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Effects of Parkinson's disease on motor asymmetry

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Introduction: Persons with Parkinson's disease (PD) experience changes cortically, subcortically and behaviorally. This dissertation examines the asymmetry of motor behavior to explore the role of asymmetry in persons with PD and its connection to clinical symptoms. **Purpose:** Project 1: To assess the hand asymmetry difference in young adults versus older adults. Project 2: To investigate the difference in hand asymmetry in older adults and persons with PD. Project 3: To explore the correlation between function and clinical symptoms of persons with PD. **Methods:** 55 right-handed participants [Young Adults (YA) = 20, Female = 10; Older Adults (OA) = 20, Female = 10; Persons with PD = 15, Female = 5] were recruited and performed motor tasks: Purdue Pegboard test, grip strength test, response task, thumb opposition task, tapping task, three variations of timed-up-and-go test (TUG), single leg stance task (SLS), Weight Distribution test and Limits of Stability test. The two-way ANOVA was conducted to examine a variance between YA and OA. A separate two-way ANOVA was conducted comparing variance between OA and persons with PD. The purpose was to explore asymmetries, characterized by a significant difference between groups' left and right sides. Pearson's correlation was implemented to examine connection of clinical symptoms and motor behavior.

Statistics: IBM SPSS 24 software was used. Two 2-way ANOVAs with the between group factor of group (Young vs. Older in Project 1; Older vs. PD in project 2), and within group factor of hand (Right vs. Left in Study 1 & Study 2) were used to examine if age (or PD) changes hand asymmetry. Pearson's correlation coefficient was used to determine correlations between Unified Parkinson's Disease Rating Scale (UPDRS) and motor tasks in PD patients (Study 3). **Results:** Project 1: Results indicate asymmetry reduces with age in fine motor tasks containing speed, dexterity and strength components. Project 2: The basal ganglia dysfunction does not overall further exacerbate the reduced asymmetry with age. Project 3: Clinical symptoms of PD measured by the UPDRS are generally not associated with fine motor tasks of this study.

DEDICATION

In dedication to my beautiful children: Eli, Evelyn and Audrey.

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Foremostly, I would like to thank my mentor Dr. Pan, committee chair, for her unyielding support and direction during this process. I would also like to thank everyone on the dissertation committee for their guidance and counsel, as this time in my academic career was challenging, but also incredibly inspiring. Leading the Thai Chi community service project under the direction Dr. Lamberth and Dr. Chen was truly a rewarding experience. Working on my first publication with Dr. Aiken was a pleasure and I am tremendously grateful to him and all other individuals that made that publication a reality. I am also grateful to Dr. Chander for his advice and encouragement in every step of this journey, from my first class as a PhD student to the dissertation defense. I want to express gratitude to Dr. Knight who provided direction and advice from beginning to end, application to the program and afterward overseeing each step of this academic, research and teaching journey. I want to thank my remarkable parents and in-laws for their endless encouragement, guidance and help during this academic journey. Lastly (but definitely not least) thank you to my amazing husband, for without his love and support, this wouldn't be possible. I am honored by the love and unremitting support I have received these last four years.

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CHAPTER I

INTRODUCTION

Parkinson's Disease and Asymmetry

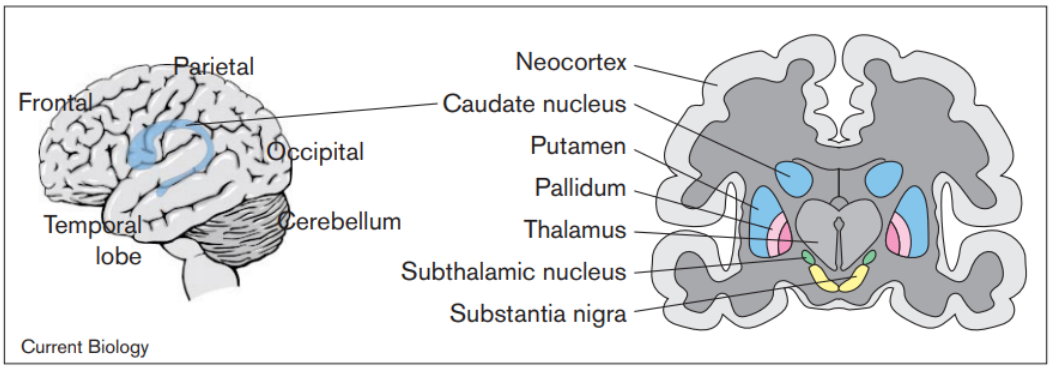
Nervous System

The central nervous system is comprised of the brain and spinal cord. The brain comprises the cerebrum which enables sensation from sensory input and voluntary motor action; the cerebellum, housed in the inferior and posterior parts of the skull, coordinating movements and influencing motor performance; and finally, the brainstem, at the base of the brain, connecting to the spinal cord. Nuclei are stored in the brainstem that controls important and life-sustaining body functions such as regulating swallowing, sleep cycle, respiratory rate, heart rate, and other vital functions. Part of the brainstem is the diencephalon which includes the hypothalamus and thalamus. The thalamus is a gateway that relays sensory signals to the cerebral cortex (Kandel et al., 2013, Magill 2013).

The basal ganglia (BG) is a subcortical structure consisting of nuclei pairs (Figure 1): Subthalamic nuclei, substantia nigra, pallidum (external and internal components), and striatum which is made up of the caudate nucleus and putamen. One of each nucleus is housed in each cortical hemisphere (Kandel et al., 2013).

Figure 1

Basal Ganglia



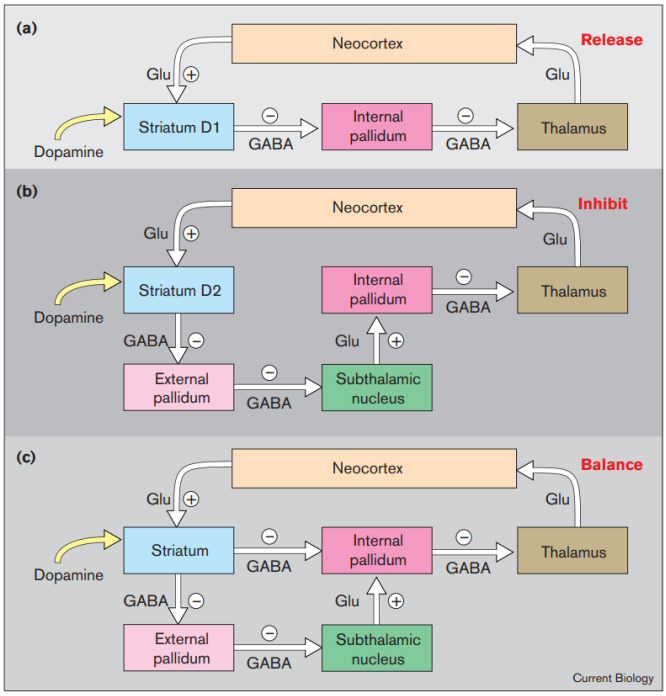
Basal ganglia subcortical structure components (Graybiel, 1995).

The typical function of the BG is to assist in the planning of movements, the smoothness of movements, and the initiation and inhibition of movements at appropriate times. The neocortex communicates with the BG. The BG sends input to the thalamus which communicates with the frontal cortex (Graybiel, 1995) illustrated in Figures 2 and 3. Furthermore, BG is involved with nuclei in the brainstem, which is useful in controlling muscles involved in axial orientation and saccadic eye motion.

When there is dysfunction of the neurons in the striatum, Huntington's disease transpires (Graybiel, 1995). The substantia nigra contains two regions; pars reticulata and pars compacta. The pars compacta houses dopamine. When the pathways of the basal ganglia is affected, Parkinson's disease (PD) transpires. When the basal ganglia's direct pathway is affected, Huntington's disease transpires.

Figure 2

Motor Control Pathways of the Basal Ganglia

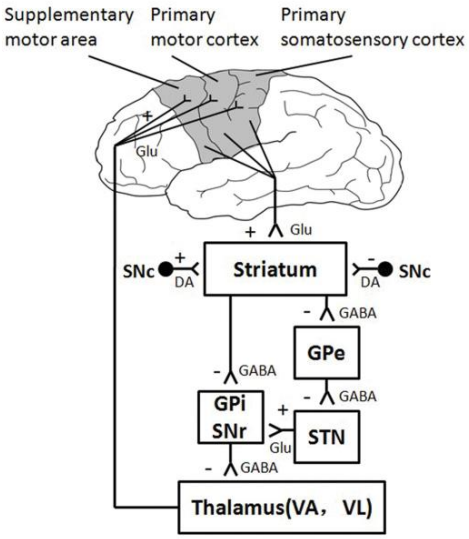


The brake–accelerator model for basal ganglia motor disorders. **(a)** The direct pathway (leading to release of movement) consists of two successive GABAergic connections, from the striatum to the internal pallidum and from the internal pallidum to the thalamus. This flow diagram suggests that excitatory (glutamate; Glu) inputs from the neocortex to the striatum would disinhibit thalamic neurons. Dopamine modulates the system mainly in the striatum, where it activates D1-class and D2-class dopamine receptors. **(b)** In the indirect pathway (leading to inhibition of movement), there is an extra step after the external pallidum, so that the subthalamic nucleus excites the internal pallidum. **(c)** Balance is achieved when these antagonistic systems are combined under normal circumstances.

Direct/Indirect pathways of the basal ganglia for movement control (Graybiel, 1995).

Figure 3

Basal Ganglia Pathways



Direct and Indirect pathways assisting motor control (Hou et al., 2016).

Introduction to Parkinson's Disease

According to the Mayo Clinic (2022), PD is a progressive disorder affecting movement via nervous system dysfunction. An estimated 10 million people worldwide are affected by PD (American Parkinson's Disease Association, 2022). The neurological disorder typically affects adults over 50 years old but can affect persons under the age of 50, otherwise known as early-onset PD. Dorsey et al. (2007) looked at 15 populous nations and determined that the number of persons over the age of 50 with PD was between 4.1 million and 4.6 million, with an expectation to double by the year 2030.

While the cause of Parkinson's disease is still unknown, theories underlying the disease are hypothesized from genetics to environmental influences (Warner & Schapira, 2003). The crux of

movement disorder associated with PD is an insufficient substantia nigra, a subcortical structure. Normal dopamine balances between the direct and indirect pathways assist in producing normal, coordinated, and smooth movements. However, the disease processes of PD in the substantia nigra progressively reduce dopamine production, resulting in an imbalance of dopamine activity and ultimately giving rise to the PD characteristics of slow movement (Escande et al., 2016). While tremor pathophysiology is not completely understood, dopaminergic neural degeneration of the retrorubral plays a role (Abusrair et al., 2022). Similarly, underlying pathophysiology of rigidity is also poorly understood, however, observations have shown cortical and subcortical excitability changes, indicated by abnormalities of stretched-induced co-activation of agonist-antagonistic muscles and long-latency stretch reflexes (Bologna & Paparella, 2020).

Currently, there is no cure for PD. Treatment options for persons with PD include exercise, medications, and for some candidates, deep brain stimulation. The treatment goals are to reduce the symptoms of the disease in the person or slow the progression of symptoms that arise from neurodegeneration. Medicines used to manage symptoms of PD include levodopa, DA receptor agonists, selegiline, amantadine, catechol-o-methyl transferase (COMT) inhibitors, and anticholinergics (Singh et al., 2007). Additionally, neuroprotective agents can be included in the treatment regimen such as nicotine, anti-inflammatory agents, melatonin, selenium, vitamins A, C, and ,E and other agents including Ginseng, Ginko biloba, etc.

The primary structure damaged due to PD is the substantia nigra, but other brainstem structures are also compromised (Braak et al., 1996; Braak et al., 2002). Typically, persons in the early stages of the disease are unaware of the disease because clinical symptoms are not identifiable.

When there is more than 75% of nigrostriatal dopamine neuronal loss, the clinical symptoms of PD will be elicited (Lloyd, 1977). The staging of PD is related to the involvement of the disease such that in stages 1-2, lower brainstem nuclei (dorsal motor nucleus of the vagus and olfactory system) are compromised. In stages 3-4, the coeruleus complex, substantia nigra pars compacta, basal forebrain magnocellular nucleus, subthalamic nucleus and amygdala are implicated. Stages 5-6 implicate the neocortex and supervene are involved (Braak et al., 2002; Braak et al., 2003). Older adults experience deficits in both cognitive and motor domains due to declines in neurotransmitters such as dopamine and serotonin. (Seidler et al., 2010). However, when a more severe number of dopamine neurons die, the symptoms of PD begin to present. The nigrostriatal pathway begins in the substantia nigra pars compacta, which houses dopamine neuron cell bodies. Axons of the dopaminergic neurons extend to the caudate nucleus and putamen (striatum). This major dopamine pathway is essential for motor control, and the reduction or absence of neurotransmitters can result in impairments: bradykinesia, the slowing of movement; resting tremor, a shaking that typically begins unilaterally and often in the finger or hand; Parkinsonian gait described as freezing of gait, shuffling, and reduced arm swing with drooped shoulders; reduced posture and balance; muscle stiffness and hypomimia or reduced facial expressions.

The insufficient dopamine production of the substantia nigra affects all skeletal muscles. Some of the cardinal symptoms of PD are tremors, bradykinesia, postural instability, and rigid muscles (Bereczki, 2010). The Mayo Clinic (2022) describes a tremor as a shaking, typically beginning with one extremity. Bradykinesia is characterized by slow movements, making daily functional activities difficult and slow. A stooped posture leans the trunk forward, producing postural

instability that can potentially lead to falls, especially during locomotion. Rigidity typically refers to the stiffness felt in muscles, potentially reducing the range of motion and increasing pain with movement. With slow movement and motor skill-related deficiencies resulting from the aforementioned signs and symptoms, gait and functional movement can become challenging and dangerous. Motor symptoms such as bradykinesia, rigidity and tremor typically appear unilaterally in the early stages of the disease (Djaldetti et al., 2006). Thus, the study of asymmetry and movement in persons with PD is imperative in understanding challenges and finding interventions that may assist this population in moving better. In early PD, symptoms begin asymmetrically (Lee et al., 1995), and with disease progression, symptoms appear bilaterally (Djaldetti et al., 2006).

Non-motor symptoms of Parkinson's disease can include gastrointestinal symptoms, sleep disorders, neuropsychiatric symptoms, and autonomic symptoms (Chaudhuri, 2006). More specifically, the pathway related to the sleep-wake cycle may be interrupted, or a person can experience olfactory deficit and depression. Motivation deficits are also common in persons with PD. Persons with PD that were taking dopaminergic therapy exhibited improved motivation compared to persons with PD off medication (McGuigan et al., 2019).

Motor Asymmetry and Hemispheric Lateralization

Motor Asymmetry Related to Motor Behavior

Motor behavior lateralization has been identified as early as prenatally and in infants through the investigation of thumb-sucking (Hepper et al., 2005). When toddlers learn to walk, gait patterns of preterm infants also appear to demonstrate asymmetric tendencies and is correlated with head-turning (Konishi et al., 1986).

In general observation, individuals use their preferred hand more than the nonpreferred hand, which may partially account for asymmetry. For example, hand grip strength is typically greater on the dominant side compared to the non-dominant side (Bohannon, 2003). A study by Akpinar et al. (2015) reveals the comparison of asymmetry between expert fencers and non-fencers. The study indicates novice performers present with more asymmetry, but may be able to reduce the asymmetries with long-term practice. Extrapolation of the data suggests excessive amounts of practice may play a role in the reduction of asymmetry.

Studies concerned with motor task performance of healthy adults reveal asymmetries in motor performance. Aoki et al. (2016) investigated tasks performed with the index finger on a touchscreen in both left-handed and right-handed individuals, with results indicating significant differences between the left and right hands of the groups. The study yielded significant findings of asymmetry utilizing fine motor tasks, demonstrating that the plausibility of applying fine motor tasks in future study is reasonable.

Even in the discussion of relatively simple motor functioning, Chaurasia and Goswami (1975) discovered that a majority of people do not use the two sides of their faces equally and considers the ambilaterality of the face as a rarity. As motor asymmetry is evident in everyday functioning, comparison between the left side and right side can readily assist in understanding motor control and behavior.

Change of Motor Asymmetry in Healthy Older Adults

Young, healthy individuals tend to perform motor skills asymmetrically between the left side and right side. With age, the asymmetry declines as symmetry becomes more predominant. As motor

behavior is a large topic, studies aim to define which tasks and subcomponents of motor movement are subject to the reduction of asymmetry.

A study by Przybyla et al. (2011) indicates that motor coordination asymmetry reduces with age. As people age, the asymmetry between hands lessens, resulting in increased symmetry linked to increasing age. Younger and older participants performed an aiming task with each hand. Reduction in lateralization was evidenced as straighter non-dominant hand paths relative to the younger subjects (Przybyla et al., 2011). Suggested mechanisms from this study include additional cortical resources utilized from the ipsilateral hemisphere to supplement the contralateral hemisphere controlling the movement, or the difference may be due to the additional years of training for the non-dominant hand gained through the lifespan.

In a study conducted by Teixeira (2008) three age groups participated in motor tasks to assess manual performance across ages. The maximum grip force task revealed a transition between the identified profiles of lateral asymmetry as a function of age, indicating decreased asymmetry with age. The author suggests the cause of more symmetrical findings in older adults is the greater reduction of performance of the right/dominant hand, compared to thenon-dominant hand. However, this same study revealed that a sequential drawing task did not indicate reduced asymmetry with age. Interestingly, the drawing circles task indicated increased asymmetry in older adults. Authors concluded that asymmetry between the left and right hand as a function of age may be task specific.

Asymmetry is more notable with certain components of motor capability, such as an increase in the superiority of the right hand with age on a highly demanding task, such as the Pin Test (Mitrushina et al., 1995). Other studies have found significant motor asymmetries when using sequential finger tapping (Thorton & Peters, 1982). However, it should be noted that some studies did not find reduced asymmetries in some motor skill performances associated with age. Findings indicate similar patterns of asymmetry in older and younger subjects (Chua et al., 1995).

