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Brain activity during complex imagined gait tasks in Parkinson disease

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Abstract

Objective—Motor imagery during functional magnetic resonance imaging (fMRI) allows assessment of brain activity during tasks, like walking, that cannot be completed in a scanner. We used gait imagery to assess the neural pathophysiology of locomotion in Parkinson disease (PD).

Methods—Brain activity was measured in five locomotor regions (supplementary motor area (SMA), globus pallidus (GP), putamen, mesencephalic locomotor region, cerebellar locomotor region) during simple (forward) and complex (backward, turning) gait imagery. Brain activity was correlated to overground walking velocity.

Results—Across tasks, PD exhibited reduced activity in the globus pallidus compared to controls. People with PD, but not controls, exhibited more activity in the SMA during imagined turning compared to forward or backward walking. In PD, walking speed was correlated to brain activity in several regions.

Conclusions—Altered SMA activity in PD during imagined turning may represent compensatory neural adaptations during complex gait. The lowered activity and positive correlation to locomotor function in GP suggests reduced activity in this region may relate to locomotor dysfunction.

Significance—This study elucidates changes in neural activity during gait in PD, underscoring the importance of testing simple and complex tasks. Results support a positive relationship between activity in locomotor regions and walking ability.

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Keywords

Parkinson disease; gait; fMRI; imagery

INTRODUCTION

People with Parkinson disease (PD) frequently have gait abnormalities impacting stride length (Morris et al., 1996), step frequency (Iansek 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 (Hackney and Earhart, 2009; Peterson et al., 2012b; Schaafsma et al., 2003; Spildooren et al., 2010). 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 on the substantial overlap in supraspinal activation during imagined and overt movements (Deiber et al., 1998; Jeannerod and Decety, 1995; Miyai et al., 2001; Porro et al., 1996) including walking (la Fougere et al., 2010; Miyai et al., 2001). 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 (Mori et al., 1999; Orlovsky, 1969; Shik et al., 1969), and include the supplementary motor area (SMA), basal ganglia, 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 (Bruck et al., 2006; Kish et al., 1988; Prodoehl et al., 2010; Spraker et al., 2010), CLR (Cremers et al., 2012a; Hanakawa et al., 1999; Jahn et al., 2008b; Schweder et al., 2010), and MLR (Cremers et al., 2012a; Karachi et al., 2010; Snijders et al., 2011), 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 (Cremers et al., 2012a; Hanakawa et al., 1999; Snijders et al., 2011; Wai et al., 2012). Despite some inconsistent findings across studies, gait imagery in those with PD may produce altered activation in several locomotor regions (i.e. SMA (Hanakawa et al., 1999), CLR (Cremers et al., 2012a; Hanakawa et al., 1999), 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 (Godde and Voelcker-Rehage, 2010; Wagner et al., 2008). One study

of complex gait imagery of gait initiation and stepping over obstacles reported that those with PD had altered BOLD responses in lateral pre-motor regions, precuneus, 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), basal ganglia (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, and not have any contraindications for MRI. Further, participants were only included if they averaged > 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 < 26). Individuals with PD were included regardless of freezing status, which was assessed via the new freezing of gait questionnaire (NFOGQ) (Nieuwboer et al., 2009). Individuals were designated as freezers if they reported experiencing freezing at least once in the previous month. 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.

Data collection, including the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) subsection 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 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 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. Further, imagining walking faster than preferred can alter BOLD signal (Cremers et al., 2012b; Karachi et al., 2010; Suzuki et al., 2004).

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°, 0.9mm³, 8:09 min) scan was collected for identification of each region of interest (ROI) and T2* co-registration. We collected two T2*-weighted gradient echo multislice sequence scans (TR=2200ms, TE=3ms, 4.0 mm³ voxels, FA=90°, 9:45 min). Thirty-six slices covering the whole brain and the cerebellum were collected. During these 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. Including eyes open rest periods permitted participants to read the upcoming task. In addition, monitoring and recording when participants opened and closed their eyes provided a second method of assessing task adherence. Inclusion of the eyes open rest tasks may have altered the baseline BOLD signal during fMRI. However, the same rest tasks were included for all runs (i.e. imagined standing and imagined gait) and for both groups. Further, post-hoc analyses showed beta weights during rest periods were similar across PD and controls for all ROIs.

Imagined standing was assessed in a separate imaging scan on the same day and immediately following the imagined walking scan. During this 4 minute scan, participants imagined standing quietly with eyes closed for 20 seconds, followed by an 11 second eyes-open rest period. The end of each standing imagery bout was indicated by a tactile cue on the shin. Thus, all imagery tasks (imagined gait and imagined standing) were conducted with eyes closed. Only during rest periods were eyes open. We chose to have individuals imagine standing during a separate scanning block (on the same day) to reduce the overall length of each MRI run. Tactile cues were used during imagined standing for logistical reasons. During imagined walking, participants' imagery times were self-selected (i.e. they stopped imagining and opened eyes after completing the gait task). During imagined standing, however, it was necessary to notify the participant when to stop imagining. We modeled these cues to partially account for the neural changes associated with the tactile cueing.

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 gait 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 and event related design modeling. 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. 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).

fMRI analysis

FMR 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 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 with event length equal to the time taken to imagine that particular task 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 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).

Region of interest (ROI) analysis—We chose to analyze BOLD signal only within a-priori ROIs. This approach was used for three 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, this approach allows for a hypothesis driven approach to assessing locomotor changes across groups. Finally, ROI analyses limit the number of multiple comparisons compared to whole-brain analyses.

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 (Bruck et al., 2006; Cremers et al., 2012a; Hanakawa et al., 1999; Karachi et al., 2010; Kish et al., 1988; Malouin et al., 2003; Prodoehl et al., 2010; Schweder et al., 2010; Snijders et al., 2011; Spraker et al., 2010). Primary motor cortex was not included as a ROI, as this area does not typically respond to imagined motor tasks (Bakker et al., 2008; Cremers et al., 2012b; de Lange et al., 2005). 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 putamen was chosen over the caudate as it is more related to motor tasks than the caudate (Alexander et al., 1986), and regions of the putamen may be more affected in PD, with respect to controls, than the caudate (Bruck et al., 2006; Kish et al., 1988). 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 (Karimi et al., 2008; Pahapill and Lozano, 2000). These regions are diffuse and difficult to identify on T1 scans. Therefore, it is possible that the region identified for some participants excluded parts of the MLR, or included portions of other regions. However, the region identification was consistent across all subjects (both in location and size). 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, the region was included in the current analysis because it has been shown specifically to be active during locomotion in previous gait imagery experiments in humans (Jahn et al., 2008b), and may be dysfunctional in those with PD (Cremers et al., 2012a). Each region was identified bilaterally except for the CLR since it lies along the midline. Examples of each ROI are shown in Figure 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) and incorporating 6-dimensional (translation: x, y, z ; and rotation: θ, ϕ, ψ) head motion. Therefore, the 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. 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. For logistical reasons (see Procedure: Imaging) imagined gait and imagined stand beta weights were captured during different fMRI scans during the same scanning session. However, it was necessary to compare imagined gait to imagined standing. Therefore, due to potential changes in baseline BOLD signals across scans, imagined stand and imagined gait beta weights were normalized to their respective fMRI scan. This was completed by subtracting rest beta weights (collected during the imagined gait scan) from imagined gait beta weights. Similarly, rest beta weights collected during the imagined stand scan were subtracted from the imagined stand beta weights. In addition to normalizing beta weights to the particular scan, subtracting rest beta weights during rest from gait beta weights and from stand beta weights also removes some inter-subject variability and decreases potential baseline differences across groups.

To determine whether BOLD signal was higher 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°. Of these six, two also had severe hand tremor. 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, MMSE, KVIQ, and GIQ scores. Within those with PD, nine were identified, via the NFOGQ, as freezers. Preferred walking speed was lower, and time to complete the Timed Up and Go was higher in people with PD (Table 1). None of the included participants experienced dyskinesia.

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 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).

fMRI results (ANCOVA)

Across all participants, there was no significant difference in regional beta weights when turning left or turning right (paired sample t-tests between turning left and turning right yielded $p > 0.05$ for each ROI). Further, participants with PD who exhibited worse motor signs on the left side of their body ($n=9$; based on the unilateral components of the MDS-UPDRS-III) had similar beta weights during imagined turning left and right (paired sample t-tests; $p>0.05$). Of those individuals with worse motor symptoms on the right side ($n=8$), only beta weights in the left putamen were different between imagined turning to the left and right (left putamen: $p=0.049$; all other regions: $p>0.05$). Therefore, turns to the left and right were collapsed for all subsequent analyses.

