

Long Term Aerobic Exercise to Slow
Progression in Parkinson's Disease

NCT03808675

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01. Introduction to Revised Application

We thank the reviewers for their excellent guidance. We addressed their concerns below and made changes to the Research Plan that improved our proposal. Due to the extent of the revisions, we did not mark the specific changes in the Research Plan individually. Briefly, we made the following changes in our proposal to make it more feasible and to provide a crisper contrast between experimental groups, resulting in larger effect sizes, thus, smaller sample size and related costs:

- We will use “usual care with PD specific health education” as control group instead of “light exercise”.
- We dropped Specific Aim 3 (comparison to “natural history” using historic cohorts) due to inherent issues with such analyses and the lack of a clear contribution to the primary research questions. However, we used our past PD driving study cohort as a historic “usual care” control group to estimate sample sizes for the current proposal.
- We shortened the duration from 24 to 12 months, and removed interim assessments for outcomes.
- We reduced outcome measures and brought our primary outcome measures more in line with our own preliminary data, which helped with providing more detailed sample size estimates.

Control group: We agree with the concerns of the reviewer panel that light intensity walking can have confounding effect and changed our control intervention to “usual care with PD specific health education” as detailed in C.2.ii. Both groups will be allowed extra-study physical activities. We will match social attention between both groups by contacting them biweekly about their physical activity, general health, adverse events, medication changes, and other concerns that come up.

Duration of the study: We reduced the duration of the interventions from 24 to 12 months based on the review of our preliminary data¹ and the recent literature,² which suggest that significant contrasts can be observed between a usual care group and aerobic exercise group in motor function and DTI values in patients with PD over 6-12 months. We will collect primary outcome measures only at baseline and 12 months, which will reduce learning effects, attrition, and sample size requirements due to repeated measurements.

Primary outcome measures: We agree with Reviewer 2’s concern of “lack of continuity between preliminary data and a number of proposed outcome measures”. Therefore, we changed our primary outcome measures as follows: We will use flanker task outcome (PIS) for cognition³ and the DTI nodes where we observed robust rD change with significant baseline clinical correlations (putamen, cingulum, and the SLF, see Table).⁴⁻⁶

Region	VO ₂ max	PIS	PegT
L_Putamen	-.56***	.38*	.29‡
R_Putamen	-.50**	.52**	.34*
L_Cingulum	-.48**	.23	.42**
R_Cingulum	-.43**	.24	.39*
L_Sup_Long_Fasc	-.39*	.33*	.38*
R_Sup_Long_Fasc	-.33*	.27‡	.42**
L_Ant_Int_Cap	-.36*	.32*	.41**
L_Post_Cor_Rad	-.13	.31‡	.35*
L_Sup_Cor_Rad	-.36*	.31‡	.29‡

Table. Spearman correlations of regional radial diffusivity (rD) with clinical features at baseline (***p<0.001, **p<0.01, *p<0.05, ‡p<0.1). PIS (Percent Increase Score) is the outcome measure of flanker task, PegT is Peg Board completion time. The rD regions in the table except R_putamen represent those regions which showed significant improvement after 6 months aerobic training. For rD, PIS, and PegT lower values are better; whereas for VO₂max higher values are better. Higher aerobic fitness is associated with better tissue integrity (lower rD) values. Better performance on the flanker task (PIS) and Peg Board time is associated with better rD at baseline. Higher bilateral putamen rD also correlated with higher levodopa equivalent daily dose (p<0.05), a marker of PD severity.

Correlations of DTI metrics and behavior or CRF. Reviewer 2 states "...no correlations were seen with any of their DTI metrics and behavior or CRF". This is true for correlation of changes in these metrics; however, we saw correlation of DTI metrics with CRF and behavior at baseline, especially in regions that showed a significant improvement after the aerobic exercise program (Table). These correlations were in the expected direction, namely, better performances on tests or aerobic fitness correlated with higher tissue integrity (i.e., lower diffusivity). Of the 48 white matter regions tested, 7 regions showed improvement in rD with aerobic training, and 6 of these 7 areas correlated with VO₂max at baseline, whereas only 2 of 41 areas that did not improve correlated with aerobic fitness at baseline. Thus, significant correlation with aerobic fitness at baseline was robustly associated with improvement of rD in that region after aerobic training (OR for regional rD improvement after aerobic exercise if associated with aerobic fitness at baseline was 4.8 (2.2, 7.3), p<0.001, Fisher’s Exact test). This suggests that some areas in the brain might be more likely to benefit from increased

aerobic fitness. We did not detect any significant associations with change in regional DTI and change in aerobic fitness or clinical variables, which could have been due to limited spread of data as all subjects were in the intervention group. However, having a “usual care” control group in the current proposal is expected to generate a dataset with strong variability in fitness gains, clinical and DTI changes, potentially enabling us to find correlations between changes in DTI, CRF, and clinical features.

Selection of DTI nodes. We agree with Reviewer 2 that our primary outcome nodes were not completely based on our own data. Therefore, we decided to change them to putamen, cingulum, and SLF (as defined by Mori et al, 2008⁷) as we have observed significant changes in these nodes in our preliminary study along with significant correlations with baseline aerobic fitness and several clinical features (Table).⁴⁻⁶ These regions have been shown to have decreased FA and increased diffusivity in PD in cross-sectional and longitudinal studies.⁸⁻¹² Mean diffusivity changes in the white matter in PD were found to be predominantly related to an increase in rD,¹³ which increases importance of our finding that we mainly found rD improvements rather than aD.⁶ The putamen is the rostral terminus of the nigrostriatal pathway, but also pathology in cingulum and SLF play an important role in clinical manifestations of PD: The severity of postural instability and gait disorder correlates with increased diffusivity (especially rD) in the SLF;¹⁴⁻¹⁶ DTI abnormalities in cingulum and SLF are associated with cognitive dysfunction.^{14,17,18,18-24} Furthermore, white matter microstructure mediates the relationship between CRF and cognition in older adults.²⁵ Also, SLF integrity is associated with flanker task performance²⁶ as in our preliminary study (Table). The primary DTI outcome measure will be the change in rD in putamen, cingulum, and SLF. The proposed tracts in the prior submission will be used for secondary outcomes.

Management of participants who require absences or breaks for travel or illnesses. We added a section to Human Subjects titled “Protocol for Managing Illness/Injury and Other Health Problems or Travel” (section 04.2.b.), similar to the one used in the LIFE study.²⁷ However, with shorter duration of the study (1-year instead of 2-years) in this submission, potential absences or breaks are expected to be of a lesser concern.

Subject burden. We reduced the duration of the study, number of visits, and number of outcome measures. We will spread detailed baseline and post-intervention assessments over 2 days if needed. We will only do motor MDS-UPDRS scoring and MRI for DTI during the OFF stage, which do not have significant physical demands. With the new design, the number of OFF period measurements has been reduced from 5 to 2 across the study. We will wait for dopaminergic medications to kick in before we do any testing.

Outcomes to evaluate the feasibility, compliance, and adherence to the aerobic exercise. Electronic heart monitor data and exercise diaries will be reviewed with the subject during biweekly phone calls. We will assist the subject selecting walking paths. A similar approach worked well in our preliminary study.

Monitoring concurrent rehabilitation therapies, other exercise activities, and medications. We agree that strict monitoring of extra-study physical activities and various medication categories (e.g., antidepressant, antihypertensives) is needed in addition to randomization. We will use diaries and biweekly phone calls with subjects to monitor for these. We will include these factors in analyses to determine their effect on outcomes.

Sample size. Sample size estimates were “vague” and were “not provided” for some outcome measures in the original submission, as commented upon by Reviewer 2. The following explains our approach in detail. We are planning to recruit N=100 (50/group) that would provide 80% power to detect an effect size of Cohen’s $d'=0.7$ (equivalent to $f=0.35$ or a correlation of $r=0.33$ or $R^2=0.11$) at a 2-sided $\alpha=.05$ after taking into consideration that 10% of subjects may be lost to follow up and 25% might discontinue the intervention. We used our uncontrolled preliminary study on aerobic exercise in PD to estimate effect sizes in the aerobic exercise group (same exercise regimen as in the current proposal).³ To estimate effect sizes in usual care group, we used our observational longitudinal cohort study on driving in PD for motor and driving outcomes,¹ the usual care control group of an aerobic exercise study for aerobic fitness gain (VO2max) outcome,² and a longitudinal observational study on DTI changes.¹¹

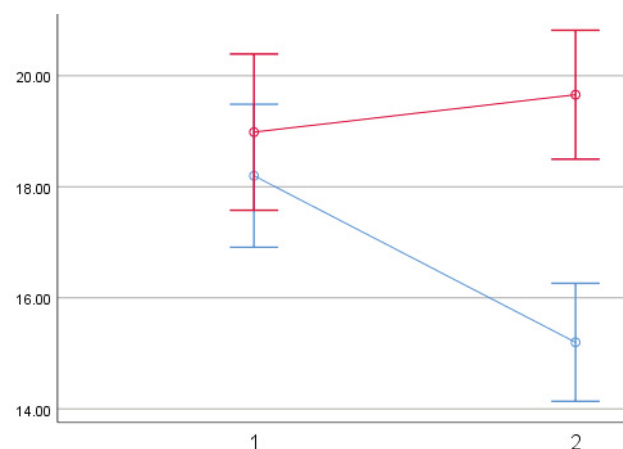


Fig. Effect of aerobic exercise (blue) vs. usual care (red) on motor UPDRS (mean±SEM). $p=0.002$, adjusted for age, education, sex, baseline LEDD, and change in LEDD.

In our prior longitudinal driving study (PD vs. normal aging),¹ subjects underwent motor and cognitive testing at baseline and then annually for 2 years (road test was only administered at baseline and 2 years later, please see B.1. Preliminary Studies). We matched 49 patients from the PD driving cohort to 49 patients from our PD aerobic exercise study³ based on baseline PD severity (as indexed by the UPDRS scores) and age. Here, we will present data from baseline to Year 1. Please note that to compensate for the different follow up periods in the exercise study (6 months) and driving study (12-24 months), the values of second measurements in the driving study were extrapolated assuming a linear change. For example, if the motor UPDRS score of a driving study subject was 20 at baseline and 26 at Year 1 assessment, then the extrapolated value of 23 ($= 20 + [(26-20)/2]$) was assigned as the 6-month follow up value. The Figure shows trajectory of motor UPDRS in aerobic exercise and usual care groups: Adjusted estimates of change in motor UPDRS were -3.1 ± 4.8 (mean \pm SD) for exercise group and 1.2 ± 4.8 for the usual care group, resulting in effect size of Cohen's $d'=0.9$.

The estimates of VO2max change were $+1.65 \pm 2.90$ ml/kg/min after aerobic exercise (our study) and -1.3 ± 2.5 after usual care (Schenkman et al, 2017),² resulting in Cohen's $d'=1.09$. For cognition, we observed a $-3.5 \pm 8.2\%$ change in flanker cost (PIS) in our uncontrolled aerobic exercise study. As we did not have a control group, we compared the change in PIS between the 72 % subset who had VO₂max gain (Δ PIS= $-5.7 \pm 7.0\%$) vs. the 28% subset who did not (Δ PIS= $-0.2 \pm 7.9\%$), resulting in an effect size of Hedges $g'=0.76$ (used for unequal group sample sizes) for those with aerobic improvement. For driving, the annualized change in road error counts based on our cohort¹ were an increase of 7.3 ± 8.4 in the PD group and 0.6 ± 6.0 in the control group. If the proposed PD exercise group were to do midway between the PD group and the control group in our past driving study, and if the proposed usual care group were to do similar as in the PD group in the past study, then the effect size would be Cohen's $d' \sim 0.7$.

We did not have our own historic usual care group for DTI changes. However, we used the data by Zhang et al (2016)¹¹ who scanned 122 recently diagnosed PD patients one year apart.¹¹ In almost all regions, PD patients showed an increase in rD and aD, accompanied by a decrease in FA. Within the PD group, the rD increased up to 4% over 1 year across different regions, averaging $1.7 \pm 1.2\%$ over the whole brain. From this annual change, we estimated the change for 6 months for the whole brain (increase of $0.86 \pm 0.58\%$) and used in sample size calculations to represent the changes in the usual care group in comparison to our own study. During our 6-months aerobic exercise study, rD decreased $1.4 \pm 2.5\%$ in the SLF, $1.5 \pm 3.1\%$ and $1.3 \pm 3.2\%$ in the putamen. Estimated Hedges' g' for SLF was 1.24, for Cingulum 1.46, and for putamen 1.09.

In summary, the potential effect size estimates for various outcomes in a 6-12 months aerobic exercise intervention vs. usual care appear to range between Cohen's d' (or Hedges g') of 0.7 and 1.46. It is possible that effect size of aerobic exercise may increase with prolonged intervention to 1 year.²⁸ Based on these considerations, we decided to use Cohen's $d'=0.7$ as a basis of our sample size calculations.

