Cognitive Workload during Dual-tasking and its Relationship with Falls in Parkinson's Disease

By
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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. Individuals with PD are at high risk of falling due to degeneration of dopaminergic and cholinergic pathways in the basal ganglia. The risk of falling increases when performing two tasks simultaneously, such as standing while talking. In such dual-tasking conditions, upright stance posture is an essential motor skill to accomplish various motor and cognitive tasks concurrently. Although maintaining an upright stance posture seems autonomous and effortless in healthy individuals, it may become challenging and cognitively effortful due to impaired autonomic control processes in individuals with PD.

Dual-tasking deficiency is operationally defined as a decrease in motor or cognitive performance (or both) when tasks are performed concurrently. Dual-tasking deficiency is observed in all humans, but individuals with PD seem to be disproportionally affected by dual-tasking due to competition of limited cognitive resources. Dual-tasking is typically evaluated by dual-task cost on either cognitive tests or balance measures. However, these common endpoints have methodological limitations (ceiling/floor effect), they are not sensitive to change, and they do not explain the amount of cognitive workload needed to complete the tasks. Based on attention and effort theory, cognitive workload is defined as the mental effort that is needed to execute a task. Advances in neurophysiological technology enable us to measure cognitive workload in real-time. Pupillary response is a non-intrusive, real-time neurophysiological measure of cognitive workload. This dissertation project examined the neurophysiological response of the brain measured by pupillary response during dual-tasking conditions in individuals with PD.

In Chapter 2, we conducted a systematic review to investigate the real-time brain activity during dual task gait and balance and whether changes in brain activity correlate with changes in behavioral outcomes in older adults and people with age-related neurodegenerative conditions. In Chapter 3, we investigated the usefulness of pupillary response to quantify the cognitive workload of postural control in healthy young adults. In Chapter 4, we examined the reliability and validity of pupillary response during dual-task balance conditions in individuals with PD. Finally, in Chapter 5, we conducted a study to investigate neurophysiological changes, indexed by pupillary response, during dual-task balance between three groups: PD fallers; PD non-fallers; and healthy controls.

This body of research extends the use of pupillary response as a metric of cognitive workload during cognitive testing to cognitive-motor testing in a rehabilitation research setting. To our knowledge, this is the first study that investigated pupillary response as a metric of cognitive workload during dual-task balance in healthy adults and individuals with PD. Previous studies mainly used functional near-infrared spectroscopy or electroencephalogram as a neurophysiological tool to understand brain activity in aging and age-related neurodegenerative conditions. Pupillary response is cost-effective, less intrusive, and easy to implement in clinical settings compared to electroencephalogram and functional near-infrared spectroscopy.

We found that pupillary response is a reliable and valid measure of cognitive workload during dual-task balance in both healthy adults and in individuals with PD. In addition, the findings of this research project demonstrated that individuals with PD exhibited higher cognitive workload measured by pupillary response compared to age- and sex-matched healthy controls during dual-task balance. Lastly, pupillary response significantly increased with increased task difficulty

especially from single task to dual-task balance as well as from eyes open to eyes occluded conditions in both individuals with PD and healthy controls.

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Chapter 1

Introduction

1.1. Overview of Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, with about 1% of the population over 60 years suffering from this disease[1,2]. In the United States, more than 60,000 people are diagnosed with PD in each year, and more than 10 million people are living with PD in the world[3]. PD is characterized by degeneration of the dopaminergic neurons in the subtantia nigra pars compacta and formation of abnormal proteinaceous spherical deposits, coined Lewy bodies, in the brain. The hallmark motor symptoms of PD are tremor, rigidity, bradykinesia, and postural instability[4]. These motor symptoms are associated with dopamine depletion in the cortico-basal ganglia-thalamocortical loop due to the dopaminergic cell loss in the substantia nigra. Motor symptoms as a consequence of dopaminergic pathology are usually the primary focus of PD disease management[5]. However, there is an increasing appreciation of the contribution of cholinergic dysfunction to the pathophysiology of motor and non-motor symptoms associated with PD[6,7].

In PD, non-motor symptoms including cognitive difficulties, sleep impairments, mood disturbances, pain, and autonomic dysfunction affect health-related quality of life, perhaps even more so than motor symptoms. The cholinergic system has a widespread influence on both motor and non-motor symptoms including cognition and postural instability[8]. Imaging studies demonstrated reduced cortical cholinergic activity in individuals with PD[9]. In addition, this reduced activity has shown to correlate with cognitive difficulties especially with attention and executive function[10]. Dysfunction in attention and executive function is not discrete, but a significant predictor of falls and postural instability in individuals with PD[11]. Further evidence suggests that cholinergic degeneration is associated with postural instability and increased risk of

falls[12]. Therefore, dysfunctions in dopaminergic and cholinergic systems contribute to both motor and non-motor dysfunctions in PD[11]. Notably, these dysfunctions lead to the increased risk of falls in individuals with PD[13,14].

1.2. PD and Falls Risk

Falls are defined as an unexpected event where the person involuntarily comes to rest on the ground or other lower level[15]. Falls are problematic and disabling events for individuals with PD[14], and they present even in the early disease stage[16]. It has been reported that 50 – 68% of the PD population fall annually[17], which is three times more often than the fall rate of the older population[18]. A meta-analysis revealed that 21% percent of fallers with PD had no history of falls[19]. Another study suggested that the first fall occurs soon after diagnosis of PD (36 months) in a falls-naïve cohort which highlights the need for early detection of falls in individuals with PD[20]. Falls in individuals with PD may result in severe injuries and other health related issues, which in turn are associated with hospitalization, institutionalization, and incremented healthcare costs[21]. Given the potential health and economic consequences of falls, it is important to identify fallers in the early stage of PD, ideally before falls occur.

However, the nature of falls in PD is complex[22,23]. Falls in PD have generally been associated with motor deficits, in particular due to postural instability. However, recent literature suggested that falls are also associated with deficits in cognitive function such as decreased attentional capacity[24]. Attentional capacity is important for safe ambulation in complex, everyday environments like walking while talking on the phone in a crowded street. A study demonstrated that individuals with PD who fall had reduced attention and executive function compared with individuals with PD who do not fall[25]. A recent systematic review defined the important

predictors of falls in PD including postural instability, cognitive impairment, axial rigidity, fall history, disease severity, freezing of gait, and dual tasking[26]. Individuals with PD have an increased risk of falls when they perform two tasks concurrently[27]. The combination of cognitive and motor deficits leads to decreased performance on attention-demanding concurrent tasks, which eventually results in an increased risk of falling in individuals with PD[28,29].

1.3. Cognitive-Motor Interference in PD

Dual-task interference occurs when the simultaneous performance of two different tasks results in the deterioration in performance on one or both tasks. Cognitive-motor interference (CMI) is a specific kind of dual-task interference that occurs when the dual-tasking paradigm includes a motor task (i.e. standing) and a cognitive task (i.e., counting numbers backward). CMI is operationally defined as a decrease in motor or cognitive performance (or both) when tasks are performed concurrently[27]. The conceptual framework of CMI revolves around three main theories which are discussed below.

1.3.1. Bottleneck theory: The bottleneck theory suggests that individuals have limited cognitive resources that they can use it for one task at a time. This theory supports the notion that tasks must be processed sequentially in the brain, and not in a parallel form[30]. Therefore, information is filtered through the brain so that only the most salient and important information is perceived.

1.3.2. Cross-talk theory: The cross-talk theory is explained as when the tasks use the same cognitive domain and neuronal populations in the brain, they do not interfere with each other, but using separate cognitive areas leads to interference between the tasks[31]. When performing two

tasks which are similar in content (motor tasks) such as walking and carrying an item there will be less crosstalk in the brain and a more productive and uninterrupted cognitive processing.

1.3.3. Attentional capacity theory: Based on the attentional capacity theory, humans have limited cognitive capacity. Kahneman et al. suggested that limited amount of attention is allocated to tasks when individual is performing two tasks simultaneously[32]. Many factors determine how much attentional capacity can be allocated and how much is needed for each task. Since there is limited attentional capacity, performing two tasks at the same time decreases the performance on one or on both[33]. Perhaps the most commonly utilized theory in dual-task research is the attentional capacity theory[32,34].

Individuals with PD are greatly affected by CMI due to the degeneration of the dopaminergic cells in the basal ganglia, resulting in impairments in both motor and cognitive circuits[27]. Most activities of daily living require performing two tasks simultaneously[35] such as standing while talking. In such dual-tasking conditions, upright stance posture is an essential motor skill to accomplish various motor and cognitive tasks concurrently[36]. Although maintaining an upright stance posture seems autonomous and effortless in healthy individuals, it may become challenging and cognitively effortful due to impaired autonomic control process in individuals with PD[27]. Studies demonstrated that during concurrent postural control and cognitive testing, individuals with PD exhibited impaired postural control compared with control subjects. Therefore, adding the concurrent cognitive task component while standing resulted in greater CMI in individuals with PD compared with controls[29,37]. The auditory Stroop test was shown to be one of the key determinants of dual-task performance in individuals with PD[38]. To stress the executive function and cognitive flexibility abilities of the participants and to induce CMI we decided to use this test as the cognitive task during our dual-task paradigm.

Examining people during a postural control task while they perform a cognitive task is the most common way to assess dual-task balance performance[34]. However, the interpretation of CMI has been heavily based on the behavioral performance observations (e.g. center of pressure displacement) without having neurophysiological evidence regarding the conflicting nature of dual-tasking[35]. These outcomes are often reported as a numeric score that have methodological limitations (e.g. ceiling/floor effect), are not sensitive to change, and do not explain the amount of cognitive workload needed to complete the tasks[39,40]. Therefore, it is important to use neurophysiological tools in combination with behavioral measure to better understand the brain-behavior interactions during dual-tasking.

1.4. Concept of Cognitive Workload

Advances in neurophysiological technology enable us to measure cognitive workload in real-time[41,42]. Based on the Kahneman's theory, cognitive workload is defined as the mental effort that is needed to execute a task[32]. The capability to perform well on the cognitive task, balance task, and both of them concurrently depends on the availability of cognitive capacity[40]. In a situation of increased cognitive demand, there is a growing requirement to manage the demand on one's mental systems (i.e., cognitive workload) in an adaptive manner to maximize performance. An increase in cognitive demand can result in an elevation of cognitive workload and a reduction of cognitive reserve. In other words, the task can be executed accurately when the cognitive demand is lower than the available cognitive capacity[40]. Reflecting an inverted U-shaped pattern, at low levels of cognitive demand, individuals execute a cognitive workload which is positively correlated with the cognitive demand to maintain task performance[43]. However, at high levels of cognitive demand, this mechanism is no longer effective leading to reduced cognitive workload due to decreased attention to the task[40]. Recent studies suggested

that individuals with PD without cognitive impairments demonstrated increased cognitive workload on arithmetic tasks and tests of speed of processing compared to healthy controls in spite of performance within the normal ranges[44,45]. These findings suggest that individuals with PD may have increased cognitive workload compared to healthy controls, despite having similar behavioral outcomes. Therefore, it is reasonable to assume that individuals with PD exhibit greater cognitive workload than healthy individuals to execute the cognitive tasks (Figure 1). It is unknown, however, if the concept of cognitive workload also transfers to tasks that elicit CMI.

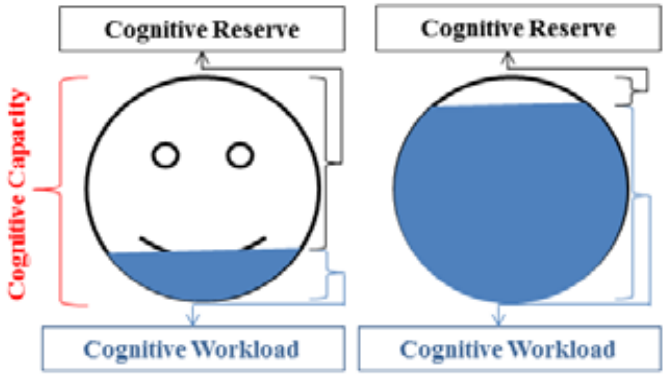

Figure 1. Hypothetical model. Healthy individuals may require less cognitive workload to execute the same task compared to the individuals with PD. Although individuals with PD require higher cognitive workload to execute a task, there is still no decreased performance on the task.

1.5. Pupillary Response as a Neurophysiological Measure of Cognitive Workload

Our systematic review demonstrated that functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG) were the mostly commonly used neurophysiological tools to assess cognitive workload during dual-task balance and gait[46]. fNIRS is a non-invasive, safe, and portable neuroimaging method to measure changes in oxygenated and deoxygenated hemoglobin concentrations (HbO2 and HbR, respectively) in the brain [47]. This technology can be used in any postural or mobile condition, which allows measurement of brain activity during a walking or balance task and even during dual-tasking. EEG is widely used by clinicians and researchers to measure the electrical activity of the cerebral cortex [48]. EEG frequency bands and event-related potentials (ERP) are direct measurements of brain activity. It is important to note that EEG is not frequently used in dual-task balance and gait activities compared with fNIRS. Spatial resolution of fNIRS is better than EEG, but inferior to the spatial resolution of fMRI. This can make it difficult to distinguish neural responses from discrete but adjacent cortical areas. In addition, the temporal resolution of both fNIRS and fMRI are limited compared to EEG due to reliance on hemodynamic changes which is intrinsically slow processes [49]. Overall, EEG and fNIRS each have specific advantages regarding spatial and temporal resolution and both have been shown to provide reliable and valid data during DT balance and gait [50-52]. However, none of the studies used pupillary response as a neurophysiological tool to understand cognitive workload. A study has compared the temporal resolution of EEG, fNIRS, and pupillary response during cognitive testing. Pupillary response showed ideal to measure middle-time-scale changes (10 s) which are sufficient to detect changes in postural demand whereas EEG is ideal for assessing short-time-scale changes (1 s) and fNIRS for long-time-scale changes (44 s)[53]. Also, pupillary response is cost-effective, easy to implement, and less intrusive compared to the other neurophysiological

tools (EEG and fNIRS). The limited intrusiveness of pupillary response allows for monitoring of cognitive workload during complex activities of daily life such as dual-task balance. Also, we believe pupillary response has more potential to be implemented in clinics in the future compared to other neurophysiological tools.

Pupillary response is a non-intrusive, neurophysiological measure of cognitive workload. Several studies have demonstrated a linear relationship between increased pupil dilation and increased cognitive workload in healthy individuals[54-56]. In addition, a large number of studies provided evidence that pupils dilate with increased task difficulty among different cognitive tasks, including short-term memory[57,58], arithmetic[58,59], digit span[60], sentence comprehension[61] and perceptual matching[59]. Through all these cognitive tasks, increased difficulty of the task elicited increased pupillary response. It has been shown that pupillary response due to light reflex differs from pupillary response from increased cognitive workload. A study has shown that pupillary response due to increased cognitive workload elicited more variability whereas a pupillary response due to light reflex is predictable[62]. In addition, increased cognitive workload typically modulate pupillary dynamics on a short time scale (i.e., in the range of seconds). Therefore, pupillary response reflects real-time, objective, difficulty-, and mental effort-related aspects of cognitive functioning. However, it is not known if pupillary response also reflects changes in postural demand during dual-tasking activities.

Pupil diameter is controlled by two muscles: the constrictor muscle that directly encircles the pupil and the dilator muscle that is connected to the iris[63]. These two muscles interact to produce two reflexes, the light reflex and the dilation reflex. The pupillary light reflex pathway is similar to the visual pathway; however, the optic tract fibers involved in pupillary light reflexes terminate at the pretectal nucleus in the midbrain and not at the lateral geniculate nucleus of the

thalamus[63]. The nasally aligned fibers decussate at the optic chiasm and transfer the signal to the contralateral pretectal nucleus, whereas the temporally aligned fibers relay the information to the ipsilateral pretectal nucleus. When each pretectal nucleus projects bilaterally and synapses in both Edinger-Westphal nuclei, the activated Edinger-Westphal nuclei begin the efferent limb of the reflex by generating action potentials. The axons of these preganglionic parasympathetic neurons send the signals along the oculomotor nerve to the post-ganglionic nerve fibers of the ciliary ganglion. Subsequently, the short ciliary nerves arising from the ciliary ganglion stimulate the pupillary constrictor muscle and cause pupillary constriction. Each activated Edinger-Westphal nucleus is responsible for the ipsilateral pupillary constriction, and these stimulated nuclei together allow the bilateral pupillary light reflex to occur. In the dim light, pupillary dilator muscle fibers contract and widen the size of the pupil. The postganglionic sympathetic fibers from the long ciliary nerve innervate the dilator muscle.

The dilation reflex (pupillary response to cognitive demand) may be less familiar to the general population, but it is equally well understood by scientists. The mechanism of the pupillary response to cognitive demand stems from increased activation of the locus coeruleus, a small nucleus in the brainstem[55,64] that plays an essential role in the regulation of physiological arousal[65] and cognition[66]. Increased cognitive workload leads to the activation of locus coeruleus that subsequently sends inhibitory projections to the parasympathetic Edinger-Westphal nucleus that, in turn, inhibits activation of the sphincter pupillae muscle, resulting in pupil dilation[67]. The activity of the locus coeruleus also leads to increased activation of the sympathetic nervous system, which results in additional pupil dilation due to the activation of the dilator pupillae muscle[65]. Both pupillary response and activation of noradrenergic neurons in the locus coeruleus have been shown to increase in a correlated manner with increased cognitive workload[68]. Light

reflex and dilation reflex occur at the same time, but their pattern of response differs from each other[69]. During the light reflex, the pupil responds with a continual but irregular oscillation. Also, the pattern of oscillation does not correlate with heart rhythm or respiratory rate[69]. In dilation reflex, researchers observed a pulsing of the pupil diameter where pulses are irregular and sharp, often exhibiting large jumps followed by rapid declines[69]. In this dissertation project, pupillary response was purported to detect subtle changes in dual-task postural control in individuals with PD. Applying pupillary response during dual-tasking provides continuous monitoring of neurophysiological response of the brain which makes a substantial contribution to furthering our understanding of brain-behavior interactions in real-time.

By solely measuring the change of the raw pupil size, there are potential limitations such as the light reflex interfering with the pupil size and movement artifacts. To combat this potential problem, the EyeWorks software was utilized to compute the Index of Cognitive Activity (ICA)[39]. Earlier studies used raw pupil diameter to understand cognitive workload. Raw pupil size is recorded by infrared cameras that display the gaze position on X and Y axes. This approach represents some limitations. When the eyes rotate away from the cameras, the pupil size appears as an ellipse which affects the accuracy of pupil size on the X-axis[70]. Capturing the Y-axis value is compromised by the eyelids that may obstruct the recording of the pupil[70]. The ICA is an algorithm that computes the moment-to-moment change in pupil diameter, and not of the difference relative to baseline, regardless of gaze position. In the ICA, wavelet coefficients are converted into a second-by-second index ranging from 0 (no cognitive workload) to 1(maximum cognitive workload). Based on this algorithm the noisy signals are reduced to nearly zero[39]. In addition, it has been shown that ICA is not affected by the change in lighting[69]. In an experiment, subjects were asked to perform four different conditions which were sitting in

a normally lit room, sit in the dark in the room, sitting in the light while responding to a series of verbal arithmetic problems, and sit in the dark in the same room while responding to series of verbal arithmetic problems. Pupil dilation was measured by an eyetracker and ICA analysis was conducted to compare cognitive workload across the conditions. The results demonstrated similar values for ICA from light to dark environment but a significant difference with a comparison from sitting to sitting while performing a cognitive task. This study provided evidence that ICA is capable to successfully separate light reflex from pupil dilation due to increased cognitive workload.

In addition, it is known that PD diagnosis is also associated with loss of noradrenergic neurons in the locus coereulus[71]. Therefore, the dysfunction in the locus coeruleus could be associated with disrupted pupillary response in PD[44]. However, most of the evidence for disrupted pupillary response in PD comes from people or animal models with moderate to severe PD. A recent study from our research group demonstrated that individuals with PD who are cognitively normal had the same pattern of pupillary response with increased cognitive demand compared to age-matched healthy controls[72]. Lastly, to eliminate the effect of PD pathophysiology on pupillary response, in this dissertation work the relative change of pupillary response rather than absolute change was calculated.

1.6. Reliability and Validity of Pupillary Response

Reliability and validity are two of the important psychometric properties to demonstrate that the tool has overall consistency on what it measures, and that the tool measures what it is intended to measure, respectively[73]. In this dissertation study, we aimed to understand reliability and validity of pupillary response during dual-tasking in individuals with PD and healthy controls.

There are several ways to estimate the reliability of the measurement including (1) test-retest reliability, (2) parallel forms reliability, (3) inter-rater reliability, and (4) internal consistency reliability[74]. Test-retest reliability refers to the degree of consistency of the tool by measuring the same test over a period of time. Parallel forms reliability is an evaluation of the consistency of results of two tests which were constructed in the same way from the same content domain. Inter-rater reliability is described as the degree of consistency on obtaining the same results by two different raters/researchers on the same phenomenon. Internal consistency reliability is used to evaluate the consistency of results across items within a test. In this dissertation study, we evaluated test-retest reliability of pupillary response during dual-task balance conditions in individuals with PD.

Furthermore, there are several ways to estimate the validity of a measurement including (1) construct validity, (2) criterion validity, and (3) content validity[75]. Construct validity is an evaluation of whether a test or tool measures a construct that it is intended to measure. Construct validity has two subtypes: convergent validity and discriminant validity. Convergent validity is described as the degree to which two measurements are expected to be related. By contrast, discriminant validity evaluates whether two tests that are not intended to be related, are in fact not related. Criterion validity refers to use of a well-established instrument (criterion) to compare a new instrument to measure the construct. Criterion validity has two subtypes: concurrent validity and predictive validity. Concurrent validity is an evaluation of the new instrument against the well-known instrument at the same time. Predictive validity refers to the instrument's ability to accurately predict what is intended to predict. Content validity is a non-statistical type of validity to define the estimate of how closely the instrument measures the various aspects of

the construct. A subtype of content validity is face validity, which is an estimate whether the instrument appears to measure what is intended to measure.

In this dissertation study, cognitive workload was measured by pupillary response while the subjects executed two tasks (postural and cognitive tasks) concurrently. According to the literature, there is no accepted gold standard (criterion) to measure cognitive workload[76,77]. However, it is possible to use subjective cognitive workload instruments by asking subjects to rate their subjective impression of mental effort[78]. One of the most commonly used subjective cognitive workload instrument is the National Aeronautics and Space Administration-Task Load Index (NASA-TLX)[79]. The NASA-TLX provides an overall index of cognitive workload by measuring the contributions of six subscales including mental, physical and temporal task demands; and effort, frustration and perceived performance. This instrument has been widely used in the literature, and has shown to be a reliable and valid measure of overall self-reported cognitive workload[80]. Although the NASA-TLX provides accurate information on cognitive workload in about two minutes, the test is subjective and based on recall since the participant completed the NASA-TLX after completion of the task. Pupillary response, on the other hand, is purported to objectively measure cognitive workload in real-time. In this project, we investigated whether pupillary response and NASA-TLX evaluate the same construct (cognitive workload) during dual-tasking and whether they are related to each other (convergent validity). In addition, we investigated the test-retest reliability of the pupillary response by administering the dual-tasking conditions twice during the same visit.

1.7. Pilot Studies

In our first pilot study, we determined the validity of pupillary response as a measure of cognitive workload during cognitive testing in individuals with PD. In our second pilot study, we determined the validity of pupillary response to cognitive workload during dual tasking against electroencephalogram in healthy young adults.

1.7.1. Pupillary response is a robust measure of cognitive demand in PD: In our pilot study[72], we aimed to examine the pupillary response to cognitive demand in a letter-number (LN) sequencing task between 16 non-demented individuals with PD and 10 healthy control participants. Participants were asked to recall a sequence of scrambled letters and numbers by first repeating the sequence of numbers in ascending order followed by the sequence of letters in alphabetical order. The test ended when the participant incorrectly recalled the sequence on three consecutive trials or achieved the maximum LN load. A remote eye tracker (FX3, SeeingMachines, Inc.) recorded the pupillary response at 60 Hz while participants were performing the LN sequencing task. A mixed model analysis was employed to investigate cognitive workload changes as a result of incremental cognitive demand for both groups. We found that cognitive workload, exemplified by pupillary response, increased with incremental cognitive demand in both groups ($p = 0.003$) (Figure 2). Although not significant due to insufficient power, non-demented individuals with PD exhibited increased cognitive workload compared to the healthy controls throughout the testing. In addition, Figure 2 suggested that people with PD adopt a different cognitive workload pattern compared with the healthy controls. At three LN load, people with PD showed a steep increase in cognitive workload compared to the healthy controls. It is possible that people with PD exhibited greater cognitive workload from two to three LN load since they were forming a strategy to tackle the task. After this strategy was formed, their cognitive workload decreased followed by a steady increase in cognitive workload

with increased cognitive demand. Symptoms of autonomous dysfunction did not correlate with pupillary response. Overall, we concluded that pupillary response is a robust measure of cognitive demand in non-demented individuals with PD, regardless of the presence and severity of autonomic symptoms in PD.