Right-hand advantage may be one reason to explain motor asymmetry as age-related declines seem to be different between hands (Pohl, 1996). Reduction of lateral asymmetry was caused by a greater decline of performance in the right than the left hand from ages 40 to 60. Teixeira (2008) and Kalisch et al. (2006) also displayed evidence for a greater decline in the right hand resulting in a more similar performance between the two hands. The implication is that while younger and older adults' right/dominant hands show reduced motor performance with age, the younger adults' dominant hand performance reduces to a much greater extent, attributing to the leveling out of dominant and non-dominant hand performance in older ages. Thus, the dominant hand reduces to a greater extent than the non-dominant hand.

Francis and Spirduso (2000) discovered differences between the preferred hands of younger and older adults in some tasks, providing evidence that more complex tasks produce more robust asymmetry findings. In the motor behavior domain, increasing task complexity may involve manipulating components of speed, agility, dexterity, and task complexity.

Hemispheric Asymmetry

Voluntary motor movements require the collaboration of many cortical and subcortical areas, working interconnectedly to execute a motor task (Kandel et al., 2013). Discussing motor behavior without a discussion of cortical involvement would be incomplete. The cortex is complex and incredibly organized. Communication must go from one part of the brain to another which is done in the way of signals. Van den Heuvel & Sporns (2011) examined the network connectivity, finding twelve bihemispheric hub regions that were strongly interrelated. Generally, the right motor cortex controls contralateral movements (Kim et al., 1993), and vice versa. Babiloni et al. (2003) found a prevailing role in the left supplementary motor area in voluntary movement, over the right supplementary motor area in right-handed individuals. However, for some movements, the ipsilateral motor area can increase, affecting the contralateral motor area (Kawashima et al., 1993). As with motor symmetry and asymmetry, there exists an element of cortical symmetry and asymmetry. M1 (primary motor cortex) is crucial for motor control, relaying signals down the spinal cord to achieve a motor task. Findings from Langan et al. (2010) revealed reduced lateralization in the M1 area in older adults during a motor task. As motor control areas of the brain dictate human movement, changes in hemispheric areas that control motor movement will ultimately result in altered motor performance.

Compensatory-related utilization of neural circuits hypothesis (CRUNCH), poses that the older adult requires additional recruitment of neuronal networks to perform a cognitive task (Reuter-Lorenz & Cappell, 2008). Figure 4 displays the cortical activation differences between older and younger adults. Younger adults' bandwidth is sufficient and can meet the demands of a difficult task. However older adults' bandwidth is insufficient, and cannot meet the demands of the

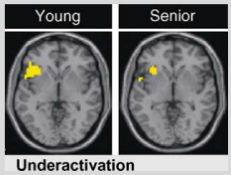
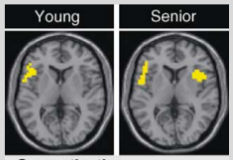
difficult cognitive task. Increased activation in older adults increase activation symmetry compared to the young adult during cognitive tasks.

Figure 4

Under and Over Compensation During Cognitive Task

Table 1

Age differences in activation: impairment or compensation?

Age-specific pattern	Interpretation	Hypothesized mechanisms	Candidate 'diagnostic' criteria	Examples
 Underactivation	Impairment	Circuitry dysfunction Region-specific atrophy Poor strategy use	Linked to poor performance Correlates with structure Might be reversed with instructions	[13–15]
	Compensation	Strategic or neural adjustments to local processing inefficiency Strategic or neural adjustments to processing inefficiency elsewhere in the brain	Linked to good performance Overactivation correlates with regions of underactivation activation elsewhere in the brain Deactivating TMS impairs performance	[18,25••,29••,35]
 Overactivation	Impairment	Disinhibited or nonselective recruitment Strategic or neural processing inefficiency Selectivity breakdown or dedifferentiation Nonfunctional activity	Linked to poor performance Deactivating TMS improves or has no effect on performance	[23,39••,43,44•]

This table summarizes the current state of knowledge pertaining to the two major patterns that characterize the results from functional neuroimaging studies comparing younger with older adults and lists several reports that exemplify these results. Underactivation refers to less activation in regions of interest in older relative to younger adults, and overactivation refers to the opposite pattern.

(Reuter-Lorenz & Lustig, 2005).

Change in Hemispheric Asymmetry in Healthy Older Adults

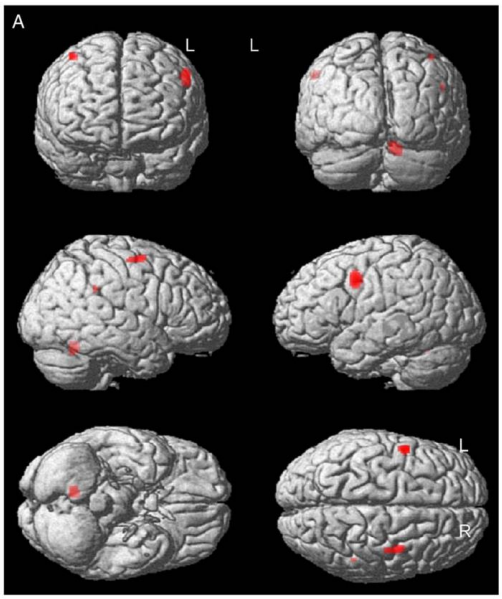
Calautti et al. (2001) claim to have been the first to report differences in cortical activation patterns associated with age with motor movement. Subsequently, studies have since attempted to locate common areas of the brain subject to asymmetry and emerging cortical activation patterns as a function of age.

Naccarato et al. (2006) reported that older subjects are less lateralized in the M1 (Primary motor cortex) activation balance due to increased activation bilaterally, albeit more significantly, on the ipsilateral side. In their study, right-handed participants performed an index-thumb tapping task for each hand while inside an fMRI machine. The maximum number of taps in 15 seconds was recorded. With age, increases in ipsilateral and contralateral M1 (primary motor cortex) activations were found. Statistically significant differences were greater for ipsilateral M1 activations compared to contralateral activations.

Transcranial magnetic stimulation (TMS) and emission tomography were combined with a motor task to investigate cortical connectivity. Subjects were to push one of four buttons in time to an auditory cue. Regions associated with movement exhibited increased activations with age (Figure 5). Furthermore, premotor cortex activations interrelated with the movement have also been reported to increase with age on bilateral hemispheres (Rowe et al., 2006). These regions have important roles in motor control, as the primary motor cortex produces the output signals for voluntary motor movement down the spinal cord. The premotor cortex assists selecting of motor movement sequencing and houses mirror neurons. A disruption in these areas would result in motor behavior abnormalities.

Figure 5

Movement-Related Activations Associated with Increasing Age



Increased cortical activation in these areas, indicated in red, were found in older adults when performing motor tasks (Rowe et al., 2006).

Cabeza (2002) originates Hemispheric Asymmetry Reduction in Older adults (HAROLD) which postulates lateralization of hemispheres decreases with age and may result from neuronal changes in some sections or more widespread restructuring of neural networks. The overactivation in older adults' cortex correlated with under-activating parts of the brain to increase task performance. Findings from Cabeza (2002) reveal older adults require more neuronal resources are required to perform at the same level as younger adults. Dedifferentiation and compensation are two theories attempting to explain the difference in older adults' cortical activation patterns compared to younger adults. Both theories recognize increased cortical activation but differ in the proposed mechanisms. The proposed outcomes of increased neuronal involvement are quite the opposite. Dedifferentiation poses increased cortical involvement but

does not result in improved performance. In this hypothesis the recruitment of additional neuronal resources is nonselective and processes inefficiently, resulting in reduced task performance. Thus, in contrast to the compensatory theory dedifferentiation theory poses that additional neuronal recruitment did not the performance of the task. The literature appears to be divided on whether additional neuronal recruitment does or does not increase task performance. Carp et al. (2011) reported that with aging, when performing motor actions (index finger tapping with visual cues), the neuronal representation is less distinctive, supporting dedifferentiation. Burianova et al. (2020), consistent with the dedifferentiation hypothesis, enhanced the topic by stating additional bilateral activation of M1 in older individuals did not associate with improved motor execution performance. In this hypothesis, it appears the older adult's cortex needs to recruit more neuronal resources to perform the same skills as a younger adult but is not as effective as the younger adult's neuronal network resulting in a skill performance that has not improved. Reuter et al. (2015) further supports dedifferentiation with reports of reduced specificity of the M1 area in older adults, involved in motor planning.

In contrast to these studies, Cabeza et al. (2002) designates consistency with the compensation hypothesis, indicating bilateral cortical activation in adults who performed at high levels, in contrast to older adults performing at lower levels. Reduced hemispheric asymmetry means an increased neuronal activity on bilateral hemispheres of the cortex, which can be viewed as our body's way of compensating for natural reductions that come along with age. Older adults may rely on compensation, the use of additional neural resources, to perform at a level sufficient or better level (Raw et al., 2012) and is consistent with the HAROLD model in reducing motor

asymmetry in older adults. In this hypothesis, the cortex appears to be compensating for the natural effects of aging by increasing neuronal activity to produce improved skill performance.

Asymmetry in Parkinson's Disease

Hemispheric Asymmetry in PD

Changes in the peripheral and central nervous systems occur throughout life, and similarities in motor performance have been noted (Ferrucci et al., 2016). The most basic description of the pathophysiology of PD is a dysfunction of the central nervous system. Thus, the abnormal changes in the central nervous system results in abnormalities of motor performance specific to this pathophysiology. Albeit the origin of the disease process is unknown, previous research proposes hypotheses to explain the asymmetric nature of PD.

The possibility exists that the number of dopaminergic neurons in the substantia nigra are with us from birth and can vary between hemispheres resulting in asymmetrical origins between hemispheres. One hemisphere may innately house more dopaminergic neurons. The degenerative process may affect both sides at an equal rate, but the hemisphere with fewer dopaminergic neurons is more vulnerable to the disease showing symptoms first and more severely than the other side (Djaldetti et al., 2006). Djaldetti et al. (2006) continue to offer another hypothesis that one hemisphere is more susceptible to degenerative processes than the other and as a result, degeneration occurs more pronounced or to a greater extent on that side. Lastly, the asymmetry could be due to variations of other structures of CNS involved in motor control, for example, abnormalities of corticocortical projecting pyramidal neurons in the pre-supplementary motor area (Macdonald & Halliday, 2002).

Kempster et al. (1989) conducted a post-mortem study of persons with PD with unilateral symptom onset, finding further degeneration of the substantia nigra compacta in the hemisphere contralateral to the initially affected side of the body. The structural cortical finding in this study connects the asymmetrical presentation of symptoms with hemispherical asymmetry. Neuroimaging study supports asymmetrical neurodegeneration of substantia nigra, and connects the asymmetry presentation to earlier stages of the disease (Wang et al., 2015). Wang et al. (2015) indicates that motor symptom asymmetry presents more asymmetrically in early PD.

Motor Asymmetry Related to PD

Asymmetrical presentations of PD symptoms as well as asymmetries in the functional movements have been of recent interest in the literature. For example, tremor is a standard symptom of PD, typically beginning unilaterally, but affects both the left and right sides as the disease progress (Hoehn & Yahr, 1967). A study revealed persons with PD typically experience atrophy of the nigrostriatal system on the left hemisphere of the cortex first, indicating asymmetric cortical degeneration, with more dysfunction on the left nigrostriatal pathway in earlier stages and increased atrophy in the right hemisphere in later stages of the disease (Claassen et al., 2016). Research indicates that with the left hemisphere affected earlier, right-side motor functions would be affected in earlier stages of the disease, before left-side motor skills become affected with the progression of the disease (Claassen et al., 2016). Unilateral manifestations have been supported by Kempster et al. (1989) finding a greater extent of degeneration of the substantia nigra in the contralateral hemisphere of the initially more affected side. The increased neuronal loss is evidence of asymmetric degeneration of subcortical structures responsible for asymmetrically degenerated motor presentations. As the disease progresses, motor signs become more symmetrical and cognition worsens with disease

progression (Foster et al., 2008). Godi et al. (2021) also found persons with PD exhibited asymmetries more pronounced in the earlier stages.

Interestingly, symptoms of PD did not appear on the same side when looking at affected individuals in the same family, and the affected side was distributed randomly (Djaldetti et al., 2006). Potential mechanisms to produce motor asymmetry in PD may include structural, genetic, environmental, and toxic or metabolic mechanisms (Djaldetti et al., 2006). In the studies of monozygotic twins, genetics does not determine which side will exhibit worsening symptoms. This review continues to discuss the explanation of the asymmetry of symptoms as injury to the blood-brain barrier is more prominent on one side. Finally, the cause may be a result of multiple factors, genetic and environmental, combined (Warner & Schapira, 2003).

It is important to note that Parkinsonian symptoms may be a result of other causes that are not typical of Parkinson's disease. For example, persons without PD may also exhibit asymmetric symptoms, or gait patterns that might resemble Parkinsonian gait, but the individual does not have a diagnosis nor pathophysiology of PD. One such example is vascular parkinsonism which results from infarcts near basal ganglia and periventricular white matter. Infarcts may have been asymmetrical, thus affecting one hemisphere more (Djaldetti et al., 2006). This paper is primarily interested in Parkinson's symptoms because of degeneration of the substantia nigra.

Gait and Balance with Aging and Parkinson's Disease

Gait in Persons with Parkinson's Disease

Abnormalities of gait and walking, for any population, could lead to falls. Persons with PD may fear falling due to their perception of their walking difficulties and balance problems (Lindh-

Rengifo, 2021). The reality may be supportive of their perceptions. Plotnik et al., (2007) compared gait between healthy older adults and persons with PD. Compared to healthy individuals, bilateral coordination in patients with PD is inferior. This same study found significantly reduced gait speeds and stride length in persons with PD. In a review, Allen et al. (2013) compares the recurrent fall statistics of the general older populations (about 15%) to persons with PD (over 50%) suggesting there may be different underlying factors for greater recurrent falls in the PD populations. Galna et al. (2014) also reported deterioration in pace and rhythm in persons with PD over 18 months. At baseline, the individuals with postural instability and gait difficulty phenotype exhibited more gait impairments than the tremor phenotype. With reduced pace and differences in gait quality, persons with PD may be more susceptible to falls.

As noted earlier in the motor behavior of persons with PD, research indicates increased asymmetry in the early stages of PD (Foster et al., 2008; Godi, 2021). Interarm asymmetry was compared between persons with PD and control subjects by instructing them to walk at normal and fast velocities. Gait differences in upper extremity movement rhythm in the early stages of PD were vastly different from the control group (Lewek et al., 2010). Lewek et al. (2010) continue to express the importance of asymmetrical arm swing as part of the qualitative evaluation for early differential diagnosis.

The study of gait asymmetry presentations appears to be of increased complexity. Step asymmetry was reported as being more asymmetrical in the early stages of PD. At the same time, swing time variability and double leg stance time are more pronounced at the 2-2.5 Hoen and

Yar stages (Godi et al., 2021). The apparent variability in the timing of the worsening of symptoms may make the study of motor symptom asymmetry more thought-provoking.

Asymmetry of Gait in Parkinson's Disease

Consistent with the asymmetries in motor behavior and hemispheric presentations, asymmetry appears to present itself in the locomotion of persons with PD. It should be noted, however, that gait asymmetry has not been shown to correlate with motor symptom asymmetry according to Plotnik et al. (2005) where researchers were interested in the relationship between freezing of gait to asymmetries of gait and rhythmic hand movement performance. Further studies reported temporal asymmetry in gait was not found to be correlated to motor symptom laterality (Plotnik et al., 2005; Yogev et al., 2007). Lewek et al. (2010) noted the presence of asymmetry in the upper extremities, but not the lower extremities.

Plotnik et al. (2005) also indicates that persons with PD also experiencing freezing of gait exhibited increased gait asymmetry compared to persons with PD and no freezing of gait symptom. Interaction of symptoms may also impact motor performance. The varied presentation of each individual may yield interesting results and something to consider.

Lastly, medications for PD are important for an individual's movement in everyday life, however, they do impact the data collection process. Another consideration in measuring asymmetry in PD can be medication, as this will affect motor performance. Spatial and temporal gait asymmetries were noted to be greater in persons with PD than in healthy subjects when measured in the OFF medication (levodopa) state (Fling et al., 2018). Persons with PD exhibited

more step length asymmetry both temporally and spatially. Thus, it is worth noting symptoms and asymmetry may be more pronounced when persons are measured during off states.

Balance in Persons with Parkinson's Disease

Muscles, sensory systems, and neurological control are all integrated, to allow a person to maintain position in space for both static and dynamic movements. As PD implicates the central nervous system, the neurotransmitter dopamine, and muscles that the motor control system depends on, balance is further compromised in persons with PD.

In persons with PD, dynamic postural asymmetry appears to be due to the disease rather than the effects of natural aging (Geurts et al., 2011). Geurtz et al. (2011) assessed the postural control of persons with PD using force plates and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. Results show that 24% of participants exhibited asymmetry of dynamic postural control. In persons with PD, asymmetries, difficulties with interlimb coordination and rigidity may contribute to difficulties turning (Boonstra et al., 2008). With additional abnormalities of motor production, persons with PD pose a higher risk of falling.

A pilot study by van der Kooij et al. (2007) reported dynamic balance asymmetry in subjects who did not appear to have difficulties with standing and stability. Participants stood on a forceplate with a supporting harness to prevent falling, but did not provide any sensory feedback. Participants stood in anatomical position for 10 seconds and spontaneous sway was recorded. The forceplate then provided continuous forward/backward perturbations in both eyes open and eyes closed scenarios. Weight-bearing distributions, sway, the center of pressure for both feet, and ankle movements were studied. Asymmetry in weight-bearing was detected. Furthermore,

asymmetry related to dynamic balance was more pronounced. Interestingly, persons who observationally didn't appear to present with asymmetry did exhibit significant asymmetries in the study. Moreso, this study reveals the importance of dynamic balance compared to static balance examination. Lastly, this study further recognizes the importance of continued research comparing the varied stages of PD as well as during On and Off phase conditions, as medications may impact on the individual's performance.

