely contribute to the benefits of exercise in PD, including
increases in brain and glial derived neurotrophic factors and modulation of neuroinflammation (Petzinger et al., 2013).

Of particular interest, recent evidence shows differences in both caudate dopamine release after exercise, and ventral striatal activation during anticipation of reward, as well as improvements in apathy and mood in habitual exercisers compared to sedentary individuals (Sacheli et al., 2018). This suggests that exercise may induce plasticity and thereby enhance dopamine release in both dorsal nigrostriatal and ventral mesolimbic projections. However, the cross-sectional design of that study precludes a causal interpretation. The purpose of the current study was to determine the effects of exercise on dorsal and ventral striatal reactivity through a prospective randomized control trial.

**Methods**

Twenty-six participants aged 45-80 years old with mild to moderate (Hoehn & Yahr stages I-III) idiopathic PD, according to UK Brain Bank criteria, were randomly allocated into either an aerobic exercise (n=14) or a control, stretching intervention (n=12). There were also 9 sedentary subjects added from the previous cross-sectional study that were also allocated into the aerobic exercise (n=6) or control, stretching intervention (n=3), but only for the fMRI and clinical assessments. The total number of participants enrolled was 35 (aerobic n=20, control n=15) (see Figure 4 and Figure 6 – Chapter IV). All subjects were enrolled between September 2013 and August 2017. The first subject was enrolled September 11, 2013 and the final post intervention assessment
was completed November 23, 2017. A blocked randomization scheme was determined prior to the enrolment of the first subject and completed by a biostatistician external to the project. All subjects and assessors were blinded to group allocation. Subjects were debriefed after the completion of the post intervention assessments and were told about the other intervention.

The primary outcome was change in DA release (measured by change in $[^{11}\text{C}]$Raclopride (RAC) binding) evoked by repetitive transcranial magnetic stimulation (rTMS), between baseline and following the exercise/control intervention. Secondary outcomes were percent signal change in the ventral striatum in anticipation of monetary reward, and a battery of motor and non-motor assessments (see below). The initial proposed sample size was a total of 30 patients ($n=15$ per group). This sample size is sufficient to detect a between-group different in [RAC baseline-RAC activation] (i.e. DA release) of 1.05 SD (delta BP=0.42) with 80% power (2-tailed, $\alpha<0.05$)

**Exclusion Criteria**

Exclusion criteria included: (i) atypical Parkinson syndrome (progressive supranuclear palsy, multiple system atrophy, drug-induced etc.), (ii) significant cognitive impairment (Montreal Cognitive Assessment, MoCA score $<24$) or depression (BDI score $>18$), (iii) significant or unstable cardiovascular or respiratory disease, (iv) significant osteoporosis or arthritis, (v) other neurological disease (e.g. myopathy) and (vi) contra-indications to MRI scanning.
Individuals participated in fMRI scans and a battery of motor and non-motor assessments (described below) and a peak aerobic capacity assessment (VO$_2$ max) on a stationary bike. During the VO$_2$ max test, heart rate and power output (watts) were also recorded and used to prescribe and scale the intensity of the aerobic exercise intervention (see below). Assessments were conducted at baseline and after a supervised 3-month exercise intervention of either stationary cycling or stretching (see Figure 5).

In addition to the above assessments, a subset of 26 participants (aerobic, n=14; control stretching, n=12) participated in two $[^{11}C]$RAC PET scans and one $[^{11}C]$Dihydrotetrabenazine (DTBZ) PET scan at baseline, and two $[^{11}C]$RAC PET scans upon completion of the interventions. The two $[^{11}C]$RAC PET scans, performed at baseline and after the aerobic/control intervention, were separated by a session of repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex based on a previously published protocol to elicit endogenous dopamine release (Strafella, Ko, Grant, Fraraccio, & Monchi, 2005) (details in supplemental online material, see Figure 4. for participant enrolment flow chart). Repetitive TMS was selected as the stimulus as evoked dopamine release is likely to be mediated by activation of corticostriatal projections and changes are therefore likely to reflect corticostriatal plasticity (Strafella et al., 2005).

The study was approved by the University of British Columbia (UBC) Clinical Research Ethics Board and carried out in accordance with the Declaration of Helsinki, and the Code of Ethics of the World Medical Association for experiments involving
Exercise/control interventions

The participants in the aerobic exercise and stretching control interventions met 3 times per week for 3 months, (36 sessions). An instructor led both interventions and the class size was 2-4 people. The aerobic exercise consisted of 40–60 minutes of cycling separated into 5-10 minutes of warm-up (no resistance), 30-50 minutes of cycling at 60-80% VO$_2$ max, and 5-10 minutes of cool-down. Aerobic exercise was selected as the active intervention to investigate the effects of exercise on dopaminergic function based on evidence from animal models suggesting that aerobic exercise induced changes to the dopamine system (Fisher et al., 2013; Petzinger et al., 2007; Vuckovic et al., 2010). Cycling was selected as the aerobic exercise of choice because it is generally better tolerated than other aerobic activities (e.g. treadmill running) by patients with PD, who may have difficulties with balance.

All participants started at a workload similar to that achieved at 60% of their VO$_2$ max during the VO$_2$ max test (i.e., moderate activity). This was determined by calculating 60% of the participant’s VO$_2$ max and cross referencing the power output (watts) exerted at a similar VO$_2$ level during the VO$_2$ max test. Heart rate (HR), power output (watts) and rate of perceived exertion (RPE, determined with the Borg RPE scale (Scherr et al., 2013)), were collected every 5 minutes during cycling. The level of exercise was increased every 3 sessions (as tolerated) by either increasing the intensity -
an increase in workload that was consistent with a 5% increase in VO_2 (i.e. after the first 3 sessions the workload was increased to the workload that was achieved at 65% of VO_2 max), or by increasing the duration by 5 minutes, to ensure a sustained training stimulus of cycling. Power output (watts) was used to regulate the increase in intensity of the aerobic exercise and to standardize the degree of exercise across the aerobic group rather than percent maximal heart rate, as autonomic dysfunction in PD may attenuate the HR response to exertion (Bouhaddi et al., 2004; DiFrancisco-Donoghue, Elokda, Lamberg, Bono, & Werner, 2009). The workloads (watts) were estimated by determining the desired percent of VO_2 max (e.g., 60%) and cross-referencing to power that was achieved at that VO_2 level during the VO_2 max test. This was repeated for 60, 65, 70, 75 and 80% of VO_2 max to determine the corresponding workloads for the exercise intensity prescription. The intensity of the exercise (work or time, alternating every week) was increased if the participant tolerated the previous 3 exercise sessions (e.g., they were able to sustain 60 RPM for the time of the session over that week’s sessions). If the participant was unable to tolerate the prescribed intensity (e.g., the workload was lowered to allow the participant to maintain 60 RPMs), then the intensity was not increased the following week, until the participant could tolerate the prescribed intensity.

The stretching program consisted of a series of seated and standing stretches and low impact exercises approved by Parkinson Society Canada. The primary purpose of the stretching intervention was to account for benefits not directly related to aerobic exercise, the intervention of interest, (i.e., social interaction, halo and Hawthorne effects).
Clinical assessments

Motor severity was assessed using the Unified Parkinson’s Disease Rating Scale motor section (MDS-UPDRS III), Purdue pegboard (left and right hands), finger tapping (left and right hands), Timed-up-and-go (TUG), and simple reaction time (RT). Motor assessments were performed in both OFF (after at least a 12-hour withdrawal of Parkinson’s medications) and ON medication states.

Cognition was evaluated using the Montreal Cognitive Assessment (MoCA), and Trail Making A and B (TMT A, TMT B) tests. Mood, depression and apathy were assessed with the Positive and Negative Affect Schedule (PANAS), BDI (Beck, Steer, Ball, & Ranieri, 1996), and Starkstein Apathy Scale (SAS) (Starkstein et al., 1992) respectively. Non-motor measures were assessed in the ON medication state. Independent student’s t-tests were used to compare the motor and non-motor clinical data.

MRI/fMRI scans

MRI scans were conducted on a Philips Achieva 3.0 Tesla scanner at the UBC MRI Research Centre. The MRI scan consisted of a T1 weighted structural scan, and four blocks of fMRI scans during a monetary reward task to measure the blood oxygen level dependent (BOLD) signal of the ventral striatum in response to reward (see supplemental online material for full details).

The fMRI task has been previously described (Sacheli et al., 2018). Briefly, the task was a chance-based monetary card game designed to manipulate the expectation of
reward with four different probabilities of winning (0%, 50%, 75% and 100%, 20 trials/probability) (see supplemental online material for full details).

**fMRI analysis**

T1 scans were registered to the subject’s fMRI scans; scans were aligned to the Montreal Neurological Institute (MNI) space, and region of interest (ROI) masks of the VS were created. The inverse registration matrix of the T1 scan to MNI space was applied to the ROI masks using FMRIB Software Library v5.0 (FSL) linear and non-linear registration tools (FLIRT, FNIRT) to bring the VS ROI data back into the patient’s native space. All participants were scanned after overnight withdrawal of dopaminergic medication.

**PET imaging**

All PET scans were performed after overnight withdrawal of dopaminergic medication. Each PET scan was preceded by a 10-minute transmission scan conducted with a $^{137}$Cs source for attenuation correction. For $[^{11}C]$RAC and $[^{11}C]$DTBZ, emission scans were obtained in dynamic mode (16 frames of increasing time) over 60 minutes following a 60-second intravenous bolus infusion of the tracer. PET scans were conducted on a PET Siemens High Resolution Research Tomograph (HRRT) with spatial resolution of (2.4 mm$^3$) FWHM (de Jong et al., 2007).

To investigate DA release in the dorsal striatum, participants underwent two PET scans (baseline and post rTMS stimulus) following intravenous bolus administration of $[^{11}C]$RAC (~185 MBq per scan). The rTMS stimulus of the primary motor cortex only in
the less affected hemisphere, was performed between the two $[^{11}\text{C}]$RAC scans to elicit DA release (details in supplemental online material). This protocol was repeated after the 3-month aerobic exercise or control intervention.

On a separate day, participants were also scanned following intravenous bolus administration of ~296 MBq (8mCi) $[^{11}\text{C}]$DTBZ to assess DA innervation. $[^{11}\text{C}]$DTBZ binds to vesicular monoamine transporter 2 and provides an estimate of pre-synaptic DA nerve terminal density, which was used as a covariate for the analysis of the data. The $[^{11}\text{C}]$DTBZ scans were only performed at baseline.

**PET image analysis**

Each PET scan was corrected for motion via a frame-to-frame realignment using SPM12 (Nichols, Qi, Asma, & Leahy, 2002). For each subject, each subsequent $[^{11}\text{C}]$RAC scan was realigned to the original baseline scan.

For the $[^{11}\text{C}]$RAC and $[^{11}\text{C}]$DTBZ scans, regions of interest (ROIs) with a standard ellipse size and shape were placed on the caudate (74.3 mm$^2$), anterior and middle putamen (47.5 mm$^2$), and the posterior putamen (50.5 mm$^2$) of the baseline and post exercise images by a blinded analyst (Lidstone et al., 2010). A series of ellipses was used to ensure that the majority of the caudate and putamen was assessed, to account for the possibility of a rostro-caudal gradient of dopamine release and that the shape and size of the ROIs were consistent for all patients. The non-displaceable binding potential ($\text{BP}_{\text{ND}}$) (Innis et al., 2007) was determined using tissue-input Logan analysis with a
cerebellar ([11C]RAC) or occipital cortex ([11C]DTBZ) reference region (Logan et al., 1996). The difference between baseline and post rTMS [11C]RAC BP_{ND} was used to calculate dopamine release (ΔBP_{ND} = BP_{ND} baseline – BP_{ND} post rTMS). ΔBP_{ND} before the aerobic/control intervention was then compared to ΔBP_{ND} after the aerobic/control interventions to determine the effect of exercise on rTMS induced DA release. Differences in BP_{ND} baseline (before rTMS) were also investigated before and after aerobic/control interventions to determine the effect of exercise on D2/3 dopamine receptor availability.

**Statistical analysis**

For the clinical assessments, repeated measures analysis of variance (RM ANOVA) (group x time) was used to compare the effect of exercise on clinical assessments. The fMRI analysis was conducted by a 3-way RM ANOVA (group x time x probability), to compare before and after aerobic exercise or control interventions in ventral striatum of each hemisphere, at the time point immediately prior to feedback, as this is when anticipation is maximal (Berridge, 2007; Knutson et al., 2001). *Pre-planned contrasts* were conducted to test the specific hypotheses that the 50% and 75% probabilities would demonstrate the specific response following the aerobic exercise intervention. The 50% probability is associated with maximal uncertainty of reward in healthy non-human primates (50% probability) (Fiorillo et al., 2003), while a probability of 75% was associated with maximal response to placebo in patients with PD (Lidstone et al., 2010) and also drove the main effect we previously observed in habitual exercisers with PD using the same reward task (Sacheli et al., 2018). Dopamine release was
compared using a 2 x 2 (group x side, better/stimulated, worse/unstimulated hemisphere) ANCOVA, with baseline $[^{11}\text{C}]$RAC BP$_{ND}$ and $[^{11}\text{C}]$DTBZ BP$_{ND}$ as covariates. A 3-way RMANOVA (group x time x ROI) was conducted to assess the effects of exercise on baseline BP$_{ND}$. A P value of <0.05 was used to determine significance for all statistical analyses. Significant interactions were investigated using a Fisher’s LSD post hoc analysis. A Brown and Forsythe test was used to test homogeneity of variance between different groups for each dependent variable. The Brown and Forsythe test was preferred over the Levene test, as the groups did not have equal sample sizes.

**Results**

There were no significant differences for the Brown and Forsythe tests, with the exception of the fMRI data at baseline in the worse hemisphere at 50% probability. Histograms showed the data to be randomly distributed (some right skewed, some left skewed, and some symmetrical) so no transformation test would convert the data to reasonable symmetry and normality.

