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Cortical Recruitment of Motor Imagery in Timed Up and Go Task

by

Gina Kirkish

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Biomedical Imaging

in the

GRADUATE DIVISION

of the

Copyright 2015
by
Gina Kirkish

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ABSTRACT

Cortical Recruitment of Motor Imagery in *Timed Up and Go* Task

Gina Kirkish

Parkinson's disease is a highly prevalent, neurodegenerative movement disorder. Gait disturbances and postural instability, symptoms that produce the highest incidence of morbidity in individuals with PD, respond poorly to dopaminergic treatment. Further, the neural correlates underlying these disabilities are currently uncharacterized. It is essential to understand the non-dopaminergic pathways that break down in patients with PD, in order to develop a neuroprotective treatment for PD.

The TUG task is a clinical marker for PD. It integrates several motor components including gait speed, initiation of movement, and turning. In this study, an fMRI paradigm was developed in order to quantitatively evaluate neural correlates related to PD motor dysfunction, which could be directly compared to performance on the TUG task. fMRI brain activation patterns of the patient imagining themselves walking, imagining themselves turning in 360-degree circles and resting were compared in 11 patients with PD and in 11 age-matched controls. Motor performance on three physical tests - the TUG task, the ten-meter walk test and the timed 360-degree turn were also recorded. These motor metric results are correlated with fMRI activation strengths.

When comparing patients with PD and controls, there were no detectable differences between the outcomes on the physical tasks, the TUG, 10-meter walk, or a 360-degree turn. Cortical activation in the SMA was localized in all subjects during motor imagery tasks. There were no significant differences between patients with PD and healthy controls relative to SMA ROI activation. However, individuals with PD had a significant increase in lateral occipital lobe activation when imagining-turning compared to imagining-walking. Activity in the premotor and primary motor area during the

imagined-turning versus imagined-walking contrast was also significantly correlated to performance on the TUG test for both patients with PD and healthy controls. Activation in the precuneus area was correlated with performance on the 360-degree turn during the imagined-turning condition. Activation in the occipital gyrus was correlated with the ten meter walk for several motor imagery contrasts.

The focus of this pilot study was to evaluate neural activation patterns in patients with mild PD and age-matched healthy controls as potential biomarkers, which relate to clinical motor outcomes. Identifying a neural biomarker is essential for future treatments to be targeted and tested. This study concluded that a neural correlate of the TUG task exists in BOLD signal change in the premotor and primary motor area when imagining-turning compared to imagining-walking. Assessing the relationship between postural instability and the corresponding functional brain areas has the potential to increase our understanding of the breakdown of motor control in patients with PD.

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1. Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is a progressive, neurodegenerative movement disorder (Mayo Clinic 2015), which affects seven to ten million people worldwide (National Parkinson's Disease Foundation 2015). It is primarily characterized by tremors, rigidity, bradykinesia, and abnormal gait and posture. PD occurs with the degeneration of dopaminergic cells, or neurons, primarily in the substantia nigra and basal ganglia. Dopamine produced in the substantia nigra is responsible for relaying messages to the corpus striatum, in order to produce smooth and controlled movements (Nagal and Singla 2012). The lack of dopamine produced when these neurons degenerate is believed to be responsible for symptoms including tremors and rigidity. Individuals with PD are typically treated with levodopa medication, which is presumably taken up into remaining dopamine neurons, converted into dopamine, and slowly released into the synapses over time (Hauser 2009). Although levodopa therapy has been shown to alleviate some symptoms caused by PD, levodopa treatment is purely symptomatic and does not delay disease progression (Hely and Morris 2005).

While many parkinsonian symptoms can be ameliorated by levodopa therapy, axial symptoms such as postural imbalance and complex gait impairment are poorly understood and do not significantly improve with the use of dopamine therapy (Karachi et al. 2010). This suggests that postural imbalance and complex gait disturbances may be independent of the dopaminergic system. Hely et al. explains that neuroprotective interventions for PD should be judged on their ability to improve aspects of the disease that are non-responsive to dopamine therapy. Several studies have suggested that there are other neurotransmitter pathways involved in PD deficits (Bohnen 2011 and Müller 2014). Karachi et al. found that bilateral lesioning of the cholinergic part of the pedunculopontine nucleus (PPN) induced gait and postural deficits in monkeys. It has also been reported that excessive

inhibitory Gabaergic inputs from the globus pallidus and substrantia nigra to the PPN may have an affect on motor function in patients with PD (Muthusamy 2007). Therefore, the neural pathways underlying gait and postural disorders are currently under investigation.

Postural stability during automatic motor activity requires a complex integration of multisensory inputs. The function of the sensorimotor system is to regulate phasic and tonic muscular activity, and is crucial for balance, and adapting to one's environment (Rinalduzzi and Trompetto 2015). The motor system is highly complex, consisting of the integration of the senses (vestibular, visual and somatosensory) with the basal ganglia, sensorimotor coordination in the cerebellum, initiation of voluntary movements in the motor cortex, and the total integration of basic movement in the brainstem and spinal cord (Purves and Augustine et al. 2008). It is apparent that some of the components of this motor system are dysfunctional in patients with PD but it is uncertain where the breakdown occurs (Rinalduzzi and Trompetto 2015).

Gait impairment and postural instability are serious consequences of PD progression because they lead to the highest incidence of morbidity in individuals with PD (Wood and Bilclough 2002). These symptoms can be highly debilitating and thirty eight percent of individuals with PD fall each year due to impairments in balance and gait dysfunction (National Parkinson's Foundation 2015, Wood and Bilclough 2002). Moreover, postural imbalance involved in non-linear gait tasks such as turning elicit falling more commonly than simple forward walking (Peterson et al. 2014, Song and Sigward 2012). More than 50% of individuals with PD have difficulty turning (Chou 2013), which is closely associated with freezing of gait, and has a significant impact on quality of life (Rahman 2008). Turning and the neural networks that cause this disability have been studied far less extensively than linear gait (Chou 2013).

Research is therefore needed to evaluate the differences in neural correlates underlying gait, turning and postural impairments found in patients with PD (Wright et al. 2007). It is essential to identify early, quantitative biomarkers which correlate with clinical motor outcomes as PD progresses. These markers could serve as a foundation to assess the benefits of future disease modifying treatments.

1.2 Motor Performance

The Timed Up and Go (TUG) test has previously been shown to be an effective and reliable measure of PD progression (Morris 2000). The test is comprised of several complex motor components including gait speed, initiation of movement and turning (Morris 2000). It specifically involves standing up from a chair, walking three meters, turning around 180-degrees, walking back and sitting down again. The TUG test simulates complex motor activity, which is routinely performed in everyday life. The time taken to complete the test is proportional to the probability of falling (Nocera and Stegemöller 2013). The TUG test involves axial movements and performance on the test does not significantly improve with dopaminergic therapy (Franzén et al. 2009).

To further elaborate on the challenge of turning, the subjects were timed performing a 360-degree turn. Difficulty in turning one's body has shown to be a significant clinical motor outcome of progressive PD. The time required to complete a timed 360-degree turn is also closely related to the risk of falling (Bryant 2015).

The ten-meter walk is a reliable measure of gait speed and can sometimes be used to screen for PD. (Greenan 2015). Gait speed can be used as a clinical marker for PD because individuals with PD often have slowed gait speed due to shorter stride length, stooped posture, forward center of support,

reduced arm swing and a freezing of motion (Schaafsma 2003). Approximately 50% of individuals with PD experience freezing of gait, or the transient inability to complete effective stepping (Giladi 2008). Patients with PD who experience freezing of gait are at higher risk of falling (Nemanich 2013). Here again, gait freezing usually responds poorly to levodopa therapy (Schweder 2010).

