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WASHINGTON UNIVERSITY IN ST. LOUIS

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Biomechanical and Neural Factors Associated with Gait Dysfunction and Freezing in  
People with Parkinson Disease

by

Daniel Soren Peterson

A dissertation presented to the  
Graduate School of Arts and Sciences  
of Washington University in  
partial fulfillment of the  
requirements for the degree  
of Doctor of Philosophy

August 2013

St. Louis, Missouri

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## ABSTRACT OF THE DISSERTATION

Biomechanical and Neural Factors Associated with Gait Dysfunction and Freezing in  
People with Parkinson Disease

by

Daniel Soren Peterson

Doctor of Philosophy in Movement Science

Washington University in St. Louis, 2013

Professor Gammon M Earhart, Chair

Parkinson disease (PD) is a progressive neurological disorder with no known cure, affecting one million Americans. Half of those with PD experience freezing of gait (FOG), manifested as an inability to complete effective stepping. Gait dysfunction and FOG are associated with falls, severe injury, and reduced quality of life, and are among the most disabling and distressing symptoms of PD. The causes of FOG and gait dysfunction are not well understood. Further, FOG is notoriously difficult to elicit in a laboratory setting, making efforts to track or identify individuals at risk for freezing difficult. An important first step in determining the mechanism of gait dysfunction and FOG is to identify factors associated with these symptoms. Therefore, the overall goal of this project was to better understand how pathologies of movement and brain function are associated with gait dysfunction and FOG.

To this end we conducted three experiments (chapters 2-4). In experiment 1 (chapter 2), we assessed the relationship between coordination of steps and freezing of gait. Results suggested that individuals with PD who freeze exhibit worse coordination than those who do not freeze, and further, that tasks related to freezing (turning and

backward walking) resulted in worse coordination than forward walking. Finally, there was a significant positive correlation between freezing severity and global coordination of steps. These results together support the hypothesized relationship between coordination of steps and freezing.

In experiment 2 (chapter 3), we investigated neural signals associated with gait dysfunction (measured via blood oxygen level dependent [BOLD] signal) in those with PD compared to healthy adults. We found that during complex gait tasks, those with PD activated the supplementary motor area more than healthy adults. In addition, we observed reduced activity in the globus pallidus in people with PD. Finally, PD exhibited consistent positive correlations between a measure of gait function (overground walking velocity) and brain activation such that those with higher brain activity exhibited better gait function.

In experiment 3 (chapter 4), we investigated the neural underpinnings of freezing of gait. Specifically, we looked at gait imagery in those with PD who do experience freezing (freezers) and those who do not (non-freezers). We found those who experience freezing exhibited reduced BOLD signal in the cerebellar locomotor region, suggesting dysfunctional activity in this region may play a role in freezing. BOLD response within freezer and non-freezer groups were not consistently correlated to functional gait measures such as overground gait speed or freezing severity.

Together these results better elucidate how pathologies of movement (i.e. coordination of steps) and neural function are related to gait dysfunction and freezing. Specifically, we found that coordination of steps and activity of the cerebellar locomotor

regions may be related to freezing. Further, altered activation of the globus pallidus may be related to gait dysfunction in those with PD, and generally, larger BOLD response is correlated to improved overground gait function.

## **Chapter 1: Introduction**

### **PARKINSON DISEASE**

Parkinson disease (PD) is the second most prevalent neurodegenerative disease, and has no known cure. PD currently affects one million Americans and its prevalence is expected to increase as the US population ages (Strickland and Bertoni 2004). Individuals with PD often develop severe motor dysfunction, leading to falls, reduced quality of life, and depression. The economic effects of PD are quite large, as approximately twenty five billion dollars are spent on direct and in-direct costs of PD every year in America alone (Whetten-Goldstein et al. 1997; Scheife et al. 2000).

A prominent neural pathology observed in those with PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) within the basal ganglia, thought to be related to the presence of ubiquitin- and  $\alpha$ -synuclein-positive cytoplasmic inclusions known as Lewy bodies (Polymeropoulos et al. 1997; Bennett et al. 1999; Wakabayashi et al. 2007). This loss of SNpc dopaminergic neurons leads to a reduction in dopamine input to the striatum, and is likely involved with several of the cardinal motor symptoms of PD. However, in those with PD, Lewy bodies are not restricted to the SNpc. Recent evidence suggests that in the early stages of PD, Lewy bodies are commonly noted in brainstem (medulla oblongata) and olfactory bulb. As the disease progresses, however, they are present in virtually all parts of the brain. Based on these findings, Braak and colleagues developed a staging system of PD, showing dysfunction and Lewy body inclusion beginning in the brainstem and moving rostrally, affecting the basal and mid forbrain, and eventually multiple regions of the neocortex

(Braak et al. 2003). Due to the extensive pathology at late stage PD, individuals often exhibit substantial motor and non-motor dysfunction.

The root of the cellular alterations is not well understood. For a small percentage of those with PD (approximately 5-10%) genetics are likely responsible (Dauer and Przedborski 2003), as several genetic mutations have been associated with PD (for review, see (Dauer and Przedborski 2003; Wirdefeldt et al. 2011)), and Lewy body proliferation in particular (Polymeropoulos et al. 1997). However for the vast majority of cases, the underlying causes are unknown. Recent reports have suggested that certain environmental factors may be linked to PD, including pesticides and herbicides (Hatcher et al. 2008). Interestingly, the incidence and prevalence of PD seem to have non-random geographic distribution throughout the United States, with increased prevalence and incidence in the Midwest and northeastern regions of the United States (Wright Willis et al. 2010). The higher PD burden in these regions may be linked to pesticides (the use of herbicides and pesticides are common in the Midwest and Northeast [Environmental Protection Agency, 2009; United States Geological Survey Pesticide National Synthesis Project, 2009]), however byproducts of industrialization, also common in these regions, may play an important role. The long lag time between exposure and development of PD, as well as the highly complex interactions between numerous environmental exposures, makes identifying specific causal links extremely difficult.

## **GAIT AND MOTOR DYSFUNCTION IN PD**

The cardinal motor symptoms of PD include bradykinesia, rigidity, and tremor (Leenders and Oertel 2001). Posture and locomotion are also affected in people with PD, leading to injury and reduced quality of life in this population. Specific changes in posture, balance, and gait in people with PD are described in detail below.

### Balance & Posture Dysfunction

Balance deficits in PD are a common and dangerous symptom associated with increased morbidity and mortality (Coelho et al. 2010). Control of balance and posture requires efficient processing of multiple sensory inputs (vestibular, visual, and somatosensory), and producing effective motor output. Examples of balance dysfunction in PD include altered control of center of mass motion during quiet standing (Horak et al. 1992; Mitchell et al. 1995), smaller functional limits of stability (Mancini et al. 2008), and altered sensory integration to maintain upright posture, among others. For example, those with PD typically exhibit increased reliance on visual information (Bronstein et al. 1990; Kitamura et al. 1993; Jacobs and Horak 2006). The underlying causes of these symptoms are not fully understood, but likely involve deficits in vestibular function and motor control. For example, hypometric and bradykinetic movements may in part underlie dysfunction of sway and anticipatory postural responses.

### Gait dysfunction

During gait, individuals with PD typically exhibit reduced walking velocity (O'Shea et al. 2002) as well as short (Morris et al. 1996), variable (Blin et al. 1991; Hausdorff et al. 1998) steps. Further, coordination in timing of steps is impaired (Plotnik et al. 2008), and in some cases, steps can become progressively shorter and faster (Chee et al.

2009). This progression, known as festination, may result in a total inability to produce effective stepping. Due to the dynamic nature of walking, instability during locomotion often leads to falls in people with PD. Interestingly, complex gait tasks such as backwards walking or turning are particularly difficult for those with PD, as the gait dysfunction noted earlier is generally more pronounced during these tasks than during normal forward walking (Hackney and Earhart 2009).

Dysfunction during walking may be related to altered ability to effectively direct attention in people with PD. This can be demonstrated during dual task walking, as those with PD exhibit considerably worse gait while dual tasking than healthy controls (O'Shea et al. 2002; Rochester et al. 2004). Similarly, if attention is focused back on gait, using attentional, visual, or auditory cueing strategies, gait can be improved (Lohnes and Earhart 2011). Interestingly, some individuals with PD exhibit a so-called “posture second” strategy, whereby attention is naturally focused more on a competing cognitive task rather than on the gait task than in healthy adults (Bloem et al. 2001; Bloem et al. 2006). This suggests a potentially un-safe focus on cognitive, rather than balance, needs. Recent evidence has, however, questioned this notion, suggesting similar attentional strategies in PD and controls (Yogev-Seligmann et al. 2012). These recent investigations, along with other evidence raise the possibility that a posture second strategy or “stops walking while talking” sign may be more related to cognitive dysfunction than PD specific dysfunction (Bloem et al. 2000; Bloem et al. 2006). Despite questions regarding specific postural strategies in PD and controls, attention clearly plays an important role in locomotion, particularly in people with PD, and focusing attention onto gait is beneficial for improving locomotion in this population.



## Freezing of Gait

At least 50% of those with advanced PD exhibit Freezing of Gait (FOG) (Giladi et al. 2001; Bartels et al. 2003), defined as a transient inability to complete effective stepping (Giladi and Nieuwboer 2008). FOG is a particularly disabling and distressing symptom, and is closely related to falls and reduced quality of life (Gray and Hildebrand 2000; Giladi et al. 2001; Bloem et al. 2004; Moore et al. 2007; Kerr et al. 2010).

Though the underlying neural dysfunction associated with FOG is not fully understood, previous investigations have identified several brain regions possibly related to freezing. For example, in those without PD, lesions in the supplementary motor area (SMA) (Della Sala et al. 2002), globus pallidus (GP) (Klawans et al. 1982; Feve et al. 1993), and mesencephalic locomotor regions (MLR) (Masdeu et al. 1994; Bhidayasiri et al. 2003; Kuo et al. 2008) resulted in freezing- like symptoms. Interestingly, individuals with PD also exhibit dysfunction in these areas (Playford et al. 1992; Bartels et al. 2003; Jahanshahi et al. 2010; Prodoehl et al. 2010; Snijders et al. 2011; Cremers et al. 2012a), suggesting they may be involved with FOG.

The MLR, and, within this region, the pedunculopontine nucleus (PPN), has been suggested to be related to FOG (Lewis and Barker 2009). This is due in part to the large role the PPN plays in movement, and specifically, locomotion. The PPN plays a key role in the control of descending locomotor signals, and is closely tied to the dopaminergic and cholinergic systems, both of which are dysfunctional in PD. Lesion (Masdeu et al. 1994; Bhidayasiri et al. 2003; Kuo et al. 2008; Karachi et al. 2010) and functional imaging (Snijders et al. 2011; Cremers et al. 2012a) studies also support the notion that dysfunction of this region may be related to FOG. The PPN is atrophied in those with

PD with respect to healthy older adults (Hirsch et al. 1987). Preliminary evidence suggests this region may be further atrophied in freezers with respect to non-freezers (Snijders et al. 2011). Finally, brain stimulation to the PPN region may improve gait and reduce the number of freezing events (Plaha and Gill 2005; Thevathasan et al. 2011; Thevathasan et al. 2012), although recent double blinded clinical trials have shown only marginal benefit for PPN stimulation (Ferraye et al. 2010; Moro et al. 2010) (for review see (Ferraye et al. 2011)). Further research is necessary to better understand if and how this region is associated with freezing and gait dysfunction in PD.

Similarly to other types of gait dysfunction, the complexity of the gait task may also influence freezing. Turning, for example, is a complex gait task generally requiring more coordination of movement and posture than simple gait tasks such as forward walking (Courtine and Schieppati 2004). Turning is the most common way to elicit freezing in the home (Schaafsma et al. 2003), and is the most consistent way to elicit freezing in the laboratory setting (Spildooren et al. 2010; Snijders et al. 2012). The mechanism by which turning elicits freezing is not well understood. However, turning necessitates asymmetries in step length and leg velocity (Courtine and Schieppati 2003), and leads to discoordinated stepping in people with PD. This asymmetry and reduced coordination of steps during turning may precipitate freezing (Plotnik and Hausdorff 2008). In support of these findings, a recent report suggested that individuals with PD who experience freezing may have altered activity in the supplementary motor area (a pre-motor region associated with the coordination and planning of complex movements) with respect to those who do not freeze (Snijders et al. 2011).

FOG is also associated with attentional deficits, as cueing, a strategy to focus attention back to the gait task, is a common and effective strategy to “break” freezing episodes (Lee et al. 2012). Similarly, tasks which pull attention away from gait, i.e. dual tasking (Snijders et al. 2010; Spildooren et al. 2010), doorways (Almeida and Lebold 2010), and stressful or emotional situations (Rahman et al. 2008) often elicit freezing (for reviews, see (Fahn 1995; Okuma 2006; Hallett 2008; Morris et al. 2008; Browner and Giladi 2010; Nutt et al. 2011)). Together, these results suggest the possibility that freezing may be associated with dysfunction not only of the basal ganglia and brainstem, but also frontal executive and attentional regions of the cortex. This notion is further supported by recent research showing that 1) alterations in cortical volume of freezers (Kostic et al. 2012), and 2) cognitive function are altered in those with PD (Amboni et al. 2008). Cortical regions have direct and indirect connections to not only the basal ganglia, but also brainstem regions such as the PPN (Pahapill and Lozano 2000; Jenkinson et al. 2009). Therefore, it is possible that freezing results from discoordination and dysfunction of multiple regions (i.e. cortical, basal ganglia, and brain stem) as opposed to one in isolation (Hashimoto 2006; Lewis and Barker 2009).

Recently, biomechanical characteristics have been suggested to be related to, or possibly part of the causal pathway of freezing. Indeed, numerous studies have noted that individuals with PD show altered coordination of both upper (Vercruysse et al. 2012) and lower limb movements (Hausdorff et al. 1998; Abe et al. 2003; Plotnik et al. 2007). Further, those who experience freezing seem to have a more variable and less symmetric gait pattern than those not experiencing FOG (Nieuwboer et al. 2001; Hausdorff et al. 2003; Plotnik et al. 2008). Importantly, arrhythmic and uncoordinated

movements can be observed during normal motion (i.e. non-freezing gait), and therefore represent a continuous gait disturbance in these individuals (Hausdorff et al. 2003). Further, dual tasking, which typically results in more frequent freezing episodes, has also been shown to elicit worse coordination of steps (Plotnik et al. 2009). Due to these findings, it has been hypothesized that biomechanical factors may be related to freezing (Plotnik and Hausdorff 2008; Plotnik et al. 2012). Previous studies, however, have tested coordination during straight walking only. Measuring coordination during tasks which more commonly elicit FOG, such as turning, could provide a better understanding of the relationship between coordination and FOG. For example, if coordination and FOG are related, tasks which often elicit FOG should result in worse coordination than forward walking. However, if tasks related to freezing do not result in worse coordination, it is unlikely that coordination is a strong predictor or contributing factor to FOG. Therefore the first aim of this project was to assess coordination of steps during tasks which often elicit freezing (backward walking and turning) with relation to tasks less associated with FOG to elucidate the relationship between bilateral coordination of steps is associated with FOG in people with PD.

## **NEURAL UNDERPINNINGS OF HEALTHY AND PARKINSONIAN GAIT**

As noted previously, the underlying dysfunction of PD and freezing of gait is not well understood. In order to better understand what alterations in neural activity may be associated with gait dysfunction, recent investigations have begun to characterize supra-spinal locomotor control networks in healthy and diseased populations. In the

following sections, the neural control of locomotion will be discussed for healthy young adults, healthy older adults, and individuals with PD.

### Locomotor Control in Healthy Young

Considerable effort and resources have been applied to understanding the neural control of gait in healthy young adults, and through work using a variety of techniques (i.e. Positron Emission Tomography; PET, Single Positron Emission Computed Tomography; SPECT, Near Infrared Spectroscopy; NIRS, Functional Magnetic resonance imaging; fMRI, Electroencephelography; EEG, and others) we have gained significant knowledge about how the brain controls gait. Early investigations used PET and SPECT to assess regions of the brain which are active during actual walking (Fukuyama et al. 1997; Mishina et al. 1999; Miyai et al. 2001; Tashiro et al. 2001; Hanakawa 2006). Perhaps not surprisingly, these studies identified several regions to consistently be associated with locomotion, including premotor regions, basal ganglia, visual cortex, and the cerebellum. Other regions shown to be active, albeit less consistently, include the anterior cingulate cortex and dorsal brainstem (Hanakawa et al. 1999; Hanakawa 2006).

More recent studies have used fMRI, as it provides superior temporal and spatial resolution than PET/SPECT, and it allow testing of multiple tasks for each participant. As walking, and in many cases any leg movements, result in prohibitive amounts of head motion for fMRI, this technique necessitates individuals to imagine gait tasks. Numerous investigations using this technique have largely supported previous findings from PET and SPECT studies, showing gait related increases in activity in premotor regions, basal ganglia, and cerebellum (Miyai et al. 2001; Jahn et al. 2004; Iseki et al.

2008; la Fougere et al. 2010). In addition, possibly due to the higher spatial resolution, some investigations have suggested activity in dorsal brainstem and cerebellar regions (Jahn et al. 2008; Karachi et al. 2010), the thalamus (Jahn et al. 2004) and parahippocampal gyrus (Jahn et al. 2004; Iseki et al. 2008; Jahn et al. 2008). These so-called “locomotor regions” identified via gait imagery overlap with locomotor centers in quadrupeds (Orlovsky 1969; Shik et al. 1969; Mori et al. 1999).

Recent investigations using fMRI and NIRS have begun to look at brain activity during locomotor-like tasks of varying complexity, including turning (Wagner et al. 2008), backward walking (Godde and Voelcker-Rehage 2010), stepping over obstacles (Malouin et al. 2003; Wang et al. 2009), and walking with narrow versus broad pathways (Bakker et al. 2008). With respect to forward walking, these relatively complex tasks result in increases in pre-motor activity (particularly the supplementary motor area, SMA) (Malouin et al. 2003; Bakker et al. 2008; Wagner et al. 2008; Godde and Voelcker-Rehage 2010), as well as parahippocampal gyrus (Malouin et al. 2003; Wagner et al. 2008), putamen (Wagner et al. 2008), and thalamus (Wagner et al. 2008; Godde and Voelcker-Rehage 2010), among others.

Locomotion at different speeds has also been shown to alter the activity of the brain (Suzuki et al. 2004; Jahn et al. 2008; Karachi et al. 2010; Cremers et al. 2012b). For example, brainstem and midline cerebellar alterations were observed in some (Jahn et al. 2004; Jahn et al. 2008; Karachi et al. 2010), though not all (Cremers et al. 2012b) studies. It has been suggested that these increases may be due to alterations in perceived balance needs while imaging brisk walking and running with respect to normal walking.

## Locomotor Control in Healthy Old

To our knowledge, only two studies have investigated effects of age on the neural control of locomotion, with varied results. Zwergal and colleagues investigated imagery of running, walking, standing, and lying in both older and younger adults using fMRI. During gait imagery, both groups showed brain activity (measured via blood oxygen level dependent signal; BOLD) in locomotor regions including the SMA, caudate, and cerebellum. Activity in regions less commonly associated with imagined locomotion was also noted to be different across age groups. For example, older adults showed relative increases in multisensory vestibular cortices and somatosensory cortices. Authors suggest that the increases in activity in non-locomotor regions may be a result of reduced cortical inhibitory reciprocal interactions within sensory systems in older adults. As part of a larger study, Wai and colleagues investigated imagery of gait initiation, stepping over obstacles, and gait termination in old and young. Broadly, both groups exhibited activity in pre-motor and visual regions during imagined walking, with older adults exhibiting more activity in these regions than young. In this study, individuals watched videos of gait from a 1st person perspective, possibly eliciting less of a response from somatosensory loops than during kinesthetic, whole-body gait imagery. Indeed, recent evidence suggests different brain regions are active during visual vs. kinesthetic imagery of movement (Guillot et al. 2009).

In all, this limited body of work suggests numerous alterations in the control of locomotion with increasing age, most prominently in non-locomotor regions. Alterations in locomotor regions may be more prominent during more complex gait tasks which challenge the coordination and planning of locomotion.

## Locomotor Control in PD

The overlap between brain regions associated with gait dysfunction and altered activity in PD has spurred several recent studies aimed at understanding how the neural control of gait may be altered in PD (Hanakawa et al. 1999; Snijders et al. 2011; Cremers et al. 2012a; Wai et al. 2012). Hanakawa and colleagues were the first to investigate neural signals in PD during locomotion. Using SPECT, investigators showed both under-activation (medial frontal areas, precuneus, and cerebellum), and over-activation (temporal cortex, insula, and cerebellar vermis) in people with PD. More recent studies have used gait imagery, showing a variety of alterations during locomotor imagery in PD, including reduced activity of the supplementary motor area in people with PD who experience freezing (freezers) (Snijders et al. 2011), and alterations in cerebellar and brainstem activity (Cremers et al. 2012a; Wai et al. 2012). Together, these results provide a promising groundwork for continued work on the neural underpinnings of gait dysfunction in people with PD. For example, previous studies have primarily focused on simple gait imagery tasks (i.e. forward walking), with little work focusing on how neural activity is altered during more complex gait tasks. Investigating neural control of complex gait tasks is critical to understand the underlying causes of gait dysfunction in PD, as 1) gait dysfunction in PD is more pronounced during these tasks, and 2) recent work in healthy adults suggests complex gait tasks may alter neural activity in regions of the brain which are dysfunctional in PD (i.e. putamen and SMA; (Wagner et al. 2008; Godde and Voelcker-Rehage 2010)).

One recent study has begun to look at the neural activity of PD during complex gait tasks, including gait initiation and stepping over obstacles, showing possible



alterations in those with PD in lateral pre-motor regions, pre-cuneus, and inferior parietal lobule (Wai et al. 2012). However, although this report provided important insights into PD gait, the authors acknowledged that they did not assess the ability of participants to imagine movements or imagery compliance during scans raising a question of task performance differences across groups. In addition, other gait tasks, such as turning and (to a lesser degree) backward walking, are also associated with gait dysfunction in PD. Assessing BOLD signal during complex gait tasks which are particularly difficult for those with PD may underscore the differences between healthy older adults and PD. Therefore, our second aim was to assess the neural pathophysiology of locomotion in PD during complex gait-like tasks. We chose to use gait imagery during fMRI to assess these group (PD and control) and task (simple and complex gait imagery) effects.