**Clinical assessments**

Five participants did not undergo fMRI imaging (n=3 aerobic, n=2 control) due to claustrophobia in the scanner (n=1), cardiac stent (n=1), change in PD diagnosis after the intervention (n=1), and personal scheduling conflicts causing dropout from the interventions (n=2). There were no adverse effects of the interventions causing dropouts during the trial.
At baseline there were no statistical differences between the groups in terms of age, years since diagnosis, motor severity (MDS-UPDRS III off medication), VO$_2$ max or the amount of exercise (time and counts) (Table 2).

After the interventions, there was a significant interaction (group x time) for VO$_2$ max ($F_{(1,27)}=9.75$, $p<=.01$). Fisher’s LSD post hoc revealed a significant VO$_2$ max increase in the aerobic exercise group only ($p<0.001$). There were no other significant effects of the interventions on the motor or non-motor clinical measures (see Table 3 for full details).

**fMRI imaging**

In the ventral striatum, there were no interactions of group x time x probability in either hemisphere. *Pre-planned contrast* at 50% probability also showed no effect of either intervention (aerobic or stretching) in either hemisphere. However, *pre-planned contrast* at 75% showed a significant increase after the aerobic intervention only, in both the better ($F_{(1,28)}=9.37$, $p<0.01$) (Figure 2A) and the worse ($F_{(1,28)}=7.69$, $p<0.01$) hemispheres (Figure 2B) (see Table 4 for full details).

**[$^{11}$C]RAC imaging**

A subset of 25 individuals participated in PET imaging. Two participants were excluded from the PET imaging cohort (one from each group) due to the previously noted personal scheduling conflict causing dropout from the aerobic exercise intervention (n=1, same person as noted in the fMRI section), and inability to establish a consistent resting
motor threshold to perform the rTMS between [$^{11}$C]RAC scans (n=1, control intervention group, different from those exclusions noted in the fMRI section).

In the stimulated less affected hemisphere, there was a significant group x time interaction in caudate $\Delta$BP$_{ND}$ ($F_{(1,19)}=4.63$, p<0.05). A Fisher’s LSD post hoc (group x time) analysis showed a significant effect of time for the aerobic groups, showing a significant increase in dopamine release after the aerobic intervention. There were no differences at baseline between the aerobic and control groups and no effect of time for the control group. (Figure 3A). In the putamen of the stimulated less affected hemisphere, there were qualitatively similar but non-significant changes in dopamine release post-aerobic intervention, which were not seen in the control group. There were no changes in either caudate or putamen of the non-stimulated more affected hemisphere (see Table 4 and Figure 5B for full details).

Baseline (i.e. pre-stimulation) BP$_{ND}$ showed a group x time x ROI interaction ($F_{(3,63)}=3.11$, p<0.05; Figure 3B). Fisher’s LSD post hoc showed a significant increase in baseline BP$_{ND}$ in the posterior putamen following the aerobic exercise intervention, as well as a significant decrease of baseline BP$_{ND}$ in the middle putamen in the control group.

Discussion

The benefits of aerobic exercise likely result from promotion of synaptic neuroplasticity leading to modification of dysfunctional brain circuitry (Petzinger et al.,
2013), improved dopaminergic function (Petzinger et al., 2013; Petzinger et al., 2015; Petzinger et al., 2007), and increased D2 dopamine receptor expression in people with PD (Fisher et al., 2013; Vuckovic et al., 2010). Previous evidence from a cross-sectional study supported this notion by showing greater dopamine release in response to exercise and greater activation of the ventral striatum in anticipation of monetary reward in people with PD who were habitual exercisers compared to those who were sedentary (Sacheli et al., 2018). However, the cross-sectional design of that study and the potential for reverse causation (i.e. that PD patients with better dopaminergic function are more likely to exercise), limits the interpretation of the results. To our knowledge, this is the first prospective study in individuals with PD to investigate the effects of exercise on dorsal striatal dopamine release and ventral striatal response to reward anticipation.

The current study showed that after 3 months of aerobic exercise, there is increased rTMS-evoked dopamine release in the caudate and greater activation of the ventral striatum in anticipation of reward; this was not observed after 3 months of stretching, the intervention that was used to control for social interaction and other possible secondary effects. The increase in dopamine release was only observed in the caudate of the stimulated hemisphere and is in keeping with enhanced corticostriatal plasticity in response to sustained moderate-high intensity exercise. It also raises the possibility that the commonly reported improvements in cognition in PD participants after exercise (Cruise et al., 2011; David et al., 2015; Petzinger et al., 2013; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009) may be explained by increased caudate dopamine function. We did not demonstrate improvements in cognition, but this may
reflect a ceiling effect. An increase in BP_{ND} was also observed in the posterior putamen after aerobic exercise, suggesting an increase in D2/D3 dopamine receptor availability in this region. While this finding is compatible with a previous study (Fisher et al., 2013), the increase here was small and of uncertain importance, as a decrease of comparable magnitude was seen in the mid-putamen of the control group. Increased dopamine release and possibly increased dopamine receptor expression may contribute to the beneficial effects associated with exercise in PD. However, the precise mechanism(s) is (are) unknown.

The fMRI findings were also in keeping with the results of our cross-sectional study. BOLD activation of the ventral striatum of both hemispheres in anticipation of a 75% probability of monetary reward was significantly greater after a course of intensive aerobic exercise, whereas no effect was seen after the stretching control intervention. These findings suggest that aerobic exercise enhances responsivity of mesolimbic reward pathways.

This study did not directly compare different intensities of aerobic exercise, but the dopaminergic changes after moderate-high intensity aerobic exercise coincide with previous findings that show high intensity to be more beneficial than lower intensity aerobic exercise in de novo PD patients (Schenkman et al., 2018). While our study did not show changes in motor or non-motor assessments, we suspect that with a longer intervention and larger sample size, clinical changes might emerge. There is likely a threshold of exercise intensity that needs to be met in order to elicit neurological changes.
that are beneficial for people with PD. Future studies should investigate the interaction between exercise intensity and mechanisms of exercise that are beneficial for people with PD.

Enhancement of dopaminergic function in both ventral striatum and caudate provides a likely explanation for many of the beneficial effects of exercise on symptoms of PD. The enhancement of reward-related responsivity in the mesolimbic system may also contribute to exercise related benefit in other conditions such as depression and apathy, as well as mood enhancement in healthy individuals (e.g. “runners’ high”). Dopaminergic changes are likely not the only explanation for the benefits of exercise in PD. Other mechanisms may include modulation of neuroinflammation (Real et al., 2017), increases in glial and brain derived trophic factors (Real et al., 2013; Wu et al., 2011), and cerebral blood flow (Swain et al., 2003). The current study provides evidence for a mechanism that contributes not only to short-term symptomatic benefit from exercise in PD, but also to more sustained effects via enhanced corticostriatal plasticity.

Limitations

Although we used separate ANCOVAs with Fisher’s LSD post-hoc measures, we did not correct for all the comparisons that were made in the PET study (i.e. caudate and putamen sub regions) given the limited number of participants.

Changes in dopamine release in the mesolimbic circuitry are inferred, as this study did not directly measure ventral striatal dopamine release. However, to our
knowledge, this is the first controlled study to show an effect of exercise on ventral striatal responsivity, and may thereby provide some insight into one of the mechanisms that underlie the changes in non-motor symptoms commonly observed in other exercise studies (Cruise et al., 2011; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009).

Unlike our prior (Sacheli et al., 2018) cross-sectional study, in which we found significant differences in depression and apathy scores in the habitual exerciser group, in this study there were no significant changes in clinical scores. This may reflect the relatively short length of the intervention (3 months). While 3 months is a common duration in many exercise intervention studies in PD literature (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008), more recent evidence suggests that a longer period of time is needed for the clinical effects of exercise to be fully evident (D. Corcos et al., 2012; D. M. Corcos et al., 2013; David et al., 2015). We hypothesize that a longer timeline may be needed to detect changes in motivation and behaviour. Additionally, failure to find significant effects in the clinical scales could result from their limited sensitivity and/or a ceiling effect. We limited recruitment to those participants with mild to moderate idiopathic PD and excluded those with a Beck Depression Inventory (BDI) >18, making it less likely to detect clinical changes. Future studies should investigate the longitudinal effects of exercise on motivation, mesolimbic dopamine release, mood, and disease progression.

It should also be noted that the current trial was stopped prior to meeting the recruitment goal suggested by the power calculation. Subject recruitment was more
difficult than anticipated due to a high prevalence of ineligible subjects (see Figure 6, Chapter IV). A preliminary analysis was conducted for the primary outcome once at least 10 subjects were recruited for each group. This resulted in a comparison of unequal groups and lower than anticipated sample size. Despite this, even with the small sample size there were significant findings for both the primary and secondary outcomes. An increased sample size may have shown additional changes in the primary outcome measure (e.g., changes in dopamine release in the putamen) or other changes in secondary outcome measures (e.g., clinical changes). However, based on scanning costs and the large patient burden, it was decided to stop the trial early due to the overall positive result.

Lastly, upon recruitment to the study, all patients were informed that they would be randomized into one of two types of exercise interventions. All patients were blinded to allocation, as neither group knew what the other group was doing. Thus, some patients may have incorrectly believed that they were in the active group rather than the control group. Conversely, the slow moving nature of the control intervention was frustrating for some participants and may have led to a negative placebo effect in these individuals, while some patients in the aerobic group complained of discomfort commonly associated with high intensity exercise (e.g., muscle fatigue, heavy breathing, sweating).

**Conclusion**

This multimodal imaging study provides evidence that exercise enhances dopaminergic function and reward-related responsivity in both nigrostriatal and mesolimbic projections, and may thereby contribute to improvements in motor function,
mood and apathy. Our findings provide biological evidence that exercise should be used as an adjunct therapy for PD.

**Acknowledgements**

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Supplemental

MRI/fMRI scans

The MRI/fMRI scans were performed on a separate day from the PET scans. The protocol for the MRI and fMRI scans was identical to that used in (Sacheli et al., 2018). The procedure consisted of a T1 weighted structural scan, and four blocks of fMRI scans during a monetary reward task to measure the blood oxygen level dependent (BOLD) signal of the ventral striatum (VS) in response to reward. The structural MRI used a T1-weighted Turbo Field Echo sequence (repetition time, TR 7724ms) with a field of view of 256x200x170 and a voxel size of 1.0 mm$^3$. The fMRI (resting state and task) had a TR of 2000ms, an echo time (TE) of 30ms, field of view 240x240x143 and voxel size of 3.0mm$^3$.

External lasers were used to position the participants so the scanner gantry was parallel to the inferior orbital-external line. Participants held a 4-button pad in their preferred hand and were instructed to select one of four cards by pushing a button to move a cursor across the screen. A headset was also positioned on the participants’ ears for auditory feedback on the outcome.

fMRI task

The fMRI task was specifically designed to investigate the anticipation of monetary reward. The task was a chance-based card task designed to manipulate the expectation of reward with four different probabilities of winning (0%, 50%, 75% and 100%). Participants had 20 trials at each probability, where success at each trial was
worth $0.50. There were no losses and no requirement for skills to be learned during the task. Multiple probabilities were tested to allow for greatest response at maximal reward value (100% probability) or maximal uncertainty of reward (50% probability)(Fiorillo et al., 2003), but also to account for a maximal response in PD individuals at an intermediate probability of 75% (Lidstone et al., 2010). Regardless of performance all participants were paid $30 for participation, but this was unknown to the subject until after the completion of the study. Participants were explicitly informed about the probability of obtaining a monetary reward ($0.50) for selecting a winning card during each block. The participants were also instructed that the task was purely chance (analogous to a slot machine) and there was no pattern to learn that could improve odds. Our prior study (Sacheli et al., 2018) demonstrated that the success of prior card selections had no impact on the selection for the trials that followed. For each selected card, participants were provided visual (happy or sad face) and auditory (cheers or sighs) feedback. Each trial lasted 22-25 seconds and comprised an anticipatory phase (10 seconds immediately prior to feedback), a reward period (10 seconds immediately after feedback) and a 2-5 second inter-trial jitter period. For each patient, the voxel intensity of the VS ROI was calculated for each block and the difference between voxel intensity at baseline (average of the 2 second jitter period between all trials, 40 seconds per block) and that of the anticipation period was calculated. Percent signal change (PSC) of blood oxygen level dependent (BOLD) signal of the ventral striatum (VS) during the anticipatory phase was the measure of interest as an indicator of dopaminergic function (Berridge, 2007).
rTMS protocol

\[^{11}\text{C}]\text{RAC PET scans were separated by 2.5 hours (> 7 half-lives for }^{11}\text{C}), to allow decay of injected radioactivity. Prior to the second PET scan, rTMS was administered based on the protocol of (Strafella et al., 2005). Repetitive TMS was preferred over other types of stimuli (e.g., stationary cycling, levodopa administration) as it provides a measure of endogenous dopamine release and may provide a measure of corticostriatal plasticity (Strafella et al., 2005). Repetitive TMS was delivered using a MagStim2 Super Rapid Plus-I stimulator with a cooled 7-cm inner diameter figure-of-eight coil (Magstim Co., UK). The ‘hotspot’ for eliciting consistent motor evoked potentials (MEPs) in the contralateral first dorsal interosseous muscle was found by positioning the coil over the scalp region overlying the hand motor cortex representation (Yousry et al., 1997). This process was repeated for the post-intervention scans as well. BrainSight stereotaxic system (Rogue Research, Montreal, QC, Canada) was used for localization and position monitoring of the motor cortex ‘hotspot’ using each individual’s MRI for co-registration. We delivered 4 blocks of stimulation over the primary motor cortex of the less affected hemisphere (ipsilateral to the more affected body side as determined by MDS-UPDRS III); each block comprised 15, 10-pulse trains of 1s duration (10 Hz) with an inter-train interval of 10s and an inter-block interval of ten minutes for a total of 150 pulses. The less affected hemisphere was stimulated as previous reports have shown a greater reduction of \[^{11}\text{C}]\text{RAC binding after stimulation of the less affected hemisphere compared to the more affected hemisphere (Strafella et al., 2005). Intensity was set at 90% of resting motor threshold, which was determined immediately prior to the start of each rTMS session (pre- and post- exercise/control intervention).}
Authors’ Roles

Matthew A. Sacheli – conception, organization and execution of the research project, design and execution of the statistical analysis and writing of the manuscript.