1.3 fMRI of Motor Imagery

The use of functional neuroimaging techniques has greatly contributed to our understanding of the neural networks that are recruited during gait control. Neural imaging techniques including functional near infrared spectroscopy (Perrey 2014), transcranial magnetic stimulation (Schubert 1997) and electroencephalography (Feix Do Nascimento 2005) have been utilized to study physical gait, while positron emission tomography (Malouin 2003) and fMRI have been used to study patients imagining gait activity, which is referred to as motor imagery. Numerous studies have reported consistent neural activation patterns in the supplementary motor area (SMA) the posterior parietal cortex, the basal ganglia, and the cerebellum during physical and imagined gait (Guillot 2009 and Malouin 2003). Other studies have concluded that the primary motor area is only active during actual physical movement, and not during motor imagery of movement (Decety 1994 and Guillot 2009).

The consistency between actual gait and imagined gait provides validation for using motor imagery in this fMRI study. Motor imagery is a useful tool because the Magnetic Resonance Imaging (MRI) scanner is highly sensitive to motion artifacts. A body of research has established that real and imagined movement recruit comparable cerebral regions (Porro 1996). Therefore we are able to compare the physical motor study of a patient to the motor imagery of that patient *imagining* the same physical movement. A noted difference is motor imagery corresponds to mental rehearsal of movement, focusing on motor planning rather than involvement of end-stage movement related

processes (Avanzino 2013). This eliminates the peripheral feedback component (Cunnington 1997). Research shows that individuals with PD tend to have a greater cognitive deficit related to motor planning than to end-stage movement execution (Cunnington 1997).

Previous studies have identified activation in networks associated with motor imagery of gait in healthy controls and in individuals with PD. For healthy controls, these networks include the motor and frontal associative areas (Maillet et al. 2014, Wang 2008), the cerebellum (Maillet et al. 2014, Peterson 2014, Klaus and Deutschländer 2004), the SMA (Wang and Wai 2008, Peterson 2014), the globus pallidus (Peterson et al. 2014, 2013), the putamen (Peterson et al. 2014), and the mesencephalic locomotor region (Peterson et al. 2013, Snijders and Leunissen 2010), as well as other regions in the brain. The identified activation patterns for people with PD during imagined gait include decreased activation in the globus pallidus (Peterson et al. 2013, 2014), cerebellum (Cremers 2012), MLR (Cremers 2012, Peterson et al. 2014) and SMA (Peterson et al. 2014), compared to healthy controls.

The SMA communicates with the primary motor cortex and is involved with planned and purposeful movement (Kikuchi 2001). It plays a large role in complex gait tasks (Godde 2010) and several studies have found that individuals with PD have impairments in SMA function. Additionally, the SMA has been shown to be active while a person imagines their gait, as well as during actual ambulation (Miyai 2001, and Godde 2010). It has also been shown that lesions in the SMA can result in gait disturbances (Nutt, Marsden and Thompson 1993).

There are many studies on the neural correlates involved in gait, but fewer looking at a direct comparison to the commonly utilized TUG test. In order to develop treatment for patients with PD, it

is crucial to understand the underlying brain mechanisms behind these motor-related disabilities. Assessing the neural correlates involved in motor dysfunction in patients with PD may help target future treatments.

2. Methods

2.1 Participants

Thirty participants (fifteen individuals diagnosed with PD and fifteen age-matched healthy controls) were recruited for this pilot study. Patients with mild PD were recruited from a private practice of neurology and the University of California San Francisco (UCSF), Department of Neurology and Department of Physical Therapy and Rehabilitation Science. Patients with mild PD, Hoehn and Yahr stages I and II, were included in this study. Hoehn and Yahr stage I is defined as unilateral involvement with minimal functional disability. Hoehn and Yahr stage II is defined as bilateral involvement without impairment of balance (Bhidayasiri and Tarsy 2012). The inclusion criteria for patients consists of the following: clinically diagnosed with PD based upon established British Bank criteria (Hughes et al. 1992), having at least two years of disease duration, and currently prescribed dopamine medication. All subjects were included in this study based on their ability to walk ten meters without assistance. Subjects were excluded from this study if they had a comorbidity condition to PD that would interfere with safe mobility during motor performance tests. Subjects were also excluded for having a previous history of deep brain stimulation, brain surgery, stroke, multiple sclerosis, epilepsy or dementia. Exclusion criteria for getting an MRI included claustrophobia, certain metallic implants, or serious medical illness. Informed consent was obtained for all subjects.

2.2 Motor Metric Examination

Subjects with PD and healthy controls underwent a motor examination in the PhysFit Center for Health and Wellness at UCSF. These motor metric examinations included the TUG test, the ten-meter walk test, and the timed 360-degree turn, among others. Standard administration procedures were followed. Tests were recorded by two physical therapists to check for accuracy of timing. Each motor test was repeated three times and the average time was reported. Each motor sequence was timed and recorded with a stopwatch. The TUG test is a combined measure of gait speed, turning speed, and speed of movement initiation. The ten-meter walk test is a measure of gait speed and requires the subjects to walk ten meters while being timed. The timed 360-degree turn evaluates the speed of turning itself. The subjects determined how to turn, and turning direction was not controlled for.

2.3 fMRI Task

Subjects took the Vividness of Visual Imagery Questionnaire, VVIQ and were trained on the fMRI task thirty minutes prior to the MRI scan. The VVIQ is a patient report questionnaire, which measures a patient's ability to imagine various activities. Performance on this questionnaire has shown to be predictive of fMRI activation during visualization of activities (Cui et al. 2007). Participants must have scored at least 50% on the VVIQ test to be included in the study.

To train participants on the fMRI task, subjects were asked to walk approximately three meters and to turn in two 360-degree circles. Subjects were then asked to close their eyes and to imagine walking and turning from a first person perspective - actively thinking about how their body should move. The task was explained and demonstrated before the MRI study.

During the fMRI scan, subjects performed a six-minute motor imagery task. Stimuli for the motor imagery paradigm consisted of three audio-instructed tasks: imagined-walking, imagined-turning in circles, and rest. These three tasks were presented in a randomized block fashion, with four blocks per task. Each task was thirty seconds long, totaling six minutes. The motor imagery audio instructions were generated from a computerized voice. A trial fMRI task was performed with subjects to make sure they were able to hear the vocal instructions during the scan. To cue the subjects to imagine walking (from a 'first person' perspective), the generated voice said, “imagine yourself walking". To cue the subject to imagine turning in 360-degree circles, the generated voice said, “imagine yourself turning in circles”. To cue the subject to rest in the scanner, the generated voice said, “begin to rest”. A computerized male voice was used for the imagined-turning task and a female voice is used for the imagined-walking task to allow the subject to easily discriminate between commands. Subjects were asked to continuously imagine or rest until the next command was vocalized. Long block-times and a simple task were implemented to maximize statistical power.

