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Cerebrospinal Fluid Biomarkers Not Associated with Neurologic Compromise Among Mild Cognitively Impaired Reverters with Parkinson's Disease

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CEREBROSPINAL FLUID BIOMARKERS NOT ASSOCIATED WITH NEUROLOGIC COMPROMISE AMONG MILD COGNITIVELY IMPAIRED REVERTERS WITH PARKINSON'S DISEASE

A Thesis

Presented to the

Faculty of

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San Bernardino

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

in

Psychological Science:

Behavioral and Cognitive Neuroscience

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disease characterized by motor (e.g. tremors) and non-motor symptoms (e.g. cognitive impairment). PD patients' change in cognitive functioning can be observed using the following classifications: cognitively intact, mild cognitive impairment (MCI), or dementia (PDD). MCI has many subtypes, one of which is MCI reversion which is defined as those with MCI at one time point reverting to cognitively intact later. While there is limited research into the utility of MCI reversion and its relationship with cerebrospinal fluid (CSF) biomarkers in PD, this study will begin to elucidate this relationship. To this end, data from 393 de novo PD patients was obtained from the Parkinson's Progression Markers Initiative (PPMI) for the first 3 years. MCI was determined if the patient's scores fell 2 standard deviations below 2 or more neuropsychological assessments. CSF biomarker samples included beta-amyloid, total tau, phosphorylated tau, and alpha-synuclein, and were analyzed using an enzyme-linked immunosorbent assay (ELISA). Multilevel modeling was used to examine the association between CSF biomarker ratios and cognitive functioning status (cognitively intact, MCI converters, MCI stable, and MCI reverters) longitudinally. MCI reverters did not differ significantly from those who were cognitively intact. There was a main effect of MCI converters in the tau ratio compared to CI patients and there was a group-by-year interaction with yearly increases in asyn in the MCI stable group. Findings support MCI reverters do not differ from cognitively intact individuals on biomarkers associated with cognitive decline in PD. These findings suggest MCI reversion may not be clinically meaningful; however, between alternative approaches and confounds, more research is needed.

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DEDICATION

To my mother. A person who was with me on this journey even if in spirit.

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CHAPTER ONE

INTRODUCTION

Neurodegenerative diseases are broadly classified by neuronal loss due to protein aggregation in selectively targeted neuronal populations (Bugger & Dickson, 2017). Parkinson's Disease (PD) is classified as a neurodegenerative disease with widespread impact on the body (Stoker & Greenland, 2018 & Przedborski, 2008). PD is the second most common neurodegenerative disease next to Alzheimer's Disease (AD) affecting older individuals (Armstrong & Okun, 2020; Goldman et al., 2015 & Stoker & Greenland, 2018).

Similarly, to patients with AD, PD is not considered fatal by nature (Bäckström et al., 2018; Brunnström & Enguland, 2009; Zanetti et al., 2009; Scorza et al., 2022). Mortality rates in PD patients are typically associated with respiratory illnesses, cardiovascular complications, suicide, falls due to challenges with movement, possible infections, and more (Brunnström & Enguland, 2009; Scorza et al., 2022; Nazem et al., 2008). Sudden unexpected death in PD patients is higher than in non-diseased patients with no other apparent explanation (Scorza et al., 2022). Even with sudden unexpected death accounted for, PD patients typically live more than 10 years post-diagnosis with the risk of death increasing by 3.5 years (Scorza et al., 2022).

Prevalence

The prevalence of PD among individuals aged between 65-69 years old is about 0.5-1%, increasing between 1-3% among individuals who are 80 years or older (Stoker & Greenland, 2018). Many different etiologies could potentially increase the risk of PD in older individuals. A meta-analysis found family history of PD was positively associated with a PD diagnosis (Noyce et al., 2012). However, few studies have linked the sole cause of PD to genetic factors alone, suggesting multiple, compounding causes of PD (Klein & Westenberger, 2012). Various longitudinal studies revealed factors such as constipation, trauma, pesticide exposure, head injuries, diet, anxiety, or depression are associated with an increased risk of developing PD later in life (Noyce et al., 2012; Ascherio & Schwarzschild, 2016).

Protective Factors

Several protective environmental factors can reduce the risk of developing PD. For example, urate levels are typically increased by the body breaking down foods high in purines. High levels of urate are associated with a lower risk of developing PD, believed to be acting as a protectant against oxidative stress (Cipriani, Chen, & Schwarzschild, 2010). Various studies indicate that elevated serum urate levels are associated with a decreased risk of developing PD (Noyce et al., 2012; Ascherio & Schwarzschild, 2016). Other factors include caffeine consumption, nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol

consumption which may also act as a protective factor against developing PD (Noyce et al., 2012).

Symptomology

Motor Symptoms

Hallmark symptoms of PD are characterized by dysfunction in motor functions. Symptoms may include tremors, rigidity, bradykinesia, and sometimes postural instability (Armstrong & Okun, 2020; Goldman et al., 2015; Stoker & Greenland, 2018). As PD progresses, motor symptoms worsen and plateau, but this progression is described as non-linear and negatively exponential (Xia & Mao, 2012). With symptoms worsening over time, those with bradykinesia and rigidity have been associated to experience faster disease progression (Xia & Mao, 2012). While these motor symptoms are useful for diagnosing PD, nonmotor symptoms are not just becoming equally important for diagnosis but for early detection as well.