Jason L. Neva – conception and execution of the rTMS data collection, design and execution of the statistical analysis relating to the fMRI data, review and critique of manuscript.

Bimal Lakhani – conception and execution of the rTMS data collection, review and critique of manuscript.

Danielle K. Murray - conception, organization and execution of the research project.

Nasim Vafai – data analysis support (fMRI)

Elham Shahinfard – data analysis support (fMRI), review and critique of manuscript.

Carolyn English – data collection support (PET)

Siobhan McCormick – data collection support (PET)

Katie Dinelle – data analysis support (PET), review and critique of manuscript.

Nicole Neilson – patient recruitment, clinical support during scanning, review and critique of manuscript.

Jess McKenzie - patient recruitment, clinical support during scanning.

Michael Schulzer – design, review and critique of the statistical analysis.

Don McKenzie – conception of the VO₂ max data collection.

Silke Appel-Cresswell – conception and organization of the research project, review and critique of the manuscript

Martin J McKeown - conception and organization of the research project, design of the fMRI data analysis

Lara Boyd – conception of the rTMS data collection, review and critique of manuscript.

Vesna Sossi - conception, organization and execution of the research project, design of the PET analysis, review and critique of the manuscript.

A. Jon Stoessl - conception, organization and execution of the research project, design of the statistical analysis, review and critique of manuscript.
Table 2. Participant demographics and clinical assessments

<table>
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<tr>
<th></th>
<th>Aerobic mean</th>
<th>Aerobic SD</th>
<th>Control Mean</th>
<th>Control SD</th>
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<td>0.85</td>
<td>4.14</td>
<td>1.02</td>
<td>ns</td>
</tr>
<tr>
<td>[¹¹C]RAC 1 BH Posterior Putamen</td>
<td>3.67</td>
<td>1.02</td>
<td>3.55</td>
<td>1.14</td>
<td>ns</td>
</tr>
<tr>
<td>[¹¹C]RAC 1 WH Caudate</td>
<td>3.03</td>
<td>0.47</td>
<td>2.87</td>
<td>0.48</td>
<td>ns</td>
</tr>
<tr>
<td>[¹¹C]RAC 1 WH Anterior Putamen</td>
<td>4.02</td>
<td>0.73</td>
<td>3.64</td>
<td>0.64</td>
<td>ns</td>
</tr>
<tr>
<td>[¹¹C]RAC 1 WH Middle Putamen</td>
<td>4.82</td>
<td>1.09</td>
<td>4.41</td>
<td>1.14</td>
<td>ns</td>
</tr>
<tr>
<td>[¹¹C]RAC 1 WH Posterior Putamen</td>
<td>4.08</td>
<td>1.06</td>
<td>3.53</td>
<td>1.10</td>
<td>ns</td>
</tr>
</tbody>
</table>
Years since Dx, years since diagnosis by a neurologist; MDS-UPDRS III, Unified Parkinson’s Disease Rating Scale motor section OFF (after 12 hour withdrawal from dopaminergic medication, conducted at time of fMRI); VO$_2$ max, maximal oxygen consumption during cycling; Baseline exercise participation counts/week, the average amount of exercise done for more than 20 minutes multiplied by intensity, x1 for mild, x2 for moderate and x3 for vigorous exercise; Baseline exercise participation minutes/week, duration of exercise activities recorded in minutes multiplied by the counts per week; DTBZ, baseline dihydrotetabenazine binding potential, [$^{11}$C]RAC1, baseline [$^{11}$C]Raclopride binding potential; WH, worse hemisphere contralateral to the more affected side of the body; BH, better hemisphere; ns, not statistically significant p<0.05.
Table 3. Summary of clinical measures

<table>
<thead>
<tr>
<th></th>
<th>Aerobic mean (SD)</th>
<th>Control mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td><strong>UPDRS OFF</strong></td>
<td>23.00 (10.42)</td>
<td>23.65 (11.49)</td>
<td>26.77 (13.14)</td>
</tr>
<tr>
<td><strong>SAS Total</strong></td>
<td>10.65 (6.50)</td>
<td>12.88 (7.55)</td>
<td>15.69 (6.46)</td>
</tr>
<tr>
<td><strong>BDI</strong></td>
<td>8.21 (6.26)</td>
<td>8.12 (6.95)</td>
<td>9.77 (8.06)</td>
</tr>
<tr>
<td><strong>MoCA</strong></td>
<td>27.94 (1.98)</td>
<td>27.53 (1.94)</td>
<td>28.23 (1.48)</td>
</tr>
<tr>
<td><strong>PANAS Pos</strong></td>
<td>34.12 (11.34)</td>
<td>35.59 (9.40)</td>
<td>31.69 (7.12)</td>
</tr>
<tr>
<td><strong>PANAS Neg</strong></td>
<td>11.82 (3.61)</td>
<td>12.47 (3.22)</td>
<td>14.08 (5.41)</td>
</tr>
<tr>
<td><strong>VO₂ max pre</strong> (ml/kg/min)</td>
<td>20.37 (5.05)</td>
<td>24.88 (6.03)</td>
<td>18.98 (8.51)</td>
</tr>
<tr>
<td><strong>Maximum power (W)</strong></td>
<td>150.77 (41.78)</td>
<td>170.26 (71.43)</td>
<td>133.88 (57.53)</td>
</tr>
<tr>
<td><strong>TMT A (s)</strong></td>
<td>38.62 (10.23)</td>
<td>34.34 (10.47)</td>
<td>35.71 (8.73)</td>
</tr>
<tr>
<td><strong>TMT B (s)</strong></td>
<td>100.41* (71.85)</td>
<td>94.58* (41.44)</td>
<td>68.83 (24.95)</td>
</tr>
<tr>
<td><strong>TMT B – TMT A</strong></td>
<td>64.06 (69.92)</td>
<td>60.25 (36.20)</td>
<td>33.12 (21.15)</td>
</tr>
<tr>
<td><strong>Pegboard</strong></td>
<td>37.53 (9.05)</td>
<td>38.88 (9.05)</td>
<td>40.92 (8.61)</td>
</tr>
<tr>
<td><strong>Finger tapping</strong></td>
<td>129.71 (20.28)</td>
<td>130.82 (21.34)</td>
<td>124.15 (9.67)</td>
</tr>
<tr>
<td><strong>Reaction time (s)</strong></td>
<td>0.36 (0.04)</td>
<td>0.40 (0.05)</td>
<td>0.37 (0.06)</td>
</tr>
<tr>
<td><strong>Timed-up-and-go (s)</strong></td>
<td>9.94 (1.52)</td>
<td>10.39 (3.03)</td>
<td>11.95 (5.12)</td>
</tr>
</tbody>
</table>

MDS-UPDRS III, Unified Parkinson’s Disease Rating Scale motor section OFF (after 12 hour withdrawal from dopaminergic medication); SAS, Starkstein Apathy Scale, Q 1-8, questions 1-8 positive question, Q 9-14, questions 9-14 negative questions (higher number =more apathy), total, combined score of questions 1-14 (higher number = more apathy); BDI, Beck depression inventory, MoCA, Montreal Cognitive Assessment; PANAS, Positive and Negative Affect Schedule, Pos, score of positive affect (higher score = great positive affect), Neg, score of negative affect (lower score = less negative affect), VO₂ max, maximal oxygen consumption during cycling; Maximum power achieved at the end of the VO₂ max test; TMT A & B, Trail Making Test version A (numbers only) and B (numbers and letters) (* the values were affected by a single outlier in the aerobic group); Pegboard, Purdue Pegboard – number of pegs placed in 60 seconds; Finger tapping, number of taps in 60 seconds; Reaction time, simple reaction time, average of 5 trials; Timed-up-and-go, the time it takes to get up from a chair, walk 3m, turn around, walk 3m and sit down, average of 3 trials at normal walking pace (only collected in OFF state); ns, not statistically significant <p>0.05.
Table 4. Summary of fMRI and PET measures

<table>
<thead>
<tr>
<th>Percent signal change from baseline activity in the ventral striatum</th>
<th>Aerobic mean (SD)</th>
<th>Control mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>BH 0%</td>
<td>0.22 x 10^{-3}</td>
<td>0.68 x 10^{-3}</td>
<td>0.131 x 10^{-2}</td>
</tr>
<tr>
<td></td>
<td>(0.174 x 10^{-2})</td>
<td>(0.337 x 10^{-2})</td>
<td>(0.223 x 10^{-2})</td>
</tr>
<tr>
<td>BH 50%</td>
<td>-0.20 x 10^{-3}</td>
<td>0.135 x 10^{-3}</td>
<td>0.63 x 10^{-3}</td>
</tr>
<tr>
<td></td>
<td>(0.190 x 10^{-2})</td>
<td>(0.374 x 10^{-2})</td>
<td>(0.196 x 10^{-2})</td>
</tr>
<tr>
<td>BH 75%</td>
<td>0.25 x 10^{-3}</td>
<td>0.233 x 10^{-2}</td>
<td>0.124 x 10^{-2}</td>
</tr>
<tr>
<td></td>
<td>(0.149 x 10^{-2})</td>
<td>(0.403 x 10^{-2})</td>
<td>(0.264 x 10^{-2})</td>
</tr>
<tr>
<td>BH 100%</td>
<td>0.106 x 10^{-3}</td>
<td>0.01 x 10^{-3}</td>
<td>0.133 x 10^{-2}</td>
</tr>
<tr>
<td></td>
<td>(0.310 x 10^{-2})</td>
<td>(0.173 x 10^{-2})</td>
<td>(0.232 x 10^{-2})</td>
</tr>
<tr>
<td>WH 0%</td>
<td>0.85 x 10^{-3}</td>
<td>0.119 x 10^{-2}</td>
<td>0.88 x 10^{-3}</td>
</tr>
<tr>
<td></td>
<td>(0.178 x 10^{-2})</td>
<td>(0.241 x 10^{-2})</td>
<td>(0.292 x 10^{-2})</td>
</tr>
<tr>
<td>WH 50%</td>
<td>0.21 x 10^{-3}</td>
<td>0.103 x 10^{-2}</td>
<td>0.22 x 10^{-3}</td>
</tr>
<tr>
<td></td>
<td>(0.117 x 10^{-2})</td>
<td>(0.335 x 10^{-2})</td>
<td>(0.230 x 10^{-2})</td>
</tr>
<tr>
<td>WH 75%</td>
<td>-0.04 x 10^{-3}</td>
<td>0.182 x 10^{-2}</td>
<td>0.30 x 10^{-3}</td>
</tr>
<tr>
<td></td>
<td>(0.143 x 10^{-2})</td>
<td>(0.305 x 10^{-2})</td>
<td>(0.362 x 10^{-2})</td>
</tr>
<tr>
<td>WH 100%</td>
<td>0.86 x 10^{-3}</td>
<td>-0.28 x 10^{-3}</td>
<td>0.81 x 10^{-3}</td>
</tr>
<tr>
<td></td>
<td>(0.280 x 10^{-2})</td>
<td>(0.215 x 10^{-2})</td>
<td>(0.268 x 10^{-2})</td>
</tr>
</tbody>
</table>

Change in [$^{11}$C]Raclopride binding potential after repetitive transcranial magnetic stimulation

<table>
<thead>
<tr>
<th></th>
<th>Aerobic mean (SD)</th>
<th>Control mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>BH Caudate</td>
<td>0.02 (0.33)</td>
<td>0.17 (0.20)</td>
<td>0.02 (0.17)</td>
</tr>
<tr>
<td>BH Anterior Putamen</td>
<td>0.04 (0.51)</td>
<td>0.14 (0.28)</td>
<td>0.11 (0.17)</td>
</tr>
<tr>
<td>BH Middle Putamen</td>
<td>-0.03 (0.39)</td>
<td>0.10 (0.43)</td>
<td>0.06 (0.36)</td>
</tr>
<tr>
<td>BH Posterior Putamen</td>
<td>-0.09 (0.47)</td>
<td>0.11 (0.20)</td>
<td>-0.04 (0.26)</td>
</tr>
<tr>
<td>WH Caudate</td>
<td>0.04 (0.28)</td>
<td>0.06 (0.14)</td>
<td>0.11 (0.18)</td>
</tr>
<tr>
<td>WH Anterior Putamen</td>
<td>0.12 (0.38)</td>
<td>0.10 (0.27)</td>
<td>-0.03 (0.26)</td>
</tr>
<tr>
<td>WH Middle Putamen</td>
<td>0.13 (0.54)</td>
<td>-0.01 (0.35)</td>
<td>-0.04 (0.13)</td>
</tr>
<tr>
<td>WH Posterior Putamen</td>
<td>0.073 (0.43)</td>
<td>0.15 (0.33)</td>
<td>-0.15 (0.13)</td>
</tr>
</tbody>
</table>

PSC, percent signal change from baseline activity in the ventral striatum in anticipation of winning monetary reward at 0%, 50%, 75% and 100% probability at the 2 second period immediately prior to the reveal of reward (maximal anticipation); Δ [$^{11}$C]RAC,
change in $[^{11}C]$Raclopride binding potential after repetitive transcranial magnetic stimulation; WH, worse hemisphere contralateral to the more affected side of the body; BH, better hemisphere (side of rTMS in $[^{11}C]$RAC studies); ns, not statistically significant $p<0.05$. 
Table 5. Subject VO$_2$ max data for exercise prescription of aerobic exercise

