PROTOCOL

1. PROJECT TITLE:

Image Parkinson's Disease Progression Study

2. INVESTIGATOR(S):

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3. ABSTRACT

The purpose of this research study is to investigate how the brain and motor behavior changes Parkinson's disease over time in response to rasagiline. The drug rasagiline will be tested in this study. Rasagiline has been prescribed by doctors for many years to treat symptomatic Parkinson's disease. It is FDA approved for the treatment of Parkinson's disease but has not been shown to slow disease progression.

4. SIGNIFICANCE

PD is a neurodegenerative brain disorder that impairs the ability to perform functions such as grooming, dressing, cooking, and other activities of daily living. PD affected between 4.1 and 4.6 million people worldwide in 2005, and it is projected that up to 9.3 million people will be affected by 2030[1]. Although current pharmacological therapies provide beneficial effects on motor symptoms of the disease (i.e., tremor, rigidity, and bradykinesia), intolerable disability eventually develops in most patients[2]. A disease-modifying therapy that slows disease progression is a major unmet medical need in PD[3]. Numerous agents have neuroprotective effects in pre-clinical laboratory models, but none have been shown to have indisputable disease-modifying effects in clinical trials for patients with PD[2]. According to Olanow and colleagues[4]: "A limiting factor is the requirement for a clinical end point that reliably measures disease progression and is not confounded by the study intervention's effects on symptoms." This is the primary reason that biomarkers of progression in PD have been sought in major research initiatives including the Michael J. Fox Parkinson Progressive Marker Initiative and the NINDS Parkinson's Disease Biomarker Program. Progression markers could serve as end-points in clinical drug trials, and this is the same model used to evaluate disease-modifying therapeutics in diseases such as cancer[5, 6] and multiple sclerosis[7, 8].

In the past three decades a revolution has occurred in the ability to image brain structure and function, and the insights that such studies have provided into the pathogenesis of various diseases have dramatically transformed the field. The Vaillancourt laboratory has been part of this revolution in the area of PD. In 2005, our group was NIH funded to evaluate novel task-based fMRI assays of the healthy basal ganglia. The studies led to new insights and a model of the healthy basal ganglia related

to specific aspects of force control[9-12], and subsequently spurred a competitive renewal and a series of cross-sectional studies comparing early stage PD and control individuals[13-15]. Our work has repeatedly found that regions of the basal ganglia such as the putamen, as well as motor cortex and SMA, show reduced BOLD activity during force control studies[15, 16], and that the severity of PD measured cross-sectionally was correlated with the BOLD activity in the putamen[14]. Most recently, we have found that the BOLD activity in the putamen, motor cortex, and SMA decrease in the PD group after one-year of progression, with no changes in a control group[17]. In addition to these innovative studies using BOLD fMRI, we also used diffusion MRI and a novel bi-tensor model as a tool to assay the degeneration occurring within the PD substantia nigra. Our group found that diffusion MRI can detect changes in the substantia nigra in cross-sectional studies[18-20]. Most recently, our laboratory found that diffusion MRI tracks progression of the substantia nigra over one year, and that baseline measures from diffusion MRI predict the rate of clinical progression of bradykinesia in the subsequent year[21]. These two major innovations using BOLD fMRI and diffusion MRI were developed with NIH funding, and we now have non-invasive MRI-based biomarkers of nigrostriatal and cortical progression in PD.

Now that non-invasive progression markers of brain structure and function exist, our next step is to demonstrate how imaging technology can effectively evaluate promising pharmacological therapies in PD. Thus far, several studies in PD have advanced the hypothesis that the selective monoamine oxidase type B (MAO-B) inhibitor could provide not only a better control of parkinsonian symptoms, but could also have disease-modifying properties. MAO-B inhibitors stop the breakdown of dopamine and thereby allow the nigrostriatal neurons to sustain firing patterns. The neuroprotective potential of MAO-B inhibitor administration has been tested in pre-clinical rodent models of PD, where MAO-B inhibitors significantly counteracted cell loss in the substantia nigra following striatal injection of 6-hydroxydopamine (6-OHDA)[22], and exerted a significant neuroprotective effect against lactacystin-induced neurostriatal degeneration[23]. Although MAO-B inhibitors have been associated with a reduction in the clinical ratings of PD (Unified PD Rating Scale) and a reduction of the “off” time in PD, establishing its long-term disease modifying quality has yet to be determined. A recent delayed start designed study demonstrated its potential as a disease modifier at 1mg/day but not at 2mg/day[24, 25]. As such, the goal of this project is to evaluate our novel scanning techniques to pick up changes related to a common PD drug (a MAO-B inhibitor at 1mg/day) at slowing the progression of PD. We will use diffusion MRI and functional MRI assays as the primary endpoints.

5. INNOVATION

We provide three specific examples of how this work is innovative.

1. **The proposed research will be the first randomized, prospective study** to determine if an MAO-B inhibitor slows the progression of MRI-based biomarkers of PD progression.
2. **We will use a novel bi-tensor analysis algorithm for diffusion MRI** to estimate the fractional volume of free-water within the substantia nigra[26-28]. This technique has shown elevated free-water in the substantia nigra of PD relative to controls in two separate cohorts, one from a single site study and another from a multi-site study[29].
3. **We will use the innovative grip force fMRI paradigm** developed by our group[13, 30]. Our group is one of the only labs in the world that manufacture the custom force sensors for this application, which provide a reliable and robust measurement of the motor-related BOLD signal in humans.

6. DIFFUSION MRI AS A BIOMARKER OF SUBSTANTIA NIGRA PROGRESSION

Diffusion MRI is a technique that examines biological tissue using MRI pulse sequences sensitized to the local microstructural characteristics of water diffusion. Diffusion MRI can provide scalar measures of interest, where fractional anisotropy (FA) is the main measure used in neurological studies. Diffusion MRI has classically been applied to white matter tracts[31, 32]. Our laboratory and others have used diffusion MRI to examine gray matter areas[19, 33, 34]. In white matter, FA reflects many factors, including axonal density and degree of myelination[35, 36]. In gray matter, FA has been related to the number of dopaminergic cells in the substantia nigra[33], although many other factors could influence FA measurements. We have used diffusion MRI and a single tensor model to study the substantia nigra in de novo PD.