2.4 MRI Protocol

The experiment was performed using a whole body 3T GE MRI. The patient was in a supine position with a 64-channel head coil. Padding was placed around the head to reduce motion artifacts. A structural, whole brain T1-weighted Magnetization Prepared Rapid Gradient Echo, MPRAGE was acquired. The MR structural scan parameters were optimized for fMRI image registration and anatomical labeling (TR 2300 ms, TE 3 ms, TI 900 ms; 1 x 1 x 1 mm^3 resolution). Next, the fMRI sequence (TR 1200 ms, TE 30 ms, 306 volumes, 2.50 × 2.50 × 2.50 mm resolution) was acquired using a gradient-echo echo-planar imaging sequence, GE-EPI.

2.5 Image Processing and Analysis

fMRI processing was performed using software tools including FreeSurfer (v5.3), Advanced Normalization Tools, and FSL (v5.0.1), FMRIB software library. FreeSurfer automatically reconstructs the cortical surface (Xiao and Jovicich 2006) and labels unique brain structures based on probabilistic information estimated automatically from a manually labeled training set (Messina 2011). Anatomical brain structures for each subject were defined using the FreeSurfer Desikan-Killiany parcellation map, produced using the automated 'recon-all' reconstruction approach.

Subject data went through a pre-processing stream, which included motion correction, artifact detection, co-registration, noise reduction, spatial smoothing and application of a temporal filter. Head motion was reduced with the FLS MCFLIRT motion correction algorithm. Artifact detection was applied to detect outliers of composite motion and to remove any image frame that deviated from scan to scan more than 1mm. Co-registration of the motion-corrected functional images to the generated surface images was performed using the FreeSurfer bbregister algorithm. Physiological noise in the blood oxygen level dependent (BOLD) signal was corrected using CompCor, a component-based correction method, which assumes that temporal fluctuations in white matter and cerebrospinal fluid are modulated by physiological noise rather than by neural activity (Craddock and Milham 2015). Smoothing was performed by the FSL SUSAN algorithm using a full width at half max of 5mm to reduce noise with nonlinear filtering (Smith and Brady 1997). In addition, a high pass temporal filter of 1/128 Hz was used to eliminate low frequency artifacts and large drifts in the fMRI time course.

After pre-processing was completed, a first level, model fitting design matrix was applied. The FSL data-modeling software, fMRI Expert Analysis Tool, FEAT (v5.90) was used to generate activation

maps of signal change between imagined periods and rest periods. FEAT is based on a general linear model (GLM) or a multiple regression, and creates a model that fits the data based on brain activation to stimuli. BOLD signal data was modeled using a convolution of square-wave functions with the hemodynamic response function during the onset of each task. Motion parameters were included to reduce residual motion after motion correction. The FMRIB FEAT directory produced statistics including: contrast of parameter estimates (COPE), variance in the contrast (VARCOPE), t-statistics and z-statistics. Using this method, the t-statistics produced were mapped onto corresponding inflated surface volumes created with FreeSurfer for visualization of the four contrasts and region of interest (ROI) selection. These contrasts include: imagined-walking versus rest, imagined-turning versus rest, imagined-walking-and imagined-turning versus rest, and imagined-turning versus imagined-walking. Each contrast represents the difference in signal intensity between 'on' task blocks and 'off' task blocks.

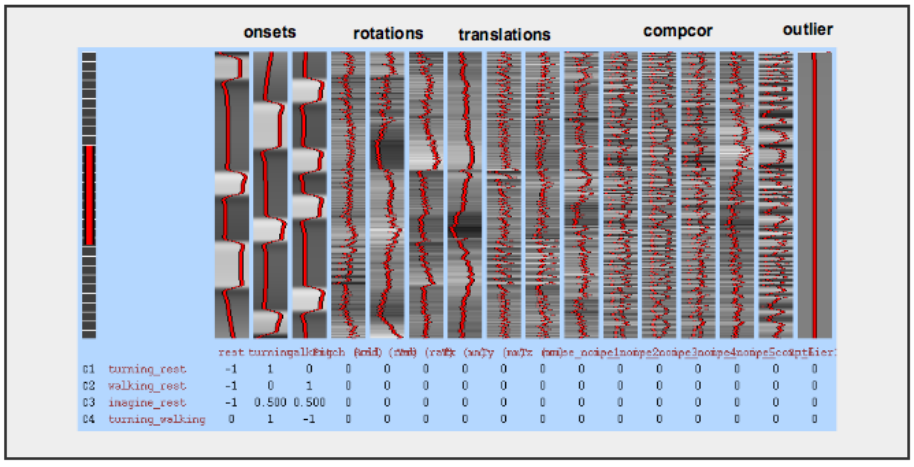

Figure 1: General Linear Model. This is a figure of a GLM for one subject. Each column is a different model time course, with time going down the image vertically. The first three columns represent the predicted BOLD signal change given the randomized stimulus pattern (rest, imagined-turning, imagined-walking) presented during the fMRI scan. The other columns including rotations, translations and CompCor are used to reduce signal change due to noise.

Once the activation maps were generated, functional SMA ROI were hand-selected using FreeSurfer by setting the t-stat threshold at 2 mm and selecting an activation cluster in the SMA region. The area of the SMA was defined as the midline grey matter superior to the cingulate sulcus (Peterson 2014). Mean COPE values were extracted from SMA ROI to quantitatively evaluate BOLD signal change in the SMA for patients with PD and healthy controls.

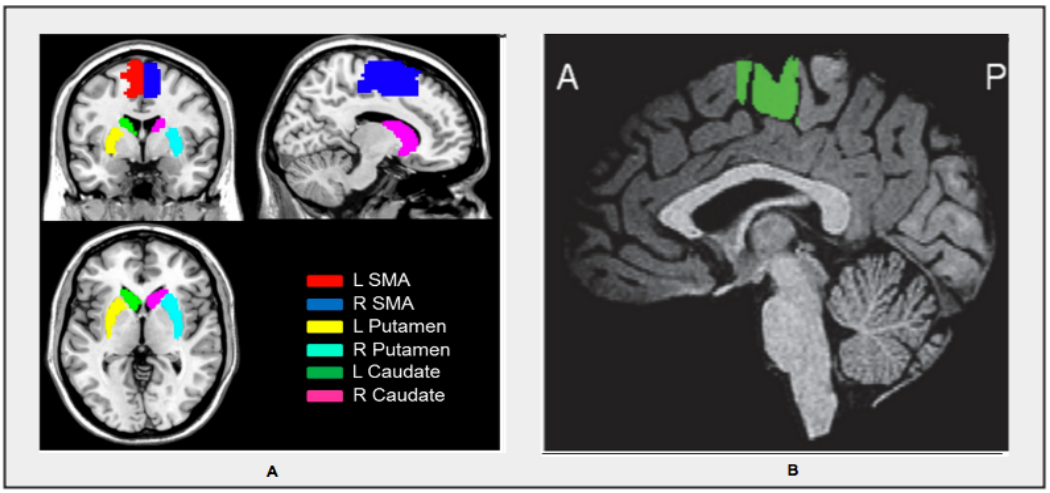

Figure 2: Supplementary Motor Area Definition. The SMA ROI was defined using these images from previously published papers. In image (A), the seed regions are defined in the SMA, the putamen and the caudate, as delineated by Yu, Liu et al. The SMA seed region in the coronal and sagittal view (colored blue and red) was used as a guide to select the SMA ROI in this study. In image (B), the SMA ROI is displayed in green, as defined by Peterson et al. This image was also used as a guide for selection of the SMA ROI in this study.