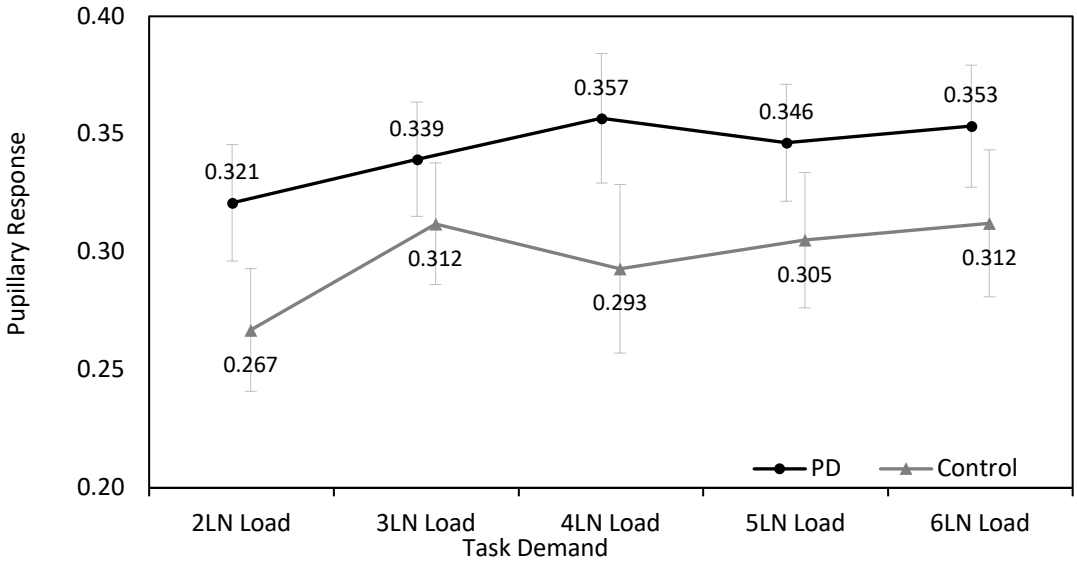

Figure 2. Mean (± SEM) changes of pupillary response to cognitive demand

1.7.2. Pupillary response is a valid measure of dual-tasking postural control in healthy young adults[81]: After we demonstrated proof-of-concept of pupillary response to cognitive workload during cognitive tasks in PD, we conceptualized another pilot study that employed the concept of cognitive workload to cognitive-motor interference tasks.

Electroencephalography (EEG) has previously been identified as an objective indicator of conscious postural control during dual-tasking[35]. However, it is not known whether pupillary response is a valid measure of cognitive workload during dual-tasking postural control. The purpose of this study was to validate pupillary response against EEG during dual-tasking postural control. Fifteen healthy young adults [age: 25.4±2.5; sex: 10 males] were tested. Subjects were asked to wear eyetracking glasses to record the pupillary response and the EEG cap to record the event-related potentials (ERP) across two conditions: (1) dual-task with eyes open; (2) dual-task with eyes occluded. The conditions were involved patients standing on the

balance platform while performing the 2-back auditory test with eyes open and eyes occluded. Each task was 320 seconds. We measured event-related brain potentials (ERP) which are derived by averaging the ongoing stimulus (2-back auditory test) -locked EEG signal across repeated presentations. We specifically extracted the latency of the P3 component (i.e., a positive EEG peak that typically occurs at around 300 ms post-stimulus), which has a frontal-central scalp topography and is thought to reflect attention[82]. Paired t-tests were used to analyze the change of pupillary response and P3 data from condition 1 to 2. Pearson's correlation coefficient was used to interpret convergent validity. The results demonstrated significant changes in pupillary response ($p=.004$) and P3 latency ($p=.048$) from condition 1 to 2. A strong correlation coefficient was observed between pupillary response and P3 latency during dual-task with eyes occluded ($r=-.70$, $p=.008$) (Figure 3). This study suggested that pupillary response demonstrated strong convergent validity against EEG during dual-tasking postural control in healthy young adults. Further analyses are in progress to understand the changes of EEG power spectrums from single tasks to dual-task balance conditions.

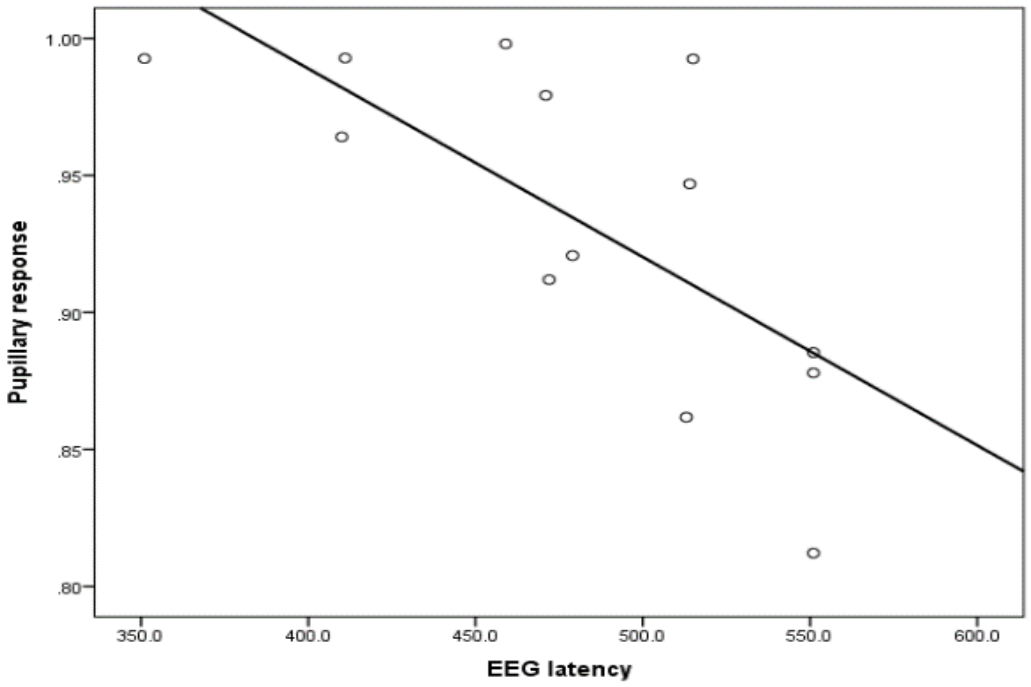

Figure 3. Correlation analysis between pupillary response and EEG during dual task with eyes occluded

1.8. Pupillary Response and Falls in PD

Individuals with PD are at high risk for falling due to degeneration of automatic control process[83]. It is reported that 70% to 87% of individuals with PD fall at some point in their disease course[84]. Despite these high fall rates, clinicians treating movement disorders, and physical therapists (PTs) do not have an accurate fall predictor tool to fully characterize the fall risk in this population[16,85]. To date, the best predictor of a fall is the history of falls in the past one year[86]. In other words, clinicians rely on self-reported recall of falls to quantify the future fall risk in individuals with PD. This approach has some limitations, including the inability to predict and potentially intervene to prevent the first fall. In addition, fall history will not explain the potential increased risk of falls due to underlying visual, motor, or cognitive impairments associated with PD[23].

Clinicians, especially movement disorders specialists, commonly use the pull test to quantify the fall risk in individuals with PD (question 33, Unified Parkinson's Disease Rating Scale-III [UPDRS-III])[87]. This single item on the UPDRS-III is designed to measure postural instability in a quick and efficient way in individuals PD. In this item, clinicians apply a backward pull to the shoulders and then assess the patient's ability to recover on a 0-4 scale. It has been demonstrated that increased postural instability measured by the pull test is associated with increased fall risk in individuals with PD[88]. However, the pull test has some limitations, including a lack of formal consensus on its execution[89]. It is possible to apply inconsistent strength to the shoulders within and between clinicians[87]. In addition, the strength of the pull test might differ from patient to patient depending on their degree of postural instability[87]. Lastly, the pull test poorly correlates with objective measures of postural instability such as force platform assessment[90].

In the PT clinic, the Timed-Up and Go (TUG) test is commonly used to quantify fall risk in individuals with PD[91]. This test is useful in the outpatient clinic due to short administration time, ease of execution, and no need for any special equipment[91]. TUG is a reliable and valid clinical assessment tool for falls in PD[92]. It has been demonstrated that increased completion time of the TUG test is highly correlated with increased risk of falls in individuals with PD[93]. In addition, the TUG test has a higher predictive accuracy than the pull test to predict falls in PD[94]. Yet, a recent study demonstrated that TUG had only 70% predictive accuracy to identify fallers in PD[91]. It is utmost important to clearly identify fallers in individuals with PD to provide therapeutic intervention in order to reduce fall risk. On the other hand, TUG test results are

mainly influenced by the motor symptoms of PD, and do not account for cognitive impairments that may contribute to falls. However, in the early stages of PD, individuals demonstrate only mild motor symptoms[95]. Still, they might have some cognitive difficulties potentially affecting the performance on balance and gait activities that might be compensated by higher neurophysiological brain activation[96,97]. Therefore, it is possible that in the early stages of the disease, individuals with PD perform well on gait and balance activities but have higher neurophysiological brain activation. In this dissertation it is proposed that measuring the neurophysiological brain activation measured by pupillary response during dual-tasking will be more sensitive to determine fall risk than the TUG and pull test in PD.

Finally, based on the literature there are several other fall risk assessment tools to quantify fall risk in individuals with PD. The most common are the Berg Balance Scale, Mini-Balance Evaluation Systems Test, and Functional Gait Assessment. However, these tools have some challenges to perform in the PT and Movement Disorders clinics, such as requiring special equipment and long administration time[98]. Although these tools are reliable and valid in the PD population to quantify fall risk, they only are moderately predictive of falls in PD[99]. In addition, due to the difficulties of the utilization in the clinics, they are not performed as commonly as the TUG and the pull tests. Therefore, in this research project, the TUG and the pull tests was administered to quantify the falls risk.

1.9. Significance

Individuals with PD are at high risk of falling, and falls entail severe health-related consequences to both individuals and society[14]. CMI is one predictor of falls in PD[28,29]. However, the interpretation of CMI during balance tasks has been heavily based on behavioral performance observations (i.e. center of pressure displacement) without having neurophysiological evidence

regarding the brain response during dual-task balance[35]. It has been demonstrated that during dual-tasking, individuals with PD had higher brain activation, measured by functional near infrared spectroscopy, than their healthy peers to perform similarly on balance and gait activities[96,97]. In addition, this higher brain activation significantly predicted the likelihood of future falls[100]. Therefore, investigating brain activation during dual-tasking might provide insight into the early pathogenesis of falls in PD. This dissertation project examined the neurophysiologic response of the brain measured by pupillary response during dual-tasking conditions in PD. Applying pupillary response during dual-tasking provides continuous monitoring of neurophysiological response of the brain which makes a substantial contribution to furthering our understanding of brain-behavior interactions in real-time. Furthermore, this study investigated whether pupillary response during pupillary response is a determinant of falls in PD beyond the traditional clinical fall assessment tests. In future, pupillary response might be utilized to better understand brain-behavior interactions during dual-tasking in individuals with PD. The real-time monitoring of objective workload makes pupillometry a promising biofeedback tool. Pupillometry can also be used to improve rehabilitation outcomes in individuals with PD by determining the intensity, duration, and optimal time frame for the rehabilitation intervention.

1.10. Innovation

Recent advances in technology enable us to measure the neurophysiological response of the brain that is needed to complete a task in real-time[101]. Pupillary response is a non-intrusive, neurophysiological measure of cognitive workload that has been widely used in the psychophysiology field[101]. This was the first study that investigated the use of pupillary response on different dual-tasking postural demanding tasks in individuals with PD. Therefore, in this

study we translated the concept of cognitive workload measured by pupillary response from cognitive task difficulty to postural demand activities.

Another novelty includes that this study investigated whether pupillary response is more sensitive to than the traditional clinical fall assessment tools to classify fall risk in PD. The first fall occurs soon after diagnosis (36 months) in a falls-naïve cohort which highlights the need for early detection of falls in individuals with PD[20]. To date, the best predictor of falls is the history of falls in the past one year[86]. However, this method is not helpful to prevent future falls before the first fall happens. In addition, the traditional clinical fall assessment tools are not able to fully characterize the fall risk in individuals with PD. Therefore, it is innovative to investigate whether pupillary response during dual-tasking is a determinant of falls in individuals with PD over and beyond traditional, clinical measures of falls.

1.11. Specific Aims

The **main objective** of this research project is to investigate cognitive workload measured by pupillary response during dual-tasking, and whether pupillary response during dual-tasking is a determinant of falls in individuals with PD. CMI is defined as the decrease in motor or cognitive performance (or both) when these tasks are performed concurrently[27]. Evidence suggests that higher physiological response of the brain during dual-tasking is a predictor of falls in older adults[100]. Although several clinical scales such as the Timed Up and Go and Unified Parkinson's Disease Rating Scale pull test have been developed to assess postural instability and screen for falls in PD, they are limited in their accuracy to predict future falls in PD[88,91]. The first fall

occurs soon after diagnosis with PD[20]. Increased pupillary response during dual-tasking may be more sensitive to determine the falls than the clinical assessment tools even prior to changes in motor or cognitive performance.

CMI is observed in all humans, but individuals with PD seem to be disproportionally affected by dual-tasking due to competition of limited cognitive resources[27]. Dual-tasking is typically evaluated by dual task cost on cognitive tests or dual task cost on balance measures[28,29]. These outcomes are often reported as a numeric score that have methodological limitations (ceiling/floor effect), are not sensitive to change, and do not explain the amount cognitive workload needed to complete the tasks[40]. Recent advances in technology enable us to measure the cognitive workload that is needed to complete a task in real-time[39]. Pupillary response is a non-intrusive, physiological measure of cognitive workload that has been widely used in psychophysiology to determine the cognitive demand of a task[102-104]. However, this is the first study that will investigate the use of pupillary response as a sensitive measure to postural demand using the dual-tasking paradigm in PD.

The **central hypothesis** of this project is that individuals with PD will exhibit increased pupillary response during dual-tasking compared with healthy controls due to the degeneration of the dopaminergic cells in basal ganglia, resulting in impairments in motor and cognitive circuits. Therefore, individuals with PD exhibit greater cognitive workload to compensate for the impairments in dual-tasking, resulting in increased risk of falls due to cognitive overload. This increased cognitive workload during dual-tasking measured by pupillary response will be a determinant of falls in PD. This project has three aims:

Aim 1: To examine the psychometric properties of pupillary response in both individuals with PD and healthy controls. We hypothesize that pupillary response will demonstrate a high test-retest (ICC>0.75) reliability (H1.1) and a strong correlation (r>0.7) with self-reported cognitive workload [convergent validity] (H1.2) during postural control tasks and dual-tasking in both individuals with PD and healthy controls.

Aim 2: To compare the magnitude of cognitive workload during dual-tasking between individuals with PD and healthy controls. We hypothesize that individuals with PD will demonstrate higher pupillary response than healthy controls during single postural control tasks and dual-tasking (H2.1). In addition, both groups will demonstrate increased pupillary response from single postural control task to dual-tasking (H2.2).

Exploratory Aim: To investigate the determinants of falls in individuals with PD. We hypothesize that the pupillary response score during dual-tasking will be more sensitive to determine falls than the clinical fall assessments (Timed Up and Go, pull test) in individuals with PD (H3.1).

Impact. Individuals with PD are at high risk for falls which entail severe health-related consequences[21]. Increased cognitive workload during dual-tasking may be a determinant of falls in PD, beyond traditional predictors of falls. The use of non-intrusive physiological tools may be considered in falls risk assessment and strategies to mitigate falls which would help to alleviate economic burden of the PD for the health care system.

Chapter 2

Brain Activity during Dual Task Gait and Balance in Aging and Age-Related Neurodegenerative Conditions: A Systematic Review

This chapter has previously been published in whole without any adaptations since publication and is reprinted here with permission. **Kahya M**, Moon S, Ranchet M, Vukas RR, Lyons KE, Pahwa R, Akinwuntan A, Devos H. Brain activity during dual task gait and balance in aging and age-related neurodegenerative conditions: A systematic review. Experimental Gerontology. 2019 Oct 22:110756. https://doi.org/10.1016/j.exger.2019.110756

Abstract

Introduction: The aims of this systematic review were to investigate (1) real-time brain activity during dual task gait and balance, (2) whether changes in brain activity correlate with changes in behavioral outcomes in older adults and people with age-related neurodegenerative conditions.

Methods: PubMed, PsycINFO, and Web of Science were searched from 2009 to 2019 using the keywords dual task, brain activity, gait, balance, aging, neurodegeneration, and other related search terms.

Results: A total of 15 articles were included in this review. Functional near-infrared spectroscopy and electroencephalogram measures demonstrated that older adults had higher brain activity, particularly in the prefrontal cortex (PFC), compared to young adults during dual task gait and balance. Similar neurophysiological results were observed in people with age-related neurodegenerative conditions. Few studies demonstrated a relationship between increased brain activity and better behavioral outcomes.

Conclusion: This systematic review supports the notion that aging and age-related neurodegenerative conditions are associated with neuronal network changes, resulting in increased brain activity specifically in the PFC. Further studies are warranted to assess the relationship between increased PFC activation during dual task gait and balance and behavioral outcomes to better optimize the rehabilitation interventions.

2.1. Introduction

The ability to stand or walk while simultaneously carrying out cognitive tasks is a critical skill for most daily-life activities [105]. When the demands of executing two tasks concurrently exceed cognitive capacity, performance on one or both tasks will diminish [27]. Studies have shown that the cost of performing dual task (DT) gait and balance is greater in older adults and in people with age-related neurodegenerative conditions [106-108]. Reduced ability to allocate sufficient attentional resources may result in increased risk of falls and loss of independence in older adults with or without age-related neurodegenerative conditions [109-111].

DT deficiency is operationally defined as a decrease in motor or cognitive performance (or both) when tasks are performed concurrently. The conceptual framework of DT revolves around three main theories: the bottleneck theory, the cross-talk theory, and the attentional capacity theory. The bottleneck theory is based on the notion that tasks must be processed sequentially in the brain, and not in a parallel [30]. The cross-talk theory postulates that tasks using the same cognitive domain and neuronal populations in the brain will not interfere with each other. However, tasks that are using separate cognitive areas will interfere when they are performed simultaneously [31]. Lastly, based on the attentional capacity theory, humans have limited cognitive capacity. As a result, doing two tasks at the same time decreases performance on one or both [33]. Older adults and people with age-related neurodegenerative conditions may be more affected by DT deficiency due to the aging process or degeneration of the neuronal circuits, resulting in impairments in both motor and/or cognitive performances [27].

DT deficiency is typically evaluated by the DT cost [((DT- single task (ST))/ST) *100] on behavioral outcomes, which can either be performance on a motor or a cognitive test [28,29]. However, these common endpoints have methodological limitations (ceiling/floor effect). They

are not sensitive to change and they do not explain the brain activity needed to complete the tasks [40]. DT cost assessed by behavioral outcomes only provide an indirect measure of DT deficiency. Neurophysiological measures, however, provide direct information about DT deficiency beyond what is provided by behavioral outcomes alone. Therefore, neurophysiological tools may advance our understanding of mobility deficits and falls risk before they emerge. Advances in technology enable us to quantify brain activity during actual motor and cognitive testing in real time. As part of normal aging, older adults may exhibit increased brain activity to maintain stable balance and gait [112]. However, in age-related neurodegenerative conditions, individuals might exhibit a disproportional increase in brain activity to compensate for impaired structural and functional brain regions. It is important to continuously monitor brain activity during DT gait and balance to determine whether attentional demand is altered and whether this alteration affect gait and balance performance in older adults and more specifically in people with age-related neurodegenerative conditions.

Functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG) are neurophysiological tools that are commonly applied to measure neurophysiological changes during DT. These neurophysiological tools enable real-time, continuous recording of brain activity while performing natural activities such as standing and walking. Other neuroimaging technologies such as (functional) magnetic resonance imaging and positron emission tomography scanners are also valid and reliable measures of DT deficiency. However, these neuroimaging tools are typically utilized during a motor imagery task or imitated DT walking [113-116], which limits the generalization of findings to real-time DT gait and balance. fNIRS is a non-invasive, safe, and portable neuroimaging method to measure changes in oxygenated and deoxygenated hemoglobin concentrations (HbO2 and HbR, respectively) in the brain [47]. This technology can be

used in any postural or mobile condition, which allows measurement of brain activity during a walking or balance task and even during DT. EEG is widely used by clinicians and researchers to measure the electrical activity of the cerebral cortex [48]. EEG frequency bands and event-related potentials (ERP) are direct measurements of brain activity. It is important to note that EEG is not frequently used in DT gait activities compared with fNIRS. Spatial resolution of fNIRS is better than EEG, but inferior to the spatial resolution of fMRI. This can make it difficult to distinguish neural responses from discrete but adjacent cortical areas. In addition, the temporal resolution of both fNIRS and fMRI are limited compared to EEG due to reliance on hemodynamic changes which is intrinsically slow processes [49]. Overall, EEG and fNIRS each have specific advantages regarding spatial and temporal resolution and both have been shown to provide reliable and valid data during DT balance and gait [50-52].

Gait and balance are under control of higher-order cognitive processes which leads to involvement of widespread cortical areas [117,118]. Studies have indicated that pre-frontal cortex (PFC) has a crucial role in human balance and gait [119,120]. According to the scaffolding theory of aging and cognition, increased activation in PFC and structures related to executive functioning with aging and age-related neurodegenerative conditions is an indicator of an adaptive brain that engages with compensatory activity in order to maintain performance in spite of declining neural structures and functions [121]. In older adults, it is common to observe decreased brain functional connectivity across the default network and frontal attentional system as well as reduced integrity of white matter and grey matter compared to the healthy young adults [122,123]. These changes are more prominent in people with neurodegenerative conditions, resulting in overreliance on the prefrontal-striatal networks that are involved in executive function during

gait and balance control [124]. Therefore, increased activation in PFC and structures related to executive functioning during DT is expected to compensate for brain functional inefficiency.

In three reviews, the neural correlates of gait and balance were evaluated in young adults [125], in people with Parkinson's disease [120], and in various populations [126]. However, the literature in older adults and in people with age-related neurodegenerative conditions has yet to be compiled for comprehensive evaluation and interpretation of real-time brain activity changes during DT gait and balance. The aims of this systematic review were to investigate (1) real-time brain activity during DT gait and balance and (2) whether changes in brain activity correlate with changes in behavioral outcomes in older adults and people with age-related neurodegenerative conditions.

2.2. Methods

This systematic review conforms with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and was registered on PROSPERO as CRD42017055835 on January 23, 2017 before running the initial searches.

2.2.1. Data Sources and Searches

We searched the published literature using strategies created by a medical librarian to identify studies measuring real-time brain activity during DT gait and balance in aging and age-related neurodegenerative conditions. We searched Medline through PubMed, PsycINFO, and Web of Science from 2009 to 2019. The initial search strategy was designed for MEDLINE/PubMed using both keywords and Medical Subject Headings (MeSH). The key words described four main concepts, including a) brain mapping terms such as brain activity, cortical activity, brain imaging, neurophysiological monitoring, fNIRS, EEG; b) DT terms including neurophysiological alterations, dual-task, balance impairments, gait disturbances; c) diseases or

conditions including Parkinson disease, Alzheimer disease, dementia, neurodegenerative diseases; and d) aged, elderly, and frail defined as 65+ years in age. All four concepts were combined to identify the relevant studies. The PubMed search strategy was then conducted in the other two databases. Studies published in languages other than English were excluded. All searches resulted in a total of 768 articles, including duplicates. Reference lists of all relevant articles and reviews were also hand-searched for additional studies.

2.2.2. Inclusion and Exclusion Criteria

Inclusion criteria: 1. Studies that used balance or gait as the primary outcome; 2. Studies that included a cognitive task simultaneously to the balance or gait task; 3. Studies that included a real-time brain activity measurement during DT gait and balance.

Exclusion criteria: 1. Studies investigating the effects of training, exercise intervention, therapy, drugs, or alcohol effects on DT; 2. Studies including assessment of brain activity before and after concurrent motor and cognitive tasks; 3. Non-English published studies.

2.2.3. Data Extraction

Two independent reviewers (MK and SM) screened the available articles based on their titles and abstracts. After initial triage, the full-text articles were examined independently by the two reviewers. Discrepancies were solved by discussion between the two reviewers and a consensus was reached. Agreement between two reviewers (Cohen's kappa = 0.90) was strong. The flow chart (Figure 1) describes the systematic review process.

2.2.4. Quality Appraisal Method

The National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used by two independent evaluators (MK, SM), to critically evaluate the methodological quality of the included studies (www.nhlbi.nih.gov/health-

pro/guidelines/in-develop/cardiovascular-risk-reduction/tools). Inter-rater agreement was calculated using the kappa statistic. The kappa values were interpreted as < 0.40 poor agreement, 0.40 to 0.60 moderate agreement, and > 0.80 excellent agreement as suggested by Tooth and Ottenbacher [127]. Disagreements between the two raters were resolved through consensus discussion.

