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The Effects of Fatigue on Balance in Individuals with Parkinson's Disease: Influence of Medication and Brain-Derived Neurotrophic Factor Genotype

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THE EFFECTS OF FATIGUE ON BALANCE IN INDIVIDUALS WITH PARKINSON'S DISEASE: INFLUENCE OF MEDICATION AND BRAIN-DERIVED NEUROTROPHIC FACTOR GENOTYPE

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ABSTRACT

Background and Purpose: The purpose was to investigate the effects of fatigue on balance in individuals with Parkinson's disease (PD). Because falls in this population can have deleterious consequences, it is important to understand the influence of fatigue and PD medications on balance. Additionally, since brain-derived neurotrophic factor (BDNF) has been shown to be related to motor performance, we explored its role in balance fatigue.

Participants: 27 individuals (age= 65.4±8.1; males= 14, females= 13) with neurologist-diagnosed PD. Of the 27, 13 were genotyped for BDNF as Val/Val, 11 as Val/Met, 2 as Met/Met, and one refused genotyping.

Methods: Participants were tested twice, first on medication and second off medication, one week apart. On both days, participants completed the following tests before and after a fatiguing condition: mini-Balance Evaluation Systems Test (mini-BESTest), computerized dynamic posturography (sensory orientation and motor control), functional reach, and gait spatial-temporal parameters at preferred gait speed across an instrumented walking mat. To address the primary aim of the study, a 2 (condition: pre and post) X 2 (medication: on and off) factorial ANOVA was performed for each outcome variable in each of the following domains: 1. anticipatory postural response; 2. adaptive postural responses; 3. Dynamic balance; 4. sensory orientation; and, 5. gait characteristics. For the exploratory aim, independent t-tests were conducted to compare both pre- and post-fatigue states, and on and of medication states for all of the aforementioned balance domains.

Results: There were no statistically significant interactions between time (pre and post) and medication (on and off) for anticipatory postural responses, adaptive postural responses,

dynamic balance, sensory orientation, or gait characteristics (ps≥.187). Participants with BDNF Met alleles were not significantly different from Val/Val participants in balance or gait (ps≥.111) and response to a fatiguing condition (ps≥.070).

Discussion: The results of this study suggest that fatigue does not have a detrimental effect on balance and gait in individuals with PD. Likewise, our results were also in line with other studies that suggest that PD medications are not effective for decreasing risk of falls due to postural instability. Lastly, these results also indicate that individuals with a BDNF Met allele are not at an increased fall risk after a fatiguing condition compared to those with the Val/Val genotype.

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INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative movement disorder that results in slowness of movement, tremors, stiffness in the limbs and trunk, and impaired balance. It is estimated that there are currently between 4.1 and 4.6 million individuals over the age of 50 with idiopathic PD in the world's 10 most populous nations.[1] Although PD itself is not fatal, serious complications such as falls have been associated with increased mortality and morbidity and can lead to increased dependency and risk of nursing home admission.[2-4] While the role of the cardinal motor symptoms of the disease (bradykinesia, resting tremor, rigidity, and postural instability) have been linked to fall risk in this population, the role of its many associated non-motor symptoms, is still misunderstood. For instance, Shulman et al found that depression, anxiety, fatigue, and sleep disorders occur commonly in PD and these non-motor symptoms may reduce the function of individuals with PD.[5] Additionally, Martinez-Martin et al found that non-motor symptoms strongly contribute to a decline in quality of life in patients with PD, perhaps even more than motor symptoms. Moreover, non-motor symptoms as a whole may be the most important predictor of quality of life in patients with PD.[6] Of the non-motor symptoms, fatigue, either as the cause or effect of inactivity and its physiologic consequences, is an important limiting factor in the physical function and capability of individuals with PD.[7]

Fatigue is a common complaint in PD. In a nine-year follow up study, Friedman and Friedman found that approximately 50% of individuals with PD experience fatigue.[8] People with PD may have fatigue associated with deconditioning, generalized lack of energy, or decline in force generation or in speed of repetitive movements, as well as fatigue due to sleep disturbance,

decreased motivation, slowed mental processes, or depression.[9] While there is no clear distinction as to whether PD is more closely associated with peripheral fatigue (localized muscle fatigue) or central fatigue (central nervous system fatigue), the fatigue-causing factors mentioned above suggest that a combination of both is highly plausible. Unfortunately, to date there has been little research done to investigate the role that fatigue plays on balance and gait in individuals with PD.

The lack of information about the effect of fatigue on balance leaves a critical gap in our knowledge and understanding of fall risk in PD. In fact, multiple studies have already established links between both peripheral and central fatigue on balance and postural stability in other populations. For example, research from Helbostad et al suggest a correlation between physical (peripheral) fatigue and fall risk in older persons.[10] Additionally, researchers in a separate study found that central fatigue also decreased balance and stability in young athletes.[11] These researchers suggested that because balance depends on the processing of three central nervous system sensory systems (visual, vestibular, and somatosensory), any fatigue-related alterations in their function could affect one's balance.[11] This research suggests that even mentally fatiguing tasks may potentially further reduce balance ability in individuals who have an increased fall risk. Likewise, because the neuromotor system is responsible for executing the response of the three sensory systems, it may also be affected by fatigue resulting in balance decrement.