<table>
<thead>
<tr>
<th>Aero sub 1</th>
<th>Rest VO$_2$ (ml/kg/min)</th>
<th>Rest HR (bpm)</th>
<th>VO$_2$ max (ml/kg/min)</th>
<th>Max HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aero sub 2</td>
<td>3.42</td>
<td>77</td>
<td>19.47</td>
<td>104</td>
</tr>
<tr>
<td>Aero sub 3</td>
<td>3.84</td>
<td>87</td>
<td>19.92</td>
<td>139</td>
</tr>
<tr>
<td>Aero sub 4</td>
<td>3.50</td>
<td>94</td>
<td>13.54</td>
<td>127</td>
</tr>
<tr>
<td>Aero sub 5</td>
<td>2.26</td>
<td>86</td>
<td>15.43</td>
<td>118</td>
</tr>
<tr>
<td>Aero sub 6</td>
<td>3.15</td>
<td>89</td>
<td>19.7</td>
<td>158</td>
</tr>
<tr>
<td>Aero sub 7</td>
<td>1.87</td>
<td>83</td>
<td>26.32</td>
<td>156</td>
</tr>
<tr>
<td>Aero sub 8</td>
<td>2.58</td>
<td>85</td>
<td>17.4</td>
<td>146</td>
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<tr>
<td>Aero sub 9</td>
<td>2.98</td>
<td>98</td>
<td>14.65</td>
<td>131</td>
</tr>
<tr>
<td>Aero sub 10</td>
<td>3.06</td>
<td>98</td>
<td>21.07</td>
<td>123</td>
</tr>
<tr>
<td>Aero sub 11</td>
<td>3.36</td>
<td>77</td>
<td>26.08</td>
<td>132</td>
</tr>
<tr>
<td>Aero sub 12</td>
<td>3.41</td>
<td>95</td>
<td>21.2</td>
<td>147</td>
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<tr>
<td>Aero sub 13</td>
<td>3.43</td>
<td>79</td>
<td>19.9</td>
<td>150</td>
</tr>
<tr>
<td>Aero sub 14</td>
<td>3.46</td>
<td>80</td>
<td>15.89</td>
<td>125</td>
</tr>
<tr>
<td>Aero sub 15</td>
<td>3.56</td>
<td>90</td>
<td>33.13</td>
<td>156</td>
</tr>
<tr>
<td>Aero sub 16</td>
<td>3.63</td>
<td>96</td>
<td>19.76</td>
<td>140</td>
</tr>
<tr>
<td>Aero sub 17</td>
<td>4.17</td>
<td>90</td>
<td>16.95</td>
<td>120</td>
</tr>
<tr>
<td>Aero sub 18</td>
<td>4.23</td>
<td>102</td>
<td>24.4</td>
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<tr>
<td>Aero sub 19</td>
<td>4.53</td>
<td>84</td>
<td>25.79</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>5.12</td>
<td>90</td>
<td>34</td>
<td>143</td>
</tr>
</tbody>
</table>

Aero sub, aerobic subjects 1-19, Rest VO$_2$, oxygen consumption at rest; VO$_2$ max, maximal oxygen consumption during cycling; HR, heart rate of beats per minute.
Table 6. Week by week exercise intensity workloads for the aerobic group by subject

<table>
<thead>
<tr>
<th></th>
<th>Weeks 1-2 (60%)</th>
<th>Weeks 3-4 (62.5%)</th>
<th>Weeks 5-6 (65%)</th>
<th>Weeks 7-8 (70%)</th>
<th>Weeks 9-10 (75%)</th>
<th>Weeks 11-12 (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VO₂ max</td>
<td>Work</td>
<td>VO₂ max</td>
<td>Work</td>
<td>VO₂ max</td>
<td>Work</td>
</tr>
<tr>
<td>Aero sub 1</td>
<td>11.68</td>
<td>86</td>
<td>12.17</td>
<td>90</td>
<td>12.66</td>
<td>95</td>
</tr>
<tr>
<td>Aero sub 2</td>
<td>11.95</td>
<td>53</td>
<td>12.45</td>
<td>65</td>
<td>12.95</td>
<td>80</td>
</tr>
<tr>
<td>Aero sub 3</td>
<td>8.12</td>
<td>65</td>
<td>8.46</td>
<td>67</td>
<td>8.80</td>
<td>75</td>
</tr>
<tr>
<td>Aero sub 4</td>
<td>9.26</td>
<td>35</td>
<td>9.64</td>
<td>37</td>
<td>10.03</td>
<td>40</td>
</tr>
<tr>
<td>Aero sub 5</td>
<td>11.82</td>
<td>75</td>
<td>12.31</td>
<td>83</td>
<td>12.81</td>
<td>94</td>
</tr>
<tr>
<td>Aero sub 6</td>
<td>15.79</td>
<td>125</td>
<td>16.45</td>
<td>135</td>
<td>17.11</td>
<td>150</td>
</tr>
<tr>
<td>Aero sub 7</td>
<td>10.45</td>
<td>40</td>
<td>10.89</td>
<td>43</td>
<td>11.32</td>
<td>45</td>
</tr>
<tr>
<td>Aero sub 8</td>
<td>8.79</td>
<td>40</td>
<td>9.16</td>
<td>45</td>
<td>9.52</td>
<td>50</td>
</tr>
<tr>
<td>Aero sub 9</td>
<td>12.64</td>
<td>70</td>
<td>13.17</td>
<td>80</td>
<td>13.70</td>
<td>90</td>
</tr>
<tr>
<td>Aero sub 10</td>
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<td>115</td>
<td>16.30</td>
<td>135</td>
<td>16.95</td>
<td>150</td>
</tr>
<tr>
<td>Aero sub 11</td>
<td>12.72</td>
<td>60</td>
<td>13.25</td>
<td>62</td>
<td>13.78</td>
<td>65</td>
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<tr>
<td>Aero sub 12</td>
<td>11.94</td>
<td>65</td>
<td>12.44</td>
<td>70</td>
<td>12.94</td>
<td>75</td>
</tr>
<tr>
<td>Aero sub 13</td>
<td>9.53</td>
<td>60</td>
<td>9.93</td>
<td>65</td>
<td>10.33</td>
<td>75</td>
</tr>
<tr>
<td>Aero sub 15</td>
<td>11.86</td>
<td>77</td>
<td>12.35</td>
<td>80</td>
<td>12.84</td>
<td>83</td>
</tr>
<tr>
<td>Aero sub 16</td>
<td>10.17</td>
<td>30</td>
<td>10.59</td>
<td>32</td>
<td>11.02</td>
<td>35</td>
</tr>
<tr>
<td>Aero sub 17</td>
<td>14.61</td>
<td>100</td>
<td>15.22</td>
<td>120</td>
<td>15.83</td>
<td>135</td>
</tr>
<tr>
<td>Aero sub 18</td>
<td>15.47</td>
<td>100</td>
<td>16.12</td>
<td>106</td>
<td>16.76</td>
<td>112</td>
</tr>
<tr>
<td>Aero sub 19</td>
<td>20.40</td>
<td>85</td>
<td>21.25</td>
<td>90</td>
<td>22.10</td>
<td>100</td>
</tr>
</tbody>
</table>

Aero sub, aerobic subjects 1-19, VO₂ max, Percentage of maximal oxygen consumption during cycling, ml/kg/min; Work, the wattage set on the bike during the given weeks based on the wattage achieved during the VO₂ max test.
Figure 2. fMRI data percent signal change in anticipation to monetary reward. At baseline (pre) for the aerobic group (black bars), the stretching control group (grey bars) and after 3 months (post) of aerobic exercise (black striped bars) or control stretching (grey striped bars). Anticipation of reward at 0%, 50%, 75% and 100% probabilities in the ventral striatum in the (A) better hemisphere and (B) worse hemisphere. **p<0.01, error bars denote SEM.
Figure 3. PET data in the stimulated hemisphere.
(A) Δ Binding potential at baseline (pre) for the aerobic group (black bars), the stretching control group (grey bars) and after 3 months (post) of aerobic (black striped bars), stretching control (grey striped bars) (post). Δ Binding potential = baseline binding potential – binding potential post repetitive transcranial magnetic stimulation, greater ΔBP represents greater dopamine release in the better/stimulated hemisphere (B) Non-displaceable binding potential in the stimulated hemisphere prior to repetitive transcranial magnetic stimulation *p<0.05, error bars denote SEM.
Figure 4. Participant enrolment flow chart.
fMRI, functional magnetic resonance imaging; PET, positron emission tomography; DTBZ, Dihydrotetrabenazine; RAC, Raclopride; rTMS, repetitive transcranial magnetic stimulation.
### Baseline

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Neuroimaging – 4 scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Motor assessments</td>
<td>• 1 fMRI scan</td>
</tr>
<tr>
<td>• Non – motor</td>
<td>o fMRI with monetary reward</td>
</tr>
<tr>
<td>• VO₂ max test</td>
<td>• 1 PET [¹¹C] DTBZ scan</td>
</tr>
<tr>
<td></td>
<td>• 2 PET [¹¹C] RAC scans</td>
</tr>
<tr>
<td></td>
<td>o Baseline scan</td>
</tr>
<tr>
<td></td>
<td>o rTMS</td>
</tr>
<tr>
<td></td>
<td>o Post rTMS scan</td>
</tr>
</tbody>
</table>

### Interventions

<table>
<thead>
<tr>
<th>Aerobic (n=20)</th>
<th>Control (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stationary cycling</td>
<td>• Stretching</td>
</tr>
<tr>
<td>• 5-10 min warm up</td>
<td>• 5-10 min cycling warm up</td>
</tr>
<tr>
<td>• 30-50 min @ 60-80% VO₂ max</td>
<td>• 30-50 min seated stretches</td>
</tr>
<tr>
<td>• 5-10 min cool down</td>
<td>• 5-10 min cool down</td>
</tr>
</tbody>
</table>

### Post interventions

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Neuroimaging – 3 scans</th>
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<td>• Non – motor</td>
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<td>• VO₂ max test</td>
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Figure 5. Study assessments flow chart.
VO2 max, maximal oxygen consumption during cycling; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; DTBZ, Dihydrotetabenazine; RAC, Raclopride; rTMS, repetitive transcranial magnetic stimulation.
Figure 6. PET data in the non-stimulated hemisphere. At baseline (pre) for the aerobic group (black bars), the stretching control group (grey bars) and after 3 months (post) of aerobic exercise (black striped bars) or control stretching (grey striped bars). (A) non-stimulated hemisphere. (B) Δ Binding potential, baseline binding potential – binding potential post repetitive transcranial magnetic stimulation, greater ΔBP represents greater dopamine release in the worse/non-stimulated...
hemisphere. Note, the large difference in the posterior putamen is driven by 2 outlier individuals in the control group. Ant, Anterior, Mid, middle, Pos, posterior.*p<0.05, error bars denote SEM.
Chapter IV: Effects of exercise on neuroinflammation: A \[^{11}\text{C}]\text{PBR} 28 \text{PET study.}

Objective: To examine the effects of exercise on activation of microglia using the positron emission tomography (PET) translocator protein (TSPO) ligand \[^{11}\text{C}]\text{PBR} 28 in subjects with Parkinson's disease (PD).

Methods: Sixteen participants with PD were randomly allocated to aerobic exercise or control interventions. Participants underwent \[^{11}\text{C}]\text{PBR} 28 \text{PET scans at baseline and after 3 months of supervised aerobic exercise to determine the effect of exercise on microglial activation. All participants completed motor (MDS-UPDRS III; finger tapping; Timed-up-and-go) and non-motor assessments (Starkstein Apathy scale, Beck Depression Inventory, reaction time, Positive and Negative Affect Schedule, Trail Making Test (A and B), and Montreal Cognitive Assessment) before and after the interventions. Standardized uptake values (SUV) and SUV divided by a cerebellar reference region (SUVr) were analyzed and compared between the aerobic and control groups.

Results: The SUV analysis showed a significant reduction in binding after aerobic exercise in the thalamus \((p<0.05)\), globus pallidus \((p<0.05)\), and cerebellum \((p<0.05)\). There was also a significant increase in binding after the control intervention in the olfactory frontal cortex \((p<0.01)\), pedunculopontine nucleus \((p<0.05)\), and posterior putamen \((p<0.05)\). However, SUVr analyses only showed a significant increase in binding in pedunculopontine nucleus following the control intervention \((p<0.05)\).
Conclusions: Our findings do not support the hypothesis that aerobic exercise alters the neuroinflammatory response in brain areas relevant to Parkinson’s disease. The interpretation is heavily dependent upon the analysis method used and other technical factors. Future studies should investigate alternate approaches to the analysis of TSPO PET and the use of other methods to assess neuroinflammation in vivo in order to determine the importance of neuroinflammation in PD and the effects of exercise.
Introduction

Chronic and prolonged activation of microglia (e.g., neuroinflammation) may be associated with neurodegenerative events such as plaque formation, dystrophic neurite growth and excessive tau phosphorylation. Neuroinflammation is suggested to be a primary contributing factor to neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease (PD), Huntington’s disease and amyotrophic lateral sclerosis (W. J. Streit, R. E. Mrak, & W. S. Griffin, 2004a). Of particular interest for the pathology of PD is the activation of microglia in the substantia nigra (McGeer, Itagaki, Boyes, & McGeer, 1988a; McGeer & McGeer, 2008).

It has been suggested that the aggregation of misfolded α-synuclein, which occurs in the parkinsonian brain, causes activation of microglia (Beraud & Maguire-Zeiss, 2012). Activated microglia have been observed in post-mortem substantia nigra tissue of PD patients (McGeer, Itagaki, Boyes, & McGeer, 1988b) and in familial forms of PD, specifically parkin (PARK2) and LRRK2 (Deleidi & Gasser, 2013; Huang & Halliday, 2012). It has been suggested that activated microglia create a toxic oxidative environment that is associated with the death of dopaminergic neurons (Hirsch & Hunot, 2009). However, it has yet to be determined if neuroinflammation causes further degeneration or if inflammation is a by-product of progressive degeneration. Regardless, microglial activation may play a role in PD pathology and, if mitigated, may provide therapeutic benefit.
In animal studies, it has been suggested that exercise may limit the accumulation of proteins associated with oxidative damage (Radak et al., 2001). While there is currently no established disease modifying therapy for the treatment of PD, aerobic exercise has been shown to improve symptoms of PD (Bergen et al., 2002; Bridgewater & Sharpe, 1996; Tanaka, de Quadros, et al., 2009), promote neurogenesis (Fisher et al., 2004) and attenuate neurotoxin-induced glia activation (Real et al., 2017). Recent evidence has shown that the beneficial short-term effects of exercise in PD are in part due to changes in corticostriatal plasticity in the dopaminergic system (Sacheli et al., 2018; Sacheli et al., 2019). However, changes in the activation of microglia and neuroinflammation may also play a therapeutic role in the long term. It is theorized that exercise may modulate the activation of microglia and reduce neuroinflammation in PD.

