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Research

Dopaminergic Medication Amplifies Sensory Integration Deficits During Static Balance in Parkinson's Patients with Freezing of Gait

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Abstract

Over the past year, research has begun to identify greater balance deficits in Parkinson's patients who experience freezing of gait (Freezers) compared to those who do not (Non-freezers). Recently, sensory impairments have been suggested to be a key mechanism that underlies freezing of gait in Parkinson's disease (PD) and thus may be a primary contributor to balance impairments. However, few studies have investigated the influence of sensory deficits on balance in those who experience freezing of gait. Furthermore, dopaminergic medication has been suggested to exacerbate somatosensory deficits in PD, yet the influence of dopaminergic medication on balance impairments has not been examined in Freezers. Therefore, the current study evaluated whether Freezers demonstrated worse performance on the modified Clinical Test of Sensory Interaction on Balance (m-CTSIB) compared to Non-freezers and a healthy control group. Dopaminergic effects on sensory integration during balance were also examined. The m-CTSIB was carried out with fifty-two participants (21 HC, 17 Non-freezers, and 14Freezers). All participants stood on a BIODEX sensor plate in four sensory conditions: (i) firm surface with eyes open, (ii) firm surface with eyes closed, (iii) foam surface with eyes open, (iv) foam surface with eyes closed. PD participants performed the test while in their ON and OFF dopaminergic states. All groups performed similarly while standing on the firm surface with their eyes open and when standing on a foam surface with eyes closed. However, Freezers had significantly worse balance compared to HC when standing on the firm surface with their eyes closed. Additionally, Freezers had significantly greater sway during the firm surface conditions when tested in their ON state compared to their OFF state. Finally, Freezers also demonstrated significantly greater sway during the foam surface, eyes open condition compared to both the Non-freezers and HC group. In conclusion, these findings suggest that Freezers have greater balance impairments especially when forced to rely on somatosensory and vestibular information. Dopaminergic medication amplifies sensory integration deficits in Freezers specifically and contributes to greater instability in their ON state. These findings may explain the higher occurrence of freezing of gait when walking in darkness, and provide clinically relevant implications for rehabilitation.

Keywords: Parkinson's Disease; Freezing Of Gait; Dopaminergic Replacement Therapy; Balance, Sensory Integration

Introduction

Freezing of gait is a severe symptom of Parkinson's disease (PD) that presents as a sudden and transient cessation of gait, where the patient reports feeling as though their feet are glued to the floor [1]. Freezing of gait episodes often result in a loss of balance and is a major contributor to falling in PD [2]. In fact, recent research shows that individuals with PD who experience freezing of gait (Freezers) perform worse on clinical balance assessments (e.g. BESTest, Fullerton Advanced Balance scale) compared to individuals with PD who do not (Non-freezers) [3,4].

In addition to clinical assessments of balance, posturography and reactive stepping perturbations have been used to investigate this relationship between freezing of gait and balance deficits in more detail. Research has found many differences between Freezers and Non-freezers, such that Freezers typically display a more posteriorly positioned center of pressure compared to Non-freezers, which was correlated with freezing of gait severity [4]. Freezers also display reduced limits of stability [4], greater instability during voluntary weight shifting (i.e. anticipatory postural adjustments) [5], and take smaller steps forward when responding to a backward perturbation compared to Non-freezers [6]. Finally, Nantel and colleagues identified a relationship between freezing of gait severity and the average anterior-posterior center of pressure excursion and mediolateral center of pressure velocity [7], however other studies have reported no difference between Freezers and Non-freezers with respect to center of pressure sway excursion, center of pressure

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velocity and sway regularity [4,8]. Taken together, it is evident that Freezers have significant balance impairments which are related to freezing of gait. However, it remains unclear whether these balance impairments may be linked to a specific underlying mechanism of freezing of gait.

Although the pathophysiological mechanism of freezing of gait remains unknown, sensory processing and integration deficits have been previously suggested to be a key factor that contributes to freezing of gait in PD, since walking in the dark led to a significant increase in number of freezing of gait episodes [9]. Notably, it is often overlooked that balance control requires a central sensory integration of visual, vestibular and somatosensory inputs [10,11] which has the potential to be impaired and hence contribute to balance impairments in Freezers. Yet, very few studies have evaluated the sensory contributions to balance deficits in Non-freezers, despite the growing literature that suggests Freezers have even greater sensory impairments including visual, vestibular and kinesthetic than Non-freezers [12-15]. A recent study which attempted to characterize postural sensory deficits in freezers found compelling evidence that impaired processing of sensory inputs, namely somatosensory and vestibular, were strongly related to the severity of freezing of gait. More specifically, a higher reliance on vision was shown to correlate with greater freezing behavior [16], however PD participants were only tested in their OFF dopaminergic state. Given recent controversies about whether dopamine improves [17,18] or does not affect sensory processing and integration, further research is needed to examine the contribution of sensory deficits on balance impairments in Freezers in the ON dopaminergic state compared to the OFF state. This is especially important to consider since balance impairments have been shown to be worse in the ON dopaminergic state, and of course better represents participants' daily functioning.