Other factors that theoretically may contribute to fatigue's effect on balance in PD are PD medications and genotype of motor-related factors. BDNF is an activity-dependent neuromodulator that plays an important role in the growth, survival, and neuronal cell differentiation in the central nervous system.[12] The genotype for BDNF (Val/Val, Val/Met, or Met/Met) affects the amount of BDNF trafficking.[13] Individuals with the Val/Met polymorphism make up the majority of the population at 60% and tend to have an intermediate level of BDNF secretion.[14] Due to the reduced secretion of BDNF, Kleim et al found that in comparison to Val homozygotes, Met allele carriers have less change in cortical motor maps in response to motor training.[15] Furthermore, Peterson et al found that motor learning, which is critical for training automatic postural responses necessary for fall prevention, is less pronounced in individual's with PD in comparison to healthy older adults.[16] If individuals with PD have the Met allele that may mean that their motor learning capabilities are suboptimal. It is also possible that a fatiguing condition may amplify these negative effects.

It seems logical that fatigue would negatively impact balance in PD and that fatigue may result in higher fall risk during periods of fatigue; however, this has not been well vetted in the literature. Therefore, the primary aim of this study was to investigate the role that fatigue plays on balance in individuals with PD. We hypothesized that different aspects of balance performance (anticipatory, adaptive, and dynamic) would decrease after a condition that induced fatigue. A secondary aim was to explore the differential effects of BDNF polymorphisms (Val/Met, Val/Val, and Met/Met) on balance performance and changes due to a fatiguing condition. We hypothesized that Met allele carriers would have poorer balance

performance and a greater decay in balance function after fatigue than the Val/Val genotype. Another secondary aim was to explore the role of PD-medication (on and off) on the balance response to a fatiguing condition. Although there is evidence that postural instability may be refractory to dopaminergic treatment,[17] we wanted to determine if fatigue was differentially affected by PD medication. We hypothesized that there would not be a difference in response to fatigue in either the on or off medication conditions.

METHODS

Participants

The inclusion criteria for the study included the following: neurologist-diagnosed idiopathic PD, Hoehn and Yahr[18] stages 1-4, willingness to be tested in the on and off PD medication states, and 45-80 years of age. The exclusion criteria were those with moderate-to-severe dementia, inability to stand or walk for more than 10 minutes, or other significant co-morbidities that would be contraindicated for the fatiguing condition in this study (i.e., atrial fibrillation, chronic obstructive pulmonary disease, poorly controlled or unstable cardiovascular disease). The reason to exclude those with other significant co-morbidities was to minimize the impact of potential compounding factors that would limit physical activity participation. Participant recruitment methods included the following: snowball recruitment, flyer distribution through local PD support groups, social media through PD-specific websites, the Michael J. Fox Trial Finder, local neurologists' offices specializing in movement disorders, and previous PD research participant lists.

Recruitment yielded 27 total participants (mean age = 65.4±8.1; males = 14, females = 13) with neurologist-diagnosed PD (mean months since diagnosis = 59.7±42.1, mean Levodopa Equivalent Daily Dose (LEDD) = 442.4±240.2)(Table 1). Participants ranged from 1 to 4 on the Hoehn and Yahr Scale (median and mode = 2). Of the 27 participants, 2 participants chose not to participate in the off-medication day, and 1 participant did not take PD medications so this individual was only tested during the off-medication day. For the BDNF genotype groupings, 13 were genotyped as Val/Val, 11 as Val/Met, and 2 as Met/Met. One participant refused the genotyping.

Study Design

This study was a pre- and post-test design in both the on and off medication states. After screening, demographic data collection, and testing, blood samples were taken to determine the BDNF genotype which was used to categorize the participants by BDNF polymorphism (Val/Met, Val/Val, Met/Met). All participants that agreed to be tested off medication were tested on two separate days, one on-medication and one off-medication, separated by at least 5 days to prevent carryover effects from delayed onset muscle soreness and activity-related fatigue. The two participants that chose not to participate in the off-medication day and the one participant that did not take PD medications were tested only once. All test evaluators were blinded to genotype.

Data collection occurred at the (Blinded) Gait and Balance Laboratory. Participants were instructed to eat a similar breakfast, including any caffeine consumption, on both testing days, to avoid any strenuous activity on the day of and the days leading up to the test days, and were

encouraged to get a restful sleep. Participants were also instructed to avoid eating protein with breakfast on the testing day as research has shown that protein can interfere with the therapeutic effects of PD medications and result in fluctuations of motor symptoms, especially bradykinesia.[19]

On the first day of testing, participants were instructed to take their PD medications 30 minutes prior to arrival as research shows that Levodopa has a peak onset time of 1 hour.[20] The additional 30 minutes before peak onset were allotted to allow for the collection of the following data: 1. Demographics - age, gender, fall history (last year, last month, and injurious falls in last year), cognitive level (Montreal Cognitive Assessment),[21] physical activity level (International Physical Activity Questionnaire),[22] balance confidence (Activities-Specific Balance Confidence Scale),[23] and fear of falling avoidance behavior (Fear of Falling Avoidance Behavior Questionnaire – modified);[24] and, 2. PD characteristics - year of PD diagnosis, PD medication usage (Levodopa Equivalent Dose),[25] Hoehn and Yahr Scale,[18] and The Parkinson's Fatigue Scale.[26]

Next, participants completed a battery of balance and gait tests, followed by a fatiguing condition, and lastly, the same balance and gait tests. The pre and post-tests consisted of the same tests and measures with the exception of a 3 minute rest period between tests during the pre-test phase to ensure that participants were not fatigued when performing the tests. During the post-test, the 3 minute rest periods were replaced with a 30-second sit-to-stand exercise to

maintain the sense of fatigue throughout the second half of testing. The following balance and gait tests were used:

1. **Anticipatory postural responses**. The anticipatory postural response is how one responds to a balance challenge that the person knows about and is associated with the activation of postural muscles prior to an expected balance perturbation. Anticipatory postural responses are mediated by supraspinal centers, including premotor and cerebellar systems.[27] This type of balance response was assessed using the anticipatory postural response subsection on the mini-Balance Evaluation Systems Test (mini-BESTest),[28-30] and Functional Reach Test (FRT)[31] (quantified using VirtuBalance technology[i]). Collectively, these tests allowed inference about the effects of the fatigue condition on anticipatory (supraspinal) contributions to balance.
2. **Adaptive postural responses.** The adaptive or compensatory postural response is how one responds to a balance perturbation that occurs without knowledge and is associated with the reflex activation of postural muscles after an unexpected balance perturbation. Because these postural responses occur without knowledge, the latency period of an adaptive postural response is longer than a stretch reflex but shorter than voluntary reaction time suggesting that they are mostly mediated by spinal cord reflex circuitry and do not typically have a large supraspinal contribution.[32] This type of balance response was assessed using the Bertec Balance System[ii] motor control test which quantifies postural sway as a result of unexpected movements of the balance

[i] VirtuSense Technologies, Peoria Next Innovation Center 801 W Main St, Suite B216 Peoria, IL 61606, (309)495-7325

[ii] Bertec Corporation, 6171 Huntley Rd, Suite J Columbus, OH 43229, (614) 543-8099

platform (i.e. forward/backward translation). Additionally, the reactive postural response subsection of the Mini-BESTest was also utilized. These tests allowed inference about the effect of the fatigue condition on adaptive or spinal cord (reflex circuitry) contributions to balance.

3. **Balance sensory orientation.** Balance sensory orientation testing helps to determine the specific contribution of three different balance sensory systems to static balance: visual, vestibular, and somatosensory.[33] Quantification of the contribution of these three sensory systems was done using the Bertec Balance System Sensory Organization Test (SOT).[34] The SOT allowed inference about what postural sensory system (i.e., visual, vestibular, somatosensory) was most influenced by the fatigue condition.
4. **Dynamic balance.** Gait was assessed by the 20 Feet Walk Test, Timed Up and Go test (TUGT),[35] and Timed Up and Go Cognitive (TUGTcognitive),[36] gait component of the mini-BESTest using the Protokinetics[iii] Zeno instrumented walking mat.[37] The walking mat was used to quantify the following gait characteristics during those tests: gait velocity, step length, step length coefficient of variation, stride length, stride length coefficient of variation, stride velocity, and stance percentage.

Collectively, these balance tests allowed inference about the effects of the fatigue condition on supraspinal (premotor), and spinal cord (reflex circuitry) contributions to balance, as well as determined which postural sensory system (i.e., visual, vestibular, somatosensory) was most influenced by the fatigue condition.

[iii] ProtoKinetics LLC, 60 Garlor Dr. Havertown, PA 19083, (610) 449-4879

To achieve fatigue, participants performed a 30-second sit-to-stand exercise followed by the Modified Bruce Treadmill Test[38] until they reported a 7 out of 10 score using the Visual Analogue Scale for Fatigue (VAS-F)[39] (subscale of the Fatigue Severity Scale). During the Modified Bruce Treadmill Testing, the participants' heart rate, oxygen saturation, fatigue level, speed, and incline were monitored and recorded. Immediately after reaching the fatigue threshold (operationally defined as 7 out of 10), participants then performed the balance and gait tests again, except the rest periods were replaced with the 30-second sit-to-stand exercise so as to maintain fatigue. On the second testing day, participants were tested after having not taken their PD medications for at least 12 hours. The same balance and gait pre-testing, fatiguing condition, and balance and gait post-testing protocol was conducted the same as Day 1.

BDNF Genotyping

During the first test day, a sample of blood (600 µl) was collected via finger-sick into an anticoagulant tube (Multivette 600 LH, Sarstedt, Fisher Scientific, Pittsburgh, PA). DNA isolation was performed using a commercially available kit (Wizard Genomic DNA Purification Kit, Promega, Madison, WI). Genotyping was conducted by the (blinded). DNA concentration (ng/mL) was determined using an Epoch microplate reader with the Take3 System (Biotek U.S., Winooski, VT). BDNF gene region rs6265 was amplified using polymerase chain reaction (PCR) as described by Sheikh et al (Sheikh et al., 2010). Three amplicons, two allele specific amplicons, 253 bp (val) and 201 bp (met) along with the 401 bp amplicons (entire res6265 region used as an internal control) were distinguished with four primers: P1 (forward)

CCTACAGTTCCACCAGGTGAGAAGAGTG, P2 (reverse) (TCATGGACATGTTTGCAGCATCTAGGTA), P3 (G allele specific) CTGGTCCTCATCCAACAGCTCTTCTATAAC, and P4 (A allele specific) ATCATTGGCTGACATTTCGAACCCA. The PCR reaction consisted of a total of 12 µL containing: 1X Kapa Hotstart Genotyping Mix (Kapa Biosystems), 0.5 µM of each of the four primers (P1, P2, P3, P4) and 20 ng of genomic DNA. Thermocycling conditions were as follows: denaturation at 94°for 3 min followed by 30 cycles of at 95° for 45 sec, 65° for 60 sec, and 72° for 60 sec, followed by a final extension of 72° for 2 minutes. DNA 1000 bp ladder (Promega, USA) and 10 µL PCR products were loaded onto a 2% agarose gel and electrophoresed at 100 V for 90 min. Based on the following banding patterns, samples were classified as Val/Val (253/253 bp), Val/Met (253/201 bp), and Met/Met (201/201 bp) with all of them having the rs6265 internal control (401 bp) band (Figure 2). Each sample was genotyped from at least two independent polymerase chain reactions to ensure fidelity.

