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Freezing of gait is associated with increased saccade latency and variability in Parkinson's disease

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HIGHLIGHTS

- PD patients with freezing of gait (PD–FOG) had longer pro- and anti-saccade latencies than non-freezers (PD–NON).
- PD–FOG showed greater variability of saccade velocity and gain than PD–NON.
- Findings were unrelated to saccade error rate, disease severity, or cognition, and suggest freezing is related to a global disturbance in motor automaticity.

ABSTRACT

Objective: Freezing of gait (FOG) is a locomotor disturbance in Parkinson disease (PD) related to impaired motor automaticity. In this study, we investigated the impact of freezing on automaticity in the oculomotor system using an anti-saccade paradigm.
Methods: Subjects with PD with (PD–FOG, $n = 13$) and without (PD–NON, $n = 13$) FOG, and healthy age-matched controls (CTRL, $n = 12$) completed automatic pro-saccades and non-automatic anti-saccades. Primary outcomes were saccade latency, velocity, and gain.
Results: PD–FOG (pro-saccade latency = 271 ms, anti-saccade latency = 412 ms) were slower to execute both types of saccades compared to PD–NON (253 ms, 330 ms) and CTRL (246 ms, 327 ms). Saccade velocity and gain variability was also increased in PD–FOG.
Conclusions: Saccade performance was affected in PD–FOG for both types of saccades, indicating differences in automaticity and control in the oculomotor system related to freezing.
Significance: These results and others show that FOG impacts non-gait motor functions, suggesting global motor impairment in PD–FOG.

1. Introduction

Among the many gait difficulties in people with Parkinson's disease (PD), freezing of gait (FOG) is one of the most common, affecting over half of the PD population (Forsaa et al., 2015). FOG manifests as episodic interruptions of the gait cycle during normal walking and other complex gait tasks like turning (Bloem et al., 2004; Nutt et al., 2011). Additional research into the mechanisms of FOG showed that freezing is not limited to gait, but can also be observed in other motor tasks, such as upper limb movements and speech (Moreau et al., 2007; Williams et al., 2013; Vercruysse et al., 2014a). Altogether, these studies indicate that freezing may be a global phenomenon impacting not just gait but the entire motor system.

Many hypotheses explaining FOG phenomenology have been proposed (Nieuwboer and Giladi, 2013), and two specifically relate FOG to impairments in cognitive-motor function. The interference model suggests excessive overlap of activity in sensorimotor, associative, and limbic circuits of the basal ganglia leads to abnormal inhibition from the globus pallidus, leading to freezing episodes (Lewis and Barker, 2009). Additionally, the cognitive model proposes freezers have impaired conflict resolution and response automaticity in challenging environments, resulting in an

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increased reliance on cortical resources (Vandenbossche et al., 2012). Evidence for this is seen in dual-task experiments, commonly used to assess automaticity, during which people with PD and FOG (PD–FOG) have poorer gait performance during dual-task tests compared to those who do not have FOG (PD–NON) (Spildooren et al., 2010). Recent neuroimaging data also support the cognitive model, showing increased activation and connectivity of cortical regions in PD–FOG (Fling et al., 2014; Vercruysse et al., 2014b). Tying back into the interference model, increased activity may lead to resource "overloads", particularly during cognitively demanding tasks, inducing motor arrests observed during a freezing episode (Shine et al., 2013). Given these hypotheses, it is reasonable to predict that impaired automaticity is a common feature of freezing that would affect all motor output.

Saccades are fast eye movements that allow us to quickly foveate objects of interest, and are mediated by both cortical (DLPFC, FEF, SEF) and subcortical (thalamus, basal ganglia, superior colliculus) circuits as well as oculomotor neurons in cranial nerves (Moschovakis et al., 1996; Munoz and Everling, 2004). Saccadic output follows highly stereotyped patterns and is well-described in both healthy (Bahill et al., 1975; Peltsch et al., 2011) adults and PD. These studies show that people with PD are generally slower to respond (i.e. increased latency) and make slower (i.e. decreased velocity) volitional saccades (Crawford et al., 1989; Briand et al., 1999), supporting the traditional view that slowed voluntary movement is a result of increased inhibition of the basal ganglia (Terao et al., 2013).

The anti-saccade task is a common way to study a different aspect of oculomotor control (Hallett, 1978). In this task, participants make saccades either toward a visual target (the automatic pro-saccade) or to a mirrored position of a visual target (non-automatic anti-saccade). Anti-saccades require inhibition of a visually-guided response as well as initiation of a non-visually guided saccade. As such, anti-saccade tasks are useful to assess both the cognitive and motor aspects of oculomotor control and have been used in both healthy individuals and patients with neurological conditions (Guitton et al., 1985; Kristjansson et al., 2001; Chan and DeSouza, 2013). In addition, anti-saccade performance correlates well with other measures of executive function in adults (Klein et al., 2010; Mirsky et al., 2011). Altogether, anti-saccades likely involve parallel processing of cognitive and motor commands mediated by the basal ganglia, and are a suitable approach to study cognitive-motor processing and its relationship to freezing. However to our knowledge only one recent study directly examined the impact of FOG on saccades. This study noted that PD–FOG made more anti-saccade errors, which were related to gray matter loss in visual, frontal, and parietal regions (Walton et al., 2015) Interestingly, no differences in pro- or anti-saccade latency were noted between freezer subgroups, suggesting the oculomotor impairment was specific to response inhibition and not selection. Since freezing is associated with a maladaptive response to increased cognitive-motor demand and impaired automaticity, the link between freezing and oculomotor function merits further investigation.

In this study, we investigated automaticity and control using an anti-saccade task in PD–NON and PD–FOG relative to healthy adult controls. We hypothesized that PD–FOG would demonstrate impaired saccade automaticity, as evidenced by slowness of movements and prolonged response latency during both pro- and anti-saccades compared to PD–NON and controls. In contrast, we predicted that PD–NON would be slower and more variable during volitional anti-saccades compared only to controls. This work aimed to increase our knowledge of the oculomotor system in PD–NON and PD–FOG in an effort to better understand the impact of freezing as a potential global motor disturbance and inform the development of treatment approaches to address freezing.

2. Materials and methods

2.1. Participants

A sample of twenty six people with PD (13 PD–NON and 13 PD–FOG) and twelve age-matched neurologically healthy older adults took part in the study. PD participants were recruited from the Movement Disorders Center at Washington University School of Medicine and had a diagnosis of idiopathic PD as defined by previous criteria (Calne et al., 1992). Healthy older adults were recruited from a volunteer database managed by the Department of Psychological & Brain Sciences at Washington University. All subjects were free of other neurological conditions including dementia (Montreal cognitive assessment (MOCA) >21 (Dalrymple-Alford et al., 2010)), and were able to walk independently with or without an assistive device. Additionally, PD participants were excluded if they were unable to tolerate medication withdrawal or had previous deep brain stimulation surgery. Given our sample size, the effect size was calculated to be 0.48, assuming 80% power and Type I error rate of 5%.

We classified the group of PD participants as freezers (PD–FOG) and non-freezers (PD–NON) based on self-report of freezing episodes over the past month using the New Freezing of Gait Questionnaire (NFOGQ), a reliable instrument which uses both written and video descriptions of FOG to determine FOG severity (Nieuwboer et al., 2009). If the participant reports s/he has not experienced any freezing episodes over the past month, s/he is classified as PD–NON and given a score of zero. If the participant responds that s/he has experienced freezing over the past month, s/he is asked additional questions about the duration and frequency of episodes and a composite NFOGQ score ranging from 1 to 28 is determined. PD participants were evaluated in the off state, defined as at least a 12-h withdrawal from any anti-Parkinson medication, and clinically evaluated for descriptive purposes using the Movement Disorder Society version of the Unified Parkinson Disease Rating Scale (MDS-UPDRS). Sub-sections I (non-motor symptoms), II (motor aspects of daily living), and III (motor sign severity) were administered and scored by a trained physical therapist. This protocol was approved by the Human Research Protection Office at Washington University School of Medicine. Participants provided informed consent before participating and were compensated for their time.

2.2. Saccade tasks

We used a modified anti-saccade paradigm to study saccadic eye movements (Hallett, 1978; Antoniades et al., 2013). The task parameters were chosen based on previously published best practices for saccade testing in people with neurological conditions (Antoniades et al., 2013). The tasks required participants to either make saccades toward (pro-saccade) or to a symmetrically-opposite location away from (anti-saccade) a visually presented target. Stimuli were presented on a 22″ LCD monitor and controlled by E-Prime v2.0 (Psychology Software Tools, Sharpsburg, PA) on a Dell E6440 Latitude laptop computer. Participants sat approximately 50 cm from the display, which was adjusted to eye level. A chin rest was used to minimize head movement. Participants performed one block of 50 pro-saccades and another block of 50 anti-saccades, the order of which was counter-balanced across participants. The number of trials was chosen both to minimize fatigue and to get reliable estimations of saccade parameters for each participant (Antoniades et al., 2013).

Each trial began with a blue or red fixation cross (2.6°) centered on a white background (see Fig. 1). A blue cross indicated a pro-saccade should be made; a red cross indicated an anti-saccade