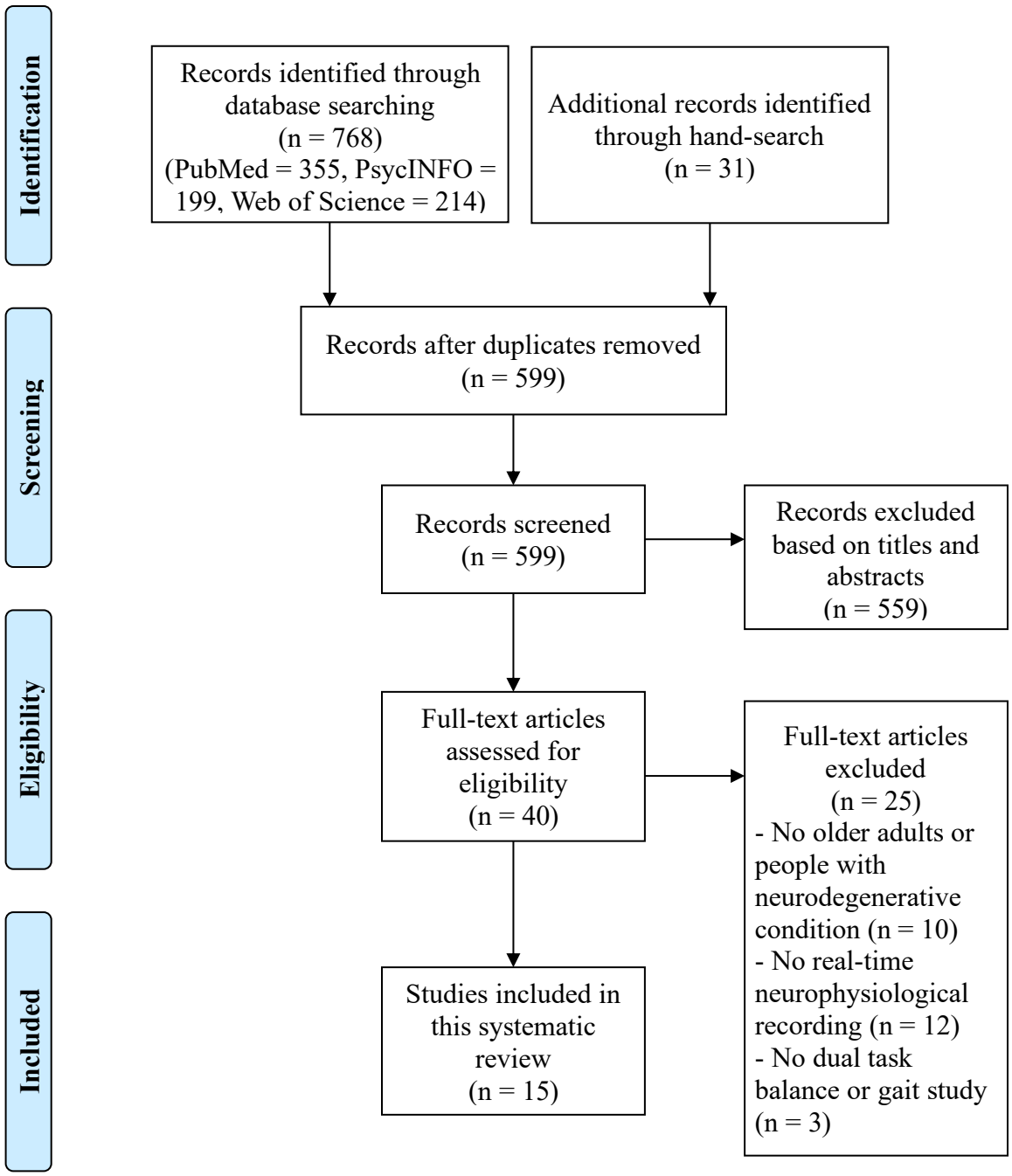

Figure 1. PRISMA flow chart of search and retrieval process

2.3. Results

A total of 15 articles met the inclusion criteria [35,100,115,128-139]. All articles selected in this review (1) utilized gait or balance as a behavioral outcome; (2) administered cognitive tasks in addition to motor tasks; and (3) used a real-time neurophysiological tool to assess DT. A summary of included articles is presented in Table 1. Among 15 unique studies, 12 studies used gait as the primary behavioral outcome measure, whereas three studies used balance or postural adjustment to assess motor control. Eight studies examined older adults without age-related neurological conditions (healthy), whereas seven studies included older adults with age-related neurodegenerative conditions. Regarding the real-time neurophysiological assessment, 11 studies utilized fNIRS, whereas four used EEG. Most studies (n = 14) were cross-sectional, whereas one study was a prospective cohort design [100].

The results will be discussed in two main sections based on the type of neurophysiological tools applied in each study (fNIRS or EEG). The sections will be divided by the type of subjects investigated (healthy or with age-related neurodegenerative condition), and outcomes including neurophysiological results (HbO2 levels, frequency bands, or ERP) during ST and DT and behavioral results (gait, balance, or cognition).

2.3.1. fNIRS studies

2.3.1.1. Healthy older adults

Neurophysiological results

Five studies used fNIRS to measure brain activity during DT in healthy older adults. In general, the results of the studies showed that older adults had increased PFC activation during DT compared to ST. In addition, older adults also showed higher PFC activation during DT

compared to young adults. Holtzer et al. showed that HbO2 levels in the PFC increased bilaterally during DT compared to ST in both older and younger groups [131]. However, a smaller increase in HbO2 levels was observed in older adults than young adults. Fraser, Dupuy, Pouliot, Lesage, Bherer [130] investigated the levels of HbO2 and HbR (deoxygenated hemoglobin) in eight different regions of the PFC, including anterior/posterior dorsolateral/ventrolateral PFC (aDLPFC, pDLPFC, aVLPFC, and pVLPFC) of left and right hemispheres. For HbO2, older and young adult groups showed task effects (ST < DT) with increased HbO2 in the left pDLPFC (older adults) and left aVLPFC, right aDLPFC, and right pDLPFC (young adults) during DT (normal pace walk + n-back) compared to ST. For HbR, task effects (ST < DT) were observed in all eight regions in older adults and seven regions in young adults. Furthermore, during DT with 2-back test, older adults did not show any significant hemispheric differences in HbO2 and HbR levels, whereas young adults demonstrated significant differences in HbO2 and HbR levels in pDLPFC and pVLPFC (right > left).

Marusic, Taube, Morrison, Biasutti, Grassi, De Pauw, Meeusen, Pisot, Ruffieux [138] utilized fNIRS to assess a postural-cognitive DT. For the hemodynamic changes, HbO2 levels in the PFC significantly increased from quiet standing to postural ST (tandem stance), but no change was observed from postural ST to DT in both groups. The study also found no significant effects of aging on HbO2 levels throughout all task conditions including quiet standing, STs (cognitive task or postural control), and DT. In summary, most fNIRS studies showed that older adults had increased PFC activation during DT compared to ST. Older adults also showed higher PFC activation during DT compared to young adults. However, Beurskens, Helmich, Rein, Bock [128] reported contradicting results demonstrating decreased PFC activation in older adults during DT compared to ST, which may be related to reduced brain activity in older adults. Marusic, Taube,

Morrison, Biasutti, Grassi, De Pauw, Meeusen, Pisot, Ruffieux [138] reported no changes in PFC activation from ST to DT.

Behavioral results

In general, healthy older adults showed poorer or similar performances in motor and/or cognitive tasks compared to young adults. Older adults demonstrated poorer accuracy on both 1-back and 2-back tests compared to young adults. In addition, older adults showed poorer accuracy during n-back tests during DT (normal pace walk + n-back) compared to young adults [130]. Holtzer, Verghese, Allali, Izzetoglu, Wang, Mahoney [132] showed slower gait velocity in healthy older adults during DT (normal pace walk + verbal fluency) compared with ST (normal pace walk). Similar results were found by Maidan, Rosenberg-Katz, Jacob, Giladi, Deutsch, Hausdorff, Mirelman [115].

Postural balance in older adults during DT was compared with young adults [134]. An auditory choice reaction task (CRT), clicking a right or left button depending on the frequency (high or low) of the given sound cue, was administered while participants were standing on a dynamic posturography platform. Older adults showed longer response time during ST2 (auditory choice reaction task) and DT (postural balance task + auditory choice reaction task) compared to young adults. However, no significant group difference was observed between ST1 (postural balance task) and DT. Similar study by Marusic, Taube, Morrison, Biasutti, Grassi, De Pauw, Meeusen, Pisot, Ruffieux [138] found that changes in postural control (center of pressure sway path) were not different across tasks (ST and DT) and groups (older and young adults). For the cognitive performance, older adults were significantly worse on both ST (cognitive task only) and DT than

younger adults. No significant difference in cognitive performance from ST to DT was found in older adults.

Stuart, Alcock, Rochester, Vitorio, Pantall [136] reported no significant differences in gait characteristics between tasks (ST (normal pace walk) and DT (normal pace walk + digit vigilance task)) or groups (older and young), except a slower preferred treadmill speed during ST and DT in older adults compared with young adults. Lastly, the study by Beurskens, Helmich, Rein, Bock [128] measured step duration, step length, and number of steps between older and young adults. The study consisted of one ST (normal pace walk) and two DTs (DT1: normal pace walk + checking the boxes on a piece of paper with a pen for 30 seconds; DT2: normal pace walk + verbal letter fluency task). Compared with young adults, older adults showed greater DT cost in step duration, step length, and number of steps during DT2 compared to ST. Also, older adults showed greater DT cost in step duration during DT1 compared to DT2. In summary, healthy older adults showed poorer or similar performances in motor and/or cognitive tasks compared to young adults.

2.3.1.2. Older adults with age-related neurodegenerative conditions

Neurophysiological results

Five fNIRS studies investigated older adults with age-related neurodegenerative conditions such as mild cognitive impairment [129], neurological gait abnormalities [132], PD [115,139], and severe neurological conditions with gait impairment [100].

Study conducted by Holtzer, Verghese, Allali, Izzetoglu, Wang, Mahoney [132] investigated non-demented older adults with neurological gait abnormalities. The study found that central neurological gait abnormalities induced attenuated changes in the HbO2 level during DT (normal

pace walk (ST1) + verbal fluency task (ST2)), compared to STs (ST1 and ST2). Maidan, Rosenberg-Katz, Jacob, Giladi, Deutsch, Hausdorff, Mirelman [115] and Al-Yahya et al. [139] assessed older adults with PD during DT walking conditions. Older adults with PD showed a nonsignificant increasing trend in HbO2 levels during DT compared to ST, whereas healthy older adults showed a significant increase in HbO2 levels during DT compared to ST [115]. Another study found increased HbO2 levels in older adults with mild cognitive impairment while performing DT compared to ST [129]. In addition, older adults with PD demonstrated increased PFC and M1 activation under DT walking compared to ST [139]. These results may suggest that during ST brain stem and spinal circuits automatically initiate and maintain a gait pattern without substantial need for executive control. Automaticity refers to the ability of the nervous system to successfully control gait and balance activities with minimal use of executive and attentional resources [140]. However, with DT older adults with PD may need to use their cognitive resources for motor planning or gait deficit compensation. Overall, most studies found increased levels of HbO2 in PFC among older adults with age-related neurodegenerative conditions while performing DT.

Behavioral results

Most studies used a normal pace walk as ST. Regardless of the age-related neurodegenerative condition, older adults showed decreased gait velocity during DT (verbal letter fluency or serial 3's subtraction) compared to ST. Doi, Makizako, Shimada, Park, Tsutsumimoto, Uemura, Suzuki [129] demonstrated that older adults with mild cognitive impairment had slower gait velocity during DT (normal pace walk + verbal letter fluency) compared to ST (normal pace walk). Similarly, Verghese, Wang, Ayers, Izzetoglu, Holtzer [100] demonstrated a DT effect in community-dwelling older adults without cognitive and gait abnormalities, showing slower gait velocity during DT

(normal pace walk + verbal letter fluency) compared with ST (normal pace walk). Older adults with PD showed reduced performance in stride length, gait velocity, step time, and step time variability compared with healthy older adults [96].

2.3.2. EEG studies

2.3.2.1. Healthy older adults

Neurophysiological results

Two studies used EEG to measure brain activity during DT in healthy young adults. Malcolm, Foxe, Butler, De Sanctis [133] studied DT gait in healthy older and young adults using a response inhibition task (Go/No-Go) during normal pace walk. In this study, event-related potentials (ERP) were recorded using EEG. During DT, older adults had limited ERP modulation showing a delayed and reduced P300 amplitude, whereas young adults showed ERP modulations at early (reduced N200 amplitude) and later (earlier P300 latency) stages as motor load increased during DT. These findings suggest that older adults may exhibit less flexibility in allocation of cognitive resources during multiple tasks.

Another study examined balance in both young and older adults [35]. They investigated standing balance during four different DT conditions using two cognitive tasks (non-challenging (1-back) and challenging (2-back)) and two surface platforms (non-challenging (fixed surface) and challenging (sway surface)). Thus, four DT conditions were '1-back + fixed', '1-back + sway', '2-back + fixed', and '2-back + sway'. Cortical activity modulations using EEG band frequencies revealed differences between older and younger individuals in DT. Delta bands decreased in the frontal, central-frontal, central, central-parietal, and parietal regions when older adults engaged in a challenging postural control task with DT ('1-back + sway' and '2-back +

sway'), compared with young adults. Theta band activity was smaller during DT with a challenging cognitive task ('2-back + fixed' and '2-back + sway') in the frontal and central-frontal regions in older adults compared to young adults. In other words, theta bands are more responsive to cognitive tasks. The smaller theta band activation in the older adult group compared to the young adult group may represent less activation of neural correlates relating high-level cognitive computations. Alpha bands were more activated over central-parietal and parietal cortices in both older and young adult groups when performing challenging postural control DTs (1-back + sway and 2-back + sway). Gamma bands increased over frontal, central-parietal, and parietal regions in older adults during DT with challenging postural control conditions ('1-back + sway' and '2-back + sway'). This suggests that gamma bands are associated with more increased attention to postural tasks in older adults. No significant changes were observed in beta bands across any ST and DT conditions.

Maidan, Fahoum, Shustak, Gazit, Patashov, Tchertov, Giladi, Hausdorff, Mirelman [137] investigated ERP during DT, with a special focus on P300 amplitude and latency. The study used an auditory oddball test in standing position (ST) and during normal pace walk (DT). P300 latency during DT was significantly longer in older adults compared to young adults. Also, both groups showed longer P300 latency during DT compared to ST. P300 amplitude was similar within each group and between the two groups during DT, which contradicts a previous finding from Malcolm, Foxe, Butler, De Sanctis [133]. This contradiction may be due to the use of different cognitive task (auditory oddball vs. Go/No-Go).

Behavioral results

In general, older adults showed slower response time, stride time, and impaired postural control compared to the young adults during DT. Ozdemir, Contreras-Vidal, Lee, Paloski [35] found that during STs (balance only task on fixed or sway platform) and DTs with a non-challenging cognitive task (1-back), postural control performance was similar between young and older adult groups. However, postural control performance in older adults became considerably worse when performing DTs with a challenging cognitive task (2-back) compared with young adults on both surface conditions. Although older adults showed no difference in postural performance during DTs with a non-challenging cognitive task (1-back) compared with young adults, older adults showed decreased accuracy in '1-back + sway'. This suggests that older adults have less cognitive capacity compared to young adults during the challenging postural control performance. Alternatively, older adults may allocate more cognitive resources for postural control, resulting in decreased performance in the non-challenging cognitive task (1-back).

2.3.2.2. Older adults with age-related neurodegenerative conditions

Neurophysiological results

Two studies used EEG to measure brain activity during DT in older adults with age-related neurodegenerative conditions. A study by Tard, Dujardin, Bourriez, Molaee-Ardekani, Derambure, Defebvre, Delval [135] examined changes in cortical activities due to modulated attention during motor preparation in older adults with PD. During DT (attention + motor preparation), EEG results showed that theta and alpha bands increased over 500 ms followed by S1 in all three groups (freezing of gait, non-freezing of gait, and healthy older adults), which implied an event-related synchronization of the brain. Older adults with PD without freezing of gait and healthy older groups showed decreased beta bands during DT, which reflected an event-related desynchronization of the brain. Older adults with PD with freezing of gait had different

EEG patterns, showing prolonged event-related synchronization and no generation of event-related desynchronization during DT. The results suggest that older adults with PD with freezing of gait have a relatively intact function to discriminate stimuli because they showed changes in EEG patterns (greater modulation in the beta band) after the target sound though it was prolonged. However, their attention-motor preparation coupling is impaired since the beta band did not decrease (no event-related desynchronization).

Another EEG study by Maidan, Fahoum, Shustak, Gazit, Patashov, Tchertov, Giladi, Hausdorff, Mirelman [137] investigated older adults with PD. In this study, participants performed an auditory oddball test while standing (ST) and during normal pace walk (DT). P300 ERP latency in older adults with PD was longer than that in young adults during DT. However, there was no difference in P300 latency between older adults with PD and healthy older adults during DT. P300 amplitude during ST was not different across older adults with PD and healthy older and young adult groups. However, older adults with PD demonstrated a lower P300 amplitude during DT, which indicates older adults with PD may have a lack of attentional resources, compared with healthy older and young adults, especially when the cognitive demand is greater such as DT.

Behavioral results

Motor performance, including inappropriate postural adjustment, inappropriate anticipatory postural adjustment, and step speed, was worse in older adults with PD than healthy controls [135]. Similarly, motor performance outcomes also distinguished between PD with and without freezing of gait. In addition, older adults with PD showed worse gait performance including slower gait velocity, stride, and step regularity during DT compared with young adults [137].

Cognitive performance measured immediately after ST and DT in older adults with PD was also worse than healthy young adults and older adults.

2.3.3. Correlation between Neurophysiological and Behavioral Outcomes

Only two studies investigated the correlation between neurophysiological and behavioral outcomes. One study found a strong inverse relationship between Stroop interference and HbO2 levels in the left inferior frontal gyrus in older adults with mild cognitive impairment [129] whereas another study found increased HbO2 levels with increased gait speed in people with PD [96].

Table 1. Summary of participant characteristics, task paradigm, neurophysiological tool, behavioral outcomes, and neurophysiological outcomes of the studies included in the systematic review.

Authors (year)	**Participant characteristics**	**Task paradigms (single (ST) and dual (DT) tasks)**	**Neurophy-siological tool**	**Behavioral outcomes**	**Neurophysiological outcomes**
Holtzer et al. (2011)	N = 22 (14f / 8m) (i) older adults, n = 11 (7f / 4m), age range = 69-88 yrs (ii) young adults, n = 11 (7f / 4m), age range = 19-29 yrs	ST: normal walk DT: walk + cognitive task (verbal letter fluency task: reciting alternate letters beginning	fNIRS	↓ gait velocity during ST and DT in older adults compared with young adults ($p < 0.001$) ↓ gait velocity	↑ HbO2 level in PFC in both groups during DT compared with ST ($p < 0.05$ in 15 out of 16 channels) ↓ HbO2 level in PFC in older adults during DT compared with young adults ($p <$

		with the letter A or B)		during DT compared with ST in both groups ($p < 0.001$)	0.05 in 13 out of 16 channels)
Doi et al. (2013)	N = 16 (6f /10 m) Age = 75.4 (7.2) yrs, with mild cognitive impairments	ST: normal walk DT: walk + cognitive task (verbal letter fluency)	fNIRS	↓ gait velocity during DT compared with ST ($p < 0.001$)	↑ HbO2 level in PFC during DT, compared with ST ($p < 0.001$) Correlation between HbO2 level during DT and Stroop inference (measured by Stroop test assessing executive function) ($p < 0.05$)
Beursken s et al. (2014)	N = 25 (i) older adults, n = 10, age = 71.0 (3.8) yrs	ST: normal walk → cognitive task 1	fNIRS	↑ DT cost (DT2 – ST) in step duration ($p <$	↓ HbO2 level in PFC during DT2, but no changes in HbO2 levels during

	(ii) young adults, n = 15, age = 24.5 (3.3) yrs	(checking the boxes on the paper with a pen for 30 seconds) → cognitive task 2 (verbal letter fluency task) → DT1: walk + cognitive task 1 → DT2: walk + cognitive task 2		0.05), step length ($p < 0.05$), and number of steps ($p < 0.01$), during DT2 in older adults compared to young adults ↑ DT cost in step duration during DT1 compared to DT2 in older adults ($p < 0.05$) ↓ DT cost in step duration,	ST and DT1 in older adults No changes in HbO2 level in PFC during ST, DT1, and DT2 in young adults

				step length, and number of steps (all p < 0.001) during DT2 compared to DT1 in young adults	
Malcolm et al. (2015)	N = 33 (17f / 16m) (i) older adults, n = 16 (9f / 7m), age = 63.9 (4.0) yrs (ii) young adults, n = 17 (8f / 9m), age = 27.2 (4.6) yrs	ST1: cognitive task (Go/No-Go) in sitting ST2: normal walk DT: walk + cognitive task	EEG	↓ response time in older adults during ST1 and DT compared to young adults (p < 0.001) ↑ DT cost in cognitive task accuracy in older adults between ST1 and DT	↑ P3 amplitude: delayed and attenuated ERP during DT in older adults ERP modulations at N2 amplitude reduction and P3 latency during DT in young adults

				whereas no changes in young adults ($p = 0.07$; approaching significance) ↓ stride time in older adults during DT compared to young adults ($p < 0.05$)	
Fraser et al. (2016)	N = 33 (24f / 9m) (i) older adults, n = 14 (12f / 2m), age = 66.9 (5.3) yrs	ST1: normal walk ST2: cognitive task (n-back)	fNIRS	↑ accuracy during 1-back in older and young adults compared to 2-back ($p < 0.001$)	↑ HbO2 and HbR levels in PFC in older and young adults during DT compared to ST1

	(ii) young adults, n = 19 (12f / 7m), age = 21.8 (1.9) yrs	DT: walk + cognitive task		↓ accuracy during ST2 and DT in older adults compared to young adults (p = 0.009)	No significant age effect between older and young adults in HbO2 and HbR levels during any tasks
Holtzer et al. (2016)	N = 236 (122f / 114m) Age = 75.5 (6.5) yrs, all non-demented (≥ 65 years) (i) healthy older adults, n = 167 (ii) older adults with neurological	ST1: normal walk ST2: cognitive task only (verbal letter fluency) DT: walk + cognitive task	fNIRS	↓ gait velocity during DT compared to ST1 in healthy older adults (p < 0.001) No main and interaction effects between	Between groups, ↓ HbO2 level in older adults with neurological gait abnormalities during DT, compared to HbO2 levels during ST1 or ST2

	gait abnormalities, n = 69			neurological gait abnormality status and tasks	
Maidan et al. (2016)	N = 106 (40f / 66m) (i) healthy older adults, n = 38 (18f / 20m), age = 70.4 (0.9) yrs (ii) PD, n = 68 (22f / 46m), age = 71.6 (0.9) yrs	ST: normal walk DT1: walk + cognitive task (serial 3's subtraction) DT2: walk + obstacle negotiation	fNIRS	↓ functional performance (stride length, gait velocity, etc.) during all walking conditions in adults with PD compared with healthy older adults ($p \leq 0.001$)	↑ HbO2 level in PFC during ST in PD compared to healthy older adults ($p < 0.030$) ↑ HbO2 level in PFC during DT1 only in healthy older adults compared to ST ($p < 0.001$)

					↑ HbO2 level in PFC during obstacle negotiation in PD ($p = 0.001$) and in healthy older adults ($p = 0.053$)
Ozdemir et al. (2016)	N = 19 (10f / 9m) (i) young adults, n = 10 (4f / 6m), age = 26.2 (2.8) yrs (ii) older adults, n = 9 (6f / 3m), age = 81.4 (6.3) yrs	ST: balance task only and/or cognitive task (n-back) only → DT: balance + cognitive task	EEG	↓ 2-back performance in balance tasks (fixed and sway platforms) in older group compared with young group ($p < 0.05$) ↓ balance during sway platform	↑ delta, theta, and gamma oscillations in frontal, central-frontal, central, and central-parietal cortices during DT (sway + 2-back) in older group compared with ST (all $p < 0.05$)

				balance test + 2-back test in the older group compared with young group ($p < 0.001$)	
Tard et al. (2016)	N = 38 (10f / 28m) (i) PD FoG, n = 12 (3f / 9m), age = 62.5 (5.2) yrs (ii) PD non-FoG, n = 13 (3f / 10m), age = 60.2 (10.2) yrs (iii) healthy older adults, n	ST1: auditory preparatory stimulus (standard or target sound) → ST2: visual imperative stimulus ("Go" sign → step initiation)	EEG	↓ motor performance (↑ inappropriate postural adjustment, ↑ inappropriate anticipatory postural adjustment, ↓ step speed) in PD FoG, compared	↑ low-frequency power over 500 ms following the auditory stimulus in all three groups (ERS; event-related synchronization) Then ↓ mid-range frequency power after both target and standard sounds in normal controls and non-FoG (ERD;

	= 13 (4f / 9m), age = 65.4 (5.8) yrs			with PD non-FoG ↓ motor performance in PD non-FoG, compared with healthy older adults	event-related desynchronization) However, no ERD in FoG after ERS
Rosso et al. (2017)	N = 16 (9f / 7m) (i) older adults, n = 10 (7f / 3m), age range = 66-81 yrs (ii) young adults, n = 6 (2f / 4m), age range = 22-30 yrs	ST1: postural balance task ST2: cognitive task (auditory choice reaction time)	fNIRS	↑ reaction time during ST2 and DT in older adults compared to young adults ($p < 0.001$ (ST2); $p = 0.01$ (DT))	↑ HbO2 and HbR levels in PFC during DT in older adults compared to young adults ($p = 0.006$ (HbO2); $p = 0.02$ (HbR))

		DT: balance (ST1) + cognitive task		No significant differences between ST1 and DT in both older and young adults	
Verghese et al. (2017)	N = 166 (85f / 81m) Age = 75.0 (6.1) yrs; older adults without severe neurological conditions and gait impairment	ST: normal walk → cognitive task only (verbal letter fluency) → DT: walk + cognitive task	fNIRS	↓ gait velocity during DT compared to ST	↑ HbO2 level in PFC during DT compared to ST
Maidan et al. (2019)	N = 31 (14f / 17m)	ST: cognitive task	EEG	↓ gait velocity, step regularity,	Prolonged P300 (ERP component)

	(i) older adults, n = 10 (6f / 4m), age = 67.1 (1.7) yrs (ii) PD, n = 10 (4f / 6m), age = 60.5 (3.6) yrs (iii) young adults, n = 11 (4f / 7m), age = 32.3 (1.8) yrs	(auditory oddball test; counting odd tones (600 Hz) among standard tones (1200 Hz)) in standing DT: walk + cognitive task		and stride in PD compared to young adults	latency during DT in PD ↓ P300 amplitude during DT only in PD
Marusic et al. (2019)	N = 20 (13f / 7m) (i) older adults, n = 10 (6f / 4m), age = 72.3 (3.2) yrs	ST1: postural balance task ST2: cognitive task (serial 3's	fNIRS	↓ cognitive performance during STs and DT in older adults compared with young adults	↑ HbO2 levels from baseline to ST1, but not changes from ST1 to DT

	(ii) young adults, n = 10 (7f / 3m), age = 22.6 (2.8) yrs	subtraction) DT: balance + cognitive task		No significant difference in postural balance task	No significant difference across groups
Stuart et al. (2019)	N = 35 (18f / 17m) (i) older adults, n = 18 (9f / 9m), age = 72.6 (8.0) yrs (ii) young adults, n = 17 (9f / 8m), age = 20.3 (1.2) yrs	ST: normal walk DT: walk + cognitive task (digit vigilance task: counting the number of random number X for 30 seconds)	fNIRS	No significant differences in gait characteristic s between tasks (ST vs. DT) or groups (older vs. young)	↑ HbO2 level in motor regions of the brain during DT compared to ST in older and young groups No significant HbO2 level change in PFC during DT compared to ST in older and young groups

Al-Yahya et al. (2019)	N= 51 (29f/ 22m) (i) PD, n= 29 (13f/16m), age= 66.3 (5.9) yrs (ii) older adults, n= 22, (16f, 6m) age= 59.5 (6.8)	ST: Self-selected walking speed (SSWS) and Fast walking speed (FWS) DT: Subtracting while walking in SSWS and FWS	fNIRS	↑ step time and step time variability in older adults from ST to DT No significant changes in the PD group	↑ HbO2 level in PFC and M1 from ST to DT in both SSWS and FWS for both older adults and PD group

Age = Mean (SD or Q1-Q3)

Abbreviations: DT = dual task, EEG = electroencephalography, ERD = event-related desynchronization, ERP = event-related potential, ERS = event-related synchronization, fNIRS = functional near infrared spectroscopy, FoG = freezing of gait, HbO2 = oxygenated hemoglobin, HbR = deoxygenated hemoglobin, PD = Parkinson's disease, PFC = prefrontal cortex, ST = single task.