Data Analysis

All data were analyzed using SPSS version 22.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) with $\alpha = 0.05$. To address the primary aim of the study, a 2 (condition: pre and post) X 2 (medication: on and off) factorial ANOVA was performed for each outcome variable in each of the following balance domains: 1. anticipatory postural response (mini-BESTest - Anticipatory subsection, FRT); 2. adaptive postural responses (Bertec Balance System motor control test, mini-BESTest - Reactive Postural Control); 3. Dynamic balance (TUGT, TUGTcognitive, mini-BESTest – Dynamic Gait subscale); 4. sensory orientation (Bertec Balance System SOT); and, 5. gait characteristics. The secondary aim of the study was to compare the

difference in balance function between the two BDNF genotypes, Val/Val and those with a Met allele (Val/Met and Met/Met) and also to see if there was a difference between them on response to a fatiguing condition. To compare the difference in balance function between the two genotypes an independent t-test was conducted for the pre-test scores, both on and off medication, across all of the aforementioned balance domains. To compare the differences in response of the two groups to a fatiguing condition, independent t-tests were used to compare the difference between the pre- and post-tests across all of the aforementioned balance domains. Missing data were inputted using the last observation carried forward method. The other secondary aim of PD medication was analyzed using the main effect of medication on the primary factorial ANOVAs.

RESULTS

Anticipatory postural responses

For the mini-BESTest – Anticipatory subscale, there was not a statistically significant interaction between time (pre and post) and medication state (on and off), p=.382 (Tables 2 and 3). There were no statistically significant differences for the main effects of time (p=.491) and medication (p=1.000). Likewise, for the FRT, there was not a statistically significant interaction between time and medication state, p=.785. There were no statistically significant differences for the main effects of time (p=.054) and medication (p=.813).

Adaptive postural responses

There were no statistically significant interactions between time and medication state for amplitude (ps≥.702) and latency (ps≥.494) for both forward and backward on the motor control test (Tables 2 and 3). The main effect of medication was statistically significant only for forward latency (p=.011) but was not for the others (ps≥.452). The main effect of time was statistically significant only for backward amplitude (p=.041) but not for the others (ps≥.182). There was no interaction for the mini-BESTest – Reactive Postural Control subscale, p=.405, or for either of the main effects, ps≥.247.

Dynamic balance

For the TUGT, TUGTcognitive, and mini-BESTest – Dynamic Gait subscale, there were no statistically significant interactions between medication and time, ps≥.187 (Tables 2 and 3). There were no main effects of medication, ps≥.683. Of the three outcome variables, only the TUGT had a statistically significant main effect of time (p=.004).

Sensory orientation

There were no statistically significant interactions between time and medication on the SOT composite and the three sensory balance systems (visual, somatosensory, vestibular), ps≥.210 (Tables 2 and 3). There were no main effects of time, ps≥.208; however, two of the four sensory orientation outcomes, composite (p=.009) and visual (=.015), were statistically significant.

Gait characteristics

There were no statistically significant interactions between time and medications for any of the 7 gait characteristic outcomes, ps≥.355 (Tables 2 and 3). Of the 7 outcomes, the only statistically significant main effect of medication was stride length coefficient of variation, p=.036. All but two (step length coefficient of variation (p=.373) and stride length coefficient of variation (p=.925)) of the 7 outcomes were statistically significant for the main effect of time, ps≤.007.

BDNF genotype

In comparing those with a Met allele (Val/Met and Met/Met) and those without (Val/Val) in both the on and off state of PD medication, there were no statistically significant differences across the following gait and balance categories on their pre-fatigue assessment: anticipatory postural responses (ps≥.474), adaptive postural responses (ps≥.262), dynamic balance (ps≥.299), sensory orientation (ps≥.166), and gait characteristics (ps≥.111). Likewise, there were no differences between the two BDNF groups (with and without Met), on their response to a fatiguing condition across all of the balance domains (ps≥.070).

DISCUSSION

Individuals with PD, who experienced a fatiguing condition, did not demonstrate significant decrements in anticipatory balance responses, adaptive balance responses, sensory organization, dynamic gait, or gait characteristics. Moreover, BDNF polymorphism did not

influence balance and gait in individuals with PD or their response to a fatiguing condition. Lastly, the use of PD medications did not improve balance and gait in individuals with PD. Contrary to our hypothesis, there were no decrements in balance and gait performance after a fatiguing condition. From a clinical prospective, these results suggest that treadmill exercise to the point of fatigue may not increase balance and gait dysfunction and, logically, may not increase one's risk for a fall. Our results also suggest that PD medications are not sufficient for improving postural instability; thus, clinicians should seek the use of other evidence-based treatment approaches to address this problem.

It is possible that the reason for the lack of change in balance and gait was that the fatiguing condition on the treadmill used in our study was not sufficiently fatiguing to decay balance and gait. Thus, it is possible that balance and gait do indeed decay with fatigue but the fatiguing condition chosen for this trial did not fatigue enough to see the true effect. On the other hand, it is possible that the fatiguing condition was sufficiently fatiguing but that balance and gait systems are resilient to fatigue. In light of our findings, we cannot make a definitive conclusion about which is more likely. However, based on the evidence in the literature, we believe the former conclusion is more likely. In retrospect, the treadmill-based fatiguing condition may have not been a good design choice because it may have primed, warmed up, or entrained the lower extremities and postural muscles, thereby improving posture and gait which may have counteracted any fatigue effects. It is also possible that balance performance did not decrease because participants were experiencing transient asthenia rather than actual fatigue.