In addition, no studies to date have investigated how tasks of varying complexity affect those with PD who freeze. Complex gait tasks such as turning are the most common trigger for FOG, suggesting certain components of this task are highly related to freezing. Understanding how brain signals are altered in those with PD who freeze during turning may provide valuable insights into the neural underpinnings of freezing. Our third and final aim was to determine the brain mechanisms associated with FOG in people with PD. To this end, we measured BOLD signal during imagined forward gait and complex tasks which commonly elicit freezing such as backward walking and turning.

### Imagery as a Probe of Locomotor Activity

There are few methods currently available to probe the neural circuitry underlying full body motions such as locomotion, and even fewer that allow collection of signals with high spatial and temporal resolution. One commonly used technique for this purpose is the collection of BOLD signal during gait imagery. This approach, which relies upon the large degree of overlap between actual and imagined movements (Jeannerod and Decety 1995; Porro et al. 1996; Deiber et al. 1998; Miyai et al. 2001; la Fougere et al. 2010), has been used to gain a better understand of the supra-spinal components of locomotion in healthy younger and older adults (Malouin et al. 2003; Jahn and Zwergal 2010; Snijders et al. 2011; Zwergal et al. 2012). There are several benefits to this type of data collection. First, compared to other cortical and subcortical brain imaging techniques used in humans, fMRI provides relatively high spatial (~2-4mm) and temporal (~2 sec) resolution. Second, imagery of gait allows individuals to imagine movements similarly across groups. This is particularly important when investigating those with reduced over ground gait speed, as alterations in speed of movement can significantly affect BOLD signal (Jahn et al. 2004; Suzuki et al. 2004; Jahn et al. 2008; Harada et al. 2009; Cremers et al. 2012b). Finally, with this paradigm, it is possible to differentiate descending neural signals from proprioceptive signals or the integration of proprioceptive information into motor plans, which may be altered in those with PD (Almeida et al. 2005).

A major downfall of motor imagery is the inability to precisely monitor the participant's adherence to the assigned task. However, several methods have been devised to circumvent this limitation. For example, in the current projects, two primary steps were taken. First, all participants were screened for their ability to imagine

movements. The Kinesthetic Visual Imagery Questionnaire (KVIQ) was administered to all participants, and those who averaged less than a 3 on either the kinesthetic or visual components (indicating “Moderately clear/vivid movement imagery”), were not scanned. The Gait Imagery Questionnaire, GIQ (Pickett et al. 2012), which measures one’s ability to imagine gait specifically, was also collected to compare each group’s ability to imagine locomotion. Second, we assessed whether participants were adhering to tasks during scans. Participants imagined completing both long and short distances of each gait task while in the scanner. If the time necessary to complete gait tasks was not modulated across short and long imagery bouts, data was not included for analysis.

Another potential pitfall of gait imagery in those with PD is the possibility that those with PD may imagine more poorly while “Off” anti-Parkinson medication with respect to “On” medication, in part due to the documented alterations of activity in PD in regions, such as the SMA, that play a role in both actual and imagined locomotion (la Fougere et al. 2010). However, recent evidence suggests that there is little difference between imagery “On” and “Off” anti-Parkinson medication (Peterson et al. 2012; Appendix 1).

## **SUMMARY**

There is currently not a clear understanding of the factors underlying gait dysfunction and FOG in people with PD. Though pathologies of movement (i.e. coordination of steps) and brain function have been suggested to be related to gait dysfunction and FOG, little work has focused on measuring these factors during tasks which typically elicit gait dysfunction and freezing.

Therefore, the overall goal of this project is to better understand how pathologies of movement and brain function are associated with gait dysfunction and FOG. Our approach was to measuring these factors during simple tasks (forward walking) as well as complex gait tasks (backward, turning) which amplify dysfunction and FOG. We chose this approach in an attempt to elicit more pronounced differences between freezers and non-freezers (and PD and controls).

In experiment 1, we investigated how bilateral coordination of steps during gait is altered during simple (forward, turning in large circles) and complex (backward, turning in small circles) gait tasks to understand how coordination of steps may be related to gait dysfunction and freezing. In experiment two, we assessed the BOLD response (captured via fMRI) during imagined forward walking, backward walking, and turning in PD and controls to understand the brain mechanisms underlying gait dysfunction in PD. In experiment 3, we assessed BOLD response during imagined walking in freezers and non-freezers to elucidate neural responses related specifically to FOG.

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## **Chapter 2: Evidence for a Relationship between Bilateral Coordination during Complex Gait Tasks and Freezing of Gait in Parkinson's Disease**

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## **ABSTRACT**

**PURPOSE:** Freezing of gait is a debilitating and common gait disturbance observed in individuals with Parkinson's disease (PD). Although the underlying mechanisms of freezing remain unclear, bilateral coordination of steps, measured as a phase coordination index, has been suggested to be related to freezing. Phase coordination index has not, however, been measured during tasks associated with freezing such as turning and backward walking. Understanding how bilateral coordination changes during tasks associated with freezing may improve our understanding of the causes of freezing.

**METHODS:** Twelve individuals with PD who freeze (freezers), 19 individuals with PD who do not freeze (non-freezers), and 10 healthy, age-matched older adults participated. General motor disease severity and freezing severity were assessed. Phase coordination index was calculated for all subjects during forward walking, backward walking, continuous turning in small radius circles, and turning in large radius circles.

**RESULTS:** Freezers and non-freezers had similar disease duration and general motor severity. Stepping coordination was significantly worse in freezers compared to non-freezers and controls. Turning and backward walking, tasks related to freezing, resulted in worse coordination with respect to forward walking. Coordination was associated with severity of freezing scores such that worse coordination was correlated with more severe freezing.

**CONCLUSIONS:** These results provide evidence that stepping coordination is related to freezing in people with PD. Identifying variables associated with freezing may

provide insights into factors underlying this symptom, and may inform rehabilitative interventions to reduce its occurrence in PD.



## INTRODUCTION

Freezing of gait (FOG) is a paroxysmal gait disturbance characterized as a sudden inability to produce effective stepping (Giladi and Nieuwboer 2008). FOG affects 50% of individuals with Parkinson's disease (PD), is directly related to falls (Bloem et al. 2004), and is one of the most disabling and distressing symptoms of PD (Backer 2006). Despite the burden of FOG, its underlying causes are unclear.

FOG can occur during all types of gait, however it is most common during turning (Schaafsma et al. 2003). It is possible that the increase in FOG events during turning may be due in part to the asymmetric nature of the task. In particular, the temporal and spatial asymmetry of steps during turning (i.e. inner and outer legs cover different distances (Courtine and Schieppati 2003a)) represents a more complex control problem than forward walking. The increased complexity of interlimb timing during turning may pose an additional challenge to the bilateral coordination of steps and could contribute to FOG (Plotnik and Hausdorff 2008; Fasano et al. 2011). Recent studies have also suggested a potential relationship between backward walking and FOG. Though less evidence exists relating backward walking to FOG than turning to FOG, several gait characteristics, such as asymmetry, step length, and Functional Ambulation Profile (FAP (Nelson 2008)), are worsened in PD during backward walking with respect to forward. Further, individuals with PD who experience FOG (PD+FOG) exhibit more dysfunction during backward walking than those with PD not experiencing FOG (PD-FOG) (Hackney and Earhart 2009). Though evidence directly linking backward walking to FOG is lacking, backward walking represents a complex locomotor task which is

more difficult for PD+FOG. Despite the dysfunction of backwards gait in PD+FOG, the link between backward gait and FOG is not well understood.

Several studies have investigated the coordination of bilateral stepping during gait, as quantified by the Phase Coordination Index (PCI). PCI has been shown to become worse with both age and PD (Plotnik et al. 2005; Plotnik et al. 2007; Plotnik et al. 2008; Plotnik and Hausdorff 2008; Plotnik et al. 2009a; Plotnik et al. 2009b; Fasano et al. 2011). Interestingly, among those with PD, PD+FOG subjects have worse coordination than PD-FOG (Plotnik et al. 2008). These results, along with prior research suggesting FOG to be associated with abnormalities of spatiotemporal characteristics (Nieuwboer et al. 2001) and sequencing of gait (Ivansek et al. 2006), led to the hypothesis that freezing may be related to reduced bilateral coordination of stepping (Plotnik and Hausdorff 2008). One limitation of these studies is that they only describe coordination of steps during forward walking. It remains unclear how coordination changes during walking tasks more commonly associated with freezing, e.g., turning and backward walking. If a relationship exists between FOG and coordination, tasks associated with freezing should result in more poorly coordinated gait, represented by higher PCI. If, however, PCI is not altered across these tasks, it would be unlikely that coordination is directly related to FOG. Said differently, if coordination and FOG are related, one would expect a co-variance of these measures across gait tasks.

Identifying factors associated with FOG may provide important insight into the underlying mechanisms of FOG, potentially informing rehabilitative interventions to reduce the incidence of FOG. Further, FOG is notoriously difficult to elicit in a laboratory setting. Identifying quantifiable variables that are closely related to FOG, such as PCI, is

a first step in establishing surrogate measures for this symptom. These variables could be used to identify individuals at risk for FOG and track the progression of this symptom. Therefore, the goal of this study was to better understand the relationship between bilateral coordination of stepping and FOG. We determined how tasks associated with freezing (turning in small radius circles and backward walking) affected coordination with respect to tasks which elicit freezing less often (forward walking and turning in large radius circles). We hypothesized that tasks associated with freezing would result in higher PCI, i.e., worse coordination, and that this effect would be most pronounced in individuals who experience freezing (PD+FOG). We further hypothesized that there would be a direct relationship between FOG severity and PCI.

## **METHODS**

### Participants

Ten healthy older adults, 19 “non-freezers” (PD-FOG), and 12 “freezers” (PD+FOG) participated (Table 1). Individuals with PD completed the Freezing of Gait Questionnaire (FOG-Q (Giladi et al. 2000)) to assess freezing severity and to classify individuals as PD+FOG or PD-FOG. The FOG-Q is a self-assessment of FOG which consists of 6 questions, each scored from 0 to 4 (Maximum score- 24 points), with higher scores representing more severe freezing. Four questions address the frequency and duration of FOG and two questions assess general gait impairment. Patients were classified as PD+FOG if they answered  $\geq 2$  on question three of the FOG-Q (Plotnik et al. 2008), representing a frequency of FOG of at least once a week. Total FOG-Q (sum of scores on all questions) was determined for individuals with PD to assess the severity

of FOG. The two questions not directly associated with FOG, as well as the criterion of a score of  $\geq 2$  on question 3 meant individuals classified as PD-FOG could have a non-zero FOG-Q total score. PD groups were matched for disease duration and severity, and all groups were matched for age. Disease severity was measured by part 3 (motor subscale) of the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS), as well as Hoehn and Yahr staging (Hoehn and Yahr 1967). Individuals were excluded if they had any injury to the lower limbs within six months of testing, were unable to walk unassisted, or had neurological disorders other than PD. Individuals with PD were tested after a minimum 12-hour withdrawal from anti-parkinsonian medications. Experimental protocols were approved by the Human Research Protection Office of Washington University in St. Louis, and were in accordance with the Declaration of Helsinki. All subjects provided informed written consent prior to enrollment.

### Protocol

Six round footswitches (20mm diameter, 1mm thick; Motion Lab Systems; Baton Rouge, LA) were placed on the sole of each shoe (3 near the toes, and 3 near the heel) to determine the time of heel strike and toe off. Subjects then completed the following 6 gait tasks in random order: forward walking, backward walking, turning to the left and right in a small radius circle (radius = 0.6m), and turning to the left and right in a large radius circle (radius = 3m). Large radius turns have been suggested as a technique to reduce FOG during turning (Morris 2006), and were included in this study to serve as a contrast for the small radius condition. Five to 8 trials of a 10 meter walk were completed for both forward and backward walking. One 60 second large radius circle

trial was completed to the left and right, and three to five 20 second bouts of small radius turns were completed to the left and right. Subjects were instructed to perform all tasks at a comfortable, preferred pace. A telemetered system (Konigsberg Instruments, Pasadena, CA) transmitted footswitch data to the collection computer at 1000 Hz. Digital video was also acquired for each task. Data were collected using Cortex software (Motion Analysis Corp., Santa Rosa, CA USA).

### Data analysis

PCI is a variable which integrates the accuracy and consistency of left- right stepping phases. The derivation of PCI has been described previously (Plotnik et al. 2007). Briefly, PCI is the summation of two measures:

$\varphi_{CV}$  – the coefficient of variation of the series of relative timing of the stepping of one leg (i.e. the timing of its heel strike) with respect to the gait cycle defined by 2 consecutive heel strikes (stride) of the other leg. The relative timing is represented by the value  $\varphi$  in degrees, which is the outcome of the time normalization with respect to the stride scaled to 360°. The ideal anti-phase stepping pattern yields  $\varphi=180^\circ$ .  $\varphi_{CV}$  represents the *consistency* of phase generation.

$\varphi_{ABS}$  - the mean value of a series of absolute differences between the values of  $\varphi_i$  (i.e, the phase calculated for the  $i$ th stride) and 180°.

$$\varphi_{ABS} = \overline{|\varphi_i - 180^\circ|}$$

$\varphi_{ABS}$  represents the overall *accuracy* in generating anti-phased stepping across all the steps of a walking trial.

Phase coordination index was calculated as the sum of  $\varphi_{CV}$  and  $P\varphi_{ABS}$ :

$$PCI = \varphi_{CV} + P\varphi_{ABS}$$

where  $P\phi_{ABS} = 100 \cdot (\phi_{ABS}/180)$ . Therefore, PCI consists of two relative values ( $\phi_{CV}$  and  $P\phi_{ABS}$ ), both given as percentages. Periods of freezing and festination were identified by watching videos of gait which were time-synchronized with footswitch data. The period of festination and freezing, along with approximately one second before and after this period, was omitted from data analysis.

### Statistical analysis

A one-way ANOVA determined statistical differences across age, and independent sample t-tests determined statistical differences for all other subject characteristics. As PCI was not different while turning to the left and right for small or large radius turns (see Results), PCI was collapsed across turning directions, leaving four gait tasks (forward walking, backward walking, large radius turns, and small radius turns). Therefore, a two-way mixed model ANOVA (group, 3 levels x walking condition, 4 levels) was used to determine the effects of both group and gait task on PCI as well as both components of PCI ( $P\phi_{ABS}$  and  $\phi_{CV}$ , see methods). Bonferroni correction for multiple comparisons was applied to all post hoc analyses. A recent review by Nutt and colleagues noted that while not all individuals with PD will experience FOG, those who do are likely on a spectrum of freezing severity (Nutt et al. 2011). With this in mind, we further tested the relationship between FOG and coordination by calculating Spearman's  $\rho$  correlation statistic between severity of freezing (total FOG-Q score) and mean PCI across all tasks. Statistical analyses were run in SPSS (Chicago, IL).

## **RESULTS**

There was no age difference between groups (Table 1;  $p=0.75$ ), and individuals with PD+FOG and PD-FOG were of similar disease severity (MDS-UPDRS-3,  $p=0.43$ ; Hoehn & Yahr stage,  $p=0.26$ ) and duration ( $p=0.44$ ). The PD+FOG group exhibited significantly higher ( $p<0.001$ ) total FOG-Q scores than the PD-FOG group (Table 1). Seven of twelve individuals in the PD+FOG group experienced FOG during the gait protocol. Within this group, backward walking and turning in small radius circles elicited freezing most frequently. Twenty five, 29, and 27 freezing events were observed during turning in small radius circles to the left, small radius circles to the right, and backward walking, respectively. In contrast, only one, two, and 7 freezing events were observed during forward walking, turning in large radius circles to the left and turning in large radius circles to the right, respectively.

As PCI data were not different when turning to the left or right (large turns:  $p=0.37$ ; small turns:  $p=0.63$ ; paired sample t-test), data from both turn directions were combined for large and small turns. Exemplar data from one control, one PD-FOG, and one PD+FOG subject are shown in Figure 2.1. PCI values were smallest during forward walking, increased slightly (i.e. coordination worsened) during large radius turning, further increased during backward walking, and were highest during small radius turning, where the highest shifts from anti-phase coordination (i.e,  $180^\circ$ ) were observed. In all walking conditions, the control subject had the lowest and the PD+FOG subject had the highest PCI values.

These differences were also observed at the group level (Figure 2.2), as a significant group effect was present ( $F_{2,38}=16.5$ ;  $p<0.001$ ). Post hoc tests revealed PD+FOG had significantly higher PCI than PD-FOG ( $p=0.01$ ), and PD-FOG had

significantly higher PCI than controls ( $p=0.005$ ; Bonferroni corrected). There was also a significant task effect ( $F_{2,83}=78$ ,  $p<0.001$ ). Post hoc analyses showed PCI was statistically higher (i.e., worse bilateral coordination) when turning in small radius circles than when walking forward ( $p<0.001$ ), turning in large radius circles ( $p<0.001$ ), or walking backward ( $p=0.002$ ; Figure 2.2). Backward walking also resulted in higher PCI than turning in large radius circles ( $p<0.001$ ) and forward walking ( $p<0.001$ ). Large turns had a significant effect on PCI with respect to forward ( $p=0.002$ ), but this effect was substantially less pronounced than the effect of small turns or backward walking on PCI. In addition, there was a task by group interaction effect ( $F_{4,83}=3.0$ ,  $p=0.02$ ) such that the difference in PCI across groups was largest during backward walking and small turns. The two subcomponents of PCI,  $P\phi_{ABS}$  and  $\phi_{CV}$ , represent the temporal accuracy and consistency of steps, respectively (see Methods). Both subcomponents exhibited significant group and task effects similarly to PCI ( $P\phi_{ABS}$ : Group effect:  $F_{2,38}=14.9$ ,  $p<0.001$ , Task effect  $F_{2,71}=44$ ,  $p<0.001$ ;  $\phi_{CV}$ : Group effect  $F_{2,38}=13.6$ ,  $p<0.001$ , Task effect  $F_{2,87}=95$ ,  $p<0.001$ ).

A significant relationship was observed between freezing severity (total FOG-Q score) and global coordination of steps (mean PCI across all tasks- 'global PCI') such that higher FOG-Q scores were associated with higher global PCI (Spearman's  $\rho=0.54$ ,  $p=0.002$ , Figure 2.3). Additional analyses confirmed that PCI values for each walking task (forward, backward, large radius turns, and small radius turns) were each statistically significantly related to total FOG-Q score ( $0.37 < \text{Spearman's } \rho < 0.46$ ,  $0.009 < p < 0.04$ , data not shown). These correlations were shown to arise primarily from the PD+FOG group. When global PCI – FOG-Q correlation was run on PD-FOG and



PD+FOG groups separately, only the PD+FOG group showed a significant relationship (global PCI vs. FOG-Q for PD+FOG: Spearman's  $\rho=0.85$ ,  $p<0.001$ ; for PD-FOG group: Spearman's  $\rho=0.11$ ,  $p=0.65$ ).

## **DISCUSSION**

Previous reports suggest spatial and temporal gait kinematics, including bilateral coordination of stepping, may be altered in individuals who experience freezing (Nieuwboer et al. 2001; Nieuwboer et al. 2004; Iansek et al. 2006; Nieuwboer et al. 2007; Plotnik and Hausdorff 2008). To better understand the relationship between bilateral coordination and FOG, we measured coordination during turning and backward walking, gait tasks associated with freezing. Our three primary results showed that 1) PD+FOG had worse coordination than PD-FOG, 2) gait tasks related to FOG resulted in worse coordination than those that less commonly elicit FOG, and 3) a direct correlation was observed between severity of freezing and coordination, with worse coordination predicting more severe freezing symptoms. Together, these results provide additional support for a relationship between coordination of steps and FOG.

It has been hypothesized that there may be a threshold for gait characteristics (including bilateral coordination of steps) which when crossed, triggers freezing of gait (Plotnik and Hausdorff 2008). This threshold may be modulated by numerous factors, including how much one attends to the gait task, environmental stressors (e.g., crowds, doorways), and the individual's postural stability. In the current study, all groups exhibited worse coordination during tasks associated with FOG with respect to forward walking. Therefore, the higher PCI during turning and backward walking, particularly in

PD+FOG, may place one near this hypothetical FOG threshold, potentially contributing to the increased frequency of freezing during these tasks. In addition, correlation analyses showed individuals with PD who exhibit worse coordination experience more severe FOG. This relationship was strongest in the PD+FOG group and suggests the possibility that amongst those who freeze, coordination may modulate freezing severity. However, correlation results must be interpreted with caution, as only 31 individuals with PD (12 with PD+FOG), were analyzed. Future research with larger sample sizes is necessary to better understand this observation.

The reason some tasks elicit worse coordination and frequent freezing is not well understood. It is possible that tasks such as turning pose an increased challenge to lower limb coordination with respect to forward walking, due in part to the inherent asymmetries of inner and outer legs during this task (Courtine and Schieppati 2003a; Courtine and Schieppati 2003b). This increased challenge to coordination posed by turning, along with the already diminished coordination of those with PD (Almeida et al. 2002; Abe et al. 2003; Plotnik et al. 2007; Plotnik et al. 2008; Wu et al. 2010) may bring subjects closer to the hypothetical FOG threshold described above. Indeed, results from the current study show that the higher PCI during turns with respect to forward gait is more pronounced in those with PD than controls (as noted by the task by group interaction), suggesting that individuals with PD who are prone to freezing may have particular difficulty meeting the coordination challenges posed by turning.

We also assessed coordination of steps during backward walking, a task without the inherent step length asymmetry of turning. Similarly to turning, coordination during backward walking was worse than forward walking. Among all tasks presented in this

study, prolonged backward gait (i.e., ~10 m) is the most foreign to gait usually performed during daily living conditions. It is therefore suggested that subjects had to invest attention and cognitive resources when confronted with this relatively unfamiliar task. It is possible that the increased cognitive faculties required to spatially orient and plan backward gait may interfere with the autonomous activation of gait. Therefore, the relative novelty and complexity of this gait task may result in less automated gait and reduced bilateral coordination (Plotnik et al. 2009a).

