SLEEP, PERIVASCULAR SPACES, AND COGNITION IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

ERICA L. TATHAM

A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN PSYCHOLOGY
YORK UNIVERSITY
TORONTO, CANADA

July 2022

Abstract

Cognitive dysfunction, particularly involving memory and executive function, is a core component of neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. Two factors that are likely related to and may contribute to these cognitive deficits are sleep changes and enlarged perivascular spaces, which are an indicator of cerebral small vessel disease. In addition to being related to cognition, they may also be interconnected, further exacerbating their impact on cognition. This dissertation lays out our current knowledge on these topics and explores the association of these factors with cognition.

In this dissertation, I investigated the relationship that perivascular space volumes and sleep (i.e., sleep duration or sleep quality) have with cognitive performance and cognitive status category in Alzheimer's disease and Parkinson's disease. Study 1 included individuals with Alzheimer's-related mild cognitive impairment (MCI) or dementia. Among the individuals with Alzheimer's disease, longer sleep durations were related to lower memory and executive function performance, and larger white matter perivascular space volumes exacerbated the relationship between longer sleep durations and memory after accounting for relevant covariates. Study 2 included individuals with Parkinson's disease with intact cognition, MCI, or dementia. Analyses revealed an interaction in which individuals with Parkinson's disease with smaller white matter perivascular space volumes and better sleep quality exhibited better executive function performance after accounting for relevant covariates. There was also a significant negative correlation between sleep quality and white matter perivascular spaces, and this correlation stayed relatively consistent when covariates were individually included in the model. Finally, analyses across cognitive status groupings revealed that individuals with Parkinson's disease with MCI exhibited significantly larger white matter perivascular space volumes relative

to those with intact cognition, but no other group differences were observed. These results indicate that cognition has a complex relationship with perivascular spaces and/or sleep in Alzheimer's disease and Parkinson's disease and that some indicators of sleep and perivascular space volume may be related to cognitive abilities in these populations.

Dedication

I would like to dedicate this work to my sister, Dr. Barbara Tatham.

Acknowledgments

I am a better scientist because of the guidance of Drs. Rich, Troyer, and Vandermorris. Dr. Rich, you have an effortless ability to push me while also expressing true empathy when there are soft spots. Dr. Vandermorris, your ability to step in and lead and provide compassion for students going through the training journey has made me feel seen and helped me attain goals that I did not think were achievable. Dr. Troyer, your calm nature and ability to effortlessly think through scientific endeavours has improved my critical thinking abilities.

To the other members of the lab, Iris, Christina, KB, Becca, and Komal. This journey has been long and I would not have made it through without your support. A particular thanks to Komal, a frequent co-author, who would take my 10pm phone calls and always helped put me back on the right path.

I would also like to thank the 20 psychologists that have provided me with clinical supervision during my training. Although they didn't directly contribute to this document, their knowledge and wisdom have made me a skilled psychologist.

I would also like to thank my family. Putting into words what you mean to me is difficult because you are the most important people in my life. We have gone through a lot over the course of my training and you have all shown resilience and unconditional support. Dad, thank you for your passion for science, and Mom, thank you for showing me how to truly be there for others.

And most importantly, I would like to thank Bryan. He has supported me through everything, never questioned my passion for psychology, admired my tenacity, and has always shown me unconditional love.

“I’ve learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel.”

- Maya Angelou

TABLE OF CONTENTS

List of Tables

List of Figures

Chapter One: Introduction

When cognition is impaired, which is the case in many neurodegenerative conditions, individuals may experience a reduced ability to function in daily life. Identifying modifiable risk factors that contribute to this cognitive decline may help elucidate mechanisms to slow or prevent changes to cognition. Two factors that may be related to cognition in neurodegenerative conditions are sleep and indicators of cerebral small vessel disease (e.g., enlarged perivascular spaces). These factors may not only have a relationship with cognition but may be interconnected, which could exacerbate their impact on cognition.

In this Introduction, I review literature on sleep, cognition, and perivascular spaces. Then, I provide details for two studies I completed that examine relationships between these constructs in individuals with Alzheimer's disease and Parkinson's disease.

Cognition in Neurodegenerative Disease

Cognitive decline is commonly observed in individuals with neurodegenerative diseases, such as Alzheimer's disease. For example, individuals with Alzheimer's disease typically exhibit a cognitive profile characterized by a decline in memory (particularly episodic memory) which presents as impaired delayed recall, fast rates of forgetting, and problems learning new information on neuropsychological tests (Hessen et al., 2016; Loewenstein et al., 2004; Weintraub et al., 2012). In addition to these deficits, individuals with Alzheimer's disease also commonly have deficits in executive functioning and sometimes impairments in visuospatial abilities, attention, language skills, and general intelligence (Weintraub et al., 2012). During early stages of the disease, when cognitive impairments are typically less severe and do not impair daily function, a person is diagnosed with mild cognitive impairment. But, as these

deficits increase and independent living becomes compromised, the diagnosis of dementia is given.

Cognitive decline is also observed in some individuals with Parkinson's disease. Studies on cognition in Parkinson's disease suggest that the average time between Parkinson's disease diagnosis and development of dementia is 10 years, with prevalence rates of dementia being 15-20% after 5 years and 46% after 10 years (Williams-Gray et al., 2009; 2013). Executive function is the cognitive domain most commonly impaired in Parkinson's disease, including the ability to integrate feedback, switch, plan, and organize. Impairments in this domain are often present at the time of Parkinson's disease diagnosis (Muslimovic et al., 2005), worsen with disease progression (Pagonabarraga et al., 2012), and are predictive of conversion to dementia (Janvin et al., 2005; Levy et al., 2002). Other than impairments in executive function, declines in memory are also commonly observed, resulting in 30-40% of Parkinson's patients with mild cognitive impairment being diagnosed with the amnestic phenotype (Kalbe et al., 2016; Monastero et al., 2019). Other cognitive domains that can be impaired in Parkinson's disease include visuospatial abilities, attention, and learning (Aarsland et al., 2010; Lezak et al., 2012; Schoenberg & Scott, 2011).

In the follow two sections, I outline factors that are observed in Alzheimer's and Parkinson's disease and may impair cognition in these populations.

Cerebral Small Vessel Disease Marker and Cognition

The umbrella term *cerebral small vessel disease* includes a number of conditions that affect the small arteries, arterioles, venules, and capillaries in the brain. Cerebral small vessel disease typically increases with age and is believed to result in reduced cerebral blood flow, impaired cerebral autoregulation, and increased blood–brain barrier permeability (Li et al.,

2018). These changes can lead to reduced or interrupted cerebral perfusion resulting in ischemic conditions that cause neuronal apoptosis, axonal loss/injury, demyelination, and mild gliosis (Pantoni et al., 2010). Such changes can be visualized through neuroimaging tools and have been classically classified as infarcts, lacunes, white matter hyperintensities, microbleeds, and brain atrophy (Wardlaw et al., 2013).

Enlarged Perivascular Spaces

One relatively novel imaging marker, enlarged perivascular spaces, may also serve as an indicator of small vessel disease (Brown et al., 2018; Wardlaw et al., 2013), although research in this area is still in its infancy. Perivascular spaces are small fluid-filled cavities that surround the brain's veins and arteries and can become enlarged. Although it is unclear why these spaces become enlarged, research has associated other markers of cerebral small vessel disease, such as lacunes, microbleeds, and white matter hyperintensities, with perivascular space enlargement, suggesting that it may be an indicator of vasculopathology (Doubal et al., 2010; Francis et al., 2019; Potter et al., 2015). For example, a study of 350 patients with previous stroke found a strong association between perivascular spaces and white matter hyperintensities. Additionally, a meta-analysis (n = 12,725) found an association between perivascular spaces and lacunes and microbleeds (Francis et al., 2019). Beyond their association with vascular factors, they have also been associated with markers of inflammation (Satizabal et al., 2013; Wuerfel et al., 2008), suggesting that they may be related to increased inflammation. A study by Wuerfel and colleagues (2008) found that patients with multiple sclerosis, a chronic inflammatory disease of the central nervous system, had larger perivascular spaces than healthy controls. Additionally, a study of older adults found a positive association between perivascular space count and levels of inflammatory marker, interleukin-6 (Satizabal et al., 2013).

Additionally, and/or alternatively, enlarged perivascular spaces may be related to the clearance of neurotoxins, such as amyloid-beta (Tarasoff-Conway et al., 2015), a protein that accumulates in Alzheimer's disease. Recent research, primarily in mice models, have found that enlarged perivascular spaces may be associated with reduced interstitial fluid drainage, resulting in reduced glymphatic system functioning (Brown et al., 2018; See Figure 1 for schematic of this process). This blockage likely results in reduced clearance of metabolites and promotes deposition of amyloid-beta (Xu et al., 2015).

Examination of Perivascular Spaces

As our knowledge on the etiology of perivascular space enlargement continues to grow, so does our understanding of the importance of region-specific changes. Some researchers who examine perivascular spaces distinguish basal ganglia and white matter perivascular spaces in their investigations, as previous studies have found that they have morphological differences that may reflect functional differences (see Wardlaw et al., 2020, for review). This notion has been supported by studies associating region-specific enlargement of perivascular spaces with different clinical features. Enlargement of basal ganglia perivascular spaces has been associated with hypertension, whereas enlargement of white matter perivascular spaces has been associated with cerebral amyloid angiopathy and greater amyloid deposit (Charidimou et al., 2014; van Veluw et al., 2015).

Despite this research on perivascular spaces and advancements in neuroimaging, enlarged perivascular spaces remain difficult to visualize on typical MRI images as they are only small (< 3-mm diameter) linear hyperintensities along the vasculature. That said, there has been some evolution in how they are quantified. For example, most research to date has used visual rating scales to examine the frequency of enlarged perivascular spaces on a scan (Adams et al., 2013;

Patanker et al., 2005). More recently, a more quantitative approach was developed by members of the Ontario Neurodegenerative Disease Research Initiative team. This new approach provides a measure of volume rather than count and has been validated against visual ranking systems in studies on aging, cardiovascular disease, and Alzheimer's disease (Berezek et al., 2015; Ramirez et al, 2015). Although more automated, the results of this approach still need to be reviewed by trained imaging experts to remove incorrect segmentations and to ensure perivascular spaces are correctly assigned, as they can be mislabeled as lacunes (Ramirez et al., 2020).

Perivascular Spaces and Cognition

Although perivascular spaces are beginning to be examined more frequently, the clinical significance of this neuroanatomical feature is still emerging. Some studies have found that exhibiting a few enlarged perivascular spaces is normal and that the frequency of enlarged perivascular spaces increases with advancing age (Zhu et al., 2011), but greater frequencies of enlarged perivascular spaces are associated with increased risk of cognitive decline (Seperhrand et al., 2021) and dementia (Banerjee et al., 2017; Chen et al., 2011; Patankar et al., 2005; Ramirez et al., 2015; Zhu et al., 2010). These individual study findings have been supported by meta-analyses that report associations between enlarged perivascular spaces and cognitive impairment in individuals with mixed diseases (Jie et al., 2020) and Alzheimer's disease (Smeijer et al., 2019). This said, inconclusive findings have been reported by other meta-analyses including community-dwelling older adults (Hilal et al., 2018) and individuals with cardiovascular disease (Francis et al., 2019).

Beyond looking at general cognitive impairment and dementia, more recent studies have investigated whether enlarged perivascular spaces are related to performance in specific

cognitive domains. These studies have found that enlarged perivascular spaces are related to executive function abilities (Passiak et al., 2019; Uiterwijk et al., 2016), memory (Javierne-Petit et al., 2020; Valdés Hernandez et al., 2019), visuospatial abilities (Javierne-Petit et al.,2020; Maclullich et al.,2004), and processing speed (Passiak et al., 2019; Valdés Hernandez et al., 2019; Ding et al., 2017; Huijts et al., 2014), in older adults and in individuals with cardiovascular disease.

In addition to studies in these populations, there is also some preliminary evidence to suggest that the frequency of enlarged perivascular spaces is related to cognition in Alzheimer's disease and Parkinson's disease. A relationship between severity of cognitive dysfunction and frequency of enlarged basal ganglia perivascular spaces was observed in a study of 225 participants with either subjective memory impairment, mild cognitive impairment, or Alzheimer's dementia, after adjusting for relevant covariates (Jeong et al., 2015). Another study of 158 participants with either normal cognition, mild cognitive impairment, or Alzheimer's dementia found a stepwise relationship between level of cognitive impairment and the frequency of enlarged perivascular spaces, and enlarged perivascular spaces discriminated healthy controls from patients with Alzheimer's disease with 79% accuracy (Chen et al., 2011). Enlarged perivascular spaces have also been related to dementia risk. A 4-year follow-up study of 1778 cognitively normal older adults found that a high frequency of white matter enlarged perivascular spaces was related to increased risk of incident dementia, after accounting for other markers of vasculopathology (Zhu et al., 2010). Similar findings have also been observed in Parkinson's disease. Greater frequency of enlarged perivascular spaces have been observed in individuals with Parkinson's disease with mild cognitive impairment or dementia compared to individuals without cognitive impairment (Shibata et al., 2019). Additionally, another study of

271 patients with Parkinson's disease found that the degree of enlargement predicted progression from intact cognition to mild cognitive impairment and from mild cognitive impairment to dementia, after accounting for relevant covariates (Park et al., 2019). These findings suggest that perivascular space enlargement may be a particularly sensitive indicator of cognitive decline within neurodegenerative conditions, but additional research is necessary.

Sleep and Cognition

Beyond the biological factors that have already been discussed, there are many lifestyle factors, including sleep, that influence our well-being and health. Over the past 40 years there has been an increased focus on understanding sleep processes and the experience of sleep. This exploration would not have been possible without the quantification of sleep. Currently, sleep is examined using objective and self-report measures. Objective measures include actigraphy, which is a sensory system typically worn on the wrist to record movement to estimate sleep parameters, and polysomnography, a multiple-component sleep study that records a variety of body functions (such as eye movement and respiratory function), muscle activity, and electrical activity of the brain during sleep. These measures capture sleep metrics such as sleep efficiency, sleep duration, length of sleep stages [N2, N3, rapid eye movement (REM)], waking after sleep onset, and sleep onset latency. On the other hand, self-report sleep measures, such as the Pittsburgh Sleep Quality Inventory (PSQI: Buyesse et al., 1989), capture some metrics that overlap with objective measures (such as sleep duration, sleep efficiency, and sleep-onset latency), but also capture the experience of sleep including sleep quality, daytime drowsiness, and trouble with snoring and nocturnal temperature regulation. Quantifying sleep through these metrics has been pivotal in clarifying how sleep impacts important processes, such as cognition.

In younger adults, most of the research on the relationship between sleep and cognition has examined the impact of sleep deprivation on cognition (see Alhola & Polo-Kantola, 2007, for review). Forced shortened sleep is related to a 40% reduction in the ability to form new memories (Walker, 2009), as well as reduced attention, working memory, decision making, long-term memory, and response inhibition (Alhola & Polo-Kantola, 2007, for review). Considering the relationship between sleep and cognition in younger adults, it is possible that the cognitive changes observed in older adults, such as slower processing speed and reduced attention, memory, and executive function abilities (Park et al., 1996; Salthouse, 2004), may be related or partially related to changes to sleep quality and quantity (Scullin & Bliwise, 2015; Yaffe et al., 2014).

With regard to sleep quality, older adults who exhibit longer sleep latency, increased wakenings after sleep onset, decreased sleep efficiency, and more frequent long-wake episodes and daytime naps in polysomnography studies are at a higher risk of exhibiting cognitive decline (Blackwell et al., 2006; 2014). Additionally, disruption of the sleep-wake rhythm in older adults has been correlated with reduced cognitive performance in the domains of speed, memory, and executive function (Oosterman et al., 2009).

With regard to self-reported sleep quantity, both long and short sleep have been related to cognition. In a sample of older women, fewer than 5 hours of sleep per night was associated with reduced global cognition and poorer performance across a range of cognitive indicators (i.e., verbal memory, working memory, and verbal fluency; Tworoger et al., 2006). Another study found that short and long sleep durations in a sample of 5000 older adults were associated with reduced word list memory and verbal fluency (Kronholm et al., 2009). Similarly, two studies of over 3000 and 900 older adults, respectively, found that worse global cognitive functioning was

associated with long but not short sleep durations (Faubel et al., 2009; Ramos et al. 2013). These findings suggest a U-, possibly, J-shaped relationship between habitual sleep duration and cognitive function. This has been supported by a meta-analysis demonstrating that both long and short sleep durations negatively impact multiple domains of cognitive functioning in older adults, with odds risk ratios being slightly higher for long (odds risk ratio: 1.58) than short sleep (odds risk ratio: 1.40) durations (Lo et al., 2016).

Sleep and Cognition in Alzheimer's Disease

Changes to sleep also occur in individuals with more advanced cognitive changes, such as those with Alzheimer's-related mild cognitive impairment and dementia (Hita-Yañez et al., 2012). Sleep disturbances occur in 14% to 59% of patients with mild cognitive impairment and are even more common in individuals with Alzheimer's dementia (for review, see Beaulieu-Bonneau & Hudon, 2009). These sleep disturbances include waking after sleep onset, longer sleep latency, decreased slow wave sleep, longer total sleep durations, and daytime sleepiness (McCurry et al., 1999; Moran et al., 2005; Peter-Derex et al., 2015). Considering that sleep disturbances and cognitive impairment increase in concert in these samples and that sleep disturbances (and their behavioural effects, such as daytime sleepiness) predict higher rates of dementia and cognitive decline at 3-year follow-up (Cricco et al., 2001; Foley et al., 2004), it is suggested that these factors are related. This is further supported by studies that have found that severity of one's sleep disturbances increases with functional decline and cognitive impairments in Alzheimer's disease (Moe et al., 1995).

Sleep duration is one sleep metric that may have an important role in the sleep-cognition relationship, as numerous large-scale longitudinal studies have found that longer sleep durations (i.e., typically greater than 8 or 9 hrs of sleep) are a primary predictor of dementia incidence in

older adults (Benito-Leon 2009; Lu et al., 2018). For example, a study of 2853 older adults found that longer sleep durations were associated with increased dementia risk at 3- to 10-year follow-up (odds ratio = 3.98; Sindi et al., 2018). Additionally, a longitudinal study by Westwood and colleagues (2017) found that prolonged sleep duration (> 9 hours) was associated with an increased risk of developing all-cause dementia (hazard ratio = 2.01) and Alzheimer's disease (hazard ratio = 2.20) at 10-year follow-up in a sample of 2457 older adults (mean age = 72 years).

These findings have been further supported by meta-analyses. In one meta-analysis, long sleep durations were associated with a 77% increased risk of all-cause dementia and a 63% increased risk of Alzheimer's disease, but no association was found between short sleep duration and all-cause dementia or Alzheimer's disease (see Fan et al., 2019, for meta-analysis). This finding aligns with another meta-analysis of 53,942 older adults (mean age 66.9 years), which reported that longer sleep durations increased risk of dementia by 42%, cognitive decline by 42%, and cognitive impairment by 38% (Kim et al., 2016). Additionally, a meta-analysis by Bubu and colleagues (2017), found that the risk for Alzheimer's and cognitive decline was higher in individuals with longer sleep durations (relative risk = 2.05) than it was for short sleep durations (relative risk = 1.63).

Currently, it is unknown why prolonged sleep and dementia development are related, but it has been suggested that sleeping longer may be a compensatory strategy to spend more time in sleep stages (i.e., slow wave sleep) related to clearance of toxic proteins that are known to cause dementia (Ramirez et al., 2021; Van Cauter et al., 2000). Alternatively, this relationship may be due to chronic inflammation, as previous research has found that longer sleep durations are related to increased levels of interleukin-6 and c-reactive protein (Irwin et al., 2016; Patel et al.,

Prather et al., 2015). Finally, it is possible that this association is due to underlying health issues or depression symptomatology (Diniz et al., 2013; Zhai et al., 2015).

Sleep and Cognition in Parkinson's Disease

Like individuals with Alzheimer's-related mild cognitive impairment and dementia, individuals with Parkinson's disease also exhibit sleep difficulties. This includes disturbances and disorders, such as difficulty falling asleep, nocturia (nighttime awakening to urinate), early-morning awakenings, sleep fragmentation, and REM sleep behaviour disorder (Comella, 2007; Neikrug et al., 2013). These changes to sleep are likely related to the cognitive decline observed in Parkinson's disease (Amara et al., 2020; Bohnen & Hu, 2019).

In contrast to the Alzheimer's disease literature, research on sleep in Parkinson's disease has focused on sleep quality rather than sleep duration. There is evidence that reduced sleep efficiency is associated with both mild cognitive impairment (Gunn, Naismith, Terpening, 2014) and dementia in Parkinson's disease (Sobreira et al., 2019). Additionally, a study by Stavitsky and colleagues (2012) demonstrated that actigraphy-based measures of poor sleep quality were associated with reduced executive function performance in nondemented individuals with Parkinson's disease.

Sleep quality as assessed by self-report measures, such as the PSQI, have also been associated with cognition in Parkinson's disease (Hogl et al., 2015). Sahebzadeh and colleagues (2016) found a significant association between scores on the PSQI and Montreal Cognitive Assessment (a screening measure for cognition) in individuals with Parkinson's disease. This association between sleep and cognition was also observed when sleep quality was dichotomized. For example, when the PSQI was used to distinguish individuals with Parkinson's disease who had good or poor sleep quality, associations were found between poor sleep and

greater cognitive impairment (Liu et al., 2018) and lower executive function performance (Aggrawal et al., 2021).

Sleep and Perivascular Spaces

Thus far, I have reviewed how sleep and enlarged perivascular spaces are each associated with cognition. Interestingly, emerging research suggests that these two factors are themselves associated. Clinical investigations examining sleep and perivascular spaces in individuals with mixed cardiovascular disease have found that enlarged perivascular spaces are related to polysomnographic measures of poor sleep quality (including sleep efficiency, wakefulness after sleep onset, and non-REM sleep/N3 stage; Berezek et al., 2015). Since then, other studies in adults who are older or have cardiovascular disease have replicated these findings using actigraphy (Del Brutto et al., 2019) and self-reported sleep metrics, such as sleep duration (Aribasini et al. 2020; Ramirez et al., 2021), but vascular factors were sometimes considered to have an important role in those relationships (Aribasini et al. 2020; Del Brutto et al., 2019).

There are a variety of possible rationales for why sleep and perivascular spaces are related. One explanation is that processes that occur during sleep are positively related to perivascular-mediated clearance (i.e., glymphatic clearance) of neurotoxins (Xie et al., 2012). Therefore, disturbances to sleep may negatively impact these processes, resulting in reduced perivascular-mediated clearance of neurotoxins and enlarged perivascular spaces (Nedergaard & Goldman, 2020). Alternatively, sleep may influence vasculopathology or vice versa, resulting in an association between sleep and perivascular spaces. A small meta-analysis by Del Brutto and colleagues (2019) examined four cross-sectional studies examining the relationship between sleep measures and silent markers of small vessel disease, particularly white matter hyperintensities. These studies reported associations between factors of sleep, such as sleep

duration (specifically longer sleep) or sleep quality, and white matter hyperintensity severity (Alosco et al., 2013; Cheng et al., 2013; Kanda et al., 2003; Ramos et al., 2014). Two of these studies suggested that sleep problems may affect subcortical white matter through changes in cerebral blood perfusion (Alosco et al., 2013; Ramos et al., 2014), whereas the other two hypothesized that cerebral small vessel disease may disrupt sleep-related processes (Cheng et al., 2013; Kanda et al., 2003).

Although research has identified an association between sleep and enlarged perivascular spaces in healthy older adults and cardiovascular disease patients, and neurobiological mechanisms have been proposed to explain this association, there is little understanding of the association between these factors in other populations and whether these factors are related to cognitive impairment.

Overview of the Present Studies

Through the following two studies, I explore whether factors such as sleep disturbances and perivascular spaces are related to cognitive domain performance and cognitive status categorization in Alzheimer's and Parkinson's diseases. In the first Study, I examine whether sleep duration and perivascular space volumes are related to cognitive performance (i.e., memory and executive function) and cognitive status (i.e., mild cognitive impairment vs. dementia) in individuals with Alzheimer's disease (n = 125; Chapter 2). Memory and executive functions were the cognitive domains examined in this study as they are most impacted in individuals with Alzheimer's disease (Weintrub et al., 2012) and are known to be related to sleep and perivascular spaces in other populations (Oosterman et al., 2009; Passiak et al., 2019; Valdés Hernandez et al., 2019). Additionally, sleep duration was the sleep metric used, as longer sleep durations have been related to Alzheimer's disease cerebral spinal fluid biomarkers (Xu et al., 2020),

presentation (Vitiello et al., 1990; Salzmann et al., 2020), and onset (Fan et al., 2019). This sleep marker has also been related to inflammation, a common biological change related to Alzheimer's disease (Patel et al., 2009; Prather et al., 2015) and is believed to be an inefficient compensatory strategy for dealing with reductions in slow wave sleep (Ramirez et al., 2020) that occurs in Alzheimer's disease (Moran et al., 2005). Analyses for this study not only examine whether longer sleep durations and enlarged perivascular space are related to cognition but also the relationship between these two factors and whether co-expression of these factors is related to lower cognitive performance.

In the second Study, I examine whether sleep quality and perivascular space volumes were related to cognitive performance (i.e., memory and executive function abilities) and cognitive status (i.e., cognitively intact *vs*. mild cognitive impairment *vs*. dementia) in Parkinson's disease (n = 140; Chapter 3). Memory and executive functions were the cognitive domains examined in this study as they are impacted in individuals with Parkinson's disease (Aarsland et al., 2017) and are known to be related to sleep and perivascular spaces in other populations (Oosterman et al., 2009; Passiak et al., 2019; Valdés Hernandez et al., 2019). Sleep quality was the sleep metric used in this study, as it reflects the sleep disturbances observed in Parkinson's disease (Hogl et al., 2010) and is related to cognitive changes that occur in this population (Lui et al., 2018; Pushpanathan et al., 2016; Sahebzadeh et al., 2016). Beyond examining the relationship that perivascular space volumes and sleep quality have with cognition, I also examine the relationship between these two factors and whether co-expression of these factors is related to lower cognitive performance.

Following reports of the two individual studies, I then discuss the overall implications and future directions for this research in Chapter 4.