The Modified Bruce Treadmill Protocol used in our study may not have been an appropriate method to induce fatigue to impair balance in individuals with PD. At the time of this study, there were few studies relating a fatigue condition and balance and gait. However, recently published research has suggested that there may be more appropriate activities to induce sufficient fatigue. For example, a study by Mudie et al found that the single-leg hopping to exhaustion may be adequate to elicit muscle fatigue of the lower limb muscles.[40] For individuals that are incapable of safely performing a single-leg hop exercise as is the case with our study population, Hamacher et al successfully used an incremental exercise test on a cycle ergometer to elicit a reduction in stability during gait in older individuals.[41] In retrospect, cycle ergometry may have been a better choice for the fatigue-inducing modality in our study since it would not have likely recruited the same neuromuscular circuitry for balance and gait as the treadmill did.

As mentioned above, the treadmill may have primed the nervous system, which may have enhanced balance performance even after the fatiguing condition. Previous research has demonstrated that "treadmill walking can promote a faster and a more stable walking pattern in patients with PD."[42] The validity of the priming notion may be evidenced by the fact that participant TUGT times were significantly faster, regardless of medication usage, during the post-fatigue testing. These results are also consistent with previous research by Lambourne et al that has suggested that, moderate steady-state exercise can enhance motor performance by increasing central nervous system arousal resulting in improved motor response time to sensory stimuli.[43] A study published by Koo et al also found evidence to suggest that treadmill training has a positive effect on neurotransmitters as well, specifically dopamine, which would

logically improve motor function. Because treadmill training exercise is thought to activate mitochondrial import machinery, “treadmill exercise may be an effective way of inhibiting dopaminergic neuron loss and improving mitochondrial function, thus leading to partial recovery of motor loss”.[44]

Additionally, as there was no research to determine how long to wait after the fatiguing condition to re-test balance, or how long the improvement in gait speed lasts, it may be possible that balance decrements and the return of baseline gait speeds or lower, may manifest some time later after the putative “priming effect” has worn off. This could be supported by participant reports of significant exhaustion several hours after the completion of testing. Future research could aim to identify the potential of a delay in the effect of fatigue on balance as well as how long possible treadmill priming remains active in individuals with PD.

To date, there is also no clear, widely-accepted definition for fatigue. Most previous studies did not state how they defined fatigue and instead, used each participant’s subjective perception. With no explicit description of what fatigue is, it is possible that individuals may not actually be fatigued, but rather be experiencing other closely-related states. For example, Egerton discussed the definition of fatigue as well as a related synonym, asthenia. “(1) fatigue--the state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli, and (2) asthenia—clinical sign or symptom manifested as debility or lack or loss of strength and energy.”[45] Although our study was concerned with fatigue as defined above, it is possible that participants

may have misinterpreted their loss of strength and energy, or their asthenia, for fatigue. As the definition for asthenia does not include decreased work capacity and reduced response to stimuli, this could result in better preservation of balance performance after a fatiguing condition, than if "true" fatigue had been achieved. It should also be noted that in PD, the distinction between fatigue and asthenia is not clear. It is possible that the latter is a closer approximation of the "fatigue" reported by people with PD and, based on the above definition, may not be exacerbated by a fatiguing condition. Additionally, this study aimed at specifically inducing "peripheral" fatigue. Future research may desire to investigate the impact of a centrally fatiguing task, either alone or in conjunction with a peripherally fatiguing task, on balance performance.

While several studies on the use and validity of the Visual Analog Scale for Fatigue exist, research on the specific amount of fatigue required to have a significant effect on balance is lacking. A level of 7/10 fatigue was chosen arbitrarily as the cut-off to induce fatigue midway between an individual's perceived "moderate" and "severe" fatigue. It is possible that a level of 7 fatigue may not have been sufficient enough to significantly impact the participants' balance. It is also possible that participants had unreliable reports of sufficient fatigue for our study as "patients with PD present a degradation in sensorimotor integration and sensory feedback,[46] which may be associated with deficits in perception of fatigue."[47,48] Additionally, according to Dobkin, the concept of "fatigue" is the more central component, that often arises from "fatigability," the more peripheral component.[49] Dobkin describes "fatigability" as a demonstrable decline in muscle strength as the result of repetitive activation of specific muscle

groups, but notes that it may be difficult to localize "because no finite boundary exists between the central and peripheral components of motor reserve and endurance."[49] Dobkin also states that because most individuals have difficulty separating psychological manifestations of fatigue from the neuromuscular mechanisms, the use of subjective fatigue rating scales, such as the VAS-F, may not be sufficient enough to specifically measure peripheral fatigue. For assessing peripheral fatigue, Dobkin recommends, "manual muscle testing of specific proximal or distal muscles after rest, immediately after repetitive movements against light resistance, and again after 60 to 120 seconds of rest to retest for reversibility of weakness."[49] On the other hand, it is possible that people with PD have a more central fatigue component than a peripheral fatigability component and the method of self-report used in this study was indeed appropriate. However, perhaps the treadmill condition did not sufficiently challenge the central component. Therefore, it may have been a mismatch of theory. A future study may desire to explore the impact of a severe fatigue condition on balance and include the recommended manual muscle testing to attempt to disassociate the desired peripheral fatigue from the central component.

This is one of the first published studies to explore the relationship between the BDNF polymorphism and balance. The results of this study suggest that the BDNF polymorphism has no effect on balance and gait in individuals with PD, nor any effect on balance response to a fatiguing condition. Additionally, although this study was underpowered for this aim, the raw data also does not suggest any trends in the relationship. Previous research has theorized that BDNF may be more involved in motor learning and plasticity than actual motor performance.