Do observed DTI changes manifest restoration of brain integrity versus compensatory mechanisms in response to exercise? Addressing this fundamental question by Reviewer 3 may require animal models, which suggest a restorative role for exercise in PD.²⁹ We will attempt to approach this question by performing volumetric analyses of the putamen^{30,31} to determine if the hypothesized improvement of the putaminal rD is accompanied by parallel changes in putaminal volume, which may then suggest brain tissue preservation beyond compensatory changes.

Gain in executive function vs. cognition. We apologize for our unclear expression in A.4.i. as pointed out by Reviewer 3. We recognize that executive functions are one of the several domains of cognition. A more accurate statement would have been that some studies found benefits primarily in executive functions, but not in "overall cognition" or "other domains of cognition". We removed confusing statements from A.4.i. and added that overall studies in animals and humans suggest that aerobic exercise in aging improves cognition and its imaging and electrophysiological biomarkers.^{32,33}

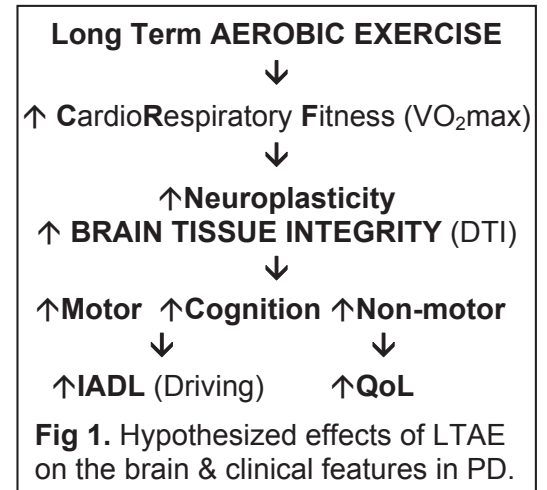
TBI/PTSD. The subjects with history of clinically significant TBI/PTSD will be excluded. Please note that the study is also open for recruitment to non-veterans from the community and the University of Iowa Hospital.

Low effort and salary support for MRI specialist and biostatistician: With the change in study design and sample size, the fiscal pressure on the study emanating from the funding cap \$275K/year diminished, which helped to increase salary support (both at 10% now) and effort allocation to experts important for the study.

Ambitious time line. Reducing the study duration from 24 to 12 months and the sample size from 120 to 100 will result in a more feasible timeline, allowing us to complete recruitment in the first 3 years at a pace of 3-4 subjects/month.

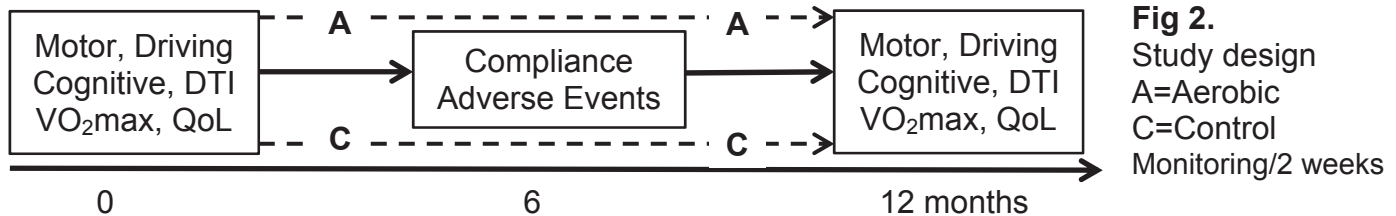
02. Specific Aims

Parkinson's disease (PD) culminates in dementia, immobility, and death at a huge societal cost. Even early in the course, motor and cognitive dysfunction impairs instrumental activities of daily living (IADL). Non-motor symptoms due to fatigue, mood, sleep, and autonomic disorders further reduce quality of life (QoL). DTI shows progressive decline in brain tissue integrity. Usual care of PD centers on medical and surgical treatments relieve motor symptoms, but cause side effects and lose efficacy over time. Usual treatment for non-motor manifestations using pharmaceuticals (e.g., antidepressants) is symptomatic and not specific for PD. Acetylcholine esterase inhibitors exert modest symptomatic benefits on dementia, but there is no approved treatment for mild cognitive impairment. Physical Therapy is usually prescribed in later stages when mobility impairment ensues. There is no approved standard exercise regimen for PD. There is no cure or disease modifying treatment. Thus, there is a critical need for treatments that provide broad spectrum of benefits and slow PD.



Preliminary research suggests that aerobic exercise has potential to meet this need. However, aerobic exercise is demanding and carries some risks. It is unknown if aerobic exercise is more beneficial than usual care in PD in long term due to gaps in our knowledge about the effects of cardiorespiratory fitness (CRF) on brain tissue integrity, motor function, cognition, IADL, QoL, and disease progression. Limitations of current studies include short duration, small sample size, lack or inadequacy of controls, lack of outcome measures for cognition and IADL, and lack of biological markers to measure progression. Our objective in this application is to fill the translational gap by determining the biological, clinical, and functional effects of long term aerobic exercise (LTAE) in PD.

Our overall hypothesis is that LTAE improves brain tissue integrity and slows down PD (Fig 1).



Specific Aim 1: Determine the effects of LTAE on clinical features and functional abilities in PD.

Our 6-month, uncontrolled preliminary trial showed that aerobic exercise improves aspects of motor function, cognition, and QoL in PD, but long term clinical and functional outcomes are unknown. We hypothesize that LTAE will improve motor function, cognition, and non-motor symptoms with translation of benefits to QoL and IADL (driving). Driving is key for independence and depends on integrity of cognitive and motor functions. We will test our hypotheses with a 1-year randomized controlled trial (RCT) that compares the effects of moderate (i.e., aerobic) vs usual care, as in Fig 2.

Specific Aim 2: Determine the mechanism of LTAE effects in PD.

CRF reflects complex improvements in vascular, cardiac, and metabolic health from AE. There is preliminary evidence in aging that higher CRF is associated with better brain health and motor/cognitive function, and that aerobic exercise improves these outcomes. We showed improved clinical function and brain tissue integrity in the striatum and white matter on DTI in PD in our 6-months, uncontrolled, study, but it is unclear how these changes counteract PD progression over long term. Our hypotheses are: 1) LTAE will improve brain tissue integrity as indexed by DTI, 2) LTAE effects on motor and cognitive function are mediated by changes in tissue integrity of critical neural structures on DTI, and 3) physiological processes leading to improved CRF from LTAE are critical to the benefits on the brain tissue integrity and motor/cognitive function. We will test these hypotheses by determining the effects of LTAE on CRF and DTI, and the association between individual differences in training-related changes in motor and cognitive function, DTI, and CRF.

Impact. This proposal leverages our diverse interdisciplinary team, strong preliminary data and past work, and unique infrastructure to determine if LTAE slows down neurodegeneration and clinical disability in PD.

02a. Research Plan

A. Background and Significance

A.1. SIGNIFICANCE

PD is a progressive devastating neurodegenerative condition without a cure or disease modifying treatment.³⁴ The prevalence of PD is 1% of the population over the age of 60, projected to increase by ~60% within the next two decades.³⁵ The estimated annual economic cost PD is \$23 billion in the US, with projected increase to \$50 billion in the next 25 years.³⁵

A.2. PROGRESSION OF PD

General course. PD involves dopaminergic and cholinergic pathways leading to motor and cognitive dysfunction. Involvement of other neuronal systems contributes to depression, anxiety, dysautonomia, fatigue, and sleep disorders resulting in a poor quality of life. Non-motor symptoms usually start before diagnosis and become a major source of disability in advanced phases of PD when non-dopaminergic symptoms take the center stage (Fig 1). Relentless progression leads to immobility and dementia, culminating in nursing home placement and death.³⁴

Motor function. Postural instability and gait disorder (PIGD) is the most potent indicator of evolving disability.³⁶ About 50% of patients develop postural instability within 5 years of diagnosis,³⁷ followed by falls and immobility over time.³⁸

Cognition. Mild cognitive impairment is present in ~20% of patients at diagnosis, or develops ~1/3 of patients within 3 years of diagnosis.³⁹ Cognitive impairment starts with executive dysfunction, accompanied by deficits in attention, information processing, working memory, and visuospatial abilities, followed by memory impairments. Dementia is almost inevitable after 15-20 years, especially in older patients.³⁸

IADLs and driving. IADLs,⁴⁰ including driving, are impaired even in early PD,^{1,41-48} leading to unemployment and social withdrawal.⁴⁹ Driving is a key IADL that allows a person to be more independent for work, leisure, travel and socialization.⁵⁰ Cognitive, visual, and motor deficits all contribute to driving problems in PD (Fig 3).^{41,51} PD patients fail the road test in 30-56% of cases compared to 0-24% among healthy aging controls.⁴⁵ Eventually, PD patients cease driving much earlier than their peers without PD.⁴⁴

Effects on brain tissue integrity as measured by DTI. The main correlates of neurodegenerative diseases on DTI are reduced FA, indicating loss of integrity of white matter due to the breakdown of directionally oriented axonal membranes, and increased MD, reflecting a reduction in density of cellular membranes that hinder diffusion.¹¹ Mean diffusivity consists of radial diffusivity (rD) and axial diffusivity (aD). In general, an increase in rD has been associated with demyelination whereas an increase in aD is thought to primarily indicate cell degradation and axonal loss.¹¹

Cross-sectional changes: Fig 4 shows regions of abnormal DTI in PD across 39 studies.⁸ DTI abnormalities are present in PD in frontal and parietal white matter,⁵² cingulum,⁹ striatum,¹⁰ substantia nigra (SN),^{52,53} and corpus callosum,⁵² and correlate with cognitive and motor function.^{9,54} Interestingly, diffusivity changes in the white matter in PD were found to be predominantly related to an increase in rD.¹³

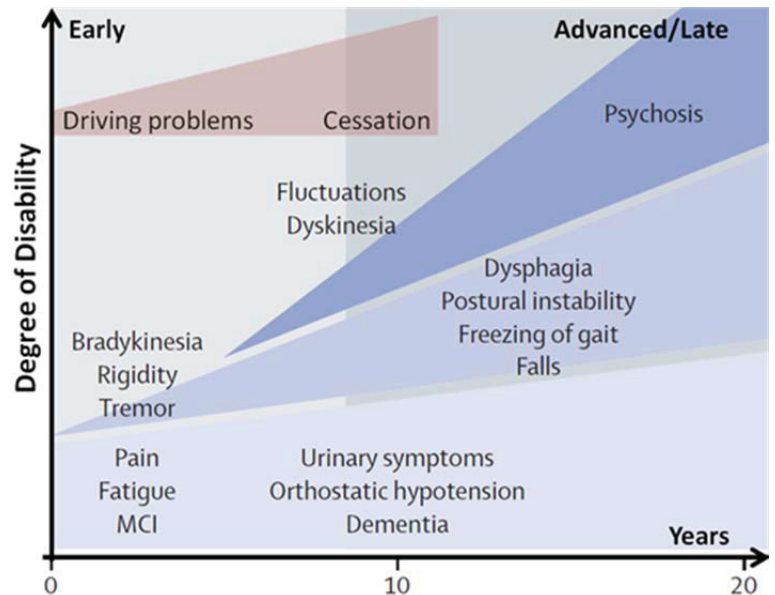


Fig 1. Course of PD.³⁴

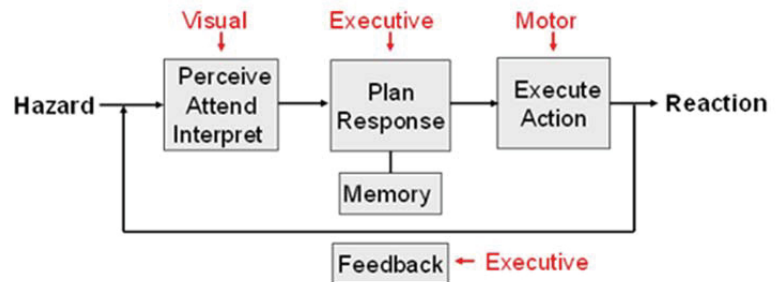


Fig 3. Impaired information processing in drivers with PD.⁴¹ The driver has to attend to the hazard, judge its severity, plan response using memory of past experiences, and execute the selected action (e.g., braking), while monitoring the process for corrective actions. Words in red show dysfunction of key domains.