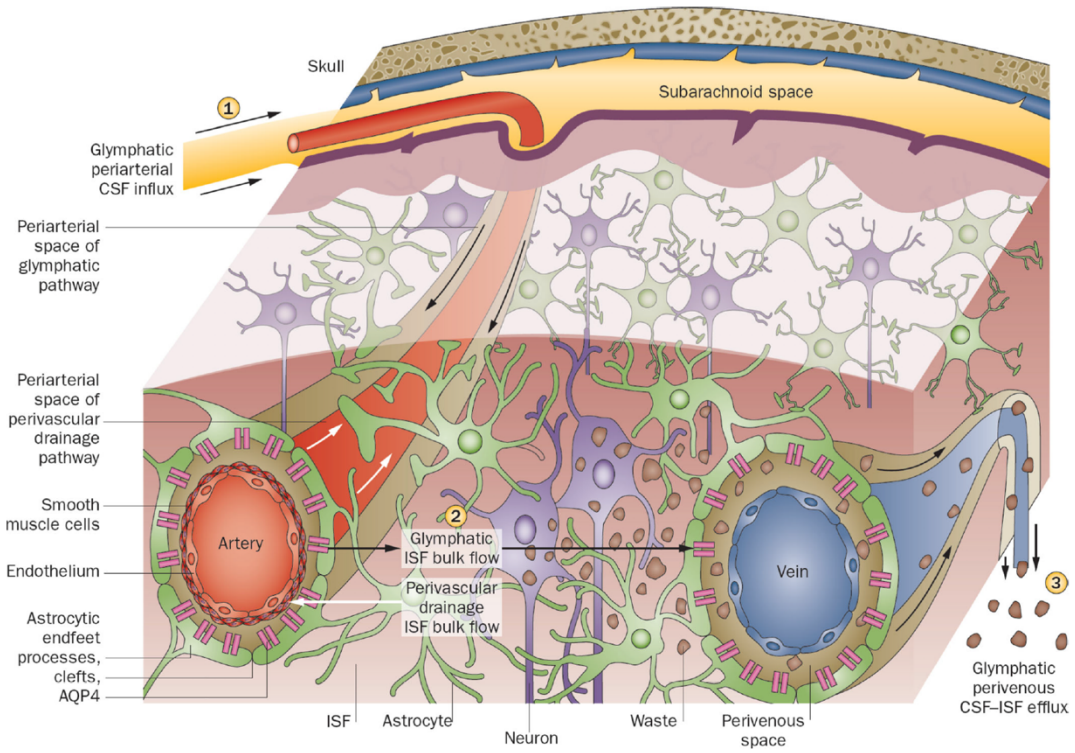

Figure 1: The Glymphatic System and Perivascular Spaces

This figure exemplifies the process of perivascular mediated/glymphatic clearance [denoted by the black arrows and labeled "Glymphatic interstitial fluid (ISF) bulk flow"]. In this process, neurotoxin waste (denoted by brown blobs) produced by neurons (purple cells), is cleared into the perivascular space (denoted as "perivenous space") which surround the vein.

From "Clearance systems in the brain—implications for Alzheimer disease" by **Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Zetterberg, H., Wisniewski, T., and De Leon, M. J., 2015,** *Nature Review Neurology*, ***11, p. 457*** (doi:10.1038/nrneurol.2015.119). **Copyright 2015 by Nature Publishing Group.** Reprinted with permission.

Chapter Two: Perivascular Space Moderates the Relationship Between Sleep and Memory in Mild Cognitive Impairment and Dementia Due to Alzheimer's Disease

Sleep disturbances are reported by 45% of individuals with Alzheimer's disease (McCurry et al., 2000) and can manifest as increased nighttime awakenings, daytime naps, and sleep durations, as well as decreases in slow wave and rapid eye movement (REM) sleep (Basta et al., 2019; Vitiello & Borson, 2001; Vitiello et al., 1990). Examination of sleep disturbances in persons with subjective cognitive decline, mild cognitive impairment, and dementia suggests that sleep disturbances may contribute to the cognitive decline observed in Alzheimer's disease, as similar types of sleep disturbances are observed across groups, with prevalence rates and severity increasing with disease progression (Beaulieu-Bonneau & Hudon, 2009; Hita-Yañez et al., 2012; Vitiello et al., 1990). One metric of sleep that may be particularly important in understanding the relationship between sleep and cognition is sleep duration, as longer sleep durations are related to lower cognitive performance (Gildner et al., 2019) and predict incidence of all-cause and Alzheimer's-related dementia (see Fan et al., 2019, for meta-analysis).

One possible rationale for the relationship between longer sleep durations and cognitive decline in Alzheimer's is increased levels of inflammation. Previous research has associated long sleep durations with greater levels of inflammatory markers, such as interleukin-6 and c-reactive proteins (Irwin et al., 2016; Patel et al., 2009; Prather et al., 2015), which are associated with Alzheimer's pathology and cognitive decline (Darweesh et al., 2018). Alternatively, it has been proposed that poor clearance of neurotoxins during sleep may have a role in the relationship between sleep changes and cognitive decline. Seminal research by Xie and colleagues (2013) found that neuronal clearance mechanisms in mice were twice as efficient during sleep compared to wakefulness or while being anesthetized. This removal of neuronal waste, also known as

glymphatic clearance, occurs through perivascular spaces, which are interstitial fluid-filled channels surrounding the brain's smaller arteries and veins. These spaces are thought to become enlarged from blockage at the aquaporin-4 channel, resulting in fluid stagnation and greater deposition of neuronal waste (Iliff et al., 2012; 2013). One possible contributor to suboptimal perivascular-mediated clearance is sleep disturbances, which have been related to enlargement of perivascular spaces (Berezek et al., 2015; Ramirez et al., 2021) as well as increased accumulation of neuronal waste (Ju et al., 2017; Sanchez-Espinosa et al, 2014; Shokri-Kojori et al., 2018), which, in turn, is a known contributor to cognitive decline.

Perivascular space enlargement has also been observed in individuals with Alzheimer's-related mild cognitive impairment (Niazi et al., 2018; Sepehrband et al., 2020) and dementia (see Smeijer et al., 2019, for review) and may represent underlying pathology contributing to disease development. For example, enlarged perivascular spaces are related to features of cerebral small vessel disease, inflammation, and increased accumulation of neurotoxic solutes (Brown et al., 2018; Francis et al., 2019; Sepehrband et al., 2020; Wuerfel et al., 2008). Enlarged perivascular spaces in the white matter seem to be particularly important in Alzheimer's disease, as they are more frequently enlarged relative to basal ganglia perivascular spaces (Banerjee et al., 2017; Niazi et al., 2018) and are related to cerebral amyloid angiopathy (Charidimou et al., 2013; van Veluw et al., 2016), a pathology that is commonly observed in Alzheimer's disease.

Although these studies support the notion that functions occurring at perivascular spaces may be important for Alzheimer's disease processes, associations between perivascular spaces and cognition have been inconsistent across the literature. Some studies report that perivascular space enlargement is related to dementia development (Zhu et al., 2010; Jie et al., 2020) and poorer cognitive performance (Chen et al., 2011; MacLullich et al., 2004; Passiak et al., 2019;

Valdes Hernandez et al., 2020), whereas other studies have not found these associations (Francis et al., 2019; Hilal et al., 2018).

In the current study I examined the relationship between sleep, perivascular spaces, and cognition in Alzheimer's-related mild cognitive impairment and dementia. I hypothesized that longer sleep durations and enlarged perivascular spaces would be related to lower memory and executive function performance. Considering the possible role of perivascular-mediated clearance in the sleep-cognition relationship, I also postulated that white matter perivascular space volumes would moderate the relationship between subjective sleep duration and memory/executive function performance. Finally, to provide a more global, rather than domain-specific perspective, I hypothesized that perivascular space volumes would be greater and sleep durations would be longer in dementia than in mild cognitive impairment.

Methods

Participants

Participants were part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI), an ongoing longitudinal, multisite, and multidisciplinary research study investigating five neurodegenerative conditions (Farhan et al., 2017; Sunderland et al., 2020). As part of this initiative, all participants underwent comprehensive clinical and neuropsychological testing and brain neuroimaging. Data for the present study were obtained from the Alzheimer's-related dementia and mild cognitive impairment (AD/MCI) cohort and went through rigorous data quality evaluation (Sunderland et al., 2019).

All participants provided informed consent and met extensive eligibility criteria for the larger ONDRI study (Farhan et al., 2017; Sunderland et al., 2020) and the AD/MCI cohort. Inclusion criteria were: (a) 50-89 years of age; (b) meeting the National Institute on Aging-

Alzheimer's Association (McKhann et al., 2011) core clinical criteria for probable Alzheimer's disease dementia or amnestic single- or multiple-domain mild cognitive impairment[1]; (c) proficiency in English as indicated by a self-rated score ≥ 7 out of 10 for both speaking and understanding English on the Language Experience and Proficiency Questionnaire (Marian et al., 2007); (d) 8 or more years of formal education; (e) a Montreal Cognitive Assessment score ≥ 17, or ≥ 14 if they received the diagnosis of atypical AD; (f) sufficient vision and hearing to complete testing; and (g) completion of at least 75% of the neuropsychological battery. Exclusion criteria included: (a) non-Alzheimer's disease causes of dementia (as identified from brain imaging or blood work); (b) substance abuse within the past year; (c) unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active malignancy or infectious disease; (d) AIDS or AIDS-related complex; (e) unstable psychiatric illness (e.g., psychosis or major depression) within 90 days of screening; (f) enrollment in a therapeutic trial; and (g) any other current underlying disease that may interfere with the ability to participate in cognitive testing. All study procedures were approved by the Research Ethics Boards at Baycrest Health Sciences and York University.

Eighty-five participants met criteria for mild cognitive impairment and 41 met criteria for Alzheimer's dementia. Most participants in the sample were in their 60s and 70s and had some university education on average; approximately half were women. Demographic information is reported in Table 1.

[1] These criteria ensure that an individual does not have substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden

Assessment Measures

Sleep Duration. A measure of sleep duration was obtained from a single question on the Pittsburgh Sleep Quality Inventory (Buysse et al., 1989), which is a self-report measure of sleep characteristics in the previous 30 days.

Neuroimaging. ONDRI study participants were recruited from multiple sites within Ontario, with neuroimaging data acquired from each site's 3T MRI scanner, which included a General Electric (GE, Milwaukee, WI) Discovery 750, a GE Signa HDxt, a Siemens Health Care (Siemens, Erlangen, Germany) Prisma, a Siemens TrioTim, and a Siemens Skyra. The full MRI acquisition protocol can be found in Appendix 1.

All images were processed using Semi-Automatic Brain Region Extraction (Gibson et al., 2010), a pipeline parcellation technique. This process requires a trained technician to identify 13 landmarks on each hemisphere to create individualized brain maps. Coordinates of the Talairach grid system (Talairach & Tournoux, 1988) are then overlayed onto each participant's brain map. This process accounts for natural individual differences in anatomy and significant focal or global brain atrophy that can occur in neurodegenerative disease. Enlarged perivascular spaces were then identified using the Lesion Explorer pipeline (Ramirez et al., 2014) based on the standards for reporting vascular changes on neuroimaging criteria (Wardlaw et al., 2013). In this pipeline, perivascular spaces were defined as small (< 3 mm), linear hyperintensities following the course of vasculature that appear as CSF intensities on T2, T1, and FLAIR sequences (i.e., hyperintense on FLAIR sequences; hypointense on T1 and T2 sequences). After identification, all regions-of-interest were reviewed by a trained technician. Only highly trained neuroimaging analysts achieving intraclass correlation coefficients and similarity indices > 0.90 are allowed to perform this procedure. Additionally, a neuroradiologist was consulted if complex radiological

anomalies were present. This methodology has been validated against the Patankar VRS (Patankar et al., 2005) and Wardlaw Enlarged Perivascular Spaces (http://www.bric.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf) visual rating scales (Ramirez et al., 2011; 2014; Ramirez, Berezuk et al., 2015).

Once perivascular spaces were identified, perivascular space volumetrics in the basal ganglia and white matter were extracted. For this investigation, basal ganglia spaces were defined as the region encompassing the caudate, lentiform nucleus, and thalamus, whereas white matter spaces included regions located within the remaining supratentorial cerebral white matter. Individual differences in head size and the highly skewed distribution of white matter hyperintensities and perivascular space volumes (Decarli et al., 2005; Ramirez, McNeely et al., 2015) were adjusted for with a natural log transform and supratentorial total intracranial volumes. Additional information on neuroimaging procedures used in the present study is reported by Ramirez and colleagues (2020).

Neuropsychological Performance. All participants completed a comprehensive neuropsychological test battery that was administered and scored using rigorous quality assurance and quality control methods (McLaughlin, 2020). Twelve variables from six tests were sorted into memory and executive function conceptual domains (see Table 2) based on work by Litvan and colleagues (2012) and consistent with other ONDRI projects (Zaidi et al., 2020).

Assessment of Covariates. Demographic, clinical, and additional neuroimaging data were collected as part of the ONDRI protocol (Farhan et al., 2017; McLaughlin et al., 2020) and included age, level of education, history of smoking, systolic blood pressure when seated, waist-to-hip ratio, total-cholesterol-to-high-density-lipoprotein ratio, white matter hyperintensities (corrected for total intracranial volume and log transformed), hemoglobin A1C, fasting glucose

levels, and ventricular cerebral spinal fluid volume. Depression symptomatology was examined with the Quick Inventory of Depressive Symptomatology – Self Report (Rush et al., 2003). Fasting serum glucose was obtained, and diabetes was considered to be present if fasting glucose was > 7 mmol/L or % hemoglobin A1C was > 6.5. Use of sleep medication within the past month was obtained from Item 6 of the Pittsburgh Sleep Quality Inventory.

Statistical Analyses

Missing data due to participant cognitive or behavioural impairment preventing task completion (7/1512 data points) were replaced with the value representing the lowest possible score. Mean replacement was used for all other missing data (23/1512 data points). Prorated scores were used on the Quick Inventory of Depressive Symptomatology – Self Report, as the suicidality item was not administered.

Composite scores were calculated using the tests listed in Table 2. Each raw score was transformed to a *z*-score using the sample mean and standard deviation. On timed measures, scores were inverted so that higher *z*-scores reflected better performance (i.e., faster completion times). *Z*-scores were then averaged within each domain. All *z*-score test variables within a particular domain were significantly correlated with all other test scores in that domain, generally with medium to large effect sizes: executive function, *r*s = .29-.58, and memory, *r*s = .50-.90.

Each variable was examined for normality and outliers. Because tests of normality are sensitive to large sample sizes (Field et al., 2012), normality was examined through visual inspection of histograms, normal QQ plots, box plots, and measures of kurtosis and skewness (Cramer, 1998; Cramer & Howitt, 2004). Data points were considered outliers if they were more than 1.5 times the interquartile range beyond the first or third quartile (Tukey, 1977). Specific

cases were evaluated for exclusion if it was an outlier, had a leverage value 3 times the average leverage value (Stevens, 2002), and had a Cook′s distance (effect of a single case on a model) value > 0.7 (Cook and Weisberg, 1982; Field et al., 2012). Regression models were examined for linearity, homoscedasticity, high leverage, and influential points. Variables were examined for homogeneity of variances through Levene's tests prior to use in analyses of variance and covariance (ANOVA/ANCOVA).

Perivascular space volumes and sleep duration were fit with a linear model using memory and executive function as response variables. Main effects of sleep duration and white matter perivascular space volumes on memory and executive function, as well as analyses examining whether perivascular spaces moderated the relationship between sleep duration and cognitive performance were examined using hierarchical multiple linear regression modeling. Considering the influence of age and education on cognition (Lezak et al., 2012), these variables were included in the first block. This was followed by a block with sleep duration and perivascular space volume to examine main effects, and a separate block to examine the interaction between these terms. Covariates known to have a relationship with sleep, cognition, and/or vascular functioning (Berezuk et al., 2015; Del Brutto et al., 2019; Ding et al., 2017; Hilal et al., 2018; Hurford et al., 2014; Potter et al., 2015; Ramirez, 2021) that had a small, or greater, effect (i.e. $r > .1$ or $d > .3$, Cohen et al., 1988) on the outcome variables were included in the first block in the sensitivity analyses to ensure the reliability of results.

T-tests were used to examine differences in perivascular space volumes and sleep duration across diagnostic groups. Due to small sample size and generalizability, participants with atypical presentation of Alzheimer's disease ($n = 5$) were not included in this analysis.

Additional analyses examining the role of basal ganglia perivascular space volumes on cognition and its possible moderating affects are outlined in the supplementary material. All statistical analyses were conducted in SPSS Version 27.0.

Results

One participant's perivascular space volumes (raw basal ganglia perivascular space volume = 211 mm^3, *z*-score = 6.6; raw white matter perivascular space volume = 571 mm^3, *z*-score = 8.0) were identified as outliers and removed from the analysis.

There was a large, significant correlation between memory and executive function composite scores, $r(124) = .55$, $p < .001$. The correlation between white matter perivascular spaces volume and sleep duration was negligible in size and not statistically significant, $r(124) = .05$, $p = .55$.

Demographic variables, descriptive statistics, and volumetric data are reported in Table 1. All data were collected within an average of 26 days (*SD:* 25, range 1 to 197). Approximately half the sample had a history of smoking, and considering the mean age, sex and diagnostic history of participants, they exhibited Montreal Cognitive Assessment scores in the normal range, average waist-to-hip ratio and cholesterol-to-high density lipoprotein levels, low endorsement of depression symptoms, prediabetic levels of hemoglobin A1C, and normal levels of white matter hyperintensities. Correlation analyses examining the relationship between covariates and outcome cognitive domains are reported in Table 3.

Memory

Sleep duration and white matter perivascular space volumes together accounted for 4% of memory performance variability after controlling for age and education, $\Delta F(2, 120) = 3.27$, $p = .04$, SE = .77, which accounted for 18% of memory variability. Sleep duration, standardized $\beta = -.19$, $p = .02$, but not white matter perivascular space volumes, standardized $\beta = .07$, $p = .37$, made a significant contribution to the model.

As shown in Figure 2, moderation (or interaction) analysis revealed a small moderation effect of white matter perivascular space volumes on the relationship between sleep duration and memory, $\Delta r^2 = .04$, $\Delta F(1, 119) = 5.70$, $p = .02$, SE = .76, after controlling for covariates and main effects. This suggests that individuals with both longer sleep durations *and* enlarged white matter perivascular spaces exhibited lower memory performance than the rest of the sample. Secondary analyses with covariates exhibited similar findings (see Table 4).

Executive Function

Sleep duration and white matter perivascular space volumes accounted for 6% of executive function performance variability after controlling for age and education, $\Delta F(2, 120) = 4.5$, $p = .013$, SE = .65, which accounted for 15% of executive function variability. Sleep duration, standardized $\beta = -.25$, $p = .003$, but not white matter perivascular space volumes, standardized $\beta = .001$, $p = .99$, made a significant contribution to the model.

In contrast to the moderation analysis with memory variables, white matter perivascular space volumes did not moderate the relationship between sleep duration and executive function, $\Delta r^2 = .002$, $\Delta F(1, 119) = 0.24$, $p = .63$, SE = .65.

Cognitive Status Group Differences

Sleep duration was significantly longer in individuals with dementia (raw M = 7.85 hrs, SD = 1.7) than in individuals with MCI (7.26 hrs, SD = 1.35), but the effect was small, $t(118) = 2.01$, $p = .05$, $d = 0.40$. When covariates that had a significant relationship with sleep duration were included (i.e., systolic blood pressure, head-corrected white matter hyperintensities, depression symptomatology, sleep medication), results were similar, $F(1, 118) = 4.43$, $p = .014$, $\eta_p^2 = .07$ (medium effect). White matter perivascular space volumes did not differ between the dementia (raw $M = 43.7$ mm^3, $SD = 60.3$) and MCI groups (raw $M = 33.8$ mm^3, $SD = 39.7$), $t(118) = 0.386$, $p = .70$, $d = 0.08$.

Supplementary Basal Ganglia Analysis

Basal ganglia perivascular space volumes generally showed smaller associations with cognition and sleep, with no significant diagnostic or moderation effects (see Appendix 2).

Discussion

The present findings suggest that sleep duration is related to memory and executive function performance in individuals with mild cognitive impairment and dementia due to Alzheimer's disease. Individuals who report longer sleep durations may be particularly vulnerable to reduced memory abilities when they also exhibit enlarged perivascular spaces in white matter. Interpreted another way, these findings suggest that naturally occurring shorter sleep durations and smaller white matter perivascular spaces may be protective against reductions in memory performance. Group differences were also detected between MCI and dementia for sleep duration but not white matter perivascular space volumes. These findings highlight the prominent relationship between sleep duration and cognition and expand our understanding of this relationship by showing that longer sleep durations are associated with a

greater reduction in memory performance among individuals with enlarged white matter perivascular space. This suggests that sleep and perivascular space metrics may be clinically relevant when interpreted together.

This investigation of sleep, perivascular spaces, and cognition provides a novel contribution to the literature because of its rigorous methodologies. For example, all clinical and neuropsychological data went through thorough quality assurance measures to ensure data integrity (Sunderland et al., 2020; McLaughlin et al., 2020), and cognitive composites were defined in a theory-driven manner to reduce intraindividual variability (Jonaites et al., 2019). Additionally, perivascular space volumes were extracted from 3T imaging, through a computational process, and were corrected for head size, providing a more controlled assessment of neuroanatomical changes relative to previously used visual examination scales (Patankar Visual Rating Scale, Patankar et al., 2005; Wardlaw Enlarged Perivascular Space scale).

The relationship between longer sleep duration and risk of cognitive decline and dementia development has been repeatedly reported in the literature (see Fan et al., 2019, for meta-analysis). Although the mechanisms underlying this relationship are not well understood, it is possible that individuals sleep longer in order to spend more time in slow wave sleep stages -- the sleep stages most implicated in the clearance of neurotoxins such as amyloid-beta (see Cordone et al., 2019, for review; Ju et al., 2017). This interpretation is supported by other sleep research that has found that disruption to slow wave sleep mechanisms moderate the relationship between greater amyloid-beta accumulation and reduced memory performance in mild cognitive impairment (Sanchez-Espinosa et al., 2014). Our study extends these findings to perivascular space volumes, and shows that enlarged white matter perivascular spaces moderate the association between longer sleep durations and poorer memory performance. Interpreting these

findings in the context of recent research associating perivascular space count and neurotoxin accumulation (Wang et al., 2021) suggests that perivascular space enlargement in the context of longer sleep duration may be an indicator of poor amyloid clearance that has downstream effects on cognition.

It may also be possible that white matter perivascular space volumes moderated the relationship between sleep duration and memory abilities because of underlying associations with inflammation. Markers of inflammation have been associated with longer sleep durations (Irwin et al., 2016; Prather et al., 2015), enlarged perivascular spaces (Satizabal et al., 2013; Wuerfel et al., 2008) and Alzheimer's disease pathology (Akiyama et al., 2000). Therefore, the pairing of longer sleep durations and enlarged perivascular spaces may be associated with greater levels of inflammation, thereby resulting in greater accumulation of Alzheimer's disease pathology and subsequent memory deterioration. Additional studies examining biological factors underlying these associations are necessary to determine the distinct origins of these associative findings.

It is also important to note that this interaction was significant when memory, but not executive functions, was the cognitive outcome variable. This null executive function finding may reflect the amount of cognitive impairment required to yield significant effects. Previous studies have failed to find associations between perivascular spaces and cognition in community-dwelling adult samples who exhibit minimal cognitive impairment (Hilal et al., 2018) but have found associations in clinical samples (Zhu et al., 2010; Jie et al., 2020). These findings suggest that the relationship between perivascular spaces and cognition may only emerge once cognitive abilities fall below some critical threshold. Consistent with the typical cognitive phenotype for Alzheimer's disease, this sample was characterized by more prominent deficits in memory (i.e.,

average performance was 1 to 2 SD below normative data on most tests), than executive functions (i.e., average performance was -0.5 to +0.5 SD from normative data on most tests).

Although statistically significant, it is important to recognize that the moderation reported in the present study was small in magnitude with a substantial amount of unexplained variance in the data. This variation may be due to interindividual differences in neuronal reserve capacity and one's ability to function when significant pathology (i.e. amyloid-beta or even vasculopathology) is present. This idea is supported by studies that have found small or nonsignificant associations between amyloid-beta build up and poor cognitive performance, with some individuals exhibiting significant amyloid accumulation but no cognitive changes (Furst et al., 2012; see Hedden et al., 2013, for meta-analysis).

Although white matter perivascular space volumes moderated the relationship between sleep and memory, it did not have a direct association with memory or executive function performance. These findings align with studies in young and old adults and mixed vascular disease samples, which have failed to find an association between enlarged perivascular spaces and cognition (Francis et al., 2019; Hilal et al., 2018; Hurford et al., 2013). This suggests that perivascular space enlargement may not have distinct clinical implications in Alzheimer's disease, especially when examining performance within specific cognitive domains. Alternatively, perivascular space volumes may not be directly related to cognition because clearance of amyloid through perivascular spaces accounts for only a portion of all amyloid clearance (Tarasoff-Conway et al., 2015).

White matter perivascular space volumes did not significantly differentiate groups differing in cognitive status (i.e., MCI *vs.* dementia). Although these findings contrast with studies that compare individuals with Alzheimer's dementia and controls (Smeijer et al., 2019),

it does align with one study that examined white matter perivascular spaces across the spectrum of Alzheimer's-related MCI and dementia (Jeong et al., 2015). Therefore, the white matter perivascular changes observed in studies comparing Alzheimer's dementia to control participants may reflect changes that occur in early disease processes, which were not captured in the present sample.

The present investigation did not find an association between self-reported sleep duration and perivascular space volumes. This finding contrasts with other studies conducted in cardiovascular populations, which have found associations between greater perivascular space volumes and longer self-reported sleep durations (Ramirez et al., 2021) and polysomnography-measured sleep disturbances (Berezuk et al., 2015). There are at least two possible explanations for these findings. Our results may reflect a fundamental limitation of self-report measures and inaccurate recall of sleep duration in a population with memory impairments. Alternatively, it may be that these variables are simply not related to each other in Alzheimer's disease populations, because sleep changes and perivascular space enlargement are mediated by a third underlying mechanism that is more prominent in cardiovascular populations than in Alzheimer's disease. Therefore, in Alzheimer's disease, processes resulting in sleep changes and perivascular space enlargement may be distinct.

Limitations

Although the self-reported sleep measure used in this study captures an individual's habits over a longer period of time than one-night assessment of polysomnography, this methodology can be an imprecise measure of sleep behaviour as reports are influenced by participants' perceptions and memory (Silaa et al., 2007). Another limitation is the use of a cross-sectional design, which precludes a determination of temporal order or causation. For

example, it may be that longer sleep durations and enlargement of perivascular spaces precede cognitive decline, or cognitive decline may result in sleep and neuroanatomical changes over time. These questions would be interesting to address in longitudinal research.

Conclusion

Identifying factors that confer risk or contribute to cognitive deterioration in Alzheimer's populations is important for informing interventions that may prevent or slow disease progression. This study builds on existing literature suggesting a role of sleep in neurodegenerative-related memory impairment and attempts to extend our understanding of the role of perivascular spaces in this relationship. The findings revealed a negative relationship between sleep duration and cognitive performance and a stronger relationship between sleep duration and episodic memory performance in individuals with enlarged white matter perivascular space volumes. Additional research may help discern the causal relationship between sleep disturbances and perivascular space changes.

