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Brain activity during complex imagined gait tasks in Parkinson disease

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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.

ABSTRACT

Objective: Motor imagery during functional magnetic resonance imaging (fMRI) allows assessment of brain activity during tasks, like walking, that cannot be completed in an MRI 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.

1. 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

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to assess brain activity during whole-body motions, such as locomotion, which cannot be overtly implemented in an MRI 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 the Blood Oxygen Level Dependant (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.

2. Methods

2.1. 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 $\geqslant 3$ 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-h 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.

2.2. Procedure

2.2.1. Gait training

Participants were trained to complete five overground tasks: forward walking, backward walking, turning to the left in small radius ($r = 0.6$ 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 m 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 min, 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).

2.2.2. 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°, 0.9 mm^3, 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 multi-slice sequence scans (TR = 2200 ms, TE = 3 ms, 4.0 mm^3 voxels,