Nonmotor Symptoms

There is a growing understanding that nonmotor symptoms often precede the onset of motor symptoms (Weil et al., 2018; Stoker & Greenland, 2018 & Postuma et al., 2012). Many of these symptoms can include fatigue, rapid eye movement sleep disorders, depression, or cognitive dysfunction (Schrag et al., 2015; Postuma et al., 2012 & Stoker & Greenland, 2018). In many cases, these non-motor-related symptoms co-occur impacting cognitive functioning. Jones and

colleagues (2019) found depression precedes cognitive dysfunction among a cohort of PD patients. Mery and colleagues (2017) also found PD patients with sleep apnea experienced reduced cognitive functioning. Both of these studies further elucidate the widespread impact PD has on individuals. However, while motor and certain non-motor symptoms such as depression and fatigue correlate with cognitive impairment, the effect sizes tend to be in the small to moderate range and they do not fully explain the occurrence of cognitive impairment.

Cognitive Functioning

Cognitive dysfunction has been supported as a major clinical nonmotor symptom of PD, even among those who have been newly diagnosed (< 1 year of PD diagnosis; Riedel, et al., 2010). Cognition is considered multidimensional, comprised of one's visuospatial abilities, executive functioning, language processing, memory, and more. When cognitive dysfunction is believed to have onset, it is usually due to diminishing performance in any combination of these domains. Typically, early onset of PD, cognitive dysfunction will be mild before increasing decline as the disease progresses, making it critical for early detection of the onset of PD and implementation of interventions (Aarsland, et al., 2021; Riedel, et al., 2010). Cognitive dysfunction causes such impairment among patients diagnosed with PD, and mild cognitive impairment and dementia have been added as stages reflecting the patient's cognitive impairment status

(Aarsland, et al., 2021; Riedel, et al., 2010). The underpinnings of cognitive impairment may be a result of several neurobiological mechanisms of PD.

CHAPTER TWO

NEURAL MECHANISMS OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

The neurobiological processes underlying cognitive dysfunction in PD are complex. PD is neurodegenerative, thus over time the reduction of cortical and subcortical mass can be observed (Chung et al., 2019; Stoker & Greenland, 2018 & Przedborski, 2008). This reduction of brain mass is a result of the loss of dopaminergic neurons located in the substantia nigra pars compacta of the midbrain, making dopamine a key affected neurotransmitter in PD (Stoker & Greenland, 2018 & Przedborski, 2008). Loss of dopaminergic cell groups is most associated with the motor characteristics of PD such as tremors, bradykinesia, and/or rigidity. However, dopamine deletion can also be associated with cognitive impairment among PD patients and several proteins may contribute to this (Marino et al., 2020 & Stoker & Greenland, 2018).

For patients diagnosed with PD, dopamine neurotransmission is affected by various proteins. Three primary proteins in PD include t-tau (Total Tau), p-tau (phosphorylated tau), Aβ42 (beta-amyloid subtypes 1-42), and asyn (alpha-synuclein). Tau proteins (t-tau and p-tau/tauopathies) consist of various isoforms that contain microtubule-binding repeats that are responsible for microtubule stabilization (Teravskis et al., 2020 & Zhang et al., 2018). Overexpression of tau found in AD and PD has been linked to the process of hyperphosphorylation, which ultimately breaks the paperclip-like structure of tau proteins, inducing

aggregation at the postsynaptic and presynaptic terminals among dopaminergic neurons (Wu et al., 2013; Teravskis et al., 2020; Pîrşcoveanu et al., 2017; Cohen et al., 2011 & Galloway et al., 1989). This aggregation can lead to postsynaptic functional defects and neuronal death (Teravskis et al., 2020). Compacta and colleagues (2009) connected higher levels of cerebrospinal fluid (CSF) t-tau and p-tau with cognitive dysfunction in PD. Researchers utilized the mini-mental state examination (MMSE) as a measure of global cognition (low scores on MMSE suggest poor cognitive performance) and CSF via lumbar puncture. Results indicated that PDD (Parkinson's Disease with Dementia) patients had higher t-tau and p-tau than healthy controls, demonstrating that as cognitive impairment in PD progresses, so does tau aggregation. Similar results were shown by Bellemo and colleagues (2020) with higher CSF t-tau and p-tau associated with poor global cognition assessed with the Montreal Cognitive Assessment (MoCA).

Aβ42 aggregation results in a calcium influx which has been observed to drive dendritic spine loss through the formation of plaques (Teravskis et al., 2020). Plaque formation can inhibit neurotransmission and drive dendritic spine loss, both of which, result in neuronal death. Among dopaminergic neurons Aβ42 monomers form into oligomers, thus making the protein easier to aggregate within the postsynaptic cell. Once oligomers form, even slightly evaluated Aβ42 levels can be enough to induce aggregation (Bachhuber et al., 2015; Burré, 2015; Lu et al., 2017). The aggregation of Aβ42 has been related to cognitive dysfunction due to Aβ42 being unable to move to CSF (cerebral spinal fluid) to

be cleared from the brain (Spies et al., 2012). A neuroimaging study investigated the role of Aβ42 on MTA (medial temporal lobe atrophy) and cognitive functioning. Methods used positron emission topography (PET) on uptake of flutemetamol via IV injection to measure Aβ42 and global cognition was assessed with the MoCA and the MMSE. Results found PDD patients with higher Aβ42 had moderate MTA and worse cognitive performance on cognitive assessments than PDD patients with lower Aβ42 (Biundo et al., 2021). Montine et al (2010) had inverse findings with lower CSF Aβ42 detected in PDD patients compared to healthy controls, suggesting Aβ42 is aggregating in the brain and unable to be cleared via CSF. These results have been replicated across multiple studies with a meta-analysis conducted by Buongiorno and colleagues (2011) with 11 studies associating lower CSF Aβ42 with poorer cognitive performance as measured by the MMSE, the Dementia Rating Scale (DRS), or other neuropsychological measurements.