In order to minimize the impact of anatomic variation, the t-statistic data from all subjects was normalized to a standardized coordinate, Montreal Neurological Institute (MNI) brain using Advanced Normalization Tools (ANTs). This second-level analysis turns a GLM across all subjects in normalized MNI space into one statistical map. The functional data registered to the MNI space was compared between the two groups for the four contrasts: imagined-turning versus rest, imagined-walking versus rest, imagined-turning and imagined-walking versus rest, and imagined-turning versus imagined-walking. The four contrasts were also correlated with performance on the three motor metric examinations, combining both subject groups.

2.6 Statistics

A two-sample t-test was applied to evaluate differences between healthy control subjects and subjects with PD for the TUG test, the ten-meter walk and the timed 360-degree turn. Group-level comparisons were conducted to determine between-group differences in BOLD signal SMA activation by a two-sample t-test. Quantitative representations of BOLD signal change for each contrast were also analyzed using a two-sample t-test. A one-sample t-test was run to evaluate BOLD signal change for each contrast with each motor metric examination. A p-value with threshold <0.05 was used for all statistical tests in this study.

3. Results

3.1 Subject Population

A total of 30 subjects (15 subjects with PD and 15 healthy control subjects) received physical metric testing. A total of 22 subjects (11 subjects with PD and 11 healthy control subjects) received MRI testing. Eight subjects were excluded from the MRI portion of the study because they did not meet the MRI safety criteria. All subjects scored above 70% on the VVIQ test, and were included in the fMRI portion of the study.

	Parkinson's Disease	**Healthy Controls**
Average Age (years)	67.73	65.77
Average Weekly Exercise (min)	367.31	213.57
Gender	Males=7, Females=8	Males=8, Females=7
Average years with PD	3.13	0
Average Hoehn and Yahr Score	1.2	0

Table 1: Subject Demographics. The table above compares demographics between patients and controls. Patients with PD exercise significantly more than healthy control subjects in this study. The average Hoehn and Yahr scores indicate that the patients had mild PD at the time of testing. Subject gender and average age were similar in both groups.

3.2 Motor Metric Performance

Performance was not significantly different between patients with PD and age-matched controls on the TUG test, the ten-meter walk, and 360-degree turn. The t-score and the corresponding p-value on the TUG test were 1.21 and 0.24, respectively. The t-score and the corresponding p-value on the ten-meter walk test were 1.97 and 0.062, respectively. The t-score and the corresponding p-value on the 360-degree turn were 1.45 and 0.16, respectively.

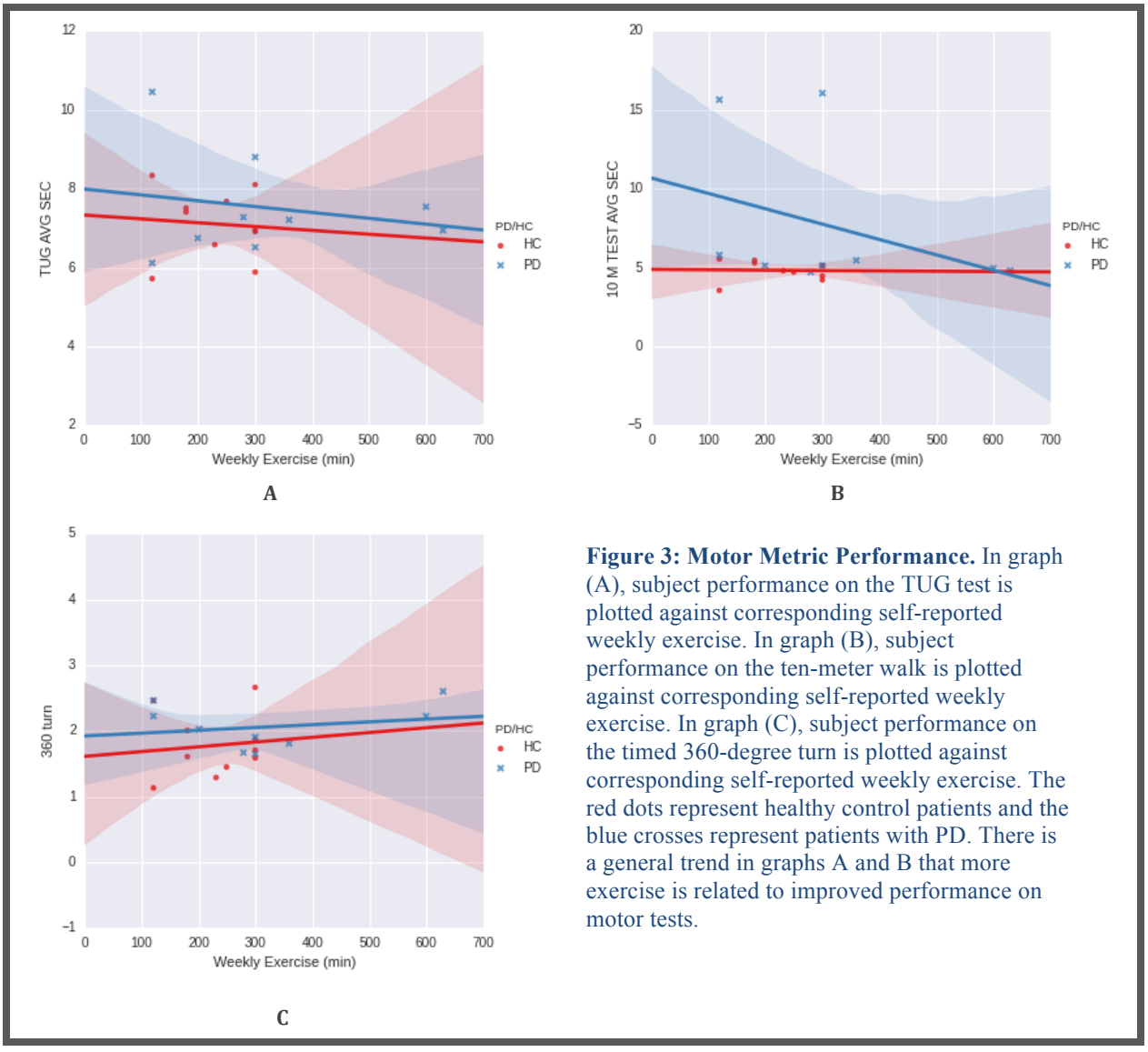

Figure 3: Motor Metric Performance. In graph (A), subject performance on the TUG test is plotted against corresponding self-reported weekly exercise. In graph (B), subject performance on the ten-meter walk is plotted against corresponding self-reported weekly exercise. In graph (C), subject performance on the timed 360-degree turn is plotted against corresponding self-reported weekly exercise. The red dots represent healthy control patients and the blue crosses represent patients with PD. There is a general trend in graphs A and B that more exercise is related to improved performance on motor tests.

3.3 SMA Signal Differences

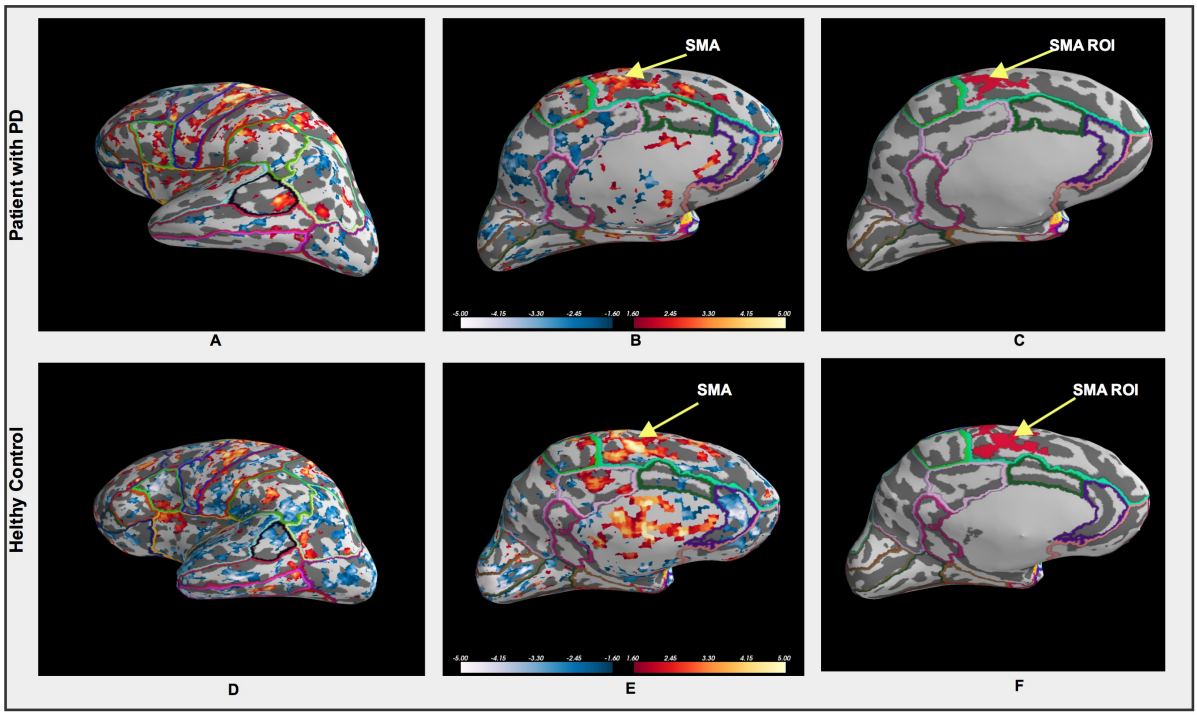

Figure 4: Supplementary Motor Area Activation. The t-statistic data is mapped onto the FreeSurfer inflated surface volumes for visualization of contrasts. The red represents significant BOLD signal increase during the imagined-turning and imagined-walking versus rest contrast. The blue represents significant BOLD signal decrease during the imagined-turning and imagined-walking versus rest contrast. The upper three images are of a patient with PD, and the lower three images are of a healthy control subject. All images are of the left hemisphere. Images A and D are lateral views of activation contrasts. Images B and E are medial views of activation contrasts. Images C and F are SMA ROI selected given the functional activations.

The present study revealed SMA activity in all but one subject during motor imagery tasks. The subject without SMA activity was excluded from the study due to his inability to hear the task instructions over the MRI scanner. Out of the four contrasts, the combined imagined-walking and imagined-turning contrast had the strongest SMA activation overall. This contrast was used to select the functional SMA ROI for each subject. Overall functional activation and selected SMA functional activation of the imagined-walking and imagined-turning versus rest condition for two subjects are displayed in Figure 4. There were no significant differences between patients with PD and controls in SMA BOLD signal activation. For the imagined-turning versus rest condition, the t-value and

respective p-value were 0.069 and 0.95. For the imagined-walking versus rest condition, the t-value and respective p-value were 1.04 and 0.31. For the imagined-walking and imagined-turning versus rest condition, the t-value and respective p-value were 0.79 and 0.44. COPE statistics with z-score values greater than two were excluded from the mean in order to eliminate outliers.

3.4 BOLD signal change

The group level results revealed that patients with PD had a significant increase in lateral occipital activation while imagining-turning versus imagining-walking, compared to controls. The t-score for this correlation was 5.371 with a corresponding p-value of 0.00001. The difference between patients and controls for this contrast is displayed in Figure 6. No significant differences were shown for other contrasts.

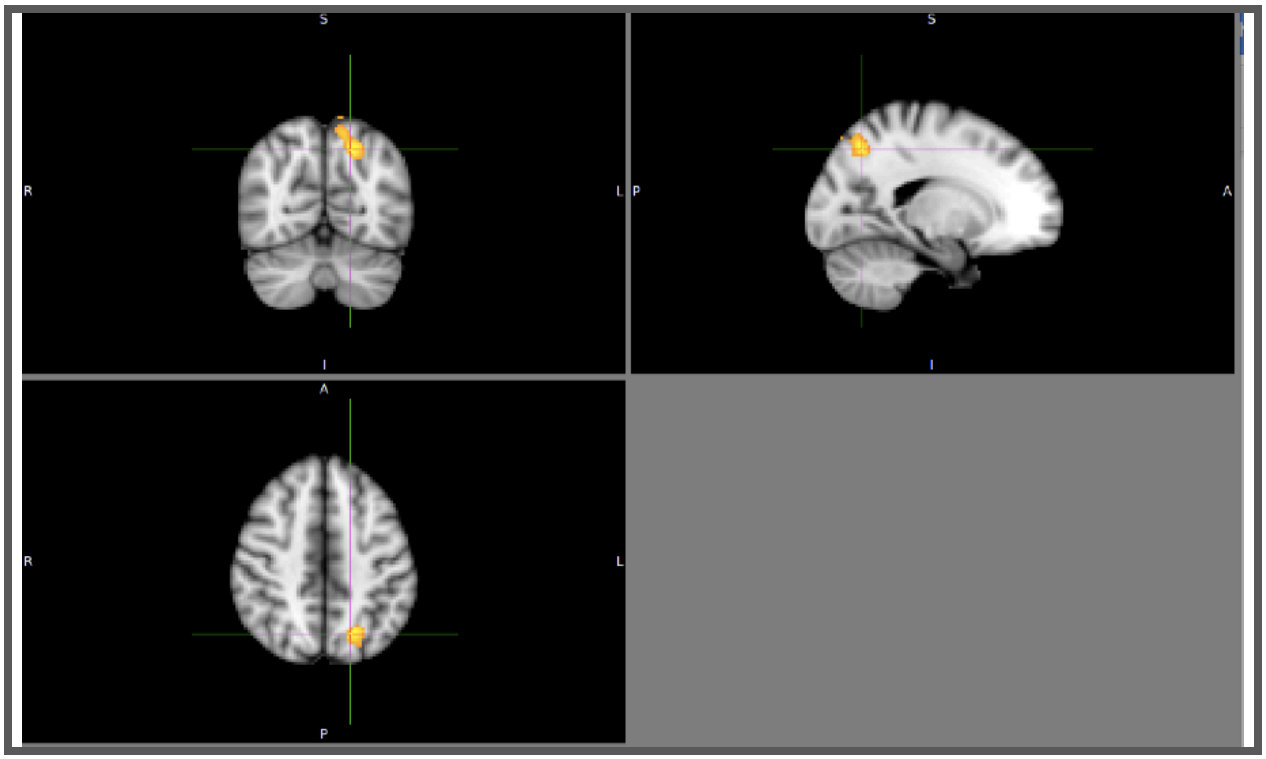

Figure 5: Lateral Occipital Signal. BOLD signal change projected on MNI space of significant occipital lobe activation for patients with PD compared to controls on the imagined-turning versus imagined-walking contrast.

BOLD signal change for each functional motor imagery contrast in comparison to each physical metric examination was examined. Data from all subjects was combined in this evaluation. The significant correlates are listed in the table below.

Motor Task	fMRI Contrast	Brain Area Activated	BOLD	p-value	Coordinates (x, y, z)	z-score
TUG	Turn vs. Walking	Premotor/Primary Motor	+	0.0001	-14, -24, 66	3.70
TUG	Walk vs. Rest	Frontal Pole	-	0.0003	-12, 62, 34	3.63
360º Turn	Turn vs. Rest	Precuneus	+	0.00005	14, -76, -40	3.45
360º Turn	Imagine vs. Rest	Precuneus	+	0.0003	12, -80, 42	3.45
360º Turn	Walk vs. Rest	Frontal Pole	-	0.0001	86, 54, 20	3.63
10 meter walk	Imagine vs. Rest	Occipital Cortex	+	0.0002	-34, -78, -12	3.52
10 meter walk	Turn vs. Rest	Occipital Cortex	-	0.003	-52, -68, 30	3.99
10 meter walk	Turn vs. Walk	Superior Frontal Gyrus	-	0.0001	0, 48, 34	3.69
10 meter walk	Walk vs. Rest	Occipital Fusiform Gyrus	+	0.00009	-42, -70, -20	3.75

Table 2: Significant Functional Activation. Significant cortical activations that correlate to fMRI motor imagery contrasts and physical motor exam measurements and displayed. BOLD signal (+) denotes increased blood flow to the corresponding brain area and BOLD signal (-) denotes decreased blood flow to the corresponding brain area. The coordinates listed are in respect to the MNI standard brain.

The significant activation during the imagined-turning versus imagined-walking contrast correlated to performance on the TUG test with a p-value of 0.0001 is displayed in Figure 6. The Juelich Histological Atlas labels the area with the highest activation as 56% premotor, Broadmann Area (BA) 6 and 54% primary motor, BA4a.

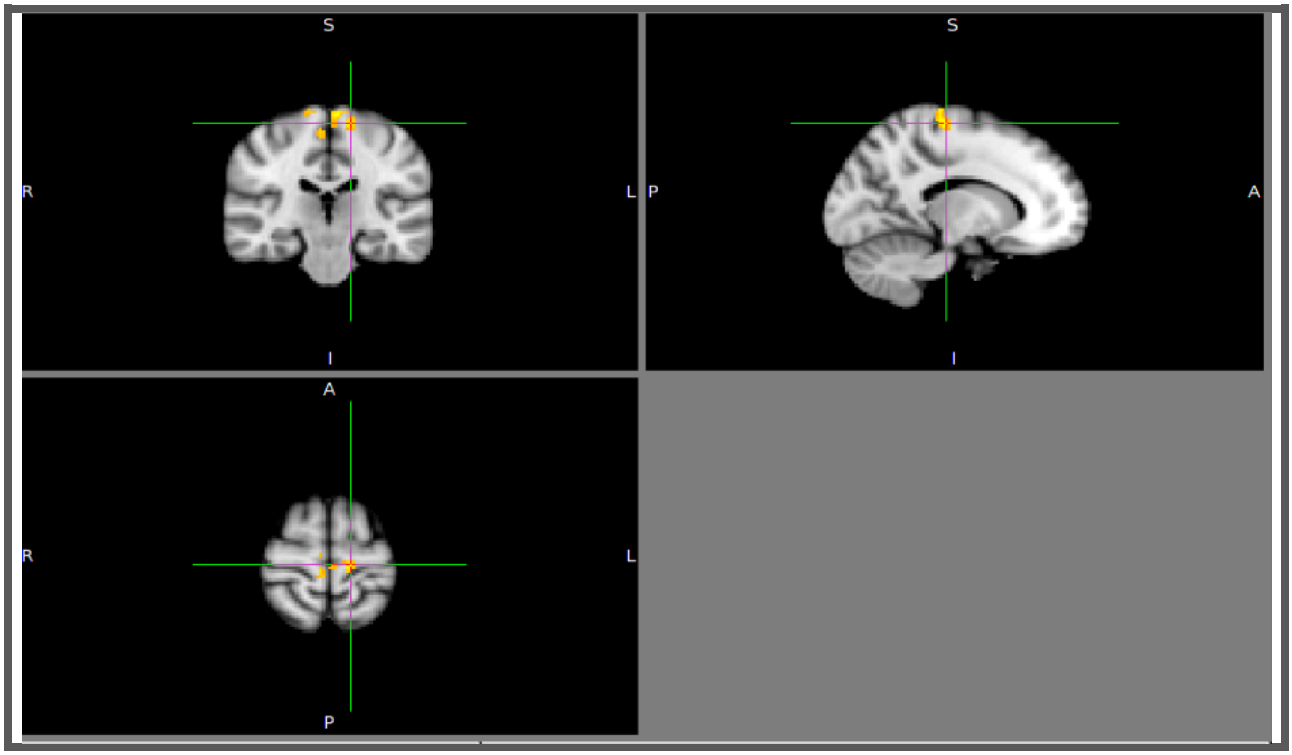

Figure 6: Neural Correlate of TUG. BOLD signal change projected on MNI space of significant premotor and primary motor activation during the imagined-turning versus imagined-walking condition for individuals with slower TUG test performance.

4. Discussion

The primary purpose of this study was to examine cortical recruitment during imagined-gait and imagined-turning in relation to motor performance during the TUG test, ten-meter walk and 360-degree turn in patients with PD compared to age-matched healthy controls.

This study concludes that SMA activation was documented in all subjects during the motor imagery task. This is an important finding warranting further research. It is promising that this block design yielded distinct motor activation patterns among subjects and between task conditions. This finding is noteworthy, given the relatively short task design, lasting a total of six minutes. Several comparable motor imagery studies perform much longer, and more complex fMRI tasks to provide

similar data (Snijders et al. 2010 and Allali et al. 2013). Designing an fMRI task that is statistically meaningful and clinically feasible for a practitioner has great potential value.

Another notable finding was the significantly higher BOLD signal response in patients with PD, in the lateral occipital region during imagined-turning, but not during imagined-walking. This may indicate that individuals with PD recruit more of their visual network to compensate for turning disability, but further data and analysis would be needed to confirm this preliminary finding.

Individuals with slower TUG task results had an increase in premotor, BA6, and primary motor, BA4a, activation during imagined-turning, compared to imagined-walking. There is strong functional connectivity between the premotor cortex and primary motor cortex. Buhmann et al. reports that the dorsal premotor cortex is hyperactive in patients with PD. This has been interpreted as adaptive plasticity of the motor system, due to deficient projections to the motor pathway. It is conceivable that the abnormal premotor activity may influence the hyperactive primary motor activity we are seeing in the patients with slower TUG task performance in this study. However, the relationship between these hyperactive connections remains unclear. Sabatini and Boulanouar et al. also report that patients with PD experience an increase in activation in the posterior SMA, the anterior cingulate cortex and the primary motor cortices. Sabatini and Boulanouar et al. interpret this finding as, "a recruitment of parallel motor circuits to overcome functional deficits attributed to the dopamine denervated brain". Udupa and Chen et al. reported that the primary motor cortex may be neuroplastic for patients with PD as a result of the degeneration of other motor systems. The data in this study suggests a possible correlation between turning disability and increased recruitment of intentional, premotor and primary motor activity.

It is noteworthy that the medial part of BA6, or the SMA, is more involved in the activation that relates to TUG performance and imagined-turning, than to imagined-walking. Borrione et al. explain how the connections between the SMA and basal ganglia are disrupted during movement performance in patients with PD, as follows: in a functional motor system, the SMA increases in activation during prepared movement, but once an external signal to move is cued by the basal ganglia, neuronal activity in the SMA drops. It is possible that the disturbance in the basal ganglia could result in over-activation in the SMA, and thus disturb the eventual movement execution. This correlation may be more present in the imagined-turning rather than the imagined-walking condition due to the higher cognitive load and the greater postural stability required for turning.

It is important to note the group level results for the 360-degree turn. The data revealed an increase in precuneus activity during the imagined-turning versus rest condition. The precuneus is identified as a vital part of the default mode or resting-state network (Utevsky 2014). A possible explanation of this finding is that the functionality of the precuneus is recruited by the motor system to improve turning ability. It would be useful to evaluate the precise functionality of the precuneous as it relates to a loss of turning ability.

It is significant that there is a distinction between the imagined-turning and imagined-walking outcomes in this study. There were apparent group differences between patients with PD and controls during imagined-turning conditions. There were also correlations between imagined-turning and performance on the motor metric examinations that include turning. Turning requires more postural balance and attention compared to simple forward ambulation. Although the TUG task did not seem to function as a sensitive clinical marker, it would be useful to evaluate other clinical markers, and corresponding biomarkers that involve turning more extensively.

After considering the results, is important to take into account the selected population. This PD patient cohort has mild PD and exercise an average of 350 minutes a week compared to the control group which exercises an average of 200 minutes a week. This high functioning PD group may have influenced the motor performance and motor imagery outcomes. It is possible that exercise has a neuroprotective effect on motor function, and this may explain some similarities in cortical activation between the studied patients with PD and controls in the SMA. There is increasing evidence that suggests vigorous exercise may favorably influence PD progression (Ahlskog 2011). It would be beneficial for future studies to look at a population with more variation in disease severity and exercise regimen, and to evaluate the neuroprotective effects of exercise accordingly.

Although the patients with PD in this study were not significantly different from the healthy controls on the TUG test, the ten-meter walk, and 360-degree turn, there were other motor metric examinations tested. Performance on the Tinetti test for gait for example, was significantly different between patients and controls. The Tinetti test for gait measures the quality of gait including: gait initiation, stepping, trunk sway, stance and arm swing. The primary difference between patients with PD and controls was that patients had an asymmetrical arm swing and a wide-based gait. This test may be a more sensitive measurement of mild PD. Like the TUG test, patients can improve performance with exercise. It would be valuable to investigate the Tinetti test in relation to neural activation patterns in patients with PD and in healthy controls.

It must be kept in mind that the motor imagery task presented in this study is an indirect measure of gait and turning. The task developed relies on that fact that there is overlap in cortical activation patterns when imagining and executing a task (Miyai 2001). This significant overlap makes motor

imagery a useful research tool, yet there is high variability between individuals (Wang 2008). The mental imagery process can be quite different for each subject, and should be accounted for when looking at the data. With a larger population size, these differences would be less significant. In addition, the speed at which individuals imagine gait tasks may influence neural activity (Cremers 2012). To maximize effect size, individuals continuously imagined during each 'imagine block' in the scanner. As a result, we are unable to assess the speed at which patients imagine a task, to compare it to the speed at which they execute a task.

Dopaminergic treatment was not accounted for in the analysis. The study was designed to evaluate neural mechanisms corresponding to those PD symptoms that are insensitive to dopamine medication, such as postural imbalance. Dopaminergic treatment is useful for treating PD symptoms, but is difficult to control for, and does not address the underlying cause of PD. However, the effect of dopaminergic treatment on motor imagery may be significant. Several sources have reported that dopamine medication can enhance imagery activation in individuals with PD (Dickstein 2007). This imagery enhancement may be related to the significant difference in recruitment of visual networks during imagined-walking and imagined-turning for patients with PD compared to controls in this study. Maillet, Thobois, and Fraix reported that levodopa increases activation in motor regions, notably the putamen, thalamus and cerebellum, and reduces premotor-parietal and brainstem involvement during motor imagery of gait. Controlling for dopamine would increase our understanding of these effects.

5. Conclusion

The current dopaminergic treatment for PD addresses the patient's symptoms, but is not neuroprotective. In order to look for a neuroprotective treatment for PD, it is pertinent to isolate the PD symptoms that are relatively insensitive to dopamine medication, in order to identify their underlying neural mechanisms, and a potential biomarker for PD. Previous studies have shown that performance on the TUG test, which involves gait and postural stability, tests a set a symptoms which are resistant to dopaminergic therapy. Our results showed no significant difference between patients and controls on the TUG task. However, the patients in this study with PD are high-functioning and exercise significantly more than the healthy controls. The similar activation in the SMA for patients with PD and controls during the motor imagery tasks could potentially be due to the neuroprotective effects of exercise in the SMA. When looking at the overall functional differences between individuals with PD and healthy controls, the patients with PD had greater lateral occipital lobe activation when participating in imagining-turning versus imagining-walking, compared to controls. TUG performance was found to correlate with BOLD signal change in the premotor and primary motor areas during the imagined-turning versus walking contrast for both patients with PD and for controls. Most significantly, areas of the brain, including the primary motor area, the premotor area, the SMA and the lateral occipital lobe, showed sensitive BOLD signal response in relation to the motor imagery of turning. An evaluation of the fMRI brain activation patterns during motor imagery tasks, as discussed in this study, may assist in correlating a clinical motor outcome of PD to a quantitative biomarker for the disease.

REFERENCES

Avanzino L, E Pelosin, D Martino, G Abbruzzese. Motor Timing Deficits in Sequential Movements in Parkinson Disease Are Related to Action Planning: A Motor Imagery Study. PLoS ONE 2013; 8(9): e75454.

Bhidayasiri, Roongroj, and Daniel Tarsy. Parkinson's Disease: Hoehn and Yahr Scale. Movement Disorders: A Video Atlas. Humana Press, 2012.

Bohnen NI, Albin RL. The Cholinergic System and Parkinson Disease. Behavioural Brain Research. 2011; 221(2):564-573.

Bryant, Mon S, et al. Influence of Fear of Falling on Gait and Balance in Parkinson's Disease. Disability and Rehabilitation 2014; 36(9):744–748. [Web] 2015 Aug 18.

Chou, Pei-Yi. Turning Deficits in People with Parkinson's Disease. Tzu Chi Medical Journal 2013; 25.200e202.

Cremers, Julien. Brain Activation Pattern Related to Gait Disturbances in Parkinson's Disease. Movement Disorders 2012 Oct; 27(12):1498-1505 [Web] 2012 Sep 24.

Cui, Xu et al. Vividness of Mental Imagery: Individual Variability Can Be Measured Objectively. Vision Research 2007; 47(4)474–478. [Web] 2015 Aug18.

Cunnington, R, R Iansek, KA Johnson, JL Bradshaw. Movement Potentials in Parkinson's Disease. Motor Imagery and Movement Preparation. Brain: A Journal of Neurology 1997 August; 120 (8):1339-53.

Decety, J, D Perani, M Jeannerod, et al. Mapping Motor Representations with Positron Emission Tomography. Nature 1994 Oct 13; 371:600–602.

Feix Do Nascimento, Omar. Influence of Directional Orientations during Gait Initiation and Stepping on Movement-related Cortical Potentials. Behavioral Brain Research 2005; 161(1):141-54.

Franzén, Erika, et al. Reduced Performance in Balance, Walking and Turning Tasks Is Associated with Increased Neck Tone in Parkinson's Disease. Experimental Neurology 2009; 219(2):430–438. [Web] 2015 Aug 18.

Giladi, Nir, Alice Nieuwboer. Understanding and Treating Freezing of Gait in Parkinsonism, Proposed Working Definition, and Setting the Stage. Movement Disorders 2008; 23(S2):S423–S425.

Godde, Ben, Claudia Voelcker-Rehage. More Automation and Less Cognitive Control of Imagined Walking Movements in High- Versus Low-Fit Older Adults. Frontiers in Aging Neuroscience 2010; 2:139.

Greenan, Sinead. 10 Meter Walk Test. Physiopedia [Web] 2015 July 1. http://www.physio-pedia.com/10_Metre_Walk_Test

Guillot, A, C Collet, VA Nguyen, F. Malouin et al. Brain activity during visual versus kinesthetic imagery: An fMRI study. Hum Brain Mapp 2009; 30:2157–2172.

Hauser, Robert. Levodopa: Past, Present, and Future. Eur Neurol 2009; 62(1):1-8.

Hely, Mariese A and John GL Morris. Sydney Multicenter Study of Parkinson's Disease: Non-L-Dopa-Responsive Problems Dominate at 15 Years. Movement Disorders 2005; 20(2):190-99.

Hughes AJ et al. British Brain Bank Criteria. J Neurol Neurosurg Psychiatry 1992; 55:181-184.

Karachi, Carine et al. Cholinergic Mesencephalic Neurons Are Involved in Gait and Postural Disorders in Parkinson Disease. The Journal of Clinical Investigation 2010; 120(8):2745-2754.

Kikuchi, Akio. Hypoperfusion in the Supplementary Motor Area, Dorsolateral Prefrontal Cortex and Insular Cortex in Parkinson's Disease. Journal of the Neurological Sciences 2001; 193(1): 29-36.

Klaus, John, Angela Deutschländer. Brain Activation Patterns during Imagined Stance and Locomotion in Functional Magnetic Resonance Imaging. NeuroImage 2004; 22(4):1722–1731.

Maillet, Audrey, Stéphane Thobois, Valérie Fraix. Neural Substrates of Levodopa-responsive Gait Disorders and Freezing in Advanced Parkinson's Disease: A Kinesthetic Imagery Approach. Human Brain Map 2014 May 28. [Web] 2015; 36(3):958-980.

Malouin, Francine. Brain Activations during Motor Imagery of Locomotor-related Tasks: A PET Study. Human Brain Mapping 2003; 19(1):47-62.

Mayo Clinic. Mayo Foundation for Medical Education and Research. Parkinson's Disease. [Web] 2015 http://www.mayoclinic.org/diseases-conditions/parkinsons-disease.

Miyai, Ichiro. Cortical Mapping of Gait in Humans: A Near-Infrared Spectroscopic Topography Study. NeuroImage 2001 Nov; 14(5):1186–1192.

Morris, Susan. Reliability of Measurements Obtained with the Timed "Up & Go" Test in People with Parkinson Disease. Physical Therapy 2000; 81(2):810-818.

Müller MLTM, Bohnen NI. Cholinergic Dysfunction in Parkinson's Disease. Current Neurology and Neuroscience Reports 2013; 13(9):377.

Muthsamy, Kalai, Bhooma R. Aravamuthan, B. Sc., Morten L. Kringelbach, D. Phil., et al. Connectivity of the Human Pedunculopontine Nucleus Region and Diffusion Tensor Imaging in Surgical Targeting. J. Neurosurgery 2007; 107:814–820.

Nagal, Anubhav, Rajeev K Singla. Parkinson's Disease: Diagnosis, Therapeutics & Management. [Web] WebMedCentral 2012 Aug 27. Article ID: WMC003670.

National Parkinson's Foundation. Freezing. [Web] 2015 http://www.parkinson.org/understanding-parkinsons/motor-symptoms.

Nemanich, Samuel T, Ryan P Duncan, Leland E Dibble, et al. Predictors of Gait Speeds and the Relationship of Gait Speeds to Falls in Men and Women with Parkinson Disease. Parkinson's Disease 2013; Article ID 141720: 1-8.

Nocera, JR, EL Stegemöller, et al. Using the Timed Up and Go Test in a Clinical Setting to Predict Falling in Parkinson's Disease. Arch Phys Med Rehabil. 2013 Jul; 94(7):1300-1305. [Web] 2013 March 6.

Nutt, JG, CD Marsden, PD Thompson. Human Walking and Higher Level Gait Disorders, Particularly in the Elderly. Neurology 1993; 3:268–279.

Perrey, Stéphane. Possibilities for Examining the Neural Control of Gait in Humans with fNIRS. Frontiers in Physiology 2014; 8:204.

Peterson, Daniel S, Kristen A Pickett, Ryan Duncan, Joel Perlmutter, Gammon Earhart. Gait-Related Brain Activity in People with Parkinson Disease with Freezing of Gait. PLoS ONE 2014 March 3; 9(3): e90634.

Peterson, Daniel. Biomechanical and Neural Factors Associated with Gait Dysfunction and Freezing in People with Parkinson Disease. 2013. All Theses and Dissertations (ETDs). Paper 113.

Porro, CA, MP Francescato, V Cettolo, M.E. Diamond, et al. Primary motor and sensory cortex activation during motor performance and motor imagery: A functional magnetic resonance imaging study." Journal of Neuroscience 1996; 16:7688–7698.

Purves, Dale and George J Augustine. Movement and Its Central Control. Neuroscience 2008 July 31, 4th Edition. Sunderland(MA): Sinauer Associates.

Rahman, Shibley. Quality of Life in Parkinson's Disease: The Relative Importance of the Symptoms. Movement Disorders 2008 July 30; 23(10):1428-34.

Rinalduzzi, Steno, Carlo Trompetto, Lucio Marinelli, et al. Balance Dysfunction in Parkinson's Disease. BioMed Research International 2015; Article ID 434683: 1-10.

Schaafsma, Joanna. Gait Dynamics in Parkinson's Disease: Relationship to Parkinsonian Features, Falls and Response to Levodopa. Journal of the Neurological Sciences 2003; 212 (1-2):47–53.

Schubert, M. Corticospinal Input in Human Gait: Modulation of Magnetically Evoked Motor Responses. Experimental Brain Research 1997; 115:234–246.

Schweder, Patrick M. Connectivity of the Pedunculopontine Nucleus in Parkinsonian Freezing of Gait. Neuroreport 2010; 21(14):914-916.

Snijders, Anke, Inge Leunissen. Gait-related Cerebral Alterations in Parkinson Patients with Freezing of Gait. [Web] Brain 2010 Dec; Brain 2012; 59-72.

Song, Jooeun, Susan Sigward, Beth Fisher, George J. Salem. "Altered Dynamic Postural Control during Step Turning in Persons with Early-Stage Parkinson's Disease." Parkinson's Disease (2012).

Wang, ChiHong, YauYau Wai. Cortical Control of Gait in Healthy Humans: An FMRI Study. Journal of Neural Transmission 2008 August; 115(8):1149-1158.

Wood, BH, JA Bilclough. Incidence and Prediction of Falls in Parkinson's Disease: A Prospective Multidisciplinary Study. Journal of Neurology Neurosurgery Psychiatry 2002; 72:721-725.

Wright, WG et al. Axial Hypertonicity in Parkinson's Disease: Direct Measurements of Trunk and Hip Torque. Experimental Neurology 2007; 208.1: 38–46. [Web] 2015 Aug 18.

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