Positron emission tomography (PET) imaging can be used for the *in vivo* study of neuroinflammation using the radioligand that binds to the Translocator protein (TSPO; previously known as the peripheral benzodiazepine receptor or PBR). TSPO binding is increased in conditions of neuroinflammation (e.g., head trauma, neurodegeneration, stroke, etc.) and its expression coincides with activation of microglia (and also astrocytes). PET has demonstrated increased TSPO binding in a number of studies of PD (Gerhard et al., 2006; Ouchi et al., 2005) and prodromal states of synucleinopathy (e.g., REM sleep behaviour disorder) (Stokholm et al., 2017; Stokholm et al., 2018). The purpose of this study was to explore the effects of aerobic exercise on the activation of microglia, using PET with the 2nd generation TSPO ligand [$^{11}$C]PBR 28.
Methods

This study was conducted in a subset of patients from our previously reported randomized controlled trial of exercise in PD (Sacheli et al., 2019).

Sixteen participants aged 45-75 years old with mild to moderate idiopathic PD (Hoehn & Yahr stages I-III), according to UK Brain Bank criteria, were randomly allocated to either an aerobic exercise (n=10) or a control stretching intervention (n=6) between April 2015 and July 2017. The first subject was enrolled April 7, 2015 and the final post intervention assessment being completed November 14, 2017. A blocked randomization was determined prior to the enrolment of the first subject and completed by a biostatistician external to the project. All subjects and assessors were blinded to group allocation. Subjects were debriefed after the completion of the post intervention assessments and were told about the other intervention. Inclusion/exclusion criteria were the same as previously published (Sacheli et al, 2019), with the addition of TSPO binding affinity. Given that not all subjects bind $[^{11}\text{C}]\text{PBR28}$ with high affinity, we excluded those subjects with the TT allele of the rs6971 polymorphism of the TSPO gene, which is associated with low binding affinity (Owen et al., 2012).

Following overnight withdrawal of dopaminergic medication (OFF medication, at least 12 hours) individuals participated in a $[^{11}\text{C}]\text{PBR28}$ PET scan, T1 structural magnetic resonance imaging (MRI) scan and a battery of motor and non-motor assessments (described below). On a separate day, during peak dose of dopaminergic medication (ON medication), a peak aerobic capacity assessment ($\text{VO}_2\text{ max}$) on a
stationary bike was conducted. During the VO₂ max test, heart rate and power output (watts) were also recorded and used to prescribe and scale the intensity of the aerobic exercise intervention, as previously reported in Sacheli et al (2019). Assessments were conducted at baseline and after a supervised 3-month exercise intervention of either stationary cycling or stretching.

The study was approved by the University of British Columbia (UBC) Clinical Research Ethics Board and carried out in accordance with the Declaration of Helsinki, and the Code of Ethics of the World Medical Association for experiments involving humans. Written informed consent was obtained from all participants prior to the start of the study.

**Exercise/control interventions**

The aerobic exercise and stretching control interventions have been previously described (Sacheli et al., 2019). In short, participants met 3 times per week for 3 months (36 sessions). The aerobic exercise consisted of 40–60 minutes of cycling separated into 5-10 minutes of warm-up (no resistance), 30-50 minutes of cycling at 60-80% VO₂ max, and 5-10 minutes of cool-down. The stretching program consisted of a series of seated and standing stretches and low impact exercises approved by Parkinson Society Canada. The primary purpose of the stretching intervention was to account for benefits not directly related to aerobic exercise, the intervention of interest (i.e., social interaction, halo and Hawthorne effects).
PET imaging

Subjects were scanned following intravenous bolus administration of 740 MBq (20mCi) $[^{11}\text{C}]$PBR28 at baseline and 3 months, in order to determine if there was a change in markers of neuroinflammation. Emission scans were acquired for 90 minutes in list mode after a 60-second bolus intravenous injection of $[^{11}\text{C}]$PBR28 and then reconstructed into a dynamic sequence of images ($4 \times 1$ min, $3 \times 2$ min, $8 \times 5$ min, $7 \times 10$ min) using 3D ordinary Poisson-ordered subset expectation maximization (OP-OSEM) algorithm (Comtat et al., 2004). Each subject also underwent a T1-weighted anatomical MRI scan, performed on a 3T Philips Achieva camera (repetition time (TR) = 0.81 milliseconds, echo time (TE) = 8.1 milliseconds and the flip angle = 8). The acquisition matrix measured $256 \times 256 \times 170$, and the field of view measured 50 cm. For the $[^{11}\text{C}]$PBR scans, the scans were co-registered to each individual's MRI, which was in turn warped to a template derived from the Montreal Neurological Institute (MNI) database to calculate a transformation matrix. The inverse transformation was then applied to the region of interest (ROI) images to fit the original PET data. Forty-six MRI regions of interest (ROIs) (21 bilateral: amygdala, caudate, cerebellum, anterior and posterior cingulate, dorsolateral prefrontal cortex (DLPFC), hypothalamus, insula, anterior frontal, orbital frontal cortex (OFC), parietal cortex, pedunculopontine nucleus (PPN), putamen (anterior, middle and posterior), substantia nigra, temporal cortex, thalamus, ventral striatum, hippocampus, dentate nucleus, and globus pallidus, and four midline ROIs: cerebellum, pons, midbrain and medulla) were placed on $[^{11}\text{C}]$PBR28 data to extract the mean regional time-activity curves (TACs). For Standardized Uptake Value (SUV) analysis, the time-averaged TACs were converted to SUV by dividing measured activity
by the ratio of the injected dose to subject body weight. Additionally, an SUV ratio (SUVr) analysis was conducted by dividing the SUV of region by the SUV of the cerebellum ROI.

Clinical assessments

Motor (MDS-Unified Parkinson’s Disease Rating Scale motor section, UPDRS III; Purdue pegboard; finger tapping; Timed-up-and-go, TUG and simple reaction time, RT) and non-motor (MoCA, BDI; and Starkstein Apathy Scale, SAS) functions were assessed. Clinical data were collected in the OFF medication states. A repeated measures ANOVA (group x time) was used to compare the effect of exercise on clinical assessments.

Statistical analysis

For both SUV and SUVr datasets, a repeated measures analysis of variance (RM ANOVA) (group x time) was conducted for each ROI. A repeated measures ANOVA (group x time) was used to compare the effect of exercise on clinical assessments. A Fisher’s LSD post hoc analysis was used to explore any significant interactions.

Results

One participant was excluded from the analysis due to a change in diagnosis after the intervention. Of the remaining 15 participants, analysis of the rs 6971 polymorphism indicated that 10 subjects were mixed-affinity binders and 5 were high-affinity binders. As this study was a sub-study of a larger randomized clinical trial, randomization was conducted with a block design, prior to knowledge of the TSPO binding status. This
unfortunately led to an unequal distribution of subjects in the aerobic and control interventions amongst the high-affinity binders. Out of the 5 high-affinity binders, 4 were randomly allocated to the aerobic group and only 1 high-affinity binder to the control group. Amongst the mixed-affinity binders, there was an equal distribution of 5 subjects per intervention. Thus, for the statistical analysis of the PET data, only the mixed-affinity group was analyzed. For the analysis of the clinical data, all subjects were used, with the exception of the one participant noted above, in whom there was a change in diagnosis over the course of the study.

Clinical assessments

There were no significant differences in age or years since diagnosis between groups. Furthermore, there were no significant differences between the aerobic or control groups in any of the clinical measures, with the exception of VO2 max \( F(1, 13) = 5.27, p<0.05 \) (Table 5). A Fisher’s LSD post hoc showed a significant increase in VO2 max after aerobic exercise compared to the control group (Table 5).

SUV

In the less affected brain side – contralateral to the less affected side of the body, the SUV analysis showed significant time x group interactions in the amygdala \( F(1, 8) = 6.6, p<0.05 \), OFC \( F(1, 8) = 11.39, p<0.01 \), posterior cingulate \( F(1, 8) = 5.45, p<0.05 \), PPN \( F(1, 8) = 9.96, p<0.05 \), posterior putamen \( F(1, 8) = 8.58, p<0.05 \), and thalamus \( F(1, 8) = 8.19, p<0.05 \). Fisher’s LSD post hoc analysis showed group differences in the amygdala and posterior cingulate, which were driven by a group difference at baseline (aerobic>control, \( p<0.05 \)). The group difference in the OFC was driven by a significant increase in binding
after the control intervention ($p<0.05$). In the PPN, there were group differences at baseline with the aerobic group showing greater SUV than control, ($p<0.05$), and a significant increase in binding after the only the control intervention ($p<0.05$). In the posterior putamen, there was a group difference at baseline with the aerobic group showing significantly greater binding than the control group at baseline, and an increase in binding after the control intervention ($p<0.05$), and a non-significant decrease in binding after the aerobic intervention ($p=0.053$). In the thalamus, there was both a difference at baseline between the groups (aerobic>control, $p<0.05$), and a significant reduction in binding after aerobic exercise ($p<0.05$). In the same side of the brain, there were also numerous non-significant group x time interactions in the anterior frontal cortex ($F_{(1, 8)}=4.51$, $p=0.070$, caudate ($F_{(1, 8)}=3.72$, $p=0.09$) and dentate nuclei ($F_{(1, 8)}=5.04$, $p=0.06$), insula ($F_{(1, 8)}=4.40$, $p=0.07$), and parietal ($F_{(1, 8)}=4.59$, $p=0.06$) and temporal cortices ($F_{(1, 8)}=4.88$, $p=0.06$).

In the more affected brain side – ipsilateral to the less affected side of the body, the SUV analysis showed significant time x group interactions in the globus pallidus ($F_{(1, 8)}=13.10$, $p<0.01$), OFC ($F_{(1, 8)}=12.44$, $p<0.01$), PPN ($F_{(1, 8)}=5.93$, $p<0.05$), and substantia nigra ($F_{(1, 8)}=9.31$, $p<0.05$). Fisher’s LSD post hoc analysis showed that in the globus pallidus, there was a difference at baseline between the groups (aerobic>control, $p<0.05$) and a significant reduction in binding after aerobic exercise only ($p<0.05$). The differences in the OFC and PPN were driven by a significant increase in binding after the control intervention ($p<0.05$); the difference in the substantia nigra was driven by a difference at baseline between the groups (aerobic>control, $p<0.05$). In the ventral
striatum, there was a main effect of group \((F_{(1, 8)}=7.60, p<0.05)\) with the aerobic group showing greater binding than the control group. There was also a non-significant trend in the middle putamen \((F_{(1, 8)}=5.05, p=0.054)\).

Lastly, there was a significant group x time interaction in the cerebellum \((F_{(1, 8)}=6.42, p<0.05)\), and Fisher’s LSD post hoc showed there was significantly more binding in the aerobic group than the control group \((p<0.05)\) at baseline, and a non-significant trend of a decrease in binding after the aerobic intervention \((p=0.064)\). There was also a non-significant group x time trend in the midbrain \((F_{(1, 8)}=4.70, p=0.06)\) (see Table 6 for all results).

**SUVr**

The SUVr analysis resulted in a different outcome. The only significant group x time interaction was in the pedunculopontine nucleus contralateral to the more affected body side \((F_{(1, 8)}=7.64, p<0.05)\). Fisher’s LSD post hoc analysis showed that the baseline binding in the aerobic group was significantly higher than that of the control group \((p<0.01)\), but there was an increase in binding in the control group after the intervention \((p<0.05)\). There was a main effect of group in the posterior cingulate \((F_{(1, 8)}=11.39, p<0.01)\), with the aerobic group showing greater binding compared to the control group. There were also near significant trends observed in middle putamen of the less affected brain side \((F_{(1, 8)}=4.14, p=0.08)\) and in the OFC of the more affected brain side \((F_{(1, 8)}=4.33, p=0.07)\), where observation of the means showed an increase in binding after the control intervention, which is consistent with SUV analysis (see Table 6 for all results).
Discussion

While increased dopamine release may be a primary driving mechanism to explain the short-term symptomatic beneficial effects of exercise for PD, other factors, such as the modulation of neuroinflammation, may contribute to longer-term disease modifying benefits. This study was a preliminary investigation into the effects of exercise on neuroinflammation in PD.

When SUV analysis was used, there appeared to be an increase in binding of $[^{11}\text{C}]$PBR 28 after the control intervention in the putamen, OFC, and the PPN. In contrast, there appeared to be a reduction of binding after the aerobic intervention in the thalamus, globus pallidus and cerebellum. Differences in the amygdala, posterior cingulate and substantia nigra were driven by group differences at baseline. The pattern of increased binding after the control intervention seemed to be in keeping with the Braak hypothesis (Braak et al., 2003), which suggests a caudo-rostral pattern of Lewy pathology that starts in the brain stem and eventually spreads to the neocortex. The caudo-rostral spreading of the disease is also suggested to be in keeping with a prion-like spreading of misfolded alpha synuclein ($\alpha$-synuclein) (Olanow & Brundin, 2013), which may trigger microglial activation in PD (Beraud & Maguire-Zeiss, 2012; Su et al., 2008). We hypothesized that aerobic exercise would reduce inflammation associated with PD. If the pattern of inflammation is determined according to a network that predicts progression in a caudo-rostral pattern (e.g., Braak hypothesis), one might further hypothesize that the therapeutic effects of exercise would reduce inflammation in a reverse order, i.e. in a rostro-caudal
pattern beginning with the areas least affected by disease and moving to the more affected areas. This hypothesis seems to be partially supported by the reduction of binding in the thalamus and globus pallidus after the exercise intervention. However, the Braak hypothesis implies a temporal context of disease spreading over decades, while this study was a snapshot over 3 months, which limits the interpretation of the findings. It is unlikely that moderate-high intensity aerobic exercise would eliminate neuroinflammation in a 3-month period. Additionally, the Braak hypothesis is not universally accepted as the basis for the pathology of PD. Neuroinflammation may change throughout the disease course making it difficult to correlate the neuroinflammation with a specific disease related pattern. Future studies should investigate the longitudinal effects of exercise on neuroinflammation to determine if patterns of change are aligned with Lewy body pathology or other disease mechanisms.