Gait imagery, compared to imagined standing, produced significant increases in beta weights from nearly all locomotor regions of interest (See Table 2: Gait vs. Stand columns). In addition, there were main effects for the left GP and right SMA. Specifically, those with PD exhibited significantly smaller beta weights (across all tasks) in left GP than healthy older adults (group effect: $F_{1,36}=12.79$, $p=0.001$; Figure 4b). 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 ($F_{2,72}=3.33$, $p=0.042$; Table 2, Figure 4a). Post hoc paired sample t-tests in people with PD demonstrated that beta weights during imagined turning were larger than imagined forward ($p=0.055$) or backward ($p=0.026$) walking in the right SMA (Figure 4a and c), though the increase from

forward to turning did not reach statistical significance. Because lateralization of motor symptom severity in people with PD could be related to the activity of left and right brain regions during motor imagery, we conducted post hoc analyses to determine whether those with worse motor signs on the right side of the body exhibited different brain activity than those with worse signs on the left. Independent sample t-tests showed that beta weights were not different for any ROIs between these two groups ($p > 0.05$ for all ROIs).

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, Figure 5) such that larger beta weights for several regions (SMA, putamen, GP, and MLR) positively correlated with faster gait velocity (Table 3).

DISCUSSION

We compared the activity (i.e. beta weights) within brain regions associated with locomotion in healthy older adults to those with PD during complex gait imagery tasks. Three main findings of this work are: 1) across gait tasks, PD exhibited reduced beta weights in left GP compared to controls, 2) PD exhibited larger beta weights in SMA during imagined turning compared to forward or backward while controls did not, and 3) actual overground walking speed correlated with beta weights during imagined walking in several locomotor regions in PD and not in controls.

Brain Activity during Gait Imagery in PD

Few studies have investigated the neural activity of locomotion in people 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, PD and control participants exhibited increased activity in pre-motor regions, and control participants showed higher activity in locomotor regions including the GP, MLR, and cerebellum (Cremers et al., 2012a). We also observed increased activity in several locomotor regions, albeit with greater consistency in the PD group. Further, Cremers and colleagues observed PD to exhibit reduced activity in midline cerebellar and MLR regions, among others, with respect to controls. We also noted a decrease in activity in those with PD in the CLR with respect to control participants, though this difference did not reach statistical significance.

A novel finding of the current study is the significantly reduced activity during imagined gait in the left GP in those with PD compared to controls. In other words, people with PD exhibited a smaller increase in GP beta weights than controls when imagining walking. This result, along with the positive correlation between GP activity and overground walking speed suggests reduced activity in the GP may be associated with locomotor dysfunction. Deep brain stimulation (DBS) studies also suggest the GP, and subthalamic nucleus (STN), play an important role in locomotion, as targeting the internal segment of the GP (GPi) or the STN can improve gait and balance in PD (St George et al., 2010). However, understanding the functional significance of increases or decreases in BOLD signal can be difficult. For example, the BOLD signal has been shown to be more closely related to the local field potential (LFP; representing inputs to and internal processing of a region) than the multi-unit activity (MUA; representing neuronal firing rates of projection neurons). (Logothetis, 2002; 2008). Therefore, the reduction in GP beta weights in the current study may be the result of reduced neural input to the left GP during imagined walking in PD compared to controls. Alternatively, the smaller beta weights may reflect alterations in firing pattern of the GP in people with PD. DBS electrodes to measure LFP, investigators have

consistently shown PD to exhibit increased oscillations within the “beta band” (8–30Hz) of LFP (for reviews, see (Brown and Eusebio, 2008; Hammond et al., 2007)). Oscillations within this beta band correlated to bradykinesia and rigidity (but not tremor), suggesting these oscillations may relate to PD motor symptoms (Kuhn et al., 2006b). Interestingly, recent investigations suggest that, in humans, beta band synchronization decreases prior to and during overt motor tasks (Cassidy et al., 2002) and during imagined motor tasks (Kuhn et al., 2006a) in regions such as the GPi and STN (a region where firing rate often closely corresponds with GPi firing rate (Brown et al., 2004; Brown et al., 2001; Cassidy et al., 2002)). Further, those with PD may not reduce beta band synchronization in the STN as much as those without PD during motor tasks (Androulidakis et al., 2007). This less pronounced reduction of oscillation synchronization of basal ganglia regions in PD compared to non-PD may contribute to the region-specific changes in BOLD signal observed in the current study. In fact, a recent report on recordings from the visual cortex in awake primates suggests that while all LFP power spectra may affect BOLD signal, frequency bands of 20–60 Hz have a stronger correlation to BOLD signal than other bands (Goense and Logothetis, 2008). However, the precise relationship between LFP frequency bands and basal ganglia BOLD signals in humans remains to be determined.