Results from a recent report show that freezers turn with a wider arc than non-freezers (Willems et al. 2007). In addition, walking in large arc circles is a technique used in the clinic to improve turning in freezers (Morris 2006). In the current study, coordination of steps was significantly better during large turns than during small turns. The improved coordination during large radius turning with respect to small radius turning may, in part, drive the strategy observed in PD+FOG to walk in large radius circles while turning. This improvement in coordination could pull individuals further away from a FOG threshold (Plotnik and Hausdorff 2008) and may partially explain why large turns seem to reduce FOG during turning.

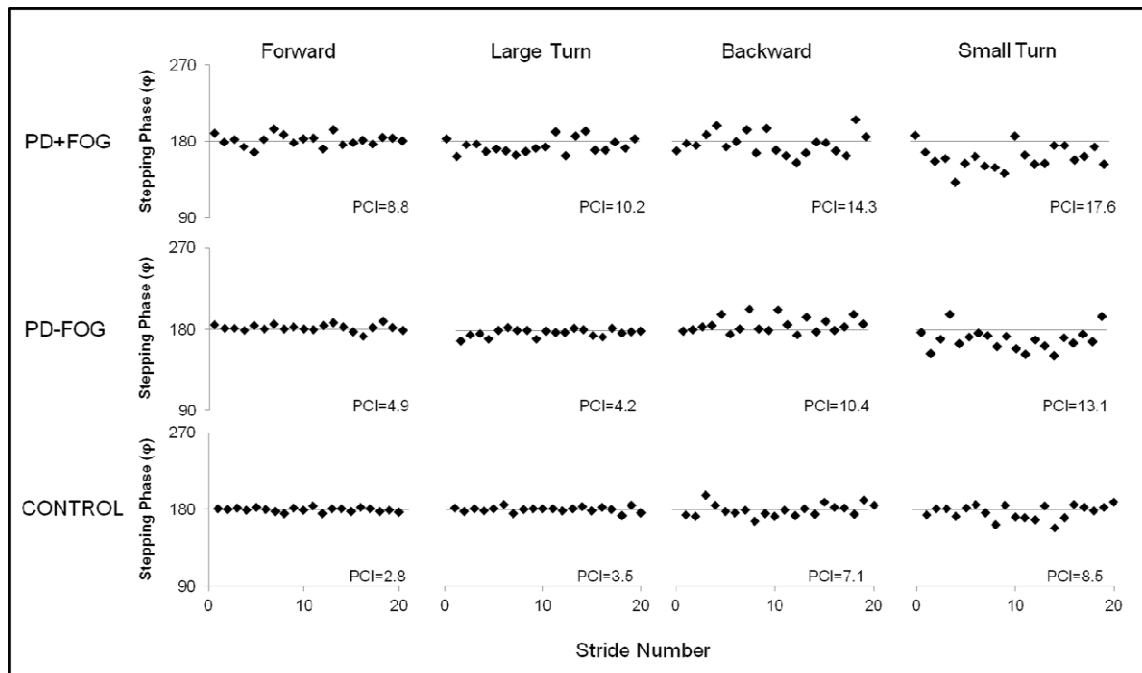
Other factors have been shown to increase the prevalence of FOG. For example, if the individual is stressed, or distracted from the gait task as with dual tasking, freezing is more common (Camicioli et al. 1998). Other external stimuli such as transitions in flooring or doorways can pull attention from gait and elicit freezing (Almeida and Lebold 2010; Cowie et al. 2010). Walking with split attention also results in worse coordination (Plotnik et al. 2009a), exemplifying a covariance of coordination and FOG. Gait initiation, like turning, may be considered an instance of high temporal asymmetry of

steps, needing a large degree of lower limb coordination to be completed effectively. The increased coordination needs during asymmetric tasks such as turning and gait initiation may be related to the high incidence of FOG during these tasks. These studies, in conjunction with results from the current investigation further support the relationship between bilateral coordination of steps and FOG.

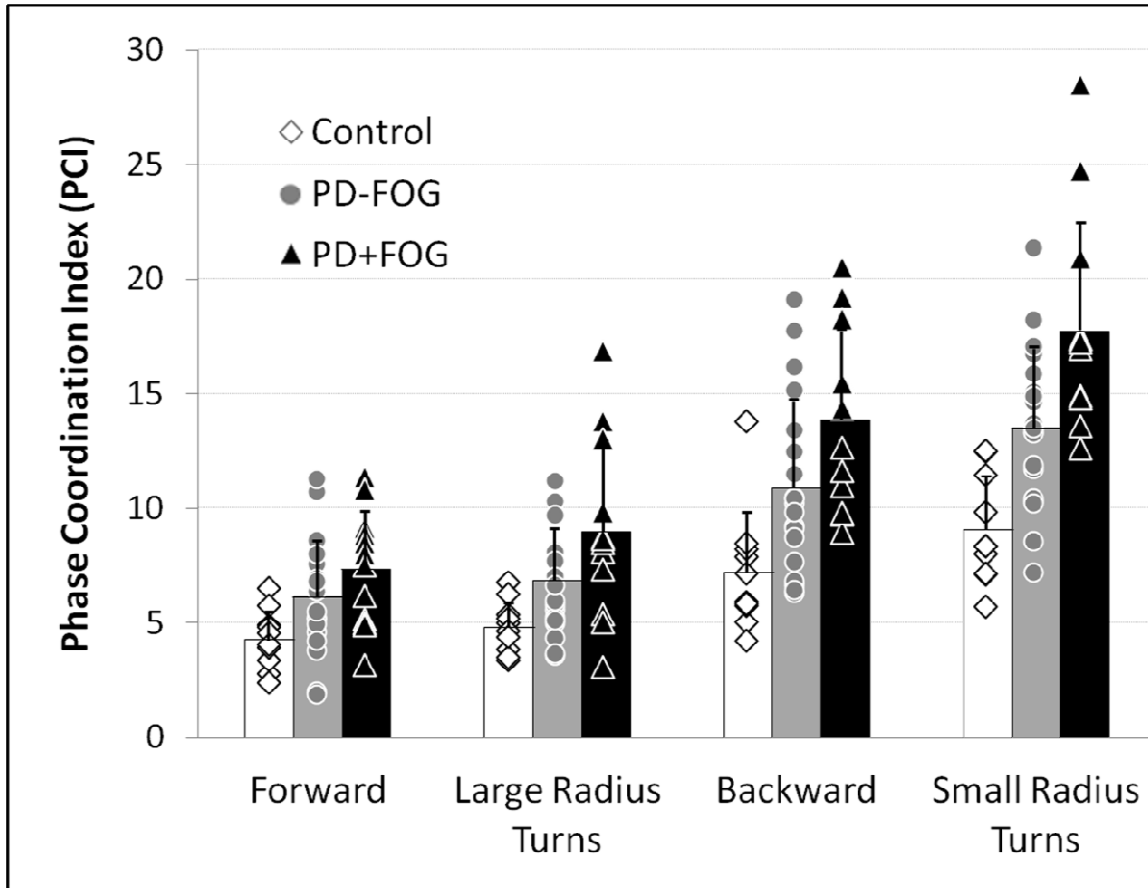
### Conclusions

Previous literature suggests that impaired coordination of steps during gait may be related to, or even on the causal pathway of FOG. The present study provides support for a relationship between these variables in three ways. Coordination of steps was 1) worse in those who experience freezing compared to those who do not, 2) worse during tasks associated with freezing, and 3) directly correlated to freezing severity. Impaired coordination of steps likely contributes to FOG.

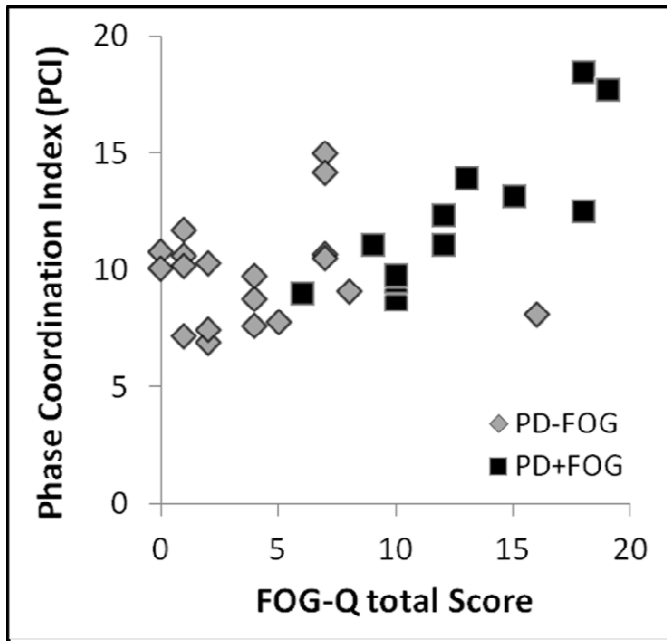
**Figure 2.1:** Stepping phase ( $\phi$ ) data of one subject from each group (control, PD-FOG, PD+FOG) for different walking tasks.



**Figure 2.2:** Mean and SD of Phase coordination index (PCI) for PD+FOG, PD-FOG, and controls across gait tasks. Individual subject data plotted around mean of each group. Significant task ( $p < 0.001$ ) and group ( $p < 0.001$ ) effects were observed.



**Figure 2.3:** Scatter plot of mean PCI across tasks (global PCI) and FOG-Q for all subjects with PD. PCI and FOG-Q were significantly correlated ( $r=0.54$ ;  $r^2=0.29$ ;  $p=0.002$ ).



**Table 2.1:** Subject characteristics; Mean (SD).

	Control n=10	PD-FOG n=19	PD+FOG n=12	p-value
Age	69 (11)	71 (9)	72 (9)	0.75
Yrs with PD	-	6.6 (5.1)	8.0 (4.5)	0.44
MDS-UPDRS-3	-	41.6 (6.4)	45.5 (15.2)	0.34
Hoehn & Yahr Stage	-	2.37 (0.40)	2.63 (0.83)	0.26
FOG-Q Total score	-	4.2 (3.9)	12.6 (4.1)	<0.001



**Table 2.2:** PCI,  $\phi_{CV}$ , and  $P\phi_{ABS}$  for all subjects and across tasks.

	Forward			Large Radius Turns			Backward			Small Radius Turns		
	PD-			PD-			PD-			PD-		
	Con	FOG	PD+FOG	Con	FOG	PD+FOG	Con	PD-FOG	PD+FOG	Con	PD-FOG	PD+FOG
PCI*	4.3(1.3)	6.1(2.5)	7.3(2.5)	4.7(1.0)	6.8(2.2)	9.0(3.9)	7.3(2.7)	10.9(3.8)	13.9(3.9)	9.1(2.4)	13.5(3.5)	17.7(4.7)
$\phi_{CV}$ *	2.0(0.5)	3.0(1.2)	3.7(1.2)	2.4(0.5)	3.4(1.2)	4.4(1.9)	3.7(1.1)	5.6(1.9)	6.4(1.4)	4.4(1.2)	6.5(1.8)	8.3(2.0)
$P\phi_{ABS}$ *	2.3(1.1)	3.2(1.4)	3.7(1.5)	2.3(0.8)	3.5(1.2)	4.6(2.2)	3.6(1.6)	5.3(2.1)	7.4(3.2)	4.7(1.5)	7.0(2.2)	9.4(2.2)

\* Significant group and task effects

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## **Chapter 3: Brain Activity during Complex Imagined Gait Tasks in Parkinson Disease**

This chapter is in preparation:

Peterson DS, Pickett KA, Duncan R, Perlmutter JS, Earhart GM. Brain Activity during Complex Imagined Gait Tasks in Parkinson Disease

## **ABSTRACT**

**PURPOSE:** The pathophysiology underlying gait dysfunction in those with Parkinson disease (PD) is not well understood. Motor imagery during functional magnetic resonance imaging (fMRI) is a commonly used technique to assess brain function during tasks, such as walking, that cannot be completed in a scanner. The goal of this study was to use gait imagery to assess the neural pathophysiology of locomotion in PD.

**METHODS:** We used fMRI to measure blood oxygen level dependent (BOLD) signals while participants imagined simple (walking forward), and complex (backward, and turning in small (0.6m radius) circles to the left and right) gait tasks. BOLD responses were analyzed in five a-priori locomotor regions: supplementary motor area (SMA), globus pallidus (GP), putamen, mesencephalic locomotor region (MLR), and cerebellar locomotor region (CLR). To determine whether BOLD signals correlated with a functional measure of actual walking, we also measured overground walking velocity.

**RESULTS:** In the SMA, complex gait imagery produced increased BOLD responses in those with PD compared to controls, whereas simple gait imagery did not. Across all tasks, PD exhibited reduced BOLD responses in the GP compared to controls. Finally, in those with PD, walking speed correlated with BOLD responses in several locomotor regions.

**CONCLUSIONS:** These results further elucidate the changes in activity of locomotor regions during gait imagery tasks in PD and in controls and underscore the importance of testing simple and complex tasks. Further, we provide evidence

supporting a relationship between increased BOLD responses in locomotor regions and improved walking function.

## INTRODUCTION

People with Parkinson disease (PD) frequently have gait abnormalities impacting stride length (Morris et al. 1996), step frequency (Ivansek et al. 2006), side-to-side step coordination (Plotnik et al. 2008), and variability (Hausdorff et al. 1998) of steps. In addition, complex gait tasks such as turning and backward walking exacerbate gait dysfunction, possibly due to the increased need for coordination and balance control (Schaafsma et al. 2003; Hackney and Earhart 2009; Spildooren et al. 2010; Peterson et al. 2012b). These gait difficulties lead to falls (Foreman et al. 2011) and reduce quality of life (Muslimovic et al. 2008). Rational approaches to therapeutic interventions require a better understanding of the pathophysiology underlying these gait abnormalities.

Motor imagery during functional magnetic resonance imaging (fMRI) is a commonly used technique which allows investigators to assess brain activity during whole-body motions, such as locomotion, which cannot be overtly implemented in the scanner. This approach relies heavily on the substantial overlap in supraspinal activation during imagined and overt movements (Jeannerod and Decety 1995; Porro et al. 1996; Deiber et al. 1998; Miyai et al. 2001) including walking (Miyai et al. 2001; la Fougere et al. 2010). Recent investigations have used gait imagery during fMRI to identify neural regions related to walking. The so-called “locomotor regions” identified via this method overlap with several locomotor centers in quadrupeds (Orlovsky 1969; Shik et al. 1969; Mori et al. 1999), and include the supplementary motor area (SMA), basal ganglia (BG), cerebellar locomotor region (CLR), and tegmental regions of the brainstem (including the mesencephalic locomotor region; MLR), among others (Jahn et al. 2008a; Jahn and Zwergal 2010).



Individuals with PD exhibit altered activation patterns and brain atrophy in many of these locomotor regions. For example, across a variety of motor and imagined tasks, pre-motor regions (i.e. SMA) (Hanakawa et al. 1999; Malouin et al. 2003; Snijders et al. 2011), basal ganglia (Kish et al. 1988; Bruck et al. 2006; Prodoehl et al. 2010; Spraker et al. 2010), CLR (Hanakawa et al. 1999; Jahn et al. 2008b; Schweder et al. 2010; Cremers et al. 2012a), and MLR (Karachi et al. 2010; Snijders et al. 2011; Cremers et al. 2012a), have altered activity in people with PD relative to healthy older adults. Further, regions including the pedunculopontine nucleus (PPN), a subsection of the MLR, are atrophied in those with PD with respect to healthy older adults (Hirsch et al. 1987). The overlap between brain regions associated with locomotion and altered activity in PD spurred several recent studies to investigate the neural control of gait in PD (Hanakawa et al. 1999; Snijders et al. 2011; Cremers et al. 2012a; Wai et al. 2012). Despite some inconsistent findings across studies, gait imagery in those with PD typically produces altered activation in several locomotor regions (i.e. SMA (Hanakawa et al. 1999), CLR (Hanakawa et al. 1999; Cremers et al. 2012a), and MLR (Cremers et al. 2012a)).

Previous studies investigating supraspinal control of locomotion in those with PD have focused primarily on simple gait imagery tasks such as forward walking. However, assessments of BOLD signal during complex gait imagery may enhance differences between healthy adults and those with PD, providing additional insights into the neural dysfunction underlying PD gait abnormalities. Indeed, recent work in healthy adults suggests complex gait imagery may alter brain activation in regions which are dysfunctional in PD including the putamen and SMA (Wagner et al. 2008; Godde and

Voelcker-Rehage 2010). One study of imagery of gait initiation and stepping over obstacles reported that those with PD had altered BOLD responses in lateral pre-motor regions, pre-cuneus, and inferior parietal lobule (Wai et al. 2012). Although this report provided important insights into neural control of gait in PD, the authors acknowledged that they did not assess the ability of participants to imagine movements or imagery compliance during scans raising a question of task performance differences across groups. Further, people with PD have gait dysfunction with other complex gait tasks, such as turning and backward walking that remain to be investigated.

Therefore, we used gait imagery during fMRI to investigate the neural components of gait dysfunction in PD during both simple and complex gait imagery tasks. In addition, we correlated regional BOLD signals to a measure of locomotor function, overground walking speed. We hypothesized that during imagery of complex gait tasks (turning, backward walking), those with PD would exhibit reduced BOLD signal in the SMA (Hanakawa et al. 1999; Snijders et al. 2011), BG (putamen and GP) (Prodoehl et al. 2010), and MLR (Cremers et al. 2012a), and increased BOLD signal in the CLR (Hanakawa et al. 1999; Palmer et al. 2010). Further, we expected BOLD signal in locomotor regions of interest to positively correlate with actual overground walking velocity.

## **METHODS**

### Participants

Standard clinical criteria were used to diagnose idiopathic PD (Hughes et al. 1992; Racette et al. 1999). All participants had to be free of lower limb injuries, not have

any contraindications for MRI, and demonstrate at least a moderate ability to imagine motor tasks. Specifically, participants were included if they averaged  $\geq 3$  on both the visual and kinesthetic components of the Kinesthetic Visual Imagery Questionnaire (KVIQ) (Malouin et al. 2007), representing at least “moderate” clarity and intensity of imagined movements. This imagery vividness threshold excluded nine controls and seven individuals with PD (no fMRI data were collected). Participants were excluded if they had any neurological problems other than PD or cognitive dysfunction (Mini Mental State Exam; MMSE  $< 27$ ). Two of the PD group and two of the control group were left-handed. After screening, fMRI data were collected from 27 control and 27 PD participants.

All data collection, including the Movement Disorders society Unified Parkinson Disease Rating Scale motor sub-score (MDS-UPDRS-III) to measure motor severity of parkinsonism, was conducted after a 12-hour withdrawal of anti-Parkinson medication. All participants provided informed written consent prior to participation in accord with the procedures approved by the Human Research Protection Office of the Washington University School of Medicine and the Declaration of Helsinki.

## Procedure

### *Gait training*

Participants were trained to complete five overground locomotor tasks: forward walking, backward walking, turning to the left in small radius ( $r=0.6\text{m}$ ) circles, turning to the right in small radius circles, and standing quietly. Participants were instructed to walk at a natural, comfortable speed for each task. Each participant completed each

task at two different distances (4 and 8 meters for forward and backward gait, and 2 or 3 revolutions for turning). The time necessary to complete each gait task was recorded. Training lasted approximately 20 minutes, in which participants completed each task a minimum of 2 times. Participants also practiced imagining each task. The Gait Imagery Questionnaire (GIQ) (Pickett et al. 2012) was also administered at this time to assess the kinesthetic and visual vividness of gait imagery. Participants were not given feedback on their actual overground gait times and were not coached to imagine walking faster or slower based on actual walking times. We used this approach because we wanted subjects to imagine walking at a self-selected pace and because coaching participants to alter imagery times based on actual walking times could have resulted in differences in gait imagery times between groups during fMRI. In addition, imagining walking faster than preferred can alter BOLD signal (Suzuki et al. 2004; Karachi et al. 2010; Cremers et al. 2012b).

### *Imaging*

MR was done with a Siemens 3T Magnetom TrioTim scanner. A T1-weighted sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=8°, 0.9mm<sup>3</sup>, 8:09 min) scan was collected for identification of ROIs and T2\* co-registration. We collected three T2\*-weighted gradient echo multislice sequence scans (TR=2200ms, TE=3ms, 4.0 mm<sup>3</sup> voxels, FA=90°, 9:45 min ). Thirty-six slices covering the whole brain and the cerebellum were collected. During imagery scans, participants completed four gait imagery tasks (forward walking, backward walking, turning to the left, and turning to the right) each separated by an 11 second rest period. Similar to the practice gait tasks outside the

scanner, participants imagined completing each gait task at two different distances (4 and 8 meters for forward and backward gait, and 2 or 3 revolutions for turning), all at a natural, comfortable speed. Participant responses were logged using a custom made MRI compatible button box (Mag Design and Engineering, Redwood City, CA, USA) and a Matlab data logging interface. Participants' eyes were closed for all imagery tasks to improve the quality of the imagery. During rest periods, however, participants' eyes were open and fixated on a crosshair to permit them to read the upcoming task. This baseline rest task imbedded in the scan with gait tasks allowed us to normalize beta weights within each participant (i.e. by subtracting the beta weight during rest from the beta weight during imagined walking; see Statistical Analysis) Subtracting rest beta weights from gait beta weights removes some inter-subject variability and decreases potential baseline differences across groups. Imagined standing was assessed in a separate scan following imagined walking. During this 4 minute scan, participants imagined standing quietly with eyes closed for 20 seconds, followed by an 11 second eyes-open rest period. Duration of imagery was controlled by a tactile cue indicating the end of the imagined stand bout.

During the fMR scans, stimuli were projected onto a screen behind the head of the participant and were viewed via a mirror mounted on the head coil. Imagery and rest instructions were presented using E-Prime v1.0 (Psychology Software Tools, Inc, Sharpsburg, PA). Following imagery cues, participants closed their eyes and pressed a button to denote the beginning of gait imagery. At the end of imagery tasks, participants again pressed a button and opened their eyes. Timing of each button press was recorded and used for post hoc assessment of imagery times. During imagery,

participants were instructed to imagine in a first person perspective, and not to count steps. All participants were monitored via an eye tracker to ensure eyes were open and closed during the appropriate times during all imagery tasks.

## fMRI analysis

### *fMRI pre-processing*

Functional data were preprocessed using Brain Voyager (v. 2.4.0.2000, 32-bit). 3D motion correction was completed via sinc-interpolation. 3D motion for each volume was included in the general linear model (see Statistical Analysis). Slice scanning time differences were corrected by sinc interpolation, and data were high pass filtered (the lowest two cycles were removed). Functional scans were then coregistered (i.e. spatially aligned) to participant-specific T1-weighted images which were normalized to Talairach space (Talairach and Tournoux 1998)

Task conditions were modeled with an event related design and convolved with the canonical hemodynamic response function, which accounts for the delayed cerebral blood oxygenation and flow changes following neuronal activity. The first two volumes from each scan were excluded to achieve steady-state MRI signal. Any scan in which more than 2mm or 2° of motion in any direction was detected was not included in the analysis. The average maximum motion during scans and standard deviation of motion during scans were not different between the two groups (maximum motion measured in mm or degree: PD: 1.17 (0.46), control: 1.06 (0.41),  $p=0.28$ ; standard deviation of motion: PD: 0.31 (0.16), control: 0.27 (0.13),  $p=0.34$ , independent samples t-tests).

## *ROI analysis*

We chose to analyze BOLD signal only within a-priori regions of interest (ROIs). This approach was used for two reasons. First, participant-specific identification of regions provides a more precise picture of regional activity than typical full-brain analyses due to the structural variance of brain regions across individuals. This is particularly true when comparing across healthy and PD groups, as those with PD have been shown to exhibit alterations of brain volume compared to healthy older adults (Kostic et al. 2012). Second, the hypothesis driven a-priori specified regions limits the need for multiple comparison correction.

Therefore, nine ROIs (bilateral supplementary motor area [SMA], bilateral putamen, bilateral globus pallidus [GP], bilateral mesencephalic locomotor region [MLR], and cerebellar locomotor region [CLR] were included in the analysis. These regions were chosen due to their link to human locomotion (Jahn et al. 2008a; Jahn and Zwergal 2010) and dysfunction in those with PD (Kish et al. 1988; Hanakawa et al. 1999; Malouin et al. 2003; Bruck et al. 2006; Karachi et al. 2010; Prodoehl et al. 2010; Schweder et al. 2010; Spraker et al. 2010; Snijders et al. 2011; Cremers et al. 2012a). Since our tasks of interest involved imagined movements, primary motor cortex was not included as a ROI, as this area does not typically responded to imagined motor tasks (de Lange et al. 2005; Bakker et al. 2008; Cremers et al. 2012b). The ROIs were identified manually for each participant on a high resolution MP-RAGE image warped to Talairach space. One experienced operator, blinded to BOLD activation results, identified all ROIs. The SMA was identified as the midline grey matter dorsal to the cingulate sulcus. The rostral and caudal boundaries of the SMA were lines through the

anterior commissure (AC), posterior commissure (PC), respectively, perpendicular to the AC-PC plane (Immisch et al. 2001). Globus pallidus and putamen were identified using standard human atlases (DeArmond et al. 1989; Woosley et al. 2008). The MLR was identified as a 54-voxel region of the brainstem lateral to the cerebellar peduncle decussation and medial lemniscus, and includes approximately the cuneate, subcuneate and pedunculo pontine nuclei (Pahapill and Lozano 2000; Karimi et al. 2008). The CLR was identified as a 72-voxel region of the midline white matter of the cerebellum, approximately anterior to the fastigial nuclei (Mori et al. 1999). Although this definition was created for the cat, no other clear definition has been proposed for the CLR in humans. In addition, this approximate region has been shown specifically to be active during locomotion in previous gait imagery experiments in humans (Jahn et al. 2008b). Each region was identified bilaterally except for the CLR since it lies along the midline. Examples of each ROI are shown in Figure 3.1.

## Statistical analyses

### *Behavioral measures*

A 3-way repeated measures ANOVA (task, length, group) was run on actual and imagined gait times to investigate changes in imagery times across gait tasks in PD and control.

### *fMRI measures*

We constructed a general linear model (GLM) for the imagined gait BOLD data to determine beta weight changes associated with 5 tasks (rest, forward, backward,



turning left, and turning right) incorporating 6-dimensional (translation: x,y,z; and rotation:  $\theta, \phi, \psi$ ) head motion. Similarly, we calculated beta weights for imagined stand and rest for the imagined stand scan. Tactile cues used to indicate the end of imagined stand bouts were also modeled in the “stand” GLM to account for any changes in BOLD signal due to the cueing procedure. These GLMs were run separately for each ROI. Each ROI therefore had one beta weight for each task, which represents the average change in BOLD signal associated with each task across the whole region of interest. As each beta weight represents the average change in BOLD signal for all voxels within the ROI, no multiple corrections were applied.

To determine whether BOLD signal was higher (for either group) during gait tasks compared to stand, paired sample two-sided t-tests were run to compare imagined gait (beta weights combined over all imagined gait tasks) to imagined stand for each ROI and for each group.

To investigate differences across groups and across tasks, beta weights during imagined stand were subtracted from those of each imagined gait task. Then, two-way mixed model ANCOVAs assessing group (PD, Con), task (forward, backward, turning), and group by task interaction were run on these stand-corrected beta weights for each ROI. Average gait imagery times were included in the ANCOVA as a covariate to account for the possible confound of altered behavior across groups.

Correlations between actual overground walking speed and BOLD signal during gait imagery within each ROI were conducted using Spearman’s Rho correlation statistics.

## **RESULTS**

## Participants

Data from 15 participants (7 controls and 8 PD) were excluded. Six excluded controls were removed due to head motion over two millimeters of translation or two degrees of rotation. Following analysis, one control was excluded because beta weights from over 50% of our a-priori regions of interest were >2 standard deviations different than the mean of the group. Six PD participants also were excluded due to head movement over 2mm or 2°, one individual later reported prior head trauma, and one individual had poor imagery performance. Thus, 19 individuals with PD and 20 healthy older adults were included for analysis. Among these included participants, healthy and PD groups had similar age, handedness, KVIQ, and GIQ scores (Table 3.1). Average score on the MDS-UPDRS part III for those with PD was 31.2.

## Behavioral

As expected, actual gait times showed a length effect (longer gait tasks took longer than short tasks;  $F_{3,25}=577$ ;  $p<0.001$ ) and a group effect (PD took longer than controls;  $F_{1,37}=19$ ;  $p<0.001$ ). Imagined walking times (in the scanner), showed a length effect, such that when participants were prompted to imagine longer distances, gait imagery times increased ( $F_{1,36}=197.7$ ;  $p<0.001$ ). There was no group effect of imagery times (Figure 3.2). Gait imagery times in the scanner were longer than the actual overground gait times outside of the scanner ( $p=0.001$ , paired sample t-test, all participants). Imagery times were, however, positively correlated to actual gait times ( $\rho=0.473$ ;  $p=0.003$ ; Figure 3.3).

## fMRI results (ANCOVA)

Across all participants, there was no significant difference in regional BOLD responses when turning left or turning right (paired sample t-tests between turning left and turning right  $> 0.05$  for each ROI). Therefore, turns to the left and right were collapsed for all subsequent analyses.

Gait imagery, compared to imagined standing, produced significant increases in BOLD signal from nearly all locomotor regions of interest (See Table 3.2: Gait vs. Stand columns). In addition, there were main effects for the right SMA and the left GP. Specifically, within the right SMA, there was a main effect of task ( $F_{2,72}=3.6$ ,  $p=0.031$ ) and a group by task interaction ( $F_{2,72}=3.33$ ,  $p=0.042$ ). This interaction indicates that turning produced a more pronounced effect on BOLD signal in those with PD than controls (Table 3.2, Figure 3.4a). Post-hoc paired sample t-tests in those with PD demonstrated that beta weights during turning were larger than forward or backward imagined walking in the SMA (Figure 3.4a&c). Those with PD exhibited significantly smaller beta weights (across all tasks) in left GP than healthy older adults (group effect:  $F_{1,36}=12.79$ ,  $p=0.001$ ).

### fMRI results (Correlations)

Beta weights during imagined walking correlated with actual overground walking velocity for those with PD, but not for healthy older adults (Table 3.3, Figure 3.5). Larger beta weights for several regions (SMA, putamen, GP, and MLR) positively correlated with faster gait velocity (Table 3.3).

## **DISCUSSION**

We assessed the change in BOLD signal within brain regions associated with locomotion in healthy older adults and those with PD during complex gait imagery tasks. Three main findings of this work are: 1) PD exhibited significant BOLD responses in SMA during imagined turning while controls did not, 2) across gait tasks, PD exhibited reduced BOLD responses in left GP than controls, and 3) actual overground walking speed correlated with BOLD responses during imagined walking in several locomotor regions in PD and not in controls.

### Brain Activity during Complex Gait Imagery in PD

We chose to enhance the motor behavioral deficits in PD compared to controls by increasing the difficulty of the gait task with imagined backward walking and turning. This strategy should magnify changes in brain BOLD responses. In support of this strategy, imagined forward walking revealed no differences in SMA responses across groups, whereas imagined turning yielded significant BOLD responses in PD but not healthy controls. Interestingly these BOLD responses contrast with some previous studies reporting reduced SMA activity in PD during actual motor tasks (Playford et al. 1992; Jahanshahi et al. 1995; Hanakawa et al. 1999; Prodoehl et al. 2010; Wu et al. 2010). However, imagined movements elicited variable group differences in SMA activity in different studies (Snijders et al. 2011; Cremers et al. 2012a; Wai et al. 2012). For example, Snijders and colleagues reported reduced SMA activity during motor imagery only for individuals who experience freezing with respect to non-freezers (Snijders et al. 2011). Further, two additional gait imagery studies in those with PD showed no differences in SMA activity with respect to controls (Cremers et al. 2012a; Wai et al. 2012). Indeed, in the current study imagined forward walking produced similar

levels of SMA BOLD responses between PD and controls. However, during complex gait imagery PD had higher SMA BOLD responses. Actual turning typically causes more pronounced gait dysfunction in those with PD than forward walking, possibly due to the higher bilateral coordination necessary to complete the task (Schaafsma et al. 2003; Peterson et al. 2012b). Therefore, the larger increase in SMA signal during turning imagery in PD (but not in controls) may indicate that people with PD require more activation in this region to plan and coordinate complex gait tasks, while controls do not. The positive correlation between SMA BOLD response and actual overground walking velocity suggests that the increase in BOLD signal during complex gait tasks may be compensatory in nature. Alternatively, it is possible that this is a pathological adaptation, as those with PD exhibit worse gait function during complex gait tasks and exhibit elevated SMA activity while healthy controls do not. Regardless, this result underscores the importance of including both simple and complex tasks as a tool to examine potential neural alterations in those with PD.

Interestingly, backwards walking did not increase BOLD responses relative to forward walking for any ROI in either group. This surprising result contrasts with a previous study that suggested backward walking may elicit larger BOLD responses in the putamen (Godde and Voelcker-Rehage 2010). Gait imagery may not permit capturing certain aspects of complex gait tasks. For example, backwards walking is typically more difficult for those with PD (Hackney and Earhart 2009) possibly due to more pronounced postural instability in that direction (Horak et al. 2005). However, with gait imagery, deficiency in balance and weight-shifting are likely less apparent. Therefore, part of the difference in difficulty across gait tasks (i.e. balance requirements)

may not be fully captured by gait imagery paradigms, yielding non-significant changes across tasks in the current study. Alternatively, turning (both actual and imagined) necessitates altered foot placement and coordination of steps, possibly increasing BOLD signal in the SMA of those with PD. Another possible explanation for the lack of difference across gait imagery tasks is the imagery speed of different tasks. Imagery speeds were considerably slower for backward walking and turning than forward. Therefore, one may predict smaller signal in locomotor regions during backward walking and turning. However, all gait tasks in the current study were imagined walking at comfortable speeds. Previous investigations demonstrating alterations in neural signal at different walking speeds (Jahn et al. 2004; Karachi et al. 2010; Cremers et al. 2012b) note differences when subjects deviated from “preferred” (i.e. brisk walking vs. preferred).

#### Brain Activity during All Gait Imagery in PD

Few studies have investigated the neural activity of locomotion in those with PD. Though results from these investigations vary, data from the current study match fairly well with previous results. For example, Cremers et al. 2012 found that during imagined locomotion, both PD and control participants exhibited increased BOLD signal in pre-motor regions, with control participants also showing higher BOLD in several locomotor regions, including the GP, MLR, and cerebellum. We also observed increased BOLD responses in several of these locomotor regions, albeit with greater consistency in PD participants than in this previous study (Cremers et al. 2012a). Across groups, Cremers and colleagues observed PD to exhibit reduced BOLD signal in midline cerebellar and MLR regions, among others. In the current study, we also noted a decrease in BOLD in

those with PD in the CLR with respect to control participants, though this difference did not reach statistical significance.

Previous studies on gait imagery have been mixed with respect to MLR activation, showing increases (Snijders et al. 2011), decreases (Karachi et al. 2010; Cremers et al. 2012a), and no change (Wai et al. 2012) across healthy and PD. This variability may be due to differences in protocol, however they may also be due to the vast heterogeneity of symptoms of those with PD. A novel finding of the current study is the significant reduction in BOLD signal during imagined gait in the left GP in those with PD with respect to controls. This result is not surprising considering the critical role that GP plays in motor control through cortico-basal ganglia-thalamic circuits known to be disrupted in those with PD (Prodoehl et al. 2010). The classical model of basal ganglia dysfunction in PD involves altered activity of several regions, including the GP, resulting in increased inhibition of the thalamus (Wichmann and DeLong 1996). This thalamic inhibition results in decreased facilitation of cortical motor areas, bradykinesia and hypokinetic movements. During walking, this typically manifests as reduced walking velocity and small steps. Though we did not observe group differences during imagined walking in the putamen, the activity in GP was altered, possibly contributing to overground gait dysfunction. Indeed, overground walking velocity was lower in PD than controls. The reason for a reduction in the left GP, but not the right GP is unclear, although it seems to be driven to some degree by the bilateral differences observed in both controls and PD. Within those with PD, we observed significantly lower activity in the left GP than the right, and within controls, we observed higher activity in the left GP with respect to the right, though this difference did not reach significance. One previous

investigation also noted increased BOLD signal in the left pallidum (but not the right) for healthy adults during imagined walking (Cremers et al. 2012b) however the bilateral changes in PD have not previously been reported. Structural asymmetries in bilateral GP regions may have contributed to the asymmetric across group differences in the current study. Previous investigations show the left globus pallidus may be larger (Kooistra and Heilman 1988) and contain more dopamine (Glick et al. 1982) than the right in healthy adults. This is in conjunction with our the fact that, in controls, there was more activity in the left GP than the right GP. Therefore, it is possible that the left GP may play a larger role in normal gait imagery than the right GP. If true, dysfunction in the left GP in people with PD (as seen in the current study) could result in more pronounced disruption of overground walking than dysfunction in the right GP.

It is unlikely that this difference is due to motor asymmetries in our population. Post-hoc analyses showed that GP activity during imagined gait in those with greater right side signs (based on unilateral components of the MDS-UPDRS-III) was not different from those who had greater involvement of the left side. This was true both in the left and right GP. The bilateral difference was also not due to the inclusion of 4 left-handed individuals (2 PD and 2 control), as removal of these individuals did not alter the result.

### Correlation to Overground Gait Speed

One goal of this study was to identify whether correlations exist between BOLD signals within locomotor regions and actual gait and balance function. We chose to correlate BOLD signal during imagined gait tasks to actual overground walking speed



because walking speed may reflect global gait and balance function (Fritz and Lusardi 2009), and reduction in gait speed may relate to negative outcomes including falls (Verghese et al. 2009) quality of life (Schmid et al. 2007), and mortality (Studenski et al. 2011).

Average walking positively correlated with BOLD response magnitude in several locomotor brain regions only in the PD group and not in the controls. Though the strength of correlations varied across regions, all these regional BOLD responses directly correlated with walking speed. These results suggest that higher BOLD responses predict faster walking speeds (better clinical outcome) for individuals with PD. Prodoehl and colleagues found similar results in upper limb motor function, showing less BOLD signal in PD with respect to controls during finger tapping, and indirect relationships between BOLD signal and disease severity in numerous regions (Prodoehl et al. 2010). These results together suggest that reductions in BOLD signal in locomotor regions (including basal ganglia) may be pathological in those with PD. The group differences in GP BOLD signal in the current study further supports this notion. The significant negative relationship between GP BOLD signal and walking speed, along with the reduced GP BOLD signal in PD compared to control participants, suggests the possibility that reduction of activity in this region is pathological.

### Gait Imagery

Few current methods permit investigation of the neural circuitry underlying gross motor control such as locomotion and even fewer allow collection of these data with high spatial and temporal resolution. fMRI BOLD measures during gait imagery provides

a reasonable experimental paradigm. This technique, which relies upon the large degree of overlap between actual and imagined movements (Jeannerod and Decety 1995; la Fougere et al. 2010), permits investigation of the brain activity associated with locomotion (Malouin et al. 2003; Jahn and Zwergal 2010; Snijders et al. 2011; Zwergal et al. 2012). There are several benefits to this type of data collection. First, compared to other cortical and subcortical brain imaging techniques used in humans, fMRI provides relatively high spatial (~2-4mm) and temporal (~2 sec) resolution. Second, imagery of gait allows individuals to imagine movements similarly across groups, thereby minimizing the potential performance confound associated with other task-based BOLD measurements. This is particularly important when investigating those with reduced overground gait speed, as alterations in speed of movement can significantly affect BOLD signal (Jahn et al. 2004; Suzuki et al. 2004; Karachi et al. 2010; Cremers et al. 2012b). Finally, with this paradigm, it is possible to differentiate descending neural signals from proprioceptive signals or the integration of proprioceptive information into motor plans, which may be altered in those with PD (Almeida et al. 2005).

An important limitation with gait imagery is the difficulty in assessing participants' adherence to gait imagery tasks during scans. We took several steps to address this concern. First, we screened all participants for their ability to imagine movements, and ability to imagine both single limb (KVIQ) and whole body (GIQ) movements were similar across groups. Second, gait imagery times reflected the distance participants were asked to imagine, suggesting individuals adhered to the gait tasks while in the scanner. These results, along with previous reports showing the overlap between imagined and executed movements (including gait (la Fougere et al. 2010)), provide

support that the BOLD signal observed during imagined gait in the current study relates to actual locomotion.

### Limitations

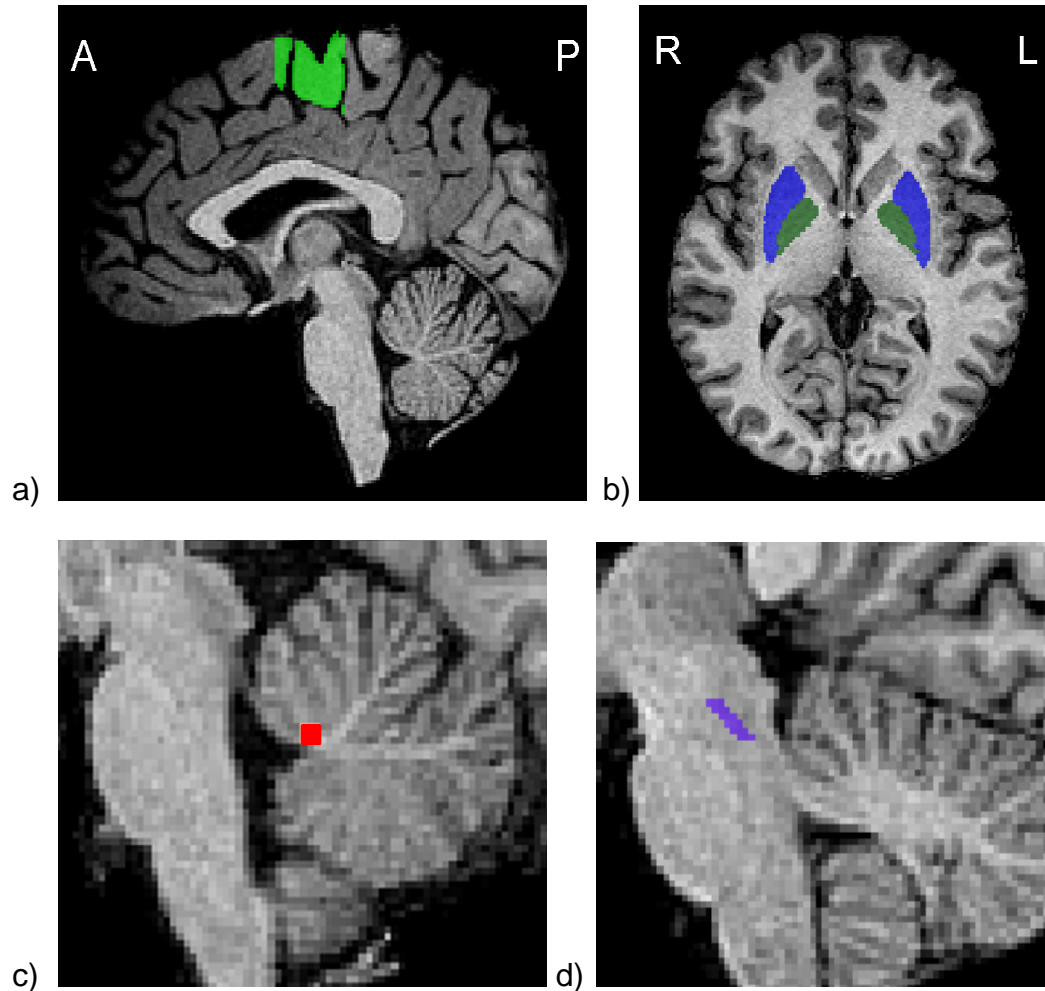
Several limitations of the current study are noted. First, the speed at which individuals imagine gait tasks can alter neural activity (Suzuki et al. 2004; Jahn et al. 2008b; Karachi et al. 2010; Cremers et al. 2012b). In the current study, there were no differences in time to imagine during scans, however, due to the importance of accounting for differences in behavior during scans, we incorporated the average imagined gait time for each participant into our statistical analysis. Second, fast walking may produce larger BOLD responses, potentially explaining, in part, the observed relationship between walking speed and amplitude of BOLD response. However, post hoc analysis showed that no correlation between imagined walking speed and BOLD signal in any region which showed an actual walking / BOLD correlation. Further, actual walking time did not significantly correlate with BOLD signal in healthy older adults. Therefore, we think that the correlations between actual overground walking speed and BOLD signal during gait imagery in those with PD represent a true relationship between walking ability and BOLD signal within locomotor regions. Third, those with PD may not be able to imagine gait tasks while in the “Off” medication state. However, recent evidence suggests that anti-Parkinson medication state does not significantly affect ability to imagine movements, and further, those with PD (both “On” and “Off” anti-Parkinson medication) have similar imagery ability to healthy older adults (Peterson et al. 2012a). Finally, although head motion while in the scanner was similar across groups, those with PD may have more motion of extremities (i.e. tremor) than healthy

older adults. We were unable to capture electromyography in this investigation, however we directly visualized all participants, and no participants exhibited tremor while in the scanner. Still, some muscular activity may not cause visually apparent motion and could potentially confound our results.

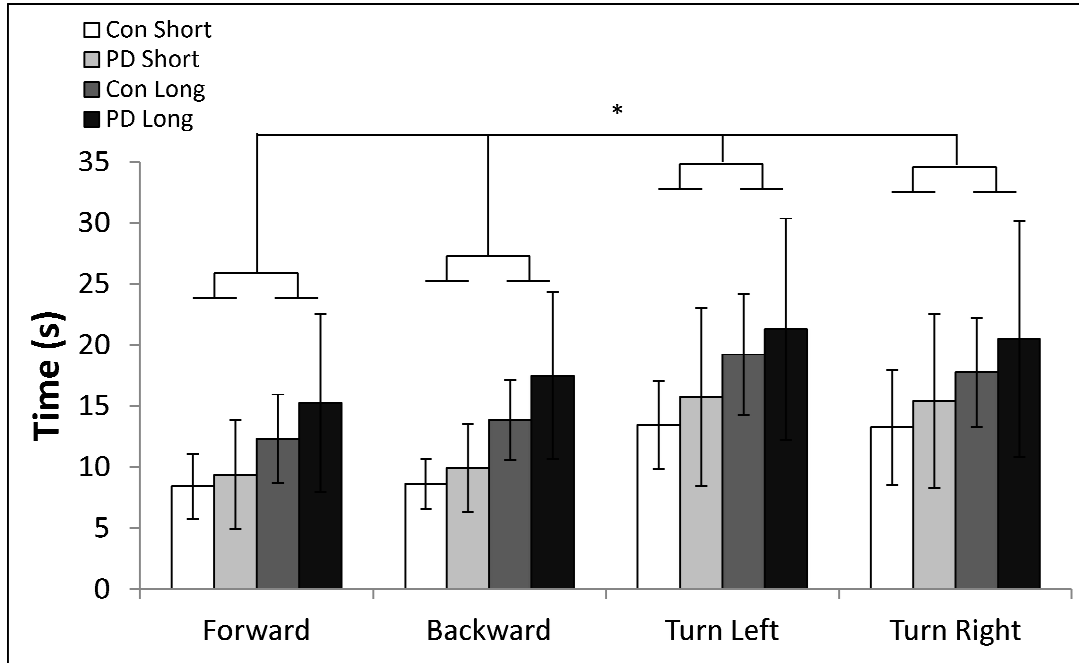
## Conclusion

Novel findings of this study include: 1) in the SMA, complex gait imagery produced greater BOLD responses in those with PD than controls, 2) PD exhibited reduced BOLD signal in GP with respect to controls, and 3) in those with PD, walking speed was related to BOLD signal in several locomotor regions. These results suggest that: 1) people with PD may require more activity in the supplementary motor area than controls to complete complex gait tasks, and this increase may be compensatory in nature; 2) gait dysfunction in people with PD (i.e. reduced gait velocity) may be related to altered function of the GP; and 3) elevated BOLD signal in locomotor regions may predict improved gait function. Together, these results further elucidate the changes in activity of locomotor regions during gait imagery tasks in PD and in controls, and provide evidence supporting a relationship between increased BOLD signal in locomotor regions and improved walking function.

**Figure 3.1:** Regions of interest. Regions were identified for each individual separately based on standard definitions (See Methods). Shown are examples of regions defined for four subjects: supplementary motor area (a), putamen (blue) and globus pallidus (green) (b), cerebellar locomotor region (c), and mesencephalic locomotor region (d). A- Anterior; P-Posterior; R-Right; L-Left

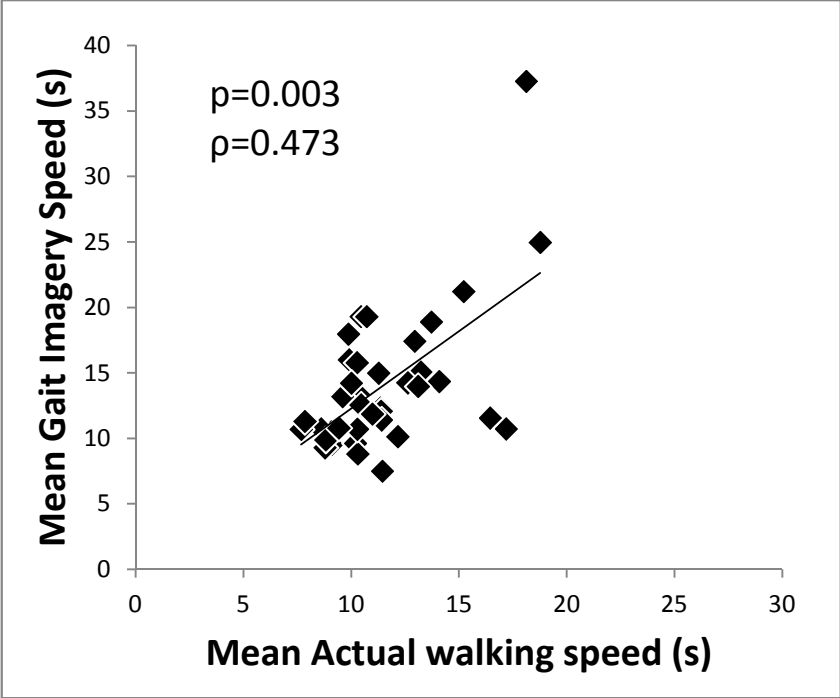


**Figure 3.2:** Imagined walking times for PD and healthy old (Con) participants during fMRI scans. Both 'short' and 'long' tasks are shown for each group. Long tasks took significantly more time to complete than short tasks (denoted by \*,  $F_{1,36}=197.7$ ;  $p<0.001$ ). Differences between PD and control subjects did not reach significance. Error bars represent standard deviation.

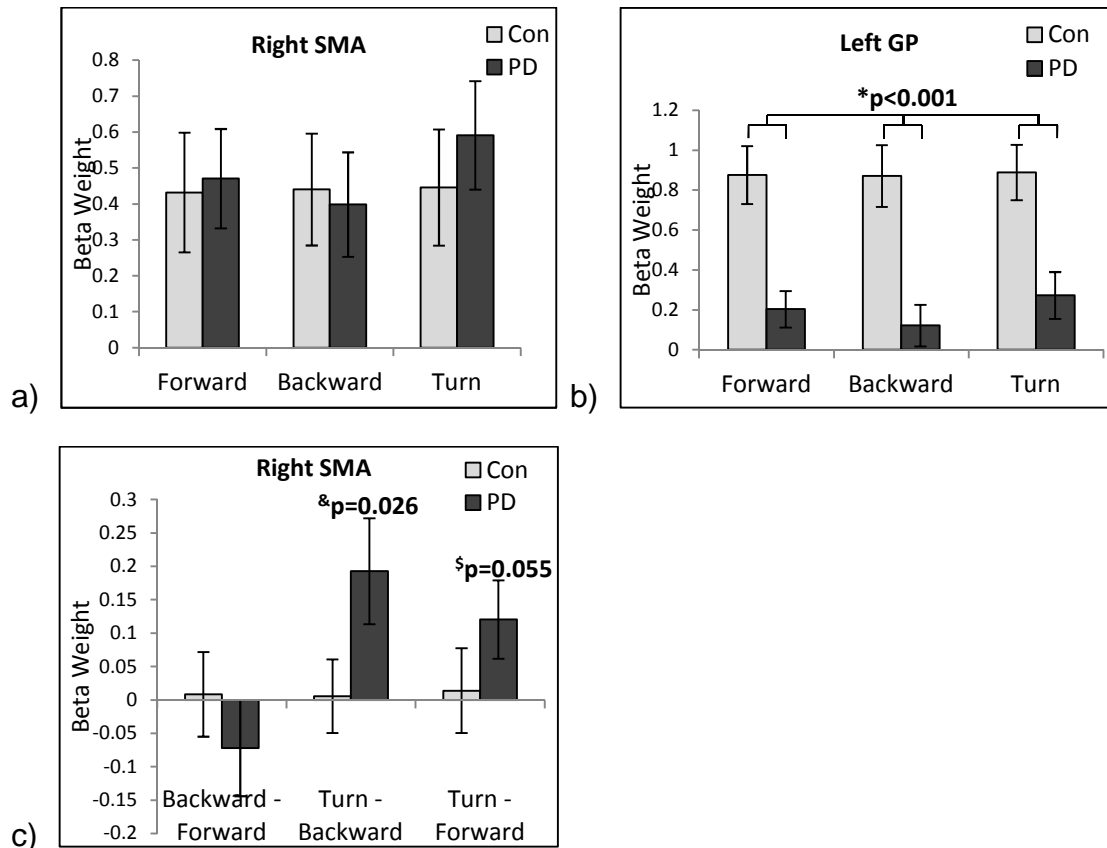


**Figure 3.3:** Correlation between actual and imagined walking times (all subjects).

Spearman's Rho and p-value reported.

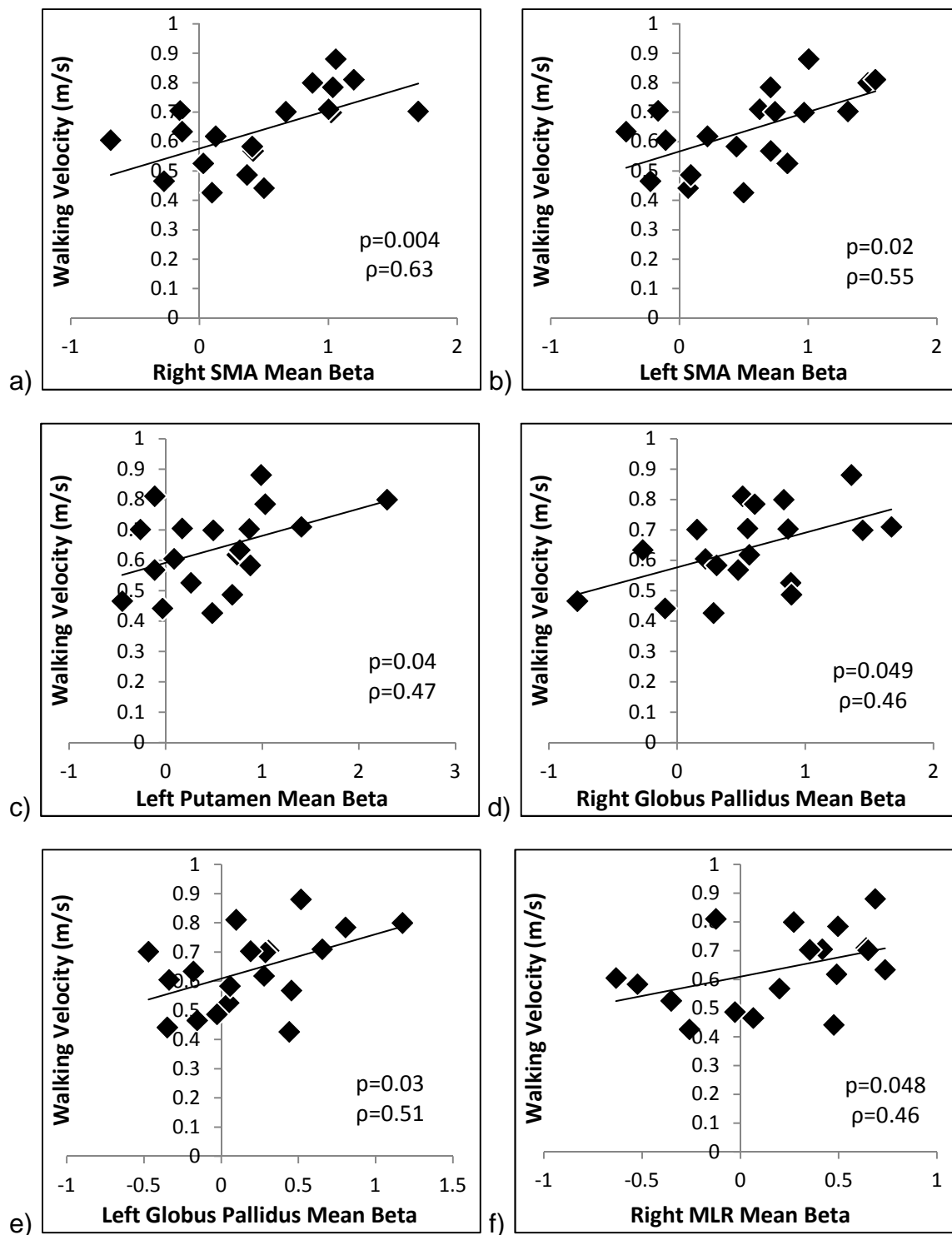


**Figure 3.4:** Beta weights during imagined walking (with respect to stand) for the right SMA (a), and left GP (b). Data in panel (c) shows the difference in beta weights for each group across imagined gait tasks (i.e. the difference between backward and forward imagery) in the right SMA. \*Repeated Measures ANCOVA; &Paired sample t-test, turning vs. backward in those with PD; \$Paired sample t-test, turning vs. forward in those with PD. Error bars represent standard error of the mean.





**Figure 3.5:** Significant correlations between beta weights and overground walking speed observed in those with PD. a) right SMA, b) left SMA, c) left putamen d) right GP e) left GP, and f) right MLR.



**Table 3.1: Subject Characteristics**

	<b>Healthy Old</b>	<b>PD</b>	
<b>N</b>	20 (6m)	19 (11m)	
<b>Age (yrs)</b>	66.6 (7.6)	64.9 (7.6)	p=0.51
<b>MDS-UPDRS-III<sup>#</sup></b>	--	31.2 (10.0)	
<b>KVIQ<sup>*</sup></b>	80.6 (11.1)	78.0 (12.4)	p=0.49
<b>GIQ<sup>*</sup></b>	31.0 (3.8)	28.8 (4.7)	p=0.12

<sup>#</sup>Movement Disorders Society Unified Parkinson's Disease Rating Scale (part III)

<sup>\*</sup>KVIQ: Kinesthetic Visual Imagery Questionnaire (maximum score = 100); GIQ: Gait Imagery Questionnaire (maximum score=40)

**Table 3.2:** ANCOVA results for all regions of interest. P-values shown.

ROI	ANCOVA Main Effects			Gait vs. Stand (paired sample t-test)	
	Group	Task	Group by Task interaction	Control	PD
Right SMA	0.668	<b>0.031</b>	<b>0.042</b>	<b>0.012</b>	<b>0.002</b>
Left SMA	0.907	0.093	0.050	<b>0.011</b>	<b>0.001</b>
Right PUT	0.768	0.690	0.610	<b>0.019</b>	<b>0.009</b>
Left PUT	0.536	0.169	0.774	<b>0.012</b>	<b>0.002</b>
Right GP	0.616	0.870	0.556	<b>0.001</b>	<b>0.001</b>
Left GP	<b>0.001</b>	0.973	0.572	<b>0.000</b>	0.053
Right MLR	0.842	0.986	0.819	<b>0.001</b>	<b>0.038</b>
Left MLR	0.869	0.290	0.100	<b>0.02</b>	<b>0.000</b>
CLR	0.085	0.925	0.189	<b>0.000</b>	<b>0.012</b>

**Table 3.3:** P-values (Spearman's  $\rho$ ) of all correlations between beta weights during imagined gait (averaged across all gait imagery tasks) and actual overground walking velocity (m/s; averaged across all gait tasks).

		<b>SMA R</b>	<b>SMA L</b>	<b>PUT R</b>	<b>PUT L</b>	<b>GP R</b>	<b>GP L</b>	<b>MLR R</b>	<b>MLR L</b>	<b>CLR</b>
<b>Gait beta weight vs. actual walking velocity</b>	<b>Control</b> p( $\rho$ )	0.56 (-0.14)	0.30 (-0.24)	0.47 (-0.17)	0.31 (-0.24)	0.65 (-0.11)	0.18 (-0.30)	0.40 (-0.20)	0.83 (-0.05)	0.05 (-0.43)
	<b>PD</b> p( $\rho$ )	<b>0.004</b> <b>(0.63)</b>	<b>0.02</b> <b>(0.55)</b>	0.06 (-0.44)	<b>0.04</b> <b>(0.47)</b>	<b>0.049</b> <b>(0.46)</b>	<b>0.03</b> <b>(0.51)</b>	<b>0.048</b> <b>(0.46)</b>	0.65 (0.11)	0.25 (0.28)

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## **Chapter 4: Gait Related Brain Activity in People with Parkinson Disease Who Experience Freezing of Gait**

This chapter is in preparation:

Peterson DS, Pickett KA, Duncan R, Perlmutter JS, Earhart GM. Gait-Related Brain Activity in People with Parkinson Disease Who Experience Freezing of Gait

## **ABSTRACT**

**PURPOSE:** Approximately 50% of people with Parkinson disease (PD) experience freezing of gait, described as a transient inability to produce effective walking. Complex gait tasks such as turning or backward walking typically elicit freezing more commonly than simple gait tasks, such as forward walking. Despite the frequency of this debilitating and dangerous symptom, the brain mechanisms of freezing remain unclear. Gait imagery during functional magnetic resonance imaging (fMRI) permits investigation of brain activity associated with locomotion. We used this approach to better understand neural function during gait-like tasks in people with PD who do freeze (freezers) and people who do not freeze (non-freezers).

**METHODS:** Nine freezers and nine non-freezers imagined complex (turning, backward walking) and simple (forward walking) gait tasks during measurements of blood oxygen level dependent (BOLD) signal. Changes in BOLD signal were analyzed in five a-priori locomotor regions: supplementary motor area (SMA), globus pallidus (GP), putamen, mesencephalic locomotor region (MLR), and cerebellar locomotor region (CLR) and then compared across groups (freezer/nonfreezer) and across tasks (forward, backward, turning).

**RESULTS:** BOLD responses in these locomotor regions did not differ for complex tasks compared to simple tasks in either group. Freezers, however, exhibited reduced BOLD responses in the CLR with respect to non-freezers. Overground gait speed significantly correlated with BOLD signal in the right SMA and right MLR in non-freezers but not in freezers.

CONCLUSIONS: Individuals with PD who freeze, as compared to non-freezers, had reduced BOLD response in the CLR during imagined gait tasks. This suggests the cerebellum may play a role in freezing of gait.

## INTRODUCTION

Gait dysfunction commonly occurs in Parkinson disease (PD), and includes short steps (Morris et al. 1996), increased step time variability (Hausdorff et al. 1998), and poor step-to-step coordination (Plotnik et al. 2008). Furthermore, approximately 50% of people with advanced PD also experience Freezing of Gait (FOG) (Giladi et al. 2001; Bartels et al. 2003), defined as a transient inability to complete effective stepping (Giladi and Nieuwboer 2008). FOG is a disabling and distressing symptom, contributing to falls and reduced quality of life (Gray and Hildebrand 2000; Giladi et al. 2001; Bloem et al. 2004; Moore et al. 2007; Kerr et al. 2010), and common PD treatments such as anti-Parkinson medication do not consistently provide adequate benefit (Schaafsma et al. 2003). Although FOG is transient, freezers may exhibit altered gait even during normal walking (i.e. periods of non-freezing or festination), suggesting that the underlying pathophysiology also affects non-freezing locomotion (Hausdorff et al. 2003; Plotnik et al. 2008; Peterson et al. 2012).

The brain mechanisms of freezing of gait remain unknown. Only one report directly compared brain activity in freezers and non-freezers during a gait-like task (Snijders et al. 2011). In this study, participants imagined walking while functional magnetic resonance imaging (fMRI) measured Blood Oxygen Level Dependent (BOLD) signal. Freezers had an increase in BOLD response in the MLR compared to non-freezers, supporting the notion that brainstem regions may relate to freezing of gait. Gait imagery during fMRI, as used by Snijders and colleagues, has become a commonly used technique to assess neural function during locomotion (Malouin et al. 2003; Bakker et al. 2008; Wagner et al. 2008; Wang et al. 2008; Godde and Voelcker-Rehage 2010; Jahn and Zwergal 2010; Snijders et al. 2011; Cremers et al. 2012a; Cremers et

al. 2012b; Zwergal et al. 2012). This approach relies on the substantial overlap in brain activation responses during imagined and overt movements (Jeannerod and Decety 1995; Porro et al. 1996; Deiber et al. 1998; Miyai et al. 2001) including walking (Miyai et al. 2001; la Fougere et al. 2010). Despite limitations, this approach has provided important insight into the brain activation during locomotion in humans (Bakker et al. 2008; Jahn et al. 2008b; Cremers et al. 2012b).

The report by Snijders and colleagues focused on imagined forward walking (Snijders et al. 2011). However, more complex gait tasks increase freezing risk and gait dysfunction (Schaafsma et al. 2003; Spildooren et al. 2010; Snijders et al. 2012), and such tasks may amplify differences across groups. The underlying mechanisms are not well understood, yet asymmetry and reduced coordination of steps during complex gait tasks, such as turning, may precipitate freezing (Plotnik and Hausdorff 2008). Turning necessitates asymmetries in step length and leg velocity (Courtine and Schieppati 2003), and leads to discoordinated stepping in people with PD. Further, turning by walking in large rather than small circles provides a clinical strategy to improve coordination and reduce freezing (Morris 2006). Therefore, increased freezing during complex gait tasks such as turning may be due to the inherent asymmetry and discoordination of movement.

Our goal was to assess the brain activity of freezers and non-freezers with PD during simple and complex gait tasks to further elucidate the neural underpinnings of freezing of gait. Assessing gait imagery during both complex and simple gait tasks may result in more pronounced differences between freezers and non-freezers due to the fact that these gait tasks typically elicit freezing more often than simple forward walking.

We hypothesized that freezers would have abnormal BOLD responses to imagined gait tasks in several locomotor regions of interest (ROIs), including supplementary motor area (SMA), globus pallidus (GP), putamen, mesencephalic locomotor region (MLR), and cerebellar locomotor region (CLR). Further, we expected imagery of complex tasks (turning, backward walking) compared to forward walking would enhance these differences. To test this hypothesis, we measured BOLD response during imagery tasks of simple forward walking and complex (backward, turning) gait in freezers and non-freezers.

## **METHODS**

### Participants

Inclusion criteria included diagnosis of idiopathic PD as described by Racette et al. (Racette et al. 1999) and based on established criteria (Hughes et al. 1992), free from lower limb injuries for the previous 6 months, no contraindications for MRI, and ability to effectively imagine movement based on the Kinesthetic Visual Imagery Questionnaire (KVIQ) (Malouin et al. 2007). All included participants demonstrated an average score of at least 3 on both the kinesthetic and visual component of this measure, indicating moderate clarity or intensity of imagery. Seven individuals with PD were excluded (no fMRI data were collected) based on this imagery vividness threshold. All participants also completed the Gait Imagery Questionnaire (Pickett et al. 2012) (GIQ) to permit post-hoc comparisons of ability to imagine gait across groups, though this score was not used to exclude participants. Exclusion criteria included neurological problems other than PD and cognitive dysfunction (Mini Mental State Exam; MMSE < 27).

Individuals were classified as “freezer” or “non-freezer” by the New Freezing of Gait Questionnaire (NFOGQ) (Nieuwboer et al. 2009). People who identified themselves as freezers in question 1 went on to answer 8 questions assessing the severity of freezing and its effects on daily life. All data collection was conducted after a 12-hour withdrawal of anti-Parkinson medication. Freezers and non-freezers were matched as closely as possible for disease severity level. Motor severity was assessed by the motor subscale of the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS part III).

Written informed consent was provided by all subjects in accordance with the Human Research Protection Office at Washington University School of Medicine and the Declaration of Helsinki.

### Procedure

Participants completed three T2\*-weighted gradient echo multislice sequence scans (EPI, TR=2200ms, TE=3ms, 4.0 mm<sup>3</sup> voxels, FA=90°, 9:45 min). BOLD signal was captured for 36 slices covering the brain and the cerebellum. A T1-weighted sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=8°, 1.0mm<sup>3</sup>, 8:09 min) scan was also collected for identification of ROIs and co-registration to T2\* scans. MR was done with a Siemens 3T Magnetom TrioTim scanner.

During BOLD acquisition scans, participants imagined four walking tasks (forward walking, backward walking, turning to the left in small radius (0.6m) circles, and turning to the right in small radius circles) in pseudo-random order and separated by 11-second rest periods in which eyes were open. It was necessary to have individuals open



their eyes during rest scans to permit them to detect the visual signal of the upcoming task. In addition, modeling this rest period provided a baseline condition for each participant within each scan. This allowed us to normalize beta weights within each participant by subtracting the beta weight during rest from the beta weight during imagined walking. Subtracting a scan- and subject-specific beta weight from each gait imagery beta weight removes inter-subject variability and potential baseline differences across group not related to imagined locomotion. Participants tapped their index finger on a custom made MRI compatible button box (Mag Design and Engineering, Redwood City, CA, USA) once at the beginning and once at the end of each gait task to log the start and finish of each imagery epoch (Figure 4.1). Two gait imagery scans were collected for each participant.

In a third, four minute long T2\*-weighted scan, participants alternated between imagined upright standing (20 seconds) and rest (11 seconds). For this scan a tactile cue on the leg indicated the end of imagery and the beginning of rest. This tactile cue was modeled into the GLM to account for any associated changes in BOLD signal. Imagined standing was used as the control task for this study because it controls for brain activity associated with first-person imagery. Participants' eyes were closed during imagery of standing and open during rest, analogous to that done for the imagined gait task.

Stimuli were projected onto a screen behind the participant and were viewed via a mirror mounted on the head coil. Instructions were presented using E-Prime v1.0 (Psychology Software Tools, Inc, Sharpsburg, PA). An MRI-compatible eye tracker documented that the eyes were closed and open at appropriate times. Presence of

tremor of the eyes, head, lower legs and hands during scans was assessed qualitatively by observation. Two participants were excluded due to tremor during the scans (See Results).

For each gait imagery task, participants imagined walking two different distances (4 and 8 meters for forward and backward gait, and 2 or 3 revolutions for turning). By measuring the time taken to imagine walking short and long distances, we could assess the degree to which participants adhered to the tasks during scans. Before scanning, participants practiced the execution and imagery of each of the gait tasks. Time to complete all actual gait tasks (forward, backward, turns) was captured. None of the individuals noted freezing while imagining gait tasks either during practice or while in the scanner.

### FMR pre-processing

Functional data were preprocessed using Brain Voyager (v. 2.4.0.2000, 32-bit). The first two image volumes from each imaging run were discarded for all trials. 3D motion correction was completed via sinc-interpolation and output for inclusion in the general linear model (see Statistical Analysis). Slice scan time differences were corrected via sinc interpolation, and data were high pass filtered (the lowest two cycles were removed). Functional scans were then coregistered (i.e. spatially aligned) to participant-specific T1-weighted images which were normalized to Talairach space (Talairach and Tournoux 1998). Task conditions were modeled with an event-related design and convolved with the canonical hemodynamic response function, which accounts for the delayed cerebral blood oxygenation and flow changes following

neuronal activity. In addition to the 3D motion correction, any scan in which more than 2mm or 2° of motion in any direction was detected was not included in the analysis. Neither maximum head movement ( $p=0.56$ ), nor standard deviation of head movement ( $p=0.91$ ) during scans differed between groups.

### ROI analysis

BOLD signal was analyzed only within a-priori ROIs. We chose this approach for two reasons. First, ROIs can be identified manually on each participant more precisely than using a standardized template. This is particularly critical for this investigation given the small regions we targeted. Second, a-priori identification of ROIs limits the need for multiple comparison correction. We chose nine ROIs (bilateral SMA, bilateral putamen, bilateral GP, bilateral MLR, and CLR) due to their link to human locomotion (Mori et al. 1999; Mori et al. 2004; Jahn et al. 2008a; Jahn and Zwergal 2010) and dysfunction in individuals with PD (Kish et al. 1988; Hanakawa et al. 1999b; Malouin et al. 2003; Bruck et al. 2006; Karachi et al. 2010; Prodoehl et al. 2010; Schweder et al. 2010; Spraker et al. 2010; Snijders et al. 2011; Cremers et al. 2012a); particularly in people who experience freezing (Hashimoto 2006; Lewis and Barker 2009; Schweder et al. 2010; Snijders et al. 2011). Since our tasks of interest involved imagined movements, primary motor cortex was not included as a ROI, as this area does not typically respond to imagined motor tasks (de Lange et al. 2005; Bakker et al. 2008; Cremers et al. 2012b). ROIs were identified manually for each participant on a high resolution MP-RAGE image warped to Talairach space (Talairach and Tournoux 1998). A single operator, blinded to BOLD activation and group status, identified all ROIs. The

SMA was identified as the midline grey matter superior to the cingulate sulcus. Parallel vertical lines through the anterior commissure (AC) and posterior commissure (PC), marked rostral and caudal boundaries (Immisch et al. 2001). The MLR was identified as a 54-voxel region of the brainstem lateral to the cerebellar peduncle decussation and medial lemniscus, including approximately the cuneate, subcuneate and pedunculo-pontine nuclei (Pahapill and Lozano 2000; Karimi et al. 2008). The CLR was identified as a 72-voxel region of the midline white matter of the cerebellum, approximately rostral to the fastigial nuclei (Mori et al. 1999). Globus pallidus and putamen were identified using standard human atlases (DeArmond et al. 1989; Woosley et al. 2008). Examples of each ROI are shown in Figure 4.2.

### Statistics

Analyses of variance (ANOVAs) assessed actual and imagined gait times in both groups. Pearson correlation statistics assessed the relationship between actual and imagined gait times.

A general linear model (GLM) was constructed for imagined gait BOLD data to determine how well the design matrix model explains data. Beta weight changes associated with 5 tasks (rest, forward, backward, turning left, and turning right) and incorporating 6-dimensional head motion were determined using the GLM. Beta weights represent how much of the BOLD signal change is attributed to each of the five tasks. The inclusion of 6-dimensional head motion in the GLM helps to account for alterations in signal due to movements of the brain. Beta weights were also calculated for imagined stand and rest for the imagined stand scan. During stand scans, tactile cueing was used

to notify participants when to stop imagining. To account for any changes in BOLD signal due to this approach, cues were also modeled into the GLM for the stand dataset. GLMs were run separately for each ROI.

We used paired sample, two-sided t-tests to determine whether BOLD signal differed during imagined gait tasks (average of all gait imagery beta weights) from imagined standing. This analysis was carried out for each ROI.

To investigate differences across groups and across tasks, we first subtracted beta weights during imagined standing from beta weights during imagined gait tasks. By subtracting standing beta weights, we removed BOLD responses associated more generally with imagining and were left with beta weights specific to imagined locomotion. Analyses of covariance (ANCOVAs) were then used to assess the change in beta weights for each region of interest between groups and across tasks for each ROI. To account for differences in motor severity across freezing and non-freezing groups, MDS-UPDRS-III was included as a covariate in the ANCOVA. Also, given the importance of accounting for differences in behavior, average gait imagery times were included as a covariate in the analysis. Spearman's  $\rho$  statistics were used to correlate BOLD signal in each region of interest to behavioral measures (actual overground gait velocity and freezing severity [NFOG total score]).

## **RESULTS**

### Participants

fMRI data were collected from 26 participants with PD. Data from six participants were excluded due to head movement over 2mm or 2°. Of these 6, two also had severe

hand tremor. Another individual was excluded because he later reported prior head trauma, and one individual was excluded due to poor imagery performance. Thus, 18 individuals with PD (nine freezers and nine non-freezers) were included for further analysis. Freezers and non-freezers were of similar age. The freezer group did not have significantly worse disease severity based on MDS-UPDRS part III and Hoehn and Yahr stage. Imagery ability (KVIQ and GIQ) was similar across groups (Table 4.1).

### Behavioral

Actual overground walking times and gait imagery times were similar across groups ( $F_{1,16}=1.26$ ;  $p=0.28$  and  $F_{1,16}=1.4$ ;  $p=0.25$ , respectively). As expected, “long” gait imagery tasks took longer than “short” ( $F_{1,16}=34.6$ ;  $p<0.001$ , Figure 4.3). Gait imagery times were not quite significantly longer than actual overground gait times, ( $p=0.053$ , paired sample t-test). Actual and imagined gait times correlated with each for all subjects ( $r=0.61$ ,  $p=0.007$ , Figure 4.4). One participant, a freezer, exhibited considerably longer imagery time (37 seconds on average) than actual time (18 seconds on average). Though no freezing was noted during imagery, this participant may have experienced altered imagined gait with respect to overground walking. Therefore, we completed BOLD signal analyses with and without this participant; no changes were noted. Furthermore, inclusion of imagined walking time in the ANCOVA attenuated the affect of this outlier. Therefore, all data presented herein include this individual.

### fMRI

Beta weights while imagining turning to the left and to the right did not differ in either group. Therefore, we combined left and right turns for subsequent analyses. Gait

imagery, with respect to imagined standing, produced increased BOLD signal in all regions except the left GP and right MLR for non-freezers. People in the freezer group exhibited increased BOLD responses during gait only in the left MLR (Table 4.2).

Freezers exhibited smaller beta weights in the CLR than non-freezers ( $F_{1,14}=17.7$ ,  $p=0.001$ ; Table 4.2, Figure 4.5). A task effect was also noted across all groups in the right SMA ( $F_{2,28}=4.30$ ;  $p=0.023$ ). However, pair-wise post hoc analyses (Bonferroni corrected) of SMA BOLD revealed no significant differences between specific tasks in this region. No other significant effects were noted across groups or tasks. Beta weights did not significantly correlate with freezing severity (NFOGQ) or gait speed within the freezers, whereas, in the non-freezers, actual gait speed significantly correlated with beta weights in the right SMA and right MLR (Table 4.3).

## **DISCUSSION**

Our primary result is that during gait imagery, freezers exhibited reduced change in BOLD signal in the CLR with respect to non-freezers. Surprisingly, we did not detect any significant differences in other locomotor regions between groups or across tasks.

The alteration of CLR activity in freezers fits with past investigations relating CLR to locomotion in animals and humans. Mori and co-workers noted that in cats, microstimulation of the CLR evokes controlled locomotion along a moving treadmill (Mori et al. 1999; Mori et al. 2004). This result has not been reproduced in humans, however this region is active in healthy adults during both imagined (Jahn et al. 2008b; Wagner et al. 2008; la Fougere et al. 2010) and actual (Hanakawa et al. 1999a; la Fougere et al. 2010) locomotion. For example, imagined walking elicits a cerebellar

response, and imagined running enhances this activation (Jahn et al. 2008b), suggesting that the cerebellum drives a relatively automated task like imagined running. These findings support the notion that freezing reflects dysfunction of the relationship between automation of locomotion and cerebellar activity. This also fits with the observation that dual tasking increases the automaticity of gait and increases the risk and severity of freezing. Either visual or auditory step cueing disrupts automaticity and may alleviate freezing (Dunne et al. 1987; Dietz et al. 1990). Therefore, tasks which increase the automaticity of walking (i.e. dual task walking) may cause an overdependence on a dysfunctional CLR, enhancing freezing. Similarly, less automated gait (i.e. during the use of visual cues) may partially bypass this dysfunctional circuitry, reducing severity of freezing.

Studies of brain control of actual human gait support the role of cerebellum in locomotion. Hanakawa and colleagues (1999) found that walking over transverse lines (compared to parallel lines) activated the left cerebellar hemisphere in PD and controls (Hanakawa et al. 1999a) possibly reflecting the relationship of the lateral hemisphere to visually guided leg movements (Yu and Eidelberg 1983; Armstrong and Marple-Horvat 1996; Marple-Horvat et al. 1998). As noted, visual cueing (i.e. stepping over lines on the ground) can improve gait and reduce freezing in people with PD (Dunne et al. 1987; Dietz et al. 1990). This relationship between changes in cerebellar activation and visual cueing (which may improve freezing) further supports a relationship between cerebellar function and freezing. That investigation, however, only included non-freezers. As noted in the current investigation, cerebellar function may be altered in freezers with respect to non-freezers, possibly limiting the applicability of these results to freezers. Additional



investigations of how visual or auditory cues affect neural control of locomotion in freezers may provide greater insight into these pathophysiologic mechanisms.

Finally, people with PD, and particularly freezers, may have altered connectivity between the cerebellum and other supraspinal regions (Wu and Hallett 2013). The basal ganglia and cerebellum are structurally connected (Hoshi et al. 2005; Bostan et al. 2010), and people with PD have altered functional connectivity between the striatum and the extended brainstem/cerebellum (Hacker et al. 2012). Cerebellar functional connectivity has also been linked to freezing. A recent preliminary report found reduced functional connectivity between the cerebellum and the pedunculo-pontine nucleus (PPN; a sub-region of the MLR) in freezers compared to non-freezers and healthy adults (Schweder et al. 2010). Although this study only included two freezers, their results support our findings, further implicating a relationship between cerebellar dysfunction and freezing of gait.

Complex gait imagery tasks did not induce changes in BOLD signal with respect to simple gait imagery, despite the fact that actual gait is typically more dysfunctional during complex tasks. Differences in actual and imagined locomotion may contribute to this finding. For example, imagined locomotion may require less balance and postural control than actual gait, limiting the differences in complexity across tasks. Despite these gait imagery limitations, Godde and colleagues showed a small increase in activity (14 voxels) in the left putamen during backward walking compared to forward walking, whereas we found no difference in putamen. Three factors may contribute to this discrepancy between studies. First, the previous report included a larger number of participants (n=51), increasing their power to detect subtle across-task differences.

Second, they had participants practice and imagine tandem backward walking while on a treadmill, while we had participants walk normally overground. Tandem walking is more difficult than normal gait, particularly in older adults (Vereeck et al. 2008), and may have led to a more pronounced BOLD signal change compared to imagined forward walking. Perhaps most importantly, they investigated healthy older adults, whereas we focused on people with PD, making direct comparisons across studies difficult (Godde and Voelcker-Rehage 2010).

Only one previous report examined differences in BOLD signal during imagined locomotion in freezers and non-freezers. In that investigation, freezers exhibited significantly higher BOLD signal changes in the MLR (Snijders et al. 2011). Discrepancies between that study and ours may be due in part to methodological differences. They used a visual imagery task (a disc moving down a hallway) as a control to remove the effects of visual stimulation, while we used an imagined standing task. The use of different baseline tasks can lead to substantially different outcomes (i.e. imagined lying vs. imagined standing (Jahn et al. 2008b)) and therefore may have played a role in the different results of these two investigations. Also, we used a ROI-based analysis, while the primary analysis of the previous report was a full-brain random effects GLM. There are pros and cons to each method. An ROI analysis allows for more precise identification of regions to test specific hypotheses. However, we average all voxels within a region (we assume homogeneity within each ROI) and could miss subtle signal changes in a subregion within the ROI. This is particularly true for larger regions such as the SMA and the putamen. Finally, we may have been underpowered to detect small differences in BOLD responses in regions such as the

MLR. However, in our study, the effect size of freezing status on MLR BOLD signal was 0.5 for the left MLR and 0.0028 for the right MLR. To detect a significant difference in the left MLR with this small effect size would require a sample of 128 and more than 1000 for the right MLR.

## **LIMITATIONS**

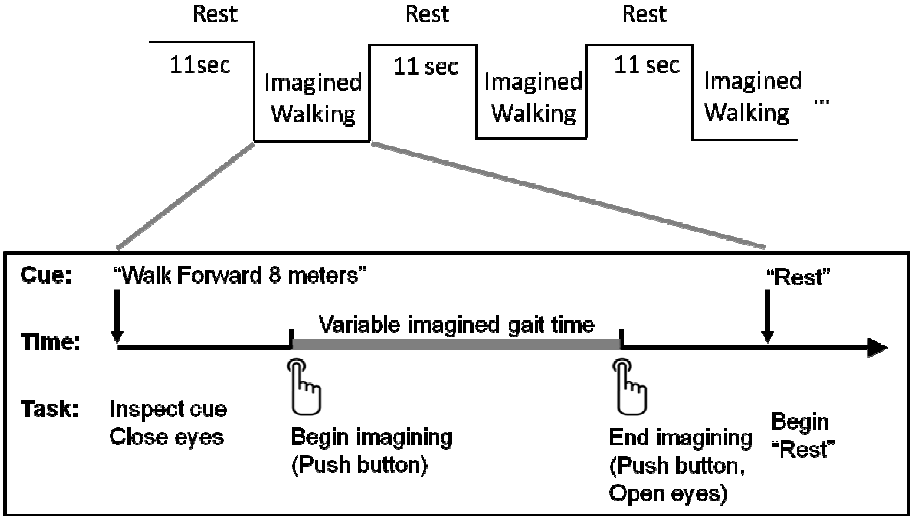
Functional neuroimaging during gait imagery permits investigation of brain pathophysiology that underlies gait tasks. However, this approach has several limitations. Although actual and imagined gait tasks activate similar brain circuits (la Fougere et al. 2010), inherent differences likely exist. Any task-related neuroimaging study depends upon accurate measurement and control of task performance. The covert nature of an imagined task makes this challenging. To ensure participants were able to effectively imagine movement, we screened for vividness of motor imagery (KVIQ score), and matched groups on ability to imagine both single limb movements (measured via the KVIQ), and imagined walking (measured via the GIQ). Furthermore, we tried to measure performance by comparing the length of time the participant imagined walking two different distances while in the scanner. Imagery times for longer distances were larger than short distances, suggesting participants were adhering to imagery tasks. This provided at least a rank order measure of performance of this covert task. Imagination of freezing during the imagery task also could confound task performance. However, no participants reported freezing events during gait imagery. Despite these various approaches to control imagery performance, we included imagined walking time as a covariate in statistical analyses when comparing across

groups as imagined walking at different speeds does alter BOLD responses (Suzuki et al. 2004; Karachi et al. 2010; Cremers et al. 2012b). Controlling for variability of other characteristics between participant groups is another challenge. In our study, we recognize that PD freezers often have greater cognitive impairments than non-freezers (Amboni et al. 2008; Amboni et al. 2010). To minimize this potential confound, we applied strict cognitive screening criteria for all participants (MMSE score had to exceed 26/30), and we matched freezers and non-freezers on this measure. Differences in motor severity between freezers and non-freezers also could be a confound. Therefore, we included MDS-UPDRS part III scores as a covariate in statistical analyses contrasting groups. Finally, our relatively small sample size, limited in part to the strict cognitive and imagery ability screening, may have reduced our power to detect more modest changes in BOLD responses in some regions. Nevertheless, we had adequate power to detect the pronounced reduction in CLR BOLD signal observed in freezers.

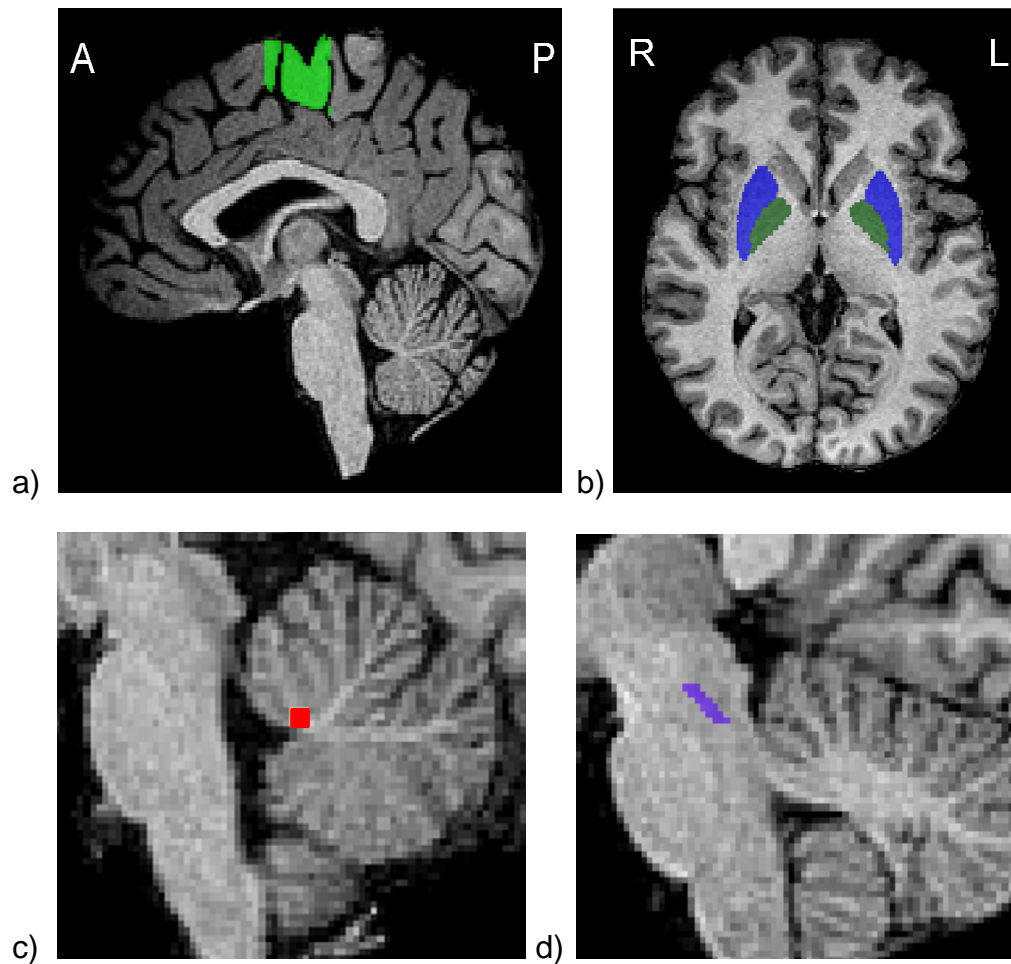
## **CONCLUSION**

Individuals with PD who freeze have reduced BOLD signal changes in the cerebellar locomotor region during imagined gait tasks. This result suggests the cerebellum may play an important role in freezing of gait.

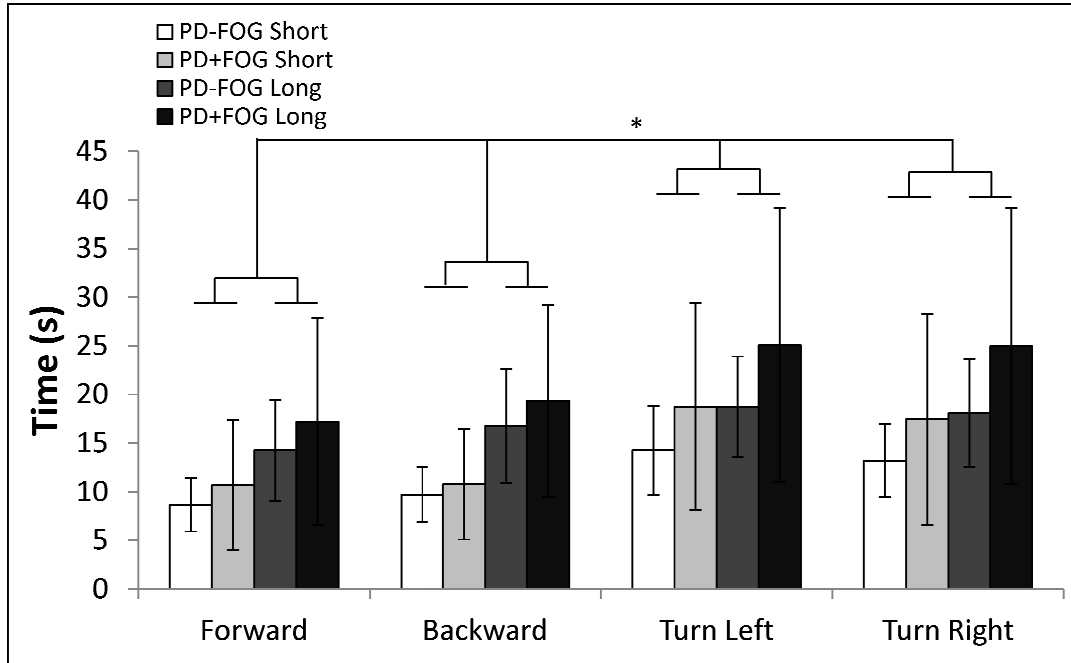
**Figure 4.1:** Gait imagery task. After reading the cue, the participant closes his eyes, pushes a button, and begins imagining. At the completion of gait imagery, he again presses the button and opens his eyes.



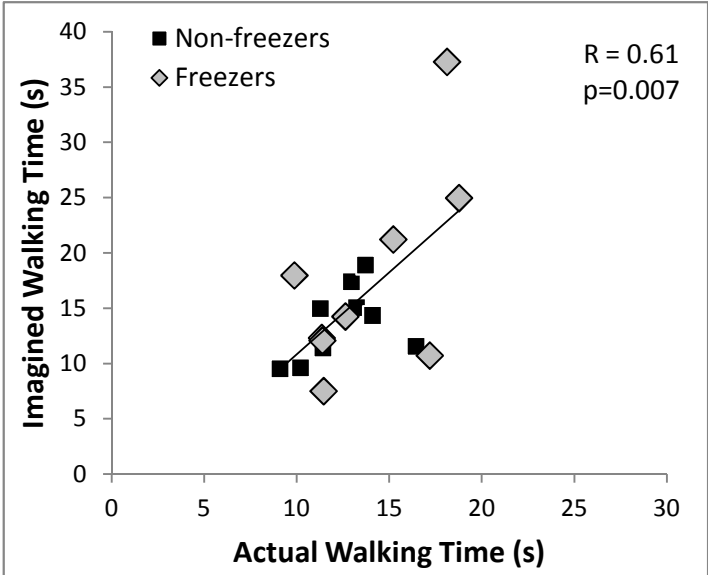
**Figure 4.2:** Regions of interest. Regions were identified for each individual separately based on standard definitions (see Methods). Shown are examples of regions defined for four subjects: supplementary motor area (a), putamen (blue) and globus pallidus (green) (b), cerebellar locomotor region (c), and mesencephalic locomotor region (d). A- Anterior; P-Posterior; R-Right; L-Left



**Figure 4.3:** Gait imagery times in non-freezers and freezers during short and long gait imagery tasks. “Long” gait imagery tasks took significantly longer than “short” gait imagery tasks (denoted by \*,  $F_{1,16}=34.6$ ;  $p<0.001$ , repeated measures ANOVA) . Differences between non-freezers (PD-FOG) and freezers (PD+FOG) did not reach significance.

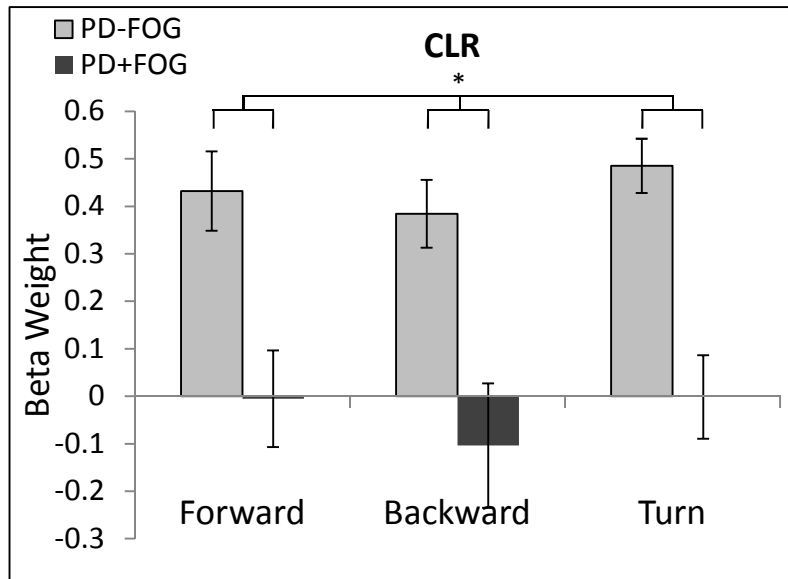


**Figure 4.4:** Correlation between actual and imagined walking times for freezers and non-freezers. Correlation statistics represent all participants.





**Figure 4.5:** Mean beta weights across gait tasks in non-freezers (PD-FOG) and freezers (PD+FOG) in the CLR. PD-FOG demonstrated significantly higher BOLD signal than PD+FOG (\* $p=0.001$ ). Error bars represent standard error of the mean.



**Table 4.1:** Participant characteristics

	<b>PD-FOG</b>	<b>PD+FOG</b>	<b>p-value</b>
<b>N</b>	9 (7 male)	9 (5 male)	
<b>Age (yrs)</b>	62.7 (8.5)	66.6 (6.7)	0.29
<b>MDS-UPDRS-III<sup>#</sup></b>	27.7 (8.8)	36.1 (9.3)	0.06
<b>Hoehn &amp; Yahr</b>	2.22 (0.26)	2.5 (0.35)	0.08
<b>Years since Diagnosis</b>	4.1 (8.8)	9.4 (7.2)	0.07
<b>NFOG-Q total score<sup>§</sup></b>	-	13.0 (8.2)	
<b>KVIQ *</b>	81.4 (11.8)	74.3 (12.4)	0.22
<b>GIQ *</b>	28.1 (4.4)	25.3 (10.8)	0.33

<sup>#</sup>Movement Disorders Society Unified Parkinson's Disease Rating Scale (part III)

<sup>§</sup>New Freezing of Gait Questionnaire

\*KVIQ: Kinesthetic Visual Imagery Questionnaire, max score 100

\*GIQ: Gait Imagery Questionnaire, max score 40

One left handed participant was included in the PD+FOG group

**Table 4.2:** ANCOVA results for each ROI. P-values shown.

ROI	ANCOVA Main Effects			Gait vs. stand (paired sample t-test)	
	Group	Task	Group by Task interaction	Non-freezers	Freezers
Right SMA	0.861	<b>0.023</b>	0.226	<b>0.025</b>	0.088
Left SMA	0.984	0.09	0.341	<b>0.003</b>	0.073
Right PUT	0.623	0.889	0.137	<b>0.008</b>	0.153
Left PUT	0.306	0.951	0.481	<b>0.013</b>	0.094
Right GP	0.505	0.080	0.565	<b>0.004</b>	0.134
Left GP	0.922	0.762	0.087	0.182	0.407
Right MLR	0.424	0.322	0.139	0.232	0.14
Left MLR	0.59	0.183	0.108	<b>0.001</b>	<b>0.032</b>
CLR	<b>0.001</b>	0.869	0.813	<b>&lt;0.001</b>	0.723

**Table 4.3:** P-values (Spearman’s  $\rho$ ) of all correlations between beta weights during imagined gait (averaged across all gait imagery tasks) and actual overground walking speed (averaged across all gait tasks).

		<b>SMA R</b>	<b>SMA L</b>	<b>PUT R</b>	<b>PUT L</b>	<b>GP R</b>	<b>GP L</b>	<b>MLR R</b>	<b>MLR L</b>	<b>CLR</b>
<b>Gait beta weight vs. actual walk velocity</b>	PD-FOG $\rho(\rho)$	<b>0.02</b> <b>(0.75)</b>	0.112 (0.57)	0.41 (0.317)	0.11 (0.57)	0.36 (0.35)	0.14 (0.53)	<b>0.01</b> <b>(0.78)</b>	0.76 (0.12)	0.97 (-0.02)
	PD+FOG $\rho(\rho)$	0.41 (0.32)	0.24 (0.43)	0.52 (0.25)	0.83 (0.08)	0.24 (0.43)	0.55 (0.23)	0.67 (0.17)	0.90 (0.05)	0.52 (0.25)

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## **Chapter 5: Conclusion**

### **SUMMARY OF MAJOR FINDINGS**

The goal of this dissertation was to better understand biomechanical and neural factors associated with gait dysfunction and freezing of gait in individuals with Parkinson disease (PD). To this end, we investigated: 1) how coordination of steps was related to freezing of gait, 2) the neural correlates of locomotor dysfunction in those with PD, and 3) the neural correlates of freezing in those with PD. Major findings of each section, within the context of current literature, are as follows:

#### Chapter 2

One component of gait dysfunction in PD is inconsistent and small steps (Yogev et al. 2007). The variability of the stepping pattern (both in length, and timing) and symmetry of left and right steps are altered in PD and may be related to freezing (Hausdorff et al. 1998; Hausdorff et al. 2003; Plotnik et al. 2008). In fact, it has been hypothesized that there may be a threshold level beyond which increases in variability and/or asymmetry may result in freezing (Plotnik and Hausdorff 2008). The phase coordination index (PCI) is a recently developed measure which quantifies these irregularities in timing and coordination of steps during gait (Plotnik et al. 2007). Recent studies using PCI showed that people with PD exhibit abnormalities in gait coordination with respect to healthy adults (Plotnik et al. 2007; Plotnik et al. 2009). Further, coordination is worse in freezers than non-freezers (Plotnik et al. 2008). This covariance between FOG and coordination suggests a relationship may exist between these variables. However, previous literature is based on normal forward walking, whereas freezing is more common during complex gait tasks such as backward walking or

turning. Determining how coordination is affected by tasks which frequently elicit FOG is critical to understand the relationship between coordination and freezing. For example, if a relationship between coordination and FOG does exist then turning, a task associated with FOG, should elicit worse coordination than forward walking. However, if turning does not result in worse coordination, it is unlikely that coordination is a strong predictor of or contributing factor to FOG.

We addressed this question in chapter 2. In sum, our results support the relationship between coordination (measured by PCI) and freezing. Three main results support this. First, as shown in previous investigations, freezers demonstrated worse coordination than non-freezers across a variety of tasks. Second, tasks related to freezing (turning in small circles, backward walking) resulted in worse coordination than simple (forward, turning in large circles) gait tasks. In addition, there was a task by group interaction, such that tasks related to freezing had a more pronounced effect on those with PD (and freezers in particular) than healthy older adults. Third, there was a significant relationship between severity of freezing and extent of dyscoordination. Together, these results suggest a relationship between coordination and freezing. More research is necessary, however, to test a potential causal link between coordination of steps and freezing.

### Chapter 3

The physical characteristics of gait dysfunction in PD are generally well described. However, considerably less is known about their neural underpinnings. Four recent studies began to address this question. These investigations showed inconsistent alterations in those with PD in a number of regions, including the

supplementary motor area (SMA) (Hanakawa et al. 1999; Snijders et al. 2011), tegmental brain stem (including the mesencephalic locomotor region; MLR) (Snijders et al. 2011; Cremers et al. 2012), and the cerebellum (Hanakawa et al. 1999; Cremers et al. 2012), among others. However, these reports largely used simple gait tasks. As with chapter 2, we wished to investigate the effects of more complex gait tasks, as these tasks may underscore potential differences between controls and those with PD.

We assessed the differences in blood oxygen level dependent (BOLD) signal in people with PD and healthy adults during simple (forward) and complex (backward, turning) gait imagery tasks. These effects were assessed in 5 a-priori regions of interest, chosen because of their involvement in locomotor control and their known dysfunction in PD. These regions were: SMA, globus pallidus (GP), putamen, MLR, and cerebellar locomotor region (CLR). There were three main results of this study. First, a group by task interaction was noted in the SMA such that turning resulted in a more pronounced change in BOLD signal in PD than in controls. Second, individuals with PD exhibited reduced change in BOLD signal in the globus pallidus with respect to healthy adults. Finally, we observed significant correlations in several regions between change in BOLD signal and overground walking speed, a measure of global locomotor function. These results suggest that: 1) people with PD may require more activity in the supplementary motor area than controls to complete complex gait tasks, and this increase may be compensatory in nature; 2) gait dysfunction in people with PD (i.e. reduced gait velocity) may be related to altered function of the GP; and 3) elevated BOLD signal in locomotor regions may predict improved gait function. Together these results further elucidate the changes in activity of locomotor regions during gait imagery

tasks in PD and in controls, and provide evidence supporting a relationship between increased BOLD signal in locomotor regions and improved walking function.

#### Chapter 4

Finally, we wished to identify alterations in brain signal which may be related to freezing of gait. Only one previous study investigated brain activity associated with freezing of gait. This report examined BOLD response during imagined forward walking in freezers and non-freezers. Freezers exhibited increased change in BOLD in the MLR with respect to non-freezers (Snijders et al. 2011). However, in this study participants only imagined forward walking. Similarly to chapters 2 and 3, we wished to understand how complex gait tasks (i.e. those which typically elicit freezing) affect BOLD signal in those who freeze with respect to those who do not freeze. Thus, we re-analyzed the PD data from chapter 3, this time contrasting those who do freeze (n=9), with those who do not freeze (n=9).

Our main result was a reduction in change in BOLD signal in the CLR in freezers with respect to non-freezers. There were no task effects or group by task interactions in any of the regions of interest. Despite the relationship between overground gait speed and change in BOLD observed across those with PD (chapter 3), few correlations remained within the freezer and non-freezer groups. No correlations were observed in either group to step-to step coordination (measured via PCI), or between freezing severity and BOLD signal in freezers. Additional research is necessary to understand the neural underpinnings of freezing of gait. However, these results suggest the cerebellum may play an important role in freezing of gait

## **SIGNIFICANCE AND CLINICAL IMPLICATIONS**

Understanding factors related to freezing and gait dysfunction may lead to improvements in the care of individuals experiencing these symptoms. For example, identifying highly quantifiable biomechanical factors which are related to freezing (i.e. PCI) may allow researchers and clinicians to more precisely track the development and progression of freezing of gait. This is especially important for freezing, as it is difficult to elicit in a clinical or laboratory setting. In addition, quantifiable measures related to freezing may lead to identification of those at risk for future freezing events, allowing early intervention (both behavioral and environmental) which could reduce the negative effects of freezing. Finally, this work suggests rehabilitative interventions aimed specifically at improving coordination of gait may also be beneficial for ameliorating freezing of gait.

Due to the complex circuitry of locomotion, dysfunction during gait (i.e. discoordination and freezing) is likely due to a number of neural factors. However, identifying specific regions with dysfunction is a critical step to understanding why dysfunction and freezing occur, and provides an important foundation for potential improvement of pharmacologic and surgical interventions. Pharmacologic interventions are often aimed at addressing alterations in neurotransmitter levels which arise, in part, from dysfunction of particular regions (i.e. acetylcholine: PPN, basal nucleus of Meynert; dopamine: substantia nigra). Identifying regions which are dysfunctional specifically during gait may allow for more focused pharmacologic interventions. In addition, deep brain stimulation is becoming a common intervention which can greatly improve

symptoms of PD, and in some cases freezing. Identification of regional dysfunction may inform future sites for DBS aimed at improving gait and freezing.

## **LIMITATIONS**

Our design for the experiment in chapter 2 did not allow investigation into the potential causal relationship between freezing and coordination. This approach will be necessary in future work to provide a more complete understanding of how these symptoms are related.

There are several limitations of using fMRI to investigate brain mechanisms underlying gait dysfunction. For example, the temporal resolution of fMRI is not fast enough to pick up many components of brain signaling. This limits the ability to assess brain function during freezing events. Further, the spatial resolution (commonly  $\sim 4\text{cm}^3$ ) makes investigation of small regions, including the MLR and PPN, difficult. Spatial distortion of the BOLD signal further limits conclusions from these investigations. Finally, to investigate gait function using fMRI, participants must imagine gait tasks. This brings about numerous potential problems including similarity between overt and imagined movements, adherence to gait tasks, ability to imagine movement, and difficulties effectively measuring behavioral responses.

These limitations aside, there are currently few other methodologies available to address this clinically important question. For example, brain imaging which allows for actual gait (i.e. Positron Emission Tomography) typically has considerably worse spatial and temporal resolution than fMRI. Further, during actual walking, gait is typically very different between PD and controls. Therefore, the use of gait imagery allows for imagery

of similar gait tasks, reducing the potential confound of different performance across groups. In the current investigation, we took several steps to address limitations of gait imagery and fMRI, including assessments of both the ability and adherence to gait imagery tasks. Though this approach is far from perfect, we believe we were able to effectively address many of these issues.

## **SUGGESTIONS FOR FUTURE RESEARCH**

To better understand the relationship between dysfunctional coordination and freezing, it is necessary to investigate possible causal mechanisms between these symptoms. Investigating the effects of specific alterations of coordination (i.e. PCI) on the frequency and severity of freezing may yield insights into this relationship.

Considerable work will be necessary to fully understand the neural underpinnings of gait dysfunction and freezing in those with PD. One future direction may be to investigate BOLD signal during actual freezing events. There are several technical and logistical hurdles to this approach; however recent work is beginning to address the issue in upper limb motor blocks (Vercruyssen 2012). Another approach may be to use electroencephalography (EEG) to assess cortical and subcortical brain function during actual gait. Previously, motion artifacts of gait have limited the use of EEG during walking. However, recent research showed this is an effective method of assessing the neural correlates of gait (Gwin et al. 2010; Gwin et al. 2011). This method provides data with very high temporal resolution and as such may be able to identify specific freezing events during walking. Another approach may be to assess the functional connectivity of freezers and non-freezers using fMRI. This approach allows participants to rest



quietly, circumventing differences in motor dysfunction across populations. Functional connectivity can also provide important insights into altered circuitry of those with PD.

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## **Appendix 1: Effects of Levodopa on Vividness of Motor Imagery in Parkinson Disease**

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## **ABSTRACT**

**PURPOSE:** Motor imagery during functional magnetic resonance imaging is commonly used to understand the neural underpinnings of complex movements. This approach has recently been applied to individuals with Parkinson disease (PD) to better understand how brain function may relate to movement dysfunction. However, the ability of individuals with PD to imagine movements when “Off” dopamine replacement medication is poorly understood. Therefore, the purpose of the current study is to test the ability of people with PD to imagine movements while “On” and “Off” anti-Parkinson medication.

**METHODS:** Vividness of imagery was assessed in 28 individuals with mild to moderate PD (Hoehn and Yahr stages 1-3) via the Kinesthetic Visual Imagery Questionnaire (KVIQ-20) both “On” and “Off” anti-Parkinson medication. Vividness of imagery of 32 age-matched older adults was also assessed.

**RESULTS:** No differences in vividness of imagery were observed between “Off” and “On” medication states ( $p=0.15$ ). Imagery was similar between controls and PD both “Off” ( $p=0.25$ ) and “On” ( $p=0.46$ ) anti-Parkinson medication. A significant correlation was observed between imagery and disease severity while “On” anti-Parkinson medication ( $r= -0.49$ ;  $p=0.008$ ).

**CONCLUSIONS:** Vividness of movement imagery was not different between “Off” and “On” anti-Parkinson medications or between PD and controls. These results suggest that people with PD are able to imagine similarly to older adults both when “On” and “Off” anti-Parkinson medication, and supports the use of motor imagery in the “Off” medication state.



## INTRODUCTION

Motor imagery (MI) is “a dynamic state during which representations of a given motor act are internally rehearsed in working memory without any overt motor output”(Decety 1996). MI has been used extensively with imaging techniques such as functional magnetic resonance imaging to provide insight into the neural underpinnings of complex motor processes in healthy adults (Sacco et al. 2006; Bakker et al. 2008; Jahn et al. 2008; Wagner et al. 2008; Godde and Voelcker-Rehage 2010; la Fougere et al. 2010; Snijders et al. 2011). More recent studies have begun to use MI with imaging techniques to better understand how brain pathology in individuals with Parkinson disease (PD) relates to movement dysfunction (Cunnington et al. 2001; Samuel et al. 2001; Helmich et al. 2007; Snijders et al. 2011). In these investigations, PD subjects are often studied “Off” anti-Parkinson medication (Levodopa replacement). However, the ability of people with PD to imagine movements while “Off” dopamine replacement medication is not well understood. One recent investigation showed that individuals with PD have similar vividness of imagery as healthy adults (Heremans et al. 2011); however, this study tested the vividness of imagery in people with PD while “On” anti-Parkinson medication. Levodopa has been suggested to normalize brain activity in PD in many regions, including the supplementary motor area (SMA) (Rascol et al. 1992; Sabatini et al. 2000; Buhmann et al. 2003; Ng et al. 2010). This region is associated with motor planning (Tanji and Shima 1994; Makoshi et al. 2011) and has been shown to be active during both overt (Rascol et al. 1992) and imagined (Jahn et al. 2008; Snijders et al. 2011) movements. Therefore, pathological activation of SMA, as well as other regions, may reduce the ability of this group to imagine movement in the “Off”

medication state. As imagery studies are often carried out with patients “Off” anti-Parkinson medications, it is important to determine the degree to which people with PD can imagine in this medication state. Further, MI has shown promise as a rehabilitative strategy in both healthy individuals (Schuster et al. 2011), and recently, those with neurological disorders, specifically stroke (Liu et al. 2004; Page et al. 2007). Though rehabilitative MI has not yet been tested in those with PD, understanding changes in imagery while “Off” and “On” anti-Parkinson medication could provide insight into which medication state is better suited for this potential intervention.

The purpose of the current study was to test vividness of MI in individuals with PD both “On” and “Off” anti-Parkinson medications, as well as how vividness of MI in those with PD compares to healthy older adults. Due to the altered activation of brain regions (including the SMA) thought to be associated with motor planning while “Off” anti-Parkinson medication, we hypothesized that individuals with PD “Off” anti-Parkinson medication would exhibit worse vividness of imagery with respect to “On” medication. We further hypothesized that the normalizing effects of Levodopa would result in similar imagery scores between PD “On” and healthy controls.

## **METHODS**

### Participants

Twenty eight individuals with PD and 32 age-matched healthy older adults participated in the study. Six of 28 PD and 2 of 32 controls were left handed. Thirteen of 28 PD were more affected on their left side. Exclusion criteria included severe orthopedic problems of upper or lower limbs, deep brain stimulation, and any

neurological disorders other than PD. Diagnosis of PD was given by a board certified neurologist using the diagnostic criteria for “definite PD” (Racette et al. 1999) and based on established criteria (Hughes et al. 1992). All individuals with PD were taking levodopa (Mean  $\pm$  SD Levodopa Equivalent Daily Dose=928  $\pm$  566; range 300-3000) when enrolled in the study. Written informed consent was provided by all subjects in accordance with the Helsinki Declaration of 1975, and all procedures were reviewed and approved by the Human Research Protection Office at Washington University School of Medicine.

### Quantifying Imagery

To assess imagery ability, the Kinesthetic Visual Imagery Questionnaire (KVIQ-20) was administered to all subjects in a similar manner to that described in Malouin et al (Malouin et al. 2007). The KVIQ-20 was chosen as it was designed specifically to be administered to individuals with movement disorders (Malouin et al. 2007), and has previously been shown to be reliable for individuals with PD (Randhawa et al. 2010). In addition, the ease and speed of administration of this test make it attractive as a potential tool to screen for ability to imagine.

The KVIQ-20 includes 10 motions of the neck, shoulders, upper limb, lower limb, and trunk. To administer the KVIQ-20, each motion is demonstrated by the tester, and then completed by the participant. The participant then imagines the motion and rates the vividness of his visual imagery followed by the vividness of his kinesthetic imagery, each on a 5 point scale (5=image or intensity as vivid as completing the motion; 1= no image or sensation). Each score is recorded by the examiner. Seven of the 10 motions

consist of movement of a single limb. For these motions, imagery of both the left and right sides were assessed.

Kinesthetic and visual scores were calculated as the sum of scores from each motion, with scores from bilateral motions averaged across left and right sides giving a minimum possible score of 0 and a maximum possible score of 50 (10 motions x maximum rating of 5). KVIQ-Total scores were determined as the sum of kinesthetic and visual sub-scores (maximum possible score = 100).

For bilateral movements, scores were compared across more and less affected sides (PD) and across dominant and non-dominant sides (PD, control). These side-specific scores were calculated as the sum of kinesthetic and visual scores for one side (more affected, less affected, dominant, or non-dominant) across all bilateral movements. As there are 7 bilateral movements, with a maximum total KVIQ score of 10 for each movement (max kinesthetic score =5; max visual score = 5), the maximum possible score for these values is 70. For individuals with PD, more and less affected side was determined by summing unilateral components of the MDS-UPDRS III. The side which accumulated a larger score was deemed the more affected side.

Individuals with PD were tested two times, while healthy controls were tested once. Individuals with PD were first tested "Off" anti-Parkinson medication (>12 hours since last dose; a commonly used criterion used to assess PD symptoms "Off" medication (Langston et al. 1992; Cunnington et al. 2001; Samuel et al. 2001; Helmich et al. 2007; Snijders et al. 2011)). After taking a normal dose of medication, subjects waited for approximately one hour, and the KVIQ-20 was administered again.

Approximately 2 hours elapsed between KVIQ-20 testing sessions for individuals with PD.

Subjects' disease severity was assessed by the part III subscale of the Movement Disorders Unified Parkinson Disease Rating Scale (MDS-UPDRS III (Goetz et al. 2008)), and the Hoehn and Yahr scale (Hoehn and Yahr 1967) both "On" and "Off" medication.

### Statistics

A paired t-test was used to determine the effects of medication on KVIQ-20 scores. Independent t-tests were used to compare individuals with PD to healthy older adults. To determine whether motor severity predicts one's ability to imagine, Pearson correlation coefficients were used to assess the relationship between KVIQ-20 scores and motor severity (MDS-UPDRS III and Hoehn & Yahr scale) both "On" and "Off" anti-Parkinson medication. All measures are noted as mean  $\pm$  standard deviation, unless otherwise noted.

## **RESULTS**

Individuals with PD were of similar age as healthy controls (PD=71.0  $\pm$  8.9; Controls=70.3  $\pm$  10.6;  $p=0.78$ ). Individuals with PD improved MDS-UPDRS III and Hoehn & Yahr scores after administration of anti-Parkinson medication ( $p<0.001$  and  $p=0.01$ , respectively; Table 1), suggesting subjects did see significant benefit from their anti-Parkinson medication.

Similarly to previous investigations (Heremans et al. 2011), no differences were observed between dominant and non-dominant limbs for control ( $p=0.34$ ), PD "Off"

( $p=0.06$ ), or PD “On” anti-Parkinson medication ( $p=0.22$ ). In addition, within the PD group, no differences were observed in KVIQ between more and less affected limbs “Off” ( $p=0.10$ ) or “On” ( $p=0.93$ ) anti-Parkinson medication (Table 2). Therefore, imagery scores for bilateral movements were each averaged across limbs for each subject.

Contrary to our hypothesis, there were no statistically significant differences in vividness of imagery in people with PD when “Off” or “On” anti-Parkinson medication (Table 1). Further, no differences were observed between vividness of imagery in healthy older adults and individuals with PD “On” or “Off” anti-Parkinson medication. Kinesthetic and visual KVIQ components were also not different across groups. Across all subjects, the visual component of the KVIQ-20 was significantly higher than kinesthetic component of the KVIQ-20 score ( $p<0.001$ ). Six of 32 control subjects and 5 of 28 PD subjects exhibited scores of  $<20$  on either vividness or kinesthetic components of the KVIQ. A score of 20 represents an average response of 2 across all tasks, or a “blurred image” and “mildly intense” for visual and kinesthetic imagery, respectively.

Scores on the KVIQ-20 while “On” anti-Parkinson medication were positively correlated to KVIQ-20 scores “Off” anti-Parkinson medication ( $r=0.94$ ,  $p<0.0001$ ; Figure A.1a). KVIQ “On” was negatively correlated to MDS-UPDRS III “On” ( $r=-0.49$ ,  $p=0.008$ ; Figure A.1b) such that increased disease severity predicted worse imagery. MDS-UPDRS III “Off” anti-Parkinson medication was not, however, correlated to KVIQ-20 “Off” ( $r=-0.31$ ,  $p=0.11$ ; Figure A.1c). Finally, no relationship was observed between KVIQ score and age for PD ( $r=-.26$ ,  $p=0.18$ ), control ( $r=-0.05$ ,  $p=0.81$ ) or the combination of PD and control subjects together, ( $r=-0.14$ ,  $p=0.28$ ; Figure A.1d).

## DISCUSSION

Dopamine replacement therapies have been shown to be beneficial for reducing many of the symptoms of PD (Cotzias et al. 1967). Until now it has been unclear whether dopamine replacement impacts MI in people with PD. As many imagery studies are carried out with individuals “Off” anti-Parkinson medication, it is critical to determine the degree to which individuals with PD can imagine movement while in the “Off” anti-Parkinson medication state. Our results suggest that in both the “Off” and “On” medication states, individuals with PD have similar imagery vividness as healthy older adults. This result provides support for MI testing while people with PD are “Off” anti-Parkinson medication. Further, MI has been suggested as a rehabilitative strategy for individuals with neurological disorders (Liu et al. 2004; Page et al. 2007). The ability of individuals with PD to imagine “Off” their anti-Parkinson medication suggests this potential rehabilitative strategy may be applicable when subjects are “Off” anti-Parkinson medication state.

A recent report suggests that although some areas of the brain are less active when “Off” anti-Parkinson medications, other areas may be more active, potentially compensating for PD-related deficits and contributing to the relatively normal degree of imagery vividness noted in the current study (Cunnington et al. 2001). Cunnington and colleagues measured brain activation using positron emission topography during imagined movements in individuals with PD both “On” and “Off” anti-Parkinson medication. Results showed that while there was less activation while subjects were “Off” medication with respect to “On” in the left anterior cingulate gyrus, there was more activation while “Off” in the left lingual gyrus and the left precuneus. The precuneus has

been suggested to be related to preparation of movements (Kawashima et al. 1995; Cavanna and Trimble 2006), potentially compensating in part for reduced activation of other regions, and helping individuals retain the ability to vividly imagine movements while “Off” anti-Parkinson medication. As noted above, individuals with PD tested in the current study ranged from mild to moderate. It is possible that individuals with more severe PD may be less able to compensate for neurodegeneration, resulting in a loss of imagery vividness. Therefore studies to determine the vividness of imagery for those with more severe PD symptoms are warranted.

Our results generally fit well with previous reports on MI in individuals with PD (Randhawa et al. 2010; Heremans et al. 2011) and healthy older adults (Malouin et al. 2007). Two recent studies have measured imagery vividness among individuals with PD using the KVIQ-20 while “On” anti-Parkinson medication (Randhawa et al. 2010; Heremans et al. 2011). Randhawa and colleagues (2010) reported vividness of MI of individuals with PD were slightly higher (better) than those reported in the current study. However, this may be due to the fact that subjects in the current study exhibited more severe Parkinsonian symptoms (higher MDS-UPDRS III scores) than those of Randhawa and colleagues. Indeed, correlation results from the current study suggest the possibility that worse MDS-UPDRS III scores may predict worse imagery in PD. Heremans et al. (2011) reported KVIQ-20 values for people with PD “On” anti-Parkinson medications as well as healthy adults to be worse than those reported in the current study. However, similarly to Heremans and colleagues, we observed no differences in vividness of imagery between older adults and individuals with PD while “On” anti-Parkinson medication. Our results further extend the findings of both Heremans &



Randhawa, showing that even when “Off” medication, individuals with PD seem to retain the ability to imagine movements.

KVIQ-20 scores “On” and “Off” anti-Parkinson medication were highly correlated, suggesting vividness of imagery was quite consistent across medication states.

Although MDS-UPDRS III “Off” and KVIQ-20 “Off” were not correlated, we did find a medium (Cohen 1988) correlation between MDS-UPDRS III “On” and KVIQ-20 “On” scores, such that individuals with worse MDS-UPDRS III scores had worse KVIQ-20 scores. This correlation suggests that ability to imagine may be related to PD motor symptom disease severity. Our investigation included only individuals with mild or moderate PD. Further studies determining ability of individuals with moderate to severe PD are necessary to better understand how PD severity may be related to vividness of imagery.

Across all subjects, age was not correlated with KVIQ-20 scores. This suggests that amongst the participants studied in the current investigation, age did not seem to play an important role in subjects’ vividness of imagery. This is consistent with a previous assessment of KVIQ-20 across age groups (Malouin et al. 2010) which also showed age not to have a significant effect on MI. Studies assessing different aspects of imagery, such as timing of imagery, have, however, described age-related differences in the ability to imagine movements (Personnier et al. 2008; Personnier et al. 2010; Gabbard et al. 2011). For example, Personnier and colleagues showed that when imagining gait, older adults systematically over-estimated the duration of imagined movements with respect to overt motions (Personnier et al. 2010). Together, these

results suggest some aspects of MI (timing of imagery) may be altered across age while others (vividness of imagery) seem to be retained.

Both PD and control subjects in the current study scored higher on visual components of imagery than kinesthetic components. This result is similar to several previous reports (Atienza et al. 1994; Malouin et al. 2007; Malouin et al. 2008; Heremans et al. 2011), and suggests that like healthy controls (Malouin et al. 2007) and individuals who have experienced a stroke (Malouin et al. 2008), individuals with PD more vividly imagine the visual component of movement than the kinesthetic component. Further, results of the current study show that there is no change in this relationship with medication. That is, visual scores tend to be greater than kinesthetic scores both “On” and “Off” anti-Parkinson medication.

Several subjects, both control and PD, demonstrated a marked inability to imagine movement (<20 on either Kinesthetic or Visual components of KVIQ). However, the proportion of individuals who were unable to imagine were similar in control (6/32; 19%) and PD groups (5/28; 18%). This is in conjunction with previous reports, which show a small population of both healthy controls (Malouin et al. 2007) and those with PD (Randhawa et al. 2010; Heremans et al. 2011) to exhibit poor imagery ability. Together, these results underscore the importance of assessing imagery ability in all individuals completing a task requiring MI.

### Limitations

In the current study it was not possible to counter-balance the order of KVIQ-20 testing sessions for individuals with PD. That is, participants with PD were always tested “Off” medication first, then again “On” medication. It is therefore possible that “On”

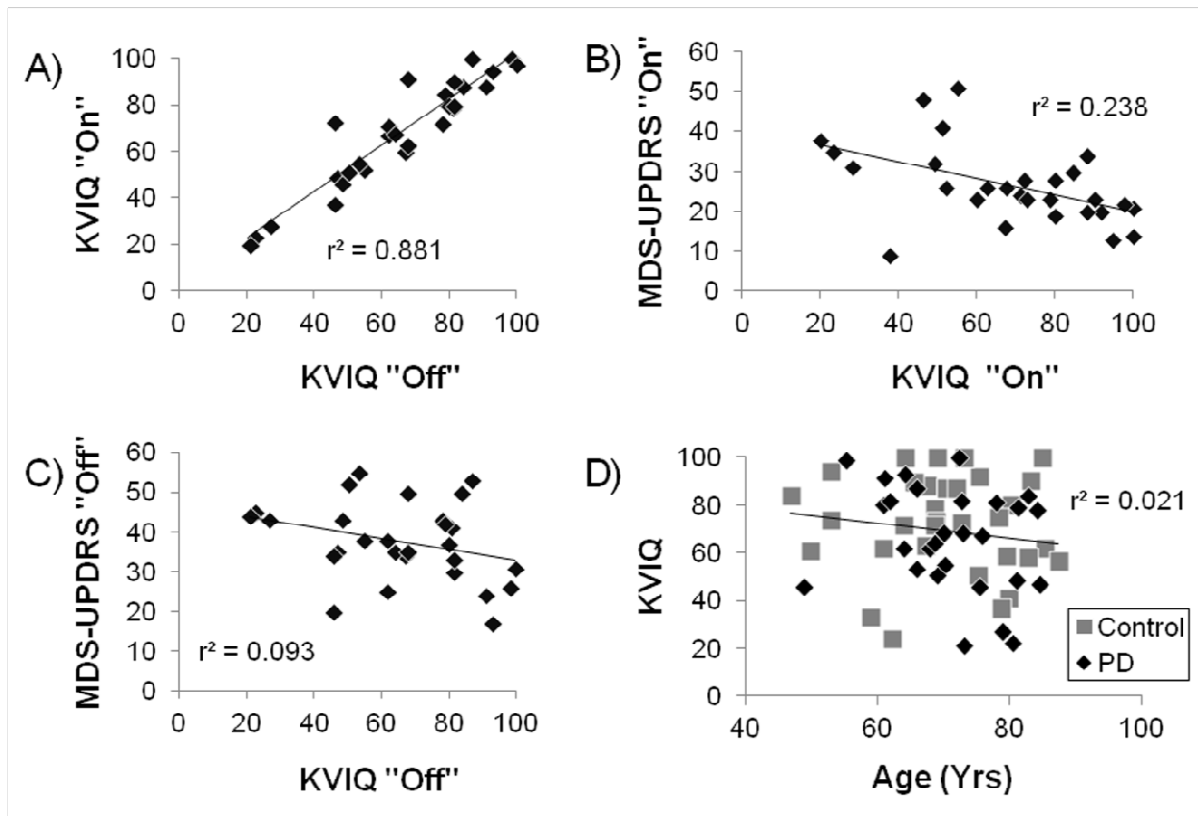
medication scores may have been biased due to a practice effect. If this were the case we may expect an overestimation of imagery vividness on the second administration when “On” medication. Despite the possibility of an overestimation of imagery vividness while “On” medication, we still found no differences between “Off” and “On” medication testing sessions, suggesting that “Off” medication imagery is likely not diminished with respect to imagery in the “On” anti-Parkinson medication state.

We determined the vividness of imagery in people with mild to moderate PD (Hoehn & Yahr stages 1-3). In addition, we showed that while “On” medication, imagery (KVIQ-20) was negatively correlated to disease severity (MDS-UPDRS III). It is possible that our results do not extrapolate to individuals with more severe PD. It therefore remains to be determined whether individuals with severe PD and/or cognitive deficits are able to effectively imagine movement.

### Conclusions

Imagery scores while “On” anti-Parkinson medication and after refraining from medication for a commonly used period of time (12 hrs) were both similar to healthy adults, suggesting anti-Parkinson medication likely does not have a substantial effect on vividness of motor imagery for individuals with mild to moderate PD. Although vividness of imagery does not seem to be affected by medication levels, the negative correlation between UPDRS and KVIQ in the “On” state suggests the possibility that imagery may be degraded in individuals with more severe PD. Further research on individuals with more severe PD is necessary to more fully understand this relationship.

**Figure A.1:** Relationships between: (A) KVIQ “Off” and “On” anti-Parkinson medication, (B) Disease severity (MDS-UPDRS III) and KVIQ “On” anti-Parkinson medication, (C) Disease severity and KVIQ “Off” anti-Parkinson medication, and (D) Age and KVIQ (Regression line and  $r^2$  value represents data from all participants; PD data shown is “Off” anti-Parkinson medication).



**Table A.1:** Demographic and imagery results across groups

<b>Variable</b>	<b>Control (N=32)</b>	<b>PD “Off” (n=28)</b>	<b>PD “On” (n=28)</b>	<b>*P-value: PD “On” vs. PD “Off”</b>	<b>#P-value: PD “Off” vs. Control</b>	<b>#P-value: PD “On” vs. Control</b>
<b>Age</b>	70.3 (10.6)	71.0 (8.9)		-	0.78	
<b>UPDRS-MDS III</b>	-	37.6 (9.9)	26.6 (9.8)	<0.001	-	-
<b>Hoehn &amp; Yahr</b>	-	2.4 (0.3)	2.2 (0.4)	0.005	-	-
<b>Stage</b>						
<b>Disease Duration</b>	-	6.5 (3.8)		-	-	
<b>KVIQ – Visual</b>	38.6 (10.9)	34.6 (10.9)	36.3 (11.6)	0.13	0.16	0.42
<b>KVIQ - Kinesthetic</b>	33.8 (12.2)	31.2 (12.1)	31.8 (13.0)	0.42	0.45	0.59
<b>KVIQ – Total</b>	72.2 (20.6)	65.8 (22.0)	68.1 (23.3)	0.15	0.25	0.46

Mean (SD). Maximum score of Visual and Kinesthetic sub-components = 50, Maximum score of KVIQ-Total = 100 (See Methods). PD “Off” = PD “Off” anti-Parkinson medication, PD “On” = PD “On” anti-Parkinson medication, Control = healthy older adults. \*Paired t-test; #Independent samples t-test

**Table A.2:** KVIQ scores for more and less affected side, and dominant and non-dominant side.

	Dominant	Non-Dominant	More Affected	Less Affected
PD "Off"	45.5(15.6)	47.1(16.2)	45.6(16.4)	47.0(15.7)
PD "On"	46.8(16.7)	47.7(16.4)	47.3(16.3)	47.3(16.9)
Control	50.5(15.0)	51.0(14.4)	-	-

Mean (SD). Maximum score = 70 (See Methods). PD "Off" = PD "Off" anti-Parkinson medication, PD "On" = PD "On" anti-Parkinson medication, Control = healthy older adults.

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