Balance in persons with PD is a topic amidst exploration, as the implications of reduced balance results in an increased incidence of falls (De Nunzio et al., 2007; Maurer et al., 2003; Termoz et al., 2008). However, studies examining balance in persons with PD with a focus on asymmetry are relatively scarce. As a result, there exists much left to be uncovered in this area warranting further investigation.

A progressive disease, such as PD, ultimately results in reduced safety, decreased mobility, and a worsening quality of life. As the PD pathology affects overall motor performance and influences the asymmetrical presentation, the study of motor behavior is critical in understanding the role of basal ganglia in motor control. Further research is indicated to enhance understanding of asymmetry and role of the basal ganglia on asymmetry, leading researchers to consider the following research questions: 1. What are the changes in asymmetry of motor behavior in healthy older adults? 2. What are the differences in the change of asymmetry between healthy older adults and persons with PD? 3. What is the relationship between PD symptoms and functional performance? The investigation connecting PD symptoms and motor behavior has the potential to provide background information and mechanisms underlying motor performance of

PD. The nature of this research domain has the potential to assist in enhancing or creating new rehabilitative techniques and enhancing early-stage PD identifiers that may be used in earlier stages of the PD pathology.

CHAPTER II

LITERATURE REVIEW

Understand Asymmetry of Clinical Symptoms

The UPDRS is a widely used tool covering a spectrum of clinical presentations in persons with PD. A highlight of the UPDRS is its comprehensive attention to motor systems (Orth & Tabrizi, 2003). Additionally, the UPDRS shows significant difference between left and right in large sample studies. (Djaldetti et al., 2006), thus indicating the use of UPDRS for the study of asymmetry has its place in the examination of motor behavior.

Another study examined 1,277 individuals with diagnosed PD. Results reported asymmetry is common in the PD population, and their study finds three cardinal features of PD presented with features of asymmetry (Uitti et al., 2005). Left-handed individuals were more likely to exhibit more severe symptoms on the left side of the body (Uitti et al., 2005). However, in Yust-Katz et al. (2008), the side of onset and severity of the disease were unrelated. Yust-Katz et al. (2008) discovered symptom asymmetry is strongly connected to PD with a trend of the dominant side being the first with symptoms. Authors assessed using the UPDRS motor portion, finding persons with right-side onset scored an average of 20.4, compared to persons with left-side onset scored an average of 21.6. Fifty-two percent of left-handed participants exhibited left side onset of symptoms and 47% of right-handed individuals exhibited right-side onset of symptoms.

Symptoms tended to first appear on the participants' dominant side, however, this finding was not significant.

Underlying causes of PD are unknown, and similarly, underlying causes of symptom asymmetry are also unknown. However, it is evident that symptoms of PD are asymmetric. For example, Yust-Katz et al. (2008) reported about 85% of participants in their study of 307 patients exhibited asymmetric symptoms, but reason remains unclear. Similarly, a study by Gomez-Esteban et al. (2010) finds around 16.4% of participants exhibited symmetrical symptoms as identified by the UPDRS. Furthermore, persons with more symmetric symptoms had symptoms for longer periods of time.

Yust-Katz et al. (2008) continue to offer the idea that protection from the disease includes exercise. Support for this idea is indicated in Cohen et al., (2003) whose data indicate that forced limb use encourages protective mechanisms against nigrostriatal degeneration of dopamine system injury. Thus, assessing the physical activity of participants may be an important consideration in reviewing results.

Clinically evident symptoms of PD do not appear until the individual has lost greater than 75% of dopaminergic neurons (Lloyd, 1977). A possible explanation was provided by Bezard et al. (2003) and van Nuenen et al. (2009), supporting the notion that the brain is using compensatory mechanisms to produce normal movement, even though the number of dopaminergic neurons is decreasing. Due to findings from van Nuenen et al.'s (2009) fMRI study, authors argue their observation of cortical activation is a compensation to maintain normal movement sequencing when a mild deficit of dopamine is present. This line of thought may explain why PD is not

caught until the individual has already sustained a plethora of basal ganglia damage, and may also mask asymmetry in the very early stages of PD. In this same line of thought, it is reasonable to hypothesize the same compensatory mechanisms may produce normal movement, even though asymmetry exists in the movement-producing motor tract system. Bezard et al. (2003) discusses the compensatory mechanisms that postpone the presence of PD symptoms resulting in a pre-symptomatic phase of the disease.

Lastly, it should be noted that a study by Miller-Patterson et al. (2018) concluded that some motor symptoms, considered via UPDRS, remain asymmetric, presenting a seemingly opposing view that in disease progression, motor symptoms do not become more symmetric. Motor symptoms of persons with PD were assessed via UPDRS to investigate motor asymmetry changes over five years. Finger tapping and tremor sum results indicated increasing symmetry over time in persons with PD. Conversely, bradykinesia, rigidity and tremor did not appear to become more symmetric with time (Miller-Patterson et al., 2018).

Understanding Fine Motor Asymmetry

In concurrence with the literature discussed earlier in this discourse, asymmetry declines with age (Mitrushina et al., 1995). Evidence suggests fine motor tasks hold relevance in the field of motor behavior asymmetry. For example, in the finger tapping test, left hand correlations between age and performance were different between left hand and right hand, as correlations were stronger with left hand (Mitrushina et al., 1995). This may indicate age plays more of a role in left hand than dominant hand, impacting symmetry/asymmetrical performance between hands in older adults.

Previous literatures reveals a variety of fine motor tests result in motor asymmetry findings. With the pin test, a difference in the rate of performance between left and right hands varied with age (Mitrushina et al., 1995). The pin test, as described by Mitrushina et al. included pushing a pin through individual holes and success was determined by the numbers of pins. The motor task similarity between this task and the Purdue Pegboard indicates there is plausibility the Purdue Pegboard may also reveal motor asymmetries. One explanation provided by Agnew et al. (2004), stating even in simple motor tasks like thumb flexion, left-hand and right-hand movements involve different neuronal systems to control the movement. Nisiyama et al. (2014) conducted an experiment to study simple and choice reaction times between the left hand and right hands of younger adults. Findings indicated sub-movement times for the right hand were longer than the left hand when the participant responded with bilateral hands. When the task was performed bilaterally and unilaterally, pause times were found to be shorter for the right hand.

Roland et al. (1982) had participants perform sequential finger movements and found activated bilateral basal ganglia indicating the role of the basal ganglia in the initiation as well as the control of the movement. As the basal ganglia is the crux of PD dysfunction, the comparison between healthy age-matched older adults and persons with PD has the potential to reveal differences in motor behavior and the connection between the central nervous system and motor movement.

Van Nuenen et al. (2009) studied sequential finger movements with fMRI, finding the pre-SMA and rostral PMd was responsible for the compensation to maintain a normal movement pattern as dopaminergic neurons begin to die in earlier stages of the disease, before presentation of

symptoms. Researchers utilized the thumb-to-finger opposition task to investigate the rostral supplementary motor area and the right dorsolateral prefrontal cortex, as these areas are important for movement selection and are affected by dysfunction of the basal ganglia. For PD participants in this study, dysfunction remained subclinical due to additional recruitment of motor areas while performing the task.

As motor symptoms of PD are observably asymmetrical, the study of motor behavior in persons with PD is a way to explore and gain further understanding about asymmetry in PD. Yokochi et al. (1985) compared left and right sided electromyography of finger extensor muscles, finding patients who had bilateral symptoms had slower reaction times on the side that was more affected. Persons with PD may have more difficulty coordinating their wrist and fingers to accomplish a graphomotor task, such as drawing circles. Deceleration phases were also found to be more prolonged (Yu et al., 2017). Basal ganglia dysfunction, as seen in PD, contributes to impaired handwriting production and fine motor skill via the individual's ability to fine-tune motor plan parameters (Senatore & Marcelli, 2019).

Dominey et al. (1995) results indicate motor asymmetry and motor imagery processes are affected similarly in persons with PD. The task was a motor finger sequencing task. This indicated that the brain structures involved in both motor imagery and motor execution are shared. Both tasks would be affected asymmetrically. When persons with PD performed the finger-to-thumb opposition task, the more involved hand (32.87 sec) performed slower than the opposing hand (26.60 sec), indicating worse performance with the more involved side. Additionally, another finding in this study was that the non-affected hand of persons with PD

moved slower than the controls. The persons with PD exhibited asymmetric motor performance, however the “better” side performed worse than the control’s non dominant hand. Impairments for PD patients are bilateral, however, have a predominantly affected side (Dominey et al., 1995).

The motor cortex must concentrate more on the motor task when using the non-dominant hand (Gao et al., 2009). Since fine motor tasks may involve more coordination of neurons, an additional complexity of using the non-dominant hand may result in differences between the left and right hands. Thus, increasing complexity may be key to provoking more pronounced findings.

Understanding Asymmetry of Gait and Balance in PD

Gait

The definition of symmetry in gait is a lack of statistically significant differences in parameters between left and right side (Sadeghi et al., 2000). For example, Sadeghi et al. describe symmetrical foot-floor contact between lower extremities during gait when comparing at the hip and knee level, as well as noted symmetry in hip and knee joint motions during walking, when using time and frequency domain analysis. Therefore, the lack of symmetry (as defined above), also defines gait asymmetry as findings reflecting statistically significant differences in parameters between the left and right side.

The mechanisms that promote asymmetries in gait remain unknown (Yogev et al., 2007). One asymmetry noted from Yogev et al. (2007) is that the difference in swing phase time for lower extremities is asymmetric in persons with PD. The values for swing time of each leg were

recorded and assessed for variability. This same study also discovered gait became more asymmetric when participants with PD engaged in dual tasking (gait combined with another activity) indicating that some cortical resources are utilized to maintain symmetric locomotion. In a review by Stuart et al. (2018), authors reported a link between increased cortical activation required for persons with PD to perform balance tasks and walking. The review states that older adults exhibit an overall increased cortical activation in preforming gait and balance tasks, and even more so for persons with PD.

Plotnik et al. (2005) discovered gait was more asymmetric for persons who experience freezing episodes of gait when compared to persons with PD who don't experience freezing episodes, when participants are not taking medications. Furthermore, foot swing rhythm was more correlated between lower extremities in the PD group not experiencing freezing episodes, but not correlated for those who did experience freezing gait episodes.

Significantly decreased symmetry was noted in the tibialis anterior muscle and medial gastrocnemius in persons with PD during gait (Miller et al., 1996) using electromyography. Authors speculated the root of their findings could either be related to the worsened postural control or dysfunction in the central pattern process. In addition to the asymmetry of lower extremities during gait, asymmetries of upper extremities in persons with PD are also revealed. Decreases in upper extremity swing velocity and range of motion were noted to be reduced significantly (Zampieri et al., 2010).

Another underlying mechanism of asymmetrical gait in persons with PD may be the integrity of the corpus collosum. The connection between asymmetrical gait and the corpus collosum was found in Fling et al. (2018), when investigating step length asymmetry and white matter connecting sensorimotor cortices involved in motor control (pre-SMA and SMA). Participants with poorer integrity of fibers in the transcallosal tract had a tendency to exhibit greater asymmetry in step length. In brief, the article reports that when the central nervous system is impacted by a degenerative disease process, abnormalities of gait and balance are manifested. Gait is a voluntary movement controlled by the cerebral cortex and subcortical structures. The prefrontal cortex region of the right cortical hemisphere is involved in executive inhibition. Structural deficits in this part of the cortical network impacts locomotion of persons with PD, specifically having a great impact on freezing of gait (Fling et al., 2013).

Balance

Balance underlies all functional mobility, including walking, of which persons with PD are likely to experience dysfunction. Boonstra, Schouten et al. (2014) tested participants' balance using a computer-controlled motion platform and a pusher to apply perturbations. Findings reveal that most persons with PD in their study exhibited asymmetries in either balance control or weight bearing. More specifically, 75% of subjects showed asymmetry in balance control of 20 persons with PD.

Interestingly, Boonstra, van Vugt et al. (2014) indicated the lesser-affected side compensates for the more affected side, so that the individual does not appear to have more falls or step more than a control subject. To compensate for the deficits on the more affected side, the side less affected

would increase its contribution to overall balance control, which may be accomplished by increasing common neural input and/or cortical reorganization.

The current number of studies exploring asymmetries and balance in persons with PD is relatively low. Due to the low number of studies explaining asymmetries and balance, literature discusses similarities found in research of stroke or cerebral vascular accidents (CVA; Boonstra et al., 2014). Findings in the literature on stroke support reorganization of the cerebrum to assist in the recovery of function, but whether these findings can be extended to PD is still unknown.

Conclusion

The asymmetry and motor difficulties caused by PD can have a major impact on movement capabilities and safety. Currently, exercise and medication are the primary interventions for persons with PD, as there is no cure. By understanding the nature of motor asymmetry in persons with PD, we can add to the understanding of motor behavior in persons with PD, better understand the function of the basal ganglia and better serve rehabilitation efforts for this population.

Underlying anatomical structural investigation in persons with PD reveals abnormalities of the central nervous system and underlying structures, namely the basal ganglia with noted asymmetries of these structures. In healthy tissues, the human body can have typical functions. However, the natural process of aging can alter the previously typical functioning, and with the addition of an abnormal pathology such as PD, abnormalities in related domains develop even further irregularities.

The indications from this dissertation reveal an area of study with miniscule existing literature and gaps in related areas warranting further exploration. Motor behavior differences are evident between younger and older adults (Pryzbyla et al., 2011; Raw et al., 2012) , as well as between healthy older adults and persons with PD (Foster et al., 2008; Fling et al., 2018; Godi., 2021). Furthermore, asymmetries in motor behavior of younger adults appear to lessen with age (Pryzbyla et al., 2011; Raw et al., 2012; Teixeira, 2008). Interestingly in a similar pattern, asymmetries; in persons with PD appear to become more symmetrical with disease progression (Hoen & Yahr, 1967 ; Miller-Patterson et al., 2018).

The intersection of asymmetry of motor performance, gait, and balance and the potential relationship with hemispheric asymmetry in persons with PD is a complex notion. Current literature has attempted to inspect smaller areas, but the connection of the whole remains unexplored. The planned methods outlined in this proposal investigate the comparison of younger adults, older adults, and persons with PD in the motor behavior domain offer originality to the existing literature on motor and hemispheric asymmetry.

Interventions for these populations are crucial in attempting to slow down or prevent deterioration of functional mobilities. Participation in complex motor skills can have benefits on balance, potentially coordination, and injury prevention (Kraft et al., 2015). The practice of motor skills can have a positive effect on persons with PD, and improvements on these methods and interventions has the potential to improve or prevent reduction of motor performance in persons with PD. By further understanding the changes in asymmetry between younger adults,

older adults, and persons with PD, the potential for understanding the role of central nervous system may serve as the backbone to finding new methods of rehabilitative technique.

CHAPTER III

METHODOLOGY

Recruitment Procedures

This study was conducted after approval from the institutional review board (IRB) of Mississippi State University (MSU) was granted. Younger adults were recruited from the campus at MSU. Older adults and age-matched persons with PD were recruited from the areas and surrounding areas of Starkville, MS and West Point, MS. Recruitment flyers were posted at the Sanderson Center of MSU, the wellness center in West Point, MS and the Swift Center of West Point, MS. Participants were also attained by word of mouth. People who were interested in participating made contact with researchers in accordance with details of inclusion and exclusion criteria as outlined in the flyers. Researcher informed participants of more details about the study as well as precautionary measures such as avoiding caffeine and vigorous physical activity 24 hours before the scheduled appointment. Older adults had to be over the age of 65 years old, younger adults were to be between the ages of 18-35 and persons with PD could be of any age. Participants were to be right-handed for continuity, assessed utilizing the Edinburgh Handedness Inventory short form with 4 questions (revision of Oldfield, 1972). A score on the MMSE was to be >24 (older adults: mean = 29.7, standard deviation = 0.47; persons with PD: mean = 29.07, standard deviation = .9612). Researchers then scheduled a date for data collection with interested persons. On the day of data collection, participants were again screened on the aforementioned

criteria. In the case that persons were unable to perform data collection that day, participants were rescheduled.

A total of 20 young adults (10 females) ages were between 18-35 years old (mean = 25.5, standard deviation = 4.88), 20 older adults (10 females) aged 65 years or older (Mean = 73.5, standard deviation = 6.59) and participants with PD (5 female) aged between 57-86 years old (Mean = 71.2, standard deviation = 6.72) participated in the study.

Breakdown of Study Procedures and Protocol

The study was interested in gaining an understanding of movement differences between older adults, younger adults and persons with PD. All participants performed the same motor tasks, providing variables to describe motor behavior. Comparison of the three groups provide a comprehensive view of the effects of aging on motor performance as well as the role of the basal ganglia on motor performance. The fist research question concerns is there a change in asymmetry in the motor behavior with age. In the study of relationships between younger and older adults, the relationship between asymmetry in task performance could be observed. The second research question asks what are the differences in change in asymmetry between older adults and persons with Parkinson's disease. Utilizing motor tasks as a method of comparison between groups, researchers aimed to identify a relationship between person with PD and older adults' motor asymmetry Lastly, what is the relationship between PD symptoms and functional performance. Motor tasks from the UPDRS were compared to motor task performance to gain understanding of the impact of PD symptoms on motor behavior. Participants met with researchers for a single data collection session, outlined in Table 1.

Table 1

Data Collection Procedures

Procedures	Time	Notes
Greeting	1-2 minutes	Thank participant, brief conversation checking on mental and physical state. Discuss procedures for the visit.
Forms	12 minutes	Informed Consent, Edinburgh Questionnaire, General Questionnaire, MMSE
Purdue Pegboard Test	3 minutes	Each hand performed 3 times with left and right hand
Tapping Task	1.5 minutes	Each hand performed 3 times with left and right hand
Thumb Opposition Task	3 minutes	Each hand performed 3 times with L and right hand
Response Task	5 minutes	Each hand performed 3 times with left and right hand
Grip Strength	1.5 minutes	Each hand performed 3 times with left and right hand

Table 1 (continued)

Procedures	Time	Notes
TUG	2 minutes	3 different TUGs were performed. 1. Typical TUG 2. TUG while holding a big tray. A tennis ball was on a little tray, which was o the big tray. 3. TUG while counting backwards from 100 by 5s.
BTrackS Weight Distribution (WD)	2 minutes	Static bilateral standing with comfortable base of support (BOS). Participants were unable to view the screen and data was taken after 5 seconds of standing.
Btracks Limits of Stability (LOS)	10 minutes	Dynamic bilateral standing with comfortable BOS, moving center of gravity around BOS without lifting heels or forefeet. Participants were given 1 minute or until max potential reached. Participants were able to view the screen (biofeedback)

Table 1 (continued)

Procedures	Time	Notes
BTrackS single leg stance (SLS)	3 minutes	Alternating single leg stance (SLS) 3x per foot, beginning with L foot. Participants were unable to view the screen
Physical Activity Questionnaire	5 minutes	Researcher conducted questionnaire so participants better understood questionnaire
UPDRS	16 minutes	Researcher conducted UPDRS and provided further explanation of items, when asked.
Total	66 minutes	Total time varied by participant. Some persons with PD required up to 1.5 hours to complete session

*Tests and tasks were performed in random order and rest breaks were given or offered between tasks. Time between tasks were 10 seconds-30 seconds. Participants were provided explanations of proper task sequencing and a practice trial before performing recorded task to ensure proper sequencing and understanding of task, as well as to reduce learning effect. (For further details, see study protocol).

Independent Variables of this study were group (young adults, older adults and PD patients). Dependent variables in this study were the scores from motor tasks and the Unified Parkinson's Disease Rating Scale (UPDRS). Subjective measurements including International Physical Activity Questionnaire (IPAQ) and the UPDRS were administered with clarifying details provided, as needed. Participants were familiarized with all objective measurement tasks. Participants performed motor behavior tasks while seated comfortably at a desk, including *Purdue Pegboard Test, Repetitive Tapping task, Maximum Grip Strength, Thumb-Finger*

Opposition task, Response task. Objective measurements including Weight Distribution, Limits Of Stability and Single Leg Stance performed were on the BTracks board. Participants were able to view the screen for LOS, but not WD and SLS. The timed Up and Go (TUG) was regulation using a chair with back and arm rests, with tape on floor for participants to walk around at appropriate distance. Participants performed the balance tasks on a BTracks balance board and lastly performed 3 Timed Up and Go. The tasks performed on the BTracks Board were the weight distribution test, limits of stability test and a single leg stance test. The first of the three TUG tests was the traditional TUG, second was a TUG while holding an object and the third TUG was achieved while performing a cognitive task. The following tasks were performed by each participant with each hand individually (3 trials per task per hand):

1. Purdue Pegboard Test

Participants sat at a desk with the Purdue Pegboard in front (Figure 6). The task was to pick up small pegs and insert them into a row of holes on the board as quickly as possible in 30 seconds. The Purdue Pegboard Test was measured by number of pins placed in 30 seconds. Number of pins was recorded for each trial of 3 trials per hand. (Bohannon et al., 2021) The right hand began, alternating hands until each hand had performed the task 3 times each. Participants were instructed, "This is a Purdue pegboard. The object is to place as many pins in the holes as you can. We will start with your dominant hand, with 3 trials, then your other hand for 3 trials. Please take some time to practice with both hands to get familiar with the task. When I say 'ready, set go' please place as many pegs in the holes as you can. Ready, set, go." The dependent variable from this task is number of pegs placed in 30 seconds.

Figure 6

Purdue Pegboard Test.

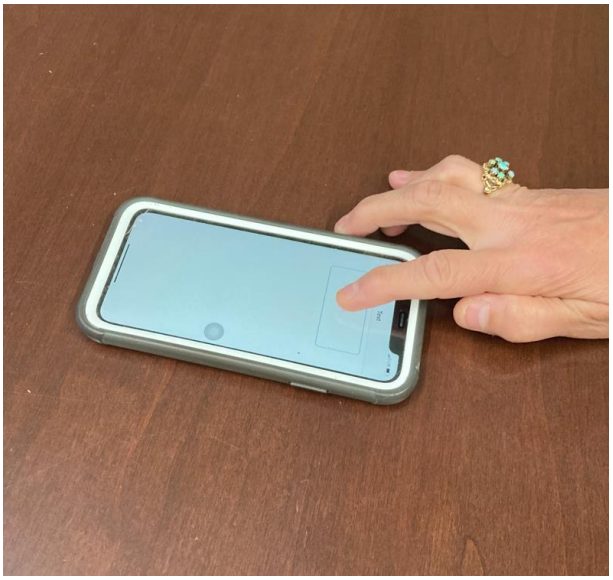
(MedQuip Inc., 2016)

2. Repetitive Tapping Task

Participants were asked to tap with one hand as fast as possible. Finger tapping was tested using an iPhone® app (SYBU Data Digital Finger Tapping Test, version 3.5; Bohannon et al., 2021) as seen in Figure 7. The app counts how many taps accumulated in 10 sec. The mean number of taps for 3 trials and the best (highest) number of taps for 3 trials were summarized for each hand (Bohannon et al., 2021). Right hand began, alternating hands until each hand had performed the task 3 times each. Participants were instructed, “This is the tapping task. Your goal is to tap as fast as possible on the phone screen with your pointer finger. We will start with your dominant hand, with 3 trials, then your other hand for 3 trials. Please take some time to practice with both hands to get familiar with the task. When I say ‘ready, go’ please tap as fast as you can. Ready, set, go.” The dependent variable from this task was number of taps in 10 seconds.

Figure 7

Tapping Test



Participant positioning based on Bohannon et al. (2021).

3. Maximum Grip Strength

Participants were positioned comfortably and squeezed a dynamometer (Figure 8) 3 times per hand, at maximum capacity. Participants were instructed, “This task measured grip strength. “Your goal is to squeeze the device as hard as possible. We will start with your dominant hand, with 3 trials, then your other hand for 3 trials. Please take off your jewelry. Please take some time to practice with both hands to get familiar with the task. When I say ‘Ready, set, go….squeeze, squeeze, squeeze. And relax.” Please squeeze as hard as you can.” The dependent variable from this task was strength of grip measured in pounds.

Figure 8

Max Grip Strength.

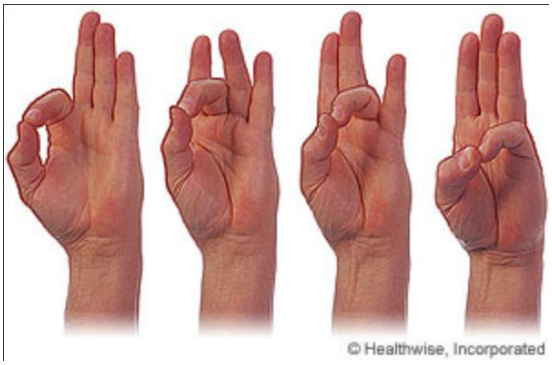
(RehabMart, 2023)

4. Thumb-Finger Opposition

Participants were positioned comfortably and asked to touch their thumb to each finger, as quickly as possible, completing 5 rounds (Figure 9). Time to complete 5 rounds was recorded. Each hand performed independently, 3 trials per hand. Participants were instructed, “This is the finger opposition task: You touch your thumb to each finger, sequentially in each direction for 5 rounds. Here, let me demonstrate. Would you like me to demonstrate more slowly? A round begins with the pointer finger touching the thumb. Please do this task as fast and accurate as possible, without skipping a finger. You will do this 3 times with each hand. I will keep track of rounds. Please take some time to practice with each hand. When I say ‘ready, go’ please tap as fast as you can. Ready, set go.” The dependent variable from this task was time in seconds to complete 5 rounds.

Figure 9

Finger Opposition Task.



(Alberta, 2023)

5. Response Task

Participants were seated comfortably at a desk with lights on a table in front of them (Figure 10). Participants were instructed to tap the blue color. Three pods lit up simultaneously, and the participant's goal was to tap the correct color as quickly as possible, ignoring the other two colors, orange and purple. Five trials per hand were performed. Response time was recorded, as well as number of incorrect trials and errors. Participants were instructed, "The object of this task is to hit the blue color as quickly as you can. There will be other colors, purple and orange that light up, please ignore them. There will be several hits per trial. You will do this 3 times with each hand. make sure you hit it relatively hard. Let's take some time to practice with each hand." The dependent variables derived from this task was average response time as well as number of hits.

Figure 10

Response Time Task with Blazepods

This is an original photo of the response task. This is not an actual participant.

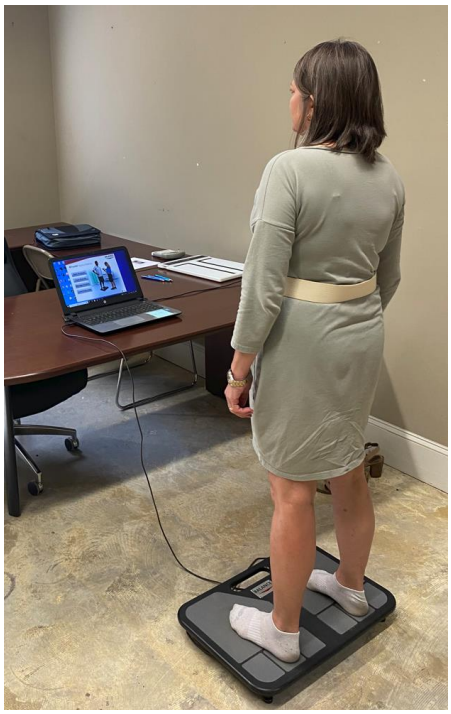
6. BTracks Balance Board

Participants stood on a balance board and performed three pre-programmed tasks using the BTrackS Balance Plate (Figure 11) and BTrackS™ and Assess Balance Advanced Software (figure 12). Tasks included the static balance test, Weight Distribution task (3 trials), Limits of Stability task for 3 trials (moving center of gravity around base of support) and a single leg stance task for 5 seconds each of the 3 trials per foot. Central pressure measurements, and other data were recorded. Dependent variables from this task included average center of pressure, total area, path length, maximum velocity, average velocity and distances measured from anterior to

posterior and medial to lateral. The dependent variables were indicators of participants' standing balance abilities.

Figure 11

BTrackS Balance Plate.



This is an original photo featuring BTrackS™ Balance Plate + BTrackS™ and Assess Balance Advanced Software. This is not an actual participant.

Figure 12

Limits of Stability Access software.

This is an original photo featuring BTrackS™ Assess Balance Advanced Software

7. Timed Up and Go

The Timed Up and Go (TUG) measures time to perform the task of walking 3 meters safely. Participants began with their backs against the chair's backrest. On "Go," participants' began walking as fast and as safely as possible the correct distance, indicated by duct tape on the ground. Time stopped when participants' backs were again on the chair's backrest. The three conditions are the (1) typical TUG, (2) TUG with manual task (carrying a tray) and (3) TUG with cognitive task (Counting down in multiples of 5). Three trials per condition will be performed and the average performance will be recorded. The dependent variable for the TUG was time to complete the TUG. Set up for the TUG is pictorially represented in Figure 13.

Figure 13

Timed Up and Go

This is an original photo featuring the starting position of the TUG. This is not an actual participant.

CHAPTER IV

PROJECT 1: UNDERSTANDING ASYMMETRY WITH AGE

The comparison of asymmetrical presentations in younger and older adults will measure the changes in asymmetry with age. This phase aims to determine if there is a change in asymmetry with age.

Introduction

In the study by Pryzbyla et al., (2011), older and younger adults performed aiming tasks with each hand. The study reported reduced lateralization, exhibited by straighter non-dominant paths relative to youngers subjects. Results indicate reduction in asymmetry between hands in older adults. One suggested source of this phenomena (Watson et al., 2022), is the reduction or elimination of dominant-hand advantage in older adults causes the asymmetry reduction in older adults, such that the dominant hand reduces to a greater extent than the non-dominant hand with age.

Older adults exhibit more symmetrical motor performances than their younger counterparts. For example, in a study by Raw et al. (2012), asymmetries between hands were found in younger adults, but not in older adults when performing a tracing task with both hands. Furthermore, Francis and Spirduso (2000) explored Purdue Pegboard and tapping tasks, finding performance differences between older and younger adults, as performance of the right hand in younger adults was more robust. Teixeira (2008) also provided support for reduced asymmetry in motor

behavior patterns with age. The research demonstrates a change in asymmetry with age, where older adults' right hand versus left hand performance is more symmetrical.

It should be noted however, that there is still some discrepancy in the literature as to which tasks display the most pronounced findings of asymmetry between younger and older individuals motor task performance. From a study conducted by Francis and Spirduso (2000), the results indicated significant hand by age interactions in two of the five motor tasks performed by older and younger individuals. Conclusions indicate task complexity may have an impact on motor performance results. Kalish et al. (2006) explored motor tasks of the upper extremity including wrist-finger tasks, aiming and precision hand-arm task further supporting evidence of increased symmetry with age in fine motor tasks. Francis and Spirduso (2000) further suggests changes with age may be task specific, however more investigation is needed to discover which tasks are more effective in pronouncing motor performance asymmetry.

Studies have reported age-related changes in cortical activation patterns. For example, Davis et al. (2008) discusses posterior-anterior shift in aging (PASA), and Cabeza et al. (1997) identified changes in neuronal activation and connectivity when older adults performed cognitive tasks. These changes include reduced hemispheric lateralization and cortical overactivation. Further research of cortical changes with age identified patterns and suggested mechanisms behind overactivation and hemispheric lateralization associated with aging as well as a possible connection between reduced hemispheric lateralization and reduced motor asymmetry with aging (Hill et al., 2020). The link between hemispheric lateralization and age-relate reduction of motor asymmetry is a currently unknown. Motor control and motor behavior is ultimately controlled by

the central nervous system. Reduced functioning with older age can be the result of declining physical structures of skeletal muscle or declining cognitive processes and neurological activation, or a combination of both.

To further understand the motor function decline of older adults and relatively symmetrical presentation compared to younger adults this study compared motor function of left and right upper extremities between older and younger adults. The purpose of this part of the overall study was to further the investigation of asymmetry and motor behavior in a variety of tasks to investigate the research question of is there a change in asymmetry in motor behavior with age? Another purpose of this study was to further explore the component of tasks specificity as related to motor asymmetry reduction with age, as not all tasks in past literature reveal common results. Researchers hypothesized age is a determinant in age-related asymmetry trends, and that specific components of tasks are important to consider in the study of age-related asymmetry reduction.

Methods

The project was approved by Mississippi State University's Institutional Review Board. Participants for this study consisted of 20 young adults (10 females) with an age range between 18-35 years (mean = 25.5, standard deviation = 4.88) and 20 older adults (10 females) aged 65 years or older (Mean = 73.5, standard deviation = 6.59). To qualify for the study, a score of higher than 24 on the Mini-Mental State Examination (MMSE) was essential for older adults (Mean = 29.7, standard deviation = 0.47). All participants were right-handed of whom reported no recent injuries, cardiovascular or orthopedic pathologies that would interfere with their abilities to perform the tasks. Participants completed the Edinburgh Handedness Inventory short form with 4 questions (revision of Oldfield, 1971). After a laterality quotient was determined to

be .60 or higher, participants were given full disclosure of the study and all questions were answered; participants signed the informed consent.

Tests and Outcomes

Objective tests included the Purdue Pegboard test (PPT), grip strength test (GS), response task (RT), thumb opposition task (TO), tapping task (TT), three variations of timed-up-and-go test (TUG), single leg stance task (SLS), Weight Distribution test (WD) and Limits of Stability test (LOS).

Before performing each task, participants were familiarized with the task through practice. The upper extremity motor tasks were completed three times with the right hand and three times with the left hand, starting with the right hand and alternating until all 6 trials were completed. Response time task utilized Blazepod^{TM} (BlazePod Inc., Miami, FL, USA) employing light emitting diode (LED) color lights. The Purdue Pegboard test (Lafayette Instrument Model #32020) was performed with the right and left hand. Bimanual task was not necessary for the purpose of this study.

Statistics

Data analyses were conducted using IBM SPSS 24 with an alpha level of .05. The two-way analysis of variance (ANOVA) was conducted to examine if the variance of younger adults' left and right sides were different from the variance of older adults' left and right sides. Separate 2 between group factor (age group: young, old) × 2 within group factor (hand: left and right) mixed-design ANOVAs were conducted to inspect age and group-related effects on manual performance and clinical symptoms.

Results

Purdue pegboard task revealed significant main effects of hand, $F(1,38) = 46.8$, $p < .001$ and Group, $F(1,38) = 63.3$, $p < .001$ and a significant interaction effect of $F(1,38) = 12.21$, $p = .001$. Tapping revealed significant main effects of hand, $F(1,38) = 70.97$, $p < .001$ and Group, $F(1,38) = 10.78$, $p = .002$ and a significant interaction effect of $F(1,38) = 6.69$, $p = .014$. Similarly, Grip Strength revealed significant main effects of hand, $F(1,38) = 25.48$, $p < .001$ and Group, $F(1,38) = 6.39$, $p = .016$ and a significant interaction effect of $F(1,38) = 6.31$, $p = .016$. Results from Purdue Pegboard, Tapping and Grip Strength all indicate differences between left and right hands of each group, as well as differences between the younger and older adults as well as a significant interaction effect, indicating a reduction of asymmetry between hands associated with age.

Thumb Opposition revealed significant main effects of hand, $F(1,38) = 17.50$, $p < .001$ and Group, $F(1,38) = 12.62$, $p < .001$. Interestingly, there was no significant findings for the interaction effect, although significant findings were found in both main effects of hand and age. Response Hits revealed a significant main effect of Group, $F(1,38) = 11.18$, $p = .002$, as did Response Average Time $F(1,38) = 12.16$, $p = .001$. Results indicate younger adults and older adults exhibited differences in manual performance across all tasks in this study. Results are summarized in Table 2.