Table 1

Demographic Characteristics of the Alzheimer's Related Dementia and Mild Cognitive Impairment Sample (N = 125)

Demographics	Ratio	Mean	SD	Range
Age (in years)		71.0	8.2	53 – 87
Education (in years)		15.2	3.1	8 – 21
Sex (Male:Female)	69:56			
Handedness (Right:Left)	119:6			
Montreal Cognitive Assessment score		22.7	3.0	15 – 30
Sleep history				
Presence of sleep difficulties (Yes:No)*	34:40			
If yes, duration of sleep difficulties (years)[a]		18.2	16.6	1 - 65
Presence of sleep apnea (Yes:No)	25:100			
Smoking history (Yes:No)	67:58			
Systolic blood pressure – seated (mmHg)		128.9	19.3	82 – 188
Diastolic blood pressure – seated (mmHg)		77.3	11.5	37 – 103
Waist-hip ratio		0.9	0.1	0.7 – 1.1
Cholesterol (mmol/L)		4.8	1.2	2.4 – 7.8
High density lipoprotein (mmol/L)		1.5	0.5	0.7 – 2.8
Low density lipoprotein (mmol/L)		2.8	1.0	0.5 – 5.3
Cholesterol-to-high density lipoprotein ratio		3.4	1.0	1.7 – 6.1
Fasting serum glucose (mmol/L)		6.0	1.6	4 – 13.5
Hemoglobin A1C (%)		5.9	1.0	4.4 – 9.9
Self-reported questionnaires				
Quick Inventory of Depressive Symptomatology		4.2	3.0	0 – 13.5
Pittsburgh Sleep Quality Inventory - total score		5.0	3.6	0 – 18
Sleep duration (hrs)		7.5	1.5	3 – 10.5
Use of sleep medication (Yes:No)	30:95			
Alcohol-use past month (Yes:No)	96:29			
Neuroimaging				
Total PVS volume (mm^3)		59.0	58.7	0 – 316
White matter PVS volume (mm^3)		37.2	46.2	0 – 284
Basal ganglia PVS volume (mm^3)		21.6	23.0	0 – 144
Deep WMH volume (mm^3)		578.7	854.6	0 – 4 985
Periventricular WMH volume (mm^3)		4175.4	5476.5	20 – 45 183
Lacune volume (mm^3)		103.9	237.7	0 – 1716

White matter volumes (cm^3)	396.4	63.5	260.5 – 556.7
Grey matter volumes (cm^3)	533.6	51.4	416.4 – 646.1
Sulcal CSF (mL)	255.8	62.1	107.3 – 428.5
Ventricular CSF (mL)	45.8	28.5	8.2 – 206.4
Total intracranial capacity (cm^3)	1235.6	144.6	912.6 – 1604.1

PVS: perivascular space, WMH: white matter hyperintensities, CSF: cerebrospinal fluid volume.
Note. Raw PVS and WMH volumes are reported for transparency; statistical analyses were performed on head-size adjusted, normalized values.
*n = 74

Table 2

Test Scores Included in the Neuropsychological Domain Composite Scores

Executive Function
Trail Making Test - Part B (time score)
D-KEFS: Colour-Word Interference: Interference trial (time score)
D-KEFS: Colour-Word Interference: Inhibition/switching trial (time score)
D-KEFS: Verbal Fluency: Letter fluency (FAS or BHR; total correct responses)
D-KEFS: Verbal Fluency: Category fluency (animals/clothing and boys/girls names; total correct responses)
WASI-II: Matrix Reasoning (total score)
Memory
RAVLT: Immediate recall trials 1-5 (total score)
RAVLT: Long-delayed recall trial (total score)
RAVLT: Recognition hits (total score)
BVMT-R: Immediate recall trials (total score)
BVMT-R: Delayed recall trial (total score)
BVMT-R: Recognition discrimination index score

Trail Making Test (Reitan & Wolfson, 1985), Delis-Kaplan Executive Functioning System (D-KEFS; Delis, Kaplan, & Kramer, 2001), Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011), Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), Brief Visuospatial Memory Test – Revised (BVMT-R; Benedict, 1997)

Table 3

Relationship Between Covariates and Outcome Variables in Alzheimer's-Related Dementia and Mild Cognitive Impairment (N = 125)

Variables	Memory	Executive Functions	WM-PVS	BG-PVS	Sleep duration (hrs)
Continuous variables	*r*	*r*	*r*	*r*	*r*
Age (years)	- .41*	- .26*	.08	.19*	.09
Education (years)	.12	.28*	-.05	.006	-.06
Waist-hip ratio	.01	- .001	-.22	.01	-.07
Systolic blood pressure – seated	- .20*	- .18*	.02	.17	.15
Cholesterol-to-HDL ratio	- .06	.11	-.13	-.04	.08
TIV-corrected WMH	-.29*	- .28*	.10	.21*	.21*
Ventricle CSF volume (mL)	.24*	.18*	.18*	-.10	.10
Quick Inventory of Depressive Symptomatology	.14	.05	-.05	-.15	-.25*
Dichotomous variable	*d*	*d*	*d*	*d*	*d*
Sex	-.02	.12	-.16	-.53*	.04
Sleep medication	-.20	-.10	-.03	-.17	.37
Smoking history	-.28	-.35*	.13	-.01	.04
Diabetes	-.001	-.07	.33	-.04	.018

Note. Dark grey shading indicates medium (or larger) effect sizes, whereas light grey shading indicates small effect sizes. Asterisks indicate statistically significant correlations.
WM-PVS = White matter perivascular spaces; BG-PVS = Basal ganglia perivascular spaces; WMH = white matter hyperintensities, HDL = high-density-lipoprotein, TIV = total intracranial volume, CSF = cerebral spinal fluid

Table 4

Sensitivity Analyses: Examining the Relationship Between Sleep Duration and White Matter Perivascular Space Volume on Memory in Alzheimer's Related Dementia and Mild Cognitive Impairment

					Model Summary			
Model		**Covariates**	**Std. β**	***p***	***r***	**F**	**SE**	***p***
A	SD	age + edu	-0.19	.02	.04	3.27	0.78	.04
	WM-PVS		0.07	.37				
	SD*WM-PVS		2.02	.02	.04	5.70	0.76	.02
B	SD	age + edu + sys BP	-0.19	.02	.04	3.15	0.78	.04
	WM-PVS		0.07	.35				
	SD*WM-PVS		2.00	.02	.04	5.50	0.76	.02
C	SD	age + edu + WMH + vCSF	-0.18	.03	.03	2.64	0.78	.08
	WM-PVS		0.07	.45				
	SD*WM-PVS		1.94	.03	.03	4.63	0.76	.03
D	SD	age + edu + depression	-0.19	.03	.04	3.30	0.77	.04
	WM-PVS		0.11	.20				
	SD*WM-PVS		2.05	.02	.04	5.83	0.76	.02
E	SD	All	-0.17	.05	.03	2.57	0.78	.08
	WM-PVS		0.10	.26				
	SD*WM-PVS		1.98	.03	.03	4.71	0.77	.03

Note.
Covariates that had a small (or greater) effect on the outcome variables were included in these analyses (see Table 1)
SD = sleep duration, WM-PVS = white matter perivascular space volume, edu = education, sys BP = systolic blood pressure, vCSF = ventricular cerebral spinal fluid, WMH = total intercranial volume corrected white matter hyperintensities

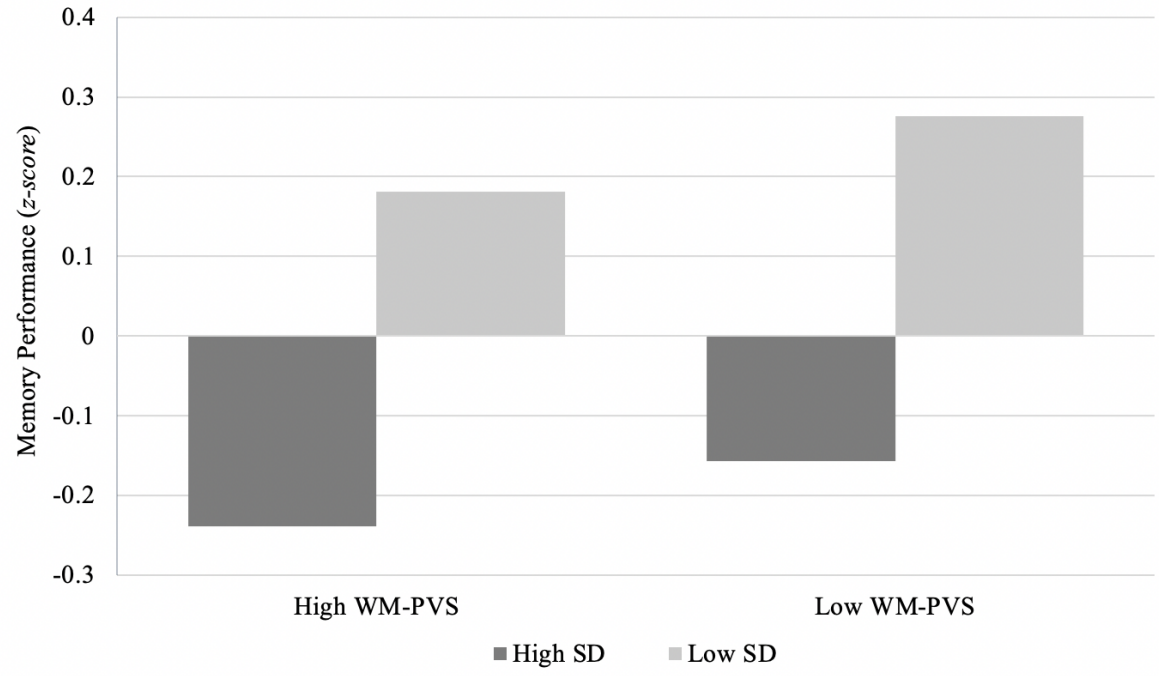

Figure 2: Interaction of Sleep Duration and White Matter Perivascular Space on Memory Performance

Linear regression modelling indicated an interaction between sleep duration, denoted by sleep duration (SD), and logarithmic-transformed total-intracranial-volume corrected white matter perivascular space volume. Sleep duration and white matter perivascular space values were median split into high and low categories for data visualization purposes. Z-scores reflect group-normed memory performance such that performance is relative to other participants in the sample. (*n*s left to right = 34, 28, 33, 30)

Chapter Three: Sleep Quality, Perivascular Space Volume, and Cognition in Parkinson's Disease

Some individuals with Parkinson's disease (PD) exhibit declines in their cognitive abilities (Aarsland et al., 2009; Ding et al., 2015; Watson & Leverenz, 2010). Cognitive domains commonly impaired in PD include executive functions and memory (Caviness et al., 2007; Muslimovic et al., 2005). As such, prevalence rates of MCI and dementia are quite high among people with PD (15-20% and 24-31%; Aarsland et al., 2005; Dalrymple-Alford et al., 2011, respectively) relative to the general older adult population (MCI: ~5%, Ritchie et al., 2004; dementia: 5-7%, Prince et al., 2013).

In addition to cognitive decline, individuals with PD often exhibit sleep disorders such as sleep apnea and rapid eye movement (REM) sleep behaviour disorder (Comella, 2007), as well as structural and subjective sleep changes such as nocturnal awakenings, sleep fragmentation, reduced sleep efficiency, and subjective daytime sleepiness (Factor et al., 1990; Peeraully et al., 2012). These sleep disorders and disturbances have been related to cognitive impairment in PD (Maggi et al., 2021). For example, a self-report measure of sleep quality has been shown to distinguish individuals with PD with normal cognition, MCI, and dementia, such that sleep quality is reduced in individuals with greater cognitive impairment (Liu et al., 2018). Additionally, actigraphy-based measures of sleep quality (i.e., sleep efficiency and onset latency) have been related to reduced performance on tasks of executive function (Stavinsky et al., 2012) and memory (Gunn et al., 2014) in PD. These findings have been further substantiated by a recent meta-analysis which found that individuals with PD with sleep problems (i.e., subjective changes, structural sleep changes, sleep disorders, etc.) exhibited reduced performance on

neuropsychological measures of memory and executive functions relative to those without sleep problems (Pushpanathan et al., 2016).

Recent evidence suggests that cerebral small vessel disease may also contribute to cognitive impairment in individuals with PD. Imaging markers of cerebral small vessel disease, such as microbleeds, lacunes, and white matter hyperintensities are observed in individuals with PD and have been related to cognitive abilities in this population (Chen et al., 2021; Shibata et al., 2019). A meta-analysis conducted by Liu et al. (2021) found that white matter hyperintensities are more prevalent in persons with PD who have dementia (PD-D) than in those without cognitive impairment. Another recent review found associations between white matter hyperintensities and cognition in persons with PD in 8 out of 11 studies (Vesely et al., 2016). White matter hyperintensities also predict future cognitive decline (Dadar et al., 2018; Kandiah et al., 2014) and are related to impairments in executive functioning (Linortner et al., 2020; Ng et al., 2012) and memory (Dunet et al., 2019).

Beyond white matter hyperintensities, an emerging measure of cerebral small vessel disease is enlarged perivascular spaces (Doubal et al., 2010; Francis et al., 2019). As described in Chapter 2, these spaces are cerebrospinal fluid-filled cavities that surround penetrating cerebral vasculature and appear as small high-signal areas. Research examining perivascular spaces has primarily focused on the white matter and the basal ganglia, as enlarged perivascular spaces are frequently observed in these regions and have morphological distinctions that may be clinically relevant (see Ramirez et al., 2016, and Wardlaw et al., 2020, for reviews).

The study of perivascular spaces and their clinical relevance in PD is still in its infancy. Initial studies have found that enlarged perivascular spaces are more common in individuals with PD than in healthy controls (Donahue et al., 2021; Shen et al., 2021) and that enlarged white

matter and basal ganglia perivascular spaces are associated with reduced performance on brief measures of global cognition among individuals with PD (Chen, et al., 2021; Shibata et al., 2019; Si et al., 2020). Additionally, enlarged basal ganglia perivascular spaces have been associated with future cognitive deterioration in persons with PD (Park et al., 2019).

It is of interest to examine whether sleep disturbances influence the relationship between perivascular spaces and cognition, as perivascular spaces and sleep have been related in previous studies. For example, perivascular space enlargement has been related to self-reported sleep quality (Aribasini et al. 2020; Del Brutto et al., 2019; Ramirez et al., 2021) and polysomnography sleep metrics (including sleep efficiency, apnea-hypopnea index, wakefulness after sleep onset, and non-REM sleep/ N3 stage; Berezek et al., 2015; Del Brutto et al., 2019) in healthy older adults and cardiovascular populations. Initial studies exploring the association between perivascular spaces and sleep in individuals with PD have focused only on REM sleep behaviour disorder (Shin et al., 2021; Si et al., 2020), so the relationship with overall sleep quality remains unknown.

Memory and executive function declines have been observed in individuals with Parkinson's disease and in patients with poor sleep and markers of white matter disease. We sought to extend these findings by examining the association of white matter and basal ganglia perivascular space volumes with cognitive performance and whether poor sleep quality exacerbates this association. First, we examined the main effects of sleep quality and perivascular spaces on cognitive performance in a sample of persons with PD with varying cognitive status (i.e., normal cognition, MCI, and dementia). We hypothesized that enlarged perivascular spaces and poor sleep quality would be related to lower domain-specific cognitive performance. Second, we examined whether the interaction of perivascular spaces and sleep

quality is related to cognitive abilities in the same sample. We hypothesized that enlarged perivascular spaces and poor sleep quality would be associated with reduced performance on tasks assessing memory and executive functions. Third, to provide a more global rather than domain-specific perspective, we examined group differences in perivascular space volumes and sleep quality across the cognitive spectrum of PD (i.e., in individuals with normal cognition, MCI, and dementia). We hypothesized that larger perivascular space volumes and poorer sleep quality would be observed in groups with greater cognitive impairment.

Methods

Participants

Participants were part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI), an ongoing longitudinal, multisite, and multidisciplinary research study investigating five neurodegenerative conditions (Farhan et al., 2017). As part of this initiative, all participants underwent genomics, neuroimaging, assessments of ocular function, gait and balance, as well as language and neuropsychological testing. Data for the present study were obtained from baseline assessments of the Parkinson's disease cohort and went through rigorous data quality evaluation prior to analysis (Sunderland et al., 2019).

One hundred and forty participants provided informed consent and met extensive eligibility criteria for the larger ONDRI study (Farhan et al., 2017; Sunderland et al., 2020) and for the PD cohort. These included: (a) 55-90 years of age, (b) established diagnosis of idiopathic Parkinson's disease based on United Kingdom Parkinson's Disease Society Brain Bank (Hughes, Daniel, Kilford, & Lee, 1992) criteria in the past 3-8 years, (c) PD progression at Stage 2 or 3 on the Hoehn & Yahr Scale (Hoehn & Yahr, 1967), (d) proficiency in English as indicated by a self-rated score ≥ 7 out of 10 for both speaking and understanding English on the Language

Experience and Proficiency Questionnaire (Marian et al., 2007), (e) 8 or more years of formal education, (f) MoCA score ≥ 18 (Nasreddine et al., 2005), (g) sufficient vision and hearing to complete testing, and (h) completion of at least 75% of the neuropsychological battery. Exclusion criteria included: (a) substance abuse within the past year, (b) unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active malignancy or infectious disease, (c) AIDS or AIDS-related complex, (d) unstable psychiatric illness (psychosis or major depression) within 90 days of the screening, (e) enrollment in a therapeutic trial, or (f) current underlying disease that may interfere with the participant's ability to participate. Each participant was required to have a study partner who provided collateral information on their functioning. All assessments were completed during participants' medication "ON" state.

Assessment Measures

Neuropsychological Performance. All participants completed a comprehensive neuropsychological test battery. Twelve variables from six tests were sorted into memory and executive function domains (see Table 5), in keeping with earlier research (Litvan et al., 2012; Zaidi et al., 2020). All neuropsychological tests were administered and scored using rigorous quality assurance and control methods (McLaughlin, 2020).

Questionnaires. Sleep quality was determined with the Pittsburgh Sleep Quality Inventory (PSQI; Buysse et al., 1989). Out of the 19 items on this self-report measure, 15 have Likert-like response scales and 4 are open-ended. Responses to each item are converted to a score between 0 and 3 using the scoring manual (See Appendix C for a copy of the measure and scoring manual). Items are then summed together to measure seven components of sleep, including sleep duration, subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each of the sleep

components yields a score ranging from 0 to 3, with 3 indicating greatest dysfunction. The sleep components scores are then summed to yield a total score ranging from 0 to 21, with higher scores indicating poorer sleep quality.

The PSQI is the most commonly used questionnaire to assess sleep quality and is generally considered the gold standard measure for the assessment of subjective sleep quality (Fabbri et al., 2021). A recent meta-analysis on the psychometric properties of the PSQI found that it demonstrated good internal consistency and test-retest reliability, but there are some discrepancies in the factor structure across studies, suggesting that the total score may be a more reliable measure of sleep quality (Mollayeva et al., 2016). Total scores on the PSQI have also been shown to distinguish clinical and non-clinical samples with (self-report and polysomnography confirmed) sleep difficulties (Buyesse et al., 1989; Mollayeva et al., 2016), suggesting that the measure has good construct validity.

A broader set of questionnaires assessing self-reported functioning – including subjective cognitive decline, independence in instrumental activities of daily living, and neuropsychiatric symptoms – was also administered to participants and their study partners for cognitive classification purposes (see Zaidi et al., 2021, for more details).

Neuroimaging. Scans were conducted at multiple sites within Ontario, Canada, with neuroimaging data acquired from each site's respective 3T MRI scanner. These included a General Electric (GE, Milwaukee, WI) Discovery 750, a GE Signa HDxt, a Siemens Health Care (Siemens, Erlangen, Germany) Prisma, a Siemens TrioTim, and a Siemens Skyra. The full MRI acquisition protocol can be found in Appendix 1. MRI-based volumetrics were acquired using previously published methods (see Ramirez et al., 2020).

All images were processed using Semi-Automatic Brain Region Extraction (Gibson et al., 2010), a pipeline parcellation technique. This process requires a trained technician to identify 13 landmarks on each hemisphere to create individualized brain maps. Coordinates of the Talairach grid system (Talairach & Tournoux, 1988) are then overlayed onto each participant's brain map. This process accounts for natural individual differences in anatomy and significant focal or global brain atrophy that can occur in neurodegenerative disease. Enlarged perivascular spaces were then identified using the Lesion Explorer pipeline (Ramirez et al., 2014) based on the standards for reporting vascular changes on neuroimaging criteria (Wardlaw et al., 2013). In this pipeline, perivascular spaces were defined as small (< 3 mm), linear hyperintensities following the course of vasculature that appear as CSF intensities on T2, T1, and FLAIR sequences (i.e., hyperintense on FLAIR sequences; hypointense on T1 and T2 sequences). After identification, all regions-of-interest were reviewed by a trained technician. Only highly trained neuroimaging analysts achieving intraclass correlation coefficients and similarity indices > 0.90 are allowed to perform this procedure. Additionally, a neuroradiologist was consulted if complex radiological anomalies were present. This methodology has been validated against the Patankar VRS (Patankar et al., 2005) and Wardlaw Enlarged Perivascular Spaces (http://www.bric.ed.ac.uk/documents/epvs-rating-scale-user-guide.pdf) visual rating scales (Ramirez et al., 2011; 2014; Ramirez, Berezuk et al., 2015).

Once perivascular spaces were identified, perivascular space volumetrics in the basal ganglia and white matter were extracted. For this investigation, basal ganglia spaces were defined as the region encompassing the caudate, lentiform nucleus, and thalamus, whereas white matter spaces included regions located within the remaining supratentorial cerebral white matter. Individual differences in head size and the highly skewed distribution of white matter

hyperintensities and perivascular space volumes (Decarli et al., 2005; Ramirez, McNeely et al., 2015) were adjusted for with a natural log transform and supratentorial total intracranial volumes. MRI-based volumetrics were acquired using previously published methods (Ramirez et al., 2020).

Cognitive Status Classification Procedures

Participants were classified based on standardized criteria proposed by the Movement Disorders Society PD-MCI Task Force (Litvan et al., 2012) following study enrollment. The normal cognition (i.e., PD-NC) category included participants who displayed unimpaired cognition for their age and education (defined as no more than one impaired test score across all domains), with or without subjective decline, and no functional impairment. The mild cognitive impairment (i.e., PD-MCI) category included participants with single-domain or multidomain cognitive impairment (i.e., a minimum of two impaired scores either within or across domains, respectively), subjective cognitive decline, and no functional impairment. The dementia (i.e., PD-D) classification included participants with multidomain cognitive impairment, defined as a minimum of one impaired score (≥ 1.5 SD below education- and/or age-corrected test-specific norms) in two or more domains, subjective cognitive decline, and functional impairment (Emre et al., 2007). Ten participants who did not fit these criteria (e.g., those with cognitive impairment but no subjective cognitive decline), were removed from analyses involving cognitive classification.

Assessment of Covariates

Demographic, clinical, and neuroimaging data were collected as part of the ONDRI protocol (Farhan et al., 2017). A long list of possible covariates that are thought to have a relationship with sleep, cognition, and/or vascular functioning was considered (Francis et al.,

2019; Ramirez et al., 2021), including: age, sex, level of education, waist-to-hip ratio, systolic blood pressure when seated, total-cholesterol-to-HDL ratio, total white matter hyperintensities and lacune volume (corrected for total intracranial volume and log transformed), motor complications (as measured by MDS-UPDRS Part IV), ventricle cerebral spinal fluid volume, depression symptomatology, history of smoking, hemoglobin A1C, and fasting serum glucose levels. Depression symptoms were examined with the Quick Inventory of Depressive Symptomatology – Self Report (Rush et al., 2003). Diabetes was considered to be present if fasting glucose was > 7 mmol/L or % hemoglobin A1C was > 6.5.

Statistical Analyses

As part of the neuropsychological evaluation, participants were exempt from subsequent conditions within a test if they were unable to complete a previous condition within a pre-set time limit (e.g., Trail Making Test - Part B was administered only if Part A was completed within a pre-set time limit) resulting in a missing value. For these cases (n = 7), the missing value was imputed with an extreme value representing the lowest possible score. Mean replacement was used for all other cases of missing data (n = 8). To facilitate interpretation, prorated scores were used on the Quick Inventory of Depressive Symptomatology – Self Report as the suicidality item was not administered.

Memory and executive functioning composite scores were calculated using test scores listed in Table 5. Raw scores were transformed to z-scores based on performance within the present sample, and participant scores were averaged within each domain. On timed measures, scores were inverted so that higher z-scores reflected better performance (i.e., faster completion times).

Each variable was examined for normality and outliers. Because tests of normality are sensitive to large sample sizes (Field et al., 2012), normality was examined through visual inspection of histograms, normal QQ plots, box plots, and measures of kurtosis and skewness (Cramer, 1998; Cramer & Howitt, 2004). Data points were considered outliers if they were more than 1.5 times the interquartile range beyond the first or third quartile (Tukey, 1977). Variables were examined for homogeneity of variances through Levene's tests prior to use in analyses of variance and covariance (MANOVA/ANCOVA). Regression models were examined for linearity, homoscedasticity, multicollinearity, high leverage, and influential points. Specific cases were evaluated for exclusion if it was an outlier, had a leverage value 3 times the average leverage value (Stevens, 2002), and had a Cook′s distance (effect of a single case on a model) value >0.7 (Cook and Weisberg, 1982; Field et al., 2012).

Perivascular space volumes and sleep quality were fit with a linear model using memory and executive function composites as response variables. Main effects of sleep quality and perivascular space volumes on memory and executive function, as well as analyses examining the interaction of perivascular space volumes and sleep quality on cognitive performance were examined using hierarchical multiple linear regression modeling. Considering the influence of age and education on cognition (Lezak et al., 2012), these variables were included in the first block. This was followed by a block with sleep quality and perivascular space volume to examine main effects, and then a separate additional block was used to examine the interaction between these terms. Additional analyses used MANOVA/ANCOVA to examine differences in perivascular space volumes and sleep quality across cognitive classification groups. Covariates that were related to the outcome variables (i.e., covariates and outcome variables had at least a small effect size: $r > .1$ or $d > .3$; Cohen et al., 1988; see Table 6 for analysis) were included in a

sensitivity analysis to evaluate reliability of results. All statistical analyses were conducted in SPSS Version 27.0. All study procedures were approved by the Research Ethics Boards at Baycrest Health Sciences.

Results

Descriptive statistics for demographics, clinical measures, questionnaires, and neuroimaging volumetrics for both the sample as a whole and within cognitive classification subgroups are reported in Table 6. Participants were predominantly men in their 60s and 70s with some university education. As would be expected, MoCA scores ranged from normal to below normal across the three groups. Otherwise, participants exhibited average waist-to-hip ratios and cholesterol-to-high density lipoprotein levels, normal-to-mild depression symptomatology, prediabetic levels of hemoglobin A1C, and just over a third of the sample had a history of smoking. For each participant, data were collected within an average of 24 days (*SD* = 22, range = 0 to 185).

Scores on all test variables within the executive function, *r*s = .32-.86, and memory, *r*s = .37-.89, domains were significantly correlated with medium to large effect sizes. There was a large, significant correlation between memory and executive function domain scores, $r(138) = .59$, $p < .001$. See Table 7 for correlations between primary variables of interest. Correlations between covariates and variables of primary interest are reported in Table 8. Age and education were significantly correlated with memory and executive function domains, whereas only age was significantly correlated with white matter perivascular spaces and sleep quality.

There was a significant correlation between logarithmic head-corrected white matter and basal ganglia perivascular space volumes, $r(138) = .37$, $p < .001$. The relationship between perivascular spaces and other measures of small vessel disease, including white matter

hyperintensities and lacunes was examined. Volume of white matter perivascular spaces had a small correlation with lacune volumes, $r(138) = .20$, $p = .02$, and white matter hyperintensities, $r(138) = .15$, $p = .07$. Volume of basal ganglia perivascular spaces was not correlated with lacune volumes, $r(138) = .03$, $p = .70$, or white matter hyperintensities, $r(138) = .14$, $p = .09$.

Executive Function

After accounting for age and education, which together accounted for 20% of the variability in executive function variance, sleep quality and white matter perivascular space volumes accounted for 2% of executive function performance variance, $\Delta F(2,135) = 1.87$, $p = .16$, SE = .7. Neither sleep quality nor white matter perivascular space volumes made a significant individual contribution to the model (ps > .06). There was a small interaction effect of white matter perivascular space volumes on the relationship between sleep quality and executive function, $\Delta r^2 = .04$, $\Delta F(1,134) = 7.6$, $p = .007$, SE = 0.7, after controlling for covariates and main effects (see Figure 3 for bar graph and Figure 4 for regression model). These results indicate that individuals with smaller white matter perivascular space volumes and good sleep quality exhibit better executive function performance. Sensitivity analyses with additional covariates that are related to executive function performance (i.e., depression symptoms and sleep medication; see Table 8) yielded similar findings, $\Delta r^2 = .03$, $\Delta F(1,132) = 6.56$, $p = .01$, SE = 0.64.

Sleep quality and basal ganglia perivascular space volume accounted for only 0.2% of the variance in executive function performance after controlling for covariates, $\Delta F(2,135) = 1.40$, $p = .26$, SE = .70, and neither variable made a significant individual contribution to the model (ps > .06). Interaction analysis revealed that basal ganglia perivascular space volumes did not

moderate the relationship between sleep quality and executive function performance, $\Delta r^2 = .02$, $\Delta F(1,134) = 3.64$, $p = .06$, SE = .70.

Memory

After accounting for age and education, which together accounted for 10% of the variability in memory variability, sleep quality and white matter perivascular space volumes volume accounted for a negligible amount (0.2%) of the variance in memory performance, $\Delta F(2,135) = 0.137$, $p = .87$, SE = .77. Neither variable made a significant individual contribution to the model (ps > .06). Interaction analysis revealed that white matter perivascular space volume did not moderate the relationship between sleep quality and memory, $\Delta r^2 = .02$, $\Delta F(1,134) = 2.75$, $p = .10$, SE = .77.

Sleep quality and basal ganglia perivascular space volume accounted for only 0.6% of the variance in memory performance after controlling for covariates, $\Delta F(2,135) = 0.47$, $p = .63$, SE = .77, and neither variable made a significant individual contribution to the model (ps > .06). Interaction analysis revealed that basal ganglia perivascular space volumes did not moderate the relationship between sleep quality and memory, $\Delta r^2 = .008$, $\Delta F(1,134) = 1.28$, $p = .26$, SE = .77.

Perivascular Spaces and Sleep Quality

There was a small, significant relationship between sleep quality and logarithmic head-corrected white matter perivascular space volumes, $r(139) = -.19$, $p = .01$. When all covariates that had a relationship with white matter perivascular space volumes and/or sleep quality (age, education, waist-to-hip ratio, systolic blood pressure, cholesterol-to-HDL, head-corrected white matter hyperintensities and lacunes, ventricle cerebral spinal fluid, depression symptomatology, motor complications, diabetes, sex; see Table 8) were collectively included in the model, the relationship stayed relatively consistent ($r = -.22$, $p = .016$). When covariates were individually

included in the model, this relationship also stayed relatively consistent (rs = -.19 – -.17, ps = .02-.04), except when age was included in the model, $r(137) = -.15$, $p = .08$ (see Table 9). The relationship between sleep quality and basal ganglia perivascular space volumes was negligible in size and not significant, $r(138) = -.03$, $p = .38$.

Cognitive Status Group Differences

MANOVA analyses revealed a small significant effect of cognitive status category on white matter perivascular space volumes and sleep quality, $F(6,250) = 1.92$, $p = .07$, $\eta_p^2 = .044$, Wilks' $\Lambda = .91$. The main effect on white matter perivascular space volumes was significant, $F(2,127) = 2.97$, $p = .05$, $\eta_p^2 = .045$ (small effect), but main effects on sleep quality, $F(2,127) = 1.78$, $p = .173$, $\eta_p^2 = .03$ (small effect), and basal ganglia perivascular space volumes, $F(2,127) = 0.21$, $p = .81$, $\eta_p^2 = .003$ (negligible effect), were not significant.

Group differences in white matter perivascular space volumes were re-examined with covariates that had a relationship with white matter perivascular space volumes (i.e., waist-to-hip ratio, head-corrected white matter hyperintensities, ventricle cerebral spinal fluid, sex, diabetes; see Table 8). Group differences stayed relatively consistent when covariates were individually added, Fs = 2.8–3.4, ps = .04-.06, η_p^2s = .043-.051, except when age was included in the model, $F = 2.3$, $p = .10$, $\eta_p^2 = .036$ (see Table 10).

Group analyses revealed that white matter perivascular space volumes were larger for PD-MCI than PD-NC, $t(102) = 2.43$, $p = .02$, $d = 0.48$, but there was no difference between PD-MCI and PD-D, $t(79) = 1.13$, $p = .26$, or PD-NC and PD-D, $t(73) = -.848$, $p = .40$ (Figure 5). The significant difference between the PD-NC and PD-MCI groups persisted when covariates related

to white matter perivascular space volume were included in the analysis, *t*s = 1.99–2.65, *p*s = .009-.05, η_p^2s = .038-.065 (see Table 11).

Discussion

The present findings suggest a complex relationship between sleep quality, perivascular space volume, and cognition in PD. Examination of individual relationships revealed that neither sleep quality nor perivascular space volumes were directly related to memory or executive function performance after controlling for covariates. Interaction analyses indicated that individuals with PD who had smaller white matter perivascular space volumes and good sleep quality exhibited better executive function performance. Finally, we found differences in perivascular space volumetrics across specific groups differing in cognitive status. Individuals with PD-MCI exhibited significantly larger white matter perivascular space volumes relative to PD-NC, but other group differences were not observed. These findings suggest that executive function abilities are better among individuals with good sleep quality and smaller perivascular spaces volumes, and that enlarged white matter perivascular spaces are related to cognitive status category in early disease.

The present findings indicate that sleep quality is not independently associated with cognitive performance in PD. This null finding may be attributed to the use of self-report measures to examine sleep quality. Self-report measures of sleep are advantageous because they capture the experience of sleep over a longer period of time (i.e., 1 month) and are not influenced by sleep-related motor movements that are common in PD, but they are limited because self-reports are influenced by a person's personality, their state of mind, perception of sleep, insight, and other psychological factors (Morgan et al., 1989; Vanable et al., 2000). These factors may

have influenced participants' sleep quality ratings and the reported relationship between sleep and cognition.

We also found that perivascular space volumes in the basal ganglia and white matter were not related to cognitive domain abilities in Parkinson's disease. These results were surprising given that other studies have found associations between perivascular spaces and cognitive abilities (assessed by brief measures of global cognition) among individuals with PD (Chen et al., 2021; Shibata et al., 2019; Si et al., 2020). Discrepancy in findings may be explained by the differences in outcome measures used, as our study examined specific cognitive domain abilities, whereas other studies used brief measures of global cognition. Therefore, it may be that perivascular spaces are related to global cognitive functioning but are not related to specific cognitive domains or specific neural networks related to memory or executive functioning. This interpretation is consistent with our finding of differences in perivascular space volumes between some cognitive status groups, as cognitive status is defined globally, and not by specific domains. Of course, there are also methodological differences between the aforementioned studies and the current study (i.e., use of visual rating scales vs. computerized methodology to examine perivascular spaces) that may also be contributing to the discrepant finding.

When examining the interaction, the pairing of larger perivascular space volumes and poor sleep quality was not associated with reduced memory or executive function abilities. That said, the significant interaction indicated that better executive function abilities were observed in individuals with PD who had smaller perivascular space volumes and good sleep quality. Therefore, it may be that poor sleep quality and larger perivascular space volumes are insufficient to impair domain-specific cognitive abilities, but when good sleep quality and

smaller white matter perivascular spaces occur together, better cognitive abilities are observed. There are at least two possible explanations for these findings. Firstly, it may be that good sleep and low levels of vasculopathology provide the opportunity to prevent decline in executive function abilities in PD. This idea is supported by previous research which has found that a low frequency of enlarged perivascular spaces (Passiak et al., 2019) and absence of sleep problems (Montanaro et al., 2021; see meta-analysis Pushpanathan et al., 2016) are associated with better executive function performance. Secondly, it is possible that good sleep quality in individuals with PD maintains good glymphatic clearance, resulting in better cognitive abilities. Because mechanisms during sleep are responsible for the clearance of amyloid-beta (Xie et al., 2013), a known contributor to cognitive decline in PD (Hall et al. 2016; Shahid et al. 2019; see Irwin et al., 2013, for review), then good sleep may increase clearance resulting in reduced perivascular space volumes, lower deposit of amyloid (and possibly other neurotoxins such as alpha synuclein) and better cognitive abilities (Sundaram et al. 2018; Mestre et al., 2017). Although these two interpretations are intriguing, they are speculative only, as the interaction was small in magnitude and there was a substantial amount of unexplained variance in the data.

Although we did not find main effects of perivascular space volumes on cognitive domain performance, we did find that white matter perivascular space volumetrics were related to cognitive status category, with white matter perivascular space being significantly larger in individuals with PD-MCI than in individuals with PD-NC. The perivascular space volume difference between PD-MCI and PD-NC suggests that vasculopathology has an important relationship with cognitive decline in early disease. Research has shown that cerebrovascular disease accelerates neurodegenerative processes in Alzheimer's disease (Janota et al., 2016; Levit et al., 2020), and therefore a similar process may be occurring in PD. Large cohort studies

have found that cerebrovascular risk factors are associated with the development of PD (Kummer et al., 2019; Malek et al., 2016), raising the possibility that cerebral small vessel disease may be contributing to PD neurodegenerative processes, such as accumulation of Lewy bodies. If this interpretation holds true, then vascular dysfunction may provide a 'double hit' on cognition, by not only impairing brain perfusion resulting in ischemic injury but also by accelerating neurodegeneration. Future research is needed to confirm this hypothesis.

Interestingly, white matter and basal ganglia perivascular space volumetrics in PD-D were intermediate to those observed in PD-MCI and PD-NC and not statistically different from either group. These findings likely indicate that disease factors or systems not related to vasculopathology (or enlarged perivascular spaces) are contributing to dementia diagnosis in this sample of PD participants. For example, dysfunction of the cholinergic and dopaminergic systems may be contributing to dementia development in this sample (Biundo et al., 2016; Goldman & Litvan, 2011; Halliday et al., 2014; Svenningsson et al., 2012). This is especially likely considering that disease duration is approximately equal across the three groups, and therefore multiple systems are likely failing in the PDD group, which results in faster cognitive decline over the same period of time. Additional studies to investigate this hypothesis and replicate the current results are necessary as only a few studies have examined perivascular spaces and cognition in PD (Chen et al., 2021; Park et al., 2019; Shibata et al., 2019; Si et al., 2020), and no other study has examined perivascular spaces across PD-NC, PD-MCI, and PD-D groups.

Finally, the present investigation found an association between self-reported sleep quality and white matter perivascular space volumes in PD. This relationship remained consistent when all covariates were included in the model and when most variables were independently included,

but this association was not significant when age was independently included in the model. This finding is consistent with another study in healthy older adults that found bivariate associations between self-reported sleep quality and frequency of enlarged basal ganglia perivascular spaces, but similarly, this association was not significant when covariates were included in the model (Del Brutto et al., 2019). These findings suggest that an association between poor sleep and enlarged perivascular spaces exists when examined in isolation but that other factors, particularly age, account for a significant portion of the variance between these two constructs. This is not surprising given that both the presence of cerebral small vessel disease (Francis et al., 2019) and metrics of poor sleep (Ancoli-Israel et al., 2009; Mander et al., 2017; Neikrug & Ancoli-Israel, 2009) are known to increase with age.

Strengths and Limitations

This investigation adds to our understanding of sleep, perivascular spaces, and cognition in PD by utilizing stringent methodologies that allow for a comprehensive examination of these constructs. For example, all neuropsychological data included in this study went through rigorous quality assurance measures to ensure data integrity (Sunderland et al., 2020; McLaughlin et al., 2020). Cognitive classification (i.e., PD-NC, PD-MCI, and PD-D) was based on performance on a 14-test neuropsychological battery, and cognitive domain composites were defined in a theory-driven manner, which reduces intraindividual variability (Jonaitis et al., 2019) and increases sensitivity to early cognitive changes (Mortamais et al., 2017). Perivascular space volumes were extracted from 3T imaging through a computational process and were head corrected, which allowed for a more controlled examination of perivascular spaces relative to semiquantitative visual rating scales.

One limitation of the present study is its cross-sectional design, which prevents us from discerning the temporal order or causal relationship between perivascular space volumes and sleep quality. For example, it is uncertain whether perivascular space enlargement precedes poor sleep quality or whether mechanisms causing poor sleep result in perivascular space volume changes. Longitudinal research would provide an optimal opportunity to examine these interesting questions. A second limitation of the present study is that we did not control for medication use, such as cognitive-enhancing medications, sleep medication, antidepressants, and dopamine agonists, which could influence one's mood, sleep, and cognitive abilities. Finally, the present study did not have a control group. This prevented us from comparing the strength of the associations found in individuals with PD to those observed in healthy older adults.

Conclusion

Identifying factors that confer risk or contribute to cognitive performance and impairment in PD is important for determining interventions that could prevent or slow cognitive decline. This study examined perivascular spaces and sleep as potential contributors or explanatory mechanisms for cognitive decline in PD. Our results suggest that neither sleep nor perivascular spaces have a direct relationship with cognitive domain performance in PD, but when good sleep quality and small perivascular spaces occur together, better executive function performance is observed. We also found that there may be perivascular space enlargement during the transition from normal cognition to MCI in PD. Future research is needed to discern the causal relationship between these factors using longitudinal studies.

Table 5:

Test Scores Included in Domain Scores

Executive Function
Trail Making Test - Part B (time score)
D-KEFS: Colour-Word Interference: Interference trial (time score)
D-KEFS: Colour-Word Interference: Inhibition/switching trial (time score)
D-KEFS: Verbal Fluency: Letter fluency (FAS or BHR; total correct responses)
D-KEFS: Verbal Fluency: Category fluency (animals/clothing and boys/girls names; total correct responses)
WASI-II: Matrix Reasoning (total score)
Memory
RAVLT: Immediate recall trials 1-5 (total score)
RAVLT: Long-delayed recall trial (total score)
RAVLT: Recognition hits (total score)
BVMT-R: Immediate recall trials (total score)
BVMT-R: Delayed recall trial (total score)
BVMT-R: Recognition discrimination index score

Trail Making Test (Reitan & Wolfson, 1985), Delis-Kaplan Executive Functioning System (D-KEFS; Delis, Kaplan, & Kramer, 2001), Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011), Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), Brief Visuospatial Memory Test – Revised (BVMT-R; Benedict, 1997)

Table 6: *Demographic Characteristics of Parkinson's Disease Sample*

Demographics	All N = 140	PD-NC *n* = 49
Age (in years)	67.9 (6.4)	66.2 (6.1)
Sex (Male:Female)	109:31	36:13
Education (in years)	15.5 (2.7)	15.9 (2.7)
Handedness (Right:Left)	131:9	45:4
Years since diagnosis	4.7 (1.6)	4.5 (1.2)
Montreal Cognitive Assessment score	25.8 (2.6)	27.4 (2.0)
Smoking history (Yes:No)	58:82	18:31
Rapid eye movement behaviour disorder diagnosis (Yes:No)	34:95	10:38
Systolic blood pressure – seated (mmHg)	131.6 (19.9)	134.6 (19.2)
Diastolic blood pressure – seated (mmHg)	78.0 (10.3)	78.7 (10.4)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)
Cholesterol (mmol/L)	4.6 (1.1)	4.7 (.9)
High density lipoprotein (mmol/L)	1.4 (0.4)	1.5 (.4)
Cholesterol-to-high density lipoprotein ratio	3.4 (0.9)	3.4 (.8)
Low density lipoprotein (mmol/L)	2.6 (0.9)	2.6 (.8)
Fasting serum glucose (mmol/L)	6.0 (1.8)	5.7 (2.1)
Hemoglobin A1C (%)	5.9 (1.0)	5.7 (1.0)
Self-reported questionnaires		
Generalized Anxiety Disorder - 7 (max = 21)	3.2 (4.1)	2.3 (2.9)
Modified Rankin Scale (max = 5)	1.7 (0.7)	1.5 (0.6)
Past month alcohol-use (Yes:No)	108:32	41:8
Quick Inventory of Depressive Symptomatology (max = 27)	6.3 (3.7)	5.1 (2.9)
Movement Disorder Society-Unified Parkinson's Disease Rating Scale		
Part I (max = 60)	10.2 (5.8)	7.9 (4.4)
Part II (max = 52)	9.8 (6.4)	6.8 (4.3)
Part III (max = 132)	23.7 (12.1)	19.8 (10.2)
Part IV (max = 24)	3.3 (3.5)	2.3 (3.0)
Total (max = 272)	46.8 (20.1)	36.9 (15.4)
TD:PIGD	1.4 (1.4)	2.0 (1.7)
TD: indeterminate: PIGD	52:12:76	24:3:22
Pittsburgh Sleep Quality Inventory (total; max = 21)	7.3 (3.9)	6.5 (3.3)

Table 6 ***continued***

Demographics	PD-MCI *n* = 55	PDD *n* = 26
Age (in years)	68.1 (5.7)	69.3 (7.1)
Sex (Male:Female)	44:11	20:6
Education (in years)	15.3 (2.9)	15.4 (2.4)
Handedness (Right:Left)	52:3	25:1
Years since diagnosis	4.6 (1.7)	5.0 (2.0)
Montreal Cognitive Assessment score	24.9 (2.5)	24.8 (2.6)
Smoking history (Yes:No)	23:32	12:14
Rapid eye movement behaviour disorder diagnosis (Yes:No)	15:40	9:17
Systolic blood pressure – seated (mmHg)	126.7 (18.1)	134.8 (23.1)
Diastolic blood pressure – seated (mmHg)	78.0 (10.2)	77.2 (11.4)
Waist-hip ratio	0.9 (0.1)	0.9 (0.1)
Cholesterol (mmol/L)	4.6 (1.2)	4.3 (1.0)
High density lipoprotein (mmol/L)	1.4 (.4)	1.4 (.5)
Cholesterol-to-high density lipoprotein ratio	3.3 (.8)	3.3 (1.0)
Low density lipoprotein (mmol/L)	2.6 (1.0)	2.4 (.7)
Fasting serum glucose (mmol/L)	5.3 (0.6)	5.8 (0.9)
Hemoglobin A1C (%)	5.6 (0.5)	5.7 (0.5)
Self-reported questionnaires		
Generalized Anxiety Disorder - 7 (max = 21)	3.9 (4.9)	3.7 (4.0)
Modified Rankin Scale (max = 5)	1.6 (.6)	2.2 (.8)
Past month alcohol-use (Yes:No)	42:13	18:8
Quick Inventory of Depressive Symptomatology (max = 27)	7.1 (4.1)	7.5 (4.0)
Movement Disorder Society-Unified Parkinson's Disease Rating Scale		
Part I (max = 60)	10.7 (6.4)	13.0 (5.8)
Part II (max = 52)	10.3 (6.1)	14.5 (7.7)
Part III (max = 132)	25.0 (12.3)	28.2 (14.2)
Part IV (max = 24)	3.7 (3.8)	3.9 (3.7)
Total (max = 272)	49.4 (20.0)	59.6 (22.7)
TD:PIGD	1.2 (1.0)	0.6 (0.6)
TD: indeterminate: PIGD	21:7:27	3:2:21
Pittsburgh Sleep Quality Inventory (total; max = 21)	7.7 (4.0)	8.0 (4.4)

Table 6 ***continued***

Neuropsychology	All N = 140	PD-NC *n* = 49
Executive function domain composite*		.65 (.4)
Memory domain composite*		.55 (.6)
Neuroimaging		
Total PVS (mm^3)	52.71 (55.64)	37.8 (34.6)
White matter PVS (mm^3)	31.16 (41.1)	19.1 (20.1)
Basal ganglia PVS (mm^3)	21.60 (23.6)	18.6 (22.3)
Deep WMH (mm^3)	512.8 (787.4)	284.6 (353)
Periventricular WMH (mm^3)	4501.9 (5620.7)	3056.1 (3373.8)
Lacunes (cm^3)	121.6 (348.8)	55.9 (198.5)
White matter (mL)	446.1 (61.2)	464.0 (64.9)
Grey matter (mL)	574.7 (470.8)	595.3 (478.2)
Sulcal CSF (mL)	252.3 (53.3)	242.5 (561.8)
Ventricular CSF (mL)	38.2 (19.4)	34.2 (15.6)
Total intracranial capacity (cm^3)	1316.6 (127.0)	1339.5 (134.2)

Table 6 ***continued***

Neuropsychology	PD-MCI *n* = 55	PDD *n* = 26
Executive function domain composite*	-.26 (.7)	-.71 (.6)
Memory domain composite*	-.37 (.7)	-.31 (.7)
Neuroimaging		
Total PVS (mm^3)	66.7 (71.4)	46.7 (43.2)
White matter PVS (mm^3)	43.4 (55.5)	27.5 (31.5)
Basal ganglia PVS (mm^3)	23.3 (26.2)	19.2 (16.2)
Deep WMH (mm^3)	552.5 (894.8)	766.2 (896.0)
Periventricular WMH (mm^3)	3997.3 (4961.9)	7001.6 (8154.0)
Lacunes (cm^3)	154.3 (441.7)	195.1 (399.6)
White matter (mL)	436.4 (51.2)	451.4 (66.0)
Grey matter (mL)	560.9 (418.1)	575.2 (49.0)
Sulcal CSF (mL)	252.7 (452.3)	266.7 (62.1)
Ventricular CSF (mL)	36.0 (16.2)	45.0 (19.8)
Total intracranial capacity (cm^3)	1290.9 (111.5)	1346.4 (149.1)

Note. TD = tremor dominant, PIGD = postural instability gait difficulty, PVS = perivascular space, WMH = white matter hyperintensities, CSF = cerebrospinal fluid volume. Raw PVS volumes are reported for transparency; statistical analyses were performed on transformed head-size normalized values. Max indicates maximum score for each questionnaire.
The cells in parentheses represent mean (SD). *Group normed z-scores

Table 7:

Bivariate correlations between variables of interest in Parkinson's Disease Sample

Variables	Memory Domain	Executive Functions Domain	WM-PVS	BG-PVS
Executive Functions	.59*			
WM-PVS†	-.11	-.14		
BG-PVS†	.09	.03	.37*	
Sleep Quality (total PSQI)	.08	-.04	-.19*	-.03

Note. WM-PVS = white matter perivascular spaces, BG-PVS = basal ganglia perivascular spaces, PSQI = Pittsburgh Sleep Quality Inventory.
†WM-PVS and BG-PVS were head and logarithmically corrected.
*Significant correlations are denoted by an asterisk.

Table 8:

Relationship Between Covariates and Outcome Variables in Parkinson's Disease (N = 140)

Variables	Memory Domain	Executive Functions Domain	WM-PVS	BG-PVS	Sleep Quality (PSQI)
Continuous variables	*r*	*r*	*r*	*r*	*r*
Age (years)	-.28*	-.37*	.27*	-.005	-.18*
Education (years)	.17	.28*	.02	.08	.10
Waist-hip ratio	-.03	.004	.16	.03	-.11
Systolic blood pressure – seated	.14	.07	.01	.09	-.12
Cholesterol-to-HDL ratio	-.02	.05	-.02	.007	.02
TIV-corrected WMH	-.09	.06	.15	.14	-.09
Ventricle CSF volume (mL)	.08	.02	.12	-.01	-.14
QIDS	-.16	-.21*	-.08	-.002	.55*
MDS-UPDRS Part IV	.02	-.12	-.07	.05	-.34*
TIV-corrected lacunes	-.15	-.17	.11	-.01	-.06
Dichotomous variables	*d*	*d*	*d*	*d*	*d*
Sex	.38*	.08	.24	.04	.47*
Smoking history	.23	.06	.13	.19	.05
Diabetes	.11	.07	.61*	.17	.24

Note. Dark grey shading indicates medium (or larger) effect sizes; light grey shading indicates small effect sizes.
WM-PVS = white matter perivascular spaces, BG-PVS = basal ganglia perivascular spaces, PSQI = Pittsburgh Sleep Quality Inventory, HDL = high-density-lipoprotein, WMH = white matter hyperintensities, TIV = total intracranial volume, CSF = cerebral spinal fluid, QIDS = Quick Inventory of Depressive Symptomatology; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Table 9:

Partial Correlations Examining the Relationship Between Sleep Quality and White Matter Perivascular Space Volume

Covariates	*r*	*p*
Model	-.19	.01
Model + Age	-.15	.08
Model + Education	-.19	.02
Model + Waist-to-hip ratio	-.17	.04
Model + Systolic blood pressure	-.19	.02
Model + Cholesterol-to-HDL	-.19	.03
Model + TIV-corrected WMH	-.18	.04
Model + Ventricle CSF volume (mL)	-.18	.04
Model + Depression symptomatology (QIDS)	-.18	.04
Model + Motor complications (MDS-UPDRS Part IV)	-.18	.03
Model + TIV-corrected lacunes	-.17	.04
Model + Diabetes	-.18	.03
Model + Sex	-.17	.04
All	**-.22**	**.016**

Note. This table outlines the main model with various covariates added to the model.
WMH = white matter hyperintensities, HDL = high-density-lipoprotein, TIV = total intracranial volume, CSF = cerebral spinal fluid, QIDS = Quick Inventory of Depressive Symptomatology; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale

Table 10:

Relationship Between Cognitive Status Category and White Matter Perivascular Space

Covariates	$F(3,126)$	p	η_p^2
Model	2.97	.05	.045
Model + Age	2.33	.10	.036
Model + Waist-to-hip ratio	3.40	.04	.051
Model + TIV-corrected WMH	2.85	.06	.043
Model + Ventricle CSF volume (mL)	3.01	.05	.046
Model + Sex	2.80	.06	.043
Model + Diabetes	3.30	.04	.050

Note. This table outlines the main model with various covariates added to the model. WMH = white matter hyperintensities, HDL = high-density-lipoprotein, TIV = total intracranial volume, CSF = cerebral spinal fluid.

Table 11: *White Matter Perivascular Space Volume Differences Between individuals with Parkinson's disease with Normal Cognition Minus Those with Mild Cognitive Impairment*

Covariates	*t*	*p*	η_p^2
Model	-2.43	.02	.050
Model + Age	-1.99	.05	.038
Model + Waist-to-hip ratio	-2.65	.009	.065
Model + TIV-corrected WMH	-2.31	.02	.050
Model + Ventricle CSF volume (mL)	-2.34	.02	.052
Model + Sex	-2.35	.02	.052
Model + Diabetes	-2.59	.01	.062

Note. This table outlines the main ANOVA analyses with various covariates added to the model. T-tests examined those with mild cognitive impairment those with normal cognition
WMH = white matter hyperintensities, HDL = high-density-lipoprotein, TIV = total intracranial volume, CSF = cerebral spinal fluid.

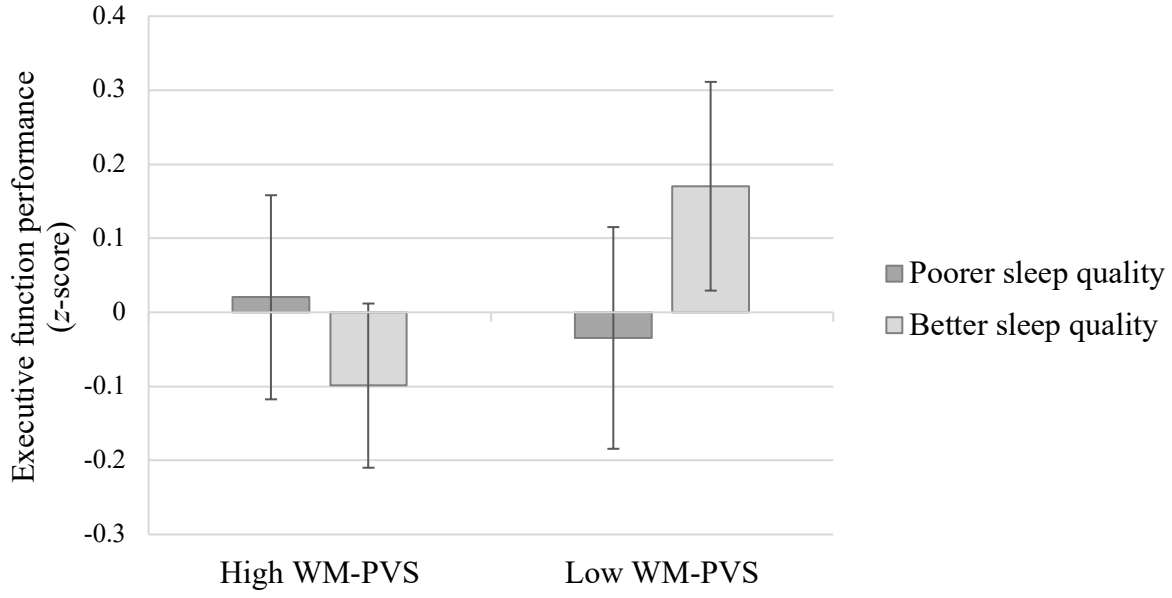

Figure 3: Interaction of Sleep Quality and White Matter Perivascular Space on Executive Function Performance

Note. Linear regression modelling indicated an interaction between sleep quality and logarithmic-transformed total-intracranial-volume corrected white matter perivascular space volume in executive function performance. White matter perivascular space values and sleep quality were mean split for data visualization purposes. Z-scores reflect group-normed performance such that performance is relative to other patients in the sample. Error bars represent standard error. WM-PVS = white matter perivascular space volumes. (*n*s left to right = 27, 47, 32, 30).

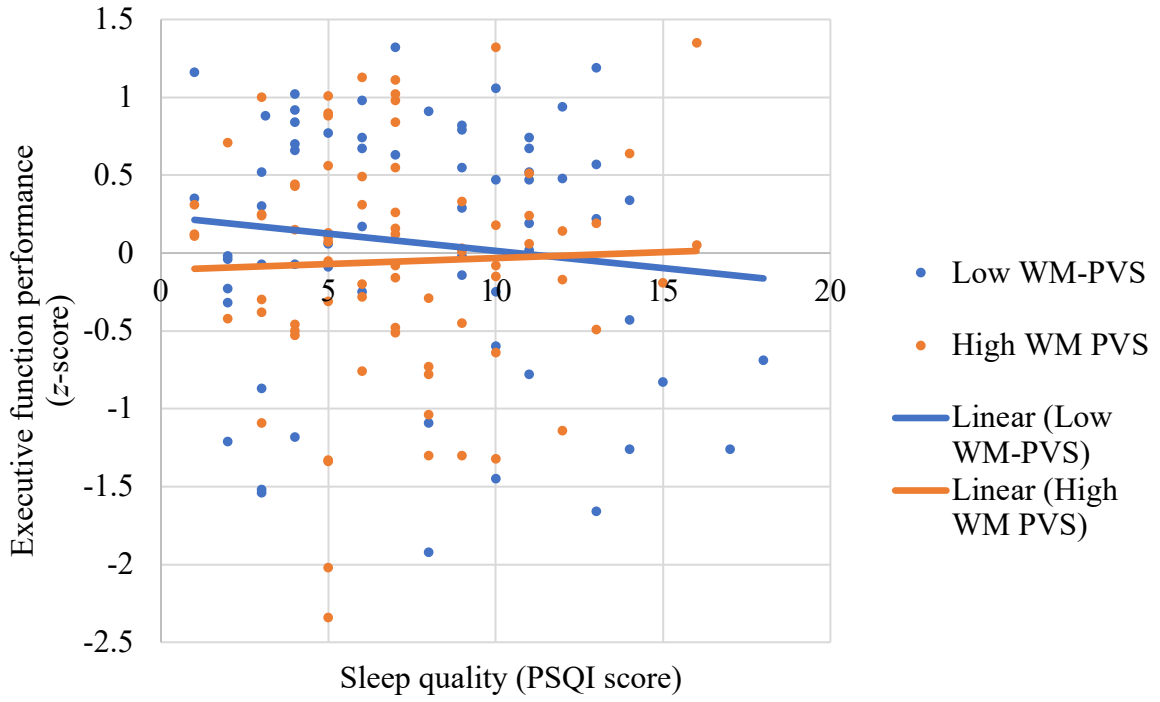

Figure 4: Interaction of Sleep Quality and White Matter Perivascular Space on Executive Function Performance

Note. Linear regression modelling indicated an interaction between sleep quality and logarithmic-transformed total-intracranial-volume corrected white matter perivascular space volume in executive function performance. White matter perivascular space values and sleep quality were mean split for data visualization purposes. Z-scores reflect group-normed performance such that performance is relative to other patients in the sample.
WM-PVS = white matter perivascular space volumes,
PSQI = Pittsburgh Sleep Quality Inventory

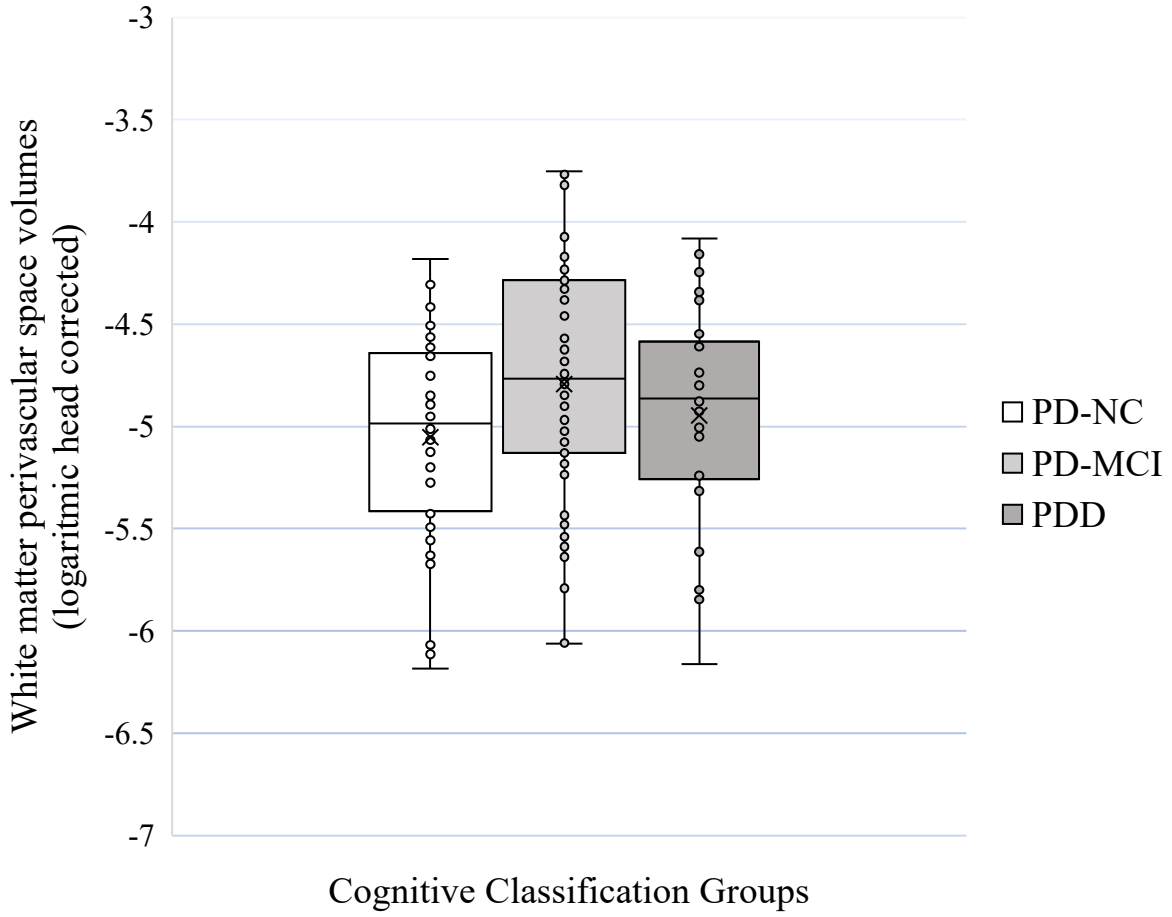

Figure 5: Box and Whisker Plot of White Matter Perivascular Space Volume Across Cognitive Status Category in Parkinson's Disease

Note. There were signficant differences between PD-NC and PD-MCI in logarithmic-transformed total-intracranial-volume corrected white matter perivascular space volume. Box identifies upper quartile, median, and lower quartile. x denotes mean.
PD-NC = Parkinson's disease with normal cognition; PD-MCI = Parkinson's disease with mild cognitive impairment; PDD = Parkinson's disease with dementia

Chapter Four: General Discussion

The primary goal of the current set of studies was to examine associations between sleep metrics, perivascular space volumes, and cognitive performance/status in individuals with Alzheimer's disease or Parkinson's disease. Below, I summarize the main findings, describe how the results contribute to current knowledge, identify some implications for intervention, and suggest future directions for research.

Summary of Findings

In Study 1, longer sleep durations but not perivascular space volumes were related to lower memory and executive function performance within a sample of individuals with Alzheimer's-related MCI and dementia. Additionally, an interaction emerged in which longer sleep durations were related to lower memory performance in those who exhibited larger white matter perivascular space volumes, relative to those with shorter sleep durations and smaller white matter perivascular spaces volumes. Finally, comparisons of subgroups indicated that sleep durations were significantly longer in individuals with Alzheimer's dementia than in those with Alzheimer's-related MCI.

In Study 2, neither sleep quality nor perivascular space volumes were independently related to memory or executive function performance within a sample of individuals with Parkinson's disease. However, good sleep quality was related to small white matter perivascular space volumes, and the co-presence of these two factors was associated with better executive function abilities. Additional analyses of subgroup differences revealed that white matter perivascular space volumes were larger in Parkinson's disease participants with mild cognitive impairment than those with no cognitive impairments, but no other group differences were observed.

In the next section I will further explore how these results fit within the broader literature and add to our understanding of the association between sleep, perivascular spaces, and cognition.

Discussion of Primary Variables

Sleep and Cognition

After accounting for effects of age and education in Study 1, longer sleep durations were related to lower memory and executive function performance in individuals with Alzheimer's-related MCI and dementia, and sleep durations were longer in individuals with dementia than in those with MCI. This finding builds on previous research with older adults that has associated long sleep durations with reduced memory performance (Gildner et al., 2019) and risk of developing Alzheimer's dementia (Fan et al., 2019). It also extends research on the association between long sleep durations and cognition (Faubel et al., 2009; Ramos et al. 2013) to individuals with existing cognitive/memory deficits. Although a relationship was found, additional research is necessary to determine the causal direction of this relationship. For example, it may be that longer sleep durations instigate neurodegenerative processes and subsequent cognitive decline; alternatively, longer sleep durations may be a compensatory strategy to reduce the impact of neurodegenerative disease on cognitive performance.

Perivascular Spaces and Cognition

The present set of studies also examined the association between perivascular spaces and cognitive performance, specifically memory and executive function abilities, in individuals with Alzheimer's disease and Parkinson's disease. These analyses revealed that perivascular spaces were not related to cognitive performance in either population and suggest that perivascular space enlargement may not have direct cognitive-domain implications within Alzheimer's

disease and Parkinson's disease populations. These finding were contrary to our hypotheses and previous research which has found associations between perivascular spaces and memory (Javierne-Petit et al., 2020; Valdés Hernandez et al., 2019) and executive functions (Passiak et al., 2019; Uiterwijk et al., 2016) in other populations, including healthy older adults and in individuals with cardiovascular disease. One possible reason for the cross-population discrepancy is that individuals with Alzheimer's disease and Parkinson's disease have other disease changes that impact cognition, which are less prominent or not present in healthy older adults and in individuals with cardiovascular disease. Previous research has found that individuals with Alzheimer's disease and Parkinson's disease exhibit neurotransmitter and cholinergic system changes which are known to impact memory and executive function abilities (see Calabro et al., 2020; Halliday et al., 2014, for reviews). Conversely, healthy older adults or those with cardiovascular disease exhibit fewer of these changes and therefore there may be stronger associations between cognitive performance and other biological factors such as perivascular space volumes. These findings indicate that cognitive abilities and perivascular spaces may be related when other biological system are not impacting their association but that this relationship is reduced (or disappears) when other disease factors are present.

Sleep and Perivascular Spaces

Beyond examining how sleep and perivascular spaces are related to cognitive performance, I also investigated whether metrics of sleep and perivascular space volumes were related to each other in Alzheimer's disease and Parkinson's disease, as this relationship has previously been explored only in healthy older adults and individuals with cardiovascular disease (Aribasini et al. 2020; Berezek et al., 2015; Del Brutto et al., 2019; Ramirez et al., 2021). These analyses revealed that there wasn't a relationship between sleep durations and perivascular space

volumes in individuals with Alzheimer's-related MCI and dementia, but there was a stronger relationship between overall sleep quality and white matter perivascular spaces in Parkinson's disease (when covariates were not included in the model). The different findings in the two population may be a function of the different sleep metrics examined but may also reflect fundamental differences in the relationship between sleep and perivascular spaces across the two populations. For example, it may be that sleep and perivascular spaces are not related in individuals with Alzheimer's disease because there are other factors that influence these components in different ways in that population. Conversely, there may be fewer variables impacting these constructs in Parkinson's disease, resulting in a stronger relationship between perivascular spaces and sleep. This interpretation has been supported by previous research demonstrating that sleep is impacted by a variety of factors in Alzheimer's disease, such as changes to melatonin levels, cholinergic signaling, and pathology, and that sleep in Parkinson's disease is related to fewer biological changes and primarily related to accumulation of Lewy body pathology (see Rothman & Mattson, 2012, for review).

Interactions Between Primary Variables

Building on the associative relationships between sleep metrics and perivascular space volumes described above, I also examined the interaction between sleep metrics and perivascular spaces on cognitive performance in Studies 1 and 2. In individuals with Alzheimer's-related MCI and dementia, I examined the interaction of sleep duration and perivascular spaces on cognitive performance, and in individuals with Parkinson's disease I examined the interaction of sleep quality and perivascular space on cognitive performance. In individuals with Alzheimer's disease (Study 1), the interaction of larger white matter perivascular space volumes and longer sleep durations were related to reduced memory abilities; whereas in the sample of individuals

with Parkinson's disease (Study 2), the interaction of smaller white matter perivascular spaces volumes and good sleep quality was related to better executive function abilities. Thus, in individuals with Alzheimer's disease, the 'unfavourable' factors (i.e., the combination of long sleep and large perivascular spaces) were associated with reduced cognition and were deleterious, and in Parkinson's disease, the 'favourable' factors (i.e., the combination of good sleep quality and small perivascular spaces) were associated with advantageous cognitive outcomes and may be protective.

Interpreting this pattern of results in the context of the association between perivascular spaces and sleep may indicate that in Alzheimer's disease, long sleep durations may be *indirectly* amplifying the negative effect of perivascular space enlargement on memory through inflammation, poorer amyloid clearance, or an unknown mechanism (Darweesh et al., 2018; Irwin et al., 2016; Prather et al., 2015; Wuerfel et al., 2008). Conversely, in Parkinson's disease (where there is a significant isolated association between sleep quality and perivascular spaces) it may be that good sleep quality may be increasing perivascular-related glymphatic clearance, which results in reduced perivascular space volumes and, ultimately, better cognitive abilities. Although these interpretations are plausible, more research is needed to understand the directionality of the relationship between these variables and to replicate the current results as the interactions in both studies were small in magnitude and may not be replicable.

In addition to the above interpretation, it should be noted that these interactions (between sleep metrics and perivascular spaces) were related only to the cognitive domain most commonly impaired in the respective populations (Emre et al., 2003; Loewenstein et al., 2004; Weintraub et al., 2012). More specifically, the interaction of sleep and perivascular space volumes was related to memory in individuals with Alzheimer's disease and to executive functions in individuals with

Parkinson's disease. The different cognitive domains implicated in the two populations may suggest that the associative relationships may be occurring due to relationships with disease pathology. Previous research has found that Alzheimer's disease pathology preferentially affects memory circuits (Jahn et al., 2013), whereas pathology related to Parkinson's disease most commonly results in changes to executive functions (Foltynie et al., 2004; Muslimovic et al., 2005). Additionally, markers of these pathologies have also been related to sleep (Louis et al., 2017; Sanchez-Espinosa et al, 2014; Shokri-Kojori et al., 2018) and are likely related to perivascular spaces (Brown et al., 2018; Charidimou et al., 2013). Thus, the associative interaction between sleep and perivascular spaces on cognition in each population examined may be a function of disease-specific pathology affecting all these factors. Future studies addressing this possible interpretation are outlined later in this section.

Relation to Cognitive Status Categories

In addition to the associative and interaction analyses, I also examined the relationship between perivascular spaces and cognitive status grouping in Studies 1 and 2. When comparing volumetric differences between Parkinson's disease participants with unimpaired cognition versus those with MCI, it was observed that individuals with MCI exhibited larger white matter perivascular spaces than those with unimpaired cognition. This finding is consistent with previous case-control research that found that white matter perivascular spaces were larger in individuals with Alzheimer's-related MCI than in healthy controls (Sepehrband et al., 2021), and may suggest that changes to white matter perivascular space volumes are related to *early* cognitive decline.

In addition to these analyses, I also examined perivascular space volume differences between participants with MCI and dementia in Studies 1 and 2. In both disease groups, there

were no significant volumetric differences between participants with MCI versus those with dementia. These findings contrast with previous research that has found a higher frequency of enlarged whole brain perivascular spaces in individuals with dementia than in those with MCI (Chen et al., 2011), but aligned with research examining white matter perivascular spaces in Alzheimer's-related MCI and dementia (Jeong et al. 2015). Therefore, it may be that perivascular spaces in the white matter do not enlarge further in later disease stages, but that perivascular spaces in other regions in the brain continue to enlarge with disease progression. Additional research examining perivascular spaces in different brain regions may be necessary to replicate these white matter disease findings and to resolve discrepancies in the literature regarding region-specific changes. These additional studies would also add to emerging literature examining the relationship between perivascular spaces and cognition in later disease stages - a pursuit that has been examined only in the two aforementioned Alzheimer's disease studies (Chen et al., 2011; Jeong et al. 2015) and in no other studies in Parkinson's disease.

Use of Specific Metrics

In addition to discussing specific findings from Studies 1 and 2, it is also important to highlight data trends in these studies because it may influence the metrics that are examined in future research. For example, although we examined white matter and basal ganglia perivascular spaces in Studies 1 and 2, we observed significant findings only when examining white matter perivascular spaces; no significant findings were observed when basal ganglia perivascular spaces volumes were examined. These findings were expected in Alzheimer's disease as much of the literature has suggested that there is prominent impact on white matter perivascular spaces in this population (Smeijer et al., 2019), but it was surprising considering the limited Parkinson's disease literature. That research has primarily focused on changes to the basal ganglia

perivascular spaces rather than white matter perivascular spaces, with some studies even excluding white matter perivascular spaces from their analyses (Chen et al., 2021; Shen et al., 2021). Thus, our findings involving white matter perivascular spaces make an important contribution to the existing literature and suggest that future studies on perivascular spaces in individuals with Parkinson's disease should include the examination of white matter perivascular spaces.

It is also important to discuss the different sleep metrics examined in the two studies. In the study on individuals with Alzheimer's disease we examined sleep duration, and in the study on individuals with Parkinson's disease we examined sleep quality. Sleep duration was selected as a variable in the Alzheimer's disease group because this sleep metric has been associated with Alzheimer's disease-related processes (Akiyama et al., 2000; Westwood et al., 2017), such as inflammation (Dowd et al., 2011; Irwin et al., 2016; Patel et al., 2009), and has been associated with the slow wave sleep disruption observed in Alzheimer's disease (Moran et al., 2005). Examining a single sleep metric was advantageous as it facilitated the exploration of whether a single change to one's sleep habits is related to biological and cognitive changes. This metric (sleep duration) was not examined in the study on individuals with Parkinson's disease because long sleep durations are not observed in this population, nor is it a risk factor for disease development (Peeraully et al., 2012). Thus, we examined sleep quality as it reflects the broad range of sleep difficulties observed in Parkinson's disease and is related to disease-specific changes such as Lewy body formation (Comella, 2007; Rothman & Mattson, 2012). Therefore, the metrics examined in the two studies differed to reflect the sleep changes observed in the two diseases, the scope of sleep changes being examined (i.e., specific or broad), and whether these sleep metrics are related to biological changes in the respective diseases.

Implications for Interventions

Although I examined associations rather than causal relationships, the present findings suggest that cognitive functions in Parkinson's and Alzheimer's diseases may be impacted by metrics of sleep and processes that result in enlarged perivascular spaces. Given this possibility, interventions that specifically target these factors may positively impact cognition. Below, I will outline possible interventions that may help preserve cognitive functioning in individuals with neurodegenerative disease.

If indeed increased sleep leads to poorer cognition in Alzheimer's disease (and not the other way around), then one possible intervention that could be used to prevent or slow cognitive decline in Alzheimer's disease would be to decrease sleep durations from long to optimal length (6-8 hrs). There are a few ways this can be accomplished. Firstly, it may be beneficial to target variables that may be contributing to prolonged sleep, such as chronic inflammation (Irwin et al., 2016; Prather et al., 2015), and depression symptomatology (Diniz et al., 2013; Zhai et al., 2015). This can be accomplished through psychotherapy interventions that target depression or nutritional interventions that aim to reduce inflammation. Alternatively, this may be accomplished by increasing time spent in slow wave sleep stages as it believed that longer sleep durations result from disruption of slow wave sleep processes, such as glymphatic clearance (Ramirez et al., 2021). Thus, interventions that increase time spent in slow wave sleep may increase glymphatic clearance, shorten sleep durations, and possibly improve memory abilities. There are two methods, closed-loop acoustic stimulation (Wunderlin et al., 2020) and transcranial magnetic and electrical stimulation (Huber et al., 2007; Massimini et al., 2007), that have been used to accomplish this.

Unfortunately, each of these methods has significant caveats. Closed loop acoustic stimulation (i.e., repeated exposure to click sounds and short tones in phase with wave activity) has been shown to increase wave amplitudes and boost spindle activity (Ngo et al., 2013), but the effect of this intervention on cognition has been mixed. Some studies have found that this method improves overnight memory retention (Ngo et al., 2013; 2015; Ong et al., 2016), but this effect is not consistently found when there are minor protocol modifications (Weigenand et al., 2016). Additionally, transcranial electrical stimulation has been shown to induce slow wave sleep that is indistinguishable from natural sleep (Massimini et al., 2007), but little is known about the unintended short- and long-term side effects of this intervention (Bellesi et al., 2014). Therefore, the risks of implementing this method into general population use are still unknown.

Exercise is another intervention that has been shown to improve subjective sleep quality (Kelley & Kelley, 2017) and may preserve cognitive abilities by improving vascular functioning (for review, see Barnes & Corkery, 2018; Valenzuela et al., 2020). Previous research has found that physical activity in adults is related to markers of good vascular functioning, such as reduced age-related arterial stiffness (Vaitkevicius et al., 1993) and endothelium-dependent vasodilation (DeSouza et al., 2000) as well as reduced vascular pathology (Torres et al., 2015) and better cognitive abilities (Kirk-Sanchez & McGough, 2014). Therefore, exercise may have a modest positive impact on cognition by not only improving sleep but also decreasing perivascular space/vascular burden and preventing build-up of vasculopathology.

Future Directions

Although our understanding of the relationship between sleep and cognition in neurodegenerative disease populations has increased over the past few decades, little is known about the role of perivascular spaces in these important functions. To date, there has been limited

research to understand the clinical impact of perivascular spaces. A meta-analysis by Francis and colleagues in 2019 found only 116 publications on perivascular spaces (in general), and only a handful of these publications examined the association of perivascular spaces with sleep and/or cognition. Therefore, there are opportunities for additional research to further elucidate the relationship between perivascular spaces, sleep, and cognition. A few of these opportunities are discussed below.

First, there is an opportunity to better understand the causal relationship between sleep disruption, perivascular space enlargement, and cognitive decline. Although the present study examined sleep and perivascular spaces in individuals with cognitive impairment, the present analyses were limited as they only examined cross-sectional as opposed to longitudinal relationships between these constructs. Thus, we were unable to determine the temporal order of these changes. Longitudinal human studies are needed to examine whether changes to perivascular spaces occur before or after sleep disruption, and whether cognitive decline occurs before or after perivascular space enlargement. This will allow us to determine whether lifestyle and biological factors, such as sleep and perivascular spaces, can be targeted for preservation of cognitive functioning, or whether changes to these factors are merely by-products of disease.

Second, replicating the present study with additional metrics of sleep would support the reliability of the findings. Considering that the present studies examined sleep with a subjective measure only, rather than both subjective and objective measures, and one of the studies examined sleep duration using a single item on a single questionnaire, additional studies using other sleep metrics would help validate the present findings and ensure that they are not due to idiosyncrasies of any particular measurement. Future studies using additional subjective sleep measures would support replicability and robustness of the present findings, and studies using

objective measures of sleep, including actigraphy and polysomnography methods, would ensure that the results can be generalized across modalities.

Third, additional studies are needed to examine whether sleep, perivascular spaces, and cognition are related to neurodegenerative disease pathology. Although we understand that perivascular space enlargement, sleep changes, and impaired cognition are frequently observed in neurodegenerative conditions, less is known about the relationship between these variables and neurodegenerative disease pathology. Therefore, additional research is needed to understand whether there is overlapping variance between these variables and neurodegenerative disease pathology and determine whether such pathology accounts for relationships between these variables. This can be accomplished by relating positron emission topography-confirmed deposits of amyloid or Lewy bodies with structural examinations of perivascular spaces, subjective and objective sleep (specifically sleep duration and quality), and measures of cognition (specifically memory and executive functions).

Final Thoughts

Understanding the factors that contribute to cognitive impairment in individuals with Alzheimer's disease and Parkinson's disease may assist us in designing interventions to slow cognitive progression. Through this work, I have demonstrated that two variables, sleep and perivascular spaces, have a complex relationship with cognition in Alzheimer's disease and Parkinson's disease. These findings substantiate the need for additional research in this emerging field, particularly longitudinal research that will help discern the causal relationship between these components.

References

Aarsland, D., Brønnick, K., Larsen, J. P., Tysnes, O. B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest study. *Neurology*, *72*(13), 1121-1126. https://doi.org/10.1212/01.wnl.0000338632.00552.cb

Aarsland, D., Brønnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., & Santangelo, G. (2010). Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis. *Neurology, 75*(12), 1062–1069. https://doi.org/10.1212/WNL.0b013e3181f39d0e

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Ffytche, D. H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nature Reviews Neurology*, *13*(4), 217–231. https://doi.org/10.1038/nrneurol.2017.27

Aarsland, D., Zaccai, J., Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Movement Disorders, 20*(10), 1255–63. https://doi.org/10.1002/mds.20527

Adams, H. H., Cavalieri, M., Verhaaren, B. F., Bos, D., van der Lugt, A., Enzinger, C., Vernooij, M. W., Schmidt, R. & Ikram, M. A. (2013). Rating method for dilated Virchow–Robin spaces on magnetic resonance imaging. *Stroke*, *44*(6), 1732-1735. https://doi.org/10.1161/STROKEAHA.111.000620

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L. and Finch, C. E., & Wyss–Coray, T. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging*, *21*(3), 383-421. https://doi.org/10.1016/S0197-4580(00)00124-X

Alhola, P., & Polo-Kantola, P. (2007). Sleep deprivation: Impact on cognitive performance. *Neuropsychiatric Disease and Treatment*, *3*(5), 553–567.

Alosco, M. L., Brickman, A. M., Spitznagel, M. B., Griffith, E. Y., Narkhede, A., Cohen, R., ... & Gunstad, J. (2013). Reduced cerebral blood flow and white matter hyperintensities predict poor sleep in heart failure. *Behavioral and Brain Functions*, *9*(1), 1-8. https://doi.org/10.1186/1744-9081-9-42

Ancoli-Israel, S. (2009). Sleep and its disorders in aging populations. *Sleep Medicine, 10*, S7-S11.

Aribisala, B. S., Riha, R. L., Hernandez, M. V., Maniega, S. M., Cox, S., Radakovic, R., Taylor, A., Pattie, A., Corley, J., Redmond, P., Bastin, M. E., Starr, J., Deary, I., & Wardlaw, J. M. (2020). Sleep and brain morphological changes in the eighth decade of life. *Sleep Medicine*, *65*, 152-158. https://doi.org/10.1016/j.sleep.2019.07.015

Banerjee, G., Kim, H. J., Fox, Z., Jäger, H. R., Wilson, D., Charidimou, A., Na, H. K., Na, D. L., Seo, S. W., & Werring, D. J. (2017). MRI-visible perivascular space location is associated with Alzheimer's disease independently of amyloid burden. *Brain, 140*(4). 1107-1116. doi:10.1093/brain/awx003

Barnes, J. N., & Corkery, A. T. (2018). Exercise improves vascular function, but does this translate to the brain? *Brain Plasticity*, *4*(1), 65-79. https://doi.org/10.3233/BPL-180075

Basta, M., Simos, P., Vgontzas, A., Koutentaki, E., Tziraki, S., Zaganas, I., Panagiotakis, S., Kapetanaki, S., Fountoulakis, N., & Lionis, C. (2019). Associations between sleep duration and cognitive impairment in mild cognitive impairment. *Journal of Sleep Research*, *28*(6), e12864. https://doi.org/10.1016/j.jagp.2015.12.002

Beaulieu-Bonneau, S., & Hudon, C. (2009). Sleep disturbances in older adults with mild cognitive impairment. *International Psychogeriatrics*, *21*(4), 654-666.

Bellesi, M., Riedner, B. A., Garcia-Molina, G. N., Cirelli, C., & Tononi, G. (2014). Enhancement of sleep slow waves: Underlying mechanisms and practical consequences. *Frontiers in Systems Neuroscience*, *8*, 208. https://doi.org/10.3389/fnsys.2014.00208

Benedict, R. (1997). *Brief Visuospatial Memory Test - Revised*. Odessa, FL: Psychological Assessment Resources.

Benito-León, J., Bermejo-Pareja, F., Vega, S., & Louis, E. D. (2009). Total daily sleep duration and the risk of dementia: A prospective population-based study. *European Journal of Neurology*, *16*(9), 990–997. https://doi.org/10.1111/j.1468-1331.2009.02618.x

Benton, A. L., Hamsher, S. K., Varney, N. R., & Spreen, O. (1983). *Contributions to neuropsychological assessment*. New York: Oxford University Press.

Berezuk, C., Ramirez, J., Gao, F., Scott, C. J., Huroy, M., Swartz, R. H., Murray, B. J., Black, S. E., & Boulos, M. I. (2015). Virchow-Robin spaces: Correlations with polysomnography-derived sleep parameters. *Sleep*, *38*(6), 853-858. https://doi.org/10.5665/sleep.4726

Biundo, R., Weis, L., & Antonini, A. (2016). Cognitive decline in Parkinson's disease: The complex picture. *NPJ Parkinson's Disease*, *2*(1), 1-7. https://doi.org/10.1038/npjparkd.2016.18

Blackwell, T., Yaffe, K., Ancoli-Israel, S., Schneider, J. L., Cauley, J. A., Hillier, T. A., Fink, H. A., & Stone, K. L. (2006). Poor sleep is associated with impaired cognitive function in older women: The study of osteoporotic fractures. *The Journals of Gerontology Series A:*

Biological Sciences and Medical Sciences, *61*(4), 405-410. https://doi.org/0.1093/gerona/61.4.405

Blackwell, T., Yaffe, K., Laffan, A., Ancoli-Israel, S., Redline, S., Ensrud, K. E., Song, Y., Stone, K. L., and the Osteoporotic Fractures in Men (MrOS) Study Group. (2014). Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: The MrOS sleep study. *Sleep,* 37(*4*), 655-663. https://doi.org/10.5665/sleep.3562

Boeve, B. F., Silber, M. H., Ferman, T. J., Lucas, J. A., & Parisi, J. E. (2001). Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Movement Disorders*, *16*(4), 622–630. https://doi.org/10.1002/mds.1120

Boeve, B. F., Silber, M. H., Saper, C. B., Ferman, T. J., Dickson, D. W., Parisi, J. E., Benarroch, E. E., Ahlskog, J. E., Smith, G. E., Caselli, R. C., Tippman-Peikert, M., Olson, E. J., Lin, S. C., Young, T., Wszolek, Z., Schenck, C. H., Mahowald, M. W., Castillo, P. R., Del Tredici, K., & Braak, H. (2007). Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*, *130*(Pt 11), 2770–2788. https://doi.org/10.1093/brain/awm056

Bohnen, N. I., & Hu, M. (2019). Sleep disturbance as potential risk and progression factor for Parkinson's disease. *Journal of Parkinson's Disease*, *9*(3), 603-614. https://doi.org/10.3233/JPD-191627

Braak, H., Rüb, U., Steur, E. J., Del Tredici, K., & De Vos, R. A. I. (2005). Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology*, *64*(8), 1404-1410.

Brown, R., Benveniste, H., Black, S. E., Charpak, S., Dichgans, M., Joutel, A., Nedergaard, M., Smith, K. J., Zlokovic, B. V., Wardlaw, J. M. (2018). Understanding the role of the

perivascular space in cerebral small vessel disease. *Cardiovascular Research, 114*, 1462-1473. https://doi.org/10.1093/cvr/cvy113

Bubu, O. M., Brannick, M., Mortimer, J., Umasabor-Bubu, O., Sebastião, Y. V., Wen, Y., Schwartz, S., Borenstein, A. R., Wu, Y., Morgan, D., & Anderson, W. M. (2017). Sleep, cognitive impairment, and Alzheimer's disease: A systematic review and meta-analysis. *Sleep*, *40*(1), 10.1093/sleep/zsw032. https://doi.org/10.1093/sleep/zsw032

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Research, 28*(2), 193-213. https://doi.org/10.1016/0165-1781(89)90047-4

Caviness, J. N., Driver-Dunckley, E., Connor, D. J., Sabbagh, M. N., Hentz, J. G., Noble, B., Evidente, V. G., Shill, H. A., & Adler, C. H. (2007). Defining mild cognitive impairment in Parkinson's disease. *Movement Disorders*, *22*(9), 1272–1277. https://doi.org/10.1002/mds.21453

Calabrò, M., Rinaldi, C., Santoro, G., & Crisafulli, C. (2021). The biological pathways of Alzheimer disease: A review. *AIMS Neuroscience*, *8*(1), 86. https://doi.org/10.3934/Neuroscience.2021005

Charidimou, A., Meegahage, R., Fox, Z., Peeters, A., Vandermeeran, Y., Laloux, P., Baron, J., Jager, H., & Werring, D. (2013). Enlarged perivascular spaces as a marker of underlying arteriopathy in intracerebral haemorrhage: A multicentre MRI cohort study. *Journal of Neurology and Neurosurgical Psychiatry, 84*, 624–629. https://doi.org/10.1136/jnnp-2012-304434

Chen, W., Song, X., Zhang, Y., & Alzheimer's Disease Neuroimaging Initiative. (2011). Assessment of the Virchow-Robin Spaces in Alzheimer disease, mild cognitive impairment, and normal aging, using high-field MR imaging. *American Journal of Neuroradiology*, *32*(8), 1490-1495. https://doi.org/10.3174/ajnr.A2541

Chen, H., Wan, H., Zhang, M., Liu, G., Wang, X., Wang, Z., ... & Wang, Y. (2021). Cerebral small vessel disease may worsen motor function, cognition, and mood in Parkinson's disease. *Parkinsonism & Related Disorders*, *83*, 86-92. https://doi.org/10.1016/j.parkreldis.2020.12.025

Cheng, C. Y., Tsai, C. F., Wang, S. J., Hsu, C. Y., & Fuh, J. L. (2013). Sleep disturbance correlates with white matter hyperintensity in patients with subcortical ischemic vascular dementia. *Journal of Geriatric Psychiatry and Neurology*, *26*(3), 158-164. https://doi.org/10.1177/0891988713493503

Cohen J. (1988). *Statistical power analysis for the behavioral sciences*. New York: Routledge Academic.

Comella, C. L. (2007). Sleep disorders in Parkinson's disease: An overview. *Movement Disorders*, *22*(S17), S367-S373. https://doi.org/10.1002/mds.21682

Cook, R. D., & Weisberg, S. (1982). *Residuals and influence in regression*. New York: Chapman and Hall.

Cordone, S., Annarumma, L., Rossini, P. M., & De Gennaro, L. (2019). Sleep and β-amyloid deposition in Alzheimer disease: Insights on mechanisms and possible innovative treatments. *Frontiers in Pharmacology*, *10*, 695. https://doi.org/10.3389/fphar.2019.00695

Cramer, D. (1998). *Fundamental statistics for social research.* London: Routledge.

Cramer, D., & Howitt, D. (2004). *The SAGE dictionary of statistics.* London: SAGE.

Cricco, M., Simonsick, E. M., & Foley, D. J. (2001). The impact of insomnia on cognitive functioning in older adults. *Journal of the American Geriatrics Society*, *49*, 1185–1189. https://doi.org/10.1046/j.1532-5415.2001.49235.x

Dadar, M., Zeighami, Y., Yau, Y., Fereshtehnejad, S. M., Maranzano, J., Postuma, R. B., Dagher, A. & Collins, D. L. (2018). White matter hyperintensities are linked to future cognitive decline in de novo Parkinson's disease patients. *NeuroImage: Clinical*, *20*, 892-900. https://doi.org/10.1016/j.nicl.2018.09.025

Dalrymple-Alford, J. C., Livingston, L., MacAskill, M. R., et al. (2011). Characterizing mild cognitive impairment in Parkinson's disease. *Movement Disorders, 26*(4), 629 - 636. https://doi.org/10.1002/mds.23592

Darweesh, S., Wolters, F. J., Ikram, M. A., de Wolf, F., Bos, D., & Hofman, A. (2018). Inflammatory markers and the risk of dementia and Alzheimer's disease: A meta-analysis. *Alzheimer's & Dementia*, *14*(11), 1450-1459. https://doi.org/10.1016/j.jalz.2018.02.014

Decarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M. Au, R., Beiser, A., D'Agostino, R., Wolf, P. A. (2005). Measures of brain morphology and infarction in the Framingham heart study: Establishing what is normal. *Neurobiology of Aging, 26*(4), 491-510. https://doi.org/10.1016/j.neurobiolaging.2004.05.004

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System: Technical manual.* San Antonio, TX: Harcourt Assessment.

Del Brutto, O. H., Mera, R. M., Del Brutto, V. J., & Castillo, P. R. (2019). Enlarged basal ganglia perivascular spaces and sleep parameters. A population-based study. *Clinical Neurology and Neurosurgery*, *182*, 53-57. https://doi.org/10.1016/j.clineuro.2019.05.002

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry*, *202*(5), 329–335. https://doi.org/10.1192/bjp.bp.112.118307

DeSouza, C. A., Shapiro, L. F., Clevenger, C. M., Dinenno, F. A., Monahan, K. D., & Tanaka, H. (2000). Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation*, 102(12), 1351-7. https://doi.org/10.1161/01.cir.102.12.1351

Ding, W., Ding, L. J., Li, F. F., Han, Y., & Mu, L. (2015). Neurodegeneration and cognition in Parkinson's disease: A review. *European Review for Medical and Pharmacological Sciences, 19*(12), 2275-2281.

Ding, J., Sigurðsson, S., Jónsson, P. V., Eiriksdottir, G., Charidimou, A., Lopez, O. L., van Buchem, M. A., Guonason, V., & Launer, L. J. (2017). Large MRI-visible perivascular spaces, cerebral small vessel disease progression and risk of dementia: The AGES-Reykjavik Study. *JAMA Neurology*, *74*(9), 1105. https://doi.org/10.1001/jamaneurol.2017.1397

Donahue, E. K., Murdos, A., Jakowec, M. W., Sheikh-Bahaei, N., Toga, A. W., Petzinger, G. M., & Sepehrband, F. (2021). Global and regional changes in perivascular space in idiopathic and familial Parkinson's disease. *Movement Disorders*, *36*(5), 1126-1136. https://doi.org/10.1002/mds.28473

Doubal, F. N., MacLullich, A. M., Ferguson, K. J., Dennis, M. S., & Wardlaw, J. M. (2010). Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*, *41*(3), 450–454. https://doi.org/10.1161/STROKEAHA.109.564914

Dowd, J. B., Goldman, N., & Weinstein, M. (2011). Sleep duration, sleep quality, and biomarkers of inflammation in a Taiwanese population. *Annals of Epidemiology*, *21*(11), 799-806. https://doi.org/10.1016/j.annepidem.2011.07.004

Dunet, V., Fartaria, M. J., Deverdun, J., Le Bars, E., Maury, F., Castelnovo, G., Kober, T., Cuadra, M. B., Geny, C., Marechal, B., & de Champfleur, N. M. (2019). Episodic memory decline in Parkinson' s disease: Relation with white matter hyperintense lesions and influence of quantification method. *Brain Imaging and Behavior*, *13*(3), 810–818. https://doi.org/10.1007/s11682-018-9909-x

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., Broe, G. A., Cummings, J., Dickson, D. W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., Quinn, N., … Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*, *22*(12), 1689–1837. https://doi.org/10.1002/mds.21507

Fabbri, M., Beracci, A., Martoni, M., Meneo, D., Tonetti, L., & Natale, V. (2021). Measuring Subjective Sleep Quality: A Review. *International journal of environmental research and public health*, *18*(3), 1082. https://doi.org/10.3390/ijerph18031082

Factor, S. A., McAlarney, T., Sanchez-Ramos, J. R., & Weiner, W. J. (1990). Sleep disorders and sleep effect in Parkinson's disease. *Movement Disorders*, *5*(4), 280–285. https://doi.org/10.1002/mds.870050404

Fan, L., Xu, W., Cai, Y., Hu, Y., & Wu, C. (2019). Sleep duration and the risk of dementia: A systematic review and meta-analysis of prospective cohort studies. *Journal of the American Medical Directors Association*, *20*(12), 1480–1487. https://doi.org/10.1016/j.jamda.2019.06.009

Faubel, R., Lopez-Garcia, E., Guallar-Castillon, P., Graciani, A., Banegas, J. R., & Rodriguez-Artalejo, F. (2009). Usual sleep duration and cognitive function in older adults in Spain. *Journal of Sleep Research*, 18, 427–35. https://doi.org/10.1111/j.1365-2869.2009.00759.x

Farhan, S. M., Bartha, R., Black, S. E., Corbett, D., Finger, E., Freedman, M., Greenberg, B., Grimes, D. A., Hegele, R. A., Hudson, C., Kleinstiver, P. W., Lang, A. E., Masellis, M., McIlroy, W. E., McLaughlin, P. M., Montero-Odasso, M., Munoz, D. G., Munoz, D. P., Strother, S., … Strong, M. J. (2017). The Ontario Neurodegenerative Disease Research Initiative (ONDRI). *Canadian Journal of Neurological Sciences*, *44*(2), 196-202. https://doi.org/10.1017/cjn.2016.415

Field, A., Miles, J., & Field, Z. (2012). *Discovering statistics using R*. London, UK: Sage Publications.

Francis, F., Ballerini, L., & Wardlaw, J. M. (2019). Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: A systematic review and meta-analysis. *International Journal of Stroke*, *14*(4), 359–371. https://doi.org/10.1177/1747493019830321

Foley, D., Ancoli-Israel, S., Britz, P., & Walsh, J. (2004). Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey. *Journal of Psychosomatic Research*, *56*(5), 497-502.

Foltynie, T., Brayne, C. E., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain*, *127*(Pt 3), 550–560. https://doi.org/10.1093/brain/awh067

Furst, A. J., Rabinovici, G. D., Rostomian, A. H., Steed, T., Alkalay, A., Racine, C., Miller, B. L. & Jagust, W. J. (2012). Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. *Neurobiology of Aging*, *33*(2), 215-225. https://doi.org/10.1016/j.neurobiolaging.2010.03.011

Gibson, E., Gao, F., Black, S. E., & Lobaugh, N. J. (2010). Automatic segmentation of white matter hyperintensities in the elderly using FLAIR images at 3T. *Journal of Magnetic Resonance, 31*, 1311-1322. https://doi.org/10.1002/jmri.22004

Gildner, T. E., Salinas-Rodríguez, A., Manrique-Espinoza, B., Moreno-Tamayo, K., & Kowal, P. (2019). Does poor sleep impair cognition during aging? Longitudinal associations between changes in sleep duration and cognitive performance among older Mexican adults. *Archives of Gerontology and Geriatrics*, *83*, 161-168. https://doi.org/10.1016/j.archger.2019.04.014

Goldman, J. G., Ghode, R. A., Ouyang, B., Bernard, B., Goetz, C. G., & Stebbins, G. T. (2013). Dissociations among daytime sleepiness, nighttime sleep, and cognitive status in Parkinson's disease. *Parkinsonism & Related Disorders*, *19*(9), 806-811. https://doi.org/10.1016/j.parkreldis.2013.05.006

Goldman, J. G., & Litvan, I. (2011). Mild cognitive impairment in Parkinson’s disease. *Minerva Medica*, *102*(6), 441-459. PMID: 22193376

Gunn, D. G., Naismith, S. L., Bolitho, S. J., & Lewis, S. J. (2014). Actigraphically-defined sleep disturbance in Parkinson's disease is associated with differential aspects of cognitive functioning. *Journal of Clinical Neuroscience*, *21*(7), 1112-1115.

Gunn, D. G., Naismith, S. L., Terpening, Z., & Lewis, S. J. (2014). The relationships between poor sleep efficiency and mild cognitive impairment in Parkinson disease. *Journal of Geriatric Psychiatry and Neurology*, *27*(2), 77-84. https://doi.org/10.1177/0891988713509135

Hall, S., Surova, Y., Öhrfelt, A., Swedish BioFINDER Study, Blennow, K., Zetterberg, H., & Hansson, O. (2016). Longitudinal measurements of cerebrospinal fluid biomarkers in Parkinson's disease. *Movement Disorders*, *31*(6), 898-905. https://doi.org/10.1002/mds.26578.

Halliday, G .M., Leverenz, J. B., Schneider, J. S., & Adler, C. (2014). The neurobiological basis of cognitive impairment in Parkinson's disease. *Movement Disorders, 29*(5), 634–650. https://doi.org/10.1002/mds.25857

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, *80*(14), 1341-1348. https://doi.org/10.1212/WNL.0b013e31828ab35d

Hessen, E., Stav, A. L., Auning, E., Selnes, P., Blomsø, L., Holmeide, C. E., Johansen, K. K., Eliassen, C. F., Reinvang, I., Fladby, T. & Aarsland, D. (2016). Neuropsychological profiles in mild cognitive impairment due to Alzheimer's and Parkinson's diseases. *Journal of Parkinson's Disease*, *6*(2), 413-421. https://doi.org/10.3233/JPD-150761

Hilal, S., Tan, C. S., Adams, H. H., Habes, M., Mok, V., Venketasubramanian, N., Hofer, E., Kamran Ikram, M., Abrigo, J., Vernooij, M. W., Chen, C., Hosten, N., Volzke, H., Grabe, H. J., Schmidt, R., Ikram, M. A. & Chen, C. (2018). Enlarged perivascular spaces and cognition: A meta-analysis of 5 population-based studies. *Neurology*, *91*(9), e832-e842. https://doi.org/10.1212/WNL.0000000000006079

Hita-Yañez, E., Atienza, M., Gil-Neciga, E., & L Cantero, J. (2012). Disturbed sleep patterns in elders with mild cognitive impairment: The role of memory decline and ApoE ε4 genotype. *Current Alzheimer's Research*, *9*(3), 290-297. https://doi.org/10.2174/156720512800107609

Hogl, B., Arnulf, I., Comella, C., Ferreira, J., Iranzo, A., Tilley, B., Trenkwalder, C., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Schrag, A., & Goetz, C. G. (2010). Scales to assess sleep impairment in Parkinson's disease: Critique and recommendations. *Movement Disorders*, *25*(16), 2704e16. https://doi.org/10.1002/mds.23190

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology, 17*(5)*,* 427-442. https://doi.org/10.1212/wnl.17.5.427

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(3), 181–184. https://doi.org/10.1136/jnnp.55.3.181

Huijts, M., Duits, A., Staals, J., Kroon, A. A., de Leeuw, P. W., & van Oostenbrugge, R. J. (2014). Basal ganglia enlarged perivascular spaces are linked to cognitive function in patients with cerebral small vessel disease. *Current Neurovascular Research*, *11*(2), 136–141. https://doi.org/10.2174/1567202611666140310102248

Hurford, R., Charidimou, A., Fox, Z., Cipolotti, L., Jager, R., Werring, D.J. (2014). MRI-visible perivascular spaces: Relationship to cognition and small vessel disease MRI markers in ischaemic stroke and TIA. *Journal of Neurology and Neurosurgical Psychiatry, 85*, 522–525. https://doi.org/10.1136/jnnp-2013-305815

Hurtig, H. I., Trojanowski, J. Q., Galvin, J., Ewbank, D., Schmidt, M. L., Lee, V. Y., Clark, C. M., Glosser, G., Stern, M. B., Gollomp, S. M., & Arnold, S. E. (2000). Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology*, *54*(10), 1916-1921. https://doi.org/10.1212/wnl.54.10.1916.

Iliff, J. J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., & Benveniste, H. (2013). Brainwide pathway for waste clearance captured by contrast-enhanced MRI. *Journal of Clinical Investigation, 123*(3), 1299–1309. https://doi.org/10.1172/JCI67677

Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., Benveniste, H., Vates, G. E., Deane, R., Goldman, S. A., Nagelhus, E. A., & Nedergaard, M. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Science of Translational Medicine, 4,* 147ra111. https://doi.org/10.1126/scitranslmed.3003748

Irwin, M. R., Olmstead, R., & Carroll, J. E. (2016). Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological Psychiatry*, *80*(1), 40–52. https://doi.org/10.1016/j.biopsych.2015.05.014

Irwin, D. J., White, M. T., Toledo, J. B., Xie, S. X., Robinson, J. L., Van Deerlin, V., Lee, V. M., Leverenz, J. B., Montine, T. J., Duda, J. E., Hurtig, H. I., & Trojanowski, J. Q. (2012).

Neuropathologic substrates of Parkinson disease dementia. *Annals of Neurology*, *72*(4), 587–598. https://doi.org/10.1002/ana.23659

Jahn H. (2013). Memory loss in Alzheimer's disease. *Dialogues in Clinical Neuroscience*, *15*(4), 445-454. https://doi.org/10.31887/DCNS.2013.15.4/hjahn

Janota, C., Lemere, C.A. Brito, M.A. (2016). Dissecting the contribution of vascular alterations and aging to Alzheimer's disease. *Molecular Neurobiology*, *53*(6), 3793–3811. https://doi.org/10.1007/s12035-015-9319-7.

Janvin, C. C., Aarsland, D., & Larsen, J. P. (2005). Cognitive predictors of dementia in Parkinson's disease: A community-based, 4-year longitudinal study. *Journal of Geriatric Psychiatry and Neurology*, *18*(3), 149-154. https://doi.org/10.1177/0891988705277540

Jeong, E. H., Lee, Y. J., Kim, S. J., & Lee, J. H. (2015). Is the severity of dilated Virchow-Robin spaces associated with cognitive dysfunction? *Dementia and Neurocognitive Disorders, 14*(3), 114-119. https://doi.org/10.1016/j.jalz.2013.05.1173

Jie, W., Lin, G., Liu, Z., Zhou, H., Lin, L., Liang, G., Ou, M. & Lin, M. (2020). The relationship between enlarged perivascular spaces and cognitive function: A meta-analysis of observational studies. *Frontiers in Pharmacology*, *11*, 715. https://doi.org/10.3389/fphar.2020.00715

Jonaitis, E. M., Koscik, R. L., Clark, L. R., Ma, Y., Betthauser, T. J., Berman, S. E., Allison, S. L., Mueller, K. D., Hermann, B. P., Van Hulle, C. A., Christian, B. T., Bendlin, B. B., Blennow, K., Zetterberg, H., Carlsson, C. M., Asthana, S. & Johnson, S. C. (2019). Measuring longitudinal cognition: Individual tests versus composites. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*, 74-84. https://doi.org/10.1016/j.dadm.2018.11.006

Ju, Y. E. S., Ooms, S. J., Sutphen, C., Macauley, S. L., Zangrilli, M. A., Jerome, G., Fagan, A. M., Mignot, E., Zempel J. M., Claassen, J. A. H. R. & Holtzman, D. M. (2017). Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*, *140*(8), 2104-2111. https://doi.org/10.1093/brain/awx148

Kelley, G. A., & Kelley, K. S. (2017). Exercise and sleep: A systematic review of previous meta-analyses. *Journal of Evidence-based Medicine*, *10*(1), 26–36. https://doi.org/10.1111/jebm.12236

Kalbe, E., Rehberg, S. P., Heber, I., Kronenbuerger, M., Schulz, J. B., Storch, A., Linse, K., Schneider, C., Gräber, S., Liepelt-Scarfone, I., Berg, D., Dams, J., Balzer-Geldsetzer, M., Hilker, R., Oberschmidt, C., Witt, K., Schmidt, N., Mollenhauer, B., Trenkwalder, C., Spottke, A., … Dodel, R. (2016). Subtypes of mild cognitive impairment in patients with Parkinson's disease: Evidence from the LANDSCAPE study. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(10), 1099-1105.

Kanda, A., Matsui, T., Ebihara, S., Arai, H., & Sasaki, H. (2003). Periventricular white matter lesions and sleep alteration in older people. *Journal of the American Geriatrics Society*, *51*(3), 432-433.

Kandiah, N., Mak, E., Ng, A., Huang, S., Au, W. L., Sitoh, Y. Y., & Tan, L. C. (2013). Cerebral white matter hyperintensity in Parkinson's disease: A major risk factor for mild cognitive impairment. *Parkinsonism & Related Disorders*, *19*(7), 680–683. https://doi.org/10.1016/j.parkreldis.2013.03.008

Kim, H. B., Myung, S. K., Lee, S. M., Park, Y. C., & Korean Meta-Analysis (KORMA) Study Group. (2016). Longer duration of sleep and risk of cognitive decline: A meta-analysis of

observational studies. *Neuroepidemiology*, *47*(3-4), 171-180. https://doi.org/10.1159/000454737

Kummer, B. R., Diaz, I. Wu, X., Aaroe, A. E. Chen, M. L., Iadecola, C. Kamel, H. & Navi, B. B. (2019). Associations between cerebrovascular risk factors and Parkinson disease. *Annuals of Neurology*, *86*(4), 572–581. https://doi.org/10.1002/ana.25564

Larsen, J. P., & Tandberg, E. (2001). Sleep disorders in patients with Parkinson's disease. *CNS Drugs*, *15*(4), 267-275. https://doi.org/10.2165/00023210-200115040-00002

Lauderdale, D. S., Knutson, K. L., Yan, L. L., Liu, K., & Rathouz, P. J. (2008). Self-reported and measured sleep duration: How similar are they? *Epidemiology*, 838-845. https://doi.org/10.1097/EDE.0b013e318187a7b0

Levy, G., Jacobs, D. M., Tang, M. X., Côté, L. J., Louis, E. D., Alfaro, B., Mejia, H., Stern, Y., & Marder, K. (2002). Memory and executive function impairment predict dementia in Parkinson's disease. *Movement Disorders*, *17*(6), 1221-1226. https://doi.org/10.1002/mds.10280

Leng, Y., & Yaffe, K. (2020). Sleep duration and cognitive aging—beyond a U-shaped association. *JAMA Network Open*, *3*(9), e2014008-e2014008. https://doi.org/10.1001/jamanetworkopen.2020.14008

Levit, A., Hachinski, V., & Whitehead, S. N. (2020). Neurovascular unit dysregulation, white matter disease, and executive dysfunction: The shared triad of vascular cognitive impairment and Alzheimer disease. *Geroscience*, *42*(2), 445–465. https://doi.org/10.1007/s11357-020-00164-6.

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment (5th ed.).* New York: Oxford University Press.

Li, Q., Yang, Y., Reis, C., Tao, T., Li, W., Li, X., & Zhang, J. H. (2018). Cerebral small vessel disease. *Cell Transplantation*, *27*(12), 1711–1722. https://doi.org/10.1177/0963689718795148

Linortner, P., McDaniel, C., Shahid, M., Levine, T. F., Tian, L., Cholerton, B., & Poston, K. L. (2020). White matter hyperintensities related to Parkinson's disease executive function. *Movement Disorders Clinical Practice*, *7*(6), 629–638. https://doi.org/10.1002/mdc3.12956

Liu, H. M., Chu, M., Li, N., Zhang, S., Zhang, Y. Z., & Gu, P. (2018). Relationship between sleep quality and cognitive function in patients with mild-to-moderate Parkinson's disease. *Chinese Medical Journal*, *131*(8), 994.

Liu, H., Deng, B., Xie, F., Yang, X., Xie, Z., Chen, Y., & Wang, Q. (2021). The influence of white matter hyperintensity on cognitive impairment in Parkinson's disease. *Annals of Clinical and Translational Neurology, 8*(9), 1917-1934. https://doi.org/10.1002/acn3.51429

Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., Mollenhauer, B., Adler, C. H., Marder, K., Williams-Gary, C. H., Aarsland, D., Kulisevsky, J., Rodrigues-Oroz, M. C., Burn, D. J., Barker, R. A., & Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Movement Disorders*, *27*(3), 349-356. https://doi.org/10.1002/mds.24893

Lo, J. C., Groeger, J. A., Cheng, G. H., Dijk, D. J., & Chee, M. W. (2016). Self-reported sleep duration and cognitive performance in older adults: A systematic review and meta-analysis. *Sleep Medicine*, *17*, 87-98. https://doi.org/10.1016/j.sleep.2015.08.021

Lu, Y., Sugawara, Y., Zhang, S., Tomata, Y., & Tsuji, I. (2018). Changes in sleep duration and the risk of incident dementia in the elderly Japanese: The Ohsaki Cohort 2006 Study. *Sleep*, *41*(10), zsy143. https://doi.org/10.1093/sleep/zsy143

Loewenstein, D. A., Acevedo, A., Luis, C., Crum, T., Barker, W. W., & Duara, R. (2004). Semantic interference deficits and the detection of mild Alzheimer's disease and mild cognitive impairment without dementia. *Journal of the International Neuropsychological Society*, *10*(1), 91.

Maclullich, A. M., Wardlaw, J. M., Ferguson, K. J., Starr, J. M., Seckl, J. R., & Deary, I. J. (2004). Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(11), 1519–1523. https://doi.org/10.1136/jnnp.2003.030858

Maggi, G., Trojano, L., Barone, P., & Santangelo, G. (2021). Sleep disorders and cognitive dysfunctions in Parkinson's disease: A meta-analytic study. *Neuropsychology Review*, 31(4), 643-682. https://doi.org/10.1007/s11065-020-09473-1

Malek, N., Lawton, M. A., Swallow, D. M., Grosset, K. A., Marrinan, S. L., Bajaj, N., Barker, R.A., Burn, D.J., Hardy, J., Morris, H.R., Williams, N.M., Wood, N., Ben-Shlomo, Y., Grosset, D.G. & PRoBaND Clinical Consortium. (2016). Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease. *Movement Disorders*, *31*(10), 1518-1526. https://doi.org/10.1002/mds.26698

Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and human aging. *Neuron*, *94*(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004

Marian, V., Blumenfeld, H. K., & Kaushanskaya, M. (2007). The Language Experience and Proficiency Questionnaire (LEAP-Q): Assessing language profiles in bilinguals and

multilinguals. *Journal of Speech, Language, and Hearing Research*, *50*(4), 940-967. https://doi.org/10.1044/1092-4388(2007/067)

McCurry, S. M., Logsdon, R. G., Teri, L., Gibbons, L. E., Kukull, W. A., Bowen, J. D., McCormick, W. C., & Larson, E. B. (1999). Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. *Journal of Geriatric Psychiatry and Neurology*, *12*(2), 53–59. https://doi.org/10.1177/089198879901200203

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr, Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

McLaughlin, P. M., Sunderland, K. M., Beaton, D., Binns, M. A., Kwan, D., Levine, B., Orange, J. B., Peltsch, A. J., Roberts, A. C., Strother, S. C. & Troyer, A. K. (2020). The quality assurance and quality control protocol for neuropsychological data collection and curation in the Ontario Neurodegenerative Disease Research Initiative (ONDRI) Study. *Assessment*, 28(5), 1267-1286. https://doi.org/10.1177/1073191120913933

Mestre, H., Kostrikov, S., Mehta, R. I., & Nedergaard, M. (2017). Perivascular spaces, glymphatic dysfunction, and small vessel disease. *Clinical Science*, *131*(17), 2257–2274. https://doi.org/10.1042/CS20160381

Moe, K. E., Vitiello, M. V., Larsen, L. H., & Prinz, P. N. (1995). Sleep/wake patterns in Alzheimer's disease: Relationships with cognition and function. *Journal of Sleep Research*, *4*(1), 15-20.

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C. M., & Colantonio, A. (2016). The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep medicine reviews*, *25*, 52–73. https://doi.org/10.1016/j.smrv.2015.01.009

Monastero, R., Cicero, C.E., Baschi, R., Davi, M., Luca, A., Restivo, V., Zangara, C., Fierro, B., Zappia, M., Nivoletti, A. (2018). Mild cognitive impairment in Parkinson's disease: The Parkinson's disease cognitive study (PACOS). *Journal of Neurology, 265,* 1050–1058. https://doi.org/10.1007/s00415-018-8800-4

Montanaro, E., Romagnolo, A., Fabbri, M., Artusi, C. A., Imbalzano, G., Rizzone, M. G., Lopiano, L. & Zibetti, M. (2021). Association between sleep disorders and cognitive dysfunctions in non-demented patients with advanced Parkinson's disease. *Journal of Neurology*, *269*(3), 1538-1545. https://doi.org/10.1007/s00415-021-10726-z

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., Pose, C., Albala, B., Ropacki, M., Ritchie, C. W. & Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimer's & Dementia*, *13*(4), 468-492. https://doi.org/10.1016/j.jalz.2016.06.2365

Moran, M., Lynch, C. A., Walsh, C., Coen, R., Coakley, D., & Lawlor, B. A. (2005). Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Medicine*, *6*(4), 347–352. https://doi.org/10.1016/j.sleep.2004.12.005

Morgan, K., Healey, D. W., & Healey, P. J. (1989). Factors influencing persistent subjective insomnia in old age: A follow-up study of good and poor sleepers aged 65 to 74. *Age and Ageing*, *18*(2), 117-122. https://doi.org/10.1093/ageing/18.2.117

Muslimović, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, *65*(8), 1239-1245. https://doi.org/10.1212/01.wnl.0000180516.69442.95

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cumming J. L. & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695- 699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Neikrug, A. B., & Ancoli-Israel, S. (2009). Sleep disorders in the older adult - a mini-review. *Gerontology*, *56*(2), 181-189.

Neikrug, A. B., Maglione, J. E., Liu, L., Natarajan, L., Avanzino, J. A., Corey-Bloom, J., Palmer, B.W., Loredo, J. S., & Ancoli-Israel, S. (2013). Effects of sleep disorders on the non-motor symptoms of Parkinson disease. *Journal of Clinical Sleep Medicine*, *9*(11), 1119-1129. https://doi.org/ 10.5664/jcsm.3148.

Ng, A. Chew, I. Tay, K. Y. Au, W. L. Tan, L. & Kandiah, N. (2012). White matter disease adversely influences cognition in idiopathic Parkinson's disease. *Alzheimer's Dementia*, *8*(45), P171-172. https://doi.org/10.1016/j.jalz.2012.05.463

Ngo, H. V., Martinetz, T., Born, J., & Molle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron, 78*, 545–553. https://doi.org/ 10.1016/j.neuron.2013.03.006.

Ngo, H. V., Miedema, A., Faude, I., Martinetz, T., Molle, M., & Born, J. (2015). Driving sleep slow oscillations by auditory closed-loop stimulation-a self-limiting process. *Journal of Neuroscience, 35*(17), 6630–6638. https://doi.org/10.1523/JNEUROSCI.3133-14.2015.

Niazi, M., Karaman, M., Das, S., Zhou, X. J., Yushkevich, P., & Cai, K. (2018). Quantitative MRI of perivascular spaces at 3T for early diagnosis of mild cognitive impairment. *American Journal of Neuroradiology*, *39*(9), 1622-1628. https://doi.org/10.3174/ajnr.A5734

Oosterman, J. M., Van Someren, E. J., Vogels, R. L., Van Harten, B., & Scherder, E. J. (2009). Fragmentation of the rest-activity rhythm correlates with age-related cognitive deficits. *Journal of Sleep Research*, *18*(1), 129-135.

Ong, J. L., Lo, J. C., Chee, N. I., Santostasi, G., Paller, K. A., Zee, P. C., Chee, M. W. (2016). Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. *Sleep Medicine, 20*, 88–97. https://doi.org/10.1016/j.sleep.2015.10.016.

Pagonabarraga, J., & Kulisevsky, J. (2012). Cognitive impairment and dementia in Parkinson's disease. *Neurobiology of Disease*, *46*(3), 590-596. https://doi.org/10.1016/j.nbd.2012.03.029

Pantoni L. (2010). Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology*, *9*(7), 689–701. https://doi.org/10.1016/S1474-4422(10)70104-6

Patel, S. R., Zhu, X., Storfer-Isser, A., Mehra, R., Jenny, N. S., Tracy, R., & Redline, S. (2009). Sleep duration and biomarkers of inflammation. *Sleep*, *32*(2), 200-204. https://doi-org.ezproxy.library.yorku.ca/10.1093/sleep/32.2.200

Park, Y. W., Shin, N. Y., Chung, S. J., Kim, J., Lim, S. M., Lee, P. H., Lee, S. K., & Ahn, K. J. (2019). Magnetic resonance imaging-visible perivascular spaces in basal ganglia predict cognitive decline in Parkinson's disease. *Movement Disorders*, *34*(11), 1672–1679. https://doi.org/10.1002/mds.27798

Park, D. C., Smith, A. D., Lautenschlager, G., Earles, J. L., Frieske, D., Zwahr, M., & Gaines, C. L. (1996). Mediators of long-term memory performance across the life span. *Psychology and Aging*, *11*(4), 621.

Passiak, B. S., Liu, D., Kresge, H. A., Cambronero, F. E., Pechman, K. R., Osborn, K. E., Gifford, K. A., Hohman, T. J., Schrag, M. S., Davis, L. T., & Jefferson, A. L. (2019). Perivascular spaces contribute to cognition beyond other small vessel disease markers. *Neurology*, *92*(12), e1309–e1321. https://doi.org/10.1212/WNL.0000000000007124

Patankar, T. F., Mitra, D., Varma, A., Snowden, J., Neary, D., & Jackson, A. (2005). Dilatation of the Virchow-Robin space is a sensitive indicator of cerebral microvascular disease: Study in elderly patients with dementia. *American Journal of Neuroradiology, 26*(6), 1512–1520. Available online at: http://www.ajnr.org/content/26/6/1512

Peeraully, T., Yong, M. H., Chokroverty, S., & Tan, E. K. (2012). Sleep and Parkinson's disease: A review of case-control polysomnography studies. *Movement Disorders*, *27*(14), 1729-1737. https://doi.org/10.1002/mds.25197

Peng, W., Achariyar, T. M., Li, B., Liao, Y., Mestre, H., Hitomi, E., Regan, S., Kasper, T., Peng, S., Ding, F., Benveniste, H., Nedergaard, M., & Deane, R. (2016). Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiology of Disease*, *93*, 215–225.

Pigott, K., Rick, J., Xie, S. X., Hurtig, H., Chen-Plotkin, A., Duda, J. E., Morley, J. F., Chahine, L. M., Dahodwala, N., Akhtar, R. S., Siderowf, A., Trojanowski, J. Q., & Weintraub, D. (2015). Longitudinal study of normal cognition in Parkinson disease. *Neurology*, *85*(15), 1276–1282. https://doi.org/10.1212/WNL.0000000000002001

Pushpanathan, M. E., Loftus, A. M., Thomas, M. G., Gasson, N., & Bucks, R. S. (2016). The relationship between sleep and cognition in Parkinson's disease: A meta-analysis. *Sleep Medicine Reviews*, *26*, 21-32. https://doi.org/10.1016/j.smrv.2015.04.003

Potter, G. M., Doubal, F. N., & Jackson, C. A. (2015). Enlarged perivascular spaces and cerebral small vessel disease. *International Journal of Stroke*, *10*, 376–81. https://doi.org/10.1111/ijs.12054

Prather, A. A., Vogelzangs, N., & Penninx, B. W. (2015). Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands Study of Depression and Anxiety (NESDA). *Journal of Psychiatric Research*, *60*, 95–102. https://doi.org/10.1016/j.jpsychires.2014.09.018

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and meta-analysis. *Alzheimer's & Dementia*, *9*(1), 63-75. https://doi.org/10.1016/j.jalz.2012.11.007

Ramirez, J., Berezuk, C., McNeely, A. A., Gao, F., McLaurin, J., & Black, S. E. (2016). Imaging the perivascular space as a potential biomarker of neurovascular and neurodegenerative diseases. *Cellular and molecular neurobiology*, *36*(2), 289-299. https://doi.org/10.1007/s10571-016-0343-6

Ramirez, J., Berezuk, C., McNeely, A. A., Scott, C. J., Gao, F., & Black, S. E. (2015). Visible Virchow-Robin spaces on magnetic resonance imaging of Alzheimer’s disease patients

and normal elderly from the Sunnybrook Dementia Study. *Journal of Alzheimer's Disorders, 43*, 415–24. https://doi.org/10.3233/JAD-132528

Ramirez, J., Gibson, E., Quddus, A., Lobaugh, N. J., Feinstein, A., Levine, B., Scott, C. J. M., Levy-Cooperman, N., Gao, F. Q., & Black, S. E. (2011). Lesion Explorer: A comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. *Neuroimage, 54*(2), 963–973. https://doi.org/10.1016/j.neuroimage.2010.09.013

Ramirez, J., Holmes, Berezuk, C., Kwan, D., Tan, B., Beaton, D., Scott, C. J. M., Ozzoude, M., Gao, F., Yu., D., Swardfager, W., Lawrence-Dewar, J., Hassan, A., Dowlatshahi, D., Mandziza, J. L., Sahlas, D. J., Saposnik, G. Boulpus, M. I, Murray, B. J., Symons, S., Bartha, R., Black, S. E., Swartz, R. H., ONDRI investigators, & Lim, A. (2021). MRI-visible perivascular space volumes, sleep duration and daytime dysfunction in adults with cerebrovascular disease. *Sleep Medicine, 83,* 83-88. https://doi.org/10.1016/j.sleep.2021.03.043

Ramirez, J., Holmes, M. F., Scott, C. J., Ozzoude, M., Adamo, S., Szilagyi, G. M., Goubran, M., Gao, F., Arnott, S. R., Lawrence-Dewar, J. M., Beaton, D., Strother, S. C., Munoz, D. P., Masellis, M., Swartz, R. H., Bartha, R., Symons, S., Black, S. E. and the ONDRI Investigators (2020). Ontario Neurodegenerative Disease Research Initiative (ONDRI): Structural MRI methods and outcome measures. *Frontiers in Neurology*, *11*, A847. https://doi.org/10.3389/fneur.2020.00847

Ramirez, J., McNeely, A. A., Scott, C. J. M., Masellis, M., & Black, S. E. (2015). White matter hyperintensity burden in elderly cohort studies. The Sunnybrook Dementia Study,

Alzheimer Disease Neuroimaging Initiative, and Three-City Study. *Alzheimers Dementia, 12*(2), 203-210. https://doi.org/10.1016/j.jalz.2015.06.1886

Ramirez, J., Scott, C. J., McNeely, A. A., Berezuk, C., Gao, F., Szilagyi, G. M., & Black, S. E. (2014). Lesion Explorer: A video-guided, standardized protocol for accurate and reliable MRI-derived volumetrics in Alzheimer's disease and normal elderly. *Journal of Visual Experiments*, 86, e50887. https://doi.org/10.3791/50887

Ramirez-Ruiz, B., Junque, C., Marti, M. J., Valldeoriola, F., & Tolosa, E. (2007). Cognitive changes in Parkinson's disease patients with visual hallucinations. *Dementia and Geriatric Cognitive Disorders*, *23*(5), 281-288. http://doi.org/10.1159/000100850

Ramos, A. R., Dong, C., Rundek, T., Elkind, M. S., Boden-Albala, B., Sacco, R. L., & Wright, C. B. (2014). Sleep duration is associated with white matter hyperintensity volume in older adults: The Northern Manhattan Study. *Journal of Sleep Research*, *23*(5), 524-530. https://doi.org/10.1111/jsr.12177

Ramos, A. R., Dong, C., Elkind, M. S., Boden-Albala, B., Sacco, R. L., Rundek, T., & Wright, C. B. (2013). Association between sleep duration and the mini-mental score: the Northern Manhattan study. *Journal of Clinical Sleep Medicine*, *9*(7), 669–673. https://doi.org/10.5664/jcsm.2834

Reitan, R.M. & Wolfson, D. (1985). *The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation.* Tucson, AZ: Neuropsychology Press.

Ritchie K. (2004). Mild cognitive impairment: An epidemiological perspective. *Dialogues in Clinical Neuroscience*, *6*(4), 401–408. https://doi.org/10.31887/DCNS.2004.6.4/kritchie

Rothman, S. M., & Mattson, M. P. (2012). Sleep disturbances in Alzheimer's and Parkinson's diseases. *Neuromolecular Medicine*, *14*(3), 194-204. https://doi.org/10.1007/s12017-012-8181-2

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., & Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573-583. doi:10.1016/S0006-3223(03)01866-8

Salthouse, T. A. (2004). What and when of cognitive aging. *Current Directions in Psychological Science*, *13*(4), 140-144.

Sanchez-Espinosa, M. P., Atienza, M., & Cantero, J. L. (2014). Sleep deficits in mild cognitive impairment are related to increased levels of plasma amyloid-β and cortical thinning. *NeuroImage*, *98*, 395–404. https://doi.org/10.1016/j.neuroimage.2014.05.027

Sahebzadeh, N., Baf, M. M. F., & Homam, S. M. (2016). Sleep quality and cognitive impairment in patients with Parkinson's disease in Iran. *Turkish Journal of Neurology*, *22*(3). http://doi.org/10.4274/tnd.84755

Salzmann, A., Chaturvedi, N., & Garfield, V. (2020). The relationship between cognitive function, Alzheimer's disease and sleep duration: A Mendelian randomisation study. *International Journal of Epidemiology*. http://doi.org/10.1101/2020.09.08.20190611

Satizabal, C. L., Zhu, Y. C., Dufouil, C., & Tzourio, C. (2013). Inflammatory proteins and the severity of dilated Virchow-Robin Spaces in the elderly. *Journal of Alzheimer's Disease : JAD*, *33*(2), 323–328. https://doi.org/10.3233/JAD-2012-120874

Scarmeas, N., & Stern, Y. (2004). Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. *Current Neurology and Neuroscience Reports*, *4*(5), 374–380. https://doi.org/10.1007/s11910-004-0084-7

Schoenberg, M. R., & Scott, J. G. (2011). *The little black book of neuropsychology*. New York: Springer.

Schmidt, M. (1996). *Rey Auditory Verbal Learning Test: A handbook.* Los Angeles: Western Psychological Association.

Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science*, *10*(1), 97-137. https://doi.org/10.1177/1745691614556680.

Sepehrband, F., Barisano, G., Sheikh-Bahaei, N., Choupan, J., Cabeen, R. P., Lynch, K. M., Crawford, M. S., Lan, H., Mack, W. J., Chui, H. C., Ringman, J. M., Toga, A. W., & Alzheimer's Disease Neuroimaging Initiative (2021). Volumetric distribution of perivascular space in relation to mild cognitive impairment. *Neurobiology of Aging*, *99*, 28–43. https://doi.org/10.1016/j.neurobiolaging.2020.12.010

Shahid, M., Kim, J., Leaver, K., Hendershott, T., Zhu, D., Cholerton, B., Henderson, V. W., Tian, L., & Poston, K. L. (2019). An increased rate of longitudinal cognitive decline is observed in Parkinson's disease patients with low CSF Aß42 and an APOE ε4 allele. *Neurobiology of Disease*, *127*, 278-286. https://doi.org/10.1016/j.nbd.2019.02.023.

Shokri-Kojori, E., Wang, G. J., Wiers, C. E., Demiral, S. B., Guo, M., Kim, S. W., Lindgren, E., Ramirez, V., Zehra, A., Freeman, C., Miller, G., Manza, P., Srivastava, T., De Santi, S., Tomasi, D., Benveniste, H., & Volkow, N. D. (2018). β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proceedings of the National Academy of Sciences*, *115*(17), 4483-4488. https://doi.org/10.1073/pnas.1721694115

Shen, T., Yue, Y., Zhao, S., Xie, J., Chen, Y., Tian, J., Lv, W., Lo, C-Y. Z., Hsu, Y., Zhang, B. & Lai, H. Y. (2021). The role of brain perivascular space burden in early-stage Parkinson's disease. *NPJ Parkinson's Disease*, *7*(1), 1-9. https://doi.org/10.1038/s41531-021-00155-0

Shibata, K., Sugiura, M., Nishimura, Y., & Sakura, H. (2019). The effect of small vessel disease on motor and cognitive function in Parkinson's disease. *Clinical Neurology and Neurosurgery*, *182*, 58-62. https://doi.org/j.clineuro.2019.04.029

Shin, N. Y., Park, Y. W., Yoo, S. W., Yoo, J. Y., Choi, Y., Jang, J., Ahn, K. J., Kim, B. S. & Kim, J. S. (2021). Adverse effects of hypertension, supine hypertension, and perivascular space on cognition and motor function in PD. *NPJ Parkinson's Disease*, *7*(1), 1-7. https://doi.org/10.1038/s41531-021-00214-6

Si, X. L., Gu, L. Y., Song, Z., Zhou, C., Fang, Y., Jin, C. Y., Wu, J. J, Gao, T., Guo, T., Guan, X. J., Xu, X. J., Yin, X. Z., Yan, Y. P. Zhang, M. M. & Pu, J. L. (2020). Different perivascular space burdens in idiopathic rapid eye movement sleep behavior disorder and Parkinson's disease. *Frontiers in Aging Neuroscience*, *12*, e580853. https://doi.org/10.3389/fnagi.2020.580853

Sindi, S., Kåreholt, I., Johansson, L., Skoog, J., Sjöberg, L., Wang, H. X., Johansson, B., Fratiglioni, L., Soininen, H., Solomon, A., Skoog, I., & Kivipelto, M. (2018). Sleep

disturbances and dementia risk: A multicenter study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *14*(10), 1235–1242. https://doi.org/10.1016/j.jalz.2018.05.012

Smeijer, D., Ikram, M. K., & Hilal, S. (2019). Enlarged perivascular spaces and dementia: A systematic review. *Journal of Alzheimer's Disease*, *72*(1), 247-256. https://doi.org/10.3233/JAD-190527

Sobreira, E. S., Sobreira-Neto, M. A., Pena-Pereira, M. A., Chagas, M. H., Fernandes, R. M., Eckeli, A. L., & Tumas, V. (2019). Global cognitive performance is associated with sleep efficiency measured by polysomnography in patients with Parkinson's disease. *Psychiatry and Clinical Neurosciences*, *73*(5), 248-253. https://doi.org/10.1111/pcn.12819

Suh, S. W., Han, J. W., Lee, J. R., Byun, S., Kwon, S. J., Oh, S. H., Lee, K. H., Han, G., Hong, J. W., Kwak, K. P., Kim, B. J., Kim, S. G., Kim, J. L., Kim, T. H., Ryu, S. H., Moon, S. W., Park, J. H., Seo, J., Youn, J. C., Lee, D. Y., … Kim, K. W. (2018). Sleep and cognitive decline: A prospective nondemented elderly cohort study. *Annals of Neurology*, *83*(3), 472–482. https://doi.org/10.1002/ana.25166

Sundaram, S., Hughes, R. L., Peterson, E., Müller-Oehring, E. M., Brontë-Stewart, H. M., Poston, K. L., Faerman, A., Bhowmick, C. & Schulte, T. (2019). Establishing a framework for neuropathological correlates and glymphatic system functioning in Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, *103*, 305-315. https://doi.org/10.1016/j.neubiorev.2019.05.016

Sunderland, K. M. Beaton, D. Arnott, S. R., Kleinstiver, P., Kwan, D., Lawrence-Dewar, J. M. , Ramirez, J. , Tan, B., Bartha, R., Black, S. E. , Borrie, M., Brien, D., Casaubon, L. K., Coe, B. C., Cornish, B., Dilliott, A. A., Dowlatshahi, D., Finger, E., Fischer, C., Frank, A.

Fraser, J., Freedman, M., Greenberg, B., Grimes, D. A., Hassan, A., Hatch, W., Hegele, R.A., Hudson, C., Jog, M., … Binns, M. A., on behalf of ONDRI Investigators (2020). The Ontario Neurodegenerative Disease Research Initiative. *MedRxiv*. https://doi.org/10.1101/2020.07.30.20165456

Sunderland, K. M., Beaton, D., Fraser, J., Kwan, D., McLaughlin, P. M., Montero-Odasso, M., Peltsch, A. J., Pieruccini-Faria, F., Sahlas, D. J., Swartz, R. H. & Binns, M. A. (2019). The utility of multivariate outlier detection techniques for data quality evaluation in large studies: An application within the ONDRI project. *BMC Medical Research Methodology, 19*(102). https://doi.org/10.1186/s12874-019-0737-5

Stavitsky, K., Neargarder, S., Bogdanova, Y., McNamara, P., & Cronin-Golomb, A. (2012). The impact of sleep quality on cognitive functioning in Parkinson's disease. *Journal of the International Neuropsychological Society: JINS*, *18*(1), 108. https://doi.org/10.1017/S1355617711001482

St Louis, E. K., Boeve, A. R., & Boeve, B. F. (2017). REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Movement Disorders*, *32*(5), 645–658. https://doi.org/10.1002/mds.27018

Stevens, J. P. (2012). *Applied multivariate statistics for the social sciences*. New York: Routledge.

Svenningsson, P., Westman, E., Ballard, C., & Aarsland, D. (2012). Cognitive impairment in patients with Parkinson's disease: Diagnosis, biomarkers, and treatment. *The Lancet Neurology*, *11*(8), 697-707. https://doi.org/10.1016/S1474-4422(12)70152-7

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain 3-dimensional proportional grid system: An approach to cerebral imaging*. Stuttgart: Thieme Medical Publishers.

Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Zetterberg, H., Wisniewski, T., & De Leon, M. J. (2015). Clearance systems in the brain— Implications for Alzheimer disease. *Nature Reviews Neurology*, *11*(8), 457. https://doi.org/10.1038/nrneurol.2015.119

Torres, E. R., Strack, E. F., Fernandez, C. E., Tumey, T. A., & Hitchcock, M. E. (2015). Physical activity and white matter hyperintensities: A systematic review of quantitative studies. *Preventive Medicine Reports*, *2*, 319-325. https://doi.org/10.1016/j.pmedr.2015.04.013

Tukey, J. W. (1977). *Exploratory data analysis*. Reading, MA: Addison-Wesley.

Uiterwijk, R., van Oostenbrugge, R. J., Huijts, M., De Leeuw, P. W., Kroon, A. A., & Staals, J. (2016). Total cerebral small vessel disease MRI score is associated with cognitive decline in executive function in patients with hypertension. *Frontiers in Aging Neuroscience*, *8*, e301. https://doi.org/10.3389/fnagi.2016.00301

Vaitkevicius, P. V., Fleg, J. L., Engel, J. H., O'Connor, F. C., Wright, J. G., Yin, F. C., & Lakatta, L. E. (1993). Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation, 88*(4 Pt 1)*,* 1456-1462. https://doi.org/10.1161/01.cir.88.4.1456.

Valdés Hernández, M., Ballerini, L., Glatz, A., Muñoz Maniega, S., Gow, A. J., Bastin, M. E., Starr, J. M., Deary, I. J., & Wardlaw, J. M. (2020). Perivascular spaces in the centrum semiovale at the beginning of the 8th decade of life: Effect on cognition and associations

with mineral deposition. *Brain Imaging and Behavior*, *14*(5), 1865–1875. https://doi.org/10.1007/s11682-019-00128-1

Valenzuela, P. L., Castillo-García, A., Morales, J. S., de la Villa, P., Hampel, H., Emanuele, E., Lista, S., & Lucia, A. (2020). Exercise benefits on Alzheimer's disease: State-of-the-science. *Ageing Research Reviews*, *62*, 101-108. https://doi-org.ezproxy.library.yorku.ca/10.1016/j.arr.2020.101108

Vanable, P. A., Aikens, J. E., Tadimeti, L., Caruana-Montaldo, B., & Mendelson, W. B. (2000). Sleep latency and duration estimates among sleep disorder patients: Variability as a function of sleep disorder diagnosis, sleep history, and psychological characteristics. *Sleep*, *23*(1), 71-79. https://doi.org/10.1093/sleep/23.1.1d

Van Cauter, E., Leproult, R., & Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *Journal of the American Medical Association*, *284*(7), 861-868. https://doi.org/10.1001/jama.284.7.861

van Hooren, S. A., Valentijn, A. M., Bosma, H., Ponds, R. W., van Boxtel, M. P., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64-81: A cohort study into the effects of age, sex, and education. *Neuropsychology, Development, and Cognition*, *14*(1), 40–54. https://doi.org/10.1080/138255890969483

Van Veluw, S. J., Biessels, G. J., Bouvy, W. H., Spliet, W. G., Zwanenburg, J. J., Luijten, P. R., Macklin, E. A., Rozemuller, A. J. M., Gurol, M. E., Greenburg, S. M., Viswanathan, A., & Martinez-Ramirez, S. (2016). Cerebral amyloid angiopathy severity is linked to dilation of juxtacortical perivascular spaces. *Journal of Cerebral Blood Flow & Metabolism*, *36*(3), 576-580. https://doi.org/10.1177/0271678X15620434

Veselý, B., Antonini, A. & Rektor, I. (2016). The contribution of white matter lesions to Parkinson's disease motor and gait symptoms: A critical review of the literature. *Neurology and Preclinical Neurological Studies, 123***,** 241–250. https://doi.org/10.1007/s00702-015-1470-9

Vitiello, M. V., & Borson, S. (2001). Sleep disturbances in patients with Alzheimer's disease. *CNS Drugs*, *15*(10), 777-796. https://doi.org/10.2165/00023210-200115100-00004

Vitiello, M. V., Prinz, P. N., Williams, D. E., Frommlet, M. S., & Ries, R. K. (1990). Sleep disturbances in patients with mild-stage Alzheimer's disease. *Journal of Gerontology*, *45*(4), M131-M138. https://doi.org/10.1093/geronj/45.4.M131

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T., Deane, R., & Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, *342*(6156), 373–377. https://doi.org/10.1126/science.1241224

Xu, W., Tan, L., Su, B. J., Yu, H., Bi, Y. L., Yue, X. F., Dong, Q., & Yu, J. T. (2020). Sleep characteristics and cerebrospinal fluid biomarkers of Alzheimer's disease pathology in cognitively intact older adults: The CABLE study. *Alzheimer's & Dementia*, *16*(8), 1146-1152. https://doi.org/10.1002/alz.12117

Xu, Z., Xiao, N., Chen, Y., Huang, H., Marshall, C., Gao, J., Cai, Z., Wu, T., Hu, G. & Xiao, M. (2015). Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Aβ accumulation and memory deficits. *Molecular Neurodegeneration*, *10*(1), 1-16. https://doi.org/10.1186/s13024-015-0056-1

Walker, M. P. (2009). The role of slow wave sleep in memory processing. *Journal of Clinical Sleep Medicine*, *5*(2 Suppl), S20.

Wallace, E. R., Segerstrom, S. C., van Horne, C. G., Schmitt, F. A., & Koehl, L. M. (2021). Meta-analysis of cognition in Parkinson's disease mild cognitive impairment and dementia progression. *Neuropsychology Review*, 32(1), 149-160. https://doi.org/10.1007/s11065-021-09502-7

Wang, M. L., Yu, M. M., Wei, X. E., Li, W. B., Li, Y. H., & Alzheimer's Disease Neuroimaging Initiative. (2021). Association of enlarged perivascular spaces with Aβ and tau deposition in cognitively normal older population. *Neurobiology of Aging*, *100*, 32-38. https://doi.org/10.1016/j.neurobiolaging.2020.12.014

Wardlaw, J. M., Benveniste, H., Nedergaard, M., Zlokovic, B. V., Mestre, H., Lee, H., Doubal, F. N., Brown, R., Ramirez, J., MacIntosh, B. J., Tannenbaum, A., Ballerini, L., Rungta, R. L., Boido, D., Sweeney, M., Montagne, A., Charpak, S., Joutel, A., Smith, K. J., Black, S. E., … colleagues from the Foundation Leducq Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel Disease (2020). Perivascular spaces in the brain: Anatomy, physiology and pathology. *Nature Reviews: Neurology*, *16*(3), 137–153. https://doi.org/10.1038/s41582-020-0312-z

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R. I., O'Brien, J. T., Barkhof, F., Benavente, O. R., Black, S. E., Brayne, C., Breteler, M., Chabriat, H., Decarli, C., de Leeuw, F. E., Doubal, F., Duering, M., Fox, N. C., Greenberg, S., … STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1) (2013). Neuroimaging standards for research into small vessel disease and its

contribution to ageing and neurodegeneration. *The Lancet: Neurology*, *12*(8), 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8

Warrington, E. K. & James, M. (1991). *The Visual Object and Space Perception Battery.* Bury St. Edmunds, Suffolk: Thames Valley Test Company.

Watson, G. S., & Leverenz, J. B. (2010). Profile of cognitive impairment in Parkinson's disease. *Brain Pathology, 20*(3), 640–645. https://doi.org/10.1111/j.1750-3639.2010.00373.x

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence: Second Edition (WASI-II).* San Antonio, TX: Pearson.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a006171. https://doi.org/10.1101/cshperspect.a006171

Westwood, A. J., Beiser, A., Jain, N., Himali, J. J., DeCarli, C., Auerbach, S. H., Pase, M. P., & Seshadri, S. (2017). Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. *Neurology*, *88*(12), 1172–1179. https://doi.org/10.1212/WNL.0000000000003732

Williams-Gray, C. H., Evans, J. R., Goris, A., Foltynie, T., Ban, M., Robbins, T. W., Brayne, C., Kolachana, B. S., Weinberger, D. R., Sawcer, S. J., & Barker, R. A. (2009). The distinct cognitive syndromes of Parkinson's disease: 5-year follow-up of the CamPaIGN cohort. *Brain*, *132*(11), 2958-2969. https://doi.org/10.1093/brain/awp245

Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., & Barker, R. A. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an

incident population-based cohort. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(11), 1258-1264. https://doi.org/10.1136/jnnp-2013-305277

Wolk, D. A., Price, J. C., Saxton, J. A., Snitz, B. E., James, J. A., Lopez, O. L., Aizenstein, H. J., Cohen, A. D., Weissfeld, L. A., Mathis, C. A., Klunk, W. E., & DeKosky, S. T. (2009). Amyloid imaging in mild cognitive impairment subtypes. *Annals of Neurology*, *65*(5), 557-568. https://doi.org/10.1002/ana.21598

Wuerfel, J., Haertle, M., Waiczies, H., Tysiak, E., Bechmann, I., Wernecke, K. D., Zipp, F., & Paul, F. (2008). Perivascular spaces--MRI marker of inflammatory activity in the brain? *Brain: A Journal of Neurology*, *131*(Pt 9), 2332–2340. https://doi.org/10.1093/brain/awn171

Wunderlin, M., Züst, M. A., Fehér, K. D., Klöppel, S., & Nissen, C. (2020). The role of slow wave sleep in the development of dementia and its potential for preventative interventions. *Psychiatry Research: Neuroimaging*, *306*, e111178. https://doi.org/10.1016/j.pscychresns.2020.111178

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T. Deane, R., & Nedergaard, M. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, *342*(6156), 373-377. https://doi.org/10.1126/science.1241224

Yaffe, K., Falvey, C. M., & Hoang, T. (2014). Connections between sleep and cognition in older adults. *The Lancet Neurology, 13*(10), 1017-1028. https://doi.org/10.1016/S1474-4422(14)70172-3

Zaidi, K. B., Rich, J. B., Sunderland, K. M., Binns, M. A., Truong, L., McLaughlin, P. M., Pugh, B., Kwan D., Beaton, D., Levine, B., Sahlas, D. J., Dowlatshahi, D., Hassan, A.,

Mandzia, J., Troyer, A. K., & Swartz, R. H. (2020). Methods for improving screening for vascular cognitive impairment using the Montreal Cognitive Assessment. *The Canadian Journal of Neurological Sciences*, *47*(6), 756-763.. https://doi.org/10.1017/cjn.2020.121

Zhai, L., Zhang, H., & Zhang, D. (2015). Sleep duration and depression among adults: A meta-analysis of prospective studies. *Depression and Anxiety*, *32*(9), 664–670. https://doi.org/10.1002/da.22386

Zhu, Y.C., Dufouil, C., Soumare, A., Mazoyer, B., Hugues, C., Tzourio, C. (2010). High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. *Journal of Alzheimer's Disease, 22*, 663–72. https://doi.org/10.3233/JAD-2010-100378

Zhu, Y.C., Dufouil, C., Soumare, A., Mazoyer, B., Hugues, C., Tzourio, C. (2010). High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. *Journal of Alzheimer's Disease, 22*, 663–72. https://doi.org/10.3233/JAD-2010-100378

Appendices

Appendix A: MRI Parameters

STUDY	***OBI - ONDRI***		
SEQUENCE	***3DT1***		
Protocol			
Vendor	GE	Philips	Siemens
Field Strength	3T	3T	3T
Model	Discovery	Achieva	Skyra/Trio/Prisma
Version	22	3.2.3	
Sequence Name	3D FAST SPGR	3D TFE	3D MP-RAGE
Imaging Options	IrP- Asset	Fast (Sense)	iPat
Pulse Timing			
TE (ms)	Min full	Min (3.3)	2.98
TR (ms)	Min	Min (7.3)	2300
Flip Angle (°)	11	9	9
TI (ms)	400	945	900
Scan Range			
FOV (in-plane) (mm)	256 x 256	256 x 248	256 x 256
Slice Thickness (mm)	1	1	1
Gap Between Slices (mm)	0	0	0
No. Slices	176	176	176
Acquisition			
Orientation	Sagittal	Sagittal	Sagittal
Matrix Size	256 x 256	256 x 248	256 x 256
Voxel Size [L/R x A/P x I/S]	1 x 1 x 1	1 x 1 x 1	1 x 1 x 1
NEX	1	1	1
Acceleration Factor (Parallel factor*)	2	2	2
Other			
Fat Suppression	None	None	None
Bandwidth	31.25 (kHz)	228 (Hz/px)	240 (Hz/px)
Echo Train Length	-	-	-
Coil Type			
Head	X	X	X
Channel	8-12 (HNS)	8	12(Trio) 20 (Prisma)
Time			
PRESCAN TIME+	00:30	00:30	00:30
SCAN TIME	04:52	06:17	05:21
TOTAL TIME (MIN)	05:22	06:47	05:51

STUDY	***OBI - ONDRI***		
SEQUENCE	***PD/T2***		
Protocol			
Vendor	GE	Philips	Siemens
Field Strength	3T	3T	3T
Model	Discovery	Achieva	Skyra/Trio/Prisma
Version	22	3.2.3	
Sequence Name	FSE-XL	TSE	TSE
Imaging Options	EDR, Asset	Fast (Sense)	iPat
Pulse Timing			
TE (ms) (2 echo scan)	Min full/86	13/100	10/93
TR (ms)	3000	3000	3000
Flip Angle (°)	125	90	165
TI (ms)	-	-	-
Scan Range			
FOV (in-plane) (mm)	240 x 240	240 x 240	240 x 240
Phase FOV	75%	75%	81%
Slice Thickness (mm)	3	3	3
Gap Between Slices (mm)	0	0	0
No. Slices	48	48	48
Acquisition			
Orientation	Oblique Axial	Oblique Axial	Oblique Axial
Matrix Size	256 x 256	256 x 254	256 x 256
Voxel Size [L/R x A/P x I/S]	0.94 x 0.94 x 3	0.94x 0.94 x 3	0.94 x 0.94 x 3
NEX	1	1	1
Acceleration Factor (Parallel factor*)	2	2	2
Other			
Fat Suppression	Yes (FAT-SAT)	Yes	Yes
Bandwidth	20 (kHz)	222 (Hz/px)	181 (Hz/px)
Echo Train Length	12	12	14
Coil Type			
Head	X	X	X
Channel	8-12 (HNS)	8	12(Trio) 20 (Prisma)
Time			
PRESCAN TIME+	00:30	00:30	00:30
SCAN TIME	02:43	04:12	03:11
TOTAL TIME (MIN)	03:13	04:42	03:41

STUDY	***OBI - ONDRI***		
SEQUENCE	***2D FLAIR***		
Protocol			
Vendor	GE	Philips	Siemens
Field Strength	3T	3T	3T
Model	Discovery	Achieva	Skyra/Trio/Prisma
Version	22	3.2.3	
Sequence Name	2D T2FLAIR	2D IR TSE	2D IR TDF
Imaging Options	EDR, IR	Fast (Sense)	iPat
Pulse Timing			
TE (ms)	140	125	120
TR (ms)	9000	9000	9000
Flip Angle (°)	125	90 (150 refocus)	165
TI (ms)	2250	2500	2500
Scan Range			
FOV (in-plane) (mm)	240 x 240	240 x 240	240 x 240
Slice Thickness (mm)	3	3	3
Gap Between Slices (mm)	0	0	0
No. Slices	48	48	48
Acquisition			
Orientation	Oblique Axial	Oblique Axial	Oblique Axial
Matrix Size	256 x 256	256 x 242	256 x 256
Voxel Size [L/R x A/P x I/S]	0.94 x 0.94 x 3	0.94 x 0.99 x 3	0.94 x 0.94 x 3
NEX	1	1	1
Acceleration Factor (Parallel factor*)	No Asset	2 (SENSE)	2
Other			
Fat Suppression	None	None	None
Bandwidth	25 (kHz)	242 (Hz/px)	220 (Hz/px)
Echo Train Length		19	19
Coil Type			
Head	X	X	X
Channel	8-12 (HNS)	8	12(Trio) 20 (Prisma)
Time			
PRESCAN TIME+	00:30	00:30	00:30
SCAN TIME	04:32	03:45	02:44
TOTAL TIME (MIN)	05:02	04:15	03:14

STUDY	***OBI - ONDRI***		
SEQUENCE	***T2-star***		
Protocol			
Vendor	GE	Philips	Siemens
Field Strength	3T	3T	3T
Model	Discovery	Achieva	Skyra/Trio/Prisma
Version	22	3.2.3	
Sequence Name	GRE	FFE	GRE
Imaging Options	-	Sense	iPat
Pulse Timing			
TE (ms)	20	21	20
TR (ms)	650	650	650
Flip Angle (°)	20	20	20
TI (ms)	-	-	-
Scan Range			
FOV (in-plane) (mm)	240 x 240	240 x 240	240 x 240
Phase FOV	75%	75%	75%
Slice Thickness (mm)	3	3	3
Gap Between Slices (mm)	0	0	0
No. Slices	48	48	48
Acquisition			
Orientation	Oblique Axial	Oblique Axial	Oblique Axial
Matrix Size	256 x 256	256 x 256	256 x 256
Voxel Size [L/R x A/P x I/S]	0.94 x 0.94 x 3	0.94 x 0.94 x 3	0.94 x 0.94 x 3
NEX	1	1	1
Acceleration Factor (Parallel factor*)	No Asset	2 (SENSE)	2
Other			
Fat Suppression	None	None	None
Bandwidth	19.23 (kHz)	217 (Hz/px)	200 (Hz/px)
Echo Train Length	1	1	1
CV act_te (GE only)	20000		
Coil Type			
Head	X	X	X
Channel	8-12 (HNS)	8	12(Trio) 20 (Prisma)
Time			
PRESCAN TIME+	00:30	00:30	00:30
SCAN TIME	02:15	02:52	03:04
TOTAL TIME (MIN)			

Note. OBI: Ontario Brain Institute, ONDRI: Ontario Neurodegenerative Disease Research Initiative, 3D: three-dimensional, T1: longitudinal relaxation time, T2: transverse relaxation time, PD: proton density, FAST SPGR: gradient recalled echo sequence, TE: time to echo, TR: repetition time, TI: inversion time, FOV: field of view, NEX: number of excitations, HNS: head, neck, spine

Appendix B: Basal Ganglia Perivascular Space Analysis in Alzheimer's disease

Basal ganglia perivascular spaces volumes did not significantly correlate with sleep duration, $r(124) = -.01$, $p = .91$, even when covariates related to basal ganglia perivascular space volume were included in the model, $r_p(115) = -.04$, $p = .64$.

Memory was not related to basal ganglia perivascular space volumes, $r(123) = .056$, $p = .27$. Sleep duration and enlarged basal ganglia perivascular space volumes accounted for 4.6% of memory performance variability after controlling for covariates, $F(2,120) = 3.54$, $p = .03$. Sleep duration, standardized $\beta = -.19$, $p = .02$, but not basal ganglia perivascular space volumes, standardized $\beta = .09$, $p = .25$, made a significant contribution to the model. Moderation analysis revealed that basal ganglia perivascular space volumes did not moderate the relationship between sleep duration and memory, $F(1,117) = .014$, $r^2 = .00$, $p = .91$.

Executive function performance was not significantly related to basal ganglia perivascular space volumes, $r(124) = -.031$, $p = .37$. Sleep duration and basal ganglia perivascular space volumes accounted for 5.9% of executive function performance variability after controlling for covariates, $F(2,120) = 4.49$, $p = .01$. Sleep duration, standardized $\beta = -.25$, $p < .01$, but not basal ganglia perivascular space volumes, standardized $\beta < .01$, $p = .99$, made a significant contribution to the model. Moderation analysis revealed that basal ganglia perivascular space volumes did not moderate the relationship between sleep duration and executive function, $F(1,119) = .024$, $r^2 < .01$, $p = .88$.

There was no significant effect of cognitive classification on basal ganglia perivascular space volumes, $t(118) = .57$, $p = .57$, $d = .11$.

Appendix C: Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night?

   _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   _____

   During the past month, what time have you usually gotten up in the morning?

   _____

3. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or				

engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				
	No bed Partner or roommate	Partner/ roomate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Scoring the PSQI

The order of the PSQI items has been modified from the original order in order to fit the first 9 items (which are the only items that contribute to the total score) on a single page. Item 10, which is the second page of the scale, does not contribute to the PSQI score.

In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality.

Component 1: Subjective sleep quality—question 9

Response to Q9	Component 1 score
Very good	0
Fairly good	1
Fairly bad	2
Very bad	3

Component 1 Score: _____

Component 2: Sleep latency—questions 2 and 5a

Response to Q2	Component 2/Q2 subscore
≤ 15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

Response to Q5a	Component 2/Q5a subscore
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Sum of Q2 and Q5a subscores	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score: _____

Component 3: Sleep duration—question 4

Response to Q4	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score: _____

Component 4: Sleep efficiency—questions 1, 3, and 4

Sleep efficiency = (# hours slept/# hours inbed) X 100%

hours slept—question 4

hours in bed—calculated from responses to questions 1 and 3

Sleep efficiency	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score: _____

Component 5: Sleep disturbance—questions 5b-5j

Questions 5b to 5j should be scored as follows:

Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Sum of 5b to 5j scores	Component 5 score
0	0
1-9	1
10-18	2
19-27	3

Component 5 score: _____

Component 6: Use of sleep medication—question 6

Response to Q6.	Component 6 score
Not during past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score: _____

Component 7: Daytime dysfunction questions 7 and 8

Response to Q7 - Component 7/Q7 subscore	Not during past month
	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Response to Q8 - Component 7/Q8 subscore	No problem at all
0	
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Sum of Q7 and Q8 subscores - Component 7 score	
0	0
1-2	1
3-4	2
5-6	3

Component 7 score: _____

Global PSQI Score: Sum of seven component scores:____