While potentially intriguing, the disease relevant relationship observed with the SUV analysis did not remain when a SUVr analysis was conducted. When the groups were compared using a SUVr analysis, using the cerebellum as the reference region, the disease relevant pattern of decreased neuroinflammation observed after aerobic exercise disappeared. The only brain area that showed a significant result was the PPN, which was driven by a combination of increased baseline binding in the aerobic group coupled with regression towards a common value following the intervention in both groups. There were other PD relevant brain areas (OFC, putamen and substantia nigra) that showed non-significant trends, and it is possible that with a larger sample size these findings might become significant. It could be suggested that exercise helps to subside the
neuroinflammatory response associated with PD, and that without exercise (e.g., with the control intervention) inflammation could increase over time. However, the latter appears unlikely as the control group did not show increased TSPO binding in other brain regions and the trend that was observed in the putamen appeared to reflect an increase following the aerobic intervention.

The approach to analyze TSPO PET has presented a challenge and has been the topic of considerable controversy in the literature. Unlike many tracers for which appropriate kinetic or graphical models exist, there has been no agreed upon approach to the estimation of free unbound tracer, nor of non-specific binding. For many tracers, both can be estimated by using a reference region felt to be devoid of specific binding. In the case of TSPO binding, there is no region that is known to be consistently free of microglial pathology, hence some investigators simply estimate SUV. The problem with this approach is that systematic variability may be high both between and within individuals, as was indeed the case in our study. We chose to address this problem by applying a cerebellar reference region, on the assumption that TSPO ligands should not demonstrate appreciable binding to the cerebellum in healthy individuals. While in PD, there is some evidence of possible microglial pathology in the superior portion of the cerebellum, this result was only seen with statistical parametric mapping and not t-tests (Gerhard et al., 2006). Other studies have shown that the cerebellum in PD is relatively free of microglial pathology (Ouchi et al., 2005; Watson et al., 2012). Another approach is to estimate total volume of distribution ($V_t$), but this requires arterial blood sampling as well as measurement of radiolabelled metabolites for measurement of the input.
function, a cumbersome procedure that is also likely to generate noisy data and that still fails to estimate non-specific binding. The last approach that has been commonly used for analysis of TSPO binding is to estimate both the input function and the non-specific binding by means of a supervised cluster analysis, in which those voxels that most closely approximate the time activity curves of a healthy control population are used to estimate the reference region (Rizzo et al., 2019; Yaqub et al., 2012). This approach, however, results in the use of different reference regions from one individual to another. The lack of congruity between the SUV and SUVr analyses of our data likely reflect systematic differences which are seen throughout the brain, including the cerebellum, and which we did not anticipate being substantially affected by PD pathology. The SUV analysis of the cerebellum showed differences in binding between the aerobic and control group at baseline and a reduction of binding after only the aerobic intervention. This suggests the alternate possibility that there was binding throughout the brain at baseline and that the SUV findings are a result of a global reduction in $^{11}$C]PBR 28 binding after aerobic exercise. However, as this result was only seen with the SUV analysis, it is difficult to interpret the importance and or validity of this finding.

The combination of the SUV and SUVr results do suggest that exercise may have an impact on neuroinflammation in PD, but the magnitude, long term effects, and significance are still unknown. It should also be noted, in contrast to previous findings obtained with the 1st generation TSPO ligand $^{[11]}$C]PK 11195 (Gerhard et al., 2006; Ouchi et al., 2005), recent evidence has failed to confirm increases in TSPO binding in PD subjects compared to controls (Ghadery et al., 2017; Varnas et al., 2019). The uncertainty
in the literature mirrors the unspecified findings of this study, and future studies need to be conducted to first understand the connection between neuroinflammation and PD pathology.

While improved dopaminergic function likely represents a major underlying mechanism for the beneficial symptomatic effects of exercise (Sacheli et al., 2019), the modulation of neuroinflammation may have a more important role with respect to disease progression. Exercise has been linked with neuroprotective properties (Gerecke, Jiao, Pani, Pagala, & Smeyne, 2010), and habitual exercise has been associated with enhanced corticostriatal plasticity and dopamine release in individuals with PD (Sacheli et al., 2018). As such, early exercise intervention should be recommended in PD and, based on the demonstration of increased nigral TSPO binding in subjects with RBD, it is possible that exercise may have a more profound impact on neuroinflammation prior to the onset of motor manifestations of PD. Recent reports have shown that high intensity aerobic exercise is more beneficial for de novo PD patients compared to lower intensity aerobic exercise (Schenkman et al., 2018). Perhaps, high intensity aerobic exercise elicits neuroprotective or neurorestorative effects through the modulation of neuroinflammation. This study used moderate-high intensity, so it is possible that the intensity of exercise was insufficient to elicit a robust effect on neuroinflammation. However, this is unlikely because the subjects enrolled in the aerobic intervention showed a mean increase in VO$_2$ max of 5.12 ml/kg/min, which was considerably higher than changes reported after high intensity exercise (Schenkman et al., 2018). Future research should investigate the effects of exercise intensity on modulation of neuroinflammation and the interaction with PD.
progression.

**Limitations**

There are several potential reasons for a null result including but not limited to: low sample size, low effect size, and limitations of the tracer and analysis methods. A major technical limitation of the SUV analysis is that it fails to account for non-specific binding by not including a reference region. Using a SUVr analysis with the cerebellum as the reference region may overcome this technical limitation. However, for analysis models that depend upon a reference tissue (e.g., SUVr analysis), a reference region with little to no tracer uptake is preferred (Lammertsma & Hume, 1996). Observation of the data showed an increase in binding in the cerebellum after the control intervention (Table 6). This, coupled with the SUV results, suggests more widespread TSPO binding throughout the brain, including the cerebellum, which limits its utility as a reference region for the SUVr analysis.

The lack of a reliable and appropriate reference region also limited the ability to assess within subject scan-to-scan variability. Without a reference region, it is difficult to assess if the changes observed are due to the intervention or simple systematic variability between scans, which is important to determine the effect size needed for a significant result. The lack of reference region has been a common limitation with TSPO radioligands, resulting in numerous pseudo-reference regions being investigated (Rizzo et al., 2019). As previously mentioned a plasma input function is not preferred as the free fraction in plasma for [\(^{11}\text{C}\)]PBR 28 is very low (1%-5%). This could result in a very
noisy input function, making this measure undesirable (Rizzo et al., 2019; Turkheimer et al., 2015). A supervised cluster analysis, is also not preferred for $[^{11}\text{C}]$PBR 28, in part because of the low tissue contrast between grey and white matter when using this tracer (Rizzo et al., 2019), and also because it results in highly inconsistent reference regions between individuals. Thus, the analysis and interpretation of $[^{11}\text{C}]$PBR 28 PET are challenging. Future studies should further examine alternative approaches to determine an ideal input/reference region as that could improve the analysis and interpretation.

Another potential confound with the interpretation of $[^{11}\text{C}]$PBR 28 PET data is that changes in binding may not be specific to microglial activation, but may also reflect altered astroglial activity (Lavisse et al., 2012). Microglia and astrocytes play unique roles in maintaining the health, function, and homeostasis of the brain, and react differently in disease states (Joe et al., 2018). As such, aerobic exercise may affect microglia and astrocytes with different downstream effects. It is vital to parse apart exercise-induced effects on microglia and astrocytes in order to understand the potential underlying contributing mechanisms of exercise for the treatment of PD. As $[^{11}\text{C}]$PBR 28 is unable to separate microglia and astrocytes, alternative means to measure microglial activation are needed. Reactive oxygen species (ROS) could be possibly used as a marker as they are secondary messengers that can signal the activation of microglia and astrocytes (Bakunina, Pariante, & Zunszain, 2015; Pawate, Shen, Fan, & Bhat, 2004), and can be measured in vivo using the PET ligand $[^{18}\text{F-18}]$ROStrace (Hou et al., 2018). Another marker of interest is the ATP-sensitive homomeric P2X7 receptor (P2X7R), which is a key element in the inflammasome complex, promotes cell cycle progression
and proliferation. As such, P2X7R is gaining interest as a marker of inflammation and a potential therapeutic target (Sperlagh & Illes, 2014). However, a limitation to both P2X7 and ROS is they affect both microglia and astrocytes. A novel strategy to specifically target microglia in the brain is to use the PET ligand \(^{[11]C}\)CPPC \(\text{[5-cyano-N-(4-(4-[11C]methylpiperazin-1-yl)-2-(piperidin-1-yl)phenyl)furan-2-carboxamide]}\), which binds to the macrophage colony-stimulating factor 1 receptor (CSF1R) (Horti et al., 2019). While this tracer is still in development stages, it may be an interesting molecular probe for clinical trials in the future (Horti et al., 2019) and may provide an intriguing alternative to second generation TSPO tracers.

Another confound with the interpretation of \(^{[11]C}\)PBR 28 imaging and the effects of exercise on microglial activity, is that neuroinflammation can be either acute or chronic (Streit & Kincaid-Colton, 1995; Streit et al., 2004a), and aerobic exercise may elicit an acute inflammatory response. In the periphery, cytokines such as interleukin-6 (IL-6) are released in response to exercise and are related to the duration and intensity of the exercise, as well as the mass of muscles recruited during exercise (Petersen & Pedersen, 2005). However, the relationship between peripheral inflammation and the status of microglia in the brain is unclear. Increased microglial activation has been detected in prodromal Alzheimer’s disease (AD), and was associated with slower AD progression (Hamelin et al., 2016; Ramanan et al., 2015). This suggests that a proinflammatory response might be beneficial for neurodegenerative diseases. Exercise could elicit an acute neuroinflammatory response, thereby activating microglia, resulting in benefits.
Conclusion

The bindings pattern observed in the SUV analysis coincided with degeneration consistent with PD pathology. However, the lack of a robust reference region limited the interpretation of the data. There is no conclusive evidence that aerobic exercise decreases neuroinflammation in subjects with PD. However, while this study does not exclude the possibility that there is a relationship between neuroinflammation and exercise, the importance in PD pathology and disease progression remains unclear.

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Matthew A. Sacheli – conception, organization and execution of the research project, design and execution of the statistical analysis and writing of the manuscript.

Danielle K. Murray - conception, organization and execution of the research project, review and critique of manuscript.

Elham Shahinfard – data analysis (fMRI).

Nasim Vafai – data analysis support (fMRI).

Siobhan McCormick – data collection support (PET).

Katie Dinelle – data analysis support (PET).

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Jess McKenzie - patient recruitment, clinical support during scanning.

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Vesna Sossi - conception, organization and execution of the research project, design of the PET analysis, review and critique of the manuscript.

A. Jon Stoessl - conception, organization and execution of the research project, design of the statistical analysis, review and critique of manuscript.
### Table 7. Participant demographics and clinical measures

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<td>Age</td>
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<td>64.67 (10.52)</td>
<td>ns</td>
</tr>
<tr>
<td>Yrs since Dx</td>
<td>3.61 (2.80)</td>
<td>2.33 (1.51)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex</td>
<td>M=5; F=4</td>
<td>M=3, F=3</td>
<td>ns</td>
</tr>
<tr>
<td>Pegboard</td>
<td>38.44 (7.63)</td>
<td>40.00 (8.29)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(16.51) (7.94)</td>
<td>42.67 (6.77)</td>
<td>ns</td>
</tr>
<tr>
<td>TMT A</td>
<td>39.76 (16.51)</td>
<td>36.45 (28.18)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(7.94) (27.60)</td>
<td>34.93 (6.59)</td>
<td>ns</td>
</tr>
<tr>
<td>TMT B</td>
<td>80.5 (28.18)</td>
<td>83.13 (27.60)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(83.13) (27.60)</td>
<td>61.95 (14.81)</td>
<td>ns</td>
</tr>
<tr>
<td>Finger tapping</td>
<td>132.00 (28.18)</td>
<td>133.00 (27.60)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(26.18) (27.49)</td>
<td>128.33 (16.51)</td>
<td>ns</td>
</tr>
<tr>
<td>Reaction time</td>
<td>0.38 (0.04)</td>
<td>0.39 (0.06)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(0.38) (0.06)</td>
<td>0.34 (0.05)</td>
<td>ns</td>
</tr>
<tr>
<td>TUG avg</td>
<td>9.62 (1.99)</td>
<td>10.97 (3.96)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(9.62) (3.96)</td>
<td>9.09 (1.02)</td>
<td>ns</td>
</tr>
<tr>
<td>SAS Apathy scale</td>
<td>8.33 (5.12)</td>
<td>10.44 (5.27)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(8.33) (5.27)</td>
<td>14.83 (6.97)</td>
<td>ns</td>
</tr>
<tr>
<td>BDI</td>
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<td>5.11 (4.37)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(2.69) (4.37)</td>
<td>9.83 (8.86)</td>
<td>ns</td>
</tr>
<tr>
<td>MoCA</td>
<td>27.11 (2.15)</td>
<td>27.22 (1.99)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(27.11) (1.99)</td>
<td>28.83 (0.41)</td>
<td>ns</td>
</tr>
<tr>
<td>MDS – UPDRS III OFF</td>
<td>27.63 (10.70)</td>
<td>25.98 (10.83)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>(25.98) (10.83)</td>
<td>20.61 (5.38)</td>
<td>ns</td>
</tr>
<tr>
<td>VO2 max</td>
<td>22.22 (5.80)</td>
<td>27.34 (5.91)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>(19.88) (5.11)</td>
<td>18.51 (9.11)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Years since Dx, years since diagnosis by a neurologist; Pegboard, Purdue Pegboard – number of pegs placed in 60 seconds; TMT A & B, Trail Making Test version A (numbers only) and B (numbers and letters); Finger tapping, number of taps in 60 seconds; Reaction time, simple reaction time, average of 5 trials; Timed-up-and-go, the time it takes to get up from a chair, walk 3m, turn around, walk 3m and sit down, average of 3 trials at normal walking pace (only collected in OFF state); SAS, Starkstein Apathy Scale, total, combined score of questions 1-14 (higher number = more apathy); BDI, Beck depression inventory, MoCA, Montreal Cognitive Assessment; MDS-UPDRS III, Unified Parkinson’s Disease Rating Scale motor section OFF (after 12 hour withdrawal from dopaminergic medication); ns, not statistically significant p<0.05.
Table 8. Percent change in Standardized Uptake Values and Standardized Uptake Value Ratios (SUVr) with cerebellar reference region