Alpha-synuclein (asyn) is another protein associated with cognitive impairment in PD. asyn forms aggregated neurofibrillary tangles (fibers) by eventually folding on itself. Once the structure has folded, the aggregation of asyn tends to spiral and aggregates quickly (Burré, 2015). Eventually, the aggregation can lead to the formation of DLB further inhibiting effective dopamine neurotransmission (Burré, 2015). This slowing process can result in poor neural communication and can lead to neuronal death. This process also results in motor and cognitive abilities being affected due to the lack of dopamine (Chung et al., 2019). A study conducted by Lin and colleagues (2017), found asyn was a

predictor of cognitive dysfunction in patients with PDD. Participants were provided assessments of motor and non-motor (including cognitive function, as measured by the MMSE) and had their blood drawn for analysis of plasma asyn. Results indicated the severity of cognitive dysfunction was associated with increased asyn levels. As asyn aggregates, this process has been shown to also induce the aggregation of tau proteins inducing neuronal death- suggesting Aβ42, asyn, and tau proteins act synergistically and may have a co-dependent relationship (Riedel et al. 2009). Both Aβ42 and asyn suggest oxidative stress may be a driving factor in the development of tauopathies (Teravskis et al., 2020 & Burré, 2015). Each of these affects dopaminergic neurons in their own respect.

Dopamine affects cognitive abilities through chronic frontal cortical dopamine changes (Meder et al., 2018). The loss of dopaminergic cell bodies, due to these proteins, within the substantia nigra pars compacta (SNpc) can affect dopamine levels in respective projection areas among individuals with PD (Palmeri et al., 2020 & Burré, 2015). Efferent dopaminergic cell body projections from the SNpc include the striatum and cortex, thus tauopathies, Aβ, and asyn are hypothesized to affect cognitive abilities through the reduction of dopaminergic cell bodies (Burré, 2015; Haber, 2014). Chung and colleagues (2018) aimed to assess whether dopamine depletion is related to cognitive decline in PD patients. Dopamine active transporter (DaT) availability via PET scans and scores on the Seoul Neuropsychological Screening Battery (SNSB) and the KMMSE (Korean MMSE; comprehensive cognitive assessments) were implemented. Results found striatal dopamine depletion was associated with

cognitive deficits. Bayram and colleagues (2020) found similar results, where reduced dopamine binding assessed with DaT scan using single photon emission computerized tomography (SPECT) was associated with poorer processing speed (Symbol Digit Modalities Test), visuospatial abilities (Benton Judgment of Line Orientation), and learning and memory (Hopkins Verbal Learning Test-Revised) as PD progresses. Further supporting dopaminergic cell body depletion is associated with cognitive decline.

Protein aggregation in the brain and loss of dopaminergic cell bodies are two processes that have been identified in the neuropathology of PD. With protein aggregation in the brain and its impact on CSF, less Aβ42 in CSF is associated with more Aβ42 plaques in the brain; more t-tau and p-tau in CSF is associated with more t-tau and p-tau in the brain; and more asyn s in CSF is associated with more asyn in the brain. Additionally, the loss of dopamine cell bodies has also been connected to cognitive decline in PD, but few studies have connected both processes to determine their impact on cognition.

A recent study attempted to connect how protein aggregation and dopaminergic cell body density affect cognitive decline. Bäckström and colleagues (2022) investigated the relationship between CSF biomarkers (Aβ42, t-tau, and p-tau) dopamine transporter (DaT scan via SPECT) and cognitive decline (MMSE and specific assessments of working memory, attention, visuospatial function, language, episodic memory, and executive function) at baseline. It is important to note, that this study does not utilize a longitudinal design, and thus cognitive decline later is defined by whether individuals

converted to PD with dementia. In the PD group, among those who were mild cognitively impaired, researchers found less CSF Aβ42 predicted later PD with dementia conversion as measured with poorer performance on cognitive assessments with less dopaminergic density when compared to healthy controls. There were no discernable differences reported in tau/DAT density. Few, if any studies have attempted to establish this relationship, and results from this study underscore how CSF protein aggregation can affect the loss of dopaminergic cell bodies, resulting in cognitive decline.

CHAPTER THREE

MILD COGNITIVE IMPAIRMENT AND MILD COGNITIVE IMPAIRMENT REVERSION

Cognitive decline has been associated greatly with the aging process and is generally considered inevitable (Ravdin & Katzen, 2013). While accepted as a normal process, it is important to distinguish the difference between healthy-aging cognitive changes and pathological cognitive impairment that is more severe than the cognitive decline that is expected in healthy aging (Ravdin & Katzen, 2013). Researchers and clinicians use neurocognitive assessments to track individuals' cognitive abilities as PD progresses.