Therefore, the aim of this study was first to examine sensory impairments during static balance in Freezers in their ON dopaminergic state compared to Non-freezers and healthy age-matched control participants (HC) using the modified Clinical Test of Sensory Interaction on Balance (m-CTSIB), and second to evaluate the influence of dopaminergic medication on sensory impairments during this static balance assessment.

Methods

Fifty-two participants were recruited from the Movement Disorders Research and Rehabilitation Centre at Wilfrid Laurier University, Waterloo, Canada, to participate in the current study. All participants provided signed informed consent and the study received ethical approval from the University of Waterloo as well as from Wilfrid Laurier University. All thirty-one PD participants included in this study had been previously confirmed to have idiopathic PD from their neurologist. Twenty-one age-matched healthy control participants (HC) were also included. All PD participants were asked if they had a history of FOG and self-reported whether they experience freezing of gait regularly. Additionally, a movement disorder specialist confirmed the presence of freezing of gait during the patient assessment (prior to participation in the study) [23]. Based on these criteria, fourteen PD participants were included in the Freezer group and the remaining seventeen PD participants were included in the Non-freezer group. Exclusion criteria included individuals with a neurological disease (other than PD), peripheral neuropathy, diabetes, and uncorrected visual disturbances such as double vision or cataracts. PD participants completed the study on two separate occasions, once in their OFF dopaminergic state (after a minimum of a 12-hour withdrawal from their dopaminergic medication), and in their ON dopaminergic state (after approximately an hour of taking their regular dopaminergic dose). Six Freezers and one Non-freezer opted to only be tested in their ON state and thus did not complete the OFF state testing due to the burden and uncomfortable nature of being 'OFF'. The completion of the study in the ON and OFF dopaminergic state was counterbalanced across PD participants. Motor symptom severity was assessed in both dopaminergic states using the Unified Parkinson's disease rating scale motor subsection (UPDRS-III). Global cognition was also assessed in all participants using the modified Mini-Mental State Exam (3MS), and participants rated their fear of falling on a 1-10 Likert scale (e.g. 1-not afraid at all, 10-extremely afraid of falling) (see Table 1).

Table 1: Participant demographics, mean (standard deviation)

	HC	Non-Freezers	Freezers	p-values
Age	69	66 (8.7)	71 (7.8)	P=0.36
Gender	6 F	3 F	3 F	
UPDRS-III OFF	--	32 (11.3)	**39 (10.6)**	P<0.001
UPDRS-III ON	--	20 (10.4)	**34 (10.1)**	P<0.001
DDE	--	223.1 (98.9)	204.1 (62.7)	P=0.54
Fear of Falling	1.7 (1.1)	2.2 (2.1)	**4.1 (3.1)**	P=0.006
3MS	97 (4.5)	96 (4.5)	95 (7)	P=0.33

Bolded values indicate that Freezers are significantly different from the other groups.

All participants performed the modified Clinical Test of Sensory Interaction on Balance using the BioDex Balance System SD (Biodex Medical Systems Inc., New York, USA). The objective of this test is to quantify how well a patient can integrate various forms of sensory inputs with respect to balance and also compensate when one or more of those senses are compromised [24,25]. Participants stood with their hands at their sides for thirty seconds in four sensory conditions. Participants stood on:

Condition 1: a firm surface with their eyes open (incorporates visual, vestibular and somatosensory inputs)

Condition 2: a firm surface with their eyes closed (visual input was eliminated to evaluate vestibular and somatosensory inputs)

Condition 3: on a foam surface with their eyes open (evaluates the interaction between somatosensory and visual input)

Condition 4: On foam surface with their eyes closed (evaluates the interaction between somatosensory and vestibular input)

To quantify balance performance, a sway index (i.e. the standard deviation of the average center of gravity position from the center of the platform) was calculated by the BioDex Balance System and outputted for each sensory condition. The higher the sway index, the more unsteady the person was during the test (e.g. 1= minimal sway; 4=a fall).

Since the data were not normally distributed, non-parametric statistics (i.e. Chi-square, Mann-Whitney U) were used to compare groups (Freezers (on), Non-freezers (on), HC) within each sensory condition and Wilcoxon tests were used to compare balance performance across dopaminergic states (off, on) within each PD group in each sensory condition. Based on our hypothesis and previous findings, a priori planned group comparisons were carried out between Freezers (on) and Non-freezers (on) as well as Freezers (on) and HC.

Results

Firm Surface with Eyes Open

All groups performed similarly while standing on the firm surface with their eyes open (x^2 (2) = 2.85, p=0.24). Notably, only the Freezers had significantly greater sway when tested in the ON dopaminergic state compared to OFF (z=-2.52, p=0.01) (Figure 1).

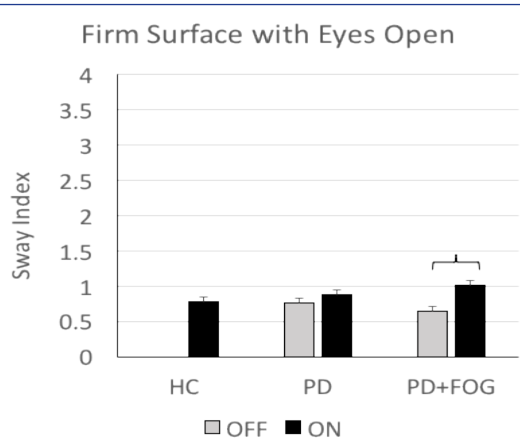

Figure 1: Mean (+ standard error) of the sway index during condition 1 (standing on a firm surface with eyes open). { indicates a significant difference (p<0.05) between the OFF and ON state within the Freezers group.

Firm Surface with Eyes Closed

Although there was not an overall effect of group (x^2(2) =4.71, p=0.09), planned comparisons revealed Freezers had greater sway compared to HC (U=85.5, p=0.038) (Figure 2). There was also a trend that Freezers also demonstrated greater sway compared to Non-freezers (U=76, p=0.088). Notably, only the Freezers group had significantly greater sway when tested in the ON dopaminergic state compared to their OFF state (z=-1.96, p=0.05).

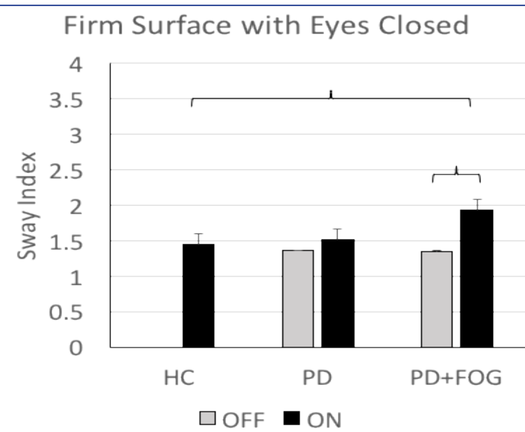

Figure 2: Mean (+ standard error) of the sway index during condition 2 (standing on a firm surface with eyes closed). { indicates a significant difference at the p<0.05 level.

Foam Surface with Eyes Open

A group effect was found during the foam surface, eyes open condition (x^2(2) =10.61, p=0.005), which revealed that Freezers demonstrated significantly greater sway compared to both Non-freezers (U=58, p=0.02) and HC groups (U=58.5, p=0.003) (Figure 3). There was no effect of medication found.

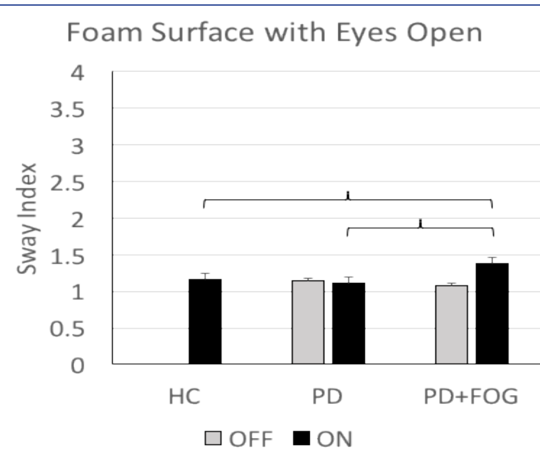

Figure 3: Mean (+ standard error) of the sway index during condition 3 (standing on a foam surface with eyes open). { indicates a significant difference at the p<0.05 level.

Foam Surface with Eyes Closed

All groups performed similarly while standing on a foam surface with their eyes closed (x^2 (2) =4.00, p=0.14) (Figure 4). There was also no effect of medication found.

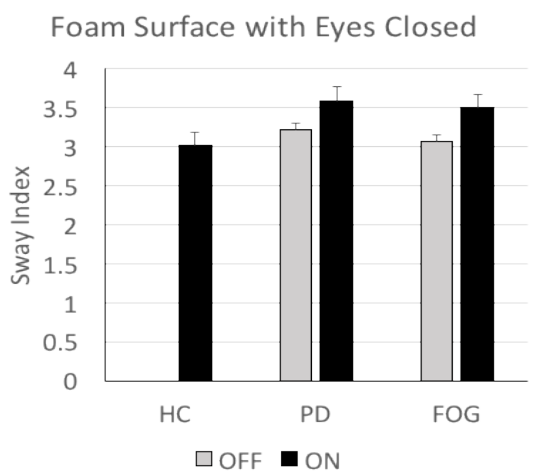

Figure 4: Mean (+ standard error) of the sway index during condition 4 (standing on a foam surface with eyes closed).

Discussion

The main findings from this study were that Freezers had greater balance impairments (i.e. a greater sway index) in their ON dopaminergic state compared to their OFF dopaminergic state as seen in conditions 1 and 2, when participants stood on a firm surface with their eyes open and closed respectively. Notably, when somatosensory input was disrupted by standing on foam (conditions 3 and 4), there were no effects of medication found. This evidence suggests that dopaminergic medication may have specifically exacerbated somatosensory and proprioceptive impairments which resulted in worsened balance in the ON state. Researchers have suggested that dopaminergic medication may contribute to irregular neuronal firing patterns within the basal ganglia [26], likely amplifying anoisy and corrupted sensory signal leading to poor sensorimotor integration [27]. This is one possible mechanistic explanation for the current findings. Alternatively, some have argued that the pedunculopontine nucleus (PPN) is integral for sensorimotor integration relating to axial motor control such as balance and postural stabilityrather than the dopamine-dependent striatum [26]. Thus, although dopamine may facilitate sensorimotor integration within the striatum, it may not influence sensorimotor integration within the PPN. Both of these accounts fit with our findings that dopaminergic therapy does not improve, but instead worsens sensory organizational processes for postural control in Freezers.

Our findings also showed that Freezers relied heavily on vision in order to compensate for somatosensory, proprioceptive and vestibular impairments. Freezers demonstrated a similar sway index to Non-freezers and HC participants when vision was available while standing on the firm surface, but once vision was removed Freezers had significantly greater sway than HC. These findings extend and support previous research which have shown that balance deficits are exacerbated in dark environments or with their eyes closed [4,8,16,28]. Since freezing of gait has also been shown to be exacerbated in dark environments [9], it is possible that a similar mechanism underlies both balance impairments and freezing of gait. A common link between impaired balance and freezing of gait may be impaired sensory processing namely from somatosensory and proprioceptive inputs. During normal walking, vision, vestibular, and kinaesthetic (proprioceptive and somatosensory) inputs are integrated in real-time by central neural networks in order to provide a frame of reference for cognitive, limbic and motor processes [29]. Thus, if sensory processing of these inputs is impaired or integration across sensory inputs requires higher level processing achieved by a faulty basal ganglia network, then conflict can arise in this system which may manifest as freezing of gait [30]. It is important to note that even when vision was provided during condition 3 (standing on a foam surface with eyes open), Freezers were more unstable compared to Non-freezers and HC participants. One interpretation of this result might be that Freezers have a reduced capacity, limiting their ability to quickly re-weight and organize sensory inputs in order to adapt to altered support surfaces. Overall, this study provides additional evidence that impaired sensory processing and integration may contribute to freezing of gait in PD, and should be targeted in future rehabilitative therapies.

Given that postural stability has limited responsiveness pharmaceutical therapies [31,32], exercise rehabilitation and balance training programs have become popular to improve motor symptoms in PD, especially for symptoms such as balance. However, very few studies to date have been successful at improving balance in Freezers. Although not in Freezers, a recent study in PD demonstrated evidence that a sensory attention focused rehabilitation program was able to significantly improve balance control, especially when eyes were closed, suggesting that the program enhanced the use of proprioceptive information [33]. Future work should investigate whether these types of programs are effective at improving balance in those with freezing of gait and whether a reduction in freezing of gait and falling is also achieved.

This study had some limitations that should be acknowledged. Freezers had a greater motor symptom severity than Non-freezers. Thus, findings from this study should be interpreted with caution as these results may reflect an effect of freezing of gait or simply greater disease severity. However, it should be noted that there was no significant relationship between motor symptom severity (UPDRS-III) and sensory integration deficits in the current study, which suggests that the differences detected were likely an effect of group rather than symptom severity. Our small sample size in this study is also a limitation that may have reduced our ability to detect differences between groups especially in the OFF state. Finally, it appeared as though there was a ceiling effect in condition 4 (standing on foam with eyes closed) where all participants found this condition very difficult to maintain balance, and thus differences between groups were not able to be distinguished as previous studies have [4,8].

Conclusion

Overall, static balance is more impaired in Freezers in the ON dopaminergic state, especially when forced to rely on somatosensory and vestibular information. This is an important consideration, considering the higher occurrence of freezing of gait while walking in the darkness. Therefore, exercise training programs that focus on enhancing one's ability to integrate sensory inputs is crucial for improving balance deficits in Freezers, and may also be effective at reducing freezing of gait and falls.

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