2.3.4. Methodological Quality

The methodological quality for each included study is reported in Table 2. The agreement between the quality raters was Cohen's kappa = 0.98, indicating excellent agreement. Fourteen studies were designed as an observational study whereas only one study was a prospective cohort study. Hypotheses and study design were reported for all studies, and all of them included a clear definition for identifying the target population. In all studies, independent and dependent variables included in the analyses were reliable, valid, and implemented consistently across all the participants. Very few studies controlled for confounding variables in the statistical analyses and only one study reported sample size justification in their methods section

Table 2. Result of methodological quality checklist

Authors (year)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**
Holtzer et al. (2011)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Doi et al. (2013)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Beurskens et al. (2014)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Malcolm et al. (2015)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Fraser et al. (2016)	Y	Y	Y	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Holtzer et al. (2016)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y
Maidan et al. (2016)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y

Ozdemir et al. (2016)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Tard et al. (2016)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Rosso et al. (2017)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Verghese et al. (2017)	Y	Y	Y	Y	N	NA	Y	Y	Y	N	Y	NA	Y	Y
Maidan et al. (2019)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	Y
Marusic et al. (2019)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N
Stuart et al. (2019)	Y	Y	NA	Y	Y	NA	NA	Y	Y	N	Y	NR	NA	N
Al-Yahya et al. (2019)	Y	Y	NA	Y	N	NA	NA	Y	Y	N	Y	NR	NA	N

Q1: Was the research question or objective in this paper clearly stated?

Q2: Was the study population clearly specified and defined?

Q3: Was the participation rate of eligible persons at least 50%?

Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

Q5: Was a sample size justification, power description, or variance and effect estimates provided?

Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Q10: Was the exposure(s) assessed more than once over time?

Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Q12: Were the outcome assessors blinded to the exposure status of participants?

Q13: Was loss to follow-up after baseline 20% or less?

Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Y: Yes; N: No; NA: Not Applicable; NR: Not Reported

2.4. Discussion

The objectives of this systematic review were to investigate the real-time brain activity during DT gait and balance and the correlation between changes in brain activity and behavioral outcomes in older adults and in people with age-related neurodegenerative conditions. A total of 15 articles were included using real-time neurophysiological tools (fNIRS and EEG) to measure brain activity during DT gait and balance. Walking while performing a cognitive task was the most common paradigm to measure the brain activity during DT. Gait velocity and postural sway were the most commonly reported behavioral outcomes in the included studies. In general, studies demonstrated higher brain activity during DT compared to ST in PFC and structures related to executive functioning in older adults and in people with age-related neurodegenerative conditions. Few studies demonstrated relationship between increased brain activity and better behavioral performance. These results suggest that with aging and/or neurodegeneration, individuals are less efficient in performing two tasks simultaneously and therefore recruit alternative neural resources predominantly from the PFC to compensate for the activity.

Based on the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model, older adults and people with age-related neurodegenerative conditions recruit neuronal networks from both hemispheres to compensate for declines in functional efficiency [141]. CRUNCH states that in aging or neurodegeneration, the brain recruits compensatory neural resources when solving a task to maintain similar performance of a younger brain. In older adults and in people with age-related neurodegenerative conditions, the brain may increase the activity in a certain neural network to compensate for declining processing efficiency in that same network. In addition, compensation might be achieved by increased activity in other, yet connected networks. Thus, increasing the activity in a certain or alternative network may reflect

compensation for reduced neural processing. Another explanation of the compensation derives from the scaffolding theory of aging and cognition. This theory states that increased PFC activation with age and age-related neurodegenerative conditions is an indicator of an adaptive brain that engages with compensatory activity to maintain the performance as a result of declining neural functions and structure [121]. The results of this systematic review support these two theories. Most studies demonstrated that older adults had increased brain activity compared to young adults [35,133,134,136]. Studies with fNIRS provided that older adults had increased activation in the PFC during DT activities compared to the ST [100,131,132,139]. Similar results were observed in several populations including PD [139], PD with freezing of gait [135] and mild cognitive impairment [129].

Interestingly, three studies found decreased HbO2 levels in the PFC during DT in older adults and in people with neurodegenerative conditions compared to their controls [115,128,130]. This might be explained in two ways. First, although fNIRS is sensitive to movement artifacts and valid to measure neurophysiological response of the brain during gait and balance [142], it only measures oxygenated and deoxygenated hemoglobin (HbO2 / HbR) levels in the specific area of the brain. In this systematic review, most of the studies used the PFC region as the area of interest whereas only one study [136] used whole brain fNIRS. It is possible that older adults and people with age-related neurodegenerative conditions recruit additional areas beyond the PFC to compensate during DT. Second, older adults and people with age-related neurodegenerative conditions might show decreased HbO2 levels when the cognitive demand of the DT paradigm exceeds the available cognitive resources. When this conflict between cognitive demand and cognitive resources occurs, participants may disengage from the task, resulting in less brain activity and decreased behavioral performance. Reflecting an inverted U-shaped pattern, at low levels of

cognitive demand, older adults and people with age-related neurodegenerative conditions need to exhibit more brain activity compared to young adults in order to maintain task performance [143]. However, at high levels of cognitive demand, this compensatory mechanism is no longer effective leading to reduced brain activity due to decreased attention to the task [144]. Therefore, it is important to consider both behavioral and brain activity outcomes to interpret the results of DT studies.

In addition, one study found a decreased hemispheric difference in PFC activation during DT in older adults compared to the young adults during treadmill walking with a 2-back test [130]. According to the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, older adults exhibit neurofunctional changes which are characterized by a reduction in functional hemispheric lateralization [145]. A possible explanation could be that older adults use additional neural networks to compensate for functional inefficiency to maintain similar behavioral performance compared to young adults. However, future research is needed to demonstrate this phenomenon in people with age-related neurodegenerative conditions during DT gait and balance conditions.

EEG studies demonstrated prolonged ERP in P300 topography during DT in people with PD [137] and in people with PD who have freezing of gait [135]. Evidence suggests that increased ERP in the P300 topography links with recruiting frontal neural circuits as a compensatory activity in aging and in age-related neurodegenerative conditions [146]. However, the results of the EEG studies should be carefully interpreted because of the heterogeneity of the outcome measurements across the studies (brain wave activity or ERPs). In addition, due to the small number of studies using EEG, it remains unclear which EEG metric best reflects the neurophysiological changes during DT and shows the strongest correlation with aging and the neurodegeneration process. Future

research should investigate a combined EEG and fNIRS approaches to have a robust measurement during DT gait and balance. Using fNIRS as a guide to EEG source localization will eventually advance spatial resolution

Coupling of behavioral and neurophysiological findings is paramount to advance our understanding of brain-behavior interactions. The behavioral outcomes consistently showed that older adults or people with neurodegenerative conditions had decreased motor performance measured by gait velocity [96,100,129,131,132,137], step duration [128], postural sway [35,134,135], and decreased performance on the cognitive task [130,133] from ST to DT conditions. Similar performance decrements were observed when comparing the behavioral outcomes between older adults and young adults as well as between people with age-related neurodegenerative conditions and older adults. People with age-related neurodegenerative conditions had a disproportional decrease in their motor performance from ST to DT conditions [115,135]. In this systematic review, few studies investigated the relationship between behavioral and neurophysiological findings. One study found a strong inverse relationship between Stroop interference and HbO2 levels in the left inferior frontal gyrus in older adults with mild cognitive impairment [129] whereas another study found increased HbO2 levels with increased gait speed in people with PD [96]. Future studies are needed to investigate the association between neurophysiological and behavioral outcomes to better understand the brain-behavior relationship in older adults and in people with age-related neurodegenerative conditions.

This systematic review has several limitations. First, the DT paradigms were different in almost all studies which made it harder to interpret the findings. It is recommended to build a consensus to find the most applicable DT paradigm and standardize the testing protocol to better interpret the effect of increased DT cost on behavioral and neurophysiological outcomes in older adults

and in people with age-related neurodegenerative conditions. Another limitation was the heterogeneity of the outcome measures that were obtained from the neurophysiological tools across the studies. Therefore, it is not surprising to observe inconsistent findings regarding the region and volume of brain activity during DT gait and balance across the studies. In addition, a limited number of studies using EEG with different outcome parameters led to difficulties interpreting which EEG parameter is most sensitive to measure brain activity during DT in older adults and in people with age-related with neurodegenerative conditions. Future studies are needed to standardize behavioral and neurophysiological outcomes in DT gait and balance studies.

2.5. Conclusion

This systematic review demonstrated that, in general, older adults and people with age-related neurodegenerative conditions had increased brain activity during DT, specifically in the PFC, while performing gait and balance activities. In addition, small number of studies reported better behavioral performance with increased brain activity. Induced DT cost during gait and balance is clinically important since it is linked to loss of independence and increased risk of falls. Further studies are warranted to assess the relationship between increased PFC activation during DT and behavioral outcomes to better optimize rehabilitation interventions to improve independence and to decrease fall risk.

Chapter 3

Increased Postural Demand is Associated with Greater Cognitive Activity in Healthy Young Adults: A pupillometry study

This chapter has previously been published in whole without any adaptations since publication and is reprinted here with permission. **Kahya M**, Wood TA, Sosnoff JJ, Devos H. Increased postural demand is associated with greater cognitive workload in healthy young adults: a pupillometry study. Frontiers in Human Neuroscience. 2018 Jul 18;12:288. https://doi.org/10.3389/fnhum.2018.00288

Abstract

Introduction: Balance tasks require cognitive resources to ensure postural stability. Pupillometry has been used to quantify cognitive loads of various cognitive tasks, but has not been studied in postural control. The current investigation utilized pupillometry to quantify the cognitive loads of postural control in healthy young adults. We hypothesized that cognitive activity, indexed by pupil size, will increase with challenging postural control conditions including visual occlusion and additional cognitive load.

Methods: Twenty-one young healthy adults [mean ± standard error of the mean], [age = 23.2 ± 0.49 years; 12 females] were recruited for this study. Participants completed four tasks: (1) standing with eyes open; (2) standing with eyes occluded (3) standing with eyes open while performing an auditory Stroop task; and (4) standing with eyes occluded while performing an auditory Stroop task. Participants wore eye tracking glasses while standing on a force platform. The eye tracking glasses recorded changes in pupil size that in turn was converted into the Index of Cognitive Activity [ICA]. ICA values were averaged for each eye and condition. A two-way Analysis of Variance with post-hoc Sidak correction for pairwise comparisons was run to examine the effect of visual occlusion and additional cognitive load ICA value as well on Center of Pressure [CoP] sway velocity in anterior-posterior [AP] and medio-lateral [ML] directions. A Pearson's correlation coefficient was utilized to determine the relationship between ICA values and CoP sway velocity.

Results: Significant within-condition effect was observed with visual occlusion for the right eye ICA values [$p = 0.008$]. Right eye ICA increased from eyes open to eyes occluded conditions [$p = 0.008$]. In addition, a significant inverse correlation was observed between right eye ICA values and CoP sway velocity in the ML direction across all the conditions [$r = -0.25$, $p = 0.02$].

Conclusion: This study demonstrated support for increased cognitive activity, measured by pupillometry, as a result of changes in postural control in healthy young adults. Further research is warranted to investigate the clinical application of pupillometry in balance assessment.

3.1. Introduction

Balance tasks involve the use of many different motor and sensory systems to integrate environmental stimuli in order to maintain postural stability[147-150]. The integration and coordination of the multiple systems to complete a movement require cognitive resources[149-151]. Increased motor task difficulty will exert greater cognitive resources[149-151]. Dual task interference has been used to examine deteriorations in motor performance when the demand of a combined cognitive and motor task exceeds the available cognitive resources[152-156]. In healthy young adults, it has been shown that postural control requires a small amount of cognitive resources[156]. However, in aging and neurological populations, movement requires a greater amount of cognitive resources, and when the cognitive resources are exhausted, balance instability and falls may occur[152,154-156].

Changes in cognitive load can be observed through changes in pupil size[157]. Pupillometry has been used to understand cognitive demand during memory tasks, decision making tasks, and problem solving[101]. The mechanism of pupil dilation due to increased cognitive activity is mediated by the combination of parasympathetic and sympathetic activity. The size of the pupil is controlled by two muscles, the sphincter pupillae and dilator pupillae[158-160]. The sphincter pupillae is a smooth muscle that is controlled by the parasympathetic fibers of the autonomic nervous system. These parasympathetic fibers originate from the Edinger-Westphal nucleus and are responsible for constricting the pupil[157,160]. The dilator pupillae is also a smooth muscle and is controlled by sympathetic fibers of the autonomic nervous system from the superior sympathetic ganglion, which results in pupil dilation[157,160]. Due to the nature of the innervation of these muscles, changes in pupil size are reflexive[157-160]. With increased attentional or

cognitive load, the locus coeruleus ─ a small nucleus in the brainstem that regulates arousal, attention, memory, cognitive control, and balance ─ activates[161]. Increased activation of the locus coeruleus subsequently sends inhibitory signals to the Edinger-Westphal nucleus which leads to pupil dilation by inhibiting parasympathetic fibers[157-160]. Changes in pupil size may therefore indirectly measure locus coeruleus activity resulting from changes in cognitive and postural demand.

Pupillometry is a valid and reliable measure to quantify cognitive activity during cognitive tasks[101]. Studies have shown that pupils dilate with increased task difficulty during various cognitive tasks[55,58]. In addition, pupillometry has been used successfully to examine changes in cognitive load related to fine motor control reaction time tasks[162]. However, pupillometry has not been used in a postural control context. Although postural control requires a small amount of cognitive resources in healthy young adults[156], pupillometry has the potential to provide better understanding the cognitive loads of postural control. Thus, pupillometry could be a potential tool to improve physical rehabilitation outcomes through understanding changes in postural demand. The aim of the current study was to examine cognitive activity in healthy young adults during varying postural control and cognitive conditions. We hypothesized that cognitive activity, indexed by pupil size, will increase with a challenging postural control condition including visual occlusion and additional cognitive load.

3.2. Methodology

3.2.1. Participants

Twenty-one participants between the ages of 18 and 29 were recruited through the University of Kansas Medical Center [n = 15] and the University of Illinois at Urbana-Champaign [n = 6] in

two-month time period. Inclusion criteria were self-reported independent ambulation, self-reported normal or corrected-to-normal hearing, self-reported absence of confounding walking or balance impairment, and the ability to speak English. Potential participants were excluded if they had a self-reported history of neurological or vestibular conditions, self-reported presence of musculoskeletal conditions which might affect standing and balance activities, and self-report complete or partial blindness. All participants were screened for significant cognitive impairment on the Modified Telephone Interview for Cognitive Status [TICS-M]; participants who scored below 20 were excluded from the study[163]. All recruited participants met the eligibility criteria and were enrolled in the study.

All procedures were approved by the Institutional Review Boards of the University of Kansas Medical Center and the University of Illinois at Urbana Champaign. Each participant provided written informed consent prior to participation in the study.

3.2.2. Experimental Design

Upon consenting to take part in the study, participants completed the Montreal Cognitive Assessment [MoCA] [164]. Subsequently, participants were fitted with SMI Remote Eye Tracking Glasses [SensoMotoric Instruments, Teltow Germany], which recorded pupil size at 60 Hz. The procedures were conducted in a lab space with consistent lighting. Participants performed a series of postural tasks on a Bertec force platform [Bertec, Columbus, OH] at the University of Illinois at Urbana-Champaign or on an AMTI force platform [AMTI OPT464508-1000, Advanced Mechanical Technology, Inc., Watertown, MA] at the University of Kansas Medical Center. At the start of each task, the eye tracking glasses were calibrated using 3-point calibration according to the manufacturer's instructions.

The participants completed four different conditions: 1) single task with eyes open, 2) single task with eyes occluded, 3) dual task with eyes open, and 4) dual task with eyes occluded. Figure 1 displays the four conditions. For the four conditions, participants were instructed to look forward and remain as still as possible for 60 seconds. To ensure participant safety throughout the testing, participants were given a grab bar to stabilize themselves if needed and were fitted with a gait belt. For the first condition, the participants were instructed to focus their eyes on a crosshair target 1.5 meters away [Figure 1a]. For the second condition, after the calibration, the front of the eye tracking glasses was occluded with a sleep mask; participants could not see in front of them, but the eye tracking glasses could still record pupil size [Figure 1b]. For the third condition, the participants were instructed to focus their eyes on a target 1.5 meters away while completing an auditory Stroop task [Figure 1c]. The auditory Stroop test was shown sensitive to dual task interference in healthy young adults[165]. For the auditory Stroop task, participants were instructed to listen to the words "high" and "low." These words were spoken in a high pitch or a low pitch through headphones. Participants were asked to verbally specify the pitch of the word as quickly as possible[152,153]. Three different audio files were randomly used for each dual task condition; each audio file contained 15 stimuli with a two seconds interval. Finally, for the fourth task, the eye tracking glasses were occluded with the sleep mask and the auditory Stroop task was performed [Figure 1d]. During eyes occluded conditions, participants were specifically instructed to keep their eyes open.

The collected eye tracking data were analyzed using SMI BeGaze software [SensoMotoric Instruments, Teltow Germany] and EyeWorks [EyeTracking Inc., Solana Beach CA]. SMI BeGaze software analyzed the change of the pupil size for each eye throughout the trial. By solely measuring the change of the pupil size, there are potential limitations such as the light

reflex interfering with the pupil size and movement artifacts[39]. To combat this potential problem, the EyeWorks software utilized the eye metrics from the SMI BeGaze software to compute the Index of Cognitive Activity [ICA]. The ICA is an algorithm that measures cognitive activity through pupil dilation on a continuous scale ranging between 0 [no cognitive activity] and 1 [maximum cognitive activity][39]. The ICA is computed as the number of unusual increments in pupil size per second. Based on this algorithm the noisy signals such as light reflex are reduced to near zero level[39]. The primary outcome variable was the average ICA value for each eye and for each task.

The force platforms collected forces Fx, Fy, and Fz and movements Mz, My, and Mz. Center of pressure [CoP] was calculated in the x and y direction with the following calculations:

$CoP_X = -My/Fz$

$CoP_Y = Mx/Fz$

A custom MATLAB code [MathWorks, Natick, MA] employed a 4th order Butterworth filter low pass filter with a cut-off frequency of 10 Hz and resampled the data at 100 Hz. The Bertec force platform collected data at 500 Hz and the AMTI force place collected at 360 Hz. Data were resampled at 100 Hz for consistency between the two force platforms and 100 Hz has been shown to be suitable to characterize CoP variability[166,167]. Average AP and ML CoP sway velocity variables were then calculated for each trial. The secondary outcome variable was the CoP sway velocity in the AP and ML directions as sway velocity has been shown to be a reliable measure of postural stability[168].

3.2.3. Data Analysis

A two way ANOVA was run to examine the effect of visual occlusion and additional cognitive load on ICA values as well on CoP sway velocity in AP and ML directions. A post-hoc Sidak test was used to determine the differences in eyes open and eyes occluded conditions. The number of correct responses on the auditory Stroop test was calculated for the dual task conditions.

All variables [except sex] were normally distributed according to Shapiro-Wilk tests. Pearson's correlation coefficient was used to calculate the relationship between ICA values and CoP sway velocity. A significance value of 0.05 was used for all significance testing. All the statistical analysis were performed using IBM SPSS Statistics v23.

3.3. Results

Table 1 summarizes the subjects' demographic characteristics and the results of global cognitive testing.

Table 1. Subject characteristics [n = 21].

Characteristics	**Mean ± SEM**
Age (years)	23.2 ± 0.49
Sex, women, n (%)	12 (57.1)
Education (years)	16.1 ± 0.42
MoCA	28.3 ± 0.35

Results were reported as mean ± SEM, and as frequency [percentage] for the sex variable.

Abbreviations: SEM: Standard error of the mean; MoCA: Montreal Cognitive Assessment

3.3.1. Primary outcome

A two-way ANOVA revealed a significant effect of visual occlusion on ICA values in the right eye [p = 0.008], [see Figure 2]. However, no significant differences were found for the additional cognitive load [p = 0.77], and also no significant interaction was found between the conditions [p = 0.94]. Post-hoc analysis demonstrated a significant increase in right eye ICA values from eyes open condition [mean ± standard error mean] [0.36 ± 0.02] to single task eyes occluded condition [0.45 ± 0.02] [p = 0.008]. No significant effect of condition was observed in the left eye [p = 0.15].

Figure 1a-d: Depiction of the four postural control conditions
Figure 1a: Single task standing with eyes open
Figure 1b: Single task standing with eyes occluded
Figure 1c: Dual task standing with eyes open
Figure 1d: Dual task standing with eyes occluded
Note: The person pictured gave consent for publication of these images.