Cognitive functioning in individuals with PD is assessed with a battery of neuropsychological measures that test a variety of domains of cognition affected by neurologic insult (Ravdin & Katzen, 2013). A common neurocognitive assessment used is the Montreal Cognitive Assessment (MoCA) which assesses the following cognitive domains: attention/working memory, processing speed, language, visuospatial abilities, and learning and memory. Common tests and their respective domains include attention and working memory assessed with the Letter-Number Sequencing Task (LNS; Wechsler, 2008). Processing speed was assessed with the Symbol Digit Modalities Test (SDMT; Smith, 1982). Language assessed with Animal Fluency (Heaton et al., 2004). Visuospatial abilities are assessed with the Judgement of Line Orientation Test (JLO; Benton et al., 1983). Lastly, learning and memory can be assessed with the Hopkins

Verbal Learning Test-Revised (HVLT; Brandt & Benedict, 2001). Several studies use these measures to determine classifications of individuals' cognitive functioning: Cognitively Normal (CN), Mild Cognitively Impaired (MCI), or dementia (Jones et al., 2017; Thomas et al., 2019; Becker, 2020 & Wyman-Chick et al., 2018).

CN individuals experience little to no impairment in their everyday lives despite living with PD. PD with dementia (PDD) patients; however, experience severe cognitive impairment and disruption in their everyday life. Patients with PDD may experience neuropsychiatric symptoms such as visual hallucinations, sleep disorders, apathy, anxiety, numerous memory complaints, and other non-motor related symptoms (Goetz, Emre & Dubois, 2009; Jellinger & Korczyn, 2018; Modreanu, et al., 2017; Aarsland et al., 2001). Typically, hallucinations, mood, and apathy are behavioral characteristics that can distinguish PDD from PD-MCI or PD-CN; however, a formal diagnosis of PDD is more comprehensive. According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5th edition), PDD, now a major neurocognitive disorder due to PD, can only be diagnosed after the onset of PD with steady cognitive decline, as evidenced by neuropsychological testing, that impairs functioning in activities of daily living (American Psychiatric Association, 2013).

Lastly, MCI refers to an early stage of cognitive decline (Golomb et al., 2004; Jones et al., 2017 & Wang et al., 2020). MCI is considered a transitional stage, and as such, is typically utilized as a classifier between remaining CN or having dementia (Martinez-Horta & Kulisevsky, 2011). While individuals with MCI

demonstrate a decline in cognitive abilities, the degree of impairment is not severe enough to impede the individual's ability to complete tasks in their everyday lives (Golomb et al., 2004; Weil et al., 2018). This underscores the importance of differentiating individuals with MCI from those who are either CN or have dementia. Individuals classified with MCI, however, may digress back to CN, these individuals are referred to as reverters (Jones et al., 2017). Not everyone classified as MCI will revert to CN though, due to this many studies define MCI into two main sub-groups- MCI stable (individuals who remain MCI at every assessed time point) and MCI reversion (those who revert to CN at one follow-up; Chung et al., 2019; Thomas et al., 2019; & Jones et al., 2017). Reversion rates across several studies vary; however, remain somewhere between 18-38% for individuals at follow-ups under three years and between 13-33% for over three years (Saredakis et al., 2019 & Thomas et al., 2019). MCI reversion demonstrates the course of MCI is variable as individuals may not move between CN to MCI to dementia in a linear fashion (Martinez-Horta & Kulisevsky, 2011 & Chung et al., 2019).

MCI reversion has been extensively investigated concerning AD (Tomaszewski et al., 2009 & Thomas et al., 2019). A study conducted on patients with AD-MCI found individuals who met the criteria for MCI reversion for at least one follow-up post-initial assessment were at a higher risk for developing ADD (Alzheimer's Disease Dementia) than those who remained CN (Roberts et al., 2014). Of the MCI individuals, 38% (n=201) reverted to CN. Moreover, 65% of reverter individuals were more likely to convert back to MCI or dementia than

those who were CN or MCI (Roberts et al., 2014). Another study conducted, found 16% of AD patients reverted from MCI to scoring <MCI at a later assessment. Of those who reverted, 20% of them further developed ADD and remained at a higher risk for ADD than those who were MCI-Stable (Koepsell & Monsell, 2012). Findings from these studies suggest MCI reversion may be a strong predictor of converting to dementia as neurodegeneration progresses. Researchers have noted neurodegeneration similarities between AD and PD and thus utilized similar methods concerning PD-MCI reversion.

Utilizing similar methodologies, results paralleled findings from AD MCI patients concerning MCI reverter PD patients. Where reverters were approximately 7 times more likely to either develop PDD or convert back to MCI within a year (Jones et al. 2017). Pedersen et al (2017) also found throughout their 5-year study, out of 69 patients classified with MCI, 18 (26%) had reverted, noting that rates of reversion were lower at the 2nd consecutive visit (9.4%). Furthermore, in 2019 a meta-analysis investigating conversion rates (MCI to PDD) and reversion rates was conducted. Inclusion criteria included following patients over 6 years with a total of 4,011 patients being represented within the analysis. Follow-ups ≤3 years had a reversion rate of 28% and those ≥3 years had a reversion rate of 21%, consistently showing higher rates of reversion earlier than later on (Saredakis et al., 2019). Researchers note that again those who reverted were at an increased risk of converting from CN to PDD as the disease progressed (Saredakis et al., 2019). With questions surrounding how or why individuals revert and what may place them at higher risk for further

developing PDD, multiple models turn to include neurobiological mechanisms (Thomas et al., 2019 & Vulmunt et al., 2019).