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 activity 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 these group differences. 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. As noted above, our results suggest controls may exhibit more activity during imagined gait 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. Therefore, the disruption in the left GP during imagined walking in PD may be related to these anatomic and perhaps functional GP asymmetries. It is unlikely that this difference is due to motor asymmetries in our population, as GP activity during imagined gait in those with greater right side signs was not different from those who had greater involvement of the left side. 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 results.

Brain Activity during Complex Gait Imagery in PD

We enhanced the motor behavioral deficits in PD compared to controls by increasing the difficulty of the gait task with imagined backward walking and turning. In support of this strategy, imagined forward walking revealed no differences in SMA activity across groups, whereas imagined turning yielded increased activity in PD but not healthy controls. Interestingly these changes are in contrast with some previous studies reporting reduced SMA activity in PD during actual motor tasks (Hanakawa et al., 1999; Jahanshahi et al., 1995; Playford et al., 1992; Prodoehl et al., 2010; Wu et al., 2010). However, imagined movements elicited variable group differences in SMA activity in different studies (Cremers et al., 2012a; Snijders et al., 2011; Wai et al., 2012). For example, Snijders and colleagues reported that during gait imagery, healthy older adults and people with PD who do not report freezing of gait exhibit similar SMA activity. Individuals with PD who did experience freezing exhibited reduced SMA activity, although this difference did not reach statistical significance (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). Turning typically causes more pronounced gait dysfunction in people with PD than forward walking, possibly due to the higher bilateral coordination necessary to complete the task (Peterson et al., 2012b; Schaafsma et al., 2003).

Therefore, the increased activity in SMA during imagined turning 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 activity and actual overground walking velocity suggests that the increase in activity 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 and elevated SMA activity during complex gait tasks, while healthy controls do not. Regardless, this result underscores the importance of using complex tasks as a tool to examine neural alterations in those with PD.

Interestingly, backwards walking did not increase activity in locomotor regions relative to forward walking in either group. 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 forward and backward gait tasks (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 activity in the SMA of those with PD.

Correlation to Overground Gait Speed

One goal of this study was to identify whether correlations exist between activity within locomotor regions during gait imagery and actual gait function. We chose to correlate beta weights 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 relates to negative outcomes including falls (Verghese et al., 2009) quality of life (Schmid et al., 2007), and mortality (Studenski et al., 2011).

Average walking speed positively correlated with beta weights in several locomotor brain regions in the PD group but not in controls. Though the strength of correlations varied across regions, all beta weights directly correlated with walking speed. These results suggest that higher brain activity predicts faster walking speeds for individuals with PD. Prodoehl and colleagues found similar results in upper limb motor function, showing less basal ganglia activity in PD with respect to controls during finger tapping, and indirect relationships between activity and disease severity in numerous regions (Prodoehl et al., 2010). These results together suggest that reductions in activity in locomotor regions (including basal ganglia) may be pathological in people with PD. The reduced GP activity in people with PD in the current study further supports this notion.

Pros and Cons of 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. BOLD response 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 (Jahn and