<table>
<thead>
<tr>
<th></th>
<th>SUV</th>
<th>SUVr</th>
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<tbody>
<tr>
<td></td>
<td>Aerobic Mean Pre (SD)</td>
<td>Aerobic Mean Post (SD)</td>
</tr>
<tr>
<td>Age</td>
<td>68.60 (3.78)</td>
<td>63.60 (11.39)</td>
</tr>
<tr>
<td>Yrs since Dx</td>
<td>2.6 (1.14)</td>
<td>3.60 (3.65)</td>
</tr>
<tr>
<td>ACing1 WH</td>
<td>0.83 (0.09)</td>
<td>0.77 (0.21)</td>
</tr>
<tr>
<td>ACing1 BH</td>
<td>0.83 (0.07)</td>
<td>0.76 (0.20)</td>
</tr>
<tr>
<td>ACing2 BH</td>
<td>0.79 (0.07)</td>
<td>0.78 (0.21)</td>
</tr>
<tr>
<td>ACing2 WH</td>
<td>0.83 (0.1)</td>
<td>0.73 (0.20)</td>
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<tr>
<td>AFrontal BH</td>
<td>0.69 (0.09)</td>
<td>0.64 (0.17)</td>
</tr>
<tr>
<td>AFrontal WH</td>
<td>0.72 (0.14)</td>
<td>0.67 (0.21)</td>
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<tr>
<td>Amygdala BH</td>
<td>0.86 (0.14)</td>
<td>0.76 (0.16)</td>
</tr>
<tr>
<td>Amygdala WH</td>
<td>0.87 (0.12)</td>
<td>0.79 (0.22)</td>
</tr>
<tr>
<td>Caud BH</td>
<td>0.62 (0.09)</td>
<td>0.58 (0.19)</td>
</tr>
<tr>
<td>Caud WH</td>
<td>0.64 (0.11)</td>
<td>0.6 (0.15)</td>
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<tr>
<td>Cerebellum</td>
<td>0.73 (0.08)</td>
<td>0.64 (0.12)</td>
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<tr>
<td>Dentate Nuc BH</td>
<td>0.76 (0.15)</td>
<td>0.7 (0.19)</td>
</tr>
<tr>
<td>Dentate Nuc WH</td>
<td>0.8 (0.13)</td>
<td>0.72 (0.18)</td>
</tr>
<tr>
<td>DLPFC BH</td>
<td>0.79 (0.09)</td>
<td>0.73 (0.18)</td>
</tr>
<tr>
<td>DLPFC WH</td>
<td>0.77 (0.09)</td>
<td>0.73 (0.18)</td>
</tr>
<tr>
<td>GP BH</td>
<td>0.86 (0.10)</td>
<td>0.82 (0.21)</td>
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<tr>
<td>GP WH</td>
<td>0.9 (0.15)</td>
<td>0.76 (0.19)</td>
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<tr>
<td>Hypothalamus</td>
<td>0.96 (0.12)</td>
<td>0.9 (0.25)</td>
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<td>Insula BH</td>
<td>0.87 (0.16)</td>
<td>0.91 (0.29)</td>
</tr>
<tr>
<td>Insula WH</td>
<td>0.86 (0.06)</td>
<td>0.82 (0.21)</td>
</tr>
<tr>
<td>Medulla</td>
<td>0.96 (0.10)</td>
<td>0.93 (0.18)</td>
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<tr>
<td></td>
<td>SUV</td>
<td>SUV&lt;br&gt;</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Aerobic (SD)</td>
<td>Aerobic (SD)</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Mid brain</td>
<td>1.18 (0.13)</td>
<td>1.07 (0.25)</td>
</tr>
<tr>
<td>OFC BH</td>
<td>0.86 (0.11)</td>
<td>0.76 (0.20)</td>
</tr>
<tr>
<td>OFC WH</td>
<td>0.88 (0.11)</td>
<td>0.78 (0.18)</td>
</tr>
<tr>
<td>Parietal BH</td>
<td>0.72 (0.03)</td>
<td>0.68 (0.10)</td>
</tr>
<tr>
<td>Parietal WH</td>
<td>0.78 (0.11)</td>
<td>0.72 (0.18)</td>
</tr>
<tr>
<td>PCing BH</td>
<td>0.84 (0.10)</td>
<td>0.76 (0.18)</td>
</tr>
<tr>
<td>PCing WH</td>
<td>0.83 (0.12)</td>
<td>0.78 (0.17)</td>
</tr>
<tr>
<td>Pons</td>
<td>0.97 (0.13)</td>
<td>0.94 (0.25)</td>
</tr>
<tr>
<td>PPN BH</td>
<td>1.01 (0.24)</td>
<td>0.85 (0.22)</td>
</tr>
<tr>
<td>PPN WH</td>
<td>0.91 (0.19)</td>
<td>0.84 (0.25)</td>
</tr>
<tr>
<td>Put1 BH</td>
<td>0.74 (0.06)</td>
<td>0.72 (0.19)</td>
</tr>
<tr>
<td>Put1 WH</td>
<td>0.74 (0.10)</td>
<td>0.72 (0.17)</td>
</tr>
<tr>
<td>Put2 BH</td>
<td>0.76 (0.08)</td>
<td>0.73 (0.18)</td>
</tr>
<tr>
<td>Put2 WH</td>
<td>0.81 (0.12)</td>
<td>0.71 (0.20)</td>
</tr>
<tr>
<td>Put3 BH</td>
<td>0.8 (0.17)</td>
<td>0.72 (0.19)</td>
</tr>
<tr>
<td>Put3 WH</td>
<td>0.79 (0.06)</td>
<td>0.71 (0.19)</td>
</tr>
<tr>
<td>SN BH</td>
<td>0.91 (0.15)</td>
<td>0.83 (0.19)</td>
</tr>
<tr>
<td>SN WH</td>
<td>0.99 (0.15)</td>
<td>0.85 (0.26)</td>
</tr>
<tr>
<td>Tempora l BH</td>
<td>0.76 (0.08)</td>
<td>0.69 (0.16)</td>
</tr>
<tr>
<td>Tempora l WH</td>
<td>0.78 (0.11)</td>
<td>0.71 (0.16)</td>
</tr>
<tr>
<td>Thalamus BH</td>
<td>1.02 (0.16)</td>
<td>0.88 (0.20)</td>
</tr>
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<td>Thalamus WH</td>
<td>1.03 (0.10)</td>
<td>0.92 (0.29)</td>
</tr>
<tr>
<td>VS BH</td>
<td>0.89 (0.13)</td>
<td>0.84 (0.11)</td>
</tr>
<tr>
<td>VS WH</td>
<td>0.83 (0.08)</td>
<td>0.78 (0.24)</td>
</tr>
</tbody>
</table>
Percent change in SUV and SUVr = (post SUV(r) – pre SUV(r)/ pre SUV(r) x 100). For the SUVr analysis the cerebellum was used as the reference region, WH, worse hemisphere contralateral to the more affected side of the body; BH, better hemisphere; ACing1, ventral portion of the anterior cingulate; ACing2, dorsal portion of the anterior cingulate, AFrontal, anterior frontal cortex including dorsal lateral pre frontal cortex and orbital frontal cortex; Caud, caudate; DLPFC, dorsal lateral prefrontal cortex; GP, globus pallidus; Hypothal, hypothalamus; OFC, orbital frontal cortex; Parietal, parietal cortex; PCing, posterior cingulate; PPN, pedunculopontine nucleus; Put1, anterior portion or the putamen; P2, middle portion of the putamen; P3, posterior portion of the putamen; SN, substantia nigra; Temporal, temporal cortex; VS, ventral striatum; ns, not statistically significant p<0.05.
Figure 7. CONSORT flow diagram for patient enrolment for Chapter III and Chapter IV. A breakdown of contacted, enrolled, and analyzed subjects for each type of analysis.
across the two chapters. Note, 9 sedentary subjects from Chapter II were used for the fMRI analysis.
Chapter V: Conclusion

The purpose of this thesis was to investigate the potential mechanisms of exercise for PD. Using multimodal imaging techniques in two different cohorts, we showed that habitual exercisers with PD have better dopaminergic function in the dorsal and ventral striatum compared to sedentary PD subjects. Moreover, we showed that 3 months of aerobic exercise was able to improve dorsal and ventral dopaminergic function in sedentary PD subjects. Lastly, we explored the possibility that the modification of microglial activation might play a supporting role in the benefits of exercise. Given the clinical importance of dopamine replacement therapy for the symptomatic treatment of PD, future studies should investigate how to optimize, and potentially individualize, exercise in order to maximize the dopaminergic response of exercise for both motor and non-motor symptoms of PD. Furthermore, longitudinal studies should examine the long-term effects and early intervention of exercise on disease modification and disease progression.

The effects of exercise on the ventral striatum

Exercise has commonly been associated with a sense of euphoria and positive affect (Reed & Ones, 2006). In PD, up to 90% of patients will experience non-motor symptoms (Chaudhuri & Schapira, 2009), including up to 40% of patients experiencing apathy (den Brok et al., 2015). Interestingly, for nearly half of patients, apathy occurs without comorbid conditions of depression and cognitive impairment (den Brok et al., 2015). It is hypothesized that dopamine depletion in the ventral striatum is one of the primary underlying causes of apathy and depression in PD (Jordan et al., 2013). While
pharmacological treatments can be effective at treating depressive symptoms, they are less effective for the treatment of apathy. To a limited extent, dopamine receptor agonists (e.g., piribedil and pramipexole) have improved apathy (Thobois et al., 2013), mood and motivation (Leentjens et al., 2009), but drug-drug interactions with other antiparkinsonian medications may potentially be problematic. There is an inclination to consider non-pharmacological adjunct therapies, such as exercise, for the treatment of apathy and depression associated with PD (Jordan et al., 2013). However, previous evidence that compared highly trained and physically inactive health control subjects showed that acute aerobic exercise did not increase dopaminergic activation in the ventral striatum in either group despite improvement in apathy, (Bothe et al., 2013). Therefore, it was unclear if reported exercise-induced improvement in apathy (in healthy individuals) resulted from changes in the dopaminergic system or reflected other mechanisms. Our findings suggest that in PD subjects, prolonged exercise is associated with less apathy and greater activation of the ventral striatum.

We first conducted a study similar to Bothe et al (2013), in which we compared habitual exercisers and sedentary PD subjects on a monetary reward task using fMRI. Unlike Bothe et al. (2013), we showed that habitual exercisers had increased ventral striatal activity in anticipation of monetary reward. Habitual exercisers also showed less apathy compared to their sedentary counterparts. This provided preliminary evidence that exercise alters the mesolimbic dopaminergic pathway, which may explain the lower levels of apathy in habitual exercisers. Although this finding contradicts previous reports in healthy controls, the null results reported in Bothe et al. (2013) may reflect a ceiling
effect of tonic dopamine release, and exercise may have a different effect on ventral striatal activity in those with PD compared to healthy controls. Increased ventral striatal activation in the habitual exercisers suggests that habitual exercisers are similar to healthy controls. To improve upon the first study and to confirm that the initial results were not due to reverse causation (i.e., patients that are less apathetic will exercise more and have a greater response to reward stimuli), we conducted a prospective randomized control trial.

The results from the randomized control trial showed that after 3 months of aerobic exercise, ventral striatal activation increases in the anticipation of monetary reward. This indicates that exercise likely affects the ventral tegmental – ventral striatal projection and enhances the responsivity of the mesolimbic reward pathways. In the double blind prospective study, despite the changes in ventral striatal activation, we did not identify a coupled change in measures of mood or apathy after aerobic exercise. This may not be surprising, as the subjects were not apathetic and the behavioural measures may not have been sensitive enough to detect subtle changes. We suspect that with a longer intervention (e.g., 12+ months) and/or a cohort with a greater degree of apathy, we might be more likely to see improvement in mood and apathy with exercise. Despite the lack of behavioural changes, the neuroimaging findings strongly suggest that an underlying mechanism of benefit from exercise for apathy and depression is alterations in ventral striatal responsivity.
The effects of exercise on the dorsal striatum

In PD, the motor improvements associated with exercise have been well documented. Exercise has been shown to improve motor symptoms of PD (D. M. Corcos et al., 2013) with specific improvements in bradykinesia (Dibble, Hale, Marcus, Gerber, & LaStayo, 2009; Ridgel et al., 2009), balance (Allen et al., 2011), and gait (Farley & Koshland, 2005; Fisher et al., 2008). Animal models have suggested that these behavioural improvements may be a result of increased dopamine release (Petzinger et al., 2007), increased dendritic spine density, and arborisation in medium spiny neurons in the direct and indirect pathways (Toy et al., 2014). However, in vivo studies on the mechanisms of action that underlie the therapeutic benefits of exercise for PD have been largely lacking. This thesis provides evidence that prolonged exercise is associated with greater dopamine release in response to exercise itself and that aerobic exercise can increase dopamine release in response to cortico-striatal stimulation in PD patients.

Anecdotal evidence has shown that PD patients who regularly participate in exercise have better clinical outcomes (e.g., lower MDS-UPDRS score, lower dosages of medication, less medical comorbidities, etc.). To determine if these clinical outcomes were the result of better dopaminergic function, we compared dopamine release in response to 30 minutes of exercise between PD habitual exercisers and PD sedentary subjects. We showed the habitual exercisers had greater dopamine release in the caudate nucleus in response to a single bout of aerobic exercise. (Cruise et al., 2011; David et al., 2015; Petzinger et al., 2013; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009). This suggested that prolonged exercise affects the dopaminergic system, which could
explain why PD habitual exercisers appear to have better clinical outcomes. However, similar to the fMRI analysis, reverse causation cannot be excluded, given the cross-sectional design of the study. We were unable to determine if habitual exercisers had less severe PD (greater dopamine release) thus they exercised more, or if exercise led to greater dopamine release.

To address this limitation, a prospective study was conducted to measure the effects of 3 months of aerobic exercise on dopamine release. We showed that after 3 months of aerobic exercise, there was increased dopamine release in the caudate nucleus in response to rTMS. This result emulated the findings observed in the habitual exerciser group, showing that exercise improves dopamine release, and the differences between habitual exercisers and sedentary subjects are not a result of less severe PD.

Interestingly, the greater dopamine release observed in habitual exercisers, and the increased dopamine release observed after aerobic exercise were unexpectedly limited to the caudate. Dopamine release related to motor function is typically expected to be observed in the putamen, as the putamen receives input for somatic motor control (Parent & Hazrati, 1995). After the aerobic intervention, there was an increase in BP_{ND} observed in the posterior putamen; however, the importance of this result is unclear due to its’ small magnitude. The lack of a robust effect of exercise on dopamine release in the putamen could be a result of the type of the exercise chosen for the intervention. Cycling is well tolerated by people with PD, but may bypass somatic motor circuits through external stimuli, such as the repetitive motion of the pedals (Snijders, Toni, Ruzicka, &
Bloem, 2011). As such, cycling may have less reliance on dopaminergic function of the putamen to execute a motor movement. This notion is supported by the theory that goal-based exercise (e.g., the performance of a specific motor task, which requires a greater reliance on putaminal function) combined with aerobic exercise has a synergistic effect and a greater benefit for people with PD (Petzinger et al., 2013). Future studies should examine the effect of goal-based exercise on dopamine release in the putamen. The dopaminergic changes in the caudate align with improvements in cognition observed in PD participants after exercise (Cruise et al., 2011; David et al., 2015; Petzinger et al., 2013; Ridgel, Kim, et al., 2011; Tanaka, Quadros, et al., 2009). Given the role of the caudate in cognitive processes, it is suggested that the exercise-induced cognitive improvements may be the result of improved dopamine release in the caudate.

It should be noted that the stimuli used to evoke dopamine release was different between the two trials. For the cross-sectional comparison (habitual exercisers vs. sedentary PD subjects), the stimulus was 30 minutes of stationary cycling, whereas for the prospective trial the stimulus was rTMS. Repetitive TMS was preferred for the prospective trial as it provides a measure of endogenous dopamine release and is a surrogate marker of corticostriatal plasticity (Strafella et al., 2005). Additionally, rTMS is reproducible for the pre and post scan, unlike stationary cycling, which is affected by the exercise intervention.
The effects of exercise on neuroinflammation

While the improvement of dopaminergic function is a primary factor in explaining exercise induced symptomatic improvement in PD, other processes are likely involved in the potential neuroprotective effects of exercise. To date, neuroinflammation, microglial activation and their role in PD pathology have been a controversial. Previous evidence has shown that early in PD, microglia are triggered and remain activated throughout the disease course (Tansey & Goldberg, 2010) and pattern of activation mirrors the pattern of Lewy body pathology seen in PD (Beraud et al., 2013; Su et al., 2008). Given the effects that exercise has on inflammation (Cotman, Berchtold, & Christie, 2007; Geffken et al., 2001) and the enthusiasm to investigate therapeutics that target neuroinflammatory response in neurodegenerative disease (Hirsch & Hunot, 2009), we examined the effects of exercise on microglial activation. While our initial analysis suggested that aerobic exercise might attenuate the activation of microglia in disease-relevant areas, our interpretation was limited by the technical and analytical shortcomings of TSPO PET imaging and was not supported by a second analysis approach. Since these studies were initiated, more recent studies have failed to demonstrate consistent increases in TSPO binding in PD (Ghadery et al., 2017; Varnas et al., 2019). While exercise may indeed alter neuroinflammation, the magnitude and clinical relevance of the impact are still unresolved. Given the challenges of studying TSPO binding, and prior to understanding the effects of exercise on neuroinflammation, the identification and characterization of novel in vivo imaging markers of neuroinflammation and microglial activation need to be prioritized.
Future directions

The results presented in this thesis show that the symptomatic benefits of exercise are related to dopamine release. The reasonable next steps with this work would be to replicate the findings in a larger cohort and expand to a multisite trial to determine if the mechanisms of exercise remain in a larger, more heterogeneous sample. Additionally, in order to validate the generalizability of our findings, one could examine if changes to dopaminergic function occurs with other types, intensities, and durations of exercise. Apart from replication and validation, this work could also lead to the study of exercise in the context of multifaceted lifestyle interventions, longitudinal studies on the effects of exercise on PD progression, and examining other contributing therapeutic mechanisms.

Multifaceted lifestyle approaches

For the clinical utility of exercise in a treatment plan for someone with PD, it is important to evaluate exercise in the context of other lifestyle changes. As an adjunct therapy for PD, exercise can be complemented by other lifestyle approaches such as diet, sleep and management of comorbid conditions (e.g., cardiovascular health). Improvements to lifestyle may help maximize the therapeutic effect of exercise for the symptomatic treatment of PD. Additionally, the prevention/management of comorbid conditions will improve overall health and allow for regular exercise. Diet is also a lifestyle approach commonly added as a therapeutic adjunct, in conjunction with exercise. Specific diets, such as the ketogenic diet (Gasior, Rogawski, & Hartman, 2006) and the Mediterranean diet (Sofi, Cesari, Abbate, Gensini, & Casini, 2008), have shown specific benefit for Parkinson’s disease and may even have a protective effect (Maraki et
al., 2019). However, there is limited research on the combined effects of exercise and specific diets for PD. Nevertheless, there are promising results from the Alzheimer’s disease literature that shows that exercise in combination with diet, cognitive training and treatment of cognitive deficits can maintain or improve cognitive health of elderly people at risk of developing dementia (Ngandu et al., 2015). This result has sparked a worldwide initiative to study and implement multifaceted lifestyle interventions for the prevention of dementia. Given the results presented in this thesis and the results from the Alzheimer’s literature, it is reasonable to believe that a combination of exercise and diet could result in the prevention and/or slowing of PD. While multidimensional approaches are often full of confounds, the clinical relevance outweighs the scientific drawbacks. Future studies should investigate combination therapies in large cohorts to show the therapeutic impact that lifestyle approaches can have on PD. This will provide scientific evidence that can be immediately implemented into clinical settings and improve the health and well-being of people with PD.

**Longitudinal effects of exercise on Parkinson’s disease**

There has yet to be a pharmacological treatment for PD that is disease modifying, slows the progression, and/or prevents the disease process. Animal models have shown neuro-restorative (Fisher et al., 2004) and neuroprotective (Tillerson et al., 2003) properties of exercise. However, the potential neuroprotective properties of exercise have yet to be established in clinical populations. This is likely due to the short timeframes that are examined for exercise interventions. Many exercise studies are around 3 months in duration (Goodwin et al., 2008), as one is likely to see a physiological effect after this time. Longer durations of the interventions are preferred, but are associated with higher
costs and decreased rates of adherence. Studies with longer durations (i.e., 24 months) have reported improved motor symptoms of PD (D. Corcos et al., 2012), but still did not show changes in disease progression. We posit that a longer duration (e.g., at least 5 years) is needed to show effects on disease progression. This thesis, like many other studies, used a 3-month exercise intervention. As such, it was not designed to examine the longitudinal effects of exercise. However, we showed that a key mechanism of benefit from exercise in PD was improved dopaminergic function, and similar mechanisms differentiated habitual exercisers from sedentary PD subjects. Taken together, this suggests that habitual exercise modifies the dopaminergic system and could affect the manifestations of PD. Future studies should examine the longitudinal effects on PD progression.

It is also unclear if the changes in dopaminergic function after aerobic exercise were due, in part, to the fact that the cohort was sedentary (i.e. starting at a lower baseline). It remains to be seen if the changes in dopaminergic function that were observed after 3 months of exercise would continue to improve over a longer period of time. Future studies should examine the longitudinal impact of exercise to determine how the therapeutic mechanisms may change over time (e.g., formation and/or reinforcement of compensatory mechanisms).

**Other potential therapeutic mechanisms**

This thesis showed that increased dopamine release and responsivity to reward are some of the mechanisms that underlie the therapeutic benefit of exercise for PD. We also
examined if exercise can modulate neuroinflammation and if that also contributes to the benefits of exercise for PD. While dopamine and neuroinflammation are the logical starting points for PD, other mechanisms of exercise may also contribute to the therapeutic effects.

Exercise has been shown to increase dendritic spine density (Toy et al., 2014), activate signalling of BDNF (Wu et al., 2011), and release anti-inflammatory cytokines (Cadet et al., 2003; Scalzo, Kummer, Cardoso, & Teixeira, 2010). Interestingly, exercise-induced increases in cerebral blood flow may be a driving factor that improves angiogenesis and increases the delivery of cytokines and neurotrophic factors throughout the brain (Petzinger et al., 2013). While the magnitude and importance of changes to cerebral blood flow is unclear, future studies should investigate the effects of exercise on cerebral blood flow, and the interactions between peripheral levels of BDNF and cytokines, to infer how cortical levels are changing. In addition, while exercise-induced changes in dendritic spine density are intriguing, in vivo measurements in living brains are needed to understand the importance and impact on neuroprotection and disease pathology. One option is the use of a novel PET imaging ligand $[^{11}\text{C}]\text{UCB-J}$, which binds to the presynaptic synaptic vesicle glycoprotein 2A, and can quantify synaptic density in clinical populations (Finnema et al., 2016). When combined with RAC or other dopamine receptor radioisotopes to understand the pre and postsynaptic changes, $[^{11}\text{C}]\text{UCB-J}$ could potentially provide information on the effects of exercise on synaptic density. Future studies should investigate the impact of exercise on synaptic density and corresponding changes to clinical behaviour and patient related outcomes. Adding exercise early in
disease or at the prodromal state, and examining the effects on synaptic density and corresponding dopamine release would also be an interesting future direction.

Lastly, based on the finding presented in this thesis that showed exercise increases the activation of the ventral striatum, the potential placebo effect of exercise should be investigated. The placebo effect is driven by the expectation of benefit and is mediated by dopamine release (de la Fuente-Fernandez et al., 2001). The general health benefits of exercise have been well established, thus creating an expectation of benefit. While this study did not directly separate the placebo response from the effects of exercise, we did control for it. Additionally, both groups were blinded to group allocation and told they were randomized into an exercise intervention, so if the findings were solely due to a placebo effect, there may also have been dopaminergic changes in the control group, which was not the case. Nevertheless, there could be an interaction between the placebo and exercise-induced effects and future studies should attempt to parse these mechanisms apart.

**Exercise recommendations to consider**

The impact of this work extends beyond the research community and can be directly applied to clinical settings. In this work, we did not look at the prescription of various frequencies, intensities, duration or types of exercise, as the variability would have resulted in uninterruptable findings. There are various recommendations from a wide range different types of exercise interventions for PD that show benefit (e.g., Li et al. (2012), Ridgel et al. (2009)), but there is a lack of consistency in clinical recommendations for patients, as every type of exercise is different. By understanding the
mechanisms that underlie the therapeutic benefit of exercise for PD, we can begin to understand and uncover commonalities between different types of exercise and optimize interventions for maximal therapeutic effect. The findings presented in this thesis show that habitual exercisers have greater dopamine release. As the habitual exercisers were involved in a variety of exercises, we hypothesize that this increase in dopamine release is common to all forms of exercise. We also showed that after 3 months of aerobic exercise, sedentary subjects could increase dopamine release. As such, exercise-induced changes in dopaminergic function are not limited to PD subjects who were previously active. Therefore, all PD patients, regardless of previous exposure to exercise or physical activity, should be encouraged to participate regularly in exercise, as tolerated.

The increased activation of the ventral striatum in response to anticipation of reward suggests changes in the mesolimbic system, which is directly linked to motivation. Exercise has also been shown to increase anticipatory release of endogenous opioids in healthy individuals, related to reward signalling and cravings (Saanijoki et al., 2018). We hypothesize that the changes we observed in ventral striatal activation are not limited to PD patients, but may occur in the majority of people who exercise. However, the impact of the changes in the ventral striatum may be greater for a population at a high risk for apathy, such as PD. However, apathy and depressive symptoms can be a large barrier for individuals to overcome (Watts, Mortby, & Burns, 2018). Therefore, the initial motivation of getting people to exercise is an important concept that needs to be further studied. We propose that the delivery methods of exercise may be as important as the exercise itself, in order to motivate an individual to begin exercising. Based on the link
between exercise and dopamine, presented in this thesis, and dopamine’s role in incentive salience (Berridge, 2007), we hypothesize that once someone begins to exercise, positive reinforcement (e.g., enjoyment during exercise) is important to elicit incentive salience towards exercise. We suspect that the types of exercise that cater to an individual’s preferences will elicit a greater effect on ventral striatal activity and result in greater incentive salience. As such, we recommend that PD patients initially participate in supervised exercises that they enjoy and as changes begin to form in the mesolimbic circuitry, the individuals will begin to show less apathy and increased spontaneous willingness to exercise. In conclusion, this thesis shows biological evidence that exercise should be part of the treatment plan for all patients with PD.
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