CHAPTER FOUR

MILD COGNITIVE IMPAIRMENT REVERSION AND THE USE OF BIOMARKERS

Utilizing neurocognitive assessments, MCI reverters (MCI at one assessment and cognitively normal at a subsequent follow-up) are at an increased risk of later converting to MCI or PDD (Saredakis et al., 2019; Jones et al., 2019). Few studies implement additional measurements to further evaluate if MCI reversion is an indicator of neurologic compromise. Implementing tools such as neuroimaging and biomarker assays can further elucidate underpinning neurobiological processes among PD patients.

Using t-tau, p-tau, and Aβ as possible biomarker predictors of MCI/MCI reversion is a novel concept in investigating neurodegenerative diseases, especially in PD patients. Much of our understanding of the relationship between these biomarkers and MCI reversion stems from AD literature. Moradi and colleagues (2021) compared their 68 MCI reversion AD patients to their 337 MCI stable AD patients on brain atrophy and CSF biomarkers (t-tau, p-tau, and Aβ). They measured cognition using the following measures: Rey Auditory Verbal Learning Test (RAVLT) delayed free recall, RAVLT recognition; two language measures: 30-item Boston Naming Test (BNT), animal fluency; and two attention/executive function measures: Trail Making Test (TMT) parts A and B. Brain atrophy was measured using Tensor Based Morphometry –Symmetric Diffeomorphic Image Normalization (TBM-SyN) and CSF averages were reported

for the corresponding biomarkers. They found brain atrophy and CSF levels were associated with the MCI stable group but not the MCI reversion group, noting MCI reversion group had lower levels of t-tau and p-tau and higher levels of Aβ than the MCI stable group.

Similarly, Thomas et al (2019) results followed the same pattern, MCI reversion group was most like the CN group as opposed to the MCI stable group. AD patients' t-tau and p-tau levels were lower and had higher Aβ levels when compared to the MCI stable group. Another study yielded similar results with patients whose t-tau and p-tau levels were lower but had similar Aβ levels when compared to the MCI stable group (Vermunt et al., 2019). Authors cautioned how CSF biomarkers may be unrelated to MCI/MCI reversion or represent other AD-related processes (Vermunt et al., 2019; Wallin et al., 2011). The few studies that have investigated CSF biomarkers and MCI in PD rely on the methodologies outlined above.

Neuroimaging of PD-MCI and PD-MCI reversion patients reveal MCI reverters and those who are CN are more similar than those who are MCI stable, further supporting performance on cognitive assessments (Chung et al., 2019). While Chung and colleagues' (2019) study did not utilize CSF biomarkers, it does provide further insight into how MCI reverters may differ from those that are MCI stable.

CHAPTER FIVE

SPECIFIC AIMS

PD-MCI is thought to be a risk factor for converting to PDD; however, the fact that many patients revert may reduce the utility of a PD-MCI diagnosis. The proposed study investigated if PD-MCI reversion is associated with greater neurologic compromise relative to cognitively intact individuals with PD. We intend to investigate the relationship between these biomarkers and cognitive status using an approach like Jones et al (2017) who found that MCI reverters were more likely to progress to PDD than those with MCI or CN. Increasing our understanding of MCI reverters may lead to better detection of those who are more likely to progress to PDD.

Using neurocognitive and CSF biomarker data collected and made available by the Parkinson's Progression Markers Initiative (PPMI), we investigated where MCI reversion is associated with neurologic compromise in PD patients. We followed PD patients assessed as MCI at baseline and noted those who reverted from MCI to CN at their first annual follow-up to create our reverter group. We then compared our MCI reverters to CN and MCI stable groups to observe any longitudinal changes in their cognitive performance on neurocognitive measures and CSF biomarker levels.

We predicted individuals with MCI reversion will have less CSF Aβ42 but more tau and altered asyn relative to individuals who are cognitively intact for the first two years of the study. Like Thomas and colleagues (2019), where AD-MCI

differed from AD-CN stable on Aβ, p-tau/ Aβ ratio, and t-tau/ Aβ, we expect our PD-MCI group to differ from PD-CN group on these biomarkers with the inclusion of asyn. Additionally, we expected there to be differences between PD-MCI stable compared to our CN group among one or more CSF biomarkers, similar to Chung et al. (2019). If these biomarkers are associated with MCI reversion, findings would suggest that MCI reversion is a sign of neurologic comprise as less Aβ42 and increased tau and/or asyn would be consistent with previous findings in PDD.

CHAPTER SIX

METHODS

Database

Data was collected from the Parkinson's Progression Markers Initiative (PPMI), a longitudinal multisite international observational cohort study for retroactive analysis. The PPMI followed newly diagnosed, relatively untreated, PD patients for a total of 5 years (baseline collection and 4 annual follow-up appointments). Participants underwent various neurocognitive assessments, sleep measurements, motor movement assessments, DatScans, CSF biomarker collection, and more. For the proposed study, only: demographics, scores on neurocognitive measurements, CSF sample information, participant ages, and scores of motor severity will be used. Institutional review board approval was secured at each site before data collection.

Participants

Participants were recruited from health clinics in North America (United States and Canada), Europe, Africa, and Israel. The estimated sample consisted of approximately 390 individuals with PD, all of whom completed a battery of neurocognitive assessments at baseline and annual follow-ups. Our sample was comprised of PD patients who were followed for at least 2 years and up to 3

years post-baseline. Participants were excluded from the study if CSF markers and cognition tests were never administered, or they were not diagnosed with PD. Each participant provided informed written consent at each site before data collection.