Zwergal, 2010; Malouin et al., 2003; 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 (Cremers et al., 2012b; Jahn et al., 2004; Karachi et al., 2010; Suzuki et al., 2004). Finally, with this paradigm, it is possible to investigate neural control of movement without the confounds of 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 (Cremers et al., 2012b; Jahn et al., 2008b; Karachi et al., 2010; Suzuki et al., 2004). 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 beta weight. However, post hoc analysis showed that no correlation between imagined walking speed and beta weights in any region which showed an actual walking / beta correlation. Further, actual walking time did not significantly correlate with beta weights in healthy older adults. Therefore, we think that the correlations between actual overground walking speed and beta weights during gait imagery in people with PD represent a true relationship between walking ability and beta weights 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). Fourth, the current analysis does not allow us to identify changes in neural signal during particular portions of gait (e.g. gait initiation or gait termination). Instead, all portions were analyzed together. We feel that while it would be intriguing to identify neural correlates of each component of the gait task, it is not unreasonable, given the limitations of this method, to assess beta weights over the entirety of the imagined walking bout. Fifth, individuals who experienced freezing of gait were included in the current analysis. We chose to analyze all participants in the PD group together to increase power to detect differences between the PD and control groups. Future work exploring differences between freezers and non-freezers should be carried out. Finally, although head motion while in the scanner was similar across groups, those with PD may have more motion of extremities (e.g. tremor) than healthy older adults. We were unable to capture

electromyography during MRI in this investigation, however we visually monitored participants during all scans, and none of the included 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) PD exhibited smaller beta weights in GP with respect to controls, 2), imagined turning produced larger beta weights in the SMA in people with PD, but not in controls, and 3) in people with PD, walking speed was directly correlated to beta weights in several locomotor regions. These results suggest that: 1) gait dysfunction in people with PD (i.e. reduced gait velocity) may be related to altered function of the GP; 2) 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; and 3) higher activity in locomotor regions may predict improved gait function. Together, these results further elucidate the changes in activity of locomotor regions during gait in PD and in controls, and provide evidence supporting a relationship between increased activity in locomotor regions and improved walking function.

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HIGHLIGHTS

- Neural correlates of simple and complex gait imagery were assessed in people with Parkinson disease (PD).
- PD exhibited more activity in the supplementary motor area during imagined turning than imagined forward or backward gait.
- Across gait imagery tasks, globus pallidus activity was lower in PD compared to controls and was positively correlated to overground walking speed.

Figure 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 and globus pallidus (b), cerebellar locomotor region (c), and mesencephalic locomotor region (d). A-Anterior; P-Posterior; R-Right; L-Left

Figure 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 *, $F_{136}=197.7$; $p<0.001$). Differences between PD and control subjects did not reach significance. Error bars represent standard deviation.

Figure 3. Correlation between actual and imagined walking times (all subjects). Spearman's Rho and p-value reported.

Figure 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 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 1

Subject Characteristics- All values represented as mean (standard deviation) unless otherwise noted

	Healthy Old	PD	
N	20 (5m)	19 (11m)	
Age (yrs)	66.6 (7.6)	64.9 (7.6)	p=0.51
MDS-UPDRS-III	--	31.2 (10.0)	
Years with Disease	--	6.7 (6.0)	
Hoehn & Yahr Stage	--	2.34 (0.33)	
LEDD^β- mean (min, max)	--	753.6 (0, 2250)	
Timed Up and Go (s)	9.7 (1.3)	11.8 (2.4)	p<0.01
Preferred Walking Speed (m/s)	1.14 (0.15)	0.97 (0.18)	p<0.01
MMSE	29.0 (1.1)	28.3 (1.1)	p=0.08
KVIQ	80.6 (11.1)	78.0 (12.4)	p=0.49
GIQ	31.0 (3.8)	28.8 (4.7)	p=0.12

Abbreviations: Movement Disorder Society Unified Parkinson's Disease Rating Scale (part III), Levodopa Equivalent Daily Dose (three participants with PD were not taking anti-Parkinson medication), Mini Mental State Exam (maximum score = 30), KVIQ: Kinesthetic Visual Imagery Questionnaire (maximum score = 100), GIQ: Gait Imagery Questionnaire (maximum score=40)

Table 2

ANCOVA results for all regions of interest. P-values shown.

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

Abbreviations: ANCOVA: Analysis of covariance, SMA: supplementary motor area, PUT: putamen, GP: globus pallidus, MLR: mesencephalic locomotor region, CLR: cerebellar locomotor region

P-values (Spearman's ρ) 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) for right (R) and left (L) regions of interest.

Table 3

		R SMA	L SMA	R PUT	L PUT	R GP	L GP	R MLR	L MLR	CLR
Gait beta weight vs. actual walking velocity	Control ρ	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)
	PD ρ	0.004 (0.63)	0.02 (0.55)	0.06 (-0.044)	0.04 (0.47)	0.049 (0.46)	0.03 (0.51)	0.048 (0.46)	0.65 (0.11)	0.25 (0.28)