Figure 1. Depiction of the four postural control conditions

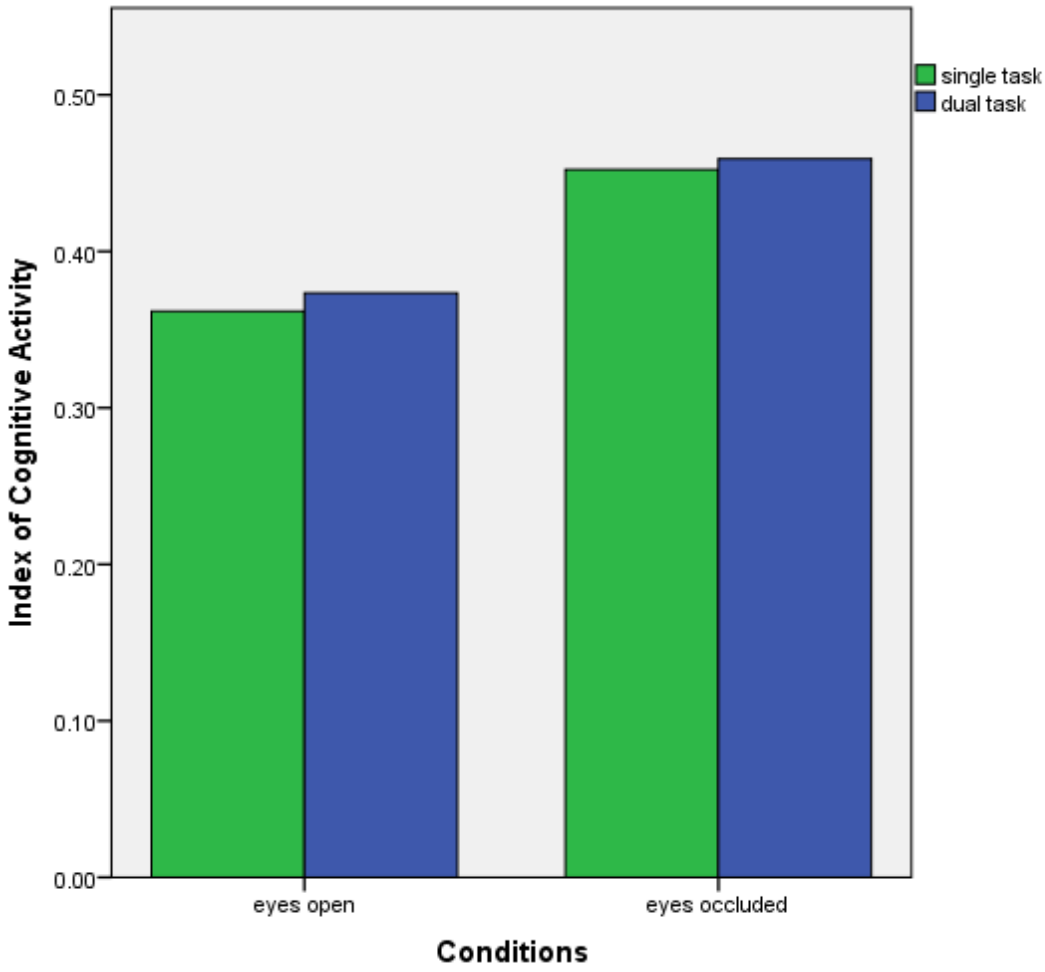

Figure 2. Bar graph of the right eye ICA results over the conditions

3.3.2. Secondary outcomes

The force platform results demonstrated that there was not a significant within-condition effect of visual occlusion as well as additional cognitive load, and also no significant interaction effect of the conditions on the CoP sway velocity in the AP direction and in the ML direction.

There were no significant differences on the auditory Stroop test incorrect responses between the dual task eyes open and dual task eyes occluded conditions [p = 0.54]. The majority [n = 18, 86%] of the subjects completed the auditory Stroop tests without errors.

3.3.3. Correlation Analysis between ICA Values and Force Platform Outcomes

There was a significant, yet weak, inverse correlation between right eye ICA values and CoP sway velocity in the ML direction across all the conditions [r = -0.25, p = 0.02] [see Figure 3]. However, there was no correlation between the right eye ICA values and CoP sway velocity in the AP direction across all the conditions [r = -0.17, p = 0.13].

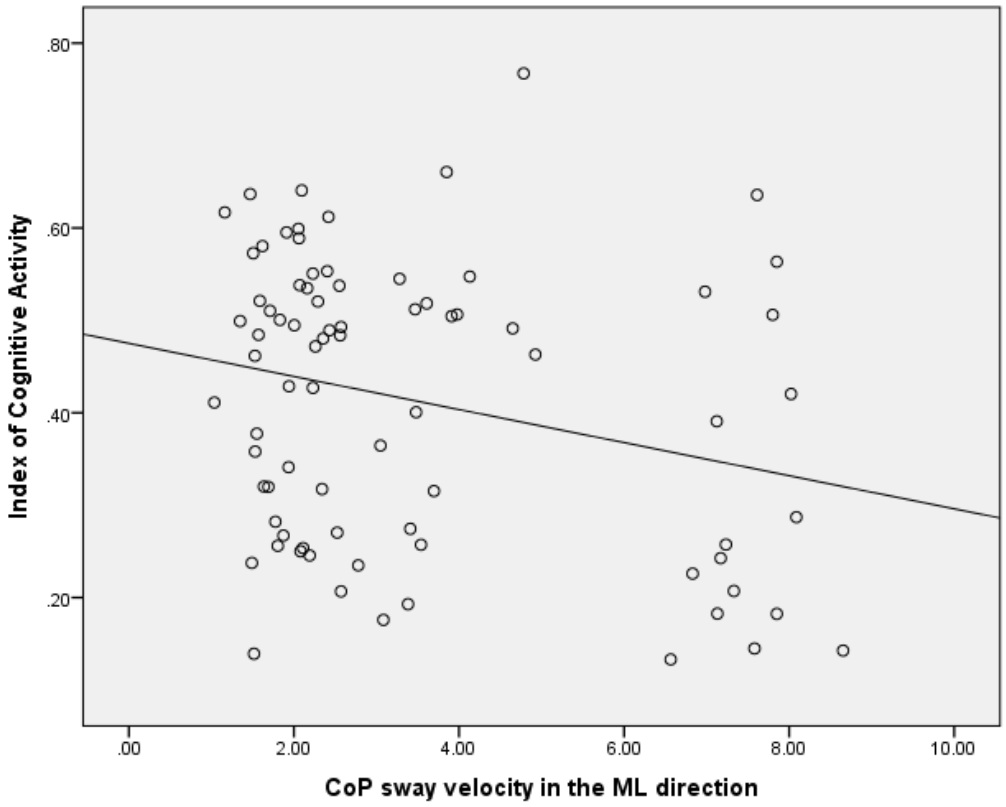

Figure 3. Correlation analysis between ICA and CoP sway velocity in the ML direction

Abbreviations: ICA: Index of Cognitive Activity CoP: Center of Pressure; ML: Medio-lateral

3.4. Discussion

The current investigation examined whether challenging postural control through visual occlusion and additional cognitive load is associated with increased cognitive activity as measured by pupillometry in healthy young adults. We found that challenging postural demand is associated with greater cognitive activity in healthy young adults. These differences mainly surfaced in postural conditions with visual occlusion. Taken together, these findings suggest that visual occlusion requires additional neural processes in the cerebral cortex to maintain posture. This increased recruitment of neural processes result in changes in pupil size [increased ICA]. However, this phenomenon was not observed when adding cognitive load to the postural control task in healthy young adults, probably because the cognitive task was not challenging enough.

Several studies have used pupil dilation as an indicator of cognitive activity during cognitive tasks[101] and motor tasks[162,169,170]. Several studies demonstrated a linear relationship between increased pupil dilation and increased cognitive activity in healthy individuals[54-56].White et al. [162] demonstrated a positive relationship between increased pupil dilation and increasing motor task difficulty while controlling the mouse to move the cursor over the target from normal to more quick and rapid cursor movements. Another study showed that increased pupil dilation was associated with increased complexity of the physical task[169]. In addition, pupil dilation has been shown to reflect increased effort required to perform a grip task[170]. The novelty of the present study is that pupillometry can potentially be used as an indicator of cognitive activity during various challenging postural control tasks in healthy young adults. Using pupillometry might allow researchers to gain insight into the cognitive processes during postural control. Several studies have used other neurophysiological tools to measure cognitive activity during changes in

a postural demand in healthy young adults, including functional near infrared spectroscopy [fNIRS] or electroencephalogram [EEG]. Herold et al.[171] demonstrated that healthy young adults had increased frontal brain activation measured by fNIRS during balancing on a balance board. By contrast, Mirelman et al.[172] did not find changes in frontal brain activation as measured by fNIRS when dual task standing was compared to dual task walking in healthy young adults. Lastly, several EEG studies showed increased activity in the brain during postural balance condition with visual occlusion as well as with additional cognitive load both in healthy young and healthy old adults[35,173]. Significantly, several reviews discussed the role of cerebral cortex on postural balance and indicated an increase in cognitive activity to maintain postural balance during challenging situations [174,175]. Our results extend the evidence on cerebral activity in postural demanding conditions in healthy young adults. However, compared to the other neurophysiological tools, pupillometry is cost-effective, less intrusive, and easy to implement in clinical practice.

Interestingly, the results showed that CoP sway velocity on the AP and ML directions did not change by visual occlusion or additional cognitive load whereas the ICA values significantly increased with increased postural demand by visual occlusion. This might suggest that the behavioral outcomes of postural balance may not be sensitive enough to detect changes in postural demand compared to the neurophysiological response of the brain in healthy young adults. Therefore, pupillometry might help to better understand the cognitive activity related to changes in postural demand in healthy young adults. Furthermore, we found that increased ICA values were significantly correlated with decreased CoP sway velocity in the ML directions. Researchers may need to assess both cognitive activity and force platform data to better understand cognitive and postural adaptations to changes in postural demand.

The lack of effect of cognitive load on ICA and on COP sway velocity indicate that the Stroop test was not challenging enough evoke higher cognitive activity in healthy young adults. Our results demonstrated that 86% of the individuals from our cohort did not miss any single item from the auditory Stroop test during the dual task conditions. Although several studies reported dual task interference when using the auditory Stroop test[165,176], some of them demonstrated this test was not sensitive to observe dual task interference in healthy young adults[152,177]. The present study was in line with the latter studies[152,177], therefore we concluded that the auditory Stroop test was not challenging enough to observe dual task interference in healthy young adults. Future studies should take into account task difficulty in order to observe a dual task interference in healthy young adults.

Furthermore, our findings demonstrated that right eye ICA values were more sensitive to demonstrate increased cognitive activity to increased postural demand compared to the left eye. Several studies with animal models and human subjects suggested that pupillary response differs between right and left eyes during increased attentional load possibly due to the brain hemispheric differences[178-180]. It is possible to say that brain hemispheric differences play a role in different responses of the right and left cortex in a postural control task. Evidence from a neuroimaging study suggests that left hemisphere is dominant for execution of motor and postural control activities in healthy young adults[181]. Therefore, the increased ICA in right eye could be explained by increased activation of the left hemisphere due to increased postural demand throughout the testing. However, given the novelty of this result and hypothetical explanation of the mechanism, future studies are needed to investigate the underlying pathways of the hemispheric differences on the pupillary response.

This study has several limitations. The order of the conditions was not randomized for the subjects, which might have resulted in an adaptation to the subsequent condition because of the experience gained in the previous condition. Therefore, the results of this study should be interpreted cautiously. However, the ultimate goal of this research is to examine if pupillometry can be used in older adults and other clinical populations. Clinical assessment of postural control in clinical populations involves progressively difficult balance tasks to maximize participant safety. Nevertheless, to minimize this adaptation, we gave breaks between the conditions and used different auditory Stroop tests for the dual task conditions. In addition, although we standardized the ambient lighting while testing the subjects, the ambient lighting might have been different between the two testing sites. However, in this study, we used the ICA algorithm to filter out the noise of ambient lighting[39]. Therefore, the combined results from the two sites truly reflect increased pupil size due to increased cognitive activity. Lastly, although we observed increased cognitive activity with visual occlusion during quiet standing, we did not capture activated areas of the brain during the conditions. A more robust design would be a combined approach in which EEG or fNIRS is used with pupillometry. Overall, this study will build a foundation to implement pupillometry to assess cognitive activity during increased postural demand in older adults with and without neurological conditions.

3.5. Conclusion

The present study provides support for cognitive activity changes measured by pupillometry related to changes in postural control in healthy young adults. Through increasing postural demand by visual occlusion, a greater pupil size [ICA] was observed possibly due to increased neural processing in the cerebral cortex to maintain posture. Future studies with similar experimental design are needed in healthy older individuals and those with neurological

conditions to assess differences in cognitive activity related to aging and disease during challenging postural control tasks.

Chapter 4

Reliability and Validity of Pupillary Response during Dual-task Balance in Parkinson's Disease

Abstract

Introduction: Neurophysiological measures are increasingly used to investigate brain-behavior interactions. Preliminary studies have shown that pupillary response increases with postural demand, especially under dual-task conditions. However, the reliability and validity of pupillary response during dual-task balance have not been established in Parkinson's disease (PD). We hypothesized that pupillary response demonstrates excellent test-retest reliability and strong validity during dual-task balance conditions in individuals with PD.

Methods: In this cross-sectional study, subjects (n=33 PD, age=69.30 ± 6.78, 14 female; n=35 healthy controls, age: 68.54 ± 6.22, 21 female) wore eyetracking glasses to record the pupillary response during single balance eyes open; single balance eyes occluded; dual-task eyes open; and dual-task eyes occluded. During the single balance task, subjects stood on the balance platform for 60 seconds with eyes open and eyes occluded. The dual-task involved standing on the balance platform while performing the Auditory Stroop test. After each condition, the National Aeronautics and Space Administration-Task Load Index (NASA-TLX) was administered to assess self-reported cognitive workload. To examine the test-retest reliability of the pupillary response, the conditions were administered twice for each subject within two hours. Intraclass correlation coefficients (ICC) were used to analyze the test-retest reliability of pupillary response in each condition for both groups. Pearson's r correlation was used to assess the convergent validity of pupillary response against NASA-TLX.

Results: The test-retest reliability was excellent for both groups in almost all conditions (ICC > 0.75). There were no correlations between pupillary response and NASA-TLX. However,

increased mental demand (one of the subitems of NASA-TLX) significantly correlated with an increased pupillary response in individuals with PD ($r = 0.38$, $p = 0.03$).

Conclusion: Pupillary response showed excellent test-retest reliability during dual-task balance for individuals with PD and healthy controls. Overall, these results suggest that pupillary response represents a stable index during dual-task balance in individuals with PD.

4.1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder affecting approximately one million people in the US[182]. PD is characterized by degeneration of the dopaminergic cells in the basal ganglia, leading to cardinal motor symptoms of resting tremor, rigidity, bradykinesia, and postural instability. In addition to the cardinal symptoms, individuals with PD also experience deterioration of motor automaticity. As a result, they perform a given task with greater use of attentional resources[27].

Most activities of daily living require performing two tasks simultaneously[183], such as standing while talking. In such dual-task conditions, upright stance posture is an essential motor skill to accomplish various motor and cognitive tasks concurrently[35]. Although maintaining an upright stance posture seems autonomous and effortless in healthy individuals, it may become challenging and cognitively effortful due to impaired motor and cognitive circuits in individuals with PD[27].

Dual-task deficiency is an important symptom of PD as it may lead to an increased risk of falls[29,184]. Dual-task deficiency is operationally defined as a decrease in motor or cognitive performance (or both) when tasks are performed concurrently[27]. Studies have shown that dual-task balance is under control of higher-order cognitive processes related to attention and executive function[112,118]. Both executive function and attentional deficits have shown even in the early stages of PD due to basal ganglia pathology [185]. Therefore, individuals with PD seem to be disproportionally affected by dual-task balance compared with their age-matched peers[27]. As a result, performing a dual-task balance might increase the reliance on cognitive resources to optimize motor control.

The pupils are known to respond to changes in cognitive demand[186]. A previous study showed that pupillary response increases with incremental cognitive demand in individuals with PD supporting the hypothesis that pupillary response reflects cognitive workload (or mental effort) in individuals with PD[72]. The pattern of pupil response in PD to cognitive demand was similar to that of healthy controls, suggesting that early PD pathology does not affect the accuracy of pupillary response in challenging cognitive tasks.

It is important to understand the amount of cognitive workload to complete dual-task balance activities to predict people who are at risk for falling and/or to develop novel rehabilitation strategies by optimizing the intensity, frequency, and difficulty of the interventions for individuals with PD. Pupillary response has shown to reflect changes in cognitive workload from single task to dual task balance conditions in healthy young adults[187]. However, the lack of reliability and validity testing currently limits the use of this neurophysiological tool as a measure of cognitive workload during dual-task balance in individuals with PD. Therefore, the purpose of this study was to determine the test-retest reliability of pupillary response during dual-task balance conditions in individuals with PD. To address the convergent validity of pupillary response, we also investigated the relationship between pupillary response and self-reported cognitive workload during dual-task balance. It was hypothesized that pupillary response would demonstrate excellent test-retest reliability and strong convergent validity in individuals with PD.

4.2. Methods

4.2.1. Participants

A total of 68 (n=33 PD, n=35 healthy controls) participants were enrolled in this study. Patients with PD were recruited from the University of Kansas Medical Center Parkinson's Disease and Movement Disorder Center between 08/2018 and 02/2019. Diagnosis of idiopathic PD was established according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [5]. Healthy controls were the spouse/significant others of the participants with PD or members of the community. The healthy control group was matched with individuals with PD for age, sex, and cognitive status.

Inclusion criteria were (1) voluntary consent, (2) ability to speak and understand the English language, and (3) mild to moderate disease severity (Hoehn & Yahr stage II and III) for individuals with PD. Exclusion criteria were (1) diagnosis of mild cognitive impairment or dementia, (2) atypical parkinsonism, (3) history of neurological or vestibular conditions unrelated to PD, (4) current visual acuity or visual field problems that cannot be resolved by corrective lenses, (5) severe trunk and head dyskinesia or dystonia in the medication "on" state, (6) blepharospasm, (7) deep brain stimulation, (8) unpredictable motor fluctuations, and (9) any musculoskeletal condition that might affect standing and balance activities.

4.2.2. Assessment

The study was approved by the Human Subjects Committee at the University of Kansas Medical Center. Participants made one visit to the University of Kansas Medical Center Parkinson's Disease and Movement Disorder Center which lasted for approximately two hours including consent and breaks. All assessments were done in the medication "on" state. Participants with PD were tested approximately 30 to 45 minutes after medication intake in order to minimize the possibility of wearing-off which could potentially affect the test results. If the medication wore

off during the assessment, the assessment was stopped until approximately 30 minutes after the next medication dose when the participant was again in the medication "on" state.

During the assessment, participants provided demographic and medical history with questions related to age, sex, education, and disease symptoms. A list of prescribed and unprescribed medications was obtained from the participants' medical records. Levodopa Equivalent Daily dose was calculated to tally antiparkinsonian related medication usage[188]. The Montreal Cognitive Assessment (MoCA)[189] was used to assess global cognitive function. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II (motor experiences of daily living) and Part III (motor examination)[190] were used to assess restrictions in activities of daily living and motor symptom severity, respectively. The modified Hoehn and Yahr (H&Y) Scale[191] was used to assess disease severity. Lastly, the Scales for Outcomes in Parkinson's Disease- Autonomic Dysfunction (SCOPA-AUT)[192] was administered as dysautonomia may potentially influence pupil recordings.

4.2.3. Procedure

All participants wore Tobii Pro 2 glasses (Tobii Technologies, Inc.) to measure pupillary response during the entire duration of testing. Subjects were tested during the following conditions in a randomized order.

1. Single balance eyes open condition: Participants stood on a force platform (AMTI OPT464508-1000, Advanced Mechanical Technology, Inc.) and maintained an upright standing posture for 60 seconds.

2. Single balance eyes occluded condition: Participants stood on a force platform for 60 seconds while their eyes were occluded with a sleep mask.

3. Dual-task eyes open condition: Participants stood on the force platform for 60 seconds while concurrently completing an Auditory Stroop test.

4. Dual-task eyes occluded condition: Participants stood on a force platform for 60 seconds while simultaneously completing an Auditory Stroop test with their eyes occluded.

Auditory Stroop test was shown to be one of the key determinants of dual-task performance in individuals with PD[38]. Therefore, we selected the Auditory Stroop test to stress the executive function and cognitive flexibility abilities of the participants. During the Auditory Stroop test, participants heard the word "high" or "low" in a high or low pitch and were instructed to name the pitch of the stimulus, while ignoring the meaning of the word. Participants heard congruent stimuli where the word and pitch are equal (e.g. "high" at a high pitch) or incongruent stimuli where the word and pitch differ (e.g., "high" at a low pitch) in a random order for 60 seconds. There were 30 stimuli presented at 2-second intervals for 60 seconds. Participants were instructed to respond accurately and as fast as possible. To standardize the test, participants wore headphones and the stimuli were played by a digital recorder. To examine the test-retest reliability of the pupillary response, conditions were administrated twice for each subject on the same day within two hours.

After testing, the pupillary response data was extracted from the EyeWorks Analyze software. By solely measuring the change of the raw pupil size, there are potential limitations such as the light reflex interfering with the pupil size and movement artifacts. To combat this potential problem, EyeWorks software was utilized to compute the Index of Cognitive Activity[39]. The

ICA is an algorithm that computes the number of unusual increments in pupil size per second. These values are then transformed into a continuous scale ranging between 0 (no cognitive workload) and 1 (maximum cognitive workload). Based on this algorithm the noisy signals are reduced to nearly zero[39].

According to the literature, there is no accepted gold standard to measure cognitive workload[76,77]. However, it is possible to use self-reported cognitive workload by asking subjects to rate their subjective impression of mental effort[78]. The National Aeronautics and Space Administration-Task Load Index (NASA-TLX) is one of the most commonly used self-reported cognitive workload instruments that provides an overall index of cognitive workload by measuring the contributions of six subscales including mental demand, physical demand, temporal demand, effort, performance, and frustration[79]. This instrument has been widely used in the literature and has shown to be a reliable and valid measure of self-reported cognitive workload[80]. Therefore, the convergent validity of pupillary response was assessed against the NASA-TLX[79]. NASA-TLX was administered after each of the four conditions. The mean score of the six subscales was computed for each of the conditions and for each subject.

4.2.4. Statistical Analysis

Descriptive statistics (mean and standard deviation) were used to evaluate baseline characteristics of the two groups. Differences in variables between groups were determined using independent sample *t*-tests or Chi-square tests. Cognitive workload indexed by pupillary response was transformed to a continuous scale ranging from 0 to 1 to filter out possible confounding effects such as a change in lighting, accommodation, and anxiety[39]. Intraclass correlation coefficients were used to interpret the test-retest reliability of pupillary response

measures on each condition in both groups. ICC was interpreted as follows: >0.75 was excellent, 0.60–0.74 was good, 0.40–0.59 was fair, <0.40 was poor[193,194]. Bland-Altman plots were used to visualize the measurement precision of pupillary response across the test moments[195]. Pearson's r correlations were used to assess the convergent validity of pupillary response against NASA-TLX. The results were interpreted as follows: >0.70 is strong, 0.50–0.70 is moderate, 0.30 – 0.50 is weak[196]. All statistical analyses were performed with the IBM SPSS Statistics v.23 software (IBM, Armonk, NY, USA). P-values < 0.05 were considered statistically significant.

4.3. Results

4.3.1. Demographic characteristics

Individuals with PD had mild to moderate disease based on the H&Y stage (n=24 in H&Y stage II; n=9 H&Y stage III) and MDS-UPDRS II and III scores. No significant differences were found in the demographic variables between individuals with PD and healthy controls except that healthy controls had more years of education. A summary of the demographic and clinical characteristics of the groups are shown in Table 1.

Table 1. Demographic characteristics

Variables	PD group (n=33)	Healthy controls (n=35)	p-value
Age (years)	69.30 ± 6.78	68.54 ± 6.22	0.63
Sex (female/male, n)	14/19	21/14	0.11
Education (years)	15.30 ± 2.14	17.31 ± 3.53	0.006
MoCA	26.61 ± 3.20	26.60 ± 2.31	0.99

MDS-UPDRS II	11.91 ± 8.23	N/A	N/A
MDS-UPDRS III	43.97 ± 14.91	N/A	N/A
Modified H & Y scale	2.3 ± 0.52	N/A	N/A
LED (mg)	302.8 ± 255.7	N/A	N/A
SCOPA-AUT	15.30 ± 9.04	N/A	N/A

PD = Parkinson's disease; MoCA = Montreal Cognitive Assessment; MDS-UPDRS II = Movement Disorder Society Unified Parkinson Disease Rating Scale motor experiences of daily living; MDS-UPDRS III = Movement Disorder Society Unified Parkinson Disease Rating Scale motor examination; H &Y = Hoehn and Yahr; LED = Levodopa Equivalent Dose; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; N/A = Not Applicable. The results are presented as mean ± standard deviation except for the sex variable.

4.3.2. Test Re-test Reliability of Pupillary Response

Table 2 provides the mean and standard deviation of the pupillary response during first and second testing as well as the ICC results with the 95% confidence interval. The test-retest reliability results demonstrated excellent ICC values for both groups in all conditions except for the dual-task eyes occluded condition in healthy controls (ICC=0.74). Bland-Altman plots for individuals with PD are presented in Figure 1. The plots demonstrated that data were equally distributed around zero showing no bias in the results, no evidence of practice effect, and no heteroscedasticity within the data.