MCI and MCI Reversion Criteria

Individuals were classified as CN or PD-MCI at the baseline and first annual follow-up assessment. PD-MCI criteria will be defined by ≥2 scores on neurocognitive measures falling at least 1.5 SD below the mean in accordance with previous studies (Jones et al., 2017; Pedersen et al., 2017 & Pedersen, 2004). We classified a patient as an MCI reverter if they were MCI at baseline and then CN at the first follow-up. MCI stable if a patient was classified as MCI at both baseline and first follow-up. CN stable if they were CN at both baseline and first follow-up. Finally, MCI converter if they were CN at baseline then converted to MCI at first follow-up.

Measures

Cognition

Participants completed the following neurocognitive battery at each annual assessment: LNS (assessing attention and working memory), SDMT (assessing processing speed), Animal Fluency (assessing language), JLO (assessing

visuospatial abilities), HVLT (assessing learning and memory). Scores were normed based on their manuals or published normative samples prior to analysis.

Severity of Motor Symptoms

The Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) assesses motor symptom severity (Goetz et al., 2007). Scores from PART III of the scale specifically measure motor severity by assessing speech, facial expressions, rigidity, hand movements, tremors, gait, and bradykinesia. Higher scores indicate greater severity of motor symptoms.

Biomarkers

T-tau, p-tau, Aβ, and asyn are the three biomarkers collected from cerebrospinal fluid (CSF) of newly diagnosed PD patients in the PPMI cohort for the first 2 years (at baseline, 1st annual follow-up, and 2nd annual follow-up). CSF biomarkers were processed utilizing an enzyme-linked immunosorbent assay test (ELISA). ELISA operates via protein immobilization which allows detection antibodies to bind to desired proteins so the assay can then quantify concentrations. CSF sample processing for North American PPMI sites was sent to and conducted by Indiana University Biorepository; European and African sites had their samples sent and processed by BioRep in Italy; all samples collected from Tel Aviv, Israel were processed at their site. All sites adhered to the standard operating procedures for ELISA processing of CSF samples outlined in the PPMI (Indiana University, 2020). CSF biomarker data will be used to provide further insight into how individuals with MCI who revert may differ from those who

do not in the severity of either cognitive decline or motor-related symptoms. Biomarker measurements will include the following ratios: p-tau/t-tau, t-tau/ Aβ, p-tau/ Aβ, and asyn.

Statistical Analyses

CSF biomarkers served as individual DVs for each multilevel linear model (MLM). A separate MLM will be conducted for each DV, resulting in four models. predictors included cognitive status (CN stable, MCI stable, MCI reverter, and MCI converter) and gender (male or female). Covariates included occasion, motor severity, and age of the patient. All data utilized was converted to standardized values (z scores and natural log) for purposes of analysis. Missing data was treated using maximum likelihood. We used an alpha level of .05 for all statistical tests conducted. Multiple post hoc comparisons utilized Fisher's test of least significant difference.

CHAPTER SEVEN

RESULTS

Demographic and Clinical Characteristics

Data included 393 participants with the majority identified as male (65.1%) and Caucasian (92.3%). Group characteristics are as follows: CN stable (*n*= 298, 95.3% Caucasian and 35.9% female), MCI stable (*n*= 38, 84.2% Caucasian and 18.4% female), MCI converter (*n*= 74.3% and 45.7% female), and MCI reverter (*n*= 22, 95.5% Caucasian and 31.8% female).

One-way ANOVAs were conducted to compare mean differences across cognitive status groups at baseline. There were significant mean differences in motor severity across our cognitive status groups. Post hoc comparisons revealed those who were CN stable had reduced motor severity compared to MCI reverters. When it came to ethnicity, CN stable (95.3%) and MCI reverters (95.5%) had a greater number of Caucasian participants compared to our MCI stable (84.2%) and MCI converter (74.3%) groups. Other demographic and clinical information from the baseline is summarized in Table 1.

Aim: Is MCI Reversion Associated with Neurologic Compromise

Our primary aim sought to investigate longitudinal changes in CSF biomarker ratios (tau/Aβ, p-tau/ Aβ, and p-tau/tau) and asyn as a function of

cognitive status while accounting for the occasion, gender, age, motor severity, and education. The CN stable group was entered as the reference group for the cognitive status variable (i.e., MCI converter vs. CN stable, MCI reverter vs. CN Stable, and MCI stable vs. CN stable).

MLM 1.1 tau/Aβ

There was no significant cognitive status by occasion interaction effects or main effects of cognitive status on tau/ab ratio measures, shown in Figure 3. However, both age (b = .262, p < .001) and occasion (b = .004, p = .004) were significantly associated with the tau/ab ratio (see Table 2.1). Greater tau/Aβ was associated with older age and continued to increase as the study progressed.

MLM 1.2 p-tau/Aβ

No significant interactions between cognitive status by occasion interaction effects or main effects of cognitive status on p-tau/AB measures were present, as shown in Figure 4. However, age (b = .267, p < .001), education (b = .106, p = .033), and occasion (b = .055, p = .004) were significantly associated with p-tau/Aβ (see table 2.2). Greater p-tau/Aβ was associated with older age and level of education and increased as the study progressed.

MLM 1.3 p-tau/tau

No significant interaction effects between cognitive status by occasion were detected. There was a main effect of MCI converters compared to CN with MCI converters having a higher p-tau/tau ratio compared to the CN group (b = .177, p = .032). The main effect is shown in Figure 1. Age (b = .179, p < .001) and education (b = .136, p = .013) were significantly associated with the p-tau/tau ratio (see Table 2.3). Greater p-tau/ab was associated with both older age and an increased level of education.