For example, Lu and Gottschalk found BDNF to be a "key regulator of activity-dependent synaptic plasticity in the brain, with a known role in the induction and maintenance of memory and learning.[50,51] Svetel et al also found that the Val/Met polymorphism specifically, does not modify motor and non-motor clinical features and treatment complications in patients with PD.[52] Additionally, it is also proposed that BDNF may be more involved in complex and/or fine motor tasks as opposed to simple, gross motor tasks like balance and gait. For example, Klintsova et al compared the effect of a complex motor learning task and a physical activity requiring very little learning on the expression of BDNF.[53] Their research found that while both tasks appear to have implications in neural plasticity, increases in cerebellar and cerebral cortices persisted longer in the complex motor skill-trained group as compared to the basic exercise group.[53]

Of the four cardinal signs of PD, postural instability is the only sign shown to be mostly unresponsive to PD medications. Our results are in line with previous research that has suggested that postural instability is refractory to dopaminergic therapies. Although our study did not show any significant differences in balance performance when participants were ON versus OFF medication, recent research done by Curtze et al suggests that the use of levodopa actually decreases static balance, specifically increasing medial-lateral and anterior-posterior postural sway velocity and variability during quite standing. However, their study also showed that balance control and postural sway during gait were not affected by levodopa suggesting that the difference between static and dynamic balance control may indicate that these balance domains depend on different neural circuitry."[54] In support of this, Di Guilio et al

suggest that postural instability in PD is caused by disruption to non-dopaminergic systems.[55] Muller et al has also suggested that the neurotransmitter acetylcholine may possibly be implicated in postural instability.[56] Likewise, Bohnen et al found that thalamic acetylcholine activity was significantly reduced in individuals with PD with a history of falls as compared to non-fallers, even when there was no difference in nigrostriatal dopaminergic activity between the two groups.[57] For this reason, dopaminergic therapies may not have a positive impact on postural instability in PD.[55]

Because postural instability is associated with higher fall risk,[58] it is important to educate individuals with PD that balance performance is not improved by medication usage and stress the importance of evidence-based therapies like strengthening and balance training to decrease fall risk.[59,60] Yitayah and Teshome also concluded that "physiotherapy interventions like balance training combined with muscle strengthening, range of movement, and walking training exercise is more effective in improving balance in patients with PD than balance exercise alone."[61]

Although our study did not find any statistical impact of fatigue on balance in individuals with PD, there are a few limitations worth discussing. First, our recruitment methods did not yield a sufficient number of participants and due to this limitation, our study may have been underpowered for our primary aims. Additionally, because our sample size was small we were unable to see if PD subgroups, like postural instability – gait difficulty and tremor dominant, reacted differently to the fatiguing condition. As mentioned earlier, another prominent

limitation may have been using the treadmill as the modality to induce fatigue. Also, because the majority of our participants were classified as Hoehn and Yahr 1-2, the results may not be an accurate representation for individuals with PD in stages 3-4. It is possible that individuals in these later stages may be more affected by fatigue than individuals in stages 1-2, which was not detected due to our small sample size. Lastly, the balance and gait assessment was conducted by researchers who were not blinded to the study aims.

CONCLUSION

Fatigue resulting from treadmill training does not negatively impact static or dynamic balance responses in individuals with PD. Likewise, it also does not negatively impact gait characteristics and may actually improve gait speed immediately following cessation of the treadmill session. Clinicians can feel confident in exercising and inducing moderate fatigue in their patients with PD using a treadmill without increasing risk for falls. While fatigue induced by treadmill training does not impair balance, future studies should investigate the impact of other fatiguing exercises, including mental fatigue, on balance and fall risk. Clinicians should also be sure to educate these individuals on the limitations of an effect of PD medication on postural instability. Furthermore, BDNF polymorphism appears unrelated to balance performance or balance responses following a fatiguing condition.

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Figure 1. Participant screening and clinical balance and gait testing

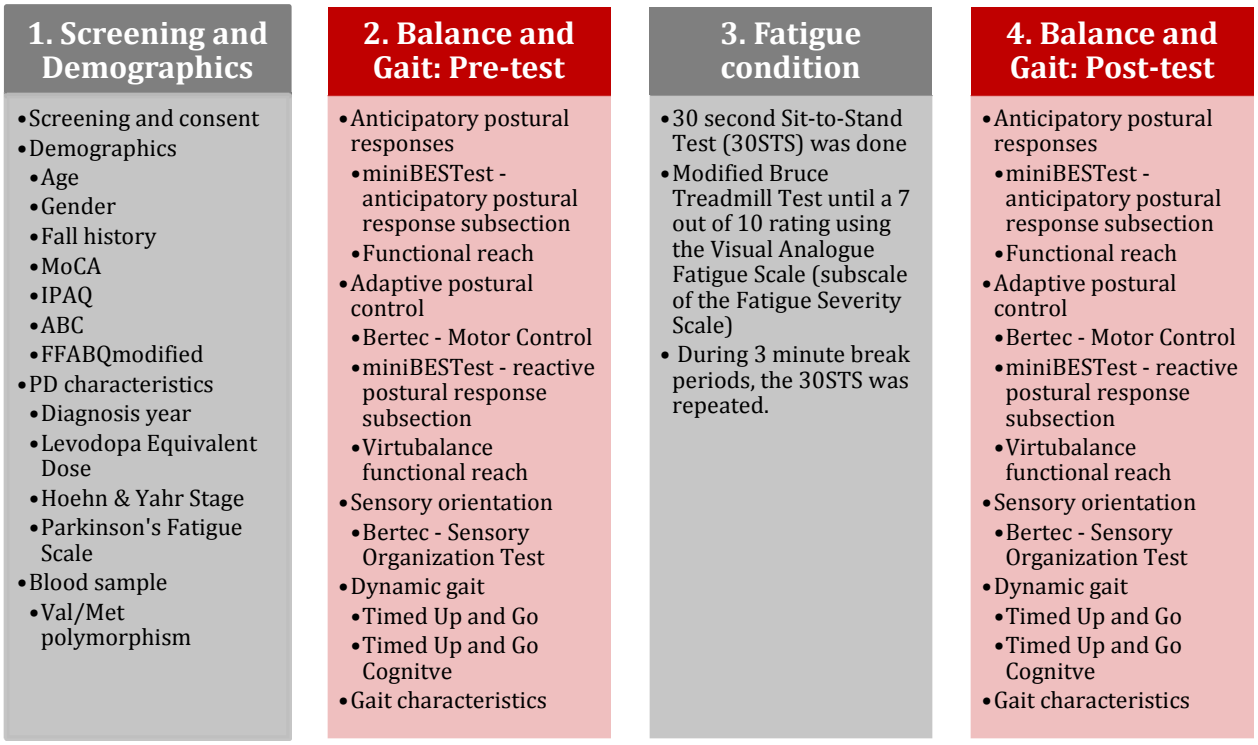

Figure 2. Characterization of BDNF genotype using banding patterns on a DNA ladder.

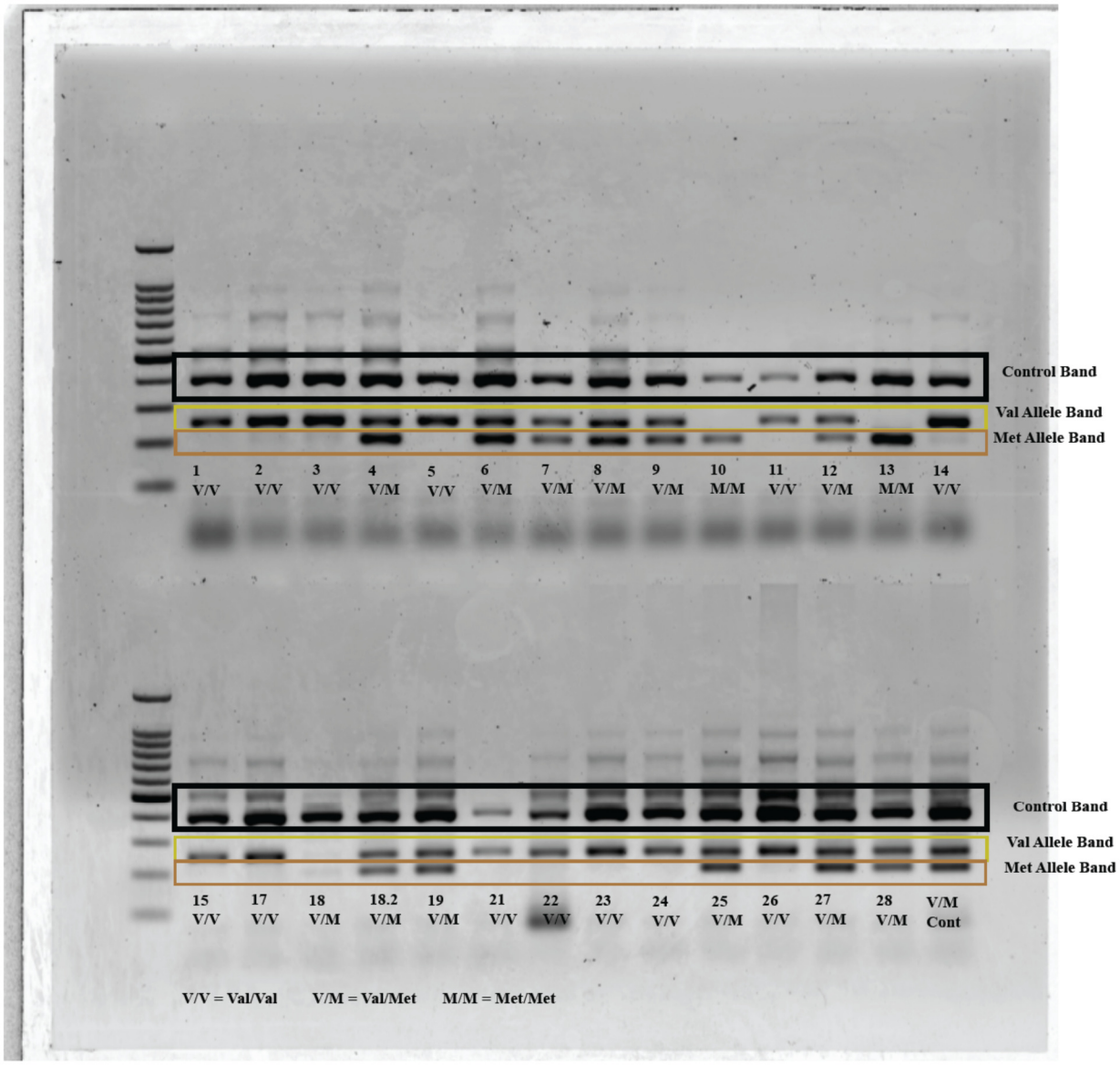

Table 1. Descriptive details of the participants.

General	Age	Mean = 65.4±8.1
	Gender	Males = 14, Females = 13
PD specific	Months since diagnosis	Mean = 59.7±42.1
	Hoehn and Yahr Scale	Mean = 2, Mode = 2 • Stage 1 = 6 • Stage 2 = 12 • Stage 3 = 8 • Stage 4 = 1
	Levodopa Equivalent Daily Dose	Mean = 442.4±240.2
Cognition	Montreal Cognitive Assessment	Mean = 25.7±3.5
Balance and falls	Falls in the last month	Mean = 5.3±18.0
	Falls in the last year	Mean = 58.0±212.9 • Fallers = 10 • Non-fallers = 17
	Fall injuries in the last year	Mean = 0.67±1.9 • Injured = 9
	Activities-Specific Balance Confidence Scale	Mean = 78.1±17.6
	Modified Fear of Falling Avoidance Behavior Questionnaire	Mean = 28.3±12.5
Physical activity levels	Number of minutes in vigorous activity per day	Mean = 27.6±43.0
	Number of minutes in moderate activity per day	Mean = 31.4±46.4
	Number of minutes in walking per day	Mean = 49.4±42.1
	Number of minutes sitting per day	Mean = 342.2±190.1
	Parkinson's Fatigue Scale	Mean = 2.7±1.0

Table 2. Means and standard deviations for outcome variables across all of the balance domains.

Balance domain	Outcome variable	On PD medications		Off PD medications	
		Pre	Post	Pre	Post
Anticipatory postural response	mini-BESTest - Anticipatory subsection	4.83 (1.17)	4.67 (1.09)	4.75 (1.19)	4.75 (1.36)
	Functional Reach Test	9.62 (3.19)	9.22 (2.55)	9.61 (2.81)	9.10 (2.91)
Adaptive postural responses	Motor control test - backward latency	130.04 (7.72)	129.90 (8.14)	128.92 (10.02)	128.17 (8.67)
	Motor control test - backward amplitude	7.56 (2.94)	7.13 (3.05)	7.77 (3.51)	7.17 (2.77)
	Motor control test - forward latency	128.63 (10.40)	129.04 (12.00)	124.69 (10.17)	126.29 (11.03)
	Motor control test - forward amplitude	6.56 (2.36)	6.48 (2.50)	6.58 (2.42)	6.54 (2.48)
	mini-BESTest - Reactive Postural Control subsection	4.33 (1.95)	4.13 (2.07)	4.21 (1.93)	4.17 (1.81)
Dynamic gait	TUGT	10.16 (3.13)	9.44 (2.82)	10.12 (4.33)	9.30 (2.79)
	TUGTcognitive	11.85 (6.39)	11.73 (7.88)	12.03 (9.01)	12.21 (12.01)
	mini-BESTest – Dynamic Gait subscale	8.92 (1.18)	8.54 (1.41)	8.67 (1.69)	8.71 (1.65)
Sensory orientation	SOT composite	66.42 (9.08)	67.00 (8.45)	71.17 (8.59)	69.50 (9.85)
	SOT visual	70.67 (12.69)	75.00 (12.52)	76.79 (11.79)	76.88 (10.37)
	SOT somatosensory	97.25 (5.27)	97.12 (9.75)	98.08 (2.93)	98.13 (3.29)
	SOT vestibular	63.00 (11.35)	63.96 (13.95)	68.04 (12.55)	63.08 (19.99)
Gait characteristics	Gait velocity	112.78 (24.20)	118.66 (25.00)	113.26 (25.58)	118.09 (27.52)
	Step length	61.72 (11.00)	63.43 (11.69)	60.76 (12.51)	61.91 (12.73)
	Step length coefficient of variation	14.25 (3.94)	13.92 (5.41)	15.23 (7.95)	14.90 (6.19)
	Stride length	123.73 (22.33)	126.63 (23.33)	121.75 (25.48)	123.85 (25.50)
	Stride length coefficient of variation	11.74 (3.17)	12.09 (4.07)	13.44 (6.16)	13.14 (4.65)
	Stride velocity	113.30 (23.95)	119.15 (24.76)	113.73 (25.56)	118.55 (27.40)
	Stance percent	64.57 (2.95)	64.34 (3.11)	64.87 (3.00)	64.53 (2.97)

Table 3. P values for the time by medication interactions and main effects.

Balance domain	Outcome variable	Interaction	Main effect of medication	Main effect of time
Anticipatory postural response	Mini-BESTest - Anticipatory subscale	P=.382	p=.491	p=1.000
	Functional Reach Test	P=.785	p=.054	p=.813
Adaptive postural responses	Motor control test - backward latency	P=.694	p=.699	p=.182
	Motor control test - backward amplitude	P=.702	p=.452	p=.041
	Motor control test - forward latency	P=.494	p=.011	p=.334
	Motor control test - forward amplitude	P=.887	p=.734	p=.741
	mini-BESTest - Reactive Postural Control subscale	P=.405	p=.247	p=.858
Dynamic gait	TUGT	P=.880	p=.783	p=.004
	TUGT cognitive	P=.477	p=.683	p=.953
	mini-BESTest – Dynamic Gait subscale	P=.187	p=.870	p=.276
Sensory orientation	SOT composite	P=.277	p=.009	p=.524
	SOT visual	P=.208	p=.015	p=.208
	SOT somatosensory	P=.945	p=.479	p=.961
	SOT vestibular	P=.210	p=.369	p=.496
Gait characteristics	Gait velocity	P=.500	p=.983	p<.001
	Step length	P=.355	p=.191	p=.001
	Step length cv	P=.998	p=.229	p=.373
	Stride length	P=.511	p=.213	p=.003
	Stride length cv	P=.429	p=.036	p=.925
	Stride velocity	P=.502	p=.972	p<.001
	Stance percent	P=.654	p=.252	p=.007

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