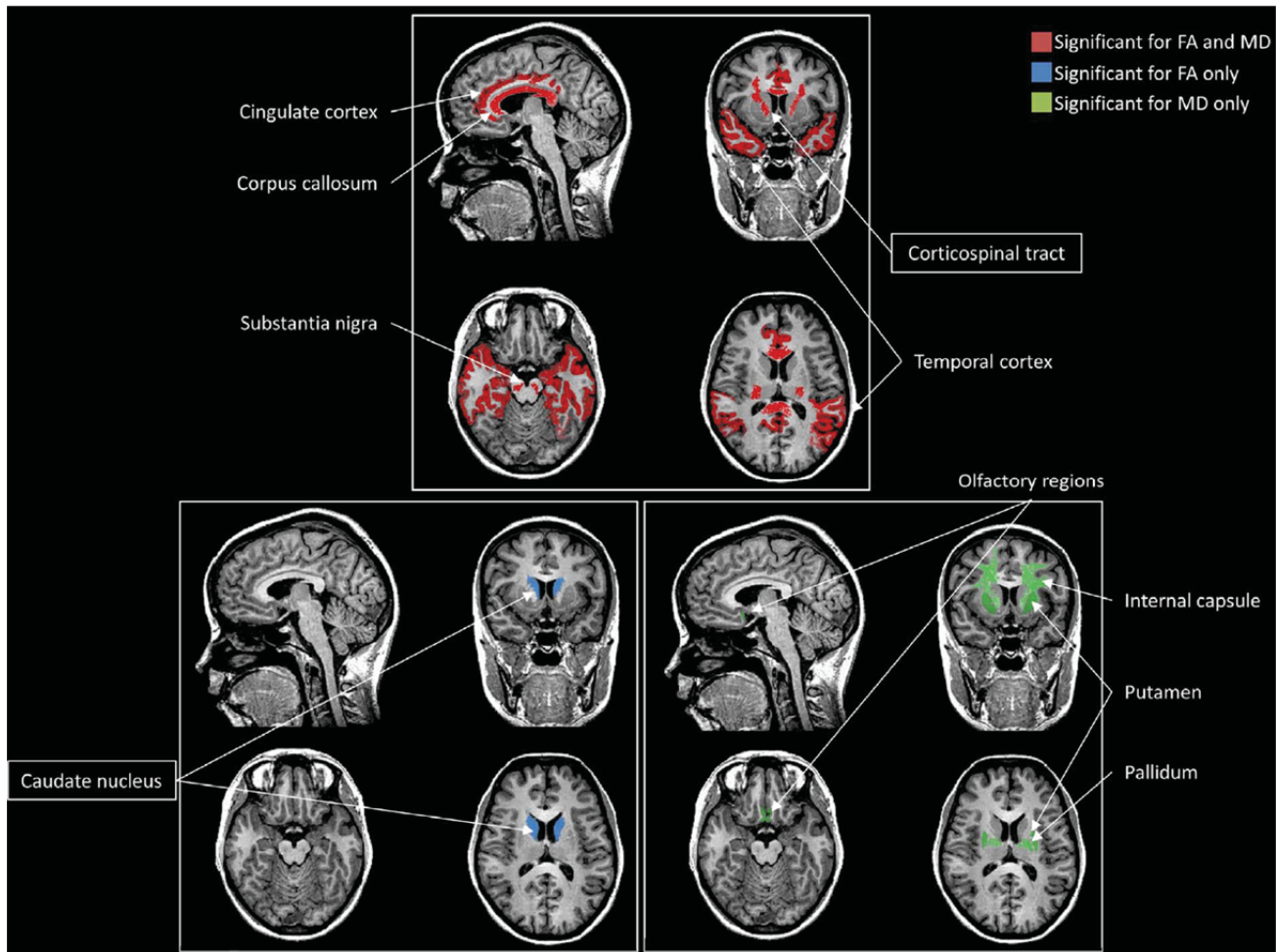


Fig 4. Cross-sectional DTI abnormalities in PD vs. controls. Meta-analysis of 39 studies showing significantly increased MD and/or decreased FA in PD ($n=1087$) vs. controls ($n=768$).⁸

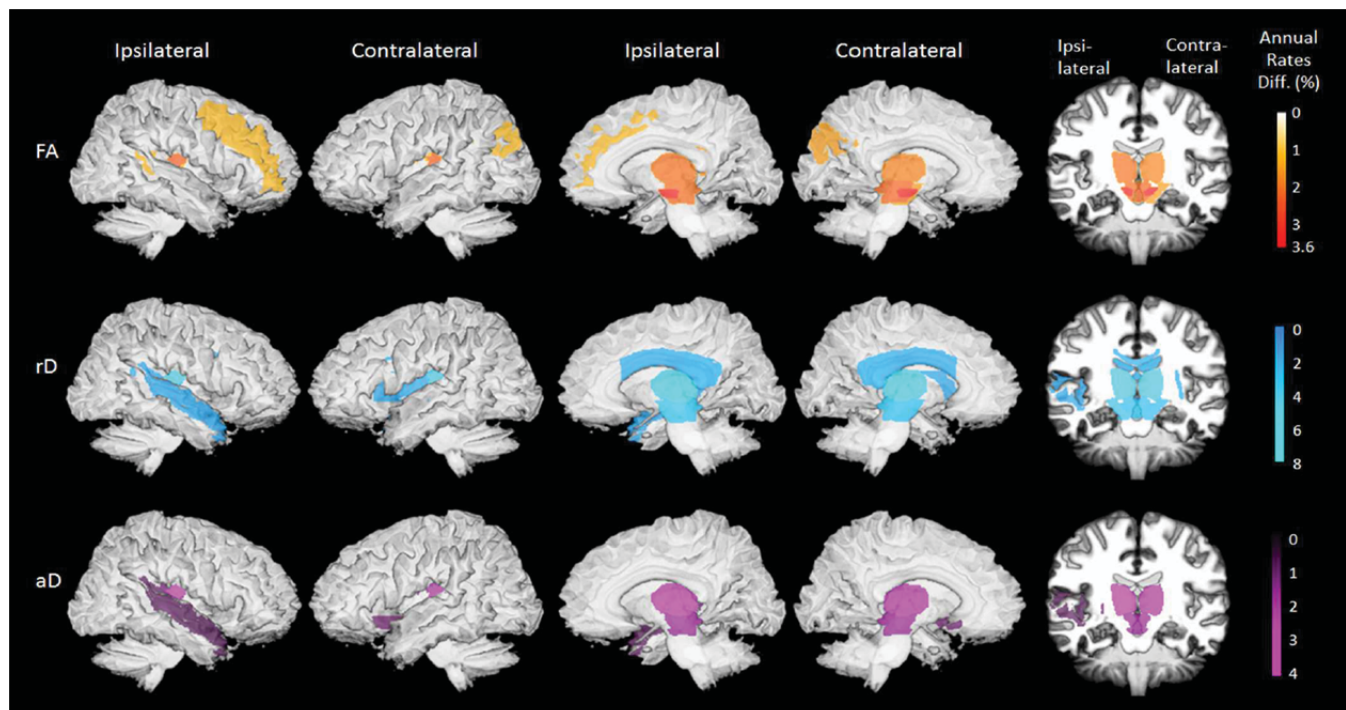


Fig 5. Longitudinal progression of DTI in PD vs. controls. Differences in regional progression rates between PD and controls ($P_{FDR} < 0.05$). Color scales indicate annual % change from baseline, separately for decline in fractional anisotropy (FA), increase in radial (aD) and axial diffusivity (aD).¹¹

Longitudinal changes: Fig 5 shows deterioration of regional DTI in SN, midbrain, internal and external capsule, corpus callosum, and various subcortical white matter regions over one year in early PD, while controls stayed stable.¹¹ Longitudinal deterioration of DTI markers in the SN^{53,55} and putamen¹² along with clinical worsening demonstrated usefulness of DTI as a biomarker of progression in PD.

In summary, DTI is abnormal in PD (FA↓, MD↑, aD↑, rD↑) compared to controls in cross-sectional studies and deteriorates faster in PD than controls in longitudinal studies.

Treatment of PD. Current treatment of PD is aimed at relief of motor symptoms using pharmacological replacement of dopamine and deep brain stimulation, which have side effects and lose efficacy over time. Pharmaceuticals exert modest and transient symptomatic benefits on dementia and there is no approved treatment for earlier stages of cognitive impairment. There is no cure or disease modifying treatment for PD.³⁴

A.3. INNOVATION

Our study will fill the knowledge gaps on aerobic exercise in PD by leveraging our diverse interdisciplinary team, strong preliminary data, and unique infrastructure. Although moderate aerobic exercise is recommended by the American Heart Association for 18-64 year old healthy adults, guidelines for aging and PD do not exist. Despite widespread belief, it is unproven that aerobic exercise improves cognition or brain health in aging or PD due to inconsistent results of the current studies with many methodological limitations.⁵⁶

The main innovation of the proposed study is in the comprehensive assessment of motor, cognitive, functional, physiologic, and neural measures in PD, and their utility to assess the impact of aerobic exercise on brain-behavioral correlations in PD subjects, as is related to symptomology and disease progression. Motor and cognitive functions reflect complex dynamics in/across distributed neural systems. Studying brain-behavior relationships in this framework is facilitated by acquisition of multiple types of data to index complementary aspects of brain microstructure. Simultaneous comprehensive assessment of behavioral, physiologic, and neural measures (DTI) facilitates a 'systems level' interpretation of brain-behavior relationships underlying disease processes and symptomology. Studies in animal models of aging and PD showed that aerobic exercise increases plasticity^{24,32,57} and neuroprotective effects.³³ However, mechanistic studies to identify neuroplastic effects of exercise in human PD are very limited. Our study will fill this gap.

An important innovation is the use of driving as an outcome measure, capitalizing on our expertise on driving in PD.⁴²⁻⁴⁴ Driving draws on cognitive and motor functions, which are impaired in PD and can be potentially improved by aerobic exercise. Driving impairment signifies a broader loss of independence than just driving itself, as the same physical and cognitive deficits that preclude safe driving also reduce people's ability to use public transportation systems.⁵⁸ We will conduct road testing in a state-of-the-art instrumented vehicle.⁴²⁻⁴⁴

A.4. EFFECTS OF AEROBIC EXERCISE IN AGING AND PD:

A.4.i. Aging

Aerobic exercise is thought to benefit the aging brain by increasing plasticity, enhancing circulation,²⁴ increasing neurotrophins, and decreasing inflammatory processes.⁵⁷ Several RCTs on aerobic exercise show encouraging results on cognition: Aerobic walking in sedentary elderly improved a measure of executive control,⁵⁷ accompanied by increased connectivity and regional brain volumes in executive networks.⁵⁹ The CRF is associated with brain integrity and function in aging independent of habitual level of physical activity.⁶⁰ Aerobic exercise on treadmill improved executive functions in MCI.⁶¹ Compared to "usual care", a self-administered aerobic walking program improved cognition in older adults with memory complaints.⁶² However, the landmark LIFE (Lifestyle Interventions and Independence For Elders) study with its large sample size and long duration failed to show cognitive benefits despite improving mobility by a combined exercise regimen (predominantly aerobic walking, accompanied by resistance and balance/flexibility training).²⁷ Still, secondary analyses showed potential benefit in executive function composite scores in a subgroup of subjects who were older and had poorer baseline physical performance.²⁷ Overall studies in animals and humans suggest that aerobic exercise in aging improves cognition and its imaging and electrophysiological biomarkers.^{32,33}

In summary, aerobic exercise improves CRF and mobility in aging and accumulating evidence suggests that it also improves cognition.

A.4.ii. PD

Motor function: Different exercise modalities typically benefit performance of trained domains: For example, aerobic exercise improves CRF (VO₂max)^{63,64} and resistance exercise improves muscle strength.^{33,65} Aerobic walking/running has consistently increased gait speed in PD.^{3,63,64} However, the effects on other, not-directly

trained physical domains is less certain. The effects of aerobic exercise on the severity of parkinsonism (as measured by UPDRS scores) have been mixed with reports showing improvement³ or no benefit.^{63,64}

Cognition: We reported improvement in a measure of executive control. A study of resistance training in PD showed that both the resistance training and an active control group improved on various cognitive tests out of many. Many of the published intervention studies, including ours, had major shortcomings in design or analysis that preclude definitive conclusions about the efficacy of aerobic exercise on cognition. A review on effects of exercise on cognition highlighted various limitations in studies using aerobic, resistance, and dance interventions.⁶⁶ Examples of problems in ascertaining cognitive effects from current studies using aerobic exercise in PD include: 1) Cognition not tested^{63,64,67,68}, 2) small sample sizes (5-25 group),⁶⁹⁻⁷¹ 3) inadequate or no controls,^{3,63,64,70,71} and 4) lack of declaration of a primary cognitive outcome measure.^{69,70} Similar problems were found in a study of resistance training in PD, in which both the resistance training and an active control group showed improvements in various cognitive tests.⁷² Almost all studies with positive results report improvement in one or few out of many cognitive tests and do not report on composite measures or try to link the improvements to real life functions. In summary, almost all published PD studies reporting cognitive benefits from exercise need to be considered preliminary or exploratory due to mentioned reasons. This conclusion could probably be extended to most exercise study results on cognition in aging.⁷³

Similar to aging, aerobic exercise improves CRF and gait speed, but its effects on global parkinsonian severity, cognition, and non-motor features need further investigation.

B. Preliminary Studies

B.1. COGNITIVE IMPAIRMENT AND DRIVING IN PD

In a 2-year longitudinal cohort study (R01 NS044930, PI: Uc), PD patients underwent motor and cognitive tests annually for 2 years after baseline. They scored worse in motor function, all cognitive domains, global cognitive function (COGSTAT), and road safety error count (Table 1) compared to age matched controls at baseline.⁵¹

COGSTAT is a composite measure of global cognition that is calculated by adding up standard T-scores (mean=50, SD=10) assigned to eight cognitive tests spanning executive functions, spatial perception, working memory, episodic memory, speed of processing, and attention.⁵¹

Road test in an instrumented vehicle: At baseline and 2 years later, participants drove 18 miles across residential city streets, suburban commercial strips, rural two-lane highways, and a freeway. The instrumented vehicle had sensors to record electronic data (e.g., steering wheel position, vehicle speed) that were superimposed on video showing lane position of the car and forward view of the road captured by miniature cameras (Fig 6).^{1,42} The videos were scored by a certified driving instructor for safety errors. Drivers were tested in the medication “on” state, under good visibility and road conditions. Drivers with PD committed more safety errors (Table 1), showed poorer navigation skills, recognized fewer landmarks on a visual search task, and were burdened more by multitasking at baseline compared to controls.^{42,46-48}



Figure 6. Still from drive video.^{1,42}

Two years later, 42.8 % drivers with PD and 62.7% control drivers returned for repeat road testing ($p<0.01$).¹ The baseline total driving error counts of PD returnees was similar to control returnees, but significantly less than PD non-returnees (Table 1). The PD returnees had a higher COGSTAT score than PD non-returnees at baseline, but still below Control returnees.¹ Driving error counts are summarized in **Fig 7**, and Tables 1 & 2.

	Control	PD	Control		PD	
Measure	All (n=110)	All (n=67)	NR (41)	R (69)	NR(39)	R(28)
Road Error #↓ (median);	30.5	38.0***	29.0	33.0	40.0	34.5*
COGSTAT↑ mean (SD).	404 (43)	346 (78)***	401 (42)	406 (44)	330 (90)	370 (49)*

Table 1. Baseline comparisons.¹ R=returnee, NR=non-returnee. * $p<0.05$, *** $p<0.001$. Arrow direction = better .

Table 2 shows divergent COGSTAT scores 2 years later, in favor of controls. Please note that Table 2 only shows PD patients who remained active drivers and returned for all visits. While the differences in COGSTAT trajectory between groups became very obvious 2 years later (Table 2), there was already a significant difference at Year 1 after baseline (change in PD -5.4 ± 37.5 vs. Controls 3.8 ± 26.1 , $p=0.05$).

	Baseline		2-Year Follow Up		Change in 2 Years	
Measure	Control	PD	Control	PD	Control	PD
Road Error #↓	33.0	34.5	33.0	46.5***	3.0	13.5***
COGSTAT↑	406 (44)	370 (49)*	417 (47)	361 (55)***	12 (26)	-8 (30) **
UPDRS-ADL↓		6.9 (2.5)		9.1 (5.0)		3.0

Table 2. Data in returnees only. *p<0.05, **p<0.01, ***p<0.001 between groups.¹

PD was at higher risk of driving cessation compared to controls (Fig 8): 2-year cumulative incidence of driving cessation was 17.6% in PD vs. 3.1% in controls (p<0.0001).⁴⁴ Due to higher driving cessation rates in PD, fewer PD patients returned for follow up drive. PD non-returnees had significantly poorer cognition at baseline compared to PD-returnees (Table 1). If all baseline participants had returned 2-years later regardless of driving status, there would have been a wider gulf between PD and controls in COGSTAT. Similar to the trajectory of COGSTAT, despite drop out of the more impaired drivers within the PD cohort, returning PD drivers, who drove like non-PD controls at baseline, showed many more driving safety errors than controls after 2 years (+13.5 vs. +3.0, p<0.001).

Predictors of driving outcomes: Decrease in COGSTAT, executive functions, visual acuity and attention, and UPDRS-ADL score predicted increase in safety errors and future driving cessation within the PD group.⁴⁴ Motor dysfunction predicted slow reaction times in response to crash hazards in the simulator.⁴³ Crashes within the PD group were predicted by history of prior citations and postural instability at baseline. Of note, there was no difference in crash rates between PD and controls due to attrition of high risk PD drivers. Citations were predicted by total road error counts at baseline.

In summary, drivers with PD showed poorer road safety compared to aging controls at baseline, which correlated with motor and cognitive impairments. A much larger proportion of drivers with PD stopped driving during follow-up. Despite attrition of the more impaired drivers within the PD cohort, returning PD drivers, who drove like controls at baseline, showed many more driving safety errors and a steeper cognitive decline than controls after 2 years.

B.2. AEROBIC EXERCISE IN PD: Clinical effects

We investigated effects of aerobic walking on motor function, cognition, and quality of life in PD (n=60, Hoehn-Yahr Stage=2.0±0.4. MMSE=29.1±1.1 at baseline).³ Subjects were required to exercise 45 min/session, 3 times/week for 6 months. We also compared safety and fitness benefits between continuous and interval training. The goal for continuous training was to remain within 70-80% of the age predicted maximal heart rate (HR_{max}), and for interval training to alternate between 60-70% and 80-90% of HR_{max} every 3 minutes. Most participants exercised individually on a neighborhood trail or track at their convenience. They wore electronic heart rate and walking speed monitors during each session. We randomized 43 participants to continuous or interval training in the first 2 years. Three subjects in the interval group dropped out due to knee pain (improved with rest), while none of the continuous group subjects had this problem (p=0.196). There was no difference in efficacy on aerobic fitness between interval and continuous arms. Therefore, the next 17 participants in the third year were allocated only to continuous training. Eighty-one percent completed the study, 7 of 11 drop-outs were due to reasons unrelated to the study. There were no serious adverse events.

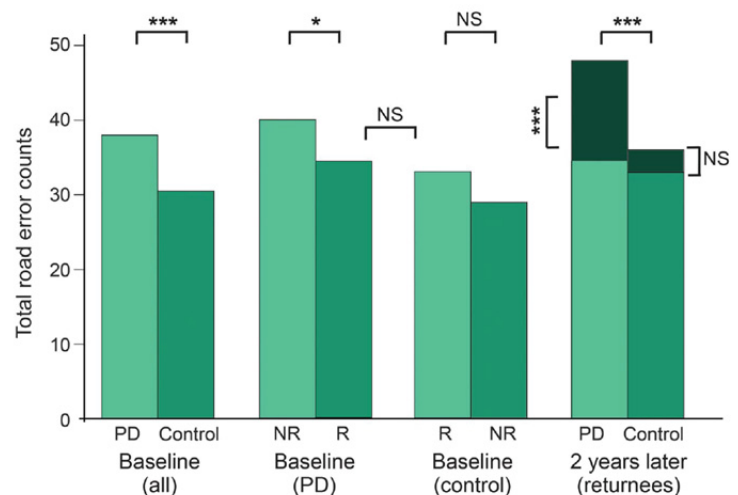


Fig 7. Comparison of road errors in PD vs. Controls.¹ R=Returnee, NR=Non-returnee; *p<0.05, **p<0.01, ***p<0.001, NS=Not significant

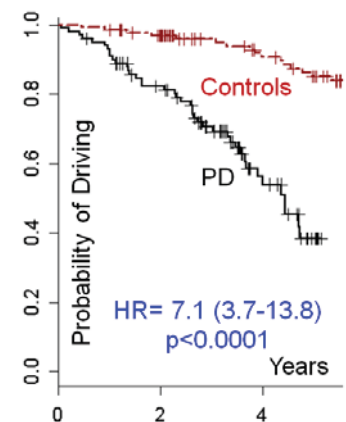


Fig 8. Increased driving cessation in PD.⁴⁴

Results: Completers attended 83.3% of the required sessions and achieved a mean exercise intensity of 46.8% of their heart rate reserve (HRR),⁷⁴ equivalent to 69.7% of age predicted HR_{max}.⁷⁴ As treatment groups did not differ in baseline characteristics, adherence, exercise intensity, and VO₂max gains, we pooled all completers for analysis, and observed significant improvements in VO₂max, gait speed, UPDRS scores, executive functions, depression, and fatigue scores, and quality of life score (Table 3) after adjusting for dopaminergic treatment.³

Outcome	Pre	Post	Change
VO ₂ max (ml/min/kg)↑	25.4±6.6	27.0±7.0	1.56±2.74***
7m Walk (seconds)↓	9.4±1.5	8.7±1.4	-0.85±0.94***
MoCA↑	24.5±3.0	24.8±3.3	0.5±1.9†
Flanker (PIS)↓	25.5±10.1	22.0±10.2	-3.7±8.2**
Fatigue (FSS)↓	4.1±1.1	3.6±1.3	-0.5±1.1**
Depression (GDS)↓	5.3±3.6	4.5±3.8	-0.8±2.6*
Quality of Life ↓	41.7± 8.9	40.6±9.3	-1.1±4.2**
UPDRS - Mental↓	2.1±1.9	1.6±1.3	-0.5±1.6*
UPDRS - ADL↓	9.3±4.9	8.8±4.6	-0.2±2.5
UPDRS - Motor↓	18.8±10.4	15.9±8.4	-2.8±7.1**

Table 3. Select results from our exercise study.³ *p<0.05, **p<0.01, ***p<0.001, †p<0.1. Arrow direction = better

Increase in VO₂max correlated with mean exercise intensity and walking speed. Multiple linear regression models showed that improvements on both the flanker task and quality of life score were significantly associated with increase in VO₂max and tended to be associated with lower VO₂max at baseline.

B.3. Aerobic exercise in PD: DTI effects

We found that CRF (VO₂max) correlated directly with FA in putamen, substantia nigra, cingulum, hippocampus, and various other white matter regions at baseline(p<0.05 to p<0.01).^{4,5} CRF correlated inversely with MD and rD of the putamen, superior longitudinal fasciculus, cingulum, posterior and superior corona radiata, anterior internal capsule at baseline (p<0.05 to p<0.001).^{4,5}

After the 6-months aerobic exercise, we observed decreased MD in the putamen and in the left superior longitudinal fasciculus and superior corona radiata, and increase in FA in the posterior corona radiata (p_{FDR}<0.05, adjusted for multiple comparisons using False Rate Discovery-FDR).^{4,5} There was tendency for increased FA in the left caudate and putamen (p=0.1).⁵ Further analysis of diffusivity showed significant (p_{FDR}<0.05) decrease in the rD in bilateral cingulate gyrus and superior longitudinal fasciculus, left anterior limb of internal capsule, posterior corona radiata, and superior corona radiata (Fig 9), but no significant decrease in axial diffusivity (index of axonal integrity) in any region, suggesting that aerobic exercise might be primarily benefiting the myelin.⁶

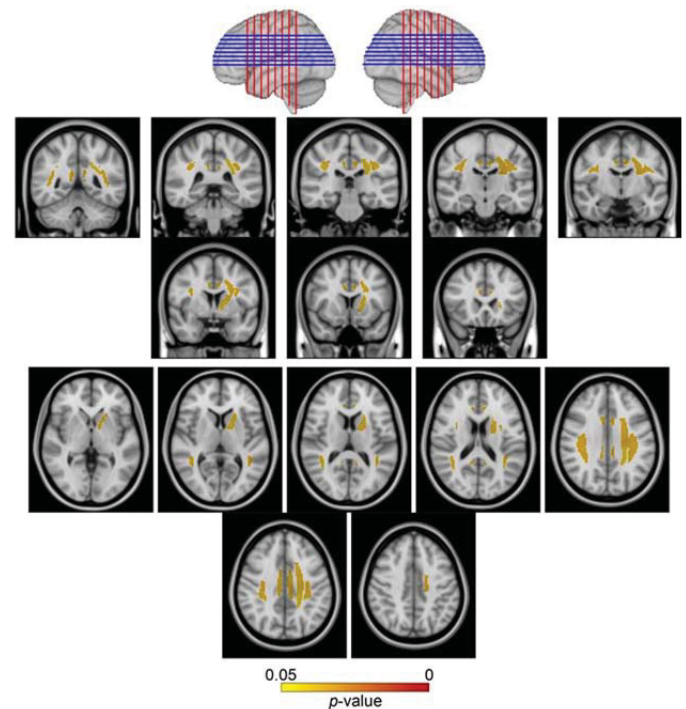


Fig 9. Improved (↓) rD in white matter, p_{FDR}<0.05.⁶

The lack of a control group in our preliminary study may have underestimated the improvement of microstructural tissue integrity by aerobic exercise, as a control group is expected to show the natural decline in tissue integrity.^{11,53} For example, compared to normal aging, PD was associated with up to 8.0% increase in rD over 1 year.¹¹ Within PD group only, the rD increased up to 4% over 1 year across different regions.¹¹ As shown in the Table in the Introduction, we had many regions that showed significant decrease in rD after aerobic exercise. Considering the contrast between the significant 1.3-1.5% decrease of rD in our primary regions of interest during our exercise study⁶ and an average of 1.7% increase of rD in a usual care group,¹¹ the effect size in the proposed study likely will be much higher than in the preliminary study.

In summary, our preliminary, uncontrolled, 6-month study suggested that striatal and white matter tissue integrity is associated with CRF, and that aerobic exercise might improve clinical symptoms and reverse the decline of DTI in PD, suggesting increased tissue integrity (neuroprotection?).

C. Research Design and Methods:

C.1. SUMMARY

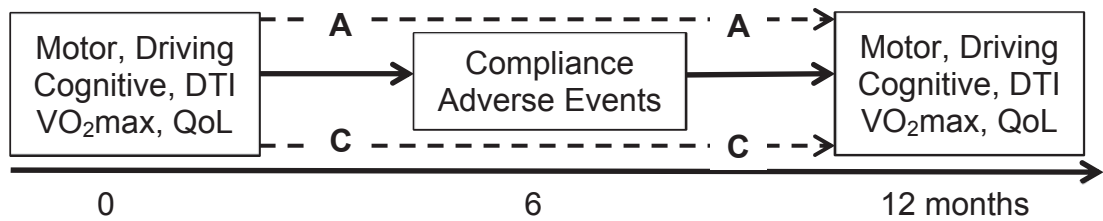


Fig 10.
Study design
A=Aerobic
C=Control
N=100 (50/group)

Design: Single-blind, parallel 2-group RCT with outcome measures as in Table 4. Please see Human Subjects section for detailed schedule of activities (Table 3) and visit day schedules.

CRF	VO ₂ max
Motor	OFF period MDS-UPDRS Motor Subscale score
Cognition	Flanker task performance (PIS)
Driving	Total road safety error count
QoL/Non-Motor	PDQ-39; MDS-UPDRS Non-motor EDL scale
DTI	rD in putamen, SLF, and cingulum

Table 4. Main outcome measures for each category.

age and gender based norms⁷⁶ (details in Human Subjects). These criteria will limit eligibility to those who are most likely to benefit, but yet are safely able to participate in the study. Subjects are allowed to continue existing physical training programs or PT as long as they meet the VO₂max and other criteria as randomization will balance potentially confounding activities between the groups. We will keep track of extra-study rehabilitation programs or exercise using patient diaries and biweekly phone calls, and incorporate their characteristics in analysis of outcomes. We believe that being too restrictive over a one-year period can hinder recruitment or increase risk of withdrawal from the study. We have a plan to manage participants who require absences or breaks for travel or illnesses, as documented in the section 04.2.b. in Human Subjects titled “Protocol for Managing Illness/Injury and Other Health Problems or Travel”.

C.2. INTERVENTIONS

C.2.i. Active Interventions: Aerobic walking

We will use self-administered continuous walking exercise at a moderate intensity level, defined as 40-59% of heart rate reserve or 64-77% of heart rate at gas exchange threshold (HR_{GET}) by ACSM⁷⁴ as in our preliminary study.³ The HR_{GET} will be determined as the heart rate at VO₂max during graded cycle ergometry.³ Using measured rather than estimated (e.g., by age) HR_{max} has the advantage of incorporating the effects of PD, comorbidities, and medications (e.g., beta-blockers) into the prescribed target intensity.⁷⁴ The total duration of the exercises will be 150 min/week per 2008 Physical Activity Guidelines for Americans and American Heart Association recommendations,⁷⁴ conducted in three 50 min sessions. The aerobic walking intervention will take place outdoors (e.g., trails, sidewalks, parks) or indoors (e.g., track in a local gym or a mall) depending on the preferences of the subject and weather. Session duration will be 20 min the first week and will be advanced by 5 min per week over 6 weeks. As the sessions are not directly supervised, we will have the subjects advance the exercise intensity using perceived levels of exertion to avoid adverse events. Using Borg’s scale, that ranges from 6 to 20,⁷⁷ participants will be asked to walk at an intensity of 13 (activity perception SOMEWHAT HARD), consistent with moderate intensity.⁷⁷ They will be discouraged from exercising at levels that approach or exceed 15 (HARD) or drop to a rating of 11 (LIGHT) or below. Completely sedentary (less than 20 min exercise/week), will be started at <12 (light intensity, about 30% of HRR). The heart rate monitor will beep if the subjects exceed 59% off HRR or drop below 30% of HRR to

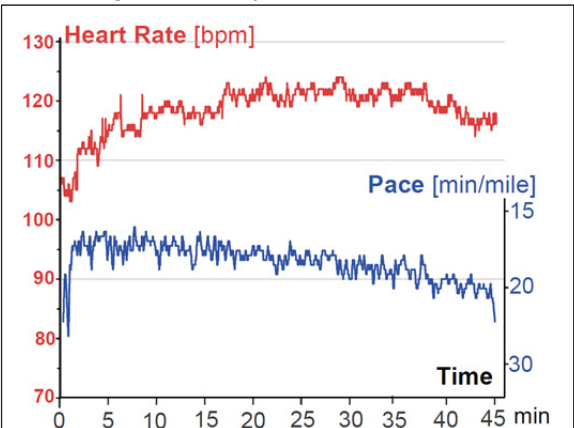


Fig 11. Electronic heart rate monitoring output from our preliminary study:³ A 45 min exercise session with mean HR 119.

provide them with real time guidance during exercise. The ACSM guidelines for exercise prescriptions⁷⁴ will be followed to avoid exercise related injury.

Monitoring: The subject will fill a simple diary about each exercise session. They will wear a Polar A300 heart rate monitor during training sessions that has been programmed to provide them with exercise duration, their current heart rate, and signals to slow down or increase the heart rate to remain within the prescribed window, similar to our preliminary study.³ We will also allow aerobic exercise subjects to engage in additional extra-study physical activity if they desire as this motivation could be an outcome of aerobic exercise itself.

Fig 11 shows the HR monitor printout of an actual exercise session from our preliminary study, where we captured 96% of all sessions electronically, confirming the exercise intensity and showing a significant correlation between exercise intensity and VO₂max gain.³ We will have the subject weekly synchronize the heart rate monitor data with Polar Flow web service using a personal computer, tablet, or smartphone. Approved study personnel will have access to Polar Flow web service data. We will call the subject biweekly for a structured interview to review progress, compliance, and adverse events, and extra-study physical activity which will also be reviewed during the study visits every 6 months.

C.2.ii. Control intervention: Usual Care with PD specific health education.

Recent clinical trials on exercise in PD employed either no control group at all,⁶³ or their control group also engaged in an exercise program.^{64,65} Lack of a non-exercise intervention control group makes it difficult to evaluate the true effect of the tested exercise program as other exercise interventions may have provide benefits beyond placebo and reduce the effect size of the investigated intervention. Furthermore, a non-exercise control group would reveal a more realistic effect size of the proposed intervention in the community as it reflects the lifestyle of the majority of the population (65% of adults in North America are sedentary).⁷⁸

Usual care for PD consists of medical and surgical treatments for motor and non-motor symptoms, and PT/OT for specific prescribed indications. There is no standard of care for behavioral interventions such as exercise. The usual care for behavioral interventions typically involves patient education by in-person discussion, providing pamphlets/booklets and on-line resources to learn about PD and encourage healthy living.

In this study, patients will receive their usual medical treatment for motor and non-motor symptoms from their primary neurologist. We will use a streamlined form of PD specific health education prepared by the VA: *My Parkinson's Story*, which consists of a series of short videos prepared by the VA PADRECCs addressing various aspects of PD. These 6-12 minutes long videos are freely available on YouTube⁷⁹. We can also provide them on a CD if subjects desire. They start with a patient testimony about the topic of the episode, followed by comments of experts in the field. These videos are popular with our patients and on YouTube (some had > 70,000 views. The title of the episodes are: Early Parkinson's, Medications, Exercise, Memory, Visual Disturbances, Depression, Sleep, Speech and Swallowing, Impulsive Behaviors, Driving, Pain, Dyskinesias, Deep Brain Stimulation, Advanced Parkinson's Disease, Falls, The Caregiver, Hospitalization, Genetics, Environmental Exposure, Atypical Parkinsonism. Dr. Uc was one of the contributors ("Driving" episode) to this program. We will ask the subjects to watch one of these videos every 2 weeks that can be discussed during biweekly monitoring phone calls.

The control subjects will be free to continue their existing exercise habits or to get involved in new programs on their own. We will also allow aerobic exercise subjects to engage in additional extra-study physical activity if they desire as this motivation could be an outcome of aerobic exercise itself. This liberal approach to extra-study physical activity will likely improve recruitment and retention, and mitigate potential ethical concerns of depriving subjects of physical activity. However, we will document extra-study physical activity very carefully by providing all subjects with exercise diaries to keep track of their exercise modality, frequency, and intensity. We will also inquire about extra-study physical activity during biweekly phone calls. Furthermore, VO₂max and detailed motor testing at baseline and 12 months will document the change in their aerobic fitness, strength, and balance. We will use diary and physical performance test results in exploratory analyses to see if extra-study physical activities might have affected outcomes. However, CRF is the associated with brain integrity and function in aging independent of physical activity, suggesting that, unless it is a sustained aerobic program, extra-study physical activity would have little bearing on our outcomes.⁶⁰ We realize that this control arm is not well matched with the active arm in terms of time spent while engaging in the intervention itself. However, we will match social attention between both groups by contacting all subjects from both groups biweekly about their physical activity, general health, adverse events, medication changes, and other concerns that come up.

C.2.iii. Concomitant drug treatment and other activities during the study

Patients will continue to be managed by their treating neurologists and primary care providers. Due to the long duration of the study, changes in PD medications and other medications will be allowed. However, we will keep track of medication changes in key categories such as dopaminergics, antidepressants, anxiolytics, antihypertensives, anticholinergics, and choline esterase inhibitors that can affect the outcome measures. We will study the influence of baseline treatments and their changes during the trial using regression analyses. Subjects will be allowed to continue their ongoing physical activities, but we will keep track of them using physical activity diaries/phone calls, and use this information as covariate in exploratory regression analyses. These statistical approaches and randomization are expected to explain and minimize the effect of concomitant treatment and activity on the outcomes.

C.3. APPROACH TO SPECIFIC AIMS:

C.3.i. Aim 1: Determine the effects of LTAE on clinical features and functional abilities in PD.

Hypothesis:

LTAE will improve motor function, cognition, and non-motor symptoms with translation of benefits to QoL and IADL.

Approach: We will analyze differences in changes on clinical outcome measures between the aerobic exercise and usual care control groups in a one-year, single blind RCT.

C.3.i.a. Motor Function

Primary outcome measure: MDS-UPDRS motor examination subscale (Part III) score in the “practically defined OFF state”, i.e., after overnight (~12 hours) withdrawal of PD medications.³⁴

Secondary outcome measures: These measures will be obtained in the ON state.

1) *MDS-UPDRS motor examination subscale (Part III) score and MDS-UPDRS motor experiences of daily living subscale (Part II) score* (completed by the patient). The MDS-UPDRS is a validated core instrument of NINDS Common Data Elements.⁸⁰ It is structured on original UPDRS but provides much broader coverage of non-motor features and incorporates of patient-reported outcomes to enhance the relevance and validity of study results. It shows greater sensitivity for change compared to original UPDRS, and correlates strongly with changes in quality of life and non-motor features.⁸⁰ Please note that we will also score subjects using the original UPDRS (subscales I-III) for comparability to past research. This additional scoring will not increase the burden on the subject as the exam and questionnaire items are overlapping and the original UPDRS has lesser items to score on.

2) *NIH Toolbox motor battery* includes 5 subdomains the following valid and reliable measures that are simultaneously low-cost and portable:⁸¹ 1) Dexterity (9-hole peg board); 2) Strength (grip dynamometry for upper-extremity strength); 3) Balance (standing balance test); 4) Locomotion (4-m walk test for gait speed); and 5) Endurance (2-minute walk; distances covered over 2 and 6 minutes are highly correlated).⁸²

C.3.i.b. Cognition

Primary outcome measure: Due to its sensitivity to changes in aerobic fitness^{57,83} (including in our preliminary study³), we chose change in Percent Increase Score (PIS) on Eriksen’s flanker task, which measures the cost of conflict resolution between the incongruent and congruent stimuli. Participants will be asked to identify the orientation of a central arrow cue (<’ or >’), which is flanked on both sides by two arrow cues that either point in the same direction (congruent: <<<<<) or a different direction (incongruent: >>>>>). Using reaction times (RT) during congruent and incongruent trials, the PIS will be calculated as $=((RT_{\text{incongruent}} - RT_{\text{congruent}}) / RT_{\text{congruent}}) * 100$.⁵⁷

Secondary outcome measures: COGSTAT, a composite measure of cognition, calculated by assigning and summing standard T-scores (mean=50, SD=10) to eight tests from the cognitive test battery we used in our driving studies,¹ will be the main secondary outcome measure. This cognitive battery will enable us to probe multiple domains: Complex Figure Test—Copy (CFT-Copy) Version, Block Design for visuospatial construction; Trail-making Test (B-A), a measure of set shifting and Controlled Oral Word Association Test (also tests language) for executive functions; Rey Auditory Verbal Learning Test (anterograde verbal memory), CFT—Recall is administered 30 minutes after the CFT-Copy (visual memory), Benton Visual Retention Test—errors for memory; Judgment of Line Orientation for visual perception.¹

All cognitive and driving tests will be conducted in the ON state.

C.3.i.c. Non-motor symptoms & quality of life

MDS-UPDRS Non-motor Experiences of Daily Living *subscale* (Part I) score will be the *main non-motor outcome measure*. As depression, anxiety, sleep, and fatigue are only covered by one item in this subscale, we will employ specific scales measure them further: Geriatric Depression Scale (GDS),⁵¹ Beck Anxiety Inventory (BAI),⁸⁴ PD Sleep Scale version 2 (PDSS-2),⁸⁵ and Fatigue Severity Scale (FSS).³ QoL will be measured by the summary index of the Parkinson's Disease Questionnaire-39 (PDQ-39).⁸⁶

C.3.i.d. IADL (Driving)

We will use driving as the outcome for IADL. Driving represents an important symbol for independence, and depends on integrity of cognitive and motor systems.

Road testing: The primary outcome measure will be the total number of safety errors during a standardized experimental drive in an instrumented vehicle per our well established protocol described in preliminary data section, published papers, and Human Subjects section. The drive videos will be scored by a certified driving instructor for safety errors.

Real world driving outcomes: *Time to driving cessation, first citation and crash* will be determined as in our prior work using Driving Habits Questionnaire,⁴⁴ clinic and state driving records.⁴⁴ The earliest evidence of driving cessation will be used to calculate elapsed time since baseline. For cases without evidence of driving cessation, we will use the last date of known driving as the censoring time for this outcome.

C.3.ii. Aim 2: Determine the mechanism of LTAE effects in PD.

Hypotheses:

1. LTAE will improve brain tissue integrity as indexed by DTI.

Approach: We will analyze differences in regional rD changes between the aerobic exercise and usual care control groups in a one-year, single blind RCT.

Primary outcome regions of interest: Putamen, Cingulum, Superior Longitudinal Fasciculus

Secondary outcome regions of interest: Diffusion imaging tractography of

Motor: Substantia nigra↔putamen (nigrostriatal tract) and putamen↔premotor cortex

Cognitive: Dorsal lateral prefrontal cortex (DLPFC)↔caudate and the parietal cortex↔prefrontal cortex.

2. LTAE effects on motor and cognitive function are mediated by changes in tissue integrity of critical neural structures on DTI.

Approach: We will perform regression analyses to determine associations between rD changes in primary regions of interest and changes in outcomes for motor and cognitive function across groups.

The primary outcome measure for motor function is the MDS-UPDRS motor score in the OFF period. The primary measure for cognitive function is PIS (Percent Increase Score) on the flanker task.

3. Physiological processes leading to improved CRF from LTAE are critical to the benefits on the brain tissue integrity on DTI and on motor/cognitive function.

Approach: We will perform regression analyses to determine associations

1) between CRF (VO₂max) changes and rD changes in primary regions of interest, and

2) between CRF changes and changes in primary outcomes for motor/ cognitive functions.

C.3.ii.a. Imaging Methodology

We will use DTI, a biomarker of structural connectivity and brain tissue integrity, as primary imaging measure based on our preliminary data.^{4,5} DTI will be performed in the practically defined OFF state (withholding medication overnight for 12 hours) to avoid potential confounding effects from dopaminergic treatments.⁸

Alternatively, positron emission tomography (PET) or single photon emission computed tomography (SPECT) of the dopaminergic system could have been used,⁸⁷ but they are invasive, more expensive, and more likely to be affected by concomitant medications. Furthermore, data on other aspects of brain structure and function can be collected while subject is in the MRI scanner. For example, we will also acquire MR images for secondary neuroimaging measures of *functional connectivity* (resting-state fMRI BOLD)⁸⁸ and *neuronal metabolism* (T1ρ),^{89,90} and volumetry of the striatum as performed by members of our team in prior work (details in Dr. Voss⁸⁸, Dr. Magnotta^{30,31,89,90}).

The primary DTI outcome measure will be the change in rD in putamen, cingulum, and SLF (Mori et al, 2008⁷) as we have observed significant changes in these nodes in our preliminary study along with significant correlations with baseline aerobic fitness⁴⁻⁶ and several clinical features (Table in the Introduction). These regions have been shown to have decreased FA and increased diffusivity in PD in cross-sectional and longitudinal studies.⁸⁻¹² Mean diffusivity changes in the white matter in PD were found to be predominantly related to an increase in rD,¹³ which increases importance of our finding that we found improvements mainly of rD in various regions rather than aD.⁶ The putamen is the rostral terminus of the nigrostriatal pathway, but also pathology in cingulum and SLF play an important role in clinical manifestations of PD: The severity of postural instability and gait disorder correlates with increased diffusivity (especially rD) in the SLF;¹⁴⁻¹⁶ DTI abnormalities in cingulum and SLF are associated with cognitive dysfunction.^{14,17,18,18-24} Furthermore, white matter microstructure mediates the relationship between CRF and cognition in older adults.²⁵ Also, SLF integrity is associated with flanker task performance²⁶ as in our preliminary study (Table). Flanker task performance is also the primary cognitive outcome measure in this proposed study.

The proposed motor and cognitive tracts in the prior submission will be used as secondary outcomes. Among them is the nigrostriatal track: DTI of SN is abnormal in PD and deteriorates with disease progression.^{11,53,55} DTI changes in SN are associated with bradykinesia, cognition,⁵³ and dopaminergic deficit.¹¹ The SN will be delineated by 7T MRI.

Imaging protocol: Participants will undergo anatomical (T1 and T2), resting state fMRI, and DTI using a GE 750W 3T scanner (Waukesha, Wisconsin). Three-dimension (3D) T1 weighted images will be collected using IR-prepped gradient echo sequence (BRAVO) in the coronal plane with the following parameters: TI=450ms, TE=3ms, TR=8.5ms, flip angle=10, FOV=256x256x240mm, matrix=256x256x240, bandwidth= 244Hz/pixel, acceleration=2. Sagittal 3D T2-weighted images will be collected using a variable flip angle fast spin-echo sequence (CUBE) with the following parameters: TE= 90ms, TR= 3000ms, echo train length=130, FOV=256x256x176mm, matrix=256x256x176, bandwidth= 488Hz/pixel, acceleration=2. Resting state BOLD will be acquired in the axial plane using a T2*-weighted multi-band gradient-echo echo-planar sequence: TE = 30ms, TR=2000ms, Flip Angle=75°, FOV=256x256mm, Matrix=128x128, slice thickness/gap=2.0/0.0mm, BW=2000 Hz/pixel, multi-band factor=3, Acceleration=2. Diffusion weighted images will be collected using a twice refocused echo-planar spin-echo sequence with four b0 images: TE=88ms, TR=6000ms, FOV=256x256mm, Matrix=128x128, slice thickness/gap=2.0/0.0mm, BW=2000 Hz/pixel, multi-band factor=3, Acceleration=2, b-value=1000s/mm², and # diffusion directions=64.

7T Imaging protocol: Images will be collected on a GE 950 scanner using a 8Tx/32Rx head coil. The study will collect a localizer and high-resolution anatomical T2 weighted image for delineation of the substantia nigra. The T2 weighted sequence will be collected using a 3D CUBE sequence in the sagittal plane (TE=93, TR=2500, echo train length=100, Bandwidth=244 Hz/pixel, FOV=230x230x192, Matrix=384x384x320, acceleration=2.5). Example image quality for this scan is shown in Figure 12.

Anatomical Image Analysis: The volumetric anatomical T1- and T2-weighted images will be analyzed using BRAINS AutoWorkup.⁹¹ The analysis

will provide automated definitions of subcortical gray matter using the Stable Atlas-based Mapped Prior [STAMP] machine-learning segmentation^{30,31} to identify putamen and caudate nucleus as in our preliminary study.⁵ The original images and the automated pipeline results will be checked for validity by a technician blind to group and visit category. The substantia nigra will be automatically segmented from the 7T datasets using an ANTS registration toolbox⁹² and a basal ganglia atlas,⁹³ which includes the substantia nigra and red nucleus. The white matter regions of interest (SLF, cingulum, and others) will be identified per White Matter Parcellation Map as described by Mori et al (2008)⁷ and performed in our preliminary study.⁴

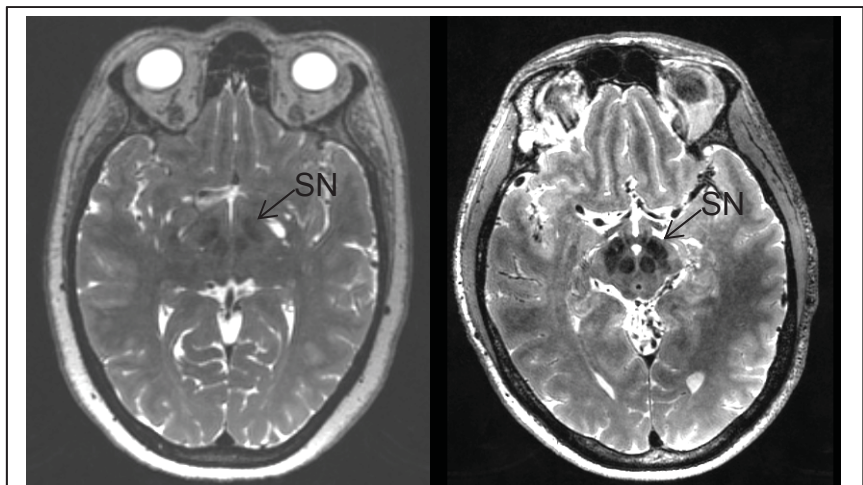
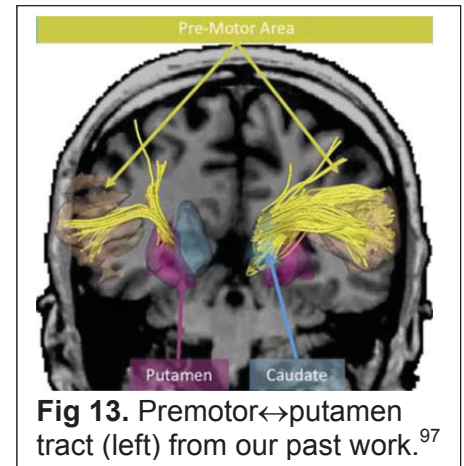


Fig 12. T2 weighted images from 3T (left) and 7T (right). The delineation of substantia nigra (SN) is superior at 7T vs. 3T.

Diffusion Analysis: Quality assurance of the diffusion weighted data will be performed using DTIPrep.⁹⁴ After motion and eddy current correction, data will be fit to a tensor model allowing derivation of rotationally invariant scalar measures (FA, MD, aD, rD). Scalar measures will be analyzed using both voxel based and ROI approaches based on participation on motor and cognitive functions, as well as documented vulnerability to degeneration^{11,53} and potential for regeneration with exercise in our preliminary study.⁴⁻⁶

Diffusion Imaging tractography: Whole brain fiber tractography will be performed using an unscented Kalman filter.⁹⁵ The fiber tracts connecting the nodes of the motor and cognitive networks will be defined using the White Matter Query Language⁹⁶ by including fiber tracts that start and end within nodes of interest. For the motor networks, fiber tracking will be performed for the substantia nigra↔putamen (nigrostriatal tract) and the putamen↔premotor cortex regions of interest defined via direct anatomical imaging. The 7T data will be used to delineate the substantia nigra due to its increased resolution and greater sensitivity to iron concentrations. For the cognitive networks, fiber tracking will be generated for the dorsal lateral prefrontal cortex (DLPFC)↔caudate and the parietal cortex↔prefrontal cortex connection. Median rotationally invariant diffusion scalars will be calculated for the fiber tracts. In our past work on Huntington's disease (Fig 13), we showed cross-sectional and longitudinal abnormalities of premotor-putamen connections.⁹⁷



C.3.ii.b. Cardiorespiratory Fitness Assessment

We will test VO₂max pre-post intervention to investigate the effect of CRF changes on brain tissue integrity and clinical function and to show that our intervention was delivered successfully. Oxygen uptake will be measured from expired air samples on a breath-by-breath basis during cycle ergometry. We will verify maximal effort for VO₂max when 2 of 3 criteria were met: 1) a plateau in VO₂ between two or more workloads, 2) respiratory exchange ratio ≥1.10, and 3) heart rate ≥ 85% of the age-predicted maximum heart rate (220-age).³

C.4. STATISTICAL ANALYSIS PLAN

C.4.i. Sample Size, Power, Randomization, Descriptive Analyses.

Design: We will determine the effects of LTAE on clinical features and brain tissue integrity in PD in a 2-arm, parallel group, one-year, single-blind, RCT (Fig 10).

Planned sample size and anticipated power:

We are planning to recruit N=100 (50/group) that would provide 80% power to detect an effect size of Cohen's $d'=0.7$ (equivalent to $f=0.35$ or a correlation of $r=0.33$ or $R^2=0.11$) at a 2-sided $\alpha=.05$ after taking into consideration that 10% of subjects may be lost to follow up and 25% might discontinue the intervention.

The effect size estimates for various outcome measures have been detailed in the Introduction. Briefly, our effect size estimates aerobic exercise vs. usual care are Cohen's $d' \sim 1.09$ for CRF (VO₂max), ~ 0.9 for motor UPDRS, ~ 0.76 for flanker task (PIS), ~ 0.7 for driving (road test error counts), and ~ 1.09 - 1.46 for rD on DTI of selected regions. Thus, we chose Cohen's $d'=0.7$ as the lowest common effect size estimate, which would require an effective sample size of N=68 (34/group) to provide 80% power at a 2-sided $\alpha=.05$. To ensure an effective sample size of N=68 at a 25% rate of discontinuation of the intervention, we would need to recruit N=90 subjects. If we incorporate 10% of loss to follow up, we would need to recruit N=100.

Randomization. Block randomization will be used in order to assure that the number in both groups will be similar throughout the study period, i.e., a split proportional to 1:1 is constrained within each block. The actual size of the blocks will be randomly chosen to be size 4 or 8, so that the assignment of the next participant cannot be accurately predicted by the study recruiters. Furthermore, to ensure that study recruitment remains unbiased, the assigned group will only be revealed after the participant has signed the consent form to indicate a willingness to accept the randomly chosen assignment.

Descriptive analyses: We will use descriptive statistics (means, SD, medians, etc.) and graphical techniques (boxplots, scatter plots, histograms, etc.) to explore the data, check for outliers, and examine distributions. We will compare baseline characteristics between groups using Fisher's Exact tests for categorical variables, and analysis of variance or the Kruskal-Wallis test for continuous variables, depending on the normality.

C.4.ii. Analysis of Efficacy and Associations

C.4.ii.a. General considerations: Statistical Models, ITT principle

The outcome measures will be obtained at baseline and after completing the intervention in 12 months. Mixed effects longitudinal regression models, multiple linear regression, and survival analysis methodology (Kaplan-Meier plots and Cox regression) will be used depending on the outcome measure as detailed in the Analysis section of each specific aim. Significance will be set at an overall 2-sided α level of .05.

The two groups will be compared using mixed effects longitudinal regression models (a generalization of repeated-measures ANCOVA). These models will accommodate flexible correlation patterns of the repeated measures and additional covariates and factors such as age, sex, education, LEDD, use of medications that can affect the tested study outcome (e.g., antidepressants, antihypertensives, acetylcholine esterase inhibitors), extra-study physical activity, and relevant interactions.

The ANCOVA model with estimated effect size of $f=0.35$ (equivalent to Cohen's $d'=0.7$ or adjusted $R^2=0.11$, medium correlation of $r=0.33$) will allow examination of up to 10 independent variables at 80% power for determining the unique variance accounted for by demographic features, CRF and its change, regional rD and its change, concomitant dopaminergic and other relevant treatments, extra-study physical activity, and additional covariates as needed. Similar models will be used for exploratory analyses of secondary outcome measures in each outcome category.

Intention-to-treat" principle: All subjects will be analyzed according to their randomization group, regardless of whether they comply with intervention protocol or not. Those who stop participating in the interventions will be invited back at 12 months to provide outcome measures. Based on our experience and the literature,^{64,65} we expect ~70-80% of the subjects to fully complete the study according to the protocol and ~90% of subjects to provide 12 month data for ITT approach. In the event of missing data, we will perform "completers only" and "compliers only" analyses, as well as other sensitivity analyses, to see whether the results are robust to non-ignorable missing data mechanisms.

C.4.ii.b. Effects on Clinical Features: Motor and Cognitive Function, Non-motor Symptoms and Quality of Life, and IADL (driving)

Motor function: The dependent variable in the repeated-measures ANCOVA model will be the post-training OFF period MDS-UPDRS motor subscale score. The baseline OFF period MDS-UPDRS motor subscale score will be entered into the model as a continuous variable and the treatment group (aerobic exercise or usual care) will be entered as a categorical variable. To assess possible impact of other relevant characteristics, we will enter demographic features, concomitant treatment, extra-study physical activity as covariates and factors into the model in supplementary analyses.

Cognitive function/Driving/Non-motor symptoms and Quality of Life: The dependent variable in the repeated-measures ANCOVA model will be the post-training value of the primary outcome measure of the tested domain as outlined in C.3.i. (e.g., PIS on flanker task for cognition, road test error counts for driving, etc.). Similar modeling approach will be used as above.

Real world driving outcomes: We will use survival analysis methodology (Kaplan-Meier plots and Cox regression) to analyze the difference in the time to driving cessation among groups after adjusting for baseline characteristics of age, sex, and education.⁴⁴ Similar methods will be used for time to first crash and citation.⁴⁴

C.4.ii.c. Effects on regional DTI

The dependent variable in the repeated-measures ANCOVA model will be the post-training rD value of the primary outcome region (e.g., putamen, cingulum, or SLF). The baseline rD value of that region will be entered into the model as a continuous variable and the treatment group (aerobic exercise or usual care) will be entered as a categorical variable. To assess possible impact of other relevant characteristics, we will enter demographic features, concomitant treatment, extra-study physical activity as covariates and factors into the model in supplementary analyses.

This approach will be repeated for other primary and secondary outcome regions. All results will be adjusted for multiple comparisons using FDR ($p<0.05$, corrected).

C.4.ii.d. Association of Clinical Changes with DTI Changes

Motor function: The dependent variable in the repeated-measures ANCOVA model will be the post-training OFF period MDS-UPDRS motor subscale score. The baseline OFF period MDS-UPDRS motor subscale score

and the ΔrD of putamen (change after intervention) will be entered into the model as continuous variables. This will show if change of rD in the putamen predicts (correlates with) change in the motor function. This across groups analysis will make use of pooled data from both groups providing increased range and variance to detect correlations. To assess possible impact of other relevant characteristics, we will enter the baseline rD of putamen, demographic features, concomitant treatment, extra-study physical activity as covariates and factors into the model in supplementary analyses. A similar approach will be used for other primary and secondary DTI regions specified in C.3.ii.a. Their ΔrD values will be entered into to the model instead of putamen.

Cognitive function: The dependent variable in the repeated-measures ANCOVA model will be the PIS on flanker task. Similar modeling approach will be used as above.

C.4.ii.e. Association of Clinical and DTI Changes with CRF Changes

Motor function: The dependent variable in the repeated-measures ANCOVA model will be the post-training OFF period MDS-UPDRS motor subscale score. The baseline OFF period MDS-UPDRS motor subscale score and the ΔCRF (change of $VO_2\max$ after intervention) will be entered into the model as continuous variables. To assess possible impact of other relevant characteristics, we will enter the baseline CRF, demographic features, concomitant treatment, extra-study physical activity as covariates and factors into the model in supplementary analyses. A similar approach will be used for other primary and secondary DTI regions specified in C.3.ii.a.

Cognitive function and DTI: A similar modeling approach will be used as above, but the dependent variable and its baseline value will reflect the outcome measure tested. For example, for cognition, the dependent variable will be post-training PIS on the flanker task. For DTI, the dependent variable will be post-training rD value of the putamen (or one of the other primary regions).

C.5. TIMELINE OF THE STUDY

Due to our experience with operational details, subject recruitment will start immediately upon receiving funding as shown below (Table 5). We expect to phone screen 15-20 subjects per month, resulting in 6-8 visits for in-person screen, and enrollment of 3-4 subjects per month. Intervention and testing will continue throughout the study period.

Activity	Months	01-06	07-12	13-18	19-24	25-30	31-36	37-42	43-48
Rolling enrollment/Intervention/Testing	++++++								
Data and Safety Monitoring Board meeting	+	+	+	+	+	+	+	+	+
Analysis/report, grant writing									+

Table 5. Approximate timeline of the study.

C.6. LIMITATIONS, POTENTIAL PITFALLS AND MITIGATION STRATEGIES

1. Recruitment. We are confident that we can reach our recruitment goal because of the large number of PD patients followed by our institutions. Our VAMC, a VA PD Consortium site, and our sister institution University of Iowa Hospitals & Clinics (UIHC) each saw more than 1,000 unique PD patients in 2017. We will place IRB approved newspaper ads and disseminate information in social and educational events for PD.

2. Attrition. The study has low risk interventions with <3 hr/week time commitment. We will advance exercise intensity very gradually to reduce drop-outs due to adverse events and intolerance. We will ensure subject comfort during the visits and compensate for their time. Our sample size estimate incorporates attrition risk.

3. Safety of self-administered physical exercise. We had no serious adverse events in the preliminary study.³ Our selection criteria exclude patients at high risk for falls and cardiovascular events. Our exercise regimen is cautious and gradual. We will complete a full clinical evaluation including exercise stress test on cycle ergometry to rule out contraindications.

4. Failure to support mechanistic hypotheses using DTI. Our secondary imaging measures such as functional connectivity, neuronal metabolism, and volumetric analyses will provide alternative approaches to investigating the mechanisms of LTAE and can be used to generate testable hypotheses for future studies.

5. Availability of broadband internet access by patients to upload exercise data. There has been big rise in digital access in the US over the last few years: According to Pew Research Center, 67% of seniors (65+), 87% of 50-64 year olds, and 96% of 30-49 year olds (96%) use the internet.⁹⁸ Digital access is ~80% in rural communities.⁹⁸ Broad band access can also be found in local public library or schools. The data upload can be helped by a technology-savvy family member or friend.

References

1. Uc, EY, Rizzo, M, O'Shea, AMJ, et al. Longitudinal decline of driving safety in Parkinson disease. *Neurology*. 2017; 89:1951-1958.
2. Schenkman, M, Moore, CG, Kohrt, WM, et al. Effect of High-Intensity Treadmill Exercise on Motor Symptoms in Patients With De Novo Parkinson Disease: A Phase 2 Randomized Clinical Trial. *JAMA Neurol*. 2017.
3. Uc, EY, Doerschug, KC, Magnotta, V, et al. Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology*. 2014; 83:413-425.
4. Uc, EY, Magnotta, VA, Dawson, JD, et al. Aerobic Exercise Improves White Matter Integrity in Parkinson's Disease. *Annals of Neurology*. 2014; 76:S49-S50.
5. Uc, EY, Magnotta, VA, Johnson, H, et al. Effects of Aerobic Exercise on Striatum and Substantia Nigra in Parkinson's Disease. *Neurology*. 2015; 84:14 Supplement.
6. Uc, EY, Magnotta, VA, Darling, WG, et al. Effects of Aerobic Exercise on the Cerebral White Matter in Parkinson's Disease Determined by Diffusion Tensor Imaging. *Neurology*. 2018; 90 (15 Supplement):P6.029.
7. Mori, S, Oishi, K, Jiang, H, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage*. 2008; 40:570-582.
8. Atkinson-Clement, C, Pinto, S, Eusebio, A, et al. Diffusion tensor imaging in Parkinson's disease: Review and meta-analysis. *Neuroimage Clin*. 2017; 16:98-110.
9. Kamagata, K, Motoi, Y, Abe, O, et al. White Matter Alteration of the Cingulum in Parkinson Disease with and without Dementia: Evaluation by Diffusion Tensor Tract-Specific Analysis. *AJNR Am J Neuroradiol*. 2012.
10. Peran, P, Cherubini, A, Assogna, F, et al. Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. *Brain*. 2010.

11. Zhang, Y, Wu, IW, Tosun, D, et al. Progression of Regional Microstructural Degeneration in Parkinson's Disease: A Multicenter Diffusion Tensor Imaging Study. *PLoS One*. 2016; 11:e0165540.
12. Chan, LL, Ng, KM, Yeoh, CS, et al. Putaminal Diffusivity Correlates With Disease Progression in Parkinson's Disease: Prospective 6-Year Study. *Medicine (Baltimore)*. 2016; 95:e2594.
13. Theilmann, RJ, Reed, JD, Song, DD, et al. White-matter changes correlate with cognitive functioning in Parkinson's disease. *Front Neurol*. 2013; 4:37.
14. Canu, E, Agosta, F, Sarasso, E, et al. Brain structural and functional connectivity in Parkinson's disease with freezing of gait. *Hum Brain Mapp*. 2015.
15. Gu, Q, Huang, P, Xuan, M, et al. Greater loss of white matter integrity in postural instability and gait difficulty subtype of Parkinson's disease. *Can J Neurol Sci*. 2014; 41:763-768.
16. Wang, M, Jiang, S, Yuan, Y, et al. Alterations of functional and structural connectivity of freezing of gait in Parkinson's disease. *J Neurol*. 2016; 263:1583-1592.
17. Pietracupa, S, Suppa, A, Upadhyay, N, et al. Freezing of gait in Parkinson's disease: gray and white matter abnormalities. *J Neurol*. 2017.
18. Duncan, GW, Firbank, MJ, Yarnall, AJ, et al. Gray and white matter imaging: A biomarker for cognitive impairment in early Parkinson's disease? *Mov Disord*. 2016; 31:103-110.
19. Chen, B, Fan, GG, Liu, H, et al. Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status. *Eur J Radiol*. 2015; 84:1318-1324.
20. Agosta, F, Kostic, VS, Davidovic, K, et al. White matter abnormalities in Parkinson's disease patients with glucocerebrosidase gene mutations. *Mov Disord*. 2013.
21. Tseng, BY, Gundapuneedi, T, Khan, MA, et al. White matter integrity in physically fit older adults. *Neuroimage*. 2013; 82:510-516.

22. Gattellaro, G, Minati, L, Grisoli, M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2009; 30:1222-1226.
23. Chondrogiorgi, M, Astrakas, LG, Zikou, AK, et al. Multifocal alterations of white matter accompany the transition from normal cognition to dementia in Parkinson's disease patients. *Brain Imaging Behav*. 2018.
24. Zheng, Z, Shemmassian, S, Wijekoon, C, et al. DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp*. 2013.
25. Oberlin, LE, Verstynen, TD, Burzynska, AZ, et al. White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. *Neuroimage*. 2016; 131:91-101.
26. Gao, S, Liu, P, Guo, J, et al. White matter microstructure within the superior longitudinal fasciculus modulates the degree of response conflict indexed by N2 in healthy adults. *Brain Res*. 2017; 1676:1-8.
27. Sink, KM, Espeland, MA, Castro, CM, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. *JAMA*. 2015; 314:781-790.
28. Voss, MW, Prakash, RS, Erickson, KI, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci*. 2010; 2.
29. Zigmond, MJ, Cameron, JL, Hoffer, BJ, et al. Neurorestoration by physical exercise: moving forward. *Parkinsonism Relat Disord*. 2012; 18 Suppl 1:S147-S150.
30. Young, KE and Johnson, HJ. Robust multi-site MR data processing: iterative optimization of bias correction, tissue classification, and registration. *Front Neuroinform*. 2013; 7:29.
31. Kim, EY, Magnotta, VA, Liu, D, et al. Stable Atlas-based Mapped Prior (STAMP) machine-learning segmentation for multicenter large-scale MRI data. *Magn Reson Imaging*. 2014; 32:832-844.

32. Voss, MW, Vivar, C, Kramer, AF, et al. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci*. 2013; 17:525-544.
33. Petzinger, GM, Fisher, BE, McEwen, S, et al. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol*. 2013; 12:716-726.
34. Kalia, LV and Lang, AE. Parkinson's disease. *Lancet*. 2015; 386:896-912.
35. Huse, DM, Schulman, K, Orsini, L, et al. Burden of illness in Parkinson's disease. *Mov Disord*. 2005; 20:1449-1454.
36. Ellis, TD, Cavanaugh, JT, Earhart, GM, et al. Identifying clinical measures that most accurately reflect the progression of disability in Parkinson disease. *Parkinsonism Relat Disord*. 2016; 25:65-71.
37. Williams-Gray, CH, Mason, SL, Evans, JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry*. 2013.
38. Hely, MA, Reid, WG, Adena, MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008; 23:837-844.
39. Caspell-Garcia, C, Simuni, T, Tosun-Turgut, D, et al. Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease. *PLoS One*. 2017; 12:e0175674.
40. Young, TL, Granic, A, Yu, CT, et al. Everyday reasoning abilities in persons with Parkinson's disease. *Mov Disord*. 2010; 25:2756-2761.
41. Uc, EY and Rizzo, M. Driving and neurodegenerative diseases. *Curr Neurol Neurosci Rep*. 2008; 8:377-383.
42. Uc, EY, Rizzo, M, Johnson, AM, et al. Road Safety in Drivers with Parkinson Disease. *Neurology*. 2009; 73:2112-2119.

43. Uc, EY, Rizzo, M, Anderson, SW, et al. Driving under low-contrast visibility conditions in Parkinson disease. *Neurology*. 2009; 73:1103-1110.
44. Uc, EY, Rizzo, M, Johnson, AM, et al. Real-life driving outcomes in Parkinson disease. *Neurology*. 2011; 76:1894-1902.
45. Devos, H, Ranchet, M, Akinwuntan, AE, et al. Establishing an evidence-base framework for driving rehabilitation in Parkinson's disease: A systematic review of on-road driving studies. *NeuroRehabilitation*. 2015; 37:35-52.
46. Uc, EY, Rizzo, M, Anderson, SW, et al. Impaired navigation in drivers with Parkinson's disease. *Brain*. 2007; 130:2433-2440.
47. Uc, EY, Rizzo, M, Anderson, SW, et al. Impaired visual search in drivers with Parkinson's disease. *Ann Neurol*. 2006; 60:407-413.
48. Uc, EY, Rizzo, M, Anderson, SW, et al. Driving with distraction in Parkinson disease. *Neurology*. 2006; 67:1774-1780.
49. Johnson, S, Davis, M, Kaltenboeck, A, et al. Early retirement and income loss in patients with early and advanced Parkinson's disease. *Appl Health Econ Health Policy*. 2011; 9:367-376.
50. Cullen, N, Krakowski, A, and Taggart, C. Functional independence measure at rehabilitation admission as a predictor of return to driving after traumatic brain injury. *Brain Inj*. 2014; 28:189-195.
51. Uc, EY, Rizzo, M, Anderson, SW, et al. Visual dysfunction in Parkinson disease without dementia. *Neurology*. 2005; 65:1907-1913.
52. Gattellaro, G, Minati, L, Grisoli, M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2009; 30:1222-1226.
53. Ofori, E, Pasternak, O, Planetta, PJ, et al. Longitudinal changes in free-water within the substantia nigra of Parkinson's disease. *Brain*. 2015.

54. Hattori, T, Orimo, S, Aoki, S, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. *Hum Brain Mapp.* 2011.
55. Loane, C, Politis, M, Kefalopoulou, Z, et al. Aberrant nigral diffusion in Parkinson's disease: A longitudinal diffusion tensor imaging study. *Mov Disord.* 2016.
56. Rascol, O. Physical exercise in Parkinson disease: Moving toward more robust evidence? *Mov Disord.* 2013; 28:1173-1175.
57. Colcombe, SJ, Kramer, AF, Erickson, KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A.* 2004; 101:3316-3321.
58. Crabtree, JL, Troyer, JD, and Justiss, MD. The Intersection of Driving With a Disability and Being a Public Transportation Passenger With a Disability. *Topics in Geriatric Rehabilitation.* 2009; 25:163-172.
59. Voss, MW, Prakash, RS, Erickson, KI, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci.* 2010; 2:12-17.
60. Voss, MW, Weng, TB, Burzynska, AZ, et al. Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *Neuroimage.* 2016; 131:113-125.
61. Baker, LD, Frank, LL, Foster-Schubert, K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol.* 2010; 67:71-79.
62. Lautenschlager, NT, Cox, KL, Flicker, L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA.* 2008; 300:1027-1037.
63. Shulman, LM, Katzel, LI, Ivey, FM, et al. Randomized Clinical Trial of 3 Types of Physical Exercise for Patients With Parkinson Disease. *JAMA Neurol.* 2013; 70:183-190.
64. Schenkman, M, Hall, DA, Baron, AE, et al. Exercise for People in Early- or Mid-Stage Parkinson Disease: A 16-Month Randomized Controlled Trial. *Phys Ther.* 2012; 92:1395-1410.

65. Corcos, DM, Robichaud, JA, David, FJ, et al. A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. *Mov Disord*. 2013; 28:1230-1240.
66. Murray, DK, Sacheli, MA, Eng, JJ, et al. The effects of exercise on cognition in Parkinson's disease: a systematic review. *Transl Neurodegener*. 2014; 3:5.
67. Collett, J, Franssen, M, Meaney, A, et al. Phase II randomised controlled trial of a 6-month self-managed community exercise programme for people with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2017; 88:204-211.
68. Demonceau, M, Maquet, D, Jidovtseff, B, et al. Effects of 12 weeks of aerobic or strength training in addition to standard care in Parkinson's disease: a controlled study. *Eur J Phys Rehabil Med*. 2016.
69. Altmann, LJ, Stegemoller, E, Hazamy, AA, et al. Aerobic Exercise Improves Mood, Cognition, and Language Function in Parkinson's Disease: Results of a Controlled Study. *J Int Neuropsychol Soc*. 2016; 22:878-889.
70. Duchesne, C, Lungu, O, Nadeau, A, et al. Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention. *Brain Cogn*. 2015; 99:68-77.
71. Nadeau, A, Lungu, O, Duchesne, C, et al. A 12-Week Cycling Training Regimen Improves Gait and Executive Functions Concomitantly in People with Parkinson's Disease. *Front Hum Neurosci*. 2016; 10:690.
72. David, FJ, Robichaud, JA, Leurgans, SE, et al. Exercise improves cognition in Parkinson's disease: The PRET-PD randomized, clinical trial. *Mov Disord*. 2015; 30:1657-1663.
73. Young, J, Angevaren, M, Rusted, J, et al. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2015; 4:CD005381.

74. American College of Sports Medicine. Cardiorespiratory Exercise Prescription. In: Ehrman JK, ed. ACSM's Guidelines for Exercise Testing and Prescription. 6th ed. Baltimore: Lippincott Williams & Wilkins, 2010:448-462.
75. Dubois, B, Burn, D, Goetz, C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord.* 2007; 22:2314-2324.
76. Shvartz, E and Reibold, RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. *Aviat Space Environ Med.* 1990; 61:3-11.
77. Fletcher, GF, Balady, GJ, Amsterdam, EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation.* 2001; 104:1694-1740.
78. Haskell, WL, Lee, IM, Pate, RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007; 39:1423-1434.
79. My Parkinson's Story. 2013. Veterans Affairs PADRECCs:
https://www.youtube.com/watch?v=BNzIaABFAMc&list=PL3AQ_JVoBEyxd5tkfQG-S3p_SDYBFtJ6c&index=2.

Ref Type: Online Source

80. Lang, AE, Eberly, S, Goetz, CG, et al. Movement Disorder Society Unified Parkinson Disease Rating Scale experiences in daily living: Longitudinal changes and correlation with other assessments. *Mov Disord.* 2013; 28:1980-1986.
81. Reuben, DB, Magasi, S, McCreath, HE, et al. Motor assessment using the NIH Toolbox. *Neurology.* 2013; 80:S65-S75.
82. Bohannon, RW, Bubela, D, Magasi, S, et al. Comparison of walking performance over the first 2 minutes and the full 6 minutes of the Six-Minute Walk Test. *BMC Res Notes.* 2014; 7:269.

83. Kluding, PM, Tseng, BY, and Billinger, SA. Exercise and executive function in individuals with chronic stroke: a pilot study. *J Neurol Phys Ther.* 2011; 35:11-17.
84. Leentjens, AF, Dujardin, K, Marsh, L, et al. Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. *Mov Disord.* 2011; 26:407-415.
85. Trenkwalder, C, Kohnen, R, Hogl, B, et al. Parkinson's disease sleep scale--validation of the revised version PDSS-2. *Mov Disord.* 2011; 26:644-652.
86. Martinez-Martin, P, Jeukens-Visser, M, Lyons, KE, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. *Mov Disord.* 2011; 26:2371-2380.
87. Brooks, DJ. Imaging of genetic and degenerative disorders primarily causing Parkinsonism. *Handb Clin Neurol.* 2016; 135:493-505.
88. Voss, MW, Weng, TB, Burzynska, AZ, et al. Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *Neuroimage.* 2016; 131:113-125.
89. Magnotta, VA, Heo, HY, Dlouhy, BJ, et al. Detecting activity-evoked pH changes in human brain. *Proc Natl Acad Sci U S A.* 2012; 109:8270-8273.
90. Wassef, SN, Wemmie, J, Johnson, CP, et al. T1rho imaging in premanifest Huntington disease reveals changes associated with disease progression. *Mov Disord.* 2015; 30:1107-1114.
91. Pierson, R, Johnson, H, Harris, G, et al. Fully automated analysis using BRAINS: AutoWorkup. *Neuroimage.* 2011; 54:328-336.
92. Avants, BB, Tustison, NJ, Song, G, et al. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage.* 2011; 54:2033-2044.
93. Keuken, MC and Forstmann, BU. A probabilistic atlas of the basal ganglia using 7 T MRI. *Data Brief.* 2015; 4:577-582.

94. Liu, Z. Quality control of diffusion weighted images. In: Cleary K, ed. SPIE Medical Imaging. San Diego, CA, 2010.
95. Lienhard, S, Malcolm, JG, Westin, CF, et al. A full bi-tensor neural tractography algorithm using the unscented Kalman filter. EURASIP J Adv Signal Process. 2011; 2011.
96. Wassermann, D, Makris, N, Rathi, Y, et al. On describing human white matter anatomy: the white matter query language. Med Image Comput Comput Assist Interv. 2013; 16:647-654.
97. Shaffer, JJ, Ghayoor, A, Long, JD, et al. Longitudinal diffusion changes in prodromal and early HD: Evidence of white-matter tract deterioration. Hum Brain Mapp. 2017; 38:1460-1477.
98. Internet/Broadband Fact Sheet. 1-12-2017. Pew Research Center: <http://www.pewinternet.org/fact-sheet/internet-broadband/>.

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