MLM 1.4 asyn

A significant interaction between cognitive status by occasion was present between the MCI stable group compared to the CN group (b = .141, p = .030). Specifically, the MCI stable group experienced markedly increased asyn than the CN group. The interaction effect is shown in Figure 2. No other cognitive status X occasion interaction effects were significant. Similarly, there were no significant main effects of cognitive status. Age (b = .159, p = .002) was the only covariate significantly associated with changes in asyn (see table 2.4) where greater asyn was associated with older age.

CHAPTER EIGHT

DISCUSSION

We hypothesized significantly different CSF biomarker concentrations among PD-MCI reverters compared to CN individuals would indicate they are neurologically compromised. Findings did not support our hypothesis with respect to CSF changes over time among MCI reverters, thus raising concerns about whether MCI reverters are at increased risk for neurologic compromise relative to CN individuals. In summary of results, the MCI stable group demonstrated elevated longitudinal changes in asyn compared to those who were CN. Additionally, we found that MCI converters had elevated ptau/tau ratios compared to CN individuals.

Our lack of findings among changes in CSF concentrations is consistent with some of the pre-existing research, suggesting MCI reverters are most likely CN individuals via CSF biomarker metrics (Chung et al., 2019 & Thomas et al., 2019). Chung and colleagues (2019) found progression to dementia among PD-MCI reverters to be of a similar rate of progression towards PDD as those who are CN. Additionally, PD-MCI reverters and CN individuals had no detectable differences in cortical thickness, indicating similarities between the groups. Thomas and colleagues (2019) found no detectable differences in CSF concentrations over annual follow-ups between AD-MCI reverters and CN individuals. They too found AD-MCI reverters were at a similar rate of progression towards ADD (Alzheimer's Disease with Dementia) as CN

individuals as evidenced by neurocognitive scores. Both studies contradict findings from previous research investigating the progression to dementia among MCI reverters.

In contrast to the above studies, both Jones and colleagues (2017) and Pedersen and colleagues (2017) found MCI reverters progressed to PDD at a higher rate than those who were CN as evidenced by neurocognitive assessments. Both Jones et al., (2017) and Pedersen and colleagues (2017) observed changes in cognitive status over the course of 5 years (consisting of baseline assessment and annual follow-ups). Both studies utilized neurocognitive assessments with no biomarker data; contrasted against Chung and colleagues (2019) who observed changes in cognition over 3 years, and Thomas and colleagues (2019) who observed changes in cognition over 2 years, both studies with inclusion of CSF biomarkers. With both Jones et al. (2017) and Pedersen et al. (2017) observing changes in cognition over 5 years, as opposed to 3 years (Chung et al., 2019) and 2 years (Thomas et al., 2019), we expected to see differences in CSF ratios.

However, methodological differences among studies may explain some discrepancies. Our current study had a shorter duration of follow-up (3 years as opposed to 5 years), which could limit the ability to detect significant changes. Including other biomarkers to assist in explaining why these differences are observed among MCI reverters may provide further insight into underlying pathophysiology.

Emerging evidence suggests MCI reverters appear to differ from healthy controls among other biomarker measures. Hu and colleagues (2022) attempted to look at functional resting state differences by comparing AD-MCI reverters to healthy controls. Analyzing data from the ADNI database, 32 MCI reverters and 37 healthy controls were included in the final analysis. MCI reverters were found to have decreased resting state activity in the cerebellum but increased activity in the frontal gyrus compared to healthy controls. Authors argue that while increased activity in the cingulate gyri is associated with cognitive processing which may assist MCI reverters in the maintenance of cognitive functioning; decreased activity in the insula is associated with decreased attention thus contributing to reduced cognitive performance on neurocognitive measures. This study assists in elucidating differences in cognition between MCI reverters and healthy controls using functional imaging as a biomarker.

APOE4 (apolipoprotein E4) may be another potential biomarker worth investigating. APOE4 is a gene that is mostly associated with Alzheimer's Disease and amyloid buildup. Dang and colleagues (2023) were interested in comparing AD-MCI reverters and AD-MCI stable individuals for potential differences in APOE4 genetic status and structural grey matter among the structural covariant network. The authors defined the structural covariant network as including the: default mode network, frontoparietal, and hippocampal networks. They found disease progression in AD-MCI reverters was associated with reduced structural grey matter in the covariant network for carriers of the APOE4 gene. Additionally, among MCI reverters, they found increased structural

integrity among the frontoparietal, and hippocampal networks compared to MCI stable individuals, regardless of APOE4 status.

Both studies suggest that alternative biomarkers/mechanisms of neurologic compromise may be better suited to detect MCI reversion and how reverters differ not only from MCI-stable individuals but cognitively normal individuals as well. Hu and colleagues (2022) describe key differences between MCI reverters and cognitively normal individuals concerning increased frontal resting state activity but reduced activity in the insula. The increase in frontal activity could be attributed to compensatory measures to overcome deficits in activity elsewhere, like the cerebellum, explaining the cognitive deficits among MCI reverters that both Jones et al. (2017) and Pedersen and colleagues (2017) detected. Additionally, Dang and colleagues (2023) allude to APOE genetic status and structural integrity of hippocampal and frontoparietal networks assist in differentiating MCI reverters from MCI stable individuals among AD participants. Implementing structural and functional scans as well as genetic tests among PD participants may yield similar results.