6.1. Using a single tensor model for fractional anisotropy. We published a study comparing FA in the ventral substantia nigra of 14 de novo PD patients with 14 control subjects[19]. De novo refers to PD patients who have never taken anti-PD medications. We observed that FA was reduced in the ventral and posterior substantia nigra of early stage PD patients compared with healthy control subjects. Since prior work has shown that the number of dopaminergic cells is related to measures from diffusion MRI[33], our findings were consistent with the established pattern of PD-related loss of dopaminergic cells in the ventral and posterior substantia nigra. Since our initial publication, several laboratories have replicated the reduced fractional anisotropy in the substantia nigra of PD [37-39]. **This set of findings has taught us that diffusion MRI can detect changes in the substantia nigra in early stage de novo PD patients compared with controls.**

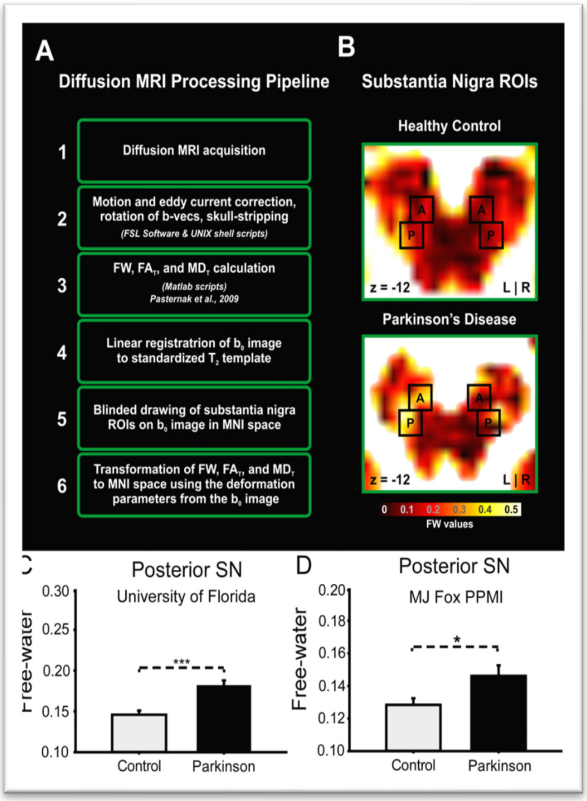

Figure 1. A, shows the pipeline for registering diffusion data to MNI space using the T2 MNI template. Regions are hand-drawn for each subject in MNI space on the b0 image and quantified on the free-water map in **B**. **C**, increased free-water in the posterior SN from the University of Florida cohort (28 PD, 20 control). **D**, increased free-water in the

6.2. Bi-tensor model to overcome some of the limitations of fractional anisotropy: Evidence from a single-site and multi-site study of PD. Although several studies have found reduced FA in the substantia nigra of PD, other studies have not found FA difference between patients with PD and controls[40]. The reason for this may be due to the limitations in the single tensor analysis model, and the bi-tensor analysis model was introduced to overcome these limitations. **The FA measure is limited as a measure of tissue microstructure, since atrophy-based partial volume free-water contamination can bias the diffusion index[41].** If gray matter voxels contain considerable free-water, then diffusion indices such as mean diffusivity can be elevated and the fractional anisotropy measure can be reduced[42, 43].

Recently, free-water diffusion MRI analysis using a bi-tensor model was developed by Dr. Ofer Pasternak to explicitly estimate the contribution of freely diffusing water molecules within the voxel[27, 41]. This free-water measure is expected to increase with atrophy-based neurodegeneration[8, 26]. When the free-water component is eliminated, the remaining signal provides a corrected fractional anisotropy value (FA_T) and corrected mean diffusivity value (MD_T) within the tissue of interest. Figure 1A shows the free-water analysis pipeline, and Figure 1B shows the free-water map in the substantia nigra. Bright colors indicate high free-water. Since substantia nigra degeneration occurs mostly in the posterior region of the substantia nigra in PD (ie. ventrolateral tier) [44-46], we tested the hypothesis that free-water would be elevated in the posterior substantia nigra of PD.

We evaluated free-water in a group of people with early stage PD (N = 28) and healthy controls (N=20) at the University of Florida. These controls were selected to match PD based on age and sex. PD patients were off-medication for more than 12 hours. As seen in Figure 1C, free-water in the ventral and posterior substantia nigra is increased in PD. This is the same region where dopaminergic cells are typically damaged in post-mortem tissue. In a validation analysis performed on the multi-site cohort from the Michael J. Fox Foundation Parkinson Progressive Marker Initiative (PPMI), we applied the same regions of interest (regions are in MNI space) shown in Figure 1B to the multi-site PPMI cohort of de novo PD (N=78) and controls (N = 56). These subjects were acquired on 8 different 3T MRI magnets across the PPMI sites. There is increased free-water in the ventral and posterior substantia nigra of the PPMI cohort of PD compared with controls (Figure 1D), which is the same region found for the University of Florida cohort. The FA_T value was not different between groups in either cohort, indicating that the free-water component of the bi-tensor model is the actual index of change in PD. **In summary, this set of findings has taught us that free-water measurement using the bi-tensor model is a very robust technique that is now replicated in two separate cohorts for measuring the microstructure of the substantia nigra of PD.**

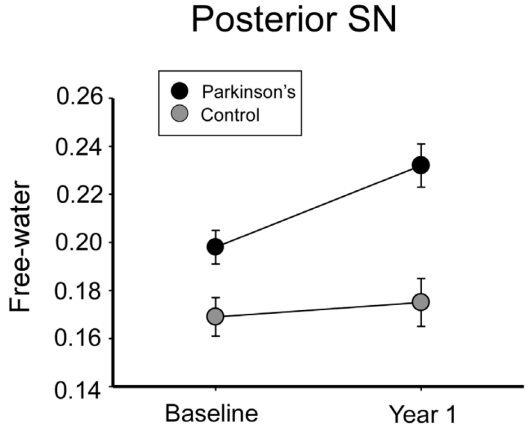

Figure 2. Free-water in the SN in 25 PD and 19 controls at baseline and one-year (mean + SE). The interaction between group and time was significant. PD had increased free-water from baseline to Year 1 ($p < .005$). Controls did not change significantly across time ($p > .10$).