Table 2

p-Values from the 2-Way ANOVA

Task	Hand	Group (Age)	Hand*Group
Purdue Pegboard	<.001*	<.001*	.001*
Tapping	<.001*	.002*	.014*
Thumb Opposition	<.001*	<.001*	.246
Grip Strength	<.001*	.016*	.016*
Response Hits	1.00	.002*	1.00
Response Average Time	.550	.001*	.986

Significant values are of Purdue Pegboard task, tapping task and grip strength are represented in figure 14, figure 15 and figure 16. The graphs depict increased asymmetrical performance of younger adults compared to older adults in each task. Differences in slopes between younger and older adults indicate a reduced asymmetry with age.

Figure 14

Purdue Pegboard Test

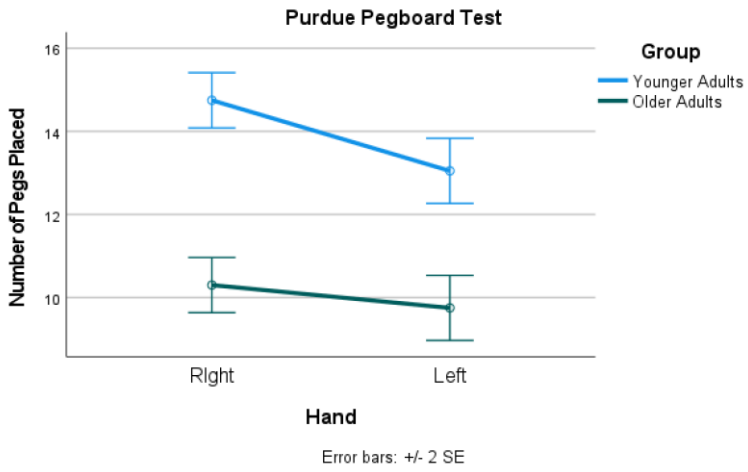


Figure 15

Tapping Task

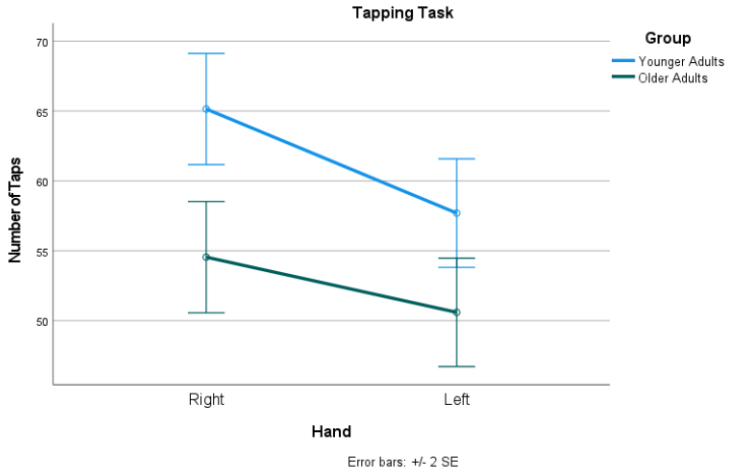
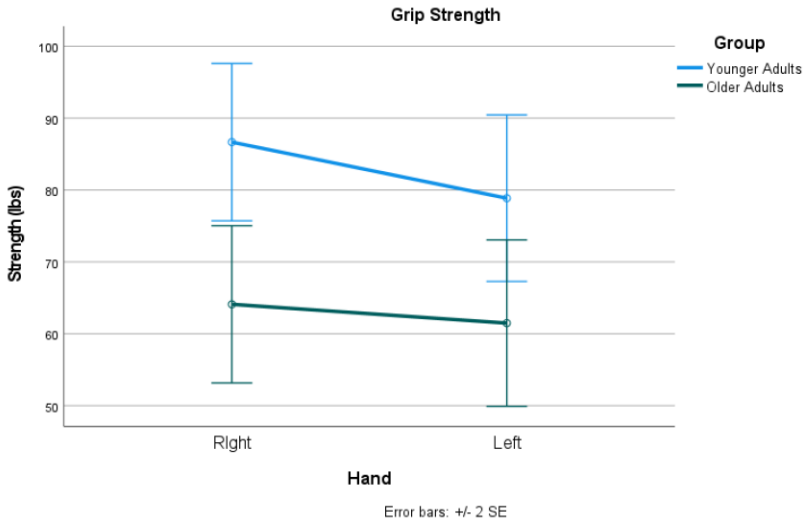


Figure 16

Grip Strength Task



Results from the response task indicate a general slowing for adults in both hands. Right and left hand for older adults was significantly slower than right and left hand of younger adults (Figure 17). Similarly, number of hits for response task was also found to be significantly different between older and younger adult's left and right hands (Figure 18).

Figure 17

Response Time Task – Time

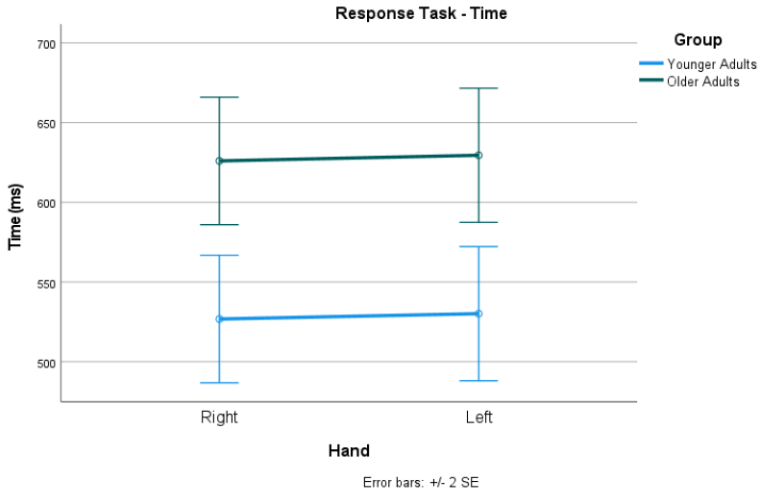
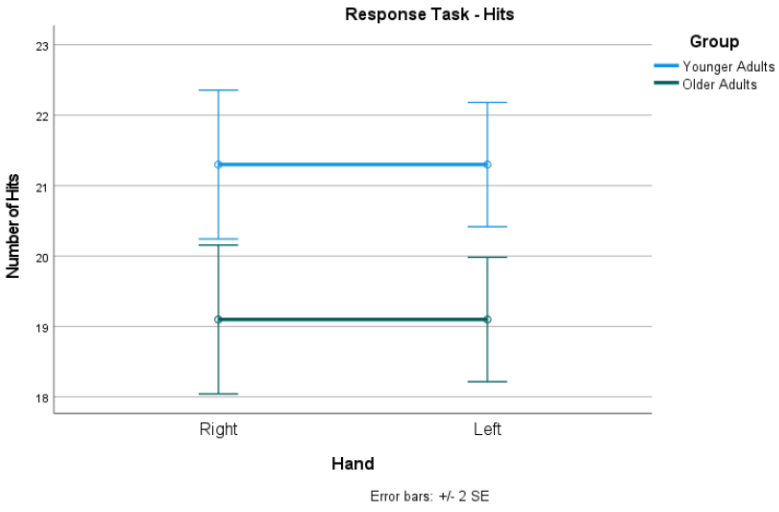


Figure 18

Response Time Task - Hits

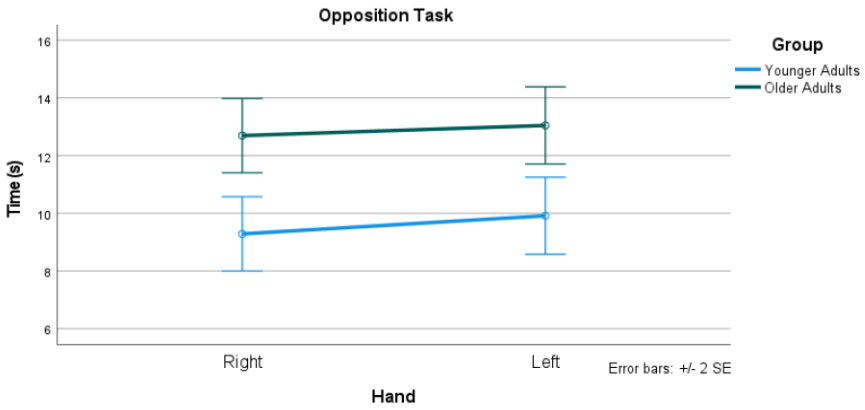


Thumb opposition results indicate a significant difference in age, with younger adults able to perform the thumb opposition task faster than older adults with both hands. A main effect of

hands is seen in younger and older adults as well indicating a difference between left and right hands of the two groups. The interaction effect was not significant, as both hands appear to decline similarly (Figure 19). However, observations of the figure 19 graph reveal familiar trends of the right hand (dominant hand) reducing to a greater extent than the left (nondominant hand) from younger to older adults, which demonstrates increased asymmetry in younger adults and reduced asymmetry of older adults.

Figure 19

Opposition Task



Discussion

The present study aimed to examine movement transformations associated with aging. In the comparison of younger adults to older adults, differences in manual performances were compared using fine motor, upper extremity tasks of Purdue Pegboard, Tapping task, thumb opposition task, response time task and grip strength. Reduction of asymmetry in motor performance of older adults was identified in the Purdue pegboard, tapping and grip strength tasks. The difference between older adults left and right hand is statistically different from the

difference of younger adults left and right hands. These findings appear to agree with Raw et al. (2012), Francis and Spirduso (2000) and Teixeira (2008).

Results for all tasks indicate a difference in performance between the younger adults' right hand and the older adults' right hand. Similarly, when comparing the difference of left hand between younger and older adults, performance declines. Interestingly, the performance of the right hand appears to reduce to a greater extent than the left hand with age, lending endorsement that upper extremity motor performance of older adults' results from a decline of both left and right hands, with the right hand declining at a more accelerated rate than the left hand. These findings support the dedifferentiation hypothesis, as older adults utilize more cortical resources, but motor performance did not improve (Cabeza, 2002).

This motor behavior pattern may be attributed to a reduction in function of the right hand, thus right-hand advantage appears to reduce with age, resulting in a more symmetrical performance in older adults. It is reasonable to suspect older adults use both hands more evenly for compensatory purposes due to decreases of motor function occurring with natural aging resulting in a more symmetrical performance between hands. Older adults' right hands would not be used as much, leaning towards more symmetrical practice between hands. (Kalisch et al., 2006). Results appear to be task specific, as some tasks showed reduced motor asymmetry with age while other tasks did not. These conclusions are consistent with Francis and Spirduso (2000), who reported that changes with age may be task-specific. Another consistency with Francis and Spirduso (2000) and Kalish et al. (2006) is the plausible role of task complexity. For example,

the Purdue pegboard task combines dexterity, precision, and speed of fine motor performance, increasing task difficulty, consequentially encouraging differences between the groups.

Recent literature continues to connect age-related neural functioning models to age-related changes in motor behavior (Hill et al., 2020), with an emphasis on expanding neurological models of asymmetry to the asymmetrical motor behavior domain. Reduced laterality of hemispheric asymmetry is observed with aging, which influence reduced manual asymmetry with aging. However, the neuronal changes with aging may not produce the general motor asymmetry change that occurs with aging (Teixeira, 2008). As this study concludes task specificity plays a role in background mechanisms explaining why some motor tasks display asymmetrical presentations while others do not, it is plausible to embrace the component of task specificity's effect on changes of cortical activation and its relationship to reduced asymmetry in the production of motor movements.

Interestingly, the tasks that took less cognitive effort (ex. tapping, Purdue Pegboard and grip strength) yielded significant results indicating reduction of age-related motor asymmetry. In contrast, the tasks in this study that did not show a significant interaction effect (thumb opposition task and response task) required more cognitive thought from the participants to perform the tasks correctly. Rationally, the cognitive thought and decision-making process may be the component of these tasks which resulted in the absence of reduced age-relate asymmetry. Observed findings indicate neuro-motor connection speed of task performance is an important component to highlight the age-related motor asymmetry. Accordingly, as cognitive processes decline in older adults, the effect of cognitive decline is symmetrical on motor performance of

the left and right upper extremities. Perhaps a significantly complex task does not allow researchers to observe the direct neuro-motor connection due to the decision-making processes behind the action. With reference to age-related hemispheric changes, older adults exhibit increased bilateral activation (Cabeza et al., 1997). Consequently, it appears that the overactivation of bilateral hemispheres results in increased symmetry between the hands and poorer overall motor performance consistent with dedifferentiation hypothesis of cognitive changes with age (Reuter et al., 2015). Subsequently, the overactivation of hemispheric processes does not appear to compensate for deficits in the motor domain. However, more research containing tools for cognitive investigation is indicated to conclude these observations and extensions to the cognitive domain.

As small sample size is one of the limitations of this study. A larger sample size may account for the differences in function as well as strengthen the observations. This study can infer associations, but only speculate causality. Another imitation is the lack of kinematics such as, velocity, acceleration, and other kinematic variables in upper extremity tasks. These areas could provide more specific data to describe the observations found in this study.

This study concludes indications of reduced asymmetry with age in the fine motor tasks of Purdue pegboard, tapping and grip strength, but not in thumb opposition and the response task, as the difference between hands is notably larger in younger adults compared to older adults. Task specificity appears to be another crucial component to understand in the study of motor asymmetry with aging, and particularly observed in this study, the cognitive decision-making component appears to reduce observations of age-related asymmetry reductions. Furthermore,

findings of age-related manual asymmetry with respect to fine-motor tasks are evident in tasks requiring speed, dexterity, precision or strength. Conclusions include reduced motor asymmetry of tasks involving grip strength or manual dexterity and speed. Future studies should focus on complex tasks, but not of significant complexities whereby cognitive thought and decision-making is an important component to task success. Complex tasks involving decisions and higher cognitive thought may be testing participant's abilities in executive functioning, or speed of cognitive functions to make decisions, rather than the neuro-motor process involved in motor behavior. Additionally, right hand motor performance declines appear to contribute to the reduction of asymmetry in manual performance with age. These findings help scientists and researchers further understand the connection between motor and cortical processes in the aging population, and to add to the existing literature, potentially substantiating current theories surrounding hemispheric and motor asymmetry behavior. To more completely describe the potential relevance to clinical settings and functional impacts of cortical and motor reduction of asymmetry with age, further research is necessary.

CHAPTER V

PROJECT 2: UNDERSTANDING FINE MOTOR ASYMMETRY IN PD

The comparison of motor asymmetry between healthy older adults and persons with PD measured the change in motor asymmetry between the two populations. The goal was to examine how CNS would affect the reduction of motor asymmetry in the aging population.

Introduction

PD is essentially the result of decreased dopaminergic neurons of the substantia nigra, subsequently having a negative effect on every muscle in the body. Cardinal symptoms are bradykinesia, tremors, rigid muscles and postural instability (Bereczki, 2010). With no current cure for PD, patients rely on treatments and interventions to slow the progression of the disease. An early diagnosis facilitates an earlier start to neuroprotective therapy which encourages a better prognosis, and reduced symptom progression. However, clinical symptoms begin to appear when persons with PD lose more than seventy-five percent of dopamine neurons in the nigrostriatal pathway (Lloyd, 1977). In that time, clinical manifestations can include tremor, bradykinesia, cogwheel rigidity and difficulties in gait and posture.

Asymmetric disease symptoms are typical for this population (Uitti et al., 2005). As such, staging of PD, using the Hoehn and Yahr (1967) staging model, includes the clinical presentation of asymmetric to bilateral symptoms, as well as decline in function (Hoehn & Yahr, 1967). Yust-Katz et al. (2008) noted that a characterization of PD is asymmetric symptoms with a trend of

symptom onset on the individual's dominant side, but literature is still inconclusive regarding the hand-dominance symptom origination theory.

Typically, motor signs and symptoms of PD begin asymmetrically (Hoehn & Yahr, 1967; Lee et al., 1995). Evidence suggests symptoms remain asymmetric with advancing PD (Miller-Patterson et al., 2018). Furthermore, a study by Djaldetti et al. (2006) reported symptoms are worse on the side of onset and continues after the disease progression develops bilaterally. What these studies collectively indicate is that symptoms begin on one side, and progressively the person becomes bilaterally involved.

In the PD pathology, the basal ganglia have also been shown to have asymmetries (Djaldetti et al., 2006). One substantia nigra appears to deteriorate first, compared to the contralateral substantia nigra, but both deteriorate symmetrically as the disease progresses (Kempster et al., 1989).

Cabeza (2002) discusses a term called HAROLD to name the phenomena occurring in older adults' cortex compared to younger adults that postulates lateralization of brain activity decreases with age. Raw et al. (2012) continued the discussion consistent with HAROLD model with motor asymmetry reduction in older adults. In this theory, increased cortical activation is how the cortex compensates for the naturally occurring deficits caused by aging. Theoretically, by increasing neuronal activity, the result is improved motor skill performance. Researchers in recent years postulate a connection in older adults between changes in hemispheric asymmetry and reduced motor asymmetry (Hill et al., 2020).

Results from Yokochi et al. (1985), a study that compared left and right index finger reaction times, indicated that patients who were affected bilaterally by neurological signs exhibited slower reaction times on the more affected side. Although both sides are affected in later stages, the asymmetry persists as one side is more affected than the other. One theory suggests that with an affected preferred hand, superiority switches to the left hand which may ultimately result in a change of hand preference (Scharoun et al., 2015). These results may explain why persons with PD become increasingly functional bilaterally.

Multiple motor tasks were utilized to further the research of fine motor skills in persons with PD. Aoki et al. (2016) found significant asymmetry in a task performed with the index finger and touchscreen in right- and left-handed individuals, indicating the credibility to the use of fine motor tasks in future studies as a method to explore asymmetry. Furthermore, reaction times in persons with PD were compared to controls in a study by Yokochi et al. (1985). The study used electromyography recordings of an index finger extension task of both hands and discovered slower reaction times on the more neurologically affected side than the less affected side. Haaxma et al. (2010) explored fine motor skill dexterity utilizing the Purdue pegboard test, and compared persons with PD to age-matched controls which revealed an ROC curve with 95% sensitivity, 89% specificity and AUC of 0.97. Vasylenko et al. (2022) utilized the Purdue pegboard test to examine manual behavior of older adults with mild cognitive impairment. Results indicated a connection between declined neural functioning and reduction of manual asymmetry. These studies support the prospect to use Purdue pegboard test, fine motor tasks and reaction time tasks as tools for investigating motor asymmetry in persons with PD.

Current literature is considering the importance of left- and right-side comparison in persons with PD. Yokochi et al. (1985) compared neuro-typical adults to persons with PD in a finger extension task using electromyography recordings to explore reaction times. Findings indicate persons with predominant neurological signs on left side displayed slower reaction times regardless of the which hand performed the task in comparison to both neurologically typical subjects and persons with PD who had more minor signs on the left side. Implications suggest worsening performance bilaterally in persons with more severe left-sided symptoms, and the use of reaction time and simple tasks is warranted in future investigation of motor behavior in persons with PD.

As research indicates, asymmetry of the cortex and motor behavior appears to be a pattern in older adults and persons with PD. A plausible hypothesis would infer a connection between the central nervous system and motor behavior asymmetry. To investigate a potential link between central nervous system and asymmetrical motor performance, this current study compared the motor performance of persons with PD and older adults' left and right upper extremities during the performance of multiple tasks. This part of the overall study aims to answer the question: what are the differences in change in asymmetry between older adults and persons with PD. The research hypothesis speculates basal ganglia plays a role in further reduction of motor asymmetry.

Methods

The Institutional Review Board of Mississippi State University approved the study before research began. A total of thirty-five people participated in this study. Older adults and persons with PD were gender and age matched. Twenty older adults (10 females) aged 65 years or older

(Mean = 73.5, standard deviation = 6.59) and 15 persons with PD (5 female) between ages 57-86 (Mean = 71.2, standard deviation = 6.72) were recruited for the study. A score on the Mini-Mental State Examination (MMSE) of greater than 24 was required for older adults (Mean = 29.7, standard deviation = 0.47) and participants with PD (Mean = 29.07, standard deviation = .9612). All participants reported negative for cardiovascular or orthopedic problems and recent injuries that would otherwise alter their ability to perform tasks in the study.

The Edinburgh Handedness Inventory short form with 4 questions (revision of Oldfield, 1972), confirmed all participants as being right-handed via a laterality quotient of .60 or higher. Informed consent was given by all participants. “On” and “off” times were self-assessed by participants with PD in accordance with their medication schedule to encourage more pronounced symptoms during data collection.

Tests and Outcomes

Familiarization was provided for each task. In a random order, participants completed the questionnaires and tasks. Objective tests include grip strength test , Purdue Pegboard test , thumb opposition task, response task, and tapping task. Beginning with the right hand, manual tasks were performed three times each hand. Blazepod^{TM} (BlazePod Inc., Miami, FL, USA) were used for the response time task, which utilized LED color lights. The Purdue Pegboard test (Lafayette Instrument Model #32020) was performed unilaterally with both hands. Bimanual skill was not investigated in this study. There was one outlier from a participant with PD, so this person’s data was not used in the TO part of the study.

Statistics

An alpha level of .05 was utilized and IBM SPSS 24 was used for data analysis. A two-way ANOVA was conducted to examine if the variance between older adults left and right sides were different from the variance between persons with PD left and right sides.

Results

Tapping task revealed significant main effect of hand, $F(1,33) = 6.33$, $p = .017$ and hand*group interaction $F(1,33) = 8.30$, $p = .007$, indicating a difference in left and right hands of participants, and a reduction of asymmetry in persons with PD compared to older adults (Figure 20). The hand difference between older adults is different from the hand difference of persons with PD. The significant interaction effect indicates dysfunction of the basal ganglia results in increased symmetry between hands in the tapping task.

Purdue pegboard revealed significant main effects of hand, $F(1,33) = 8.33$, $p = .007$ and Group, $F(1,33) = 12.52$, $p = .001$. Results indicate groups exhibited differences between hands as well as significant differences in performance of the Purdue pegboard between older adults and persons with PD (Figure 21), as persons with PD performed significantly slower than older adults. There was no significant interaction effect $F(1,33) = .08$, $p = .784$.

Figure 20

Tapping Task

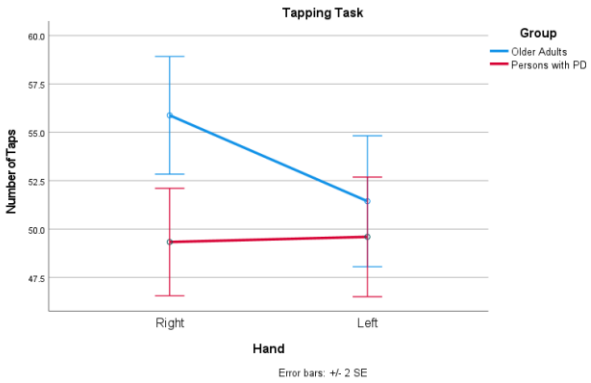
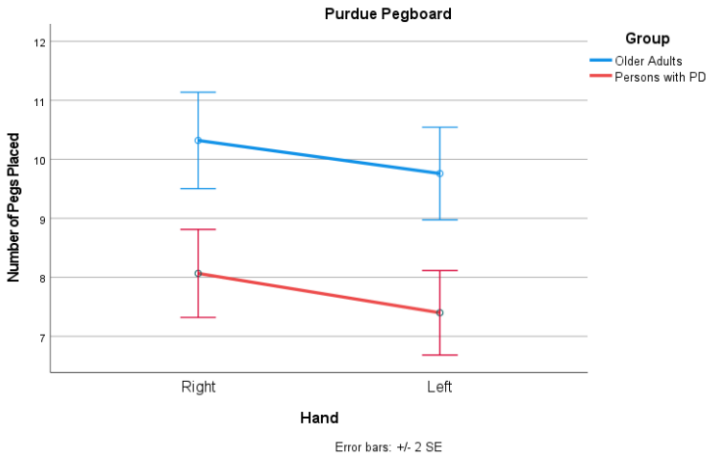


Figure 21

Purdue Pegboard Task



The lack of a significant interaction effect as illustrated in Figures 22-25 indicate that there is no increase symmetry in persons with PD compared to older adults. However, thumb opposition

task exhibited near-significant results of F(1,33) = 3.30, p = .079 for group indicating a trend of persons with PD performing TO slower than older adults.

Response average time revealed a significant main effect of group, F (1,33) = 5.81, p = .022, indicating a significant difference in scores between older adults and persons with Parkinson's disease (Fig 24). Lastly, grip strength revealed a significant main effect of hand, F (1,33) = 8.88, p = .005, revealing a significant difference in left and right hands (Fig 25).

Figure 22

Opposition Task

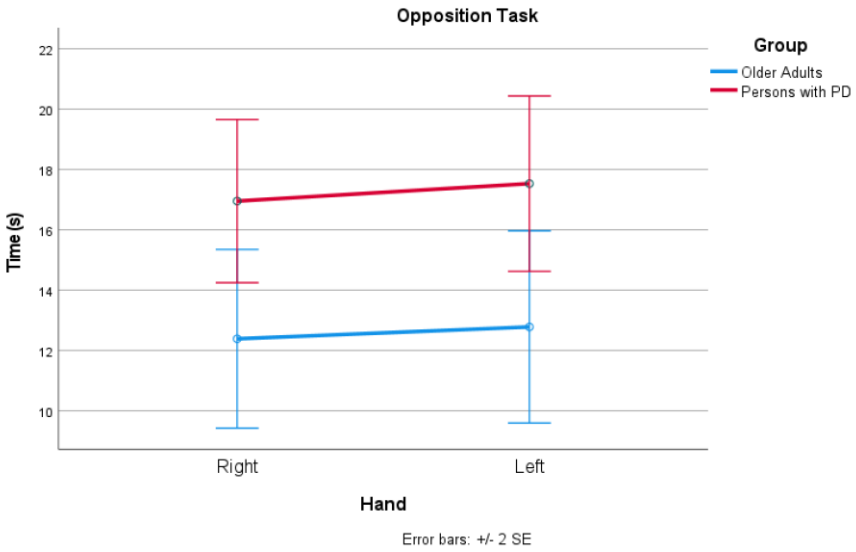


Figure 23

Response Time Task – Hits

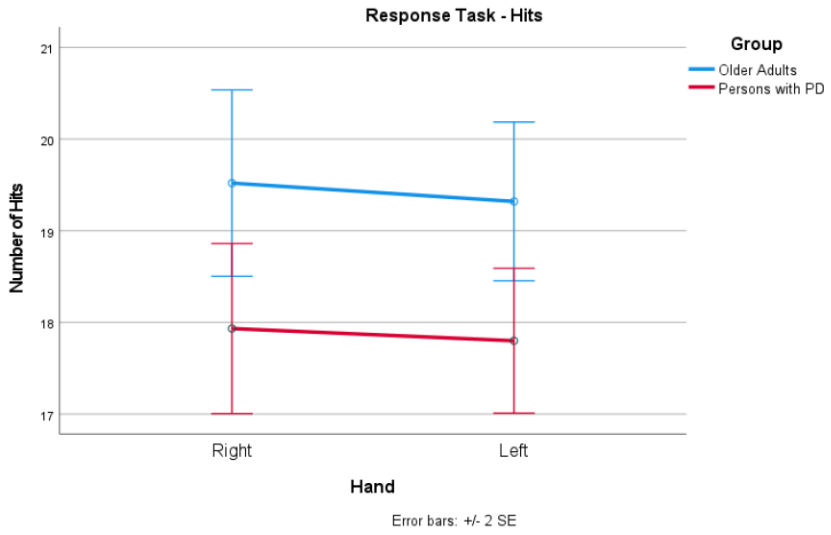


Figure 24

Response Time Task -Time

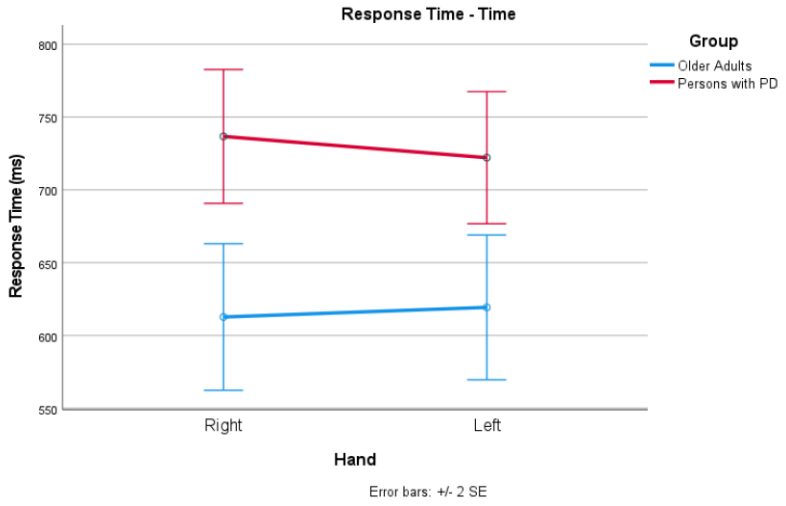


Figure 25

Grip Strength Task

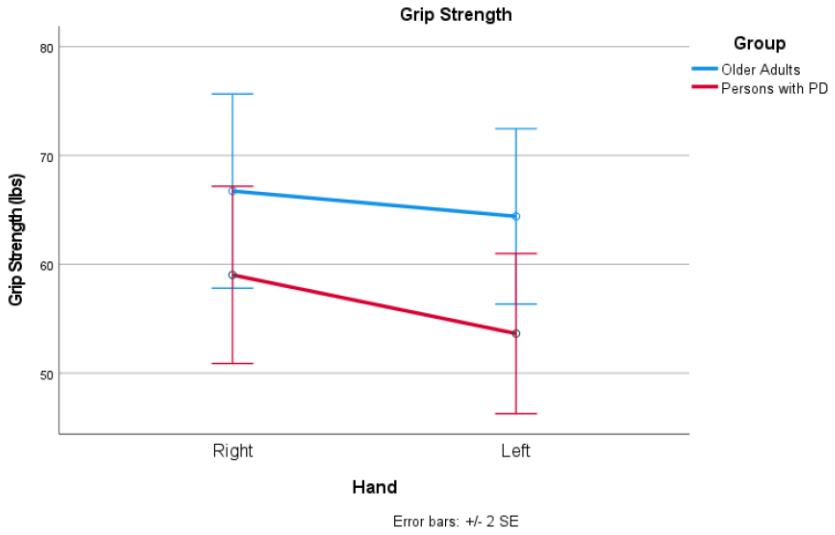


Table 3 summarizes statistical results for tasks performed in this part of the study. The column labeled “Hand” indicates the comparison of left and right of the groups. The “Group” column indicates a difference between older adults and younger adults, and the “Hand*Group” column indicates if the tasks supports age-related changes of motor asymmetry .

Table 3

p-Values Retrieved from 2-Way ANOVA

Task	Hand (Left v. Right)	Group (OA v. PD)	Hand*Group
Tapping	.017*	.269	.007*
Purdue Pegboard	.007*	.001*	.784
Thumb Opposition	.206	.079	.756

Table 3 (continued)

Task	Hand (Left v. Right)	Group (OA v. PD)	Hand*Group
Grip Strength	.005*	.373	.309
Response Hits	.753	.144	.753
Response Average Time	.523	.022*	.297

Discussion

The purpose of this study was to assess the role of the central nervous system as related to reduced asymmetrical motor performance with aging. Tapping results indicate further reduction in hand asymmetry as seen in Fig 1. However, Purdue pegboard, grip strength, response task, and thumb opposition task indicated non-significant interactions as illustrated in figures 3-6. Aggregate results indicate that there is an absence of increased hand performance symmetry in persons with PD compared to older adults. Subsequently, PD pathology generally does not further the reduction of hand asymmetry compared to older adults. Nevertheless, results indicated symmetrical reduction in motor behavior performance, with one side performing marginally poorer than the other. Findings concur in the notion of asymmetric symptoms in the beginning of the disease process (Wang et al., 2015), and symptoms continue to worsen bilaterally as the disease progresses. Conversely, current evidence does not support the notion of a shift in superior hand in persons with PD as noted in Scharoun et al. (2015), which would lead to a new preferred hand.

Significant main effects of group when comparing persons with PD to older adults confirm overall slowing down of fine motor tasks in persons with PD compared to age-matched older adults. Both the left and right hands were slower for PD participants than older adults in all tasks, with significant differences in Purdue pegboard and response time tasks. The results agree with Dominey et al. (1995) indicating person's with PD "better" side performed worse than the non-dominant hand of older adults indicating impairments of PD are bilateral, but have a predominantly affected side. As persons with PD exhibit symptoms of bradykinesia as well as akinesia, these symptoms directly interfere with the ability to initiate movement and move quickly, thus the left and right hands of persons with PD were slower than left and right hands of older adults. PD further worsens motor functioning of older adults in response time, hand dexterity and speed.

Task characteristic differences may be an underlying cause for the varied results. The Purdue pegboard components include dexterity, precision and speed, while the response time task's main component is speed. Task specificity may be a key factor in identifying significant differences between older adults and persons with PD. The component of task specificity has been discussed in literature comparing older and younger adults' (Francis & Spirduso, 2000; Teixeira, 2008) upper extremity asymmetry, and similarly can be extended into the PD research domain. For example, previous research on asymmetry reduction in older adults indicated tasks of increased complexity yielded significant differences (Fancis & Spirduso, 2000; Kalish et al., 2006), whereas this study yielded significant results in the least complex task. Perhaps reduced task complexity is important for studies working with persons with PD is beneficial. The tapping task is primarily focused on speed to which bradykinesia, a hallmark symptom of PD, would directly

impact suggesting future studies assessing motor performance of person with PD may find more robust results in matching tasks to flagship PD symptoms.

The absence of increased asymmetry between left and right hand of persons with PD compared to older adults leads this author to believe the potentially limited roles the basal ganglia play in age-related performance changes at the motor level. Based on these results the role of basal ganglia in motor movement does not appear to have a significant effect on reducing asymmetry of motor performance. One suggested theory is that dysfunction was not robust in one side due to compensatory strategies to overcome PD pathology that impacts motor behavior (Boonstra,VanVugt et al., 2014; Bezard et al., 2003). Studies focused on HAROLD and other models deliberating cognitive and motor asymmetry reductions with age should continue to research cortical areas, opposed to subcortical areas, as cortical areas appear to be more associated with cognitive and motor behavior changes with age. Although substantia nigra deterioration is typically asymmetrical, the decreased dopamine appears to have a more global effect on motor performance, affecting both upper extremities more evenly. From the non-statistically significant, but marginal difference between hands in persons with PD, results do indicate a more involved side. Dominey et al. (1995) compared 7 persons with pd and 7 age-matched older adults in mental motor imagery and manual performance of a fine motor task with results indicating both exhibited asymmetric performance. Furthermore, Dominey et al. (1995) found worse performance on the more involved side. Combined with the current study, it is reasonable to suggest the more involved side of this study correlates to a worsening cortical hemisphere affected by PD pathology and basal ganglia degeneration.

The current findings compliment the HAOLD model (Cortez 2002) theory suggesting increased cortical activation to compensate for reduced functioning. Results of this study expand HAROLD's cognitive theory into the movement behavior domain, suggesting muscle and body deterioration is the driving force in age-related asymmetry reductions due to the lack of further-reduced asymmetry with central nervous system neurological conditions. Consequently, in age-related reduction of motor asymmetry, the cortex attempts to overcompensate for bodily decrease of function by increasing cortical activation in contrast to central nervous system as the driving force of asymmetry in PD.

Findings in this study compliment past research as significant results for main interactions of hand and group from the PPT correspond with other literature indicating PPT may be useful in differentiating age-matched controls and persons with PD, and has correlation to dopaminergic degeneration (Dan et al., 2019; Vingerhoets et al., 2004; Haaxma et al., 2010; Ruzicka et al., 2016). Similarly, response time results for the main effect of group appear to correspond with Yokochi et al. (1985) in the interpretation of extended reaction times can be a result of dysfunction of the basal ganglia. Since the PD group performed worse than the OA group in all tasks, the basal ganglia dysfunction and dopaminergic degeneration affects all tasks performed, with underlying components of speed, dexterity, strength and response time. Clinical applications of this study is the use of multiple motor tests as a screening tool for PD. Decreased performance across tasks may be evident in pre-symptomatic PD stages. Thus, decreased motor performance can be used as an indicator of PD.

Limitations include a smaller sample size. Due to the small sample size, causality can only be speculated and we can infer associations. Also, some statistics that were not found to be significant, may be significant with increased number of subjects. For example: Thumb Opposition revealed a near significant main effects of age group, F (1,33), $p = .079$. Increased sample size may give future researchers the ability to compare groups of persons with PD based on functional level or Hoen and Yahr stages. Other suggestions for future researchers is to consider side of onset of symptoms as a factor in research comparing motor performances of persons with PD. Furthermore, upper extremity tasks did not have kinetics, acceleration, velocity nor further kinematics. The addition of this information would provide further details to describe observations from the study.

These results are clinically relevant to the increasing knowledge of upper extremity function for persons with PD. A significant general slowing of upper extremity fine motor performance in both hands was found in tasks involving speed and dexterity. While not statistically significant, results also indicate a bilateral reduction in upper extremity strength. Only one task exhibited a significant interaction effect, indicating motor asymmetry is not globally further reduced as a result of basal ganglia dysfunction. Results indicate that PD pathology and a reduction in dopamine has a symmetrical effect on upper extremity limbs. As persons with PD exhibit more frequent involved areas of upper extremities, head, tongue, and lips (Hoehn & Yahr, 1967), further exploration of fine motor skills in upper extremities is indicated to facilitate clinicians and persons with PD in discovering or improving tools to assist the PD population in combating the progressive effects of PD.

CHAPTER VI

PRJOJECT 3: UNDERSTANDING CLINICAL SYMPTOMS RELATED TO FUNCTION

This project aimed to assess the relationship between clinical symptoms and function in persons with PD. This project will measure the change in balance and gait performance in the PD population and compare it to the clinical presentations. The purpose of this phase is to examine the relationship between clinical manifestations of PD and their functional performance.

Introduction

In 1817, James Parkinson began to describe the characteristics of PD (Fahn, 2018). The description discusses patients with involuntary tremulous motions most common in one hand and arm as an early symptom and a combination of forward lean with gait where patients walk on their forefeet and risk falling forward (Parkinson, 1817). Many of these symptoms, especially when combined, can increase fall risk in this population.

Advances in the pathogenesis and etiology of PD have moved at a fast pace over the last two decades (Fahn, 2018). Greenfield & Bosanquet (1953) made groundbreaking discoveries linking the substantia nigra as the underlying culprit of the dysfunction due to findings of binucleated nerve cells and Lewy's spherical concentric hyaline inclusions as well as neurofibrillary tangles in persons with PD. Furthermore, cortico-basal ganglia loop deficits due to basal ganglia dysfunction appear to underly disturbances at the behavioral level, such as voluntary movements. (Takakusaki et al., 2004).

With voluntary movements affected by atypical neurological disorders, individuals' abilities to perform activities of daily living become problematic. As PD progresses, symptom severity increases, reducing independent function until ultimately becoming more dependent on caregivers due to physical limitations. Persons with PD exhibit higher recurrent fall statistics than the general papulation (Allen et al., 2013) and can potentially result in further complications that can lead to severe limitations or fatality. Plotnik et al. (2008) suggested reduced coordination of gait is correlated with reduced postural stability in a study that recorded persons with PD walking with force-sensitive insoles. Orthostatic hypotension, dementia, postural instability and falls can develop in later stages of the disease (Clarke, 2007). These aforementioned factors, as well as many others, can contribute to an increased fall risk. Understanding the decline in function in persons with PD has the potential to be instrumental in reducing fall risk and subsequent fatality. One such clinical test is the TUG that assesses fall risk depending on time to complete the task. The TUG has been used in previous research investigating function in persons with PD (Brusse et al., 2005; Steffen et al., 2002) indicating the validity of the TUG as an investigative tool in this population.

Considering that motor symptom progression and functional decline are two significant components of PD, this investigation aims to address the connection between them. To the researcher's knowledge, the potential correlation between clinical PD symptoms compared to motor performance of an individual's upper extremities and mobility function has not yet been addressed. Shahed and Jankovic (2007) reported the UPDRS is an accessible way to assess cardinal motor features and associated symptoms of PD.

In this current research study persons with PD completed a UPDRS and performed a series of balance, gait and upper extremity fine motor tasks using both hands with the purpose to examine the relationship between the Unified Parkinson's Disease Rating Scale and upper extremity motor performance in persons with PD. This study further compared the UPDRS with functional measures of balance and gait in persons with PD to inspect the connection between functional presentation. This part of the study aims to answer the question: what is the relationship between PD symptoms and functional performance? Researchers hypothesizes a connection between motor symptoms of PD and motor performance.

Methods

Prior to beginning the study, approval of Mississippi State University's Institutional Review Board was acquired. Participants for this study consisted of 15 persons with PD (5 females) between 57-86 years old (Mean = 71.2, standard deviation = 6.72). The required participant score on the Mini-Mental State Examination was over a score of 24 (Mean = 29.07, standard deviation = .9612). To be included in the study participants were right-handed as well as negative for recent injuries and cardiovascular and orthopedic pathologies to ensure proper abilities to participate in the study. Persons with PD self-assessed "on" and "off" times with attention to their medicine schedule in which symptoms would be more prominent.

The Edinburgh Handedness Inventory short form with 4 questions (revision of Oldfield, 1972) was used to determine handedness. Laterality quotients of .60 or higher were required for the Edinburgh Handedness Inventory. Participants were given full disclosure of the study and all questions were answered. Informed consent was obtained.

Tests and Outcomes

Only motor performance-related questions of the UPDRS was used for this study. Objective tests, performed in random order, include Purdue Pegboard test , grip strength test, response task, thumb opposition task, tapping task, three variations of timed-up-and-go test, single leg stance task, Weight Distribution test and Limits of Stability test. Scores from these tests were the dependent variables.

Participants were familiarized to the tasks. Only unilateral performance of the PPT (Lafayette Instrument Model #32020) was performed. Blazepod^{TM} (BlazePod Inc., Miami, FL, USA) was used for the response time task, utilizing LED color lights. Standing balance assessments were performed on the BTrackS Balance Plate and BTrackS Assess software (Balance Tracking Systems, San Diego California, US). Motor tasks performed with the upper extremities were completed 3 times with each hand, beginning with right hand first, then alternating hands until the task was completed 3 times with each hand. One person with PD was an outlier for the TO as they were unable to perform the sequencing correctly and required extensive time to complete part of the task. Subsequently, their time to complete the task was not used in that portion of the study, respectively. The SLS, WD and LOS were performed with the BTracks software and plate as pre-programmed tests. The WD program consisted of participants' standing with a comfortable base of support (BOS), looking straight ahead with their eyes level and their hands by their sides. Participants could not look at the screen, data were recorded after 10 seconds. The LOS program consisted of participants looking at a computer screen and trying to move their center of gravity (COG) around their BOS as far in each direction as possible without lifting their heels or forefeet. In the SLS program, participants had to hold SLS three times with each foot for

5 seconds, beginning with left foot without looking at the computer screen. Five patients with PD and 3 OA were unable to safely complete the SLS portion of the study. Three different TUGs were performed. First was a typical TUG, followed by TUG while holding a tray, and the third TUG was performed while counting backwards by 5 from 100. The tray contained a smaller tray with a tennis ball on top. One person with PD was unable to perform the TUG holding the tray and their data was not used in this part of the study.

Statistics

IBM SPSS 24 software and an alpha level of .05 was utilized. Pearson's correlation coefficient was used to determine correlations between UPDRS scores, and motor tasks performed. The correlation analysis goal was to assess correlation between UPDRS and motor function using a set of upper and lower extremity motor tasks: Purdue pegboard, tapping, thumb opposition task, response task for number of hits and response time, the three TUG variations and the three tasks using the BTracks balance software and plate.

Results

Analyses from correlations between the tests indicated a lack of significant correlations between motor tests performed and the UPDRS rating scale, except the regular TUG test, r (13) = .79, $p <$ .001, and the cognitive TUG test, r (13) = .69, p = .004. Significant Correlations of persons with PD between the UPDRS score and TUG regular, and TUG cognitive, are displayed in Table 4, respectively. Table 5 indicates the mean for each dependent variable and Pearson's *r* is displayed in Table 6.. A direct correlation of PD symptoms, rated via UPDRS, and TUG were found to be significant. Persons with PD with lesser symptoms exhibited increased performance on the TUG,

compared to persons with more severe symptoms (Figure 26 and Figure 27, respectively). The overall mean of TUG times of the group was used to compare to the UPDRS.

Results from the correlation between UPDRS and limits of stability (LOS) total area, r (13) = -.466, p =.08 is worth consideration as these findings suggest a trend of increased PD symptoms correlating with decreased balance (Figure 28). Persons with worse symptoms were less able to move their center of gravity around their base of support. Further investigation is warranted to conclusively correlate balance to clinical PD symptoms.

Table 4

Significant Correlations of persons with PD

	TUG regular	TUG cognitive
UPDRS Motor Score	$p < .001$*	$p = .004$*

Table 5

Means

	TUG regular	TUG cognitive	UPDRS Motor Score
Persons with PD	11.62 seconds	14.68 seconds	78.67 of a possible 208

Table 6

Pearson's r

	TUG regular	TUG cognitive
UPDRS Motor Score	.794**	.690**

Figure 26

Correlation of UPDRS to TUG Regular (TUGreg)

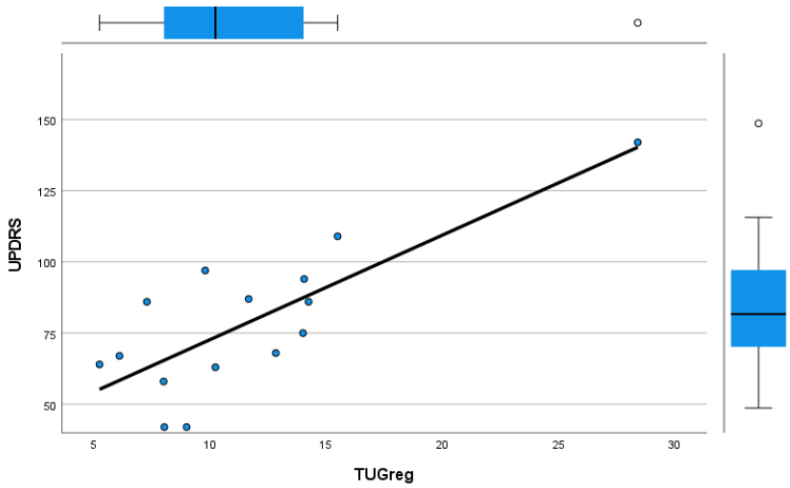
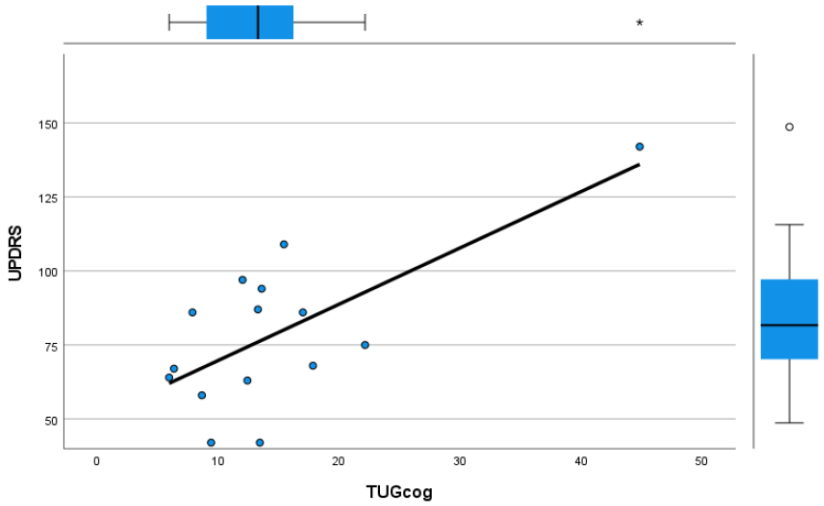


Figure 27

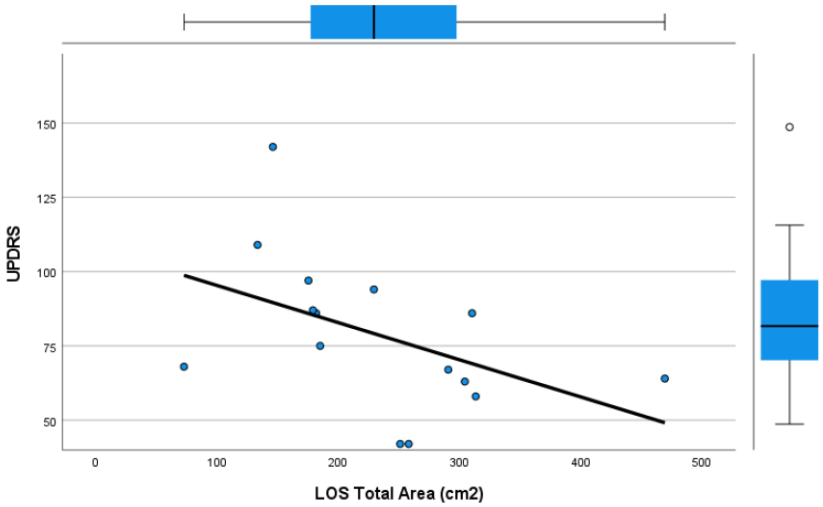
Correlation of UPDRS to TUG Cognitive (TUGcog)



Limits of Stability (total area)

Figure 28

Correlation of UPDRS to Limits of Stability



Discussion

To our surprise the main finding from this study reveals overall PD symptoms are generally not directly related to general motor function, as only one motor task correlated with UPDRS symptoms. Basal ganglia dysfunction from PD results in symptoms of bradykinesia, akinesia, tremors, rigidity. Hypothesis in this section of the study projected that the motor symptoms would have a correlation to motor performance of the tasks included in this study.

Significant correlations to UPDRS found only in TUG scores. Persons with a higher UPDRS score had longer TUG times for the regular test and TUG with cognitive task. The mean score for persons with PD from this study was 11.62 seconds, complimenting findings form Huang et al. (2011) finding TUG scores of 11.8 seconds. Consistent with Yokochi et al 1985, increased times may be associated with and implicated by output from neurons of motor pathways that are impacted by nigrostriatal input.

Clinical applications indicate persons affected to a lesser extent by clinical PD symptoms will have better function, as indicated by lower TUG scores. Results indicate the positive relationship between TUG and PD symptoms reveal TUG as a clinically relevant tool for persons with PD. Average TUG scores for older adults is 8.4 seconds (Shumway-Cook et al., 2000), whereas persons with PD in this study exhibited increased TUG scores. Extending current findings to clinical application, older adults exhibiting increased TUG scores may be an indicator of present neurological complications.

The increased TUG scores from this study suggest increased fall risk for persons with PD. Similar to findings reported by Allen et al. (2013), recurrent fall statistics are lower for the general population (about 15%) compared to persons with PD (over 50%). In clinical settings, healthcare practitioners with patients exhibiting increased TUG scores and non-significant medical history should consider further exploration for neurological pathology. However, further research would be needed to solidify the use of TUG in the application of diagnosing PD stages and an fall risk assessment specific to persons with PD.

Interestingly, persons with PD yielded significantly higher times for the TUG cognitive task compared to the regular TUG and TUG with tray. Older adults TUG cog time increased slightly, but TUG cog scores for persons with PD increased substantially. This suggests that persons with PD were cognitively compensating for basal ganglia dysfunction in the normal TUG and TUG holding a tray. However, in the TUG cog, with their cognitive efforts focused on the cognitive task, time to complete the task increased, supporting the theory of compensatory mechanisms in persons with PD to hide symptoms of PD. Clinical extensions indicate persons with PD should not do cognitive tasks during standing mobility, as their attention and cognitive efforts are removed from the motor task performance and placed into the concurrent cognitive task. Dual tasking may increase risk for falls.

The results of this study suggest PD symptoms appear to have a more significant impact on gross motor function rather than fine motor function. The application of these results suggest gross motor activities are more affected by the symptoms of PD possibly due to the increased numbers of degrees of freedom involved compared to fine motor skills. Accordingly, the more joints and

muscles involved in a motor task, the more difficult the task is to control. In fine motor tasks with less degrees of freedom, cognitive efforts may be able to focus on integral components to compensate for task deficits caused by PD symptoms. However, in gross motor skills, there may be too many muscles, joints, and cognitive-neuro components for the individual to compensate at one time. Generally, attentional focus may be able to correct deviations in fine motor skills, but not for a large number of components involved in gross motor skills. Further research is needed to explore underlying mechanisms compensating for dysfunctions of motor behavior.

Limitations of the current study are a small sample size, as we can conjecture associations, but cannot confirm causality. With a larger sample size, perhaps the near-significant values would have been significant. For example, the limits of stability total area appeared to correlate with the UPDRS, indicating decreased stability compared to age-matched controls as persons with PD were not able to move their center of gravity around their base of support as well as age-matched older adults. The results signify a trend towards reduced static balance in persons with PD. Regrettably, consequences of reduced balance results in higher fall incidence (Termoz et al., 2008; Grimbergen, et al., 2004). Although, significance didn't reach the threshold of $p < .05$, this information may be considered relevant as potentially identifying an underlying mechanism of increased fall risk and warranting further research of postural balance in persons with PD. Future research should also consider task difficulty levels, as increased task difficulty may reduce subject size. For example, performing a TUG while holding a tray is challenging, and one PD participant was unable to maintain balance without the use of a front-wheeled walker, which subsequently made them incapable of walking while holding a tray. Similar difficulties were

found in the single leg stance test, as some participants were unable to hold a single leg stance for 5 seconds.

Analysis of the UPDRS scores to manual motor tasks has not received thorough attention in the research domain. To specify motor performance in persons with PD, this study concluded there is a lack of association between scores on manual tasks and the UPDRS scores. Implications from this study signify clinical symptoms are not the sole determinant of motor performance in persons with PD. Future studies should consider the effects of clinical symptoms on other functional tasks not presented in this study.

Research focusing on diagnostic techniques that can be used early in the disease process is crucial as motor asymmetry is a characteristic of early PD stages (Djaldetti et al., 2006). Early detection can lead to early interventions and better chances to slow the progression of the disease. This study encourages the clinical relevance of TUG as a diagnostic or fall risk assessment strategy, however, further research is needed to conclude reliability, validity and specific criteria for the aforementioned suggested research areas. Future motor behavior research with a focus on symptoms of PD may uncover underlying phenomena directly associated with PD function. Continued study in the motor behavior domain of persons with PD is clinically relevant with plausible applications in early diagnostics and early intervention strategies that may assist the PD population combating the progressive PD pathology, leading to improved personal and clinical outcomes.

CHAPTER VII

SUMMARY AND DISCUSSION

Summary of Results

The purpose of this study was to examine the role of the central nervous system in the reduction of motor asymmetry with age. As PD is a disorder of the central nervous system, more specifically the basal ganglia, observations of central nervous system dysfunction provide an opportunity to explore mechanisms of reduced motor asymmetry with age. The current study builds upon the contextual background of research investigating age-related changes in functional and motor performances (Przybyla et al., 2011) and research investigating age-related changes in cognitive functioning (Cabeza, 2002; Dasellar et al., 2003; Hill et al., 2020). PD is characterized by asymmetry ((Hoehn & Yahr, 1967). The disease begins unilaterally and becomes bilateral. For some time, symptoms remain asymmetric throughout the progression of the disease with one side being more involved than the other (Miller-Patterson et al., 2018).

A literature review was performed to investigate the connection of central nervous system's role in reduction of motor asymmetry (Chapter II) with results indicating a gap in the literature. Published research focuses on asymmetry in older adults or asymmetry in persons with PD. An identified gap was the direct comparison of motor asymmetry between younger adults, older adults and persons with PD. By including several tasks and three groups of participants, this study broadens the understanding of the central nervous system's role in the reduction of motor

asymmetry for older adults as well as an increased understanding of asymmetry characteristics in both populations, older adults, and persons with PD.

Based on research questions and hypothesis developed from the literature review results of Chapter II, younger adults, older adults and persons with PD performed motor tasks outlined in Chapter III (Purdue Pegboard, tapping, thumb opposition, response task, TUGs and BTracks tasks). The upper extremity tasks (Purdue Pegboard, tapping, thumb opposition, response task) explored fine motor control, and the functional tasks (TUGs and BTracks tasks) explored functional movements in an effort to investigate both motor asymmetry patterns and the interactions between clinical symptoms and function.

One major finding from this dissertation was an increased symmetrical motor performance with aging (Chapter IV). Younger adults exhibit increased asymmetry between the left and right hands compared to older adults, who exhibited a more symmetrical performance between the left and right hands. The dominant hand advantage seen in younger adults appears to significantly reduce with aging, resulting in the symmetrical motor performance of older adults.

Interestingly, the results of project 2 (Chapter V) included: Purdue pegboard revealed significant main effects for hand, $F(1,33)$, $p = .007$ and group, $F(1,33)$, $p = .001$. This indicates the groups exhibited differences between hands as well as significant differences in performance of the Purdue pegboard between older adults and persons with PD. Although these main effects were significant, the interaction effect was not, $F(1,33)$, $p = .784$, indicating that although there are differences between the hands and groups, there is not a reduction of asymmetry as a result of

PD pathology. Similarly, thumb opposition task, grip strength and response task did not have a significant interaction effect when comparing older adults to persons with PD. Results indicate PD pathology does not further contribute to asymmetry in motor performance. From these results, we can further imply that asymmetry with age is not associated with the basal ganglia. The basal ganglia does not have a major effect on the motor pathway contributing to increased symmetrical motor performance associated with aging.

Discussion of Results

Exploration of asymmetry comparing young adults and older adults provide a background of information relevant to the pursuit of asymmetries in persons with PD. Healthy, young adults exhibit asymmetric presentations in performance of motor skills compared to their older adult counterparts. Albeit, the cause behind asymmetry in early PD patients is pathologically different from young, healthy adults, this research lends a hand to investigative exploits.

With asymmetry being such a prominent component to PD presentation, the understanding of asymmetrical motor behavior compared with PD symptom manifestation may reveal a new understanding of the disease process. In this investigation, persons with PD performed fine motor tasks with both upper extremities individually and functional movement tasks with the purpose to examine how PD symptoms impact motor behavior at the functional level.

This investigation identified an influence of task specificity on motor asymmetry between younger and older adults as well as between older adults and persons with PD. Similar findings in the current literature coincides with the idea of task being an influence on motor asymmetry (Teixeira 2008). Fine motor skills are more challenging and require more concentration for

proficiency than slow-paced, gross motor tasks. Certain components of fine motor tasks (Purdue Pegboard, tapping and grip strength task) appear to highlight the differences between younger and older adults, compared to a more gross motor task that lack precision, dexterity, and strength (response task). The response task only had the component of speed but not precision or accuracy, which appears sufficient in highlighting age differences but not differences related to asymmetry reduction with age.

Furthermore, evidence from this study indicates a reduction of right-hand performance as an underlying mechanism for increased symmetry with age. In Purdue Pegboard, Tapping and grip strength tasks, right hand differences between younger and older adults are greater than differences in left hand performance between younger and older adults. Although no significant interaction effect was declared in the thumb opposition task, observations indicate similar trends. These findings indicate the right-hand advantage seen in younger adults reduces with age, contributing to a more even performance between hands. These results are supportive of similar findings in the literature (Francis & Spirduso, 2000; Raw et al., 2012).

The current research suggests tasks including speed, dexterity and strength resulted in increased asymmetry between the hands of younger adults as well as reduced asymmetry between hands of older adults. The contrast between younger and older adults highlights the reduction of asymmetry with age and that the phenomena is related to greater reductions in dominant hand performance.

In cortical activation processes, Hill et al. (2020) references dedifferentiation and compensation hypotheses to explain underlying neural mechanisms on motor behavior whereby dedifferentiation presents overactivation in cortical areas, but insufficient motor performance, while compensatory theory advocates increased activation of the cortical regions resulting in improved motor performance comparable to younger adults (Bernard & Seidler, 2012; Carp et al., 2011). As some studies indicate increased cortical activation to perform manual tasks at comparable levels to older adults (Calauitti et al., 2001; Naccarato et al., 2006), this study indicates poorer performance of manual tasks than younger adults, indicating results favoring the dedifferentiation hypothesis. However, an important note is the results also showed improved lateralization with some tasks, partially supporting the compensatory theory.

Pathology of PD does not appear to further reduce motor asymmetry as the Purdue pegboard, thumb opposition, grip strength and response task did not have significant interaction effects. However, the tapping task revealed a significant interaction effect indicating a further reduction of asymmetry compared to older adults. As suggested in asymmetry trends comparing younger and older adults, task specificity may carryover as an underlying factor in asymmetry comparisons of persons with PD and older adults. However, task characteristics important in the study of asymmetry between younger and older adults is presumably different considering the neurological difference in persons with PD. Tapping task is the simplest fine motor task performed in this study.

The current study focused on uncovering motor asymmetry related to motor function in persons with PD. The only correlation between UPDRS and a functional task was the TUG regular and

TUG cognitive suggesting motor asymmetry and UPDRS are not universally correlated. UPDRS and function, as related to TUG are correlated, indicating a higher TUG score indicates higher UPDRS scores.

Fall incidence increases with reduced balance (De Nunzio et al., 2007). Allen et al. (2013) compared persons with PD to the general population, finding higher recurrent fall statistics for persons with PD (over 50% and about 15% respectively). Results from this study compliment the literature suggesting an underlying factor for increased fall risk. Although this study did not reveal significant findings for LOS balance test, the total area condition and UPDRS correlation indicated a trend of decreased ability to move center of gravity around base of support with worsening PD symptoms. Reduced standing abilities indicates problematic balance insufficiencies, with associations for increased fall risk with standing functional mobility. Persons who may appear in observation to function symmetrically may still present with asymmetrical balance tendencies with objective testing (Kooij et al., 2007), indicating the importance of balance testing as a critical aspect of clinical care for the older population. Overall, the findings suggest tasks of speed, dexterity and strength are advantageous in the study of motor asymmetry with age, and fine motor skills are more advantageous in the study of motor behavior in persons with PD. Clinical symptoms of Parkinson's disease are generally not associated with motor tasks performed in this study, however the timed-up-and-go revealed significant differences between persons with Parkinson's disease and age-matched healthy older adults.

Limitations and Future Direction

One limitation of the study was the number of participants. A larger sample size would advocate for stronger results. Additionally, some participants were unable to complete the tasks: One person with PD was unable to perform the TUG holding the tray because of the use of an assistive device, and was not used in that part of the statistical analysis. An individual with PD contributed outlier data for the TO and was taken out for the statistical analysis. Similarly, three older adults and five persons with PD were unable to perform the SLS. Their parts were not used in statistical analysis, respectively. The sample size limited conclusions into inferred associations, rather than causality.

Further limitations include the lack of velocity, acceleration and other kinematic and kinetic variables for the tasks, especially foe the upper extremities. Future research could use the aforementioned data to increase observations found in each task, furthering the discussion of task specificity as related to findings of asymmetry reduction in motor performance.

Lastly, without an objective measurement tool to investigate cortical activation in conjunction with motor performance, conjecture between motor and cognitive functioning is possible, but not substantiated connections. Observation of the older adult cortex compared to cortical activation of persons with PD during motor performance would generate more conclusive results in the investigation of cortical changes with age as related to central nervous system dysfunction and its relationship to the motor behavior domain. Future studies should include both cortical and motor measurements to better connect the cortical-motor relationship in motor behavior.

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APPENDIX A

IRB

Institutional Review Board Approval

From: nrs54@msstate.edu
Sent Date: Thursday, November 10, 2022 11:53:29 AM
To: zp147@msstate.edu, ack24@msstate.edu, cc2196@msstate.edu, chb267@msstate.edu, dw2401@msstate.edu, hc783@msstate.edu, jgl5@msstate.edu, noc13@msstate.edu
Cc:
Bcc:
Subject: Do Not Reply: Approval Notice for Study # IRB-22-163, Motor Asymmetry in Parkinson's disease
Message:

Protocol ID: IRB-22-163
Principal Investigator: Zhujun Pan
Protocol Title: Motor Asymmetry in Parkinson's disease
Review Type: EXPEDITED
Approval Date: November 10, 2022
Expiration Date:October 10, 2027

This is a system-generated email. Please DO NOT REPLY to this email. If you have questions, please contact your HRPP administrator directly.

The above referenced study has been approved. *For Expedited and Full Board approved studies, you are REQUIRED to use the current, stamped versions of your approved consent, assent, parental permission and recruitment documents.*

To access your approval documents, log into myProtocol and click on the protocol number to open the approved study. Your official approval letter can be found under the Event History section. All stamped documents (e.g., consent, recruitment) can be found in the Attachment section and are labeled accordingly.

If you have any questions that the HRPP can assist you in answering, please do not hesitate to contact us at irb@research.msstate.edu or 662.325.5220.

Please take a minute to tell us about your experience in the survey below.
https://msstate.co1.qualtrics.com/jfe/form/SV_9AeDZP2nfRHV6ei

APPENDIX B

INFORMED CONSENT

Informed Consent Form

Approved:	Expires:
10/11/22	10/10/27
IRB # 22-163	

Mississippi State University
Informed Consent Form for Participation in Research

IRB Approval Number: Protocol ID is IRB-22-163

Title of Research Study: Motor Asymmetry in Parkinson's Disease

Study Site: Cognitive Motor Control Laboratory at Mississippi State University, or Swift Center (West Point, MS), or participant's private residence.

Researchers:
Dr. Zhujun Pan, Principal Investigator, Mississippi State University (zp147@msstate.edu)
Deborah M. Watson, Student-Investigator, PhD Candidate, Mississippi State University
Dr. Chih-Chia Chen, Co-Investigator, Mississippi State University
Dr. Adam Knight, Co-Investigator, Mississippi State University
Dr. John Lamberth, Co-Investigator, Mississippi State University
Dr. Harish Chander, Co-Investigator, Mississippi State University
Dr. Christopher Aiken, Co-Investigator, New Mexico State University

Purpose

To investigate and further understand role of central nervous system (CNS) in age-related changes of asymmetry. In this investigation, we aim to examine the age-related reduction of asymmetry in motor tasks, the change in asymmetry between younger adults, older adults and persons with Parkinson's disease. This research aims to explore how CNS affects reduction of motor asymmetry and motor function.

Procedures

In the case you consent to participate in this research study, total time for the session will be about 67 minutes, where we will ask the following from you:

- Complete questionnaires: General questionnaire (13 questions), International Physical Activity Questionnaire (12 questions), Unified Parkinson's Disease Rating Scale (~37 questions), Edinburgh Handedness Inventory (4 questions). A Mini Mental State Examination will be conducted to ensure cognitive healthiness for participation.
- Perform tasks with hands such as tapping, drawing circles, Purdue Pegboard test, maximum grip strength, finger opposition task, etc., with one or both hands.

Purdue Pegboard Test

Participants sit at a desk with the Purdue Pegboard in front. The task is to pick up small pegs and insert them into a row of holes on the board as quickly as possible in 30 seconds.

Tapping Task

Participants will be asked to tap with one or both hands as fast as possible.

Response task
Participants will be asked to respond as quickly as possible to a stimulus.

Drawing Task
Participants will sit at a desk with a digitizer tablet in front of them. Participants will draw varied sizes of circles at maximum and comfortable speeds.

Finger Opposition Task
Participants will be positioned comfortably and asked to touch thumb to each finger, as quickly as possible.

Maximum Grip Strength
Participants will be positioned comfortably and squeeze a dynamometer at maximum capacity.

Balance task
Participants will be standing on a BTracks balance board and follow instructions for movement. Tasks may include eyes open, closed, reaching, etc.

Timed up and go
Participants will be asked to walk a short distance as fast and safe as they are able to.

Risks or Discomforts

Tasks are non-invasive. Minor discomfort is expected as participants may be seated for approximately 30-40 minutes. If you feel uncomfortable for any reason or want to stop at any time, please let the researcher know.

Benefits

Benefits include increasing knowledge of investigators and professionals in related fields to assist in the understanding of neurological disease and potential future developments related to the field that would not otherwise be observed as well as gratification of making a contribution to science.

Incentive to participate
No monetary incentives.

Confidentiality

Your data and information will only be handled by researchers involved in the study. The documents and information gathered will be stored in a file cabinet or a computer that only the researchers have access to. The computer is password-protected, and data will be coded.

Please note that these records will be held by a state entity and therefore are subject to disclosure if required by law. Research information may be shared with the MSU Institutional Review Board (IRB) and the Office for Human Research Protections (OHRP) and others who are responsible for ensuring compliance with laws and

regulations related to research. The information from the research may be published for scientific purposes; however, your identity will not be given out.

Questions

If you have any questions about this research project or want to provide input, please feel free to contact Deborah Watson at 203-506-3191 or faculty advisor Dr. Pan at zp147@msstate.edu.

For questions regarding your rights as a research participant or to request information, please feel free to contact the MSU Human Research Protection Program (HRPP) by e-mail at irb@research.msstate.edu, or visit our participant page on the website at https://www.orc.msstate.edu/human-subjects/participant-information.

To report problems, concerns, or complaints pertaining to your involvement in this research study, you may do so anonymously by contacting the MSU Ethics Line at http://www.msstate.ethicspoint.com/.

Research-related injuries

MSU has not provided for any payment to you or for your treatment if you are harmed as a result of taking part in this study.

Voluntary Participation

Please understand that your **participation is voluntary.** Your **refusal to participate will involve no penalty or loss** of benefits to which you are otherwise entitled. You **may discontinue your participation** at any time without penalty or loss of benefits.

Please take all the time you need to read through this document and decide whether you would like to participate in this research study.

If you agree to participate in this research study, please sign below. You will be given a copy of this form for your records.

_____ _____
Participant Signature Date

_____ _____
Investigator Signature Date

Research Participant Satisfaction Survey

To make sure that your rights as a research participant have been protected, after your participation in the research study, the MSU HRPP would like for you to complete this survey. Your answers will help us make sure that research participants are protected.
https://msstate.co1.qualtrics.com/jfe/form/SV_5dMg4uHnw8tU5D0

APPENDIX C

RECRUITMENT FLYER

Recruitment Flyer

Participants Needed!

MISSISSIPPI STATE UNIVERSITY

A project interested in the differences between left- and right-side performance

Do you qualify to participate?
You must be a healthy **male or female**
A**ges 18-35 & 65+**

Also, persons with a diagnosis of **Parkinson's Disease** of any age can participate.

You must meet the following criteria:

- ✓ No current or recent history of cognitive, neurological or musculoskeletal disorders
- ✓ Right-handed

If you are interested in participating, please contact:

Deborah Watson: dw2401@msstate.edu

MSU HRPP Full Accreditation	Approved: 10/11/22	Expires: 10/10/27
	IRB # 22-163	