Confounds and Alternative Explanations of MCI Reversion

There may exist other confounds that explain why PD- MCI individuals may revert to cognitively intact. One such confound could be practice effects. Practice effects can be defined by improvements in cognitive performance due to repeated exposure over time (Duff et al., 2007). Given the nature of the PPMI

being a longitudinal study and participants' repeated exposure to the same cognitive battery, practice effects could be a confound. A study conducted by Elman and colleagues (2018) utilized 995 nonclinical participants from the Vietnam Era Twin Study of Aging and measured cognition with 23 measures across the 5 cognitive domains (language; visuospatial; learning and memory; attention and working memory; and processing speed). The authors accounted for practice effects in their study design. Practice effects were adjusted using 170 age-matched replacements that underwent the same neurocognitive assessments as participants and group differences to used to assess practice effects. They found, that when adjusting their models for practice effects, MCI classification rates increased from 4.5% to 9%. Thus, adjusting for practice effects increased the number of MCI individuals.

Conversely, when adjusting for practice effects with MCI reverters, the number of reverters was reduced by 28.5% (Sanderson-Cimino et al., 2022). Unlike Elman et al. (2018), Sanderson-Cimino and colleagues (2022) utilized a sample of 344 patients diagnosed with AD from the 2003 Alzheimer’s Disease Neuroimaging Initiative (ADNI) and also found MCI rates increased when adjusting for practice effects. Practice effects were accounted for using a bootstrap replacement technique (pseudo replacement due to utilization of the ADNI dataset) that matched new participants to ADNI participants on age, sex, years of education, and premorbid IQ. After these replacement participants underwent all neurocognitive testing, they were then compared to ADNI participants, and adjusted scores were used to determine if they met the

threshold for MCI criteria. The full bootstrapping technique is described in Sanderson-Cimino, Elman, Tu, and colleagues (2022) studies. Furthermore, when practice effect adjustments were implemented with the inclusion of CSF biomarkers (tau, p-tau, and Aβ), at least one CSF biomarker was associated with MCI.

Conclusions that can be drawn from these two studies: inclusion of adjustments for practice effects can increase MCI rates while also decreasing the number of MCI reverters within a clinical sample. While practice effects may reduce the number of reverters within a clinical sample, it may not fully explain how or why MCI reverters and CN individuals are similar. Why this might be, could be attributed to the number and type of lifestyle activities participants engage in.

Shimada and colleagues (2019) investigated if engagement in lifestyle activities was a predictor of MCI reversion over the course of 4 years among a relatively healthy sample. The author defined lifestyle activities as engaging in gardening, using public transportation, taking cultural classes, driving, engaging in sports or other hobbies, playing board games, and more. They utilized the Pedersen (2004) criteria to determine the MCI status of individuals (≥2 scores on neurocognitive measures falling at least 1.5 SD below the mean) and classified MCI reversion status like our methods, making this study a reasonable comparison. Results indicated baseline group differences across all measurements between MCI reverters and MCI stable individuals. Additionally, individuals who engaged in lifestyle activities, specifically: driving, map use for

navigating, reading, and participating in cultural classes, were more likely to be MCI reverters as opposed to MCI stable individuals. This change in engagement of lifestyle activities suggests this may be a protective factor against cognitive decline and could assist in explaining why MCI reverters differ from MCI stable individuals, further indicating reverters are more like CN individuals than MCI stable individuals.

Including practice effects and lifestyle activities as covariates could assist in better understanding MCI reverters compared to CN individuals. Including both of these accomplish this by reducing MCI reverter sample size inflation (Sanderson-Cimino et al., 2022) and assessing how lifestyle activities may lead to protective factors against future cognitive decline (Shimada et al., 2019). Neurobiologically, there have been differences observed comparing MCI reverters to CN individuals that may serve as a predictor of MCI reversion.

Findings from Hu and colleagues (2022) resting state functional imaging study comparing AD-MCI reverters to CN individuals argue that resting-state differences may serve as a predictor of reversion. With increased activity in the frontal gyri but decreased activity in the cerebellum among MCI reverters, authors argue the increased frontal activity may serve as a compensatory cognitive measure due to the decreased activity observed in the cerebellum. Dysfunction in cerebellum-caudate circuitry is increasingly becoming linked to cognitive dysfunction (Shen et al., 2020; Hu et al., 2022; Kawabata et al., 2020; Sako et al., 2021), thus differences in activation between frontal cortex and cerebellum may serve as a predictor of MCI reversion.

CSF Biomarkers Associated with Neurologic Compromise

It is well documented that altered alpha synucleinopathy and tauopathy levels within CSF are associated with neurologic compromise (MCI and dementia) among both healthy and diseased samples (Haber, 2014; Chung et al., 2018; Bäckström et al., 2022; Burre, 2015; Sanderson-Cimino et al., 2022 & Vermunt et al., 2019). Our results indicated both MCI stable and MCI converter groups had elevated protein concentrations compared to CN individuals and were associated with several variables (age, education, and annual assessments) suggesting potential neurologic compromise. There are a few explanations as to why we observed linear increases in asyn overtime among our MCI stable group and observed a main effect of our elevated p-tau/tau ratio among MCI converters.

The observed interaction effect of elevated asyn among MCI-stable individuals over time may be attributed to the early onset of PD. Multiple studies indicate early aggregation of asyn has been associated with cognitive decline, specifically, through the microbiota-gut-brain axis which may assist in explaining our interaction effect (Yan et al., 2021; Fitzgerald et al., 2019; Fan et al., 2021 & Lin et al., 2017). The vagus nerve is central to the microbiota-gