Postural control predicts neurodegeneration in Mild Cognitive Impairment

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April 2021

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science (Rehabilitation Science)

Contents

Abstract

Background: Brain volume loss is commonly associated with advanced aging and neurodegeneration. In individuals with Alzheimer's Disease (AD), deficits in postural control assessed with dynamic posturography have been associated with reduced brain volume. Postural control may be a predictive biomarker of cognitive decline and neurodegeneration. However, whether changes in postural control are associated with reductions in brain volume in individuals with mild cognitive impairment (MCI) is not known. **Objectives: 1)** To investigate differences in postural control, using dynamic posturography, between MCI and cognitively normal (CN) older adults. **2)** To investigate differences in brain volumes between MCI and CN older adults. **3)** To explore associations between brain volume and postural control, using dynamic posturography, in both CN and MCI individuals. **Methods:** 18 MCI (age=73.61$\pm$6.59 y; Montreal Cognitive Assessment (MoCA)=24.05$\pm$3.21) and 32 CN (age=73.04$\pm$6.68 y; MoCA=26.52$\pm$2.62) older adults were tested. Structural magnetic resonance imaging was used to assess their total brain volume and the volume of discrete areas of the brain known to be involved in postural control, including the thalamus, caudate nucleus, putamen, pallidus, nucleus accumbens, cerebellum and hippocampus. The sensory organization test (SOT), a test of dynamic posturography, was employed to assess postural control. **Results:** MCI individuals showed smaller regional and total brain volumes, but differences met statistical significance only in the postcentral region, and caudate and accumbens stuctures. Similarly, MCI individuals demonstrated poorer postural control (SOT score=64.18$\pm$13.35) than CN individuals (SOT score=69.41$\pm$10.69), but differences did not reach statistical significance (p=0.062). Correlations between total brain volume and the SOT score in the CN group were negligible (R^2=0.24; p=0.24). In contrast, robust associations in the MCI group were found (R^2=0.60; p=0.0079). **Significance:** Postural control assessed with dynamic posturography is strongly associated with total brain volume in people with MCI. Longitudinal studies should investigate the potential predictive value of postural control as a biomarker of neurodegeneration.

Résumé

Contexte: La perte de volume cérébral est généralement associée au vieillissement avancé et à la neurodégénérescence. Chez les personnes atteintes de la maladie d'Alzheimer (MA), les déficits du contrôle postural évalués par posturographie dynamique ont été associés à une réduction du volume cérébral. Le contrôle postural peut être un biomarqueur prédictif du déclin cognitif et de la neurodégénérescence. Cependant, nous ne savons pas encore si les changements dans le contrôle postural chez les personnes avec une déficience cognitive légère (DLC) sont associés à des réductions du volume cérébral. **Objectifs:** 1) Étudier les différences de contrôle postural entre les adultes avec DLC et les adultes âgés cognitivement normaux (CN) à l'aide de la posturographie dynamique. 2) Étudier les différences de volume cérébral entre les adultes âgés DLC et CN. 3) Explorer les associations entre le volume cérébral et le contrôle postural, en utilisant la posturographie dynamique, chez les individus CN et DLC. **Méthodes:** 18 DLC (âge=73.61$\pm$6.59 ans; Montreal Cognitive Assesment (MoCA)=24.05$\pm$3.21) et 32 CN (âge=73.04$\pm$6.68 ans; MoCA=26.52$\pm$2.62) adultes âgés ont été testés. L'imagerie par résonance magnétique structurelle a été utilisée pour évaluer leur volume cérébral total et le volume de zones distinctes du cerveau connues pour être impliquées dans le contrôle postural, y compris le thalamus, le noyau caudal, le putamen, le pallidus, le noyau accumbens, le cervelet et l'hippocampe. Le test d'organisation sensorielle (SOT), un test de posturographie dynamique, a été utilisé pour évaluer le contrôle postural. **Résultats:** les individus DLC ont montré des volumes cérébraux plus petits, mais les différences ne sont statistiquement significatives que dans la région post-centrale et les structures caudées et accumbens. De façon similaire, les individus DLC ont démontré un contrôle postural plus faible (score SOT = 64.18$\pm$13.35) que les individus CN (score SOT=69.41$\pm$10.69), mais les différences ne sont pas significatives ($p = 0.062$). Les corrélations entre le volume cérébral total et le score SOT dans le groupe CN étaient négligeables ($R^2=0.24$; $p=0.24$). En revanche, des associations robustes ont été trouvées dans le groupe DLC ($R^2=0.60$; $p=0.0079$). **Signification:** Le contrôle postural évalué par posturographie dynamique est fortement associé au volume cérébral total chez les personnes atteintes de DLC. Les études longitudinales devraient étudier la valeur prédictive potentielle du contrôle postural en tant que biomarqueur de la neurodégénérescence.

Acknowledgements

I would like to enthusiastically thank my supervisor, Dr. Marc Roig, for all of his help on this endeavor. Our frequent meetings kept me excited about my work and eased my fears and anxieties every time. He gave me the tools to work through roadblocks, and made thesis writing a more enjoyable experience than I possibly could have hoped.

I would also like to thank my supervisory committee members, Dr. Joyce Fung, and Dr. Sara Ahmed, for their guidance and advice on this project.

An enormous thank you to Josephine Salib, without you the data collection for this project would not have been possible. Commiserating with you made hard days easier and laughing together brightened the good ones the most. You kept me on my toes and helped me organize myself when I didn't know which way was up.

To the researchers involved in the TRIAD study, thank you for your tireless help on this collaboration. Your hard work allowed for our participant recruitment and comparison of brain biomarker measures.

Finally, I want to thank my close friends and family, who listened endlessly to both my excited chatter and ever-present angst on this journey. To my parents, thank you for always being my biggest supporters and standing by my side. To Jeremy Korb, thank you for always encouraging me and helping me keep my chin up when things felt tough.

Chapter I: Introduction

Relevance

Given the aging population and increasing life expectancy, the number of individuals suffering from age-related cognitive decline and dementia, including Alzheimer's Disease (AD), is expected to triple by the year 2050 (Prince *et al.*, 2013). Although mild cognitive impairment (MCI) does not always lead to AD, MCI, especially of the amnestic subtype, is considered one of the earliest features of AD and other dementias. MCI diagnosis has been shown to be an independent predictor of AD, with 40% of individuals diagnosed with MCI progressing to AD over a 4-year period (Petersen, 2000). Furthermore, Petersen (2000) found that 60% of MCI patients exhibited known biomarkers of AD post-mortem – verified by autopsy. AD is costly and has a high mortality rate (Tejada-Vera, 2013; Dodel *et al.*, 2015). Therefore, it is critical to investigate and elucidate improved techniques and methodologies for the prevention, early detection, and mitigation of these diseases and their effects.

Cognitive decline and dementia manifest in the brain through various markers, including the reduction of brain volume (Visser *et al.*, 1999; Fotenos *et al.*, 2005; Driscoll *et al.*, 2009; Raji *et al.*, 2009). These structural brain changes signalling the beginning of the progression to dementia can appear several years before the symptoms of the disease become evident (Jagust *et al.*, 2006; Twamley *et al.*, 2006; Bernard *et al.*, 2014) . However, the detection of early brain changes, including brain atrophy, can be costly and time consuming. Therefore, the evaluation of these markers remains largely inaccessible to the public.

In AD, declining physical function occurs alongside declining cognitive function and neurodegeneration. For instance, Montero-Odasso *et al.* (2014) proposed gait speed to be a motor biomarker of dementia, as it has demonstrated predictive value regarding the onset of cognitive

decline and the transition to dementia (Montero-Odasso & Hachinski, 2014; Montero-Odasso, 2016). Specifically, this relationship was observed when the dual-task gait paradigm was employed – where participants are required to perform a cognitive task while walking. Adding the performance of a cognitive task to the simple motor task appears to increase the sensitivity for detection of cognitive decline. Further, dual-task gait has been associated with brain volume loss in MCI individuals (Doi *et al.*, 2017; Sakurai *et al.*, 2019). While it is evident that gait speed provides valuable information, other aspects of physical function have yet to be investigated.

Postural control can be defined as a specific aspect of balance in which an individual maintains a bipedal stance while making an effort to remain still. This entails the use and integration of sensory system information in order to generate minimal postural sway and remain over the base of support. Similarly to gait speed, postural control is an important element of physical functioning. Moreover, postural control may be likened to dual-task gait in that it has a known cognitive component in addition to the motor aspect (Kerr *et al.*, 1985; Lajoie *et al.*, 1993; Teasdale *et al.*, 1993). It is possible that like dual-task gait, postural control, as measured by dynamic posturography, will demonstrate predictive value over the course of cognitive decline.

In the past, impairments to postural control have been observed in cognitive decline using clinical balance tests (Kato-Narita *et al.*, 2011; Wilkins *et al.*, 2013; Tangen *et al.*, 2014; Tolea *et al.*, 2016) and force-plate assessments (Leandri *et al.*, 2009; Shin *et al.*, 2011; Deschamps *et al.*, 2014; Mignardot *et al.*, 2014). More recently, dynamic posturography has been introduced, and has similarly been used to demonstrate detriments to postural control occurring with cognitive decline and AD (Lee *et al.*, 2017; Baydan *et al.*, 2020). Dynamic posturography manipulates the sensory systems contributing to postural control separately, which provides unique mechanistic information regarding the maintenance of postural control.

Importantly, Lee *et al.* (2017) found a relationship between subcortical brain volumes and postural control, using dynamic posturography, in adults with AD. This finding indicates that postural control may be useful in predicting structural brain changes occurring with dementia. While this information is important, similar studies have not been conducted in individuals with MCI. Investigating the relationship between postural control, as measured with dynamic posturography, and brain volume, in individuals with MCI is critical to understanding the sensitivity of postural control as a measure of neurodegeneration in cognitive decline.

This could be of great clinical value, as the identification of structural brain changes occurring with cognitive decline may provide patients the opportunity to initiate more effective preventive treatments and implement interventions in an effort to slow the progression of cognitive decline. As such, it is important to investigate the possibility of postural control as a predictive marker of brain volume loss and global neurodegeneration.

Rationale

Research problems

1) In individuals with MCI, postural control has only been assessed using dynamic posturography in a small population (n=10) who demonstrated very low global cognition (mean MoCA score 15.9 ± 2.92). It would be worthwhile to examine postural control in individuals diagnosed with MCI in a larger population, and with a population demonstrating higher cognitive levels, which are more consistent with MCI diagnosis.

2) In individuals with MCI, the association between postural control, as measured using dynamic posturography, and brain volume has yet to be examined.

Research Questions

This research project aims to address three questions: **Primary:** To what extent is postural control, as assessed using dynamic posturography, impaired in individuals with MCI compared to CN? **Secondary:** To what extent is brain volume reduced in individuals with MCI compared to CN? **Tertiary:** To what extent is postural control, as measured by dynamic posturography, associated with brain volume in CN and MCI individuals?

Objectives

Primary: To investigate differences in postural control between MCI and CN older adults. **Secondary:** To investigate differences in brain volumes between MCI and CN older adults. **Tertiary:** To explore associations between postural control, using dynamic posturography, and brain volume in CN and MCI individuals.

Chapter II: Background

Aging, cognitive decline, and dementia

In humans, the aging process is commonly associated with declining cognitive functioning (O'Sullivan *et al.*, 2001; Andrews-Hanna *et al.*, 2007; Deary *et al.*, 2009; Salthouse, 2010), and these declines have been observed to accelerate after midlife (Salthouse, 2009; Singh-Manoux *et al.*, 2012). Certain modifiable risk factors have been proposed for cognitive decline and dementia, such as cardiovascular risk factors and lifestyle choices; however, a certain extent of cognitive impairment is inevitable with age (Knopman *et al.*, 2001; Baumgart *et al.*, 2015).

Additionally, older adults are known to have an increased risk of developing dementia. For example, Plassman *et al.* (2007) explored dementia prevalence in a population of individuals residing in the United States and found 5% of individuals aged 71-79 years to be afflicted, compared to 24.2% of individuals aged 80-89, and 37.4% of individuals over 90 years.

Dementia is a term widely used to describe a number of diseases and conditions wherein neurons in the brain cease to function normally or die, resulting in deficits to various aspects of cognitive functioning. Alzheimer disease (AD) is the most prevalent type of dementia (Alzheimer's, 2016). For example, Barker *et al.* (2002) found that in a sample of subjects with dementia, autopsy-confirmed AD made up 77% of the sample, followed by Lewy body disease (26%), vascular dementia (18%), hippocampal sclerosis (13%), and frontotemporal dementia (5%). Mixed pathology was frequently observed such that AD was observed to be present in 66% of Lewy body disease cases, 77% of vascular dementia cases, and 66% of hippocampal sclerosis cases. The deleterious changes to the brain experienced by persons with AD result in detriments to activities of daily living and independent functioning. Ultimately, AD impairs bodily functioning and results in death.

The diagnostic criteria for AD have been developed over the last several decades and are still being redefined today (Tierney *et al.*, 1988; Markesbery, 1997; Dubois *et al.*, 2007; Reitz *et al.*, 2011; Gauthier *et al.*, 2020). In 2011, the National Institute on Aging and the Alzheimer's Association made a notable update to the criteria and guidelines for AD diagnosis (Jack *et al.*, 2011; McKhann *et al.*, 2011; Alzheimer's, 2013). They proposed three distinct stages of AD – suggesting that the disease may be present before the appearance of clinical symptoms (Albert *et al.*, 2011; Sperling *et al.*, 2011). Thus, individuals who exhibit AD pathology in the brain, without the presence of dementia, may be diagnosed with pre-clinical AD, or AD-related Mild Cognitive Impairment (MCI) (Alzheimer's, 2013).

Petersen *et al.* (1999) explains MCI as memory impairment beyond what is to be expected for a given age group and education level. While individuals with MCI exhibit noticeable impairments in cognition, they are minor, such that everyday activities remain largely unaffected

(Alzheimer's, 2013). The term MCI has been used in the literature for many years, however, there remains a lack of standardized criteria for diagnosis. Widely used criteria include those laid out by the DSM-V (APA, 2013), the National Institutes on Aging - Alzheimer's association workgroup (NIA-AA) (Albert *et al.*, 2011), and the Mayo Clinic (Petersen, 2004). These diagnostic criteria overlap on several characteristics, including subjective and objective cognitive impairment, the preservation of independence, and the absence of dementia (Vega & Newhouse, 2014). Furthermore, the NIA-AA has outlined biomarker criteria regarding β-amyloid and tau protein deposition for the purposes of research and/or clinical trials.

MCI has been referred to as a transition state to AD (Morris *et al.*, 2001; Moradi *et al.*, 2015), however, it is important to note that this is not always the case (Loewenstein *et al.*, 2009; Malek-Ahmadi, 2016; Clem *et al.*, 2017). While many individuals suffer from AD-related MCI and continue to decline as the disease progresses, some individuals diagnosed with MCI remain cognitively stable, and others have been observed to revert to a cognitively normal (CN) state (Manly *et al.*, 2008; Malek-Ahmadi, 2016). This would indicate their condition to be independent of AD pathology. The distinguishing features of AD-related MCI from other causes are not well established, but it remains certain that the detection of MCI in its earliest stages is crucial. This early-detection is what may provide the opportunity to begin treatment at the earliest possible time-point, prior to the onset of dementia.

Brain volume, neurodegeneration, and cognitive decline

Structural changes to the brain are apparent with both healthy aging and cognitive decline. For example, older adults have demonstrated reduced global and regional brain volumes compared to younger adults (Good *et al.*, 2001; Walhovd *et al.*, 2005; Walhovd *et al.*, 2011; Ramanoel *et al.*, 2018). Moreover, in longitudinal studies, healthy adults have been observed to exhibit reductions

in brain volumes over time (Pfefferbaum *et al.*, 1998; Raz *et al.*, 2003b; Raz *et al.*, 2003c; Resnick *et al.*, 2003; Scahill *et al.*, 2003; Raz *et al.*, 2005; Driscoll *et al.*, 2009; Murphy *et al.*, 2010). Importantly, this volume loss, and the rate at which it occurs, has been observed to be associated with poorer cognitive functioning (Rodrigue & Raz, 2004; Fletcher *et al.*, 2018; Ramanoel *et al.*, 2018).

Brain volume reductions observed in healthy aging are exacerbated in individuals diagnosed with AD, who exhibit even greater reductions and an increased rate of change in brain volumes (Thompson *et al.*, 2003; Fjell *et al.*, 2009). Further, while there is overlap in the pattern of atrophy observed in healthy aging and AD, specific regions of the brain are known to be particularly vulnerable to AD-related brain atrophy (Fjell *et al.*, 2009; Raji *et al.*, 2009). These include medial temporal structures such as the entorhinal cortex and hippocampus, as well as lateral temporal structures, and the superior temporal gyrus (Dickerson *et al.*, 2001; McEvoy *et al.*, 2009). Therefore, AD-related declines in brain volume have been observed to follow a pattern which can be differentiated from that which occurs in healthy aging (Du *et al.*, 2004; Moradi *et al.*, 2015).

This pattern of brain volume loss and increased rate of change has been proposed as a marker of AD pathology (Atiya *et al.*, 2003; Holland *et al.*, 2009; Frisoni *et al.*, 2010), and is known to precede dementia (Visser *et al.*, 1999; Killiany *et al.*, 2000). Accordingly, these structural changes have been similarly observed in MCI (Fan *et al.*, 2008; Driscoll *et al.*, 2009; Fennema-Notestine *et al.*, 2009; Davatzikos *et al.*, 2011). Furthermore, in individuals diagnosed with MCI, smaller brain structure volumes, as well as increased rates of change, have been demonstrated to have predictive value regarding the progression to AD (Jack *et al.*, 1999;

deToledo-Morrell *et al.*, 2004; Devanand *et al.*, 2007; Whitwell *et al.*, 2008). Therefore, brain volume appears to be an important marker of AD development, even early – on in the disease.

While the exact mechanisms underlying brain volume loss with aging and AD have yet to be firmly established, they have been explored. Raz and Rodrigue (2006) synthesize the literature regarding contributing factors to brain volume loss in older adults and propose this process to be vascular-mediated. Evidence indicating a relationship between impaired brain vasculature and reduced brain volume dates back decades. For instance, cross-sectional studies have repeatedly documented an association between hypertension and reduced brain volumes globally, as well as in the prefrontal cortex and medial temporal regions of older adults (Hatazawa *et al.*, 1984; Salerno *et al.*, 1992; Strassburger *et al.*, 1997; Raz *et al.*, 2003a; Wiseman *et al.*, 2004; Korf *et al.*, 2005). Longitudinal studies have resulted in similar findings, indicating that when untreated hypertension is observed several years prior to the assessment of brain volume, there is an associated risk of increased hippocampal atrophy (Heijer *et al.*, 2003; Korf *et al.*, 2004). Additionally, it has been found that adults free of hypertension, but with a higher-than-average ambulatory blood pressure, are more likely to exhibit smaller global brain volumes (Goldstein *et al.*, 2002).

Sustained elevations in blood pressure can lead to arteriosclerosis and result in impairments to cerebral blood flow, producing detrimental effects on the cerebrovasculature (Evans, 1965; Giertsen, 1966; Naritomi *et al.*, 1979). Low cerebral blood flow has been strongly correlated with smaller brain volumes (Yamaguchi *et al.*, 1983), and has therefore been hypothesized to be the primary cause of increased reductions to brain volume in older adults with heightened blood pressure (Hatazawa *et al.*, 1984; Manolio *et al.*, 1994; Skoog, 1997). Hypertension and high blood pressure are common in older adults (Fryar *et al.*, 2017; Ostchega *et al.*, 2020) and, therefore, may account for brain volume loss in a great number of adults.

Importantly, there is also evidence to suggest a relationship between hypertension and AD (Skoog, 1997; Kivipelto *et al.*, 2002; Dickstein *et al.*, 2010). For instance, Lennon *et al.* (2019) found that hypertension at midlife was associated with an increased risk of developing AD. Additionally, reduced brain volumes which were associated with hypertension in CN adults occurred in regions known to be vulnerable to the development of AD. While there are several other explanations for the observed relationship between hypertension and AD, such as concomitant cerebrovascular disease, or shared pathogenesis, hypertension has been proposed to play a role in AD etiology (Skoog & Gustafson, 2002).

Postural control

In recent years, it has been repeatedly demonstrated that declining cognitive function is related to a decline in physical function (Bahureksa *et al.*, 2017; Gray *et al.*, 2021). For example, low gait speed has been observed to precede cognitive impairment and dementia, demonstrating predictive value for cognitive decline (Buracchio *et al.*, 2010; Kikkert *et al.*, 2016; Montero-Odasso *et al.*, 2018; Grande *et al.*, 2019). Furthermore, the dual-task paradigm, where participants are asked to walk while performing a cognitive task, has been shown to provide additional value – particularly in individuals with MCI (Montero-Odasso *et al.*, 2014). For instance, in individuals diagnosed with MCI, dual task gait performance has been associated with the onset of dementia (Montero-Odasso *et al.*, 2017).

Additionally, dual-task gait speed has been associated with a distinct pattern of brain volume loss in MCI individuals (Doi *et al.*, 2017; Sakurai *et al.*, 2019). Dual task and simple gait tasks have also been associated with other established brain biomarkers of dementia, such as cerebral β-amyloid deposition (Del Campo *et al.*, 2016; Nadkarni *et al.*, 2017; Wennberg *et al.*, 2017). This was primarily observed in CN individuals (Nadkarni *et al.*, 2017; Wennberg *et al.*,

2017), however, Del Campo *et al.* (2016) included a portion of MCI individuals in their study findings. Thus, alongside other gait parameters, dual-task gait speed has been proposed as a motor biomarker of cognitive decline (Montero-Odasso *et al.*, 2014; Montero-Odasso, 2016).

Postural control can be defined as the maintenance of an upright, bipedal stance, such that the center of mass remains over the base of support, and within the limits of stability (Alexander, 1994; Hageman et al., 1995). This is accomplished by integrating the sensory systems including the 1) visual, 2) vestibular, and 3) proprioceptive systems, in order to detect body motion, and apply a corrective force (Peterka, 2002). Similarly to dual-task gait, postural control is a complex task known to have a critical cognitive processing component (Kerr *et al.*, 1985; Lajoie *et al.*, 1993; Teasdale *et al.*, 1993). Furthermore, postural control is an important marker of physical function. Thus, postural control may demonstrate the same potential for predictive value over declining cognition.

Deficits to postural control have long-been observed alongside healthy aging (Wolfson *et al.*, 1992; Baloh *et al.*, 1994; Camicioli *et al.*, 1997). Moreover, Redfern *et al.* (2019) found postural control performance to be associated with various aspects of cognitive performance in healthy older adults. Similarly, it follows that impairments in postural control are greater in individuals with cognitive decline (Deschamps *et al.*, 2014; Mignardot *et al.*, 2014; Bahureksa *et al.*, 2017).

One plausible cause of these deficits to postural control is sensory system impairment, which is known to be associated with cognitive decline (Stephen *et al.*, 2010; Nakamagoe *et al.*, 2015; Monge & Madden, 2016). Alternately, an association has been observed between brain volume and postural control in cognitive decline (Kido *et al.*, 2010; Makizako *et al.*, 2013; Lee *et al.*, 2017), and it is possible that impairments to brain volume and postural control are linked

through a direct mechanism. However, it is also possible that these deficits simply occur concurrently as a result of global brain changes taking place with cognitive decline (Makizako *et al.*, 2013; Sparto *et al.*, 2020). Regardless of the mechanistic connection, the relationship between reduced brain volume and impaired postural control is important to investigate, as postural control may have the potential to be a useful marker of neurodegeneration and cognitive decline (Anstey *et al.*, 2006; Sheridan & Hausdorff, 2007; Borges Sde *et al.*, 2015).

Postural control assessments

Clinical balance assessments have frequently been employed in order to establish deficits to postural control in older adults with AD and MCI, compared to those who are CN (Kato-Narita *et al.*, 2011; Wilkins *et al.*, 2013; Tangen *et al.*, 2014; Tolea *et al.*, 2016). For example, the Berg Balance Scale addresses functional balance by examining sitting, standing, and dynamic conditions. It is a simple assessment with demonstrated reliability for older individuals, as well as for those with dementia (Blankevoort *et al.*, 2013; Muir-Hunter *et al.*, 2015; Telenius *et al.*, 2015; Baker *et al.*, 2020). Therefore, it has seen widespread use in these populations (Pedroso *et al.*, 2012; McGough *et al.*, 2013; Ries *et al.*, 2015).

Similarly, static balance assessments utilizing force plate technologies have been used to determine impairments to postural stability for older individuals, including those with AD and MCI (Leandri *et al.*, 2009; Shin *et al.*, 2011; Deschamps *et al.*, 2014; Mignardot *et al.*, 2014). Moreover, when these force plate assessments were employed, postural control was found to be associated with brain volume for both MCI and AD groups (Makizako *et al.*, 2013; Sparto *et al.*, 2020).

However, while these tests provide useful information, they are unable to provide specific insight regarding why postural control is impaired, such as identifying the role of different sensory

system deficits in the contribution to postural control. The Sensory Organization Test (SOT) from the dynamic posturography balance assessment uses six conditions in order to manipulate each of the visual, somatosensory, and vestibular systems. Therefore, this assessment may allow for a greater understanding of the mechanistic aspects of postural control.

When individuals with AD were evaluated with the SOT, they demonstrated poorer postural control than CN counterparts (Chong *et al.*, 1999; Lee *et al.*, 2017). Moreover, this deficit was associated with reductions in brain volume (Lee et al., 2017). (MoCA score 15.9 ± 2.92). This could indicate that individuals were assessed later on in the course of the progression of MCI and in some cases, perhaps in the early stages of dementia. The relationship between postural control, as assessed with dynamic posturography and the SOT, and brain volume has never been examined in individuals with MCI.

As the SOT provides important information that is not available from other balance assessments, it would be valuable to use dynamic posturography in order to assess postural control, and its relationship with brain volume, in individuals with MCI, compared to CN. Furthermore, if dynamic posturography scores are well associated with brain volume, it may hold clinical utility as a biomarker of neurodegeneration.

The neurophysiology of postural control

While it was previously thought that postural control was regulated by one "balance system", it is now understood that postural control is maintained through the interaction of several complex systems. Thus, in order to maintain postural stability, sensory cues are integrated from the visual, somatosensory, and vestibular systems. This allows for the effector system to maintain balance based on our position, velocity, and acceleration.

Individuals with AD and MCI may experience sensory impairments to one of these systems, as well as to the integration of their outputs. For example, several studies have found an association between cognitive impairment and impaired functioning of the visual system (Bokde *et al.*, 2008; Valenti, 2010; Marchetti & Whitney, 2013). Marchetti and Whitney (2013) summarized the literature regarding the changes to visual functioning in older adults with cognitive decline. It was found that individuals with mild dementia and AD demonstrated impairments to various aspects of visual functioning including light tracking, and visuospatial functioning, compared to age-matched controls. Similarly, Stephen *et al.* (2010) observed reduced somatosensory system function in individuals with MCI and AD.

Meanwhile, vestibular system impairments have been commonly observed in AD patients (Nakamagoe *et al.*, 2015; Harun *et al.*, 2016; Agrawal *et al.*, 2020). However, the mechanistic interaction between the deterioration of the vestibular system and the time course of AD development is still unclear.

Detriments to the integration of sensory output information have been observed in healthy older adults, compared to those who were younger, in the context of the SOT (Redfern *et al.*, 2019). Furthermore, Redfern *et al.* (2019) hypothesized that this deficit was due to the reduction in cognitive capacity occurring with aging. Therefore, it is unsurprising that exacerbated deficits to sensory system integration are evident in individuals with both AD and MCI (Chong *et al.*, 1999; Mahoney & Verghese, 2020). Importantly, these impairments to sensory system integration were correlated with impaired static balance in individuals with MCI (Mahoney & Verghese, 2020). Identifying specific sensory system contributions to postural control for individuals with MCI may help distinguish important strategies for the maintenance of postural control and fall prevention.

In addition to the sensory systems implicated in postural control, discrete brain areas and structures are known to be critical to the maintenance of postural control (Surgent *et al.*, 2019). Dijkstra *et al.* (2020) performed a systematic review of the evidence concerning the neural networks supporting postural control in healthy individuals. Included studies assessed static, dynamic, or reactive postural control, using either actual postural tasks, or a postural simulation. Critical structures which were activated in an effort to maintain postural control included the brainstem, cerebellum, basal ganglia, thalamus, and several cortical regions.

Furthermore, Surgent *et al.* (2019) synthesized the literature regarding these discrete brain areas and their associations with postural control. This was examined in a range of populations, including those of a clinical nature, who were known to have impaired balance, as well as non-clinical populations. They investigated studies which assessed static and/or dynamic postural control and it was found that the brainstem/cerebellar region was the most frequent contributor to postural control, followed by the frontal and temporal regions, respectively. Importantly, the hippocampus accounted for nearly half of the temporal associations with postural control, suggesting that it plays a strong role in the maintenance of postural control. When subcortical regions were assessed, it was observed that gray matter volumes of each of the basal ganglia, thalamus, and nucleus accumbens were frequently related to performance on balance measures. More specifically, smaller gray matter volumes of the putamen and caudate were found to be related to poorer postural control in individuals with AD (Lee *et al.*, 2017).

Surgent *et al.* (2019) propose that their findings demonstrate that postural control is a global brain effort, rather than the product of the activity of only a few specific brain regions. Meanwhile, their results also demonstrate that certain brain structures may be particularly important to the regulation of postural control. While these findings are valuable, studies of this nature have not

been performed in the context of MCI. It is possible that postural control is well correlated to global or discrete brain volumes in MCI individuals, which may be a useful indicator of neurodegeneration. Therefore, it would be beneficial to explore the relationships between brain volumes and postural control performance in the context of MCI.

Hypotheses

Primary hypothesis: Individuals with MCI will demonstrate reduced postural control compared to CN. **Secondary hypothesis:** Individuals with MCI will exhibit reduced brain volumes compared to CN. **Tertiary hypothesis:** Reduced total and or regional brain volumes will be associated with poorer postural control in CN and MCI individuals.

Chapter III: Methods

Study Design

This study was an observational – exploratory – study, employing a cross-sectional design. It was conducted across two sites: the Jewish Rehabilitation Hospital in Laval, Quebec, and the Douglas Hospital in Montreal, Quebec.

While this research investigates only the aspects of postural control and brain volume in MCI and CN individuals, it is part of a much larger collaboration. The study was comprised of two components: that performed by Dr. Pedro Rosa-Neto's lab – the Translational Biomarkers of Aging and Dementia (TRIAD) study, and that of Dr. Roig's Memory Lab. The TRIAD study is thought to be one of the largest longitudinal biomarker-based study on aging and dementia, focusing on gold-standard biomarkers. As such, a multitude of well-established brain biomarker measures were investigated, including MRI scans, which allowed for the measurement of brain volume. As well, the TRIAD study performed cognitive, and neuropsychological assessments, in order to classify patients by cognitive level (i.e., CN vs. MCI).

At the Memory Lab, a physical performance battery was developed using the International Classification of Functioning framework (WHO, 2001). This battery allowed for the assessment of the full spectrum of physical function. Further, the physical performance battery was designed to complement the measures assessed by the TRIAD study, as it is understood that cognitive decline is typically accompanied by declines in physical function (Montero-Odasso & Hachinski, 2014; Montero-Odasso *et al.*, 2014; Bahureksa *et al.*, 2017; Kueper *et al.*, 2017).

Procedures

Ethics approval was obtained from the Centre de Recherche Interdisciplinaire en Readaptation (CRIR) in October of 2017 and renewed in 2019 (CRIR-1260-0717). Further, ethics approval was obtained specific to the COVID-19 pandemic. Participants each attended two laboratory visits, and written, informed consent was obtained at the beginning of each visit. The visit to Dr. Pedro Rosa-Neto's lab at the Douglas Hospital allowed for the classification of cognitive status, and completion of magnetic resonance imaging (MRI) scans allowing for brain volume acquisition. At the Memory Lab, postural control was assessed using dynamic posturography.

The following section outlines inclusion and exclusion criteria. Please note that while the conditions were designed for the full spectrum of the TRIAD and Memory Lab studies, as previously stated, this project pertains only to the aspects of postural control and brain volume in MCI and CN individuals.

Study Participants

Fifty individuals (32 MCI and 18 CN) enrolled in the TRIAD study who met the inclusion criteria for functional and exercise testing, were recruited to participate in the study. Participants were adults between 50 and 85 years of age, residing within the Greater Montreal area. **Inclusion criteria - all participants:** 1) individuals weighing < 136 kg and aged 50 to 85 years; 2) healthy

with no clinically relevant finding on physical examination at screening; 3) able to read at a 6th grade level or equivalent and had a history of academic achievement and/or employment sufficient to exclude mental retardation; 4) in stable medical condition based on medical history, physical examination, vital sign measurements and ECG; 5) in good health based on laboratory safety tests; 6) have MRI, or will be acquiring MRI within six months; 7) signed and dated written informed consent. **Inclusion criteria for CN Group**: 1) a mini mental state examination (MMSE) score > 27; 2) clinical dementia rating scale score = 0; 3) no history of subjective memory or other cognitive complaints; 4) no objective evidence of memory or cognitive impairment from the neuropsychological battery. **Inclusion criteria for MCI group:** 1) modified Hachinski score <4; 2) MMSE score 18 to <26; 3) clinical dementia rating scale score= 0.5; 4) history of subjective cognitive impairment 5) objective cognitive impairment demonstrated in the neuropsychological battery; 6) preserved activities of daily living.

Exclusion criteria for all participants: 1) subjects with absolute contraindications to exercise based on the criteria of the American College of Sports Medicine (ACSM, 2000); 2) participants with difficulty understanding the procedures of the experiments; 3) participation in another study within four weeks of screening, or in a PET research study or other study involving administration of a radioactive substance or ionizing radiation within 12 months prior to screening, or if they have undergone an extensive (> 50 mSv) radiological examination within this period; 4) diagnosis of a psychotic disorder (including substance abuse) within two years prior to screening; 5) presence of a neurological disorder at screening will also be excluded; 6) history of cancer or uncontrolled endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or neurological disease; 7) participants who are hepatitis B, C or human immunodeficiency virus (HIV) carriers; 8) major surgery or donation or loss of one unit of blood

(approximately 500 mL) within four weeks prior to screening; 9) implants such as implanted cardiac pacemakers or defibrillators, and other medical implants that have not been certified for MRI; 10) evidence of cerebrovascular disease, infectious disease, space-occupying lesions, normal pressure hydrocephalus or any other abnormalities associated with central nervous system disease; 11) regular consumption of alcohol, cannabis, illicit drugs, or caffeine (6+ per day); 12) claustrophobia; 13) female subjects who were pregnant, lactating or breastfeeding were excluded.

General Assessments

Neuropsychological Assessments

Diagnoses of MCI were based on clinical, neuropsychological, and imaging data and were confirmed by an expert consensus panel of clinicians, neuropsychologists, and nurses. Standard neuropsychological assessments were performed for each participant by a certified neuropsychologist. Assessments included: the MMSE, the Montreal Cognitive Assessment (MoCA), the Frontal Assessment Battery, four components of the Wechsler Abbreviated Scale of Intelligence (vocabulary, similarities, matrix reasoning and block design), the Cogstate computerized cognitive battery an automated program. Lastly, a variety of assessments that make up the Clinical Dementia Rating were performed, including: the Hachinski scale, the Global Deterioration Scale, the Geriatric Depression Rating Scale, the Mattis Dementia Rating Scale, and Hamilton scales for anxiety. A demographic questionnaire was also completed, in order to acquire personal information such as education level, age, sex, and medication.

Brain Volumes

MRI images were acquired on a 3T Siemens Magnetom scanner using a standard head coil. An MPRAGE MRI sequence was employed to obtain a high-resolution (1 mm isotropic voxels) T1-weighted anatomical image of the entire brain. T1-weighted images were non-uniformity and

field-distortion corrected and processed using an in-house pipeline. This pipeline used Freesurfer (https://surfer.nmr.mgh.harvard.edu) for parcellating the brain, and SPM12 (https://fil.ion.ucl.ac.uk/spm/) for the general tissue-based segmentation. From the regular Freesurfer output, the DKT atlas (Klein, A., and Tourville, J., 2012. Front. Neurosci. 6:171) and the segmentation map ("aparc_aseg") were used to identify regions of interest (ROIs). The overall brain segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) was done using the Dartel module of SPM12 (J. Ashburner. A Fast Diffeomorphic Image Registration Algorithm. NeuroImage, 38(1):95-113, 2007; see https://neurometrika.org/node/34) which was used to warp the segmented images to ADNI standard space (http://adni.loni.usc.edu/data-samples/), representing an adaptation of MNI152 standard template (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009) to aging populations. Random field theory (RFT; Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., and Evans, A.C. (1996)). Human Brain Mapping, 4:58-73) convolution was performed to accurately estimate the tissue classes, with their masks subsequently binarized by assigning the highest probability of each tissue class. Then, the intracranial volume (ICV) was obtained as a combination of GM, WM and CSF. To compute volumes for individual ROIs, the voxel count was performed within the corresponding parcellation and segmentation maps obtained from Freesurfer, ensuring all voxels counted were within the grey matter mask; as the MRI resolution is 1mm isotropic, and the voxel count values were divided by 1000, the resulting units are cubic centimeters. Namely, the following ROIs from the DKT atlas were used: precentral gyrus, postcentral gyrus, pericalcarine cortex, thalamus, caudate nucleus, putamen, pallidum, nucleus accumbens and hippocampus (**Fig 1a-g)**. The aparg_aseg segmentation map from Freesurfer was used to define the cerebellar masks. Brain structure volumes were presented as a percentage of ICV, such that

values were first divided by ICV, and then multiplied by 100. Standard deviations were similarly multiplied by 100. This adjustment was made in order to account for inter-individual differences in brain volume.

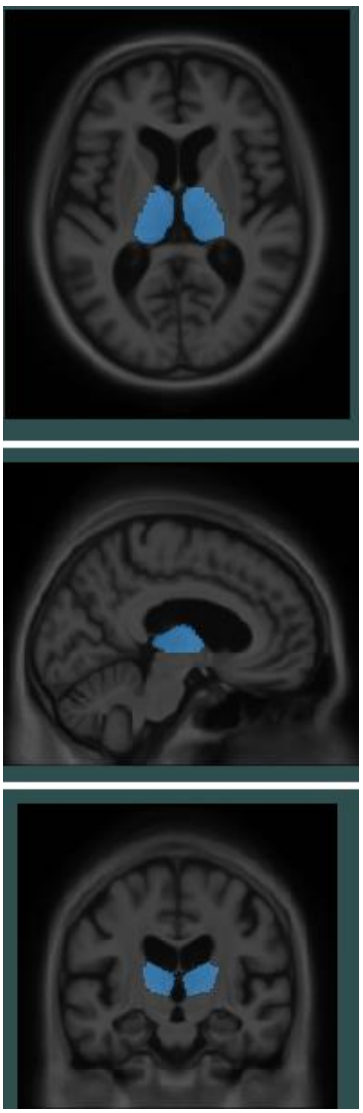


Figure 1a. Visualization of the thalamus.

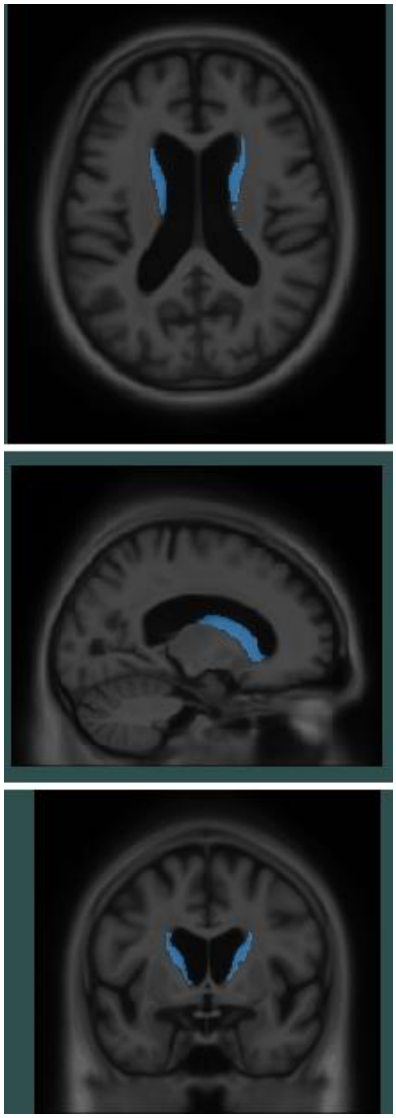


Figure 1b. Visualization of the caudate.

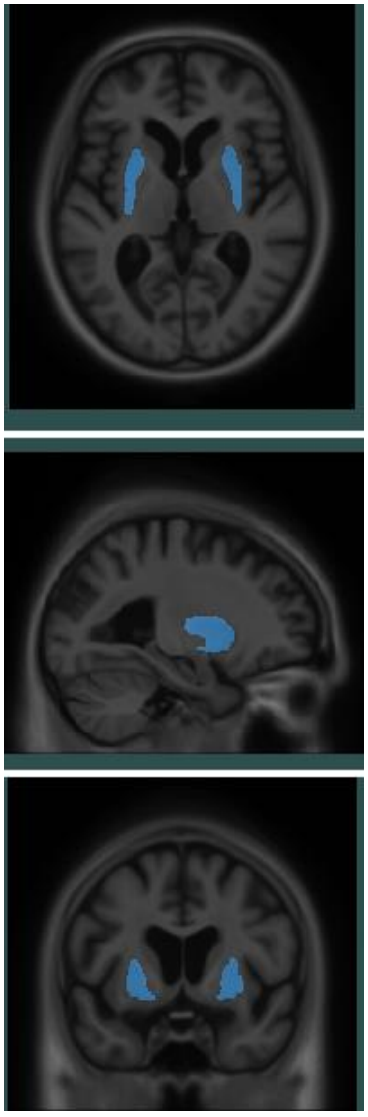


Figure 1c. Visualization of the putamen.

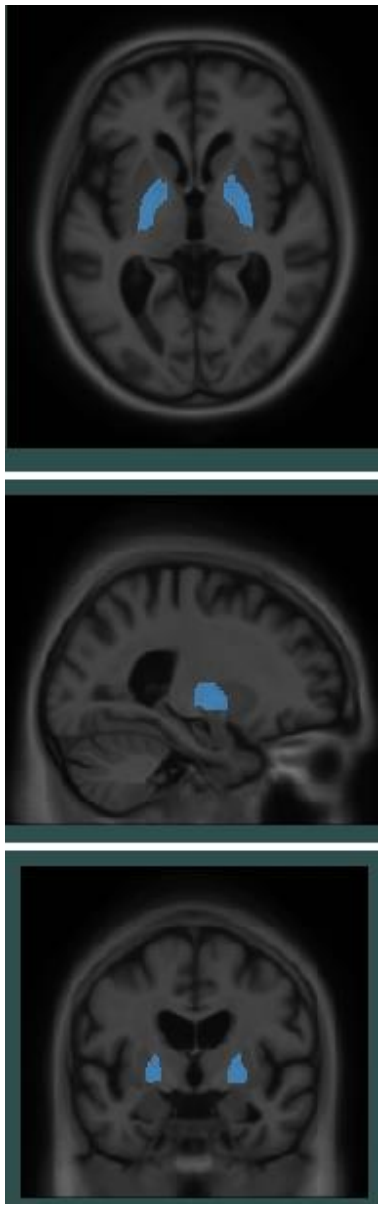


Figure 1d. Visualization of the pallidum.

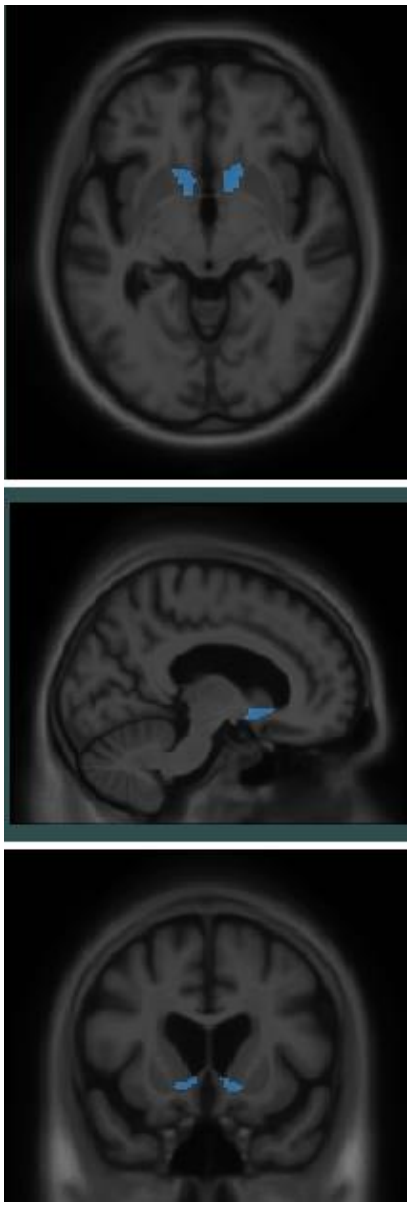


Figure 1e. Visualization of the accumbens.

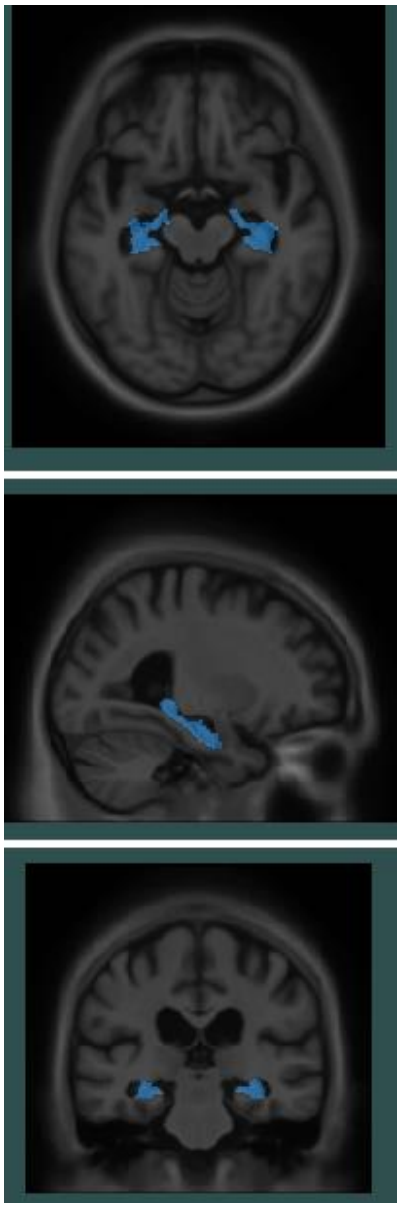


Figure 1f. Visualization of the hippocampus.

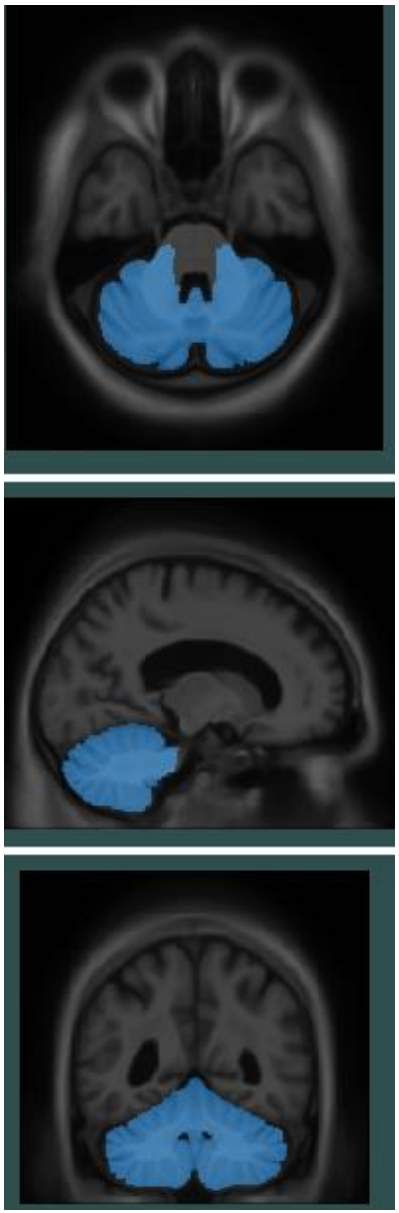


Figure 1g. Visualization of the cerebellum.

Postural Control Assessment

An EquiTest system (NeuroCom International Inc., Clackamas, OR) was used to assess postural control quantitatively, using the SOT. The SOT, whose reliability and validity are well established and which has previously been used in individuals with AD (Lee *et al.*, 2017) and MCI (Baydan *et al.*, 2020), consists of six conditions that manipulate visual, somatosensory, and vestibular inputs to challenge postural control.

Each condition is comprised of three trials, and each trial has a duration of either 20 seconds, or until the participant requires a step to regain balance, or touches the visual surround for support (Roig *et al.*, 2011). In the latter case, the trial receives an equilibrium score of zero and was registered as a fall. Trials and conditions were performed consecutively, however short rests were provided when necessary.

Depending on which SOT condition is being performed, the EquiTest system modifies the support surface (by tilting the force plate in the sagittal plane), the visual surround (by tilting the background in the sagittal plane), or both elements simultaneously. This allows for the alteration of somatosensory, visual, and vestibular inputs, respectively (**Table 1**). The vestibular system is specifically challenged in conditions 5 and 6, when the support surface is altered while visual input is eliminated (i.e., participants' eyes are closed) or when both the support surface and the visual surround are altered simultaneously.

Table 1. Description of the six conditions in the Sensory Organization Test

Condition	Description	Sensory system altered	Sensory system targeted
1	Eyes open, fixed surface, and visual surround	None	All
2	Eyes closed, fixed surface	None	Somatosensory and vestibular
3	Eyes open, fixed surface, sway-referenced visual surround	Visual	Somatosensory and vestibular
4	Eyes open, sway-referenced surface, fixed visual surround	Somatosensory	Visual and vestibular
5	Eyes closed, sway-referenced surface	Somatosensory	Vestibular
6	Eyes open, sway-referenced surface, and visual surround	Visual and somatosensory	Vestibular

The sway gain of the EquiTest system was set to 1, signifying that the support surface or visual surround followed the individual's sway exactly. Equilibrium scores (based on an individual's postural sway) for each SOT condition were calculated by determining the maximum and minimum anterior posterior sway angles (angle between a line projecting vertically from the centre of foot support and a line from the centre of foot support to the centre of gravity). Following the completion of the SOT, a composite equilibrium score was calculated. A score of 100 represents no postural sway (e.g., perfect postural control), while a lower score indicates increasingly poor postural control. Scores were age-normalized according to previously obtained data integrated in the Equitest system (Black, 2001; Ionescu *et al.*, 2005).

Additionally, the SOT allows for sensory analysis – calculating four values which indicate the potential contributions of each individual sensory systems to postural control. These outputs include SOM (somatosensory), VIS (visual), VEST (vestibular), and PREF (visual preference). Scores were computed using ratios of equilibrium scores, such that VIS was calculated using the ratio of average scores from condition 4 to condition 1, SOM from condition 2 to condition 1, and

VEST from condition 5 to condition 1. PREF was calculated by dividing the sum of the average scores of conditions 3 and 6 by the sum of the average scores of conditions 2 and 5.

As the SOT challenges balance, participants were required to wear a safety harness while performing testing. As an extra precaution, an assessor stood behind each participant for all trials, in order to help participants regain balance, should they require it.

Overall Physical Function

The Short Physical Performance Battery (SPPB) was employed in order to assess overall physical function for each participant. This battery evaluates gait speed, as well as static and dynamic balance. The SPPB is scored out of 12 with 4 points assigned to each of: a four meter walk, 10 chair stands, and 10-second static balance holds in each of three positions (side-by-side, semi-tandem, and tandem). A score of 12 indicates a perfect score, while lower scores indicate reduced capacity for physical function.

Data Analysis

Sample Size Estimation

The statistical package G*Power was used to determine the sample size required to obtain a power of 80% (alpha <0.05) when comparing the CN and MCI groups. Using previous data, we estimated a difference between group in SOT of 5 points and an averaged SD of 6.2 (Lee *et al.*, 2017). We would have required 52 participants per group to detect a difference in SOT using independent t-tests. Effect sizes were estimated based on data collected by Lee *et al.* (2017). For this study, we aimed to recruit 30 participants per group, which was an ambitious but (we believed) feasible target for an MSc study before the COVID-19. Although this target has not yet been achieved due to COVID-19, recruitment and data collection is currently ongoing in an effort to increase the sample size.

Statistical Analysis

Statistical analyses were carried out JMP Pro version 15 (SAS). Data were first plotted in order to visualize distributions for each of the two (CN and MCI) groups separately, using normal quantile plots and histograms. The Shapiro-Wilk's test was used to confirm normality. Demographic data were compared using independent t-tests, or Mann-Whitney U tests for continuous variables, while Chi-square tests were performed for categorical variables. **Primary analyses:** Independent t-tests or Mann Whitney U tests were also used in order to determine differences between groups for measures of postural control, including falls, as well as brain volumes adjusted for ICV. Data were presented as means and standard error of the mean (SEM), and all analyses were performed with 2-tailed probability tests where the statistical level is set at $p<0.05$. **Secondary analyses:** We first explored the linearity of the association between dependent (postural control) and independent (brain volumes) variables using scatter plots and correlational analyses. Separate linear regression models were then constructed between dependent and independent variables. We used a forward step-wise regression procedure in order to explore potential covariates and confounding variables.

Our main analysis was focused on the interaction between the composite score of the SOT and total brain volume. However, exploratory analyses were also performed to generate hypotheses regarding potential associations between other measures of postural control and the volume of discrete areas of the brain. ICV differed between sexes, with men having greater ICV than women (<0.0001). Therefore, brain volumes were divided by ICV in order to account for these differences. Given the exploratory nature of our analyses, the alpha threshold for significance ($p<0.05$) was not corrected for multiple comparisons. Data were reported with means and SEM unless otherwise stated.

Chapter IV: Results

Demographics

Demographic characteristics for all participants are presented in **Table 2**. MCI and CN adults had similar sample characteristics, with no significant differences in age, BMI, or education. MCI individuals showed significantly poorer MMSE scores, MoCA scores, and global CDR scores which was to be expected. Additionally, significant differences were observed in the GPAQ MET total, demonstrating that the CN group was more physically active than the MCI group. No significant differences were found between groups for the SPPB, indicating similar overall physical function for the MCI and CN groups.

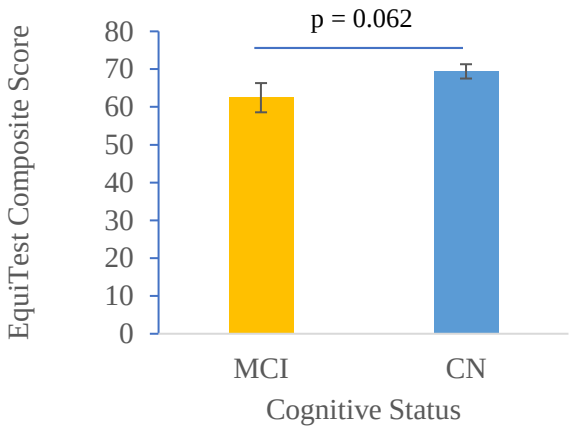
Table 2. Sample characteristics.

	Group		p-value
	CN (n= 32)	MCI (n= 18)	
Sex (male/female)	24/12	11/7	0.92
Age, y	73.03 (6.69)	74.50 (6.86)	0.76
BMI	27.51 (4.30)	27.92 (4.23)	0.62
Education, y	14.97 (3.14)	14.13 (3.40)	0.21
MMSE score*	29.32 (0.87)	28.39 (1.14)	0.0028
MoCA score*	26.52 (2.62)	24.28 (3.27)	0.0095
GPAQ MET total*	2892.41 (2589)	1741.11 (3367.68)	0.016
CDR global*	0.016 (0.090)	0.39 (0.21)	<0.0001
SPPB	11.36 (0.86)	10.6 (1.4)	0.6891

Data are presented as mean (SD). CN, cognitively normal; MCI, mild cognitive impairment; y, years; BMI, body mass index; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; GPAQ, Global Physical Activity Questionnaire; SPPB, Short Physical Performance Battery. * significantly different between groups ($p < 0.05$).

Postural control

Average composite postural control scores for both the MCI and CN groups can be observed in **Figure 1**. The MCI group was found to have a lower average score than the CN group, however, differences were not statistically significant [t(26.59) = 0.12, p = 0.062].



Results for estimated specific contributions of specific sensory systems can be observed in **Figure 2**. Average EquiTest composite score for MCI and CN participants. Error bars are SEM.

Table 3. Differences between MCI and CN adults for the somatosensory, visual, and vestibular system contributions to postural control did not reach statistical significance.

Table 3. Average individual sensory system scores for maintenance of postural control.

	CN	MCI	*p*
Somatosensory	94.37 (3.32)	95.89 (1.15)	0.67
Visual	83.93 (1.75)	75.67 (5.50)	0.084
Vestibular	57.48 (4.46)	47.28 (5.78)	0.085

Data are presented as mean (SEM). CN, cognitively normal; MCI, mild cognitive impairment.

When the median number of falls were examined for the MCI and CN groups, differences between groups were not statistically significance (p=0.19), however a greater median number of falls was observed in the MCI group [1.5, IQR (3.25)] than in the CN group [0, IQR (2)] (**Figure 3)**.

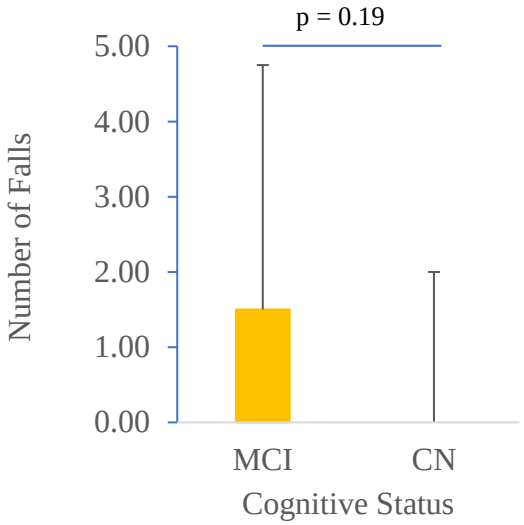


Figure 3. Median number of falls for MCI and CN groups. No significant difference was found between groups (p=0.19). Error bars are interquartile range.

Brain volume

Although there were observable differences in total brain volume between the MCI and CN groups (**Figure 4**), they did not reach statistical significance [t(36.83) = 0.20, p = 0.098].

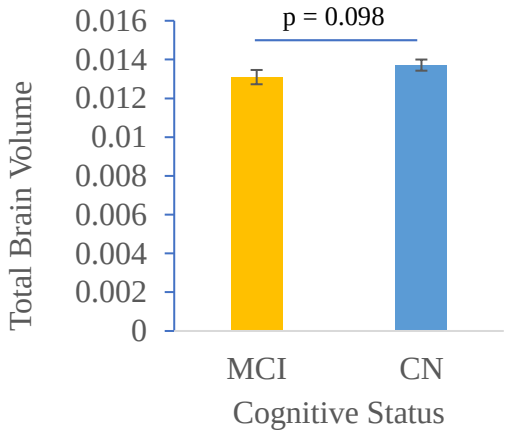


Figure 4. Total brain volume of MCI and CN participants. Between group differences did not reach statistical significance (p=0.098). Error bars are SEM.

Regional analyses of brain volume revealed significant differences between MCI and CN adults in the post central gyrus [t(40.20) = 0.078, p = 0.039], but no differences were observed in the precentral [t(34.60) = 0.39, p = 0.20] or pericalcarine [t(38.35) = 0.52, p = 0.26] areas of the brain.

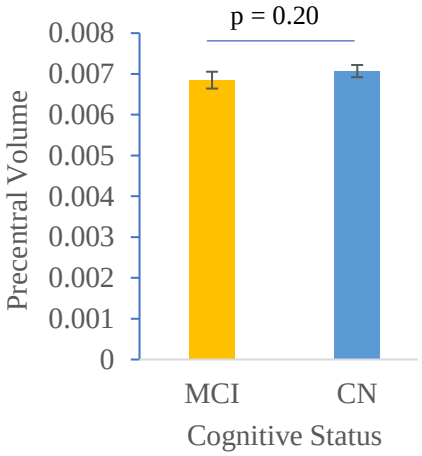


Figure 5. Average precentral brain volume of MCI and CN participants. No significant difference was found between groups (p=0.20). Error bars are SEM.

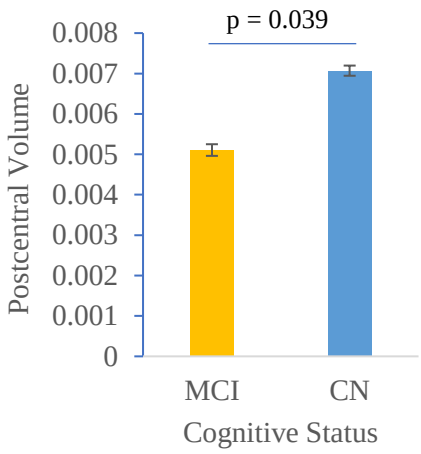


Figure 6. Average postcentral brain volume of MCI and CN participants. No significant difference was found between groups (p=0.039). Error bars are SEM.

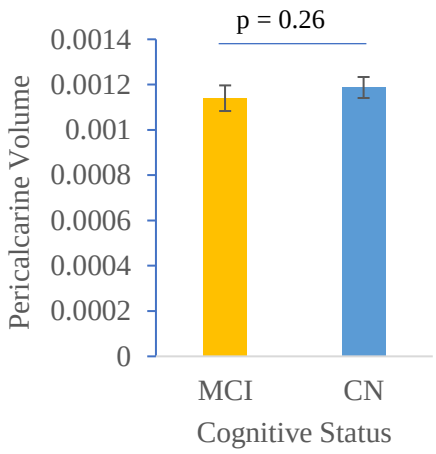


Figure 7. Average pericalcarine brain volume of MCI and CN participants. No significant difference was found between groups (p=0.26). Error bars are SEM.

Discrete structural brain volumes adjusted for ICV for all participants can be seen in **Table 4**. Although the MCI group exhibited smaller brain volumes for all structures, significant differences were only found in the caudate and accumbens. Differences in hippocampal volumes were near to reaching significance [t(36.01) = 0.11, p = 0.053].

Table 4. Discrete brain volumes CN and MCI participants, as a percentage of ICV.

	CN	MCI	*p*
Thalamus	0.20 (0.0057)	0.19 (0.0088)	0.070
Caudate	0.18 (0.0051)	0.16 (0.0061)	0.013*
Putamen	0.23 (0.0061)	0.22 (0.0094)	0.13
Pallidus	0.12 (0.0025)	0.93 (0.0017)	0.22
Accumbens	0.030 (0.00079)	0.026 (0.00089)	0.0058*
Hippocampus	0.23 (0.0061)	0.21 (0.0080)	0.053
Cerebellum	8.53 (0.15)	8.4 (0.19)	0.31

Data are presented as mean (SEM). CN, cognitively normal; ICV, intracranial volume MCI, mild cognitive impairment. * significantly different between groups $p < 0.05$.

Correlation between brain volumes and postural control

In CN adults, there were no observed relationships between aspects of postural control and regional, discrete, or global brain volumes. Meanwhile, in MCI participants, the SOT composite score was significantly associated with the pre (R^2=0.58, p=0.012) and post central gyri (R^2=0.55, p=0.019), in addition to the total brain volume (R^2=0.60, p=0.0079). Additionally, there were no statistically significant relationships between measures of postural control and discrete brain volumes, however a trending relationship was found between the SOT composite score and the putamen (R^2=0.45, p=0.064).

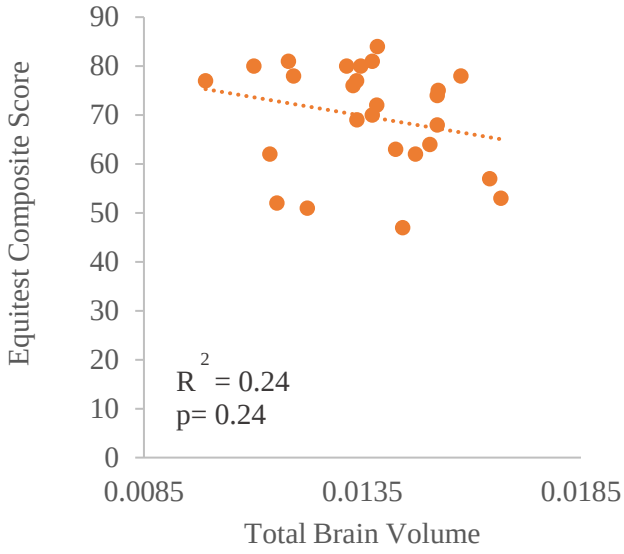


Figure 8. Correlation comparing composite EquiTest scores and brain volume in CN participants.

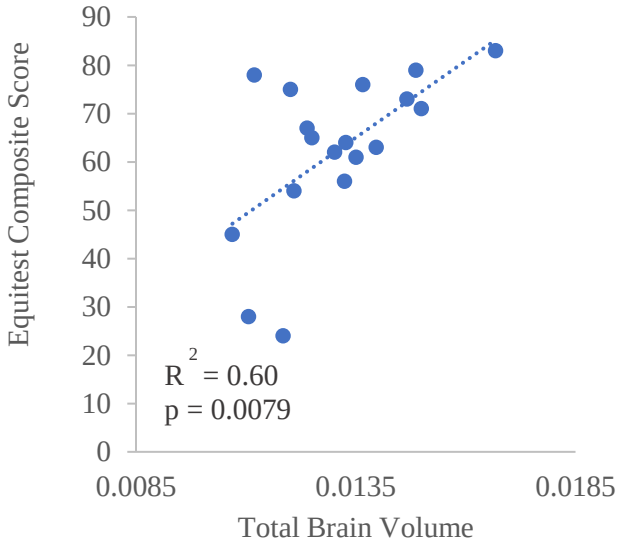


Figure 9. Correlation comparing composite EquiTest scores and brain volume in MCI participants.

A stepwise-regression model was employed in order to investigate covariates. However, the inclusion of potential covariates and confounding variables (age and biological sex) did not improve the model for either MCI or CN groups. Therefore, covariates were not included, and a simple correlation was performed. Additionally, in the MCI group, only the postural control composite score was found to predict brain volumes.

Chapter V: Discussion

Postural control

Firstly, our study investigated differences in the composite postural control score, generated by the SOT, between MCI and CN groups. While the MCI group demonstrated a lower average score compared to CN, differences did not reach statistical significance. Previous studies have documented significant postural control impairments in individuals with MCI compared to CN when employing clinical balance assessments (Shin *et al.*, 2011; Deschamps *et al.*, 2014; Mignardot *et al.*, 2014). Further, this difference was observed with the use of the SOT in a small study with 10 CN and 10 MCI participants (Baydan *et al.*, 2020). However, it should be noted that in that study, MCI global cognitive performance was very low. The average MoCA score for the MCI group was reported to be 15.9 ± 2.92, while the mean MMSE score was 21.2 ± 1.39.

Work by Petersen *et al.* (1999) indicated the mean MMSE for MCI patients to be 26.0 ± 0.3. In employing the MoCA, an upper cut-off score of 26 has been proposed in order to identify cognitive impairment – a score more than ten points greater than that observed by Baydan *et al.* (2020) (Nasreddine *et al.*, 2005; Smith *et al.*, 2007). Further, Smith *et al.* (2007) found patients with dementia to exhibit a mean MoCA score of 21.0 ± 3.4 – over five points above that achieved by the group identified as MCI in the study by Baydan *et al.* (2020). Therefore, although Baydan *et al.* (2020) characterized these 10 adults as MCI, their criteria are not consistent with known classification criteria for MCI. Consequently, it is possible that individuals characterized as MCI in the study performed by Baydan *et al.* (2020) in fact suffered from dementia.

In comparison, our MCI population demonstrated an average MoCA score of 24.28 ± 3.27 and MMSE score of 28.39 ± 1.14. Therefore, it is possible that postural control differences in our population were not as pronounced due to higher global cognitive functioning in the MCI group,

indicating that our group may be at an earlier point in cognitive decline. Moreover, our study was limited by its small sample size, which was below the estimated sample size estimated from the study by Lee *et al.* (2017), and which was required to detect significant between group differences in the composite score of the SOT. Since our results already indicate a clear trend (p=0.062) to detect significant between-group differences in postural control, it is likely that accumulating data on a larger population would result in significant findings.

When distinct contributions of each sensory system to the maintenance of postural control were assessed, differences were observed for each of the SOM, VIS, VEST, and PREF parameters. Results only approached statistical significance in the visual (p=0.084) and vestibular systems (p=0.085). It should be noted however, that the conditions assessing the contributions of the vestibular system to postural control are also the most challenging. Therefore, it is possible that between-group differences in the VEST parameter were larger in-part due to the difficulty of these conditions, and not simply because of an impairment to vestibular system function.

The present findings are in line with the only available literature, as Baydan *et al.* (2020) found no significant differences between MCI and CN groups for each of the SOM, VIS, VEST and PREF parameters. However, the limitations of this study (i.e., sample size) have been discussed previously. Therefore, while the present results may indicate that individuals with MCI perform similarly to those identified as CN in the use of specific sensory system information for the maintenance of postural control, we suspect differences would reach significance with a larger sample size.

When investigating the average number of recorded falls occurring in an SOT assessment, differences were not found to be significantly different between the MCI and CN groups. It remains important to consider the small sample size of this group. With the MCI group reporting an average

of 1.5 more falls per SOT assessment than the CN, and a sample size that did not reach the estimated target, it remains possible that differences would reach statistical significance with a greater number of participants.

Although it is known that individuals with MCI are more prone to falls than CN individuals (Delbaere *et al.*, 2012; Doi *et al.*, 2015; van der Wardt *et al.*, 2015; Tyrovolas *et al.*, 2016), previous studies have not reported differences in falls in the context of the SOT, and so cannot be compared to. Additionally, it is important to consider that a fall on the SOT is registered when a participant loses their balance in a bipedal stance, requiring a step, or holding on to the visual surround in order to regain balance (Roig *et al.*, 2011). Thus, in the SOT, the definition of a fall varies from what is typically considered to be a fall in real life.

Brain Volume

Total, regional, and structural brain volumes were compared between MCI and CN groups. Total brain volumes were found to be smaller in the MCI group; however, differences did not reach statistical significance (p=0.098). While it is possible that these results would change with a greater sample size, these findings align with the literature. Cross-sectional measures of global brain volume have not demonstrated the ability to distinguish MCI individuals from CN (Convit *et al.*, 1997; van der Flier *et al.*, 2002; Wolf *et al.*, 2004; Sluimer *et al.*, 2008). However, total brain volume is consistently reduced in individuals diagnosed with AD, compared to MCI and CN adults (Wolf *et al.*, 2001; Wolf *et al.*, 2004; Van Der Flier & Scheltens, 2009). Further, increased rates of change in total brain volume have demonstrated value in predicting the onset of dementia and AD progression (Jack *et al.*, 2004; Sluimer *et al.*, 2008; Henneman *et al.*, 2009). Therefore, total brain volume remains a useful indicator of global neurodegeneration, especially as a repeated-

measure in MCI patients in order to observe rate of change, as well as cross-sectionally in patients already diagnosed with AD.

When between-group differences in the volumes of the precentral, postcentral, and pericalcarine regions of the brain were assessed, findings were statistically significant only for the postcentral gyrus.

The literature investigating brain volume changes in these regions related to AD is sparse. However, all three of these regions have been demonstrated to be significantly smaller in AD patients compared to CN individuals and those with MCI (Yang *et al.*, 2019). Furthermore, Fennema-Notestine *et al.* (2009) explored differences between MCI and CN brain volumes across several measures, including the above regions. However, MCI individuals were split into two subgroups: multi-domain MCI (MMCI), and single-domain MCI (SMCI). Results were reported separately for each group. The SMCI group exhibited no significant differences in brain volume for any of the precentral, postcentral, or pericalcarine regions compared to the CN groups. Meanwhile, the MMCI group demonstrated significantly reduced volumes in the precentral ($p<0.001$) and postcentral ($p<0.001$) regions. Fennema-Notestine *et al.* (2009) propose the MMCI group to be in a later stage of prodromal AD, which suggests that these changes to brain structure may be more likely to appear later in the timeline of cognitive decline.

All specific structural brain volumes were similarly found to be smaller in the MCI group compared to CN, with the exception of the pallidus. Statistically significant differences were demonstrated only in the caudate nucleus ($p=0.013$) and nucleus accumbens ($p=0.0058$). Additionally, hippocampal differences were near to significant ($p=0.053$). Once again, it appears likely that with a larger sample size the brain volumes of certain structures, such as the hippocampus, may become significantly different between groups.

In line with this supposition, Braak and Braak (1991) described six stages of neuropathological progression of AD and found that the earliest stages of development involve the entorhinal region and hippocampus. While Braak and Braak (1991) investigated neurofibrillary tangle development and not brain volume, this finding may suggest that in the earliest stages of AD, pathologic changes may be observed in the hippocampus.

Over the following decades, hippocampal atrophy was repeatedly implicated in AD development, indicating reduced hippocampal volume to be a hallmark of AD (Hyman *et al.*, 1984; Fox *et al.*, 1996; Ryu *et al.*, 2010; Clerx *et al.*, 2012). Furthermore, reduced hippocampal volume is well-evidenced in the MCI condition (Convit *et al.*, 1997; Wolf *et al.*, 2004; Fennema-Notestine *et al.*, 2009; Cherubini *et al.*, 2010; Liu *et al.*, 2010; Zidan *et al.*, 2019).

While differences in other subcortical structures are not ubiquitous (Fennema-Notestine *et al.*, 2009; Cherubini *et al.*, 2010), several studies have noted significant differences between MCI and CN adults in the volume of the thalamus (Pedro *et al.*, 2012; Hahn *et al.*, 2016; Zidan *et al.*, 2019). Furthermore, Yi *et al.* (2016) explored subcortical brain volumes in a relatively large sample which included 201 MCI individuals, and 101 CN. They found significantly smaller volumes of the amygdala, thalamus, putamen, nucleus accumbens, and hippocampus in the MCI group, compared to the CN group (Yi *et al.*, 2016). This supports the notion that a larger sample size may result in increased findings of significant differences in subcortical brain volumes between the MCI and CN groups.

Relationship between postural control and brain volume

Thirdly, the current study revealed a strong relationship between global brain volume and composite postural control score but only in individuals with MCI. Given the small differences in

brain volume between groups at this early stage of cognitive decline this finding is striking. This information suggests that postural control, as assessed with dynamic posturography, may be a very sensitive indicator of global neurodegeneration in individuals with MCI.

These findings extend upon previous studies which indicated a relationship between postural control and brain volume with declining cognitive functioning. For instance, Kido *et al.* (2010) examined the relationship between static postural control and brain volume in a group of individuals which included CN, MCI, and AD, adults. Postural stability was assessed using a posturograph force plate, and poorer postural stability was associated with greater brain atrophy – indicated by increases to the temporal horn area, an index of medial-temporal lobe atrophy. Associations were not reported for CN, MCI, and AD adults separately, making results challenging to compare.

More recently, Makizako *et al.* (2013) found an indirect relationship between performance on a one-legged balance test, and brain volume in individuals with MCI. Specifically, performance on a one-legged balance task was significantly decreased for individuals who fell at least once over the 12-month follow up period, compared to those who did not experience a fall ($p=0.002$). Additionally, an increased risk of falls during the follow-up period was associated with reduced baseline gray matter volume in the middle frontal gyrus ($p<0.001$) and the superior frontal gyrus ($p<0.001$). These findings suggested the possibility of a correlation between postural control and brain volume in individuals with cognitive decline and indicated a need for further research exploring this relationship.

Moreover, Lee *et al.* (2017) performed a study investigating the relationship between subcortical brain volumes and postural control, while employing the SOT in AD patients. Their results indicated a relationship between the composite score of the SOT and each of the nucleus

accumbens (R^2=0.214, $p<0.001$), hippocampus (R^2=0.06, $p<0.05$), and thalamus (R^2=0.112, $p<0.05$). These results were critical in demonstrating a relationship between postural control and brain volume with cognitive decline.

In our study, the lack of significant findings for correlations between subcortical brain volumes and composite postural control scores may indicate a need for a larger sample size. Alternately, these relationships may only reveal themselves for individuals farther along in the process of cognitive decline, when brain volumes atrophy to a greater extent. Yet, our study still demonstrated correlations between the SOT composite score and precentral and postcentral volumes in the MCI group. Furthermore, with small differences in brain volume and postural control between groups, this strong correlation indicates postural control, as measured by dynamic posturography, to be a sensitive measure of structural brain deterioration. Additionally, our results provide evidence for this relationship at an earlier time-point in the process of cognitive decline than previously demonstrated.

Strengths and limitations

Our study had a number of strengths and limitations. One strength is the rigorous methods employed in order to determine the cognitive status of each participant. This included thorough neuropsychological testing which was performed by certified neuropsychologists, and confirmed by a panel. Further, these assessments were combined with neuroimaging measures, a resource that is not always taken into account. Additionally, inclusion criteria were extensive, in order to mitigate confounding factors.

Importantly, this study also suffers from some limitations, perhaps the greatest of which is our small sample size. Due to complications with COVID-19, our data collection was paused for

six months. As such, we were unable to assess the number of participants required to meet the estimated sample size necessary to observe between group differences on SOT performance. This in turn, may have impacted the results. Additionally, inclusion criteria did not include diagnosis of vestibular disorders, or sensory impairments, which may have the potential to impact results. Furthermore, this study may incur some heterogeneity in the results due to the inclusion of different MCI subtypes. However, those diagnosed with an MCI subtype other than amnestic numbered only 2 out of the 18 MCI participants.

As well, when facilitating the SOT, experimenters were not blinded to cognitive status. However, the objective nature of the SOT and computerized score output leaves little vulnerability to bias. Finally, this study is cross-sectional in nature, and so cannot indicate how postural control will predict further neurodegeneration and cognitive decline over time. Therefore, future research should include longitudinal studies, in order to explore the predictive value of postural control on neurodegeneration, cognitive decline, and turnover to AD, within MCI individuals.

Chapter VI: Conclusions

Ultimately, this study demonstrated a strong relationship between brain volume and postural control in individuals with MCI. These results were evident alongside small between-group differences in brain volumes and dynamic posturography scores, which did not meet statistical significance. Therefore, postural control reveals itself to be a highly sensitive marker of global neurodegeneration in individuals with MCI.

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