Table 2. ICC results of the pupillary response during dual task balance

	PD group (n = 33)			Healthy Controls (n = 35)		
Conditions	**ICA First testing**	**ICA Second testing**	**ICC (95% CI)**	**ICA First testing**	**ICA Second testing**	**ICC (95% CI)**
Single Balance Eyes Open	0.31 ± 0.14	0.28 ± 0.12	0.83 (0.65, 0.92)*	0.26 ± 0.12	0.24 ± 0.11	0.79 (0.58, 0.90)*
Single Balance Eyes Occluded	0.47 ± 0.17	0.44 ± 0.16	0.88 (0.76, 0.94)*	0.42 ± 0.15	0.38 ± 0.16	0.93 (0.85, 0.96)*
Dual-Task Eyes Open	0.31 ± 0.13	0.29 ± 0.12	0.78 (0.54, 0.89)*	0.31 ± 0.11	0.30 ± 0.12	0.86 (0.70, 0.93)*
Dual-Task Eyes Occluded	0.49 ± 0.15	0.45 ± 0.15	0.90 (0.79, 0.95)*	0.39 ± 0.13	0.43 ± 0.13	0.74 (0.46, 0.87)*

ICA: Index of Cognitive Activity; ICC: Intraclass correlation coefficient; CI: Confidence interval. The results are presented as mean ± standard deviation *Significant at $p<0.01$.

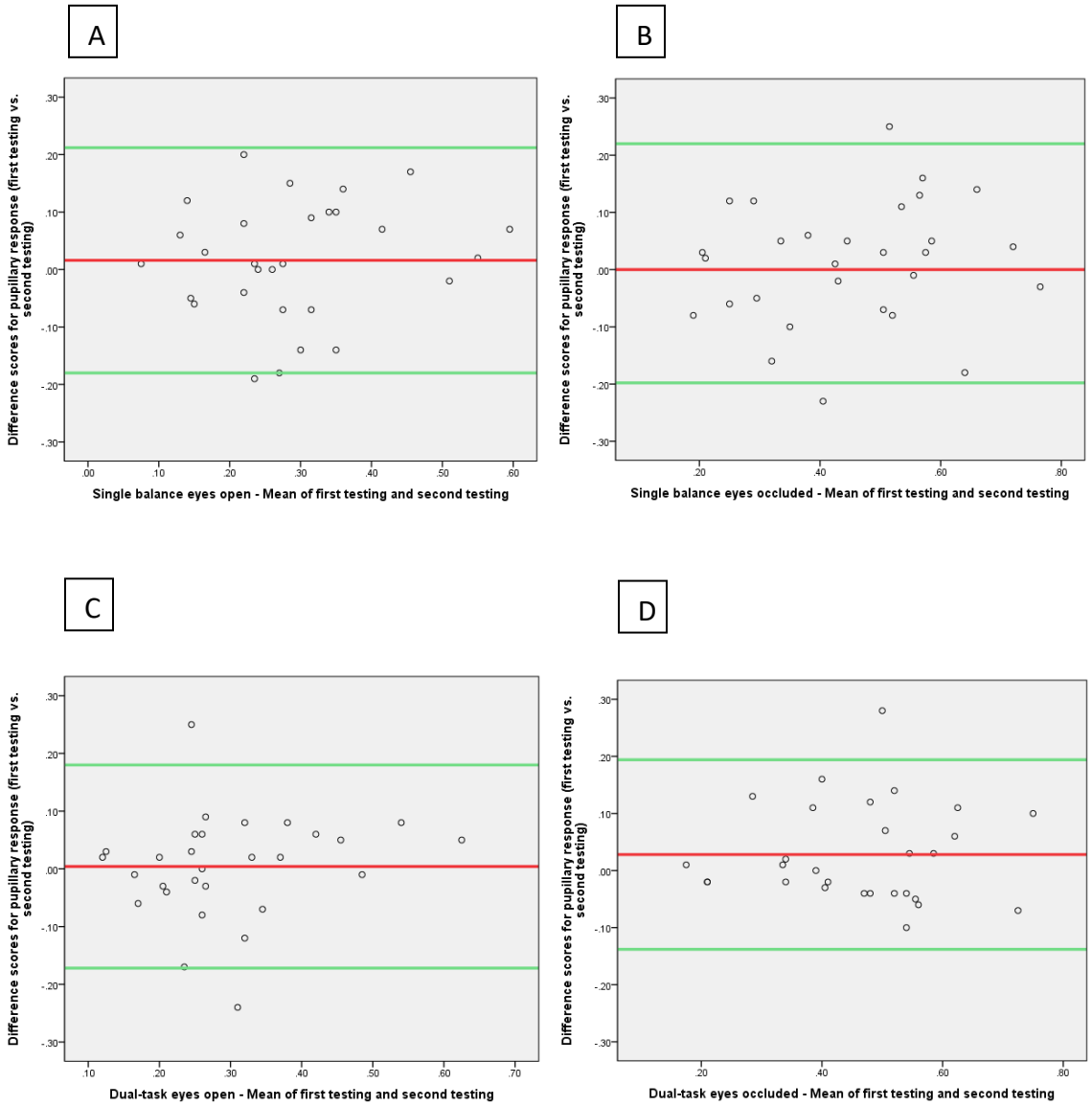

Figure 1. Bland-Altman plots for individuals with PD. A: Single balance eyes open condition, B: Single balance eyes occluded condition, C: Dual-task eyes open condition, D: Dual-task eyes occluded condition. The figures represent the difference between first testing and second testing (y-axis) plotted against the mean of first testing and second testing (x-axis). The mean difference between first testing and second testing is presented as the horizontal red line, and the upper and lower green lines represent the 95% upper and lower limits.

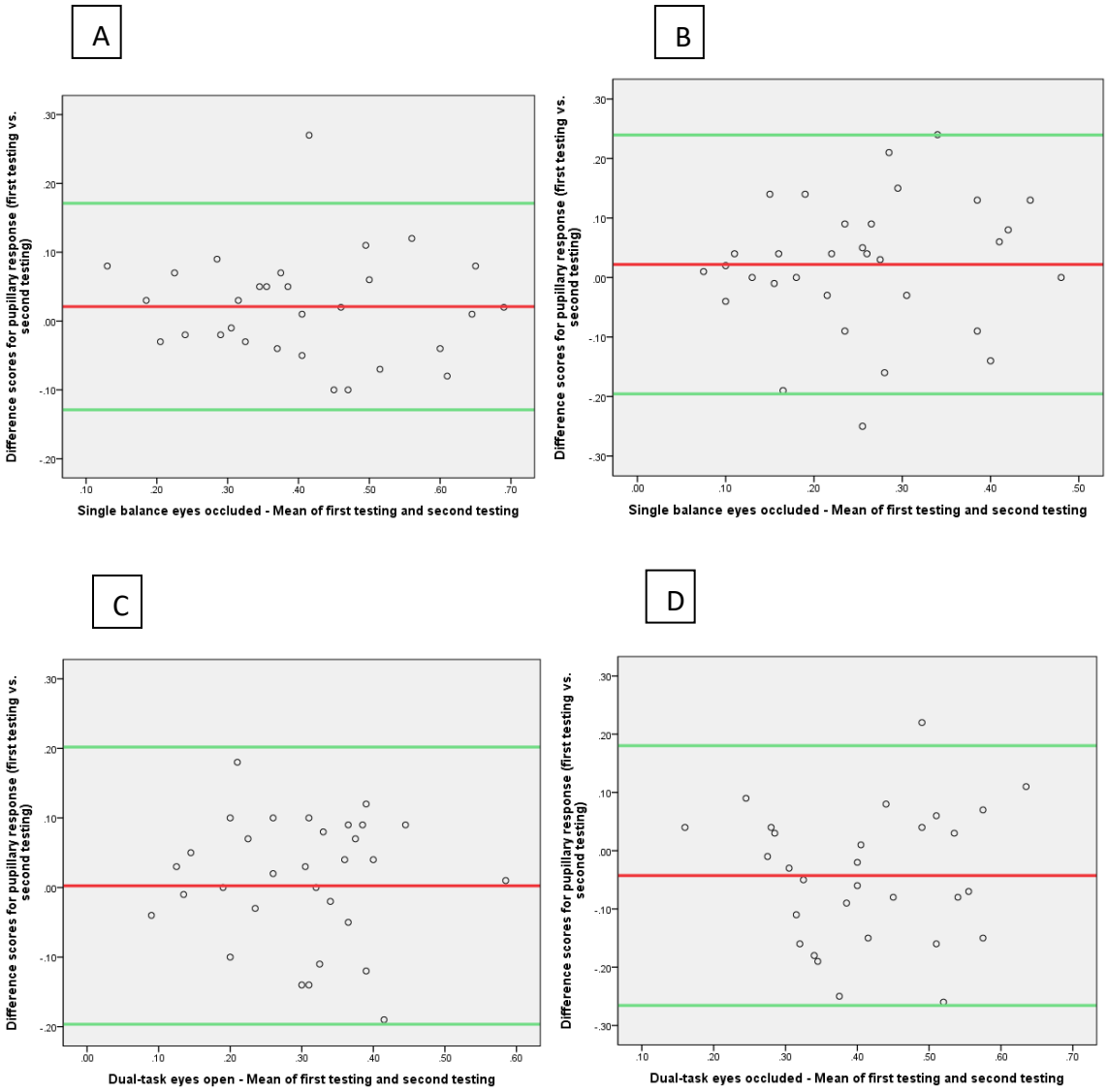

Figure 2. Bland and Altman plots for healthy controls. A: Single balance eyes open condition, B: Single balance eyes occluded condition, C: Dual-task eyes open condition, D: Dual-task eyes occluded condition. The figures represent the difference between first testing and second testing (y-axis) plotted against the mean of first testing and second testing (x-axis). The mean difference between first testing and second testing is presented as the horizontal red line, and the upper and lower green lines represent the 95% upper and lower limits.

4.3.3. Convergent Validity of Pupillary Response

There were no significant correlations between pupillary response and NASA-TLX total scores in all conditions for both individuals with PD and healthy controls (Table 3).

Table 3. Correlation analysis between pupillary response and NASA-TLX total score

	NASA-TLX total score			
	PD group		Healthy controls	
Pupillary response during:	***r***	***p***	***r***	***p***
Single Balance Eyes Open	0.06	0.73	0.14	0.41
Single Balance Eyes Occluded	0.01	0.96	-0.06	0.72
Dual-Task Eyes Open	-0.09	0.61	0.32	0.06
Dual-Task Eyes Occluded	0.14	0.44	0.14	0.45

NASA-TLX: National Aeronautics and Space Administration-Task Load Index

As a secondary analysis, the correlation between pupillary response and six subscales of NASA-TLX (mental demand, physical demand, temporal demand, effort, performance, and frustration) was calculated. In healthy controls, there was a significant correlation between pupillary response and mental demand during dual-task eyes occluded condition ($r = 0.39$, $p = 0.03$). Similarly, in the PD group, a significant correlation was observed between pupillary response and mental demand during dual-task eyes occluded condition ($r = 0.38$, $p = 0.03$).

4.4. Discussion

The current study examined the test-retest reliability and convergent validity of pupillary response during dual-task balance in individuals with PD. Our results demonstrated that

pupillary response had good to excellent test-retest reliability during all dual-task balance conditions in both individuals with PD and healthy controls. No correlations were observed between pupillary response and total scores on the self-reported cognitive workload (NASA-TLX). Pupillary response only correlated with the mental demand subdomain of the NASA-TLX. In previous studies, pupillary response during cognitive testing was validated against other neurophysiological measures that are purported to reflect cognitive workload, including electroencephalogram (EEG). EEG event-related potentials associated with attentional and cognitive processing including the P300 and N400 components significantly correlated with pupillary response ($r=0.52$, $p<0.05$)[197,198]. Previous research demonstrated that the pupillary response is a valid index of cognitive workload during cognitive testing, gradually increased exercise intensity, and physical effort perception[72,170,199]. These findings support the hypothesis that pupillary response is a reliable index of cognitive workload.

Our results extend the use of pupillary response as a reliable measure of cognitive workload during cognitively challenging tasks to dual-task balance in individuals with PD. ICC results were higher than 0.75 in almost all conditions for both individuals with PD and healthy controls. The ICC for the dual-task eyes occluded condition in healthy controls was slightly lower (ICC of 0.74) than the other conditions. Visual inspection of the Bland-Altman graphs (Figure 2) shows that healthy controls had increased pupillary response in their second testing compared to the first time in the dual-task eyes occluded condition. This increased response at the re-test may have contributed to the slightly lower ICC. Although the conditions were randomized for each subject, due to a possible adaptation and test effect, we expected a decreased pupillary response in the second testing compared to the first. A possible explanation of increased pupillary response during the second testing in healthy controls could be they had greater engagement with

the task to perform more successfully compared to the first time. Visual inspection of the Bland-Altman plots did not show any evidence of adaption, test, or practice effect in PD.

We expected to find correlations between pupillary response and the total score of the NASA-TLX (self-reported cognitive workload). However, pupillary response failed to correlate with the total score of the NASA-TLX in any of the conditions for either group. The NASA-TLX was designed to assess self-reported cognitive workload using multidimensional components of mental, physical and temporal task demand, effort, frustration, and perceived performance[79]. However, one of the limitations of NASA-TLX is that it provides a snapshot of perceived cognitive workload rather than a continuous measurement. In our study, we conducted NASA-TLX at the end of each task which possibly led to a recency effect of the measurement. There is a possibility that individuals rate their perceived cognitive workload based on their experience at the end of the task. Therefore, important information might be lost by using NASA-TLX which might explain the lack of correlation between pupillary response and total score of NASA-TLX.

In the secondary analysis, we found that pupillary response positively and significantly correlated with the mental demand subitem during dual-task eyes occluded in both groups. However, there were no correlations between pupillary response and other subitems of the NASA-TLX. It is known that pupillary response is an objective indicator of mental effort in response to incremental task demand[186]. Our findings suggest that pupillary response reflects a unidimensional construct of cognitive workload, i.e., mental demand, and may not be sensitive to other components of cognitive workload related to physical demand, temporal demand, effort, frustration, and perceived performance. Taken together, our results show that pupillary response is a reliable neurophysiological tool of cognitive workload during dual-task balance in individuals with PD.

Assessment of pupillary response during dual-tasking may offer an inexpensive, less intrusive alternative to other neurophysiological tools, such as functional near-infrared spectroscopy or EEG, in unraveling brain-behavior interactions during dual-tasking in patients with PD. A better understanding of the neurophysiological mechanisms of dual-tasking in PD may inform more adequate assessment and treatment strategies to mitigate the effect of dual-tasking on balance and falls. This study builds a foundation to compare pupillary response during dual-task balance between individuals with PD and healthy controls.

4.4.1. Study Limitations

The current study has some limitations. We measured the test-retest reliability on the same day within two hours for each subject. In our results, we found excellent test-retest reliability overall in all conditions in individuals with PD. However, it is common to observe within-day fluctuations in cognitive and motor performance in people with PD[200,201]. To eliminate the within-day fluctuations, it might be better to evaluate between-day test-retest reliability in the future. However, our results show no impact of fluctuations of motor or cognitive performance on reliability of pupil response. Second, due to the multidimensional and self-reported nature of the NASA-TLX, we did not find any correlation between pupillary response and the total score of NASA-TLX during dual-task balance. However, we found that pupillary response significantly correlated with the mental demand subitem of NASA-TLX during dual-task eyes occluded condition. Future research is therefore warranted to validate the pupillary response against other neurophysiological tools such as EEG or functional near-infrared spectroscopy during dual-task balance in individuals with PD.

4.5. Conclusion

The current study demonstrated that pupillary response during dual-task balance represents a stable index. In the future, pupillary response might be used to interpret brain-behavior interaction in real-life circumstances including dual-task balance conditions in individuals with PD.

Chapter 5

Pupillary Response to Dual-Task Balance in Parkinson's Disease: Implications for Falls

Abstract

Purpose: Individuals with Parkinson's disease (PD) are more prone to falling, resulting in decreased quality of life and loss of independence. Although decrements in dual-task balance have shown promise to predict falls, little attention has been given to the underlying neurophysiological mechanisms of falls. The purpose of this study was to investigate neurophysiological changes, indexed by pupillary response, during dual-task balance between three groups: PD fallers; PD non-fallers; and healthy controls.

Methods: Thirty-three individuals with PD (age: 69.30 ± 6.78, 14 female) and 35 age- and sex-matched healthy controls (age: 68.54 ± 6.22, 21 female) were recruited. Participants with PD were categorized into fallers (number of falls>0) or non-fallers (number of falls=0) based on their self-reported fall history in the past 12 months. The four balance conditions lasted 60 seconds and involved (1) single balance task with eyes open; (2) single balance task with eyes occluded; (3) dual-task with eyes open; (4) dual-task with eyes occluded. The dual-task comprised the Auditory Stroop test. Pupillary response was recorded using an eyetracker (Tobii Technology AB, Sweden). Balance was assessed by using a force plate (Advanced Mechanical Technology, USA). Two-way Repeated Measures ANOVA and LSD post-hoc tests were employed to compare pupillary response and Center of Pressure (CoP) displacement across the four conditions and between the three groups.

Results: Pupillary response was significantly different between the groups ($p=0.009$). Pupillary response significantly increased with increased difficulty of the conditions ($p<0.001$). Post-hoc analysis demonstrated PD non-fallers (mean±s.d.) (0.43±0.2) exhibited greater pupillary response compared to PD fallers (0.38±0.2) and healthy controls (0.34±0.1) across conditions.

CoP displacement in the anterior-posterior direction showed significant condition ($p=0.04$) and group ($p<0.001$) effects.

Conclusion: Overall, the PD group had increased neurophysiological response, measured by pupillary response, and increased CoP displacement during dual-task balance compared to the healthy controls. Interestingly, PD non-fallers had higher neurophysiological response compared to PD fallers. This might suggest that PD fallers have limited cognitive capacity to perform similarly on dual-task balance compared to PD non-fallers and healthy controls which leads to a higher risk for falls. Future studies are needed to investigate whether pupillary response can be used to predict falls.

5.1. Introduction

Falls are a common problem for individuals with Parkinson's disease (PD). A fall is defined as an event in which an individual comes to rest involuntarily on a lower surface, such as the ground or floor[202]. It has been reported that 50 – 68% of the PD population fall annually[17], which is three times more often than the fall rate of the older population[18]. In addition, 67% fallers in the PD population fall more than once since diagnosis[203]. The increased rate of falls is a concern because they suggest that individuals with PD have impaired skills to timely react and initiate appropriate compensatory postural strategies to prevent falls[204].

Degeneration of the automatic control process due to dopamine deficiency in the striatum contributes to falls in individuals with PD[205]. Most activities of daily living require performing two tasks simultaneously[35] such as standing while talking. In such dual-tasking conditions, upright stance posture is a basic, yet essential motor skill to accomplish various motor and cognitive tasks concurrently[36]. Although maintaining an upright stance posture seems autonomous and effortless in healthy individuals, it may become challenging and cognitively effortful due to impaired autonomic control process in individuals with PD[27]. The assessment of cognitive-motor dual-tasking is of great interest in gaining a better understanding of brain-behavior interactions and for improving the diagnosis, prevention, and management of cognitive impairment and falls[206]. The neurophysiological mechanisms associated with increased fall risk are important to understand, as detecting changes in neurophysiology may facilitate earlier identification of individuals who are at risk for falls.

Pupillary response is a non-intrusive, real-time neurophysiological measure of cognitive workload[72]. The reliability and validity of pupillary response to measure cognitive workload are

well established[207,208]. There is a linear relationship between increased pupillary response and increased cognitive workload in healthy individuals[54-56]. In addition, pupillary response increases with increased task difficulty among different cognitive tasks, including short-term memory[57,58], arithmetic[58,59], digit span[60], sentence comprehension[61], and perceptual matching[59]. Pupillary response, therefore, reflects real-time, objective, complexity-, and mental effort-related aspects of cognitive workload. The mechanism of the pupillary response is explained as increased activation of the locus coeruleus—a small nucleus in the brainstem—due to increased cognitive workload[55,64]. The locus coeruleus plays an essential role in the regulation of physiological arousal[65] and cognition[66]. Increased cognitive workload leads to the activation of locus coeruleus that subsequently sends inhibitory projections to the parasympathetic Edinger-Westphal nucleus. Activation of the Edinger-Westphal nucleus leads to the inhibition of the sphincter pupillae muscle, resulting in pupil dilation[67]. The activity of the locus coeruleus also leads to increased activation of the sympathetic nervous system, which results in additional pupil dilation due to the activation of the dilator pupillae muscle[65]. Both pupillary response and activation of noradrenergic neurons in the locus coeruleus have been shown to increase in a correlated manner with increased cognitive workload[68].

A previous study showed that pupillary response increases with incremental cognitive demand in individuals with PD supporting the hypothesis that pupillary response reflects cognitive workload (or mental effort) in individuals with PD[72]. The pattern of pupil response in PD to cognitive demand was similar to that of healthy controls, suggesting that early PD pathology does not affect the accuracy of pupillary response in challenging cognitive tasks. In addition, pupillary response has shown to reflect changes in cognitive workload from a single task to dual-task balance conditions in healthy young adults[187]. Pupillary response is a reliable and valid tool

of cognitive workload during dual-task balance in individuals with PD[209]. However, it is not known whether pupillary response is different between PD fallers, PD non-fallers, and healthy controls. Recording pupillary response during dual-task balance provides continuous monitoring of the neurophysiological response of the brain which makes a substantial contribution to furthering our understanding of brain-behavior interactions in real-time.

The purpose of this study was to investigate neurophysiological changes, indexed by pupillary response, during dual-task balance between three groups: PD fallers; PD non-fallers; and healthy controls. We hypothesized that PD fallers would demonstrate higher pupillary response compared to PD non-fallers and healthy older adults.

5.2. Methods

Thirty-three individuals with PD and 35 age- and sex-matched healthy controls were recruited. Participants with PD were categorized into fallers (n=14, number of falls>0) or non-fallers (n=19, number of falls=0) based on their self-reported fall history in the past 12 months[210]. Patients with PD were recruited from the University of Kansas Medical Center Parkinson's Disease and Movement Disorder Center between 08/2018 and 02/2019. Diagnosis of idiopathic PD was established according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [5]. Healthy controls were the spouse/significant others of the participants with PD or members of the community. The healthy control group was matched with individuals with PD for age, sex, and cognitive status.

Inclusion criteria were (1) voluntary consent, (2) ability to speak and understand the English language, and (3) mild to moderate disease severity (Hoehn & Yahr stage II and III) for individuals with PD. Exclusion criteria were (1) diagnosis of mild cognitive impairment or

dementia, (2) atypical parkinsonism, (3) history of neurological or vestibular conditions unrelated to PD, (4) current visual acuity or visual field problems that cannot be resolved by corrective lenses, (5) severe trunk and head dyskinesia or dystonia in the medication "on" state, (6) blepharospasm, (7) deep brain stimulation, (8) unpredictable motor fluctuations, and (9) any musculoskeletal condition that might affect standing and balance activities.

This study was approved by the Human Subjects Committee at the University of Kansas Medical Center. Participants were asked to make one visit to the University of Kansas Medical Center Parkinson's Disease and Movement Disorder Center. Prior to enrollment written informed consent was obtained from all study participants. Study testing lasted for total of three hours including consent and breaks. All assessments were done in the medication "on" state. Participants with PD were tested approximately 30 to 45 minutes after medication intake in order to minimize the possibility of wearing-off which could potentially affect the test results. If the medication wore off during the assessment, the assessment was stopped until approximately 30 minutes after the next medication dose when the participant was again in the medication "on" state.

Demographic characteristics and medical history were collected from the participants. A list of prescribed and unprescribed medications was obtained from the participants' medical records. Levodopa Equivalent Daily dose was calculated to tally antiparkinsonian related medication usage[188]. Global cognitive functioning was measured through the Montreal Cognitive Assessment (MoCA)[189]. Restrictions in activities of daily living and motor impairments were evaluated through the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II (motor experiences of daily living) and Part III (motor examination)[190]. The Hoehn and Yahr (H&Y) Scale[191] was used to assess PD severity. The Scales for Outcomes

in Parkinson's Disease- Autonomic Dysfunction (SCOPA-AUT)[192] was conducted to assess autonomic symptoms as dysautonomia may potentially influence pupillary response in PD.

All participants were asked to wear Tobii Pro 2 glasses (Tobii Technologies, Inc.) to measure pupillary response during the testing. Participants were tested in a room with no windows. The temperature and lighting conditions of the room were identical for each participant. Participants were asked to complete the following conditions in randomized order.

1. Single balance eyes open condition: Participants stood on a force plate (AMTI OPT464508-1000, Advanced Mechanical Technology, Inc.) and maintained an upright standing posture for 60 seconds.

2. Single balance eyes occluded condition: Participants stood on a force plate for 60 seconds while their eyes were occluded with a sleep mask.

3. Dual-task eyes open condition: Participants stood on the force plate for 60 seconds while concurrently completing an Auditory Stroop test.

4. Dual-task eyes occluded condition: Participants stood on a force plate for 60 seconds while simultaneously completing an Auditory Stroop test with their eyes occluded.

Auditory Stroop test was shown to be one of the key determinants of dual-task performance in individuals with PD[38]. Therefore, in this study, the Auditory Stroop test was conducted to stress the executive function and cognitive flexibility abilities of the participants. During the Auditory Stroop test, participants heard the word "high" or "low" in a high or low pitch and were instructed to name the pitch of the stimulus, while ignoring the meaning of the word. Participants heard congruent stimuli where the word and pitch are equal (e.g. "high" at a high pitch) or

incongruent stimuli where the word and pitch differ (e.g., “high” at a low pitch) in a random order for 60 seconds. There were 30 stimuli presented at 2-second intervals for 60 seconds. Participants were instructed to respond as accurately and as fast as possible. To standardize the test, participants wore headphones and the stimuli were played by a digital recorder.