6.3. Free-water measurements of the substantia nigra are a progression marker in PD. We have followed a group of 25 PD patients and 19 controls from baseline to one year using diffusion MRI. All MRIs were collected following 12 hours without Parkinsonian medications. The free-water measurement was assessed within the posterior substantia nigra using the bi-tensor analysis outlined in Figure 1A. P-values were corrected using the false-discovery rate (FDR). Figure 2 shows that we observe a significant group by time interaction (pFDR < 0.05), such that the PD patients have a greater increase in free-water after one year than the control group. Further inspection using a paired t-test in the PD group indicates that the increase in free-water in the posterior substantia nigra increased at one year compared with baseline (pFDR < 0.006). PD had elevated free-water compared with controls at both time points (pFDR < 0.005). Another key finding is shown in Figure 3. Baseline free-water values in the posterior substantia nigra predicted the changes in bradykinesia scores (r = 0.74, P < 0.001) over the next year. In control regions of interest including subthalamic nucleus and lateral ventricle we did not find any change after one year for PD and controls, and we do not observe a group effect in the control regions between PD and controls (p's > 0.5). This suggests that the observed change in free-water is specific to the substantia nigra and not related to scanner performance. It was recently noted in a paper by Kordower and colleagues[46] that the number of melanized neurons in the substantia nigra may be progressively decreasing with disease duration in PD. **The free-water measurement seems to be detecting this subtle change in cellular architecture, and provides the first published MRI progression marker of PD over a one year period of time.**

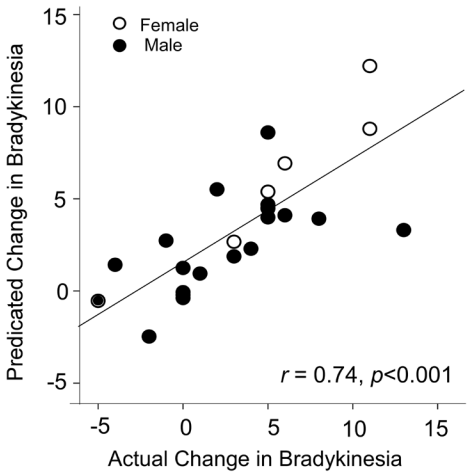

Figure 3. Scatterplot and regression of predicted change in bradykinesia and actual change in bradykinesia for patients with Parkinson's disease (r = 0.74; p < 0.001). The regression model consisted of baseline free-water and sex, which were both significant predictors of the change in bradykinesia over one year.

7. TASK-FMRI AS A BIOMARKER OF PUTAMEN AND MOTOR CORTICAL PROGRESSION

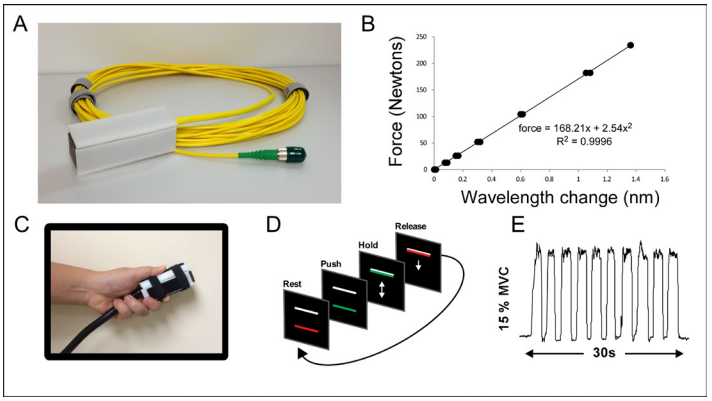

Figure 4. A, shows the force sensor. **B**, shows calibration of the sensor (N) to the change in wavelength (nm). **C**, is the grip setup during task-fMRI. **D**, is the paradigm used in our studies. **E**, shows the force pulses during one 30s block with 10 force pulses.

7.1. Development of task-fMRI for studying motor physiology. fMRI is a technique that has provided enormous advances in understanding the breakdown in functional activity and functional connectivity within the human brain of various diseases that include PD and Alzheimer's disease [47-49]. Over the past decade, our group has developed new techniques to study motor physiology in humans with PD during task-fMRI, with the overall goal to make task-fMRI more repeatable, reliable, and consistent for disease progression and drug evaluation studies.

We have designed novel MRI compatible force sensors in the PI's lab with R01 funding (Figure 4A), and these sensors have excellent linearity, sensitivity, and accuracy (Figure 4B). In Years 1-4 of the R01, we built up a considerable understanding of the blood oxygenation level dependent (BOLD) fMRI signal during motor tasks[9], and in particular found that the BOLD fMRI signal is dependent upon the amplitude of force and duration of force pulses [11, 50]. In Years 5-6 of the R01, we decided to implement a grip force paradigm that would yield a repeatable fMRI BOLD signal in cross-sectional studies of PD versus controls. We required subjects to generate multiple force pulses at 15% of maximum voluntary contraction with a fixed duration of 2 s for each force pulse[15]. The rationale for using this task was that: 1) it activates the basal ganglia, motor cortical, and cerebellar networks in healthy subjects[11, 51], 2) PD patients have difficulty contracting and relaxing muscle force as shown in numerous laboratory studies[52-54], and 3) this type of repetitive task of contracting and relaxing muscle is instrumental in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS)[55].

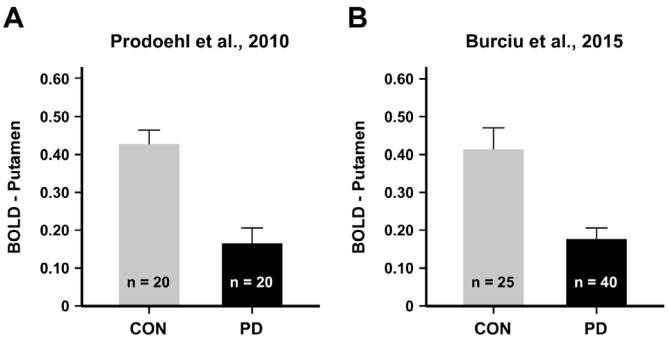

Figure 5. A, shows findings from the task-fMRI study by Prodoehl and **B**, shows results by Burciu et al. Both plots show the mean + 1SE across the two cohorts.