After testing, the pupillary response data was extracted from EyeWorks Analyze software. By solely measuring the change of the raw pupil size, there are potential limitations such as the light reflex interfering with the pupil size and movement artifacts. To combat this potential problem, the Index of Cognitive Activity algorithm was utilized through the EyeWorks Analyze software[39]. This algorithm computes the number of unusual increments in pupil size per second. These values are then transformed into a continuous scale ranging between 0 (no cognitive workload) and 1 (maximum cognitive workload). Based on this algorithm the noisy signals are reduced to nearly zero[39]. The mean ICA was calculated after each condition for all groups. In order to further eliminate the effect of lighting on pupillary response, the testing was done in a room without any windows and controlled lighting.

In addition, the Center of Pressure (CoP) displacement in the anterior-posterior (AP) and medio-lateral (ML) directions were calculated for each condition. Falls related outcomes were measured through wireless APDM Movement Monitoring inertial sensor system (APDM Inc., Portland, OR, USA). After calibration, six synchronized Opal inertial sensors were fitted on each participant via elastic straps (sternum, waist (at the level of the fifth lumbar spine), dorsal surface of bilateral wrists and top of each foot). Participants were asked to complete the Timed Up and Go (TUG) test and TUG-cognitive (TUG-COG) while wearing the sensors. TUG is a widely used, reliable, and valid test to examine functional mobility and falls risk in individuals with PD[211]. This test also assesses multiple postural components such as balance control, physical

mobility, and gait. Participants were asked to sit on a chair to start the TUG test and instructed to stand up from the chair, walk 3 meters at normal speed, turn back, walk back to the chair and then sit down. The test was done three times and the average turning and completion time was calculated. It has been shown that both TUG turning duration and TUG completion time provide a better understanding of functional impairments and falls risk in individuals with PD[212]. During TUG-COG, individuals were asked to count backward by 7 starting from a random three-digit number while standing up from the chair, walking 3 meters at normal speed, turning back, walking back to the chair and then sitting down. The TUG-COG was done three times and average turning and completion times were calculated. Signals were automatically processed and calculated via the corresponding Mobility Lab™ software package. Lastly, fear of falling was measured through the Falls Efficacy Scale-International (FES-I)[213].

5.2.1. Statistical Analysis

One-way Analysis of Variance (ANOVA) was used to compare demographic and clinical variables between PD fallers, PD non-fallers, and healthy controls. Fisher's exact test was used to compare nominal variables. Independent t-tests were used to compare disease-specific variables between PD fallers and PD non-fallers. Two-way Repeated Measures ANOVA and LSD post-hoc tests were employed to compare pupillary response and CoP displacement across the four conditions and between the three groups. Pearson's correlation was used to analyze the relationship between pupillary response and CoP displacement. The results were interpreted as follows: >0.70 is strong, 0.50–0.70 is moderate, 0.30 – 0.50 is weak[196]. All statistical analyses were performed with the IBM SPSS Statistics v.23 software (IBM, Armonk, NY, USA). P-values < 0.05 were considered statistically significant.

5.3. Results

A summary of the demographic and clinical characteristics of the three groups are shown in Table 1. PD fallers and PD non-fallers were in a mild to moderate disease severity based on the H&Y stage (PD fallers n=9 in H&Y stage II, n=5 H&Y stage III; PD non-fallers n=15 H&Y stage II, n=4 H&Y stage III) and MDS-UPDRS II and III scores. There were no significant differences in demographic variables between the groups except that healthy controls had more years of education compared to PD non-faller (post-hoc p value = 0.01). The results of the falls-related outcomes demonstrated that PD fallers had significantly higher FES-I score, TUG turning and completion time, and TUG-COG turning time compared to the PD-non-fallers and healthy controls. However, there was no significant difference in the TUG-COG completion time between the groups.

Table 1. Demographic and clinical characteristics

Variables	PD fallers (n=14)	PD non-fallers (n=19)	Healthy controls (n=35)	p-value
Age (years)	69.93 ± 6.8	68.84 ± 6.9	68.54 ± 6.22	0.79
Sex (female/male, n)	7/7	7/12	21/14	0.26
Education (years)	15.16 ± 2.24	15.50 ± 2.06	17.31 ± 3.53	0.02
MoCA	26.84 ± 3.79	26.29 ± 2.26	26.60 ± 2.31	0.85
MDS-UPDRS II	14.36 ± 8.30	10.11 ± 7.90	N/A	0.14
MDS-UPDRS III	47.46 ± 12.41	41.47 ± 16.38	N/A	0.26
Modified H & Y scale	2.43 ± 0.64	2.21 ± 0.41	N/A	0.24

LED (mg)	312.22 ± 302.16	294.47 ± 236.82	N/A	0.87
SCOPA-AUT	16.64 ± 10.22	14.32 ± 8.20	N/A	0.47
FES-I	30.64 ± 11.59	23.26 ± 7.54	18.34 ± 2.05	<0.001
TUG turning time (sec)	2.76 ± 0.53	2.59 ± 0.58	2.27 ± 0.34	0.003
TUG total time (sec)	15.01 ± 5.16	13.21 ± 3.24	11.65 ± 1.83	0.005
TUG-COG turning time (sec)	2.79 ± 0.54	2.62 ± 0.56	2.35 ± 0.38	0.02
TUG-COG total time (sec)	15.82 ± 4.33	17.34 ± 12.14	14.44 ± 5.38	0.44

PD = Parkinson's disease; MoCA = Montreal Cognitive Assessment; MDS-UPDRS II = Movement Disorder Society Unified Parkinson Disease Rating Scale motor experiences of daily living; MDS-UPDRS III = Movement Disorder Society Unified Parkinson Disease Rating Scale motor examination; H &Y = Hoehn and Yahr; LED = Levodopa Equivalent Dose; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; N/A = Not Applicable. FES-I= Falls Efficacy Scale-International, TUG= Timed Up and Go; TUG-COG= Timed Up and Go-Cognitive. The results are presented as mean ± standard deviation except for the sex variable

The two-way repeated measures ANOVA showed that there was a significant difference between the groups demonstrating that individuals with PD had higher pupillary response compared to older adults ($p=0.009$). In addition, a significant condition effect was observed indicating that pupillary response increased with increased task difficulty ($p<0.001$). The post-hoc analysis demonstrated that pupillary response significantly increased from single balance eyes open to single balance eyes occluded ($p<0.001$) as well as from dual-task eyes occluded to dual-task eyes occluded conditions ($p<0.001$). In addition, there was a significant difference on pupillary response from single balance eyes open to dual-task eyes open condition ($p= 0.01$) but not from

single balance eyes occluded to dual-task eyes occluded condition (p=0.48). In addition, there was no interaction effect (group x condition) (p=0.06), suggesting that the pupillary response to task demand was similar in both participants with PD and healthy controls (Figure 1).

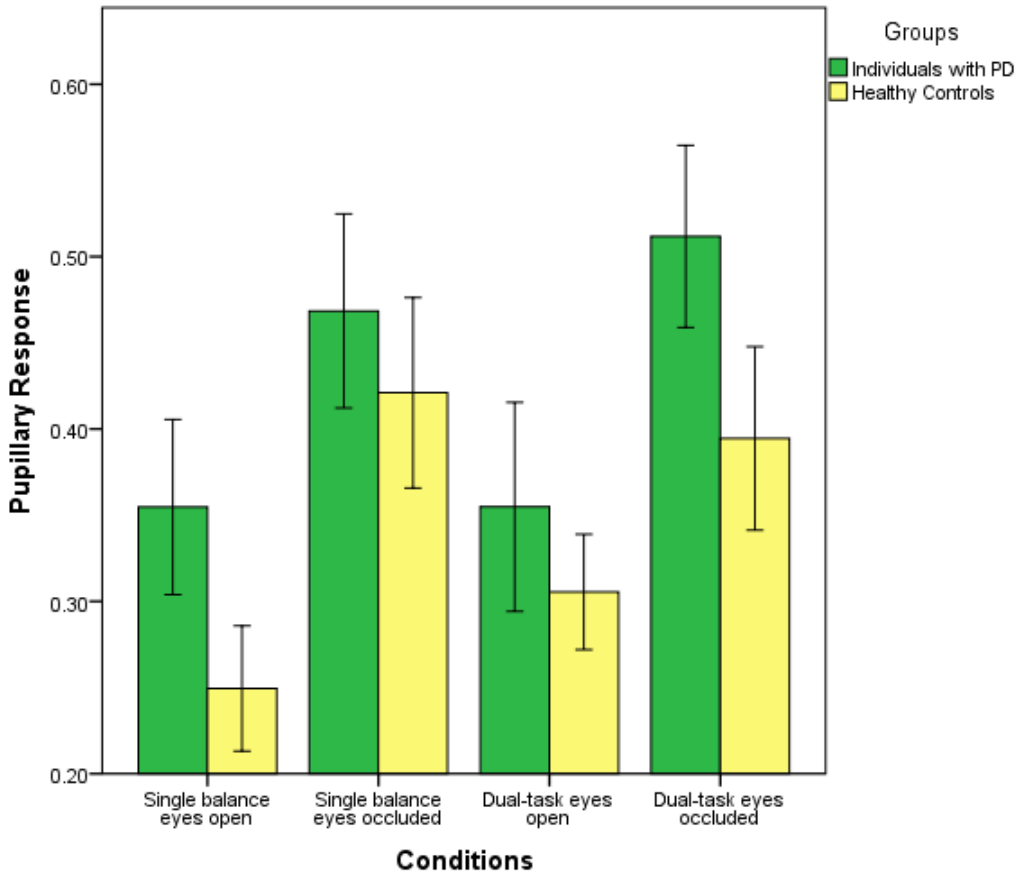

Figure 1. Mean values (range 0 – 1) and standard error of the mean (SEM) of pupillary response of PD group and healthy controls across the conditions

Pupillary response was significantly different between the groups (p<0.001). The post-hoc analysis demonstrated PD non-fallers exhibited greater pupillary response compared to healthy controls (p=0.001). In addition, PD fallers had higher pupillary response compared to healthy controls (p=0.01). Although there was no significant difference between PD non-fallers and PD fallers across the conditions (p=0.25), the comparison of mean and standard deviation demonstrated that PD non-fallers (mean±s.d.) (0.43±0.2) exhibited greater pupillary response

compared to the PD fallers (0.38±0.2) and healthy controls (0.34±0.1) across the conditions. Pupillary response significantly increased with increased difficulty of the conditions especially from eyes open to eyes occluded conditions ($p<0.001$). However, no interaction effect was observed ($p=0.77$) (Figure 2).

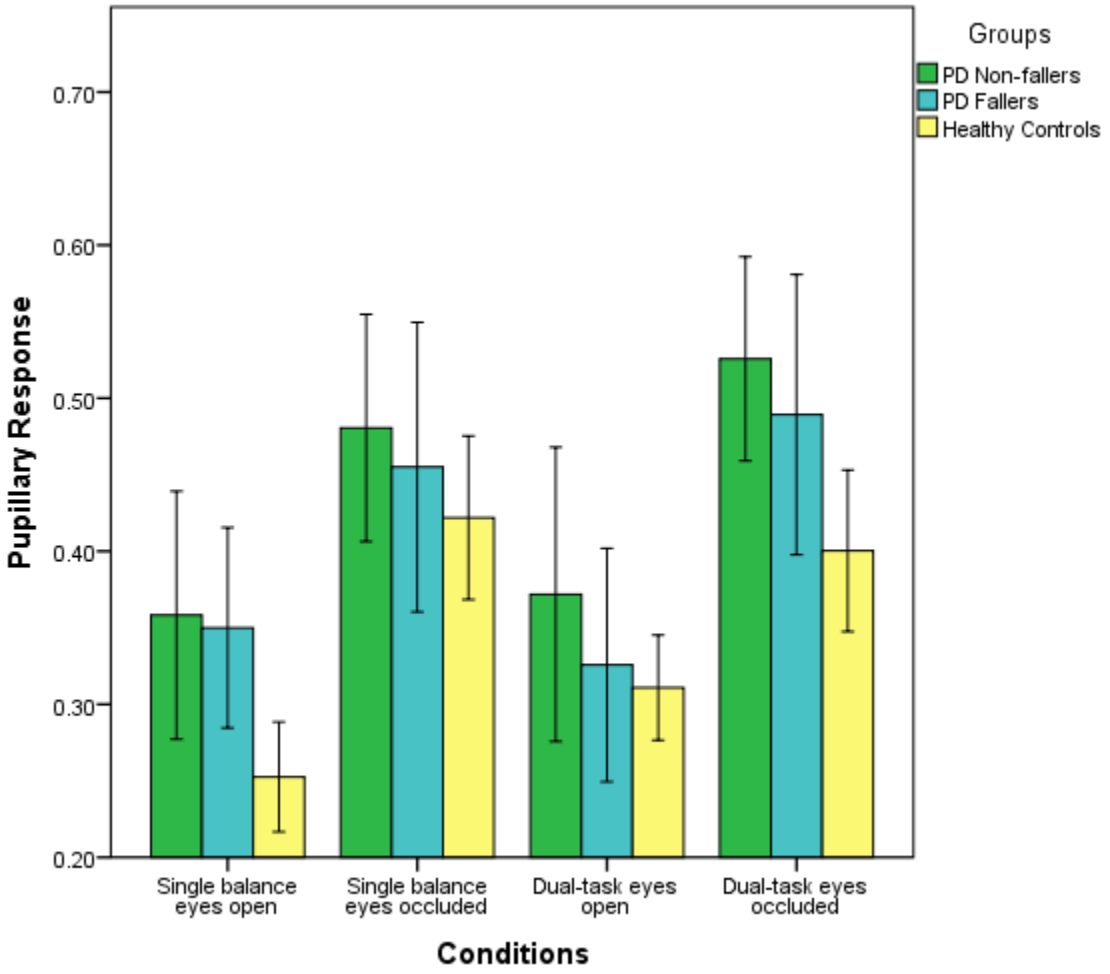

Figure 2. Mean values (range 0 – 1) and standard error of the mean (SEM) of pupillary response of PD fallers, PD non-fallers and healthy controls across the conditions

CoP displacement in the AP direction was significantly different between the three groups ($p<0.001$). The post-hoc analysis demonstrated there was a significant difference between PD non-fallers and healthy controls ($p=0.001$) as well as between PD fallers and healthy controls

(p=0.001). However, there was not any difference between PD non-fallers and PD fallers (p=0.61). In addition, a significant condition effect was observed (p=0.04) indicating that there was a greater CoP displacement from single balance eyes open to single balance eyes occluded condition (p=0.04). However, there were no significant differences across the rest of the conditions. Lastly, no interaction effect was observed between groups and conditions. (p=0.48) (Figure 3).

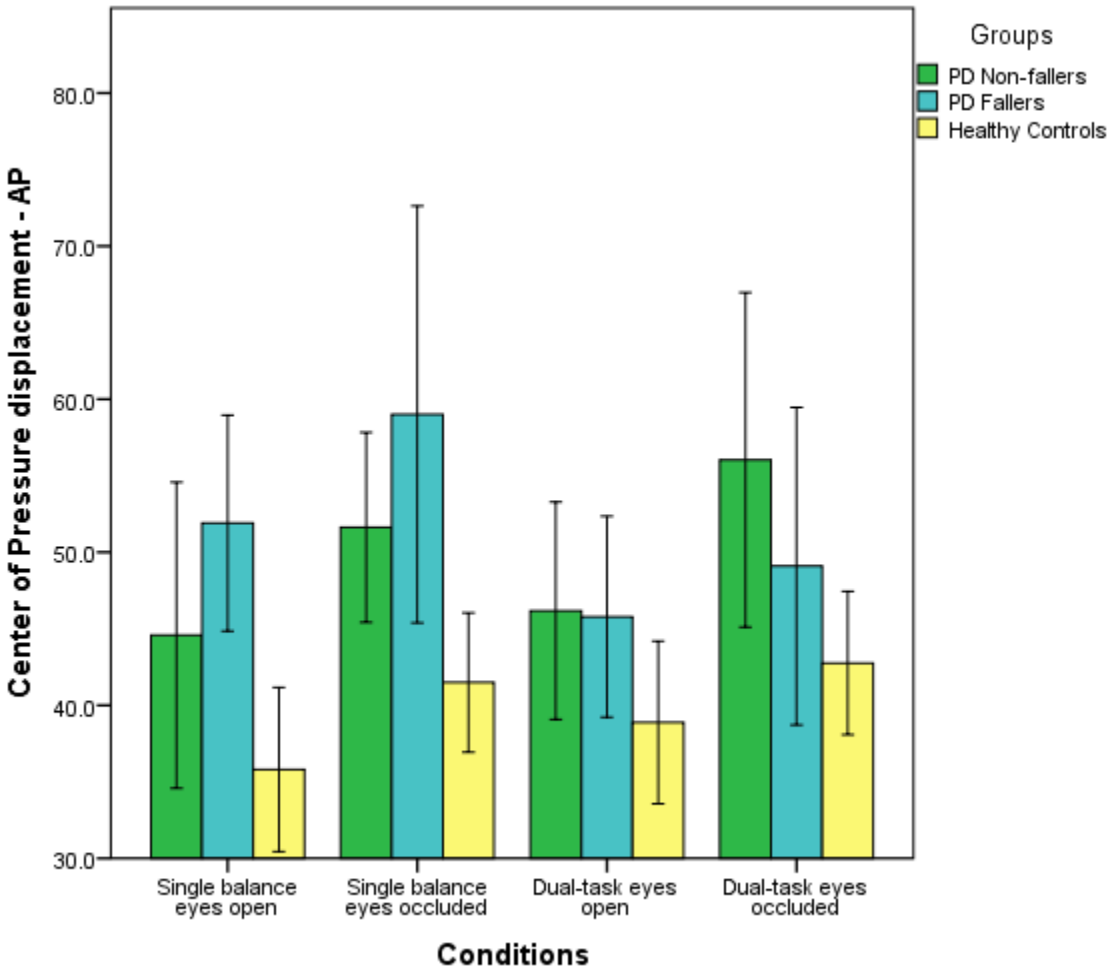

Figure 3. Mean values (in mm) and standard error of the mean (SEM) of Center of Pressure displacement in the Anterior-Posterior (AP) direction of PD fallers, PD non-fallers and healthy controls across the conditions

There was a moderate positive correlation between pupillary response and CoP displacement in PD fallers group during single balance eyes occluded (r=0.50; p=0.15) (Figure 4).

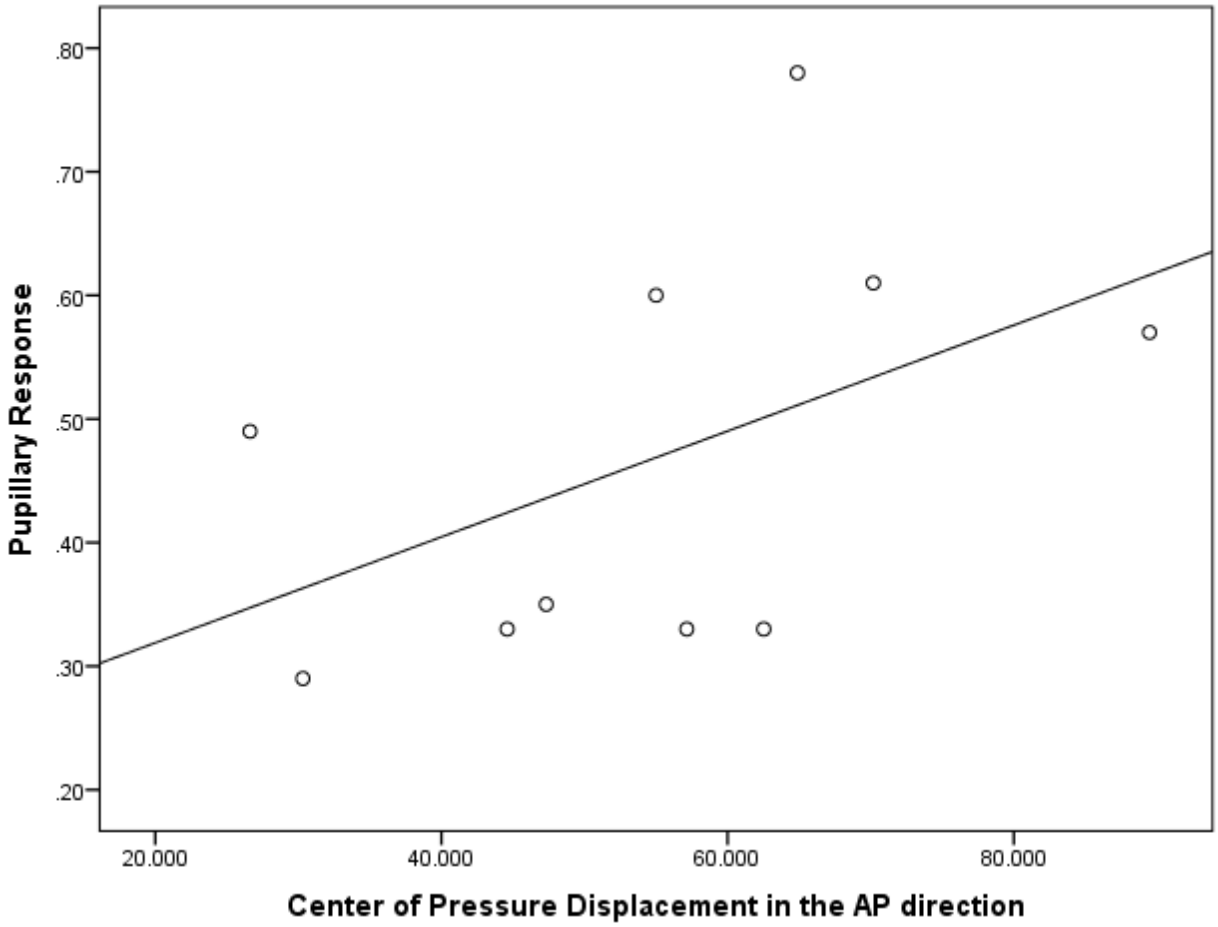

Figure 4. Correlation analysis between pupillary response and CoP displacement in PD fallers

Also, a moderate negative correlation was observed between pupillary response and CoP displacement in healthy controls during single balance eyes occluded (r=-0.51; p=0.006) (Figure 5). No other moderate or strong correlations were observed between pupillary response and COP displacement.

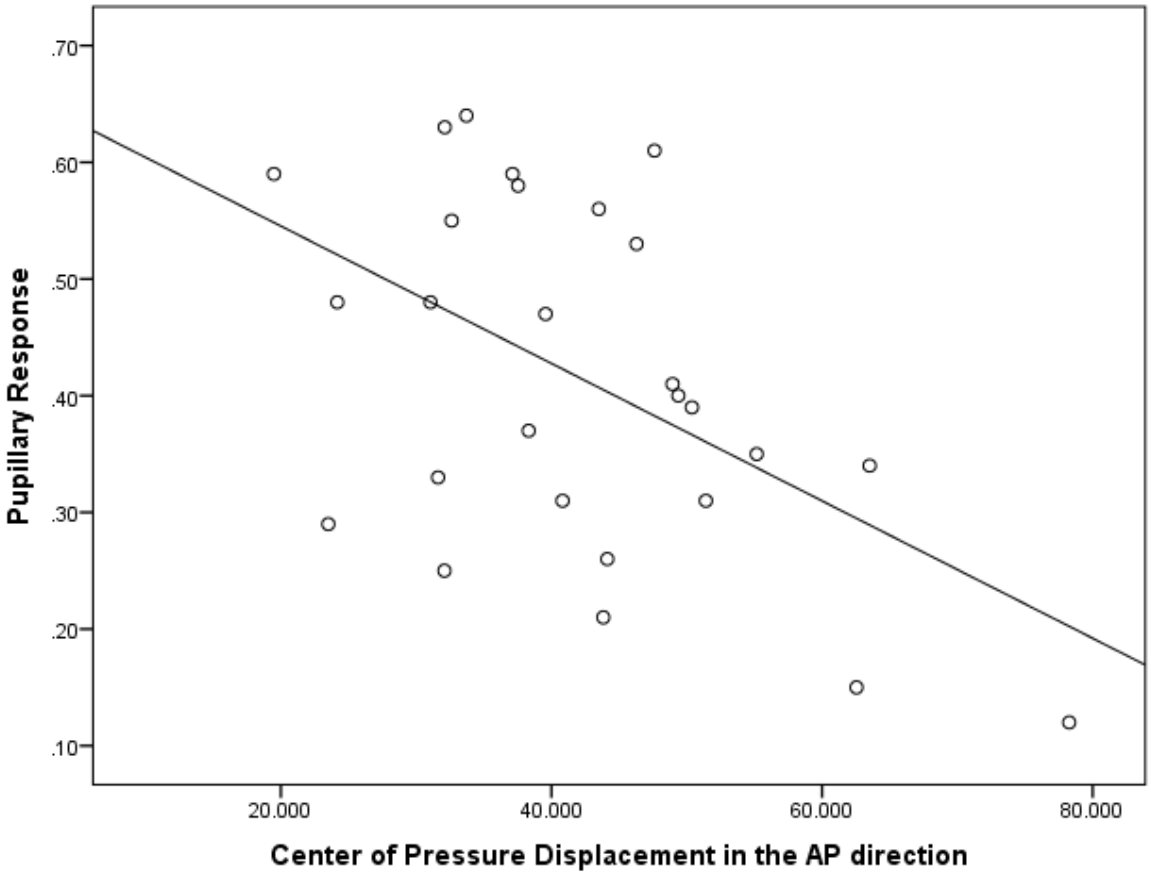

Figure 5. Correlation analysis between pupillary response and CoP displacement in healthy controls

5.4. Discussion

To our knowledge, this is the first study that investigated pupillary response as a metric of cognitive workload during dual-task balance in individuals with PD. The findings of this study demonstrated that, overall, individuals with PD exhibited higher cognitive workload measured by pupillary response compared to age- and sex-matched healthy controls during all conditions. Interestingly, although the results were not significant, PD non-fallers exhibited higher pupillary

response compared to PD fallers and healthy controls. In addition, a significant condition effect was observed suggesting that all groups displayed increased pupillary response from single balance eyes open to dual-task eyes open condition and from eyes open to eyes occluded conditions. Finally, PD fallers and PD non-fallers demonstrated higher CoP displacement compared to healthy controls.

In the current study, although the results were not significant, PD non-fallers exhibited higher pupillary response compared to PD fallers and healthy controls. This was unexpected since previous studies have shown that PD fallers and older adults who are fallers had higher brain activation in the prefrontal cortex measured by functional near-infrared spectroscopy (fNIRS) compared to their non-fallers group during dual-task gait activities[206,214]. These studies suggested that individuals who are fallers need to use additional brain networks from to prefrontal cortex as a compensatory strategy to maintain their motor activity. In our study, we used pupillary response to understand cognitive workload which has a greater temporal resolution compared to fNIRS during cognitive attention test[53]. Therefore, it is possible that pupillary response better corresponds to the timing of the actual brain activity compared to the fNIRS. In addition, none of the studies have measured the overall cognitive capacity for individuals with PD. It is possible that due to neurodegeneration process individuals might have decreased cognitive capacity and perhaps PD fallers greatly affected compared to PD non-fallers. This might suggest that PD fallers have limited cognitive capacity to perform similarly on dual-task balance compared to the PD non-fallers and healthy controls which leads to a higher risk for falls.

In addition, pupillary response significantly increased from single balance eyes open to dual-task eyes open condition as well as single balance eyes open to single balance eyes occluded conditions. These results were also similar to the findings of CoP displacement. The results

indicate that individuals with PD needed to exhibit greater cognitive workload to maintain their balance with additional cognitive load and visual occlusion. Several studies reported dual-task interference when using the auditory Stroop test individuals with PD[38,215], and the Stroop test has been proposed as the cognitive test that most elicits cognitive-motor interference, which showed similar effect in our cohort. Also, we found that visual occlusion had a greater effect on increased cognitive workload. A study has shown that balance performance was negatively affected by visual occlusion but no changes were observed from single standing to dual-task standing[216]. Our results demonstrated similar findings which might suggest that postural balance is greatly affected by additional cognitive load and visual occlusion in a cohort of mild to moderately affected individuals with PD.

PD fallers and PD non-fallers had higher CoP displacement in the AP direction and worse falls-related outcomes compared to healthy controls. In the literature, similar results were published. Studies showed higher fear of falling, increased time to complete TUG and TUG-COG in PD fallers compared to the PD non-fallers[93,217]. In addition, Matinolli et al. demonstrated that individuals with PD who are fallers had higher postural sway and CoP displacement compared to the PD non-fallers and healthy controls[218]. However, Figure 3 demonstrated that PD fallers had increased CoP displacement during single tasks but showed decreased displacement during the dual-task conditions whereas PD non-fallers had a similar pattern of CoP displacement compared to healthy controls. This might suggest that PD fallers demonstrated a rigid posture to maintain their balance during dual-task activities. In PD it is typical to observe increased CoP displacement and postural sway during balance but also a high and unadaptable axial tone (rigidity) which both negatively impact postural balance[219]. Based on the results that we provided, increased rigidity perhaps contributes more to falls which suggests that PD fallers are

unable to react and initiate appropriate compensatory postural strategies to prevent falls. It is also possible that due to increased cognitive workload during dual-task eyes occluded condition PD fallers were unable to carry the tasks at the same time, therefore, they demonstrated increased rigidity as a worse postural balance outcome.

Lastly, it is important to couple behavioral and neurophysiological results to increase our understanding of brain-behavior interaction. A moderate positive correlation was observed between pupillary response and CoP displacement in PD fallers group whereas a moderate negative correlation was observed between pupillary response and CoP displacement in healthy controls during single balance eyes occluded. These results might suggest that neurophysiological and behavioral results provide different aspects of individual's performance and may complement each other in the interpretation of brain-behavior models.

This study has several limitations. PD fallers and non-fallers were grouped based on their self-report of falls. However, the falls-related outcomes demonstrated that PD fallers had significantly higher TUG and TUG-COG completion time and fear of falling compared to PD non-fallers and healthy controls. Therefore, we assume that individuals were assigned to correct groups based on their self-reported falls. In addition, we did not measure cognitive capacity through questionnaires such as the cognitive reserve index questionnaire[220]. Although we measured subjects' global cognitive functioning and years of education to better understand the cognitive capacity it would be better to use a comprehensive questionnaire. Future studies might consider measuring cognitive capacity to better understand the neurophysiological response of the brain to cognitive or motor tasks in aging and age-related neurodegenerative conditions.

5.5. Conclusion

Overall, the PD group had increased neurophysiological response, measured by pupillary response, and increased CoP during dual-task balance compared to the healthy controls. Interestingly, PD non-fallers had higher neurophysiological response compared to the PD fallers. This might suggest that PD fallers have limited cognitive capacity to perform similarly on dual-task balance compared to the PD non-fallers and healthy controls which leads to a higher risk for falls. Pupillary response is a non-intrusive, objective, and cost-effective neurophysiological measure that reflects cognitive workload. In the future, pupillary response can be a potential tool to predict falls through understanding the neurophysiological underpinnings of dual-task balance deficiency in the PD population.

Chapter 6

Discussion and Conclusion

6.1. Summary of Findings

This body of research extended the usage of pupillary response as a metric of cognitive workload during cognitive testing to a rehabilitation research setting. To our knowledge, this is the first study that investigated pupillary response as a metric of cognitive workload during dual-task balance in healthy adults and in individuals with Parkinson's disease (PD). Previous studies mainly used functional near-infrared spectroscopy or electroencephalogram as a neurophysiological tool to understand brain activity in aging and age-related neurodegenerative conditions. Pupillary response is cost-effective, less intrusive, and easy to implement in clinical settings compared to electroencephalogram and functional near-infrared spectroscopy.

In summary, we found that pupillary response is a reliable and valid measure of cognitive workload during dual-task balance in both healthy controls and in individuals with PD. In addition, the findings of this research project demonstrated that individuals with PD exhibited higher cognitive workload measured by pupillary response compared to age- and sex-matched healthy controls during dual-task balance. Lastly, pupillary response significantly increased with increased task difficulty especially from single task to dual-task as well as from eyes open to eyes occluded conditions in both individuals with PD and healthy controls.

6.1.1. Chapter 2: Brain Activity during Dual Task Gait and Balance in Aging and Age-Related Neurodegenerative Conditions: A Systematic Review

The aims of this systematic review were to investigate (1) real-time brain activity during dual task gait and balance, (2) whether changes in brain activity correlate with changes in behavioral outcomes in older adults and people with age-related neurodegenerative conditions. PubMed, PsycINFO, and Web of Science were searched from 2009 to 2019 using the keywords dual task,

brain activity, gait, balance, aging, neurodegeneration, and other related search terms. A total of 15 articles were included in this review. Functional near-infrared spectroscopy and electroencephalogram measures demonstrated that older adults had higher brain activity, particularly in the prefrontal cortex (PFC), compared to young adults during dual task gait and balance. Similar neurophysiological results were observed in people with age-related neurodegenerative conditions. Few studies demonstrated a relationship between increased brain activity and better behavioral outcomes. This systematic review supports the notion that aging and age-related neurodegenerative conditions are associated with neuronal network changes, resulting in increased brain activity specifically in the PFC. Further studies are warranted to assess the relationship between increased PFC activation during dual task gait and balance and behavioral outcomes to better optimize the rehabilitation interventions.

Another important finding of this systematic review was that functional near-infrared spectroscopy and electroencephalogram were the mostly used neurophysiological tools to assess brain activity during dual-task balance and gait. However, none of the studies used pupillary response as a neurophysiological tool to understand brain activation. Pupillary response is a neurophysiological tool that has features of being cost-effective, easy to implement, and less intrusive compared to the other two neurophysiological tools. The limited intrusiveness of pupillary response allows for monitoring of cognitive workload during complex activities of daily life such as dual-task balance.

6.1.2. Chapter 3: Increased Postural Demand is Associated with Greater Cognitive Activity in Healthy Young Adults: A pupillometry study

Balance tasks require cognitive resources to ensure postural stability. Pupillometry has been used to quantify cognitive loads of various cognitive tasks but has not been studied in postural control.

The current investigation utilized pupillometry to quantify the cognitive loads of postural control in healthy young adults. We hypothesized that cognitive workload, indexed by pupil size, will increase with challenging postural control conditions including visual occlusion and additional cognitive load.

Twenty-one young healthy adults [mean ± standard error of the mean], [age = 23.2 ± 0.49 years; 12 females] were recruited for this study. Participants completed four tasks: (1) standing with eyes open; (2) standing with eyes occluded (3) standing with eyes open while performing an auditory Stroop task; and (4) standing with eyes occluded while performing an auditory Stroop task. Participants wore eye-tracking glasses while standing on a force platform. The eye-tracking glasses recorded changes in pupil size that in turn was converted into the Index of Cognitive Activity [ICA]. ICA values were averaged for each eye and condition. A two-way Analysis of Variance with post-hoc Sidak correction for pairwise comparisons was run to examine the effect of visual occlusion and additional cognitive load ICA value as well on the Center of Pressure [CoP] sway velocity in anterior-posterior [AP] and medio-lateral [ML] directions. Pearson's correlation coefficient was utilized to determine the relationship between ICA values and CoP sway velocity.

Significant within-condition effect was observed with visual occlusion for the right eye ICA values [$p = 0.008$]. Right eye ICA increased from eyes open to eyes occluded conditions [$p = 0.008$]. In addition, a significant inverse correlation was observed between right eye ICA values and CoP sway velocity in the ML direction across all the conditions [$r = -0.25$, $p = 0.02$].

This study provides support for cognitive activity changes measured by pupillometry related to changes in postural control in healthy young adults. Through increasing postural demand by

visual occlusion, a greater pupil size [ICA] was observed possibly due to increased neural processing in the cerebral cortex to maintain posture. This study builds a foundation to implement a similar experimental design in healthy older individuals and individuals with neurological disorders to assess differences in cognitive activity related to aging and disease during challenging postural control tasks.

6.1.3. Chapter 4: Reliability and Validity of Pupillary Response during Dual-task Balance in Parkinson's Disease

Neurophysiological measures are increasingly used to investigate brain-behavior interactions. Preliminary studies have shown that pupillary response increases with postural demand, especially under dual-task conditions in healthy young adults. However, the reliability and validity of pupillary response during dual-task balance have not been established in individuals with PD. We hypothesized that pupillary response demonstrates excellent test-retest reliability and strong validity during dual-task balance conditions in individuals with PD.

In this cross-sectional study, subjects (n=33 PD, n=35 healthy controls) wore eye-tracking glasses to record the pupillary response during single balance eyes open; single balance eyes occluded; dual-task eyes open; dual-task eyes occluded. During the single balance task, subjects stood on the balance platform for 60 seconds with eyes open and eyes occluded. The dual-task involved standing on the balance platform while performing the Auditory Stroop test. After each condition, the National Aeronautics and Space Administration-Task Load Index (NASA-TLX) was administered to assess the self-reported cognitive workload. To examine the test-retest reliability of the pupillary response, the conditions were administered twice for each subject within two hours. Intraclass correlation coefficients (ICC) were used to analyze the test-retest

reliability of pupillary response in each condition for both groups. Pearson's r correlation was used to assess the convergent validity of pupillary response against NASA-TLX.

The test-retest reliability was excellent for both groups in almost all conditions (ICC > 0.75). There were no correlations between pupillary response and NASA-TLX. However, increased mental demand (one of the subitems of NASA-TLX) significantly correlated with increased pupillary response in individuals with PD ($r = 0.38$, $p = 0.03$).

In summary, pupillary response showed excellent test-retest reliability and validity during dual-task balance for individuals with PD and healthy controls. Overall, these results suggest that pupillary response represents a stable index of cognitive workload during dual-task balance in individuals with PD. In the future, pupillary response might be used to interpret brain-behavior interaction in real-life circumstances including dual-task balance conditions in individuals with PD.

6.1.4. Chapter 5: Pupillary Response to Dual-Task Balance in Parkinson's Disease: Implications for Falls

Individuals with Parkinson's disease (PD) are more prone to falling, resulting in decreased quality of life and loss of independence. Although decrements in dual-task balance have shown promise to predict falls, little attention has been given to the underlying neurophysiological mechanisms of falls. The purpose of this study was to investigate neurophysiological changes, indexed by pupillary response, during dual-task balance between three groups: PD fallers; PD non-fallers; and healthy controls.

Thirty-three individuals with PD and 35 age- and sex-matched healthy controls were recruited. Participants with PD were categorized into fallers (number of falls>0) or non-fallers (number of

falls=0) based on their self-reported fall history in the past 12 months. The four balance conditions lasted 60 seconds and involved (1) single balance task with eyes open; (2) single balance task with eyes occluded; (3) dual-task with eyes open; (4) dual-task with eyes occluded. The dual-task comprised the Auditory Stroop test. Pupillary response was recorded using an eyetracker (Tobii Technology AB, Sweden). The balance was assessed by using a force plate (Advanced Mechanical Technology, USA). Two-way Repeated Measures ANOVA and LSD post-hoc tests were employed to compare pupillary response and Center of Pressure (CoP) displacement across the four conditions and between the three groups.

Pupillary response was significantly different between the groups ($p=0.009$). Pupillary response significantly increased with the increased difficulty of the conditions ($p<0.001$). Post-hoc analysis demonstrated PD non-fallers (mean±s.d.) (0.43±0.2) exhibited greater pupillary response compared to the PD fallers (0.38±0.2) and healthy controls (0.34±0.1) overall the conditions. CoP displacement in the anterior-posterior direction showed significant condition ($p=0.04$) and group ($p<0.001$) effect.

Overall, the PD group had increased neurophysiological response, measured by pupillary response, and increased CoP displacement during dual-task balance compared to the healthy controls. Interestingly, PD non-fallers had higher neurophysiological response compared to the PD fallers. This might suggest that PD fallers have limited cognitive capacity to perform similarly on dual-task balance compared to the PD non-fallers and healthy controls which leads to a higher risk for falls. Future studies are needed to investigate whether pupillary response can be used to predict future falls.

6.2. Clinical Implications

Falls are considered to be the most severe complication of PD as they can lead to injuries, depression, fear of falling, morbidity, and even mortality. These complications can seriously affect the ability to perform activities of daily living, quality of life, and the life expectancy among individuals with PD. Dual-task interference is one predictor of falls in PD. However, the interpretation of dual-task interference has been heavily based on behavioral performance observations (i.e. center of pressure displacement) without having neurophysiological evidence regarding the brain response during dual-tasking. It has been demonstrated that during dual-tasking, individuals with PD had higher brain activation, measured by functional near-infrared spectroscopy, than their healthy peers to perform similarly on balance and gait activities. Therefore, investigating brain activation during dual-tasking might provide insight into the early pathogenesis of falls in PD. Pupillary response is cost-effective, easy to implement, and a non-intrusive neurophysiological tool to asses cognitive workload. The limited intrusiveness of pupillary response allows for monitoring of cognitive workload during complex activities of daily life such as dual-task balance.

Furthermore, the last decade has seen a tremendous number of research in the field of falling-risk detection, which are mainly based on behavioral measures and kinematic sensors. The behavioral measures and kinematic sensors are always behind a fall with risk assessment and fall recognition[221]. It has been shown that the best fall predictor is the history of falls in individuals with PD. Also, the kinematics fall detection sensors from impact shock of acceleration and velocity vector and suggested that such methods result in high false-positive rates[221]. However, the human central neural system controls complex sensorimotor function and regulates interactions for motor planning, execution, and sensor feedback. The human sensorimotor system shows remarkable skills in perceiving subtle balance changes[222]. Therefore, neurophysiological

tools may provide a better understanding of the human sensorimotor system. Because of its ability to detect subtle changes neurophysiological tools may detect falls risk before it happens. However, some of the challenges of using neurophysiological tools are need of special equipment, training of examiners, additional time to analyze the data, and not able to see the results immediately after the data collection.

This dissertation project examined the neurophysiologic response of the brain measured by pupillary response during dual-tasking conditions in PD. Applying pupillary response during dual-tasking provides continuous monitoring of the neurophysiological response of the brain which makes a substantial contribution to furthering our understanding of brain-behavior interactions in real-time. Due to its features of real-time and objective data outcomes it might be used as a biofeedback tool or to increase the rehabilitation outcomes in individuals with PD by determining the intensity, duration, and optimal time frame of the rehabilitation interventions.

6.3. Limitations

6.3.1. Reliability and Validity of Pupillary Response

In this body of research, we measured the test-retest reliability on the same day within two hours for each subject. In our results, we found excellent test-retest reliability overall in all conditions in individuals with PD. However, it is common to observe within-day fluctuations in cognitive and motor performance in people with PD. Although our results did not show evidence of fluctuations on cognitive workload, it might be better to evaluate between-day test-retest reliability in the future. Second, due to the multidimensional and self-reported nature of the NASA-TLX, we did not find any correlation between pupillary response and the total score of NASA-TLX during dual-task balance. However, we found that pupillary response significantly

correlated with the mental demand subitem of NASA-TLX during dual-task eyes occluded condition. Future research is therefore warranted to validate the pupillary response against other neurophysiological tools such as electroencephalogram or functional near-infrared spectroscopy during dual-task balance in both healthy adults and individuals with PD.

6.3.2. Self-reported falls

In this study, we relied on self-recall of falls to categorize PD subjects into fallers and non-fallers. A study demonstrated that there was a weak correlation between recording falls by weekly follow-up versus recall of falling for the past 6 or 12 months[223]. This weak correlation was mainly driven by individuals with cognitive impairments who have difficulties recalling their falls. In our sample, we included individuals who are not cognitively impaired (Montreal Cognitive Assessment > 25), which would increase the accuracy of the self-reported fall history in the past 6 months. In addition, the falls-related outcomes demonstrated that PD fallers had significantly higher Timed Up and Go and Timed Up and Go – Cognitive tests completion time and fear of falling compared to PD non-fallers and healthy controls. Therefore, we assume that individuals were assigned to correct groups based on their self-reported falls. In the future, it is recommended to follow-up individuals for at least 6 months to assign them into fallers or non-fallers groups.

6.3.3. The sample size for subgroup analysis

We subgrouped individuals into PD fallers and non-fallers group. Although not significant due to lack of power, we found that non-fallers had higher pupillary response during dual-task balance conditions compared to PD fallers. However, the sample size for these subgroups was not sufficient to find a significant difference between the groups. Based on the results of this study,

future studies should do a power analysis to find the required number of subjects to compare the pupillary response during dual-task balance between PD fallers and PD non-fallers.

Furthermore, based on the literature fallers have greater disease severity, motor impairments, low quality of life scores compared to the non-fallers[224]. Also, fallers reported dyskinesia, on-off phenomena meaning a noticeable improvement in function after taking levodopa, usage of more than three medications (polypharmacy), and impaired mood compared to non-fallers. Furthermore, it has been shown that fallers have greater autonomic symptoms such as dizziness while standing, palpitation, bowel and bladder dysfunction compared to non-fallers in the PD population[224]. Lastly, fallers reported greater fear of falling, anxiety, and self-perceived disability compared to the non-fallers[225]. In future studies, these confounding factors should be taken into account while designing fall prediction models in individuals with PD.

6.3.4. Spatial resolution

In our body of research, we found that pupillary response increased from single balance eyes open to single balance eyes occluded condition as well as from dual-task eyes open to dual-task eyes occluded conditions in healthy young adults, healthy older adults, and individuals with PD. Although we observed increased cognitive activity with visual occlusion during quiet standing, we did not capture activated areas of the brain during the conditions. A more robust design would be a combined approach in which electroencephalogram or functional near-infrared spectroscopy is used with pupillometry. This combined approach might increase the spatial resolution and provide data regarding the activated areas of the brain during postural demanding tasks.

6.4. Future Directions

6.4.1. Use of neurophysiological tools to predict falls in long-term in individuals with PD

Unpredictable postural perturbation is a common dangerous situation that changed the original dynamic balanced state of the body and could lead to a fall. Since walk path and speed are variant toward changing of target position and obstacle, the timing and force of postural perturbation are always unexpected[173]. Thus, postural perturbation caused falls risk cannot be ignored for individuals with PD since they present motor impairments. In recent years, the involvement of the cerebral cortex in maintaining postural control has been consistently shown in many studies using electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS). Due to its high temporal resolution, EEG turned out to be particularly suitable to study cortical activities related to perturbations by using the analysis of the perturbation-evoked potentials (PEP), which is a type of event -related potentials[173]. Studies have shown that when postural control is threatened by a perturbation, PEP N1 component can be observed on the scalp[226]. N1 reflects error detection generated by the inconsistency between the expected and the actual state[226].

One potential modifier of cortical capacity in preparation or response to postural instability is cognitive load[227]. Performance of a cognitive task while concurrently being exposed to unpredictable balance perturbations attenuates N1 amplitude and concomitantly increases the magnitude of the compensatory balance response[227]. Therefore, it is important to investigate the PEP N1 through the addition of a secondary cognitive task.

Pupillary response is a non-intrusive, objective, neurophysiological tool of cognitive workload. Since PEP N1 is a well-known response to perturbation, it is important to synchronously record

the N1 amplitude with pupillary response during dual-task balance in individuals with PD who are fall naïve. We believe that pupillary response has more potential to be implemented in clinics compared to EEG in the future. Therefore, the first aim of this study is to understand the relationship between N1 potential and pupillary response during dual-task balance. The second aim is to investigate the predictive ability of N1 amplitude and pupillary response on falls in a fall naïve cohort of individuals with PD. In this study, we will follow-up individuals for a year to record their falls to data. This study will help to understand neurophysiological bases of postural impairment and falls risk in individuals with PD who are fall naïve.

6.4.2. Understanding the relationship between neurophysiological and behavioral outcomes in individuals with PD

Upright stance posture is an essential motor skill for performing for most daily-life activities. Balance is under the control of higher-order cognitive processes which leads to the involvement of widespread cortical areas. Studies have shown that maintaining balance requires greater use of cognitive resources in individuals with PD compared to the healthy controls. Reduced ability to allocate sufficient cognitive resources may result in an increased risk of falls and loss of independence in individuals with PD.

Much of our current understanding about balance control and its impairments has come from investigations of individuals maintain their stable posture and their response to situations that perturb standing balance. Knowledge obtained from these investigations has come from solely documenting the body's kinetic, kinematic, and behavioral responses. However, it is known that the cerebral cortex has significant involvement in balance control. In older adults, it is common to observe decreased brain functional connectivity across the default network and frontal

attentional system as well as reduced integrity of white matter and grey matter. These changes are more prominent in individuals with PD, resulting in overreliance on the motor and cognitive circuits during balance control. Therefore, the coupling of behavioral and neurophysiological findings is paramount to advance our understanding of brain-behavior interactions. Therefore, future studies are needed to investigate the association between brain neurophysiological response and behavioral outcomes during balance control in individuals with PD.

6.4.3. Develop an intervention by using a combination of non-invasive brain stimulation and exercise to improve balance symptoms and reduce the risk of falls in individuals with PD

Older adults with neurological conditions often have difficulties with the long-term consolidation of motor skills, but adjunctive neuromodulatory techniques, such as non-invasive brain stimulation, may help to upregulate neuroplasticity and facilitate motor skill acquisition and retention. Transcranial magnetic stimulation or transcranial direct current stimulation are therapeutic tools that have been shown to help to attenuate motor symptoms in neurological populations including Parkinson's disease. A study has shown that applying a neuromodulatory technique over the primary motor cortex (M1) can induce an increase in M1 excitability and reduce cortical inhibition, resulting in improved functional performance. However, it is not known whether concurrent use of non-invasive brain stimulation and exercise can lead to greater and longer-lasting improvements in balance function by inducing neurophysiological response of the brain. Therefore, as a future direction, it is warranted to investigate the effectiveness of combined non-invasive brain stimulation and exercise approach to induce changes on the neurophysiological response of the response and eventually improve the balance symptoms and reduce the risk of falls in individuals with PD.

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