Using the experimental paradigm in Figure 4C-E, we have made a series of important discoveries regarding the BOLD fMRI signal in people with PD. We have consistently found that BOLD signals in the putamen and motor cortex are reduced in PD compared with controls[15, 56, 57], and the severity of PD motor symptoms correlates with the BOLD signal in putamen [14]. We also observe strikingly consistent findings across our cohorts, even when using different 3T MRI systems. Figure 5 shows the results from two different cohorts of control and PD. Figure 5A shows findings by Prodoehl and colleagues in a cohort of de novo PD and controls using a GE 3T at University of Illinois at Chicago[14]. Figure 5B shows findings from Burciu and colleagues in a cohort of early stage PD and controls using a Philips 3T at University of Florida[58]. Please note that the scale is the same on each plot, and that the mean values are consistent across studies. **It is clear that this task-fMRI paradigm is a robust technique for detecting differences in PD versus controls.**

7.2. Progression of the task-fMRI BOLD signal in PD over one year. In our current cycle of funding, we have been conducting a longitudinal study of PD over a one year period. We have studied 40 PD patients and 25 control subjects at baseline and following one year of progression using task-fMRI described in Figure 4[58]. PD patients were tested following a 14-hour withdrawal from antiparkinsonian medication. A region of interest (ROI) approach was employed to examine changes in BOLD signal in putamen, hand area of the primary motor cortex (M1), supplementary motor area (SMA), and hand area of the cerebellum (lobules V-VI). The ROIs used in the study were drawn a priori, and are shown in Figure 6. A MANOVA was used to examine the change in BOLD signal over a one year period, and p-values were corrected for multiple comparisons using the false-discovery rate (FDR). Figure 7 shows no functional change over the course of a year in any of these regions for controls. However, in PD the functional activity of the putamen, hand area in M1, and SMA decreased significantly from baseline to one year follow-up (pFDR values < 0.05). Other changes in PD included an increase in disease severity based on the motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) and decrease in bimanual coordination tested using the Purdue Pegboard (pFDR values < 0.05). No decline in depression or cognition was detected in either controls or PD. **In summary, early stages of PD are associated with decreases in the functional activity of key nodes within the basal ganglia and motor cortex but not the cerebellum.**

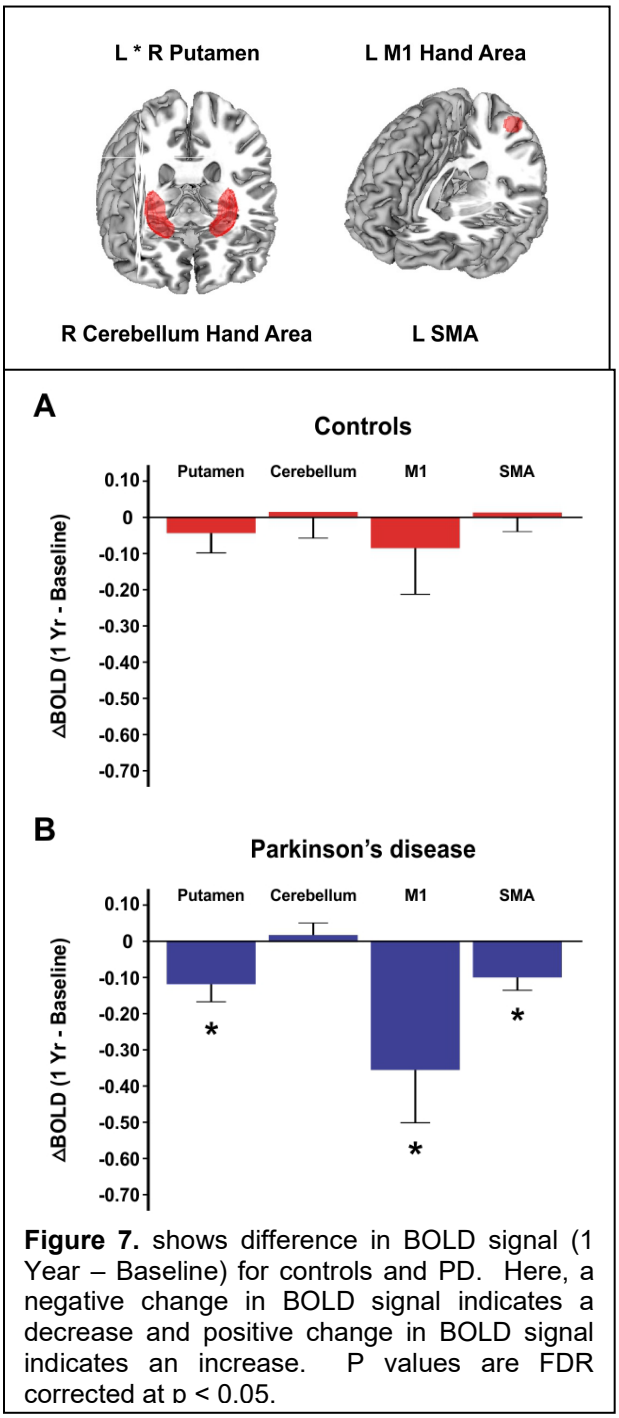

Figure 7. shows difference in BOLD signal (1 Year – Baseline) for controls and PD. Here, a negative change in BOLD signal indicates a decrease and positive change in BOLD signal indicates an increase. P values are FDR corrected at p < 0.05.

8. CHOOSING A DRUG TO TEST THE IMAGING BIOMARKERS OF PD PROGRESSION: MAO-B INHIBITORS AND PRELIMINARY CROSS-SECTIONAL FINDINGS

8.1. MAO-B inhibitors in animals and humans. Several studies in PD have advanced the hypothesis that the selective monoamine oxidase type B (MAO-B) inhibitor rasagaline provides symptomatic improvement in parkinsonian motor symptoms, and could possibly have disease-modifying properties at a 1 mg/day dose[59, 60]. Since there is a paucity of evidence in the human for a disease modifying drug, a MAO-B drug may be the best available therapy to test an imaging biomarker. A couple of decades ago the MAO-B inhibitor selegiline was tested (DATATOP), and recently the MAO-B inhibitor rasagiline was identified and developed as an anti-PD drug and possibly for disease modification[61]. In preclinical studies, MAO-B inhibitors have shown a potential for neuroprotective activity[62, 63]. The neuroprotective potential of the MAO-B inhibitor rasagiline has been tested in rodent models of PD, where the drug significantly counteracted cell loss in the substantia nigra

following striatal injection of 6-hydroxydopamine (6-OHDA)[64], and exerted a significant neuroprotective effect against lactacystin-induced nigrostriatal degeneration[65]. In humans, rasagiline at 1.0 mg/day, causes almost total inhibition of platelet MAO-B[66]. In a multi-center, randomized, double-blind, placebo-controlled clinical investigation of rasagiline monotherapy in 404 subjects with early, otherwise untreated, PD[67, 68], rasagiline was well tolerated at dosages of 1.0 and 2.0 mg/day, and patients receiving rasagiline had better motor function after 6 months of treatment than those receiving placebo. In 2009, Olanow and colleagues[4] performed a Phase III multi-center clinical trial to determine if the MAO-B inhibitor rasagiline at 1 mg/day or 2 mg/day had disease modifying qualities. The primary endpoint was the motor section of the UPDRS. The delayed-start paradigm was used to evaluate the possibility of disease modification versus symptomatic effects of rasagiline. Early-start treatment with rasagiline at a dose of 1 mg/day met all end points in the primary analysis: a smaller mean (±SE) increase (rate of worsening) in the UPDRS score between weeks 12 and 36, less worsening in the score between baseline and week 72, and noninferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72. However, all three end points were not met with rasagiline at a dose of 2 mg/day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups. The failure at 2 mg/day led the USA Food and Drug Administration to vote against rasagiline for a labeled indication as a disease modifying therapy for PD, though much debate has surfaced about this issue. Many experts believe it is possible that 2mg/day was not as effective as 1 mg/day or it was possible that 2 mg/day had a greater symptomatic effect and masked the disease modifying effect.

What is clear from this work was that 1 mg/day was well tolerated, has beneficial effects on PD symptoms, and could have disease-modifying qualities for PD. **As pointed out by Olanow and colleagues[4], the lack of a viable biomarker of the nigrostriatal system causes significant problems when interpreting the effects of potential disease modifying therapies, and an imaging endpoint could have been helpful in the two arms of this study.** This is because the symptomatic effects of the drug could mask the disease-modifying effects if they exist. Now that we have developed free-water diffusion MRI and task-based BOLD fMRI as viable progression markers in PD, we are now well positioned to test our imaging biomarkers using a placebo-controlled, double-blind randomized design with the MAO-B inhibitor rasagiline at the 1 mg/day dose.

8.2. Retrospective preliminary data for MAO-B inhibitor effects captured by PD imaging biomarkers. We examined the retrospective data from our longitudinal imaging studies by asking the question if the baseline imaging was different between patients with PD already taking rasagiline versus PD not taking rasagiline. Sixteen PD patients who were taking rasagiline prior to the time of testing (13 patients on 1 mg/day, 3 patients on 0.5 mg/day), 18 PD patients who were not taking rasagiline or another MAO-B inhibitor, and 18 controls were included in the study. The average duration that patients took rasagiline was 8 months prior to the testing. The two PD groups were matched for age, sex, disease duration, motor severity based on the UPDRS, and cognitive status based on the Montreal Cognitive Assessment (MoCA). Primary outcomes included: 1) task-fMRI BOLD signal within the posterior putamen and 2) free-water within the posterior substantia nigra.

Figure 8A illustrates the between-group differences in BOLD signal in the contralateral posterior putamen. Figure 8B shows the between-group differences in free-water in the posterior substantia nigra. P-values were corrected using the false-discovery rate (FDR). A significant group effect was found for posterior putamen BOLD signal ($F_{2,48}$ = 11.81, pFDR = 0.002) as well as for substantia nigra free-water ($F_{2,48}$ = 12.45, pFDR = 0.002). Overall, PD patients had a lower BOLD signal and higher free-water level compared to controls. When comparing the two patient groups, PD who were not taking rasagiline were the most affected, having a significantly lower BOLD signal and higher free-water level than PD who were taking rasagiline (pFDR values < 0.05) (Figure 8A-B). In control regions where we would not anticipate between group effects, we found no functional and diffusion MRI differences (i.e., contralateral angular gyrus and bilateral STN) (pFDR values > 0.05). As shown in Figure 8C, a significant group effect was found for bimanual coordination (Purdue Pegboard both hands) (F2,48 = 10.34, pFDR = 0.004). PD patients placed significantly less pegs on the pegboard with both hands than controls (pFDR values < 0.05), and PD who were taking rasagiline placed significantly more pegs than PD who were not taking rasagiline (pFDR values < 0.05).

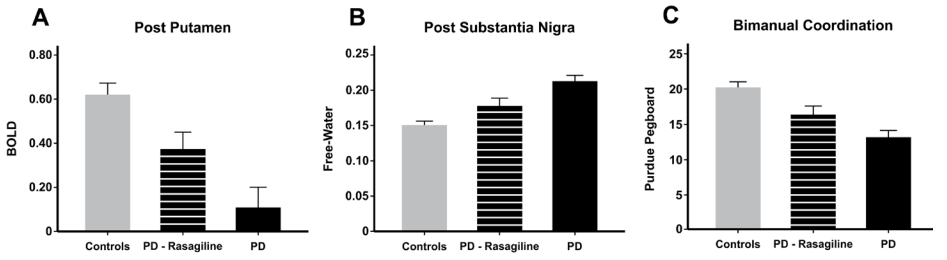

Figure 8. A, shows findings from the task-fMRI, **B**, shows findings from free-water in the substantia nigra, and **C**, shows findings from the Purdue Pegboard test using both hands. Both plots show the mean + 1SE.

The current retrospective data provides neuroimaging and motor dexterity evidence that PD patients taking the MAO-B inhibitor rasagaline have a better functional and structural integrity of the nigrostriatal circuit, as well as improved bimanual coordination. The results highlight the potential benefit of using functional and diffusion MRI measures in future prospective, randomized placebo-controlled studies of rasagiline.

9. SPECIFIC AIMS:

Aim 1. Effects of an MAO-B Inhibitor on the Progression of Free-water of the SN in PD. We will conduct a 12-month study in PD to test the hypothesis that the MAO-B inhibitor will slow the progressive increase of free-water accumulation in the SN. Since we have found that free-water in the SN relates to PD motor symptoms and bradykinesia, our secondary outcomes will evaluate if the change in free-water from the SN relates to changes in the progression of the PD motor symptoms and bradykinesia.

Aim 2. Effects of an MAO-B Inhibitor on the Progression of the BOLD signal of the putamen, M1, and SMA in PD. We will study the same patients with PD as in Aim 1. We test the hypothesis that the MAO-B inhibitor will slow the progressive decrease of the BOLD signal in the posterior putamen, M1, and SMA. Since we have found that the BOLD signal from the posterior putamen relates to PD motor symptoms and bradykinesia, our secondary outcomes will evaluate if the change in the BOLD signal from the posterior putamen relates to changes in the progression of the PD motor symptoms and bradykinesia.

This study is a prospective biomarker study to evaluate how an MAO-B inhibitor affects the progression of two novel, non-invasive biomarkers of the nigrostriatal regions and motor cortex. We will also assess a battery of secondary outcomes to monitor motor performance, cognitive status, and emotional status. The follow up questionnaires will assess additional measurements relating to long term (>18 months) health care outcomes and quality of life. We monitor adverse events carefully and have a data safety

and monitoring board. **The outcome and impact of this study will provide the first evaluation of MAO-B inhibitors at slowing the progression of the nigrostriatal pathway using advanced dMRI and fMRI methods in PD.**

10. RESEARCH PLAN:

Recruitment

To recruit subjects to the study, the Movement Disorder Centers database administrators (UF IRB 416-2002), neurologists who work at UF Health, UF Health Jacksonville, the Malcolm Randall VA Medical Center, and the University of Buffalo; and study coordinators at the Laboratory for Rehabilitation Neuroscience will identify qualifying candidates. They will then refer them to the PI, Co-PI, and other research personnel via email, who will contact potential candidates through phone or email who they believe are eligible to take part in this study. We will also send advertisements to local Parkinson's disease support groups and use word of mouth.

We will also plan on pre-screening the Center for Movement Disorder Clinic. This will be done by the PI and study coordinators. If a participant is identified who meets inclusion/exclusion criteria, their provider will be contacted by either the PI or the study coordinators. The provider will be asked to approach the participant about the study after their standard clinic visit. If the participant agrees, they can contact us directly or give permission to be contacted by the PI or study coordinators.

All participants that are recruited outside of the Movement Disorders Center will receive a neurologic evaluation by the collaborating neurologists to confirm a diagnosis of Parkinsonism.

We will also use flyers to recruit additional participants. We will hang flyers as well as make an announcement on the University of Florida radio station (89.1 – WUFT).

Study Design

The overall study design is shown in Figure 9. Referral and screening occur, followed by baseline testing. This includes the primary endpoints using diffusion MRI and task-fMRI, in addition to a test battery of secondary motor and cognitive tests. Patients will then be randomized to either the active drug arm or placebo drug arm according to recommendations by our statistician Dr. Sam Wu. Next, patients will undergo 1-year follow-up testing, which is the same testing that occurred at baseline. The 1-year follow-up testing may be delayed no longer than 90 days, due to scheduling conflicts or unforeseeable circumstances. This may include an extension of the study medication that will be determine by the P.I. The blinded data analysis will occur following the 1-year follow-up testing. After locking the data, final statistics will be performed in consultation with the statistician Dr. Wu.

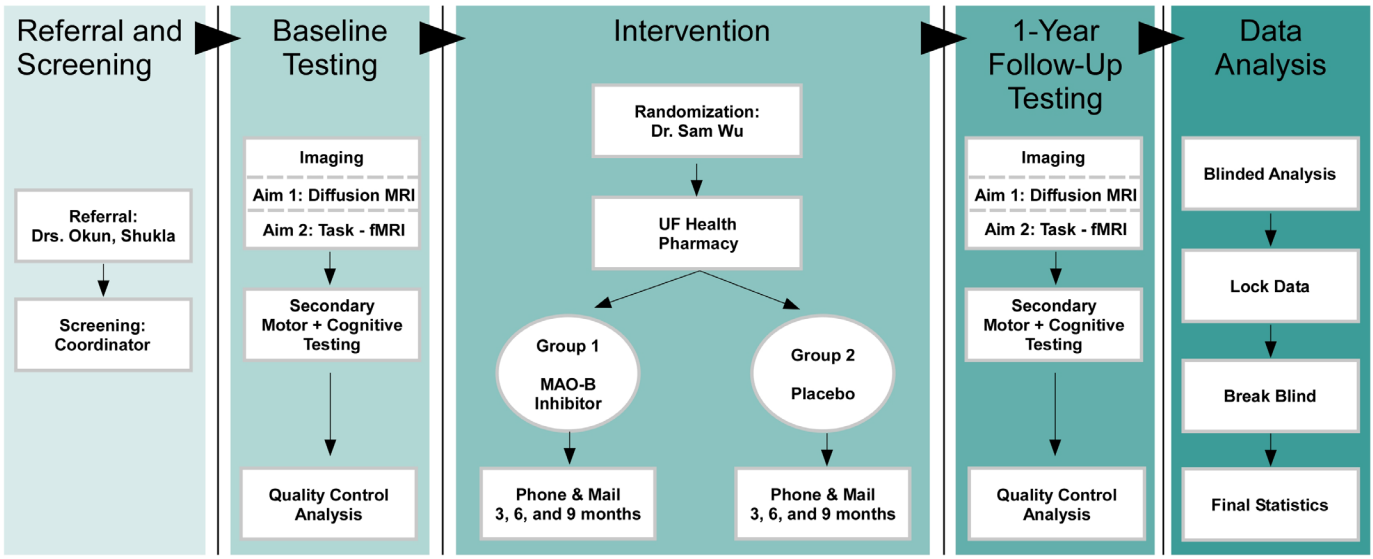

Figure 9. Flow chart for the overall study design, baseline testing, intervention, 1-year follow-up testing, and data analysis.

Blinding data collection and analysis

As shown in Figure 9, the baseline testing is performed prior to subjects entering the intervention. The coordinator will perform the evaluations. The UF Health Pharmacy will receive the randomization by Dr. Sam Wu, and then prepare the appropriate medication (placebo or active drug) for each patient. The patients will not know whether they receive placebo or active drug. During the 1-year drug trial, the coordinator will call each patient every 3 months to monitor any adverse events or issues that arise. The coordinator will immediately report any adverse events to the referring neurologist, Dr. Vaillancourt and the Data Safety Monitoring Board led by Dr. Irene Malaty (Neurologist), Dr. Christopher Hess (Neurologist), and Dr. Stephen Coombes (Imaging expert). Drs. Malaty, Hess, and Coombes will monitor patient safety and other issues. All data analyses will be performed blinded to the drug status of each patient. Once the data are locked, the group status will be unlocked by Dr. Wu, and final statistics will be performed.

Inclusion criteria

We will recruit 96 patients with clinically diagnosed PD. For the PD diagnosis, we will use the UK PD brain bank diagnostic criteria implemented by a movement disorders trained neurologist[69, 70]. We will include early stage PD within 5 years of diagnosis who have never taken rasagiline. We choose 5 years since diagnosis to focus on early stages of PD, where MAO-B inhibitors have shown the most promise. PD are eligible to participate if they are age 40-77, Hoehn and Yahr stage < or equal to 2 when on medication, and able and willing to sign informed consent to be randomized to the placebo or active drug arm.

Exclusion criteria

As necessitated by the risks of Magnetic Resonance Imaging, patients who have any type of implanted electrical device (such as a cardiac pacemaker or a neurostimulator), or a certain type of metallic clip

in their body (i.e., an aneurysm clip in the brain), are not eligible for participation in the MRI portion of the study. Individuals who are claustrophobic will also be excluded from participation. In addition, women who are or might be pregnant and nursing mothers are not eligible. Pregnancy tests will be carried out for each female subject prior to the MRI scan. Finally, individuals with psychiatric disorders or dementia will be excluded, along with other neurologic and orthopedic problems that impair hand movements and walking.

Individuals who have a history metalworking involving cutting processes such as grinding, filing, shaving, and threading, will need radiological clearance to participate in this study. Specifically, individuals who report a history of metalworking will be referred to Radiology at Shands UF for an orbitofrontal x-ray. In addition, individuals who have sustained an eye injury involving metal will also be referred to Radiology at Shands UF for an orbitofrontal x-ray. Shands at UF will provide a written report stating whether the individual is safe for imaging at 3 Tesla. All expenses related to this procedure will be covered by the PI.

Patients with a prior stroke or brain tumor are excluded. Patients will be excluded if they are unwilling to comply with the study procedures.

Reimbursement

Participant will receive $100.00 for each visit to the laboratory and completing the additional follow up questionnaires. If they are traveling to the Gainesville (University of Florida) area from more than 50 miles away, their transportation costs to and from the testing site and additional meal costs will be reimbursed. Finally, during long testing sessions, food and beverages for the participant and any family members and/or caregivers that accompany them to the visit will be provided at no expense to them.

Baseline and Longitudinal Testing Schedule

Patients and control individuals will be tested at baseline and following one year. The testing for Parkinson's Disease patients will occur when the patient is off overnight withdrawal from the medication prescribed to them by the referring neurologist. The PI has successfully accomplished off medication testing in over 300 patients, and this includes all of the patient groups in this research [72-74]. Patients will be driven to the facility by a caretaker or a car service will be arranged for the patient. We have a wheel chair on-site and an MRI compatible gait belt should the patient need help moving to the testing facility at UF. The testing for baseline and 1-year will be the same as described below.

Clinical measures

Important clinical measures to be used in this study include: 1) data about clinical movement disorder history, age, gender, height, weight, and other medical conditions; 2) clinical neurological examination; 3) tests assessing cognitive abilities including: the Montreal Cognitive Assessment, Stroop, Digit Span, Hopkins Verbal Learning Test, COWA and Animals, and Brief Test of Attention; 4) measures of anxiety, depression, and apathy (Beck Depression Inventory, Hamilton Anxiety and Depression Rating Scales, Metacognitive Awareness Inventory); 5) Parkinson's disease related quality of life (PDQ-39, Modified Schwab and England Activities of Daily Living Scale); 8) tests regarding sleep habits (Epworth Sleepiness Scale and Rapid Eye Movement Behavior Disorder Questionnaire); 9) questionnaires about any adverse events that occurred over the past year; and 10) measures relating to long term healthcare outcomes and quality of life (Follow up Patient Questionnaire and the PDQ-39).

Brain Structure Measures

We will be using the research dedicated 3T MRI scanner in the McKnight Brain Institute to obtain diffusion tensor imaging, T1 weighted, and T2 weighted images [19, 74] at the time at which it is available for use. Participants will be given a disc containing the MRI images collected during their scan. They will be informed that they will not be receiving any kind of clinical feedback related to these images, and that the images are for their own use.

Brain Function Measures

We will be using the research dedicated 3T MRI scanner at the McKnight Brain Institute to obtain functional magnetic resonance imaging (fMRI) data during the production of grip force production tasks [12, 75, 76]. Participants will use their hand to squeeze an MRI compatible grip force transducer in the MRI unit. This is a fiber optic transducer that is fully compatible with MRI. The PI has used this equipment safely at 3T for over 10 years and in numerous published studies. When producing force, the participants will view the amount of force they generate when viewing the visual feedback on a MRI compatible visual display while lying inside the scanner.

Physical Performance Measures

1. The Physical Functional Performance Test (tests the ability of the individual to perform everyday tasks). Subjects will be asked to complete as set of everyday tasks such as picking up a slipper from the floor [77]. (See Appendix 1 - attached protocol/scale).

2. The 6 minute walk (tests functional walking endurance). Subjects will be asked to walk at a comfortable pace for 6 minutes. The distance walked along with blood pressure and pulse rate will be measured. Cadence and stride length will be measured during a portion of the 6 minute walk test. (See Appendix 1 - attached protocol/scale).

3. Purdue Pegboard measures how well an individual can perform fine motor tasks using the hands [78] and has been previously used in assessing Parkinson's disease [79].

4. Movement Disorder Society (MDS)-sponsored version of the Unified Parkinson's Disease Rating Scale (UPDRS). The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). This rating scale will be video recorded with the participant's permission to ensure reliability of ratings.

6. The hand grip dynamometer test measures maximum hand grip strength. Participants apply as much grip pressure as possible on the dynamometer. Three trials will be completed with each hand.

7. The Dynamic Gait Index monitors the participant's gait as well as how well a participant is able to change gait speed, direction, etc.

Follow Up Questionnaires

Additional questionnaires will be administered at >18 months past baseline visit that assess long term health care outcomes and quality of life. Participants will fill out an amended informed consent form, delivered by mail or over the phone, prior to administering the questionnaires. The questionnaires will be administered over RedCap or distributed to the participant via mail, based on the participant's preference. For individuals who elect to receive the questionnaires by mail, they will be provided with a pre-addressed and pre-stamped envelope to return the questionnaires. Written instructions on how to complete the questionnaires will also be provided. If participants have any questions regarding how to complete the forms, the study team is available to answer any questions via phone call. The purpose of the PDQ-39 questionnaire is to quantify current quality of life outcomes for Parkinson's disease. The Follow Up Patient Survey measures health outcomes, such as to quantify the number of hospitalizations and reasons for hospitalizations, current therapies, living situation (i.e. independent at home or skilled care), and whether or not a subject has a regular caregiver each year following the baseline visit.

Statistical Analysis

Dr. Samuel Wu is our statistician who will oversee the statistics in this project. Demographic and baseline levels of clinical variables will be compared between the MAO-B inhibitor and the placebo groups using the two-sample t-test or chi-squared test as appropriate. For the primary outcomes and all secondary outcomes, standard summary statistics comparing the two randomized groups will be provided by time of follow-up.

Two primary intent-to-treat analyses will be performed to compare the MAO-B inhibitor and the placebo groups: one on the change of free-water accumulation in the SN for Aim 1 and the other on the change of BOLD signal in the posterior putamen for Aim 2. Linear regression will be conducted to estimate and test the group difference, adjusting pre-specified covariates age, gender, baseline UPDRS motor score and baseline free-water accumulation in the SN. To control overall type I error, each test will be at the two-tailed 0.025 significance level. For the primary intent-to-treat efficacy analysis, the missing primary outcome will be predicted by a fitted regression model using demographic and baseline clinical variables that characterize differences between "completers" and "non-completers." In addition, we will perform sensitivity analysis by comparing analysis results based on the above imputation method with those from "complete-case" analysis and searching for a tipping point that reverses the study conclusion. Also, we will compare the two randomized groups in missing patterns in primary endpoint, including reasons for missing data, timing of missing data, and distributions of baseline covariates and earlier outcomes.

For the secondary analysis, we will test the hypothesis that the MAO-B inhibitor will slow the progression of the BOLD signal in the M1 and SMA, using the same method as the primary analysis for the BOLD signal in the posterior contralateral putamen. In addition, correlation analysis will be performed for secondary outcomes. We will evaluate if the change in free-water from the SN and the change in the BOLD signal from the posterior putamen relate to changes in the progression of the PD motor symptoms and bradykinesia. We will obtain confidence interval of correlation coefficients and perform hypothesis tests based on Fisher's Z-transformation. No imputation is planned for secondary outcomes. Holm's step-down procedure will be applied to adjust for multiple testing and determine statistical significance.

11. POSSIBLE DISCOMFORTS AND RISKS:

If the subject has any metal in their eye or eyes (most likely the result of metalworking or an injury), we will require additional screening to ensure that it is safe for the subject to enter the magnetic resonance environment. These subjects will be sent to Radiology at Shands UF for an orbitofrontal x-ray. Shands will determine if it is safe for the subject to participate in this study.

If the subject is a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before they can have the MRI, they must have a pregnancy test. An individual will not be allowed to participate if she is pregnant. Nursing mothers are not eligible for participation in this project. The possibility exists that complications and undesirable side effects, which are unknown at this time, could occur.

Individuals with any type of implanted electrical device (such as a cardiac pacemaker or a neurostimulator), or a certain type of metallic clip (i.e., an aneurysm clip in the brain), are not eligible for participation in this study. The magnet is very likely to cause malfunction of electrical devices, and metal objects will get hot with exposure to the magnetic fields.

Aside from the above mentioned limitations of subject participation, there are no known significant risks with this procedure. The radio waves and magnetic fields used by the MRI machine are thought to be without harm. There are conservative Federal Guidelines for radio wave exposure and our examinations fall within those guidelines. We feel these are safe levels.

All metallic objects must be removed prior to approaching the high field strength magnet, as these objects may be attracted to the magnet. In addition, such objects as watches and credit cards should also be removed as these could be damaged.

Some subjects have experienced claustrophobia while inside the scanner. This is a fear of enclosed spaces that can cause feelings of anxiety and physical symptoms which are characteristic of a heightened state of anxiety, such as increased heart rate, blood pressure, and body temperature. Subjects are advised that if they begin to feel claustrophobic, they may discontinue the scan at any time.

The patients who go “off” their regular medications during the study may experience increased tremor (shaky hands), increased slowness and trouble walking. In the “off” state, there is also an increased risk of falling. In order to reduce the risk of injury, the patient will never drive, but be driven to the study by a spouse, by a family member or by a friend, who can assist them if they need help. In the case that a friend or family member is unavailable, taxi transportation will be arranged to and from the UF laboratory. Furthermore, patients who have difficulty walking off medication will be transported around the laboratory using a wheel chair. Finally, if the patient has any problems while “off” their regular medications, laboratory staff will contact their physician.

The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

12. POSSIBLE BENEFITS:

There is no direct benefit to participating in this research. Patients may learn more about their disease and learn more about how the body is affected by their disease. Future therapies and diagnoses may be improved upon by this knowledge.

13. CONFLICT OF INTEREST:

The PI and collaborators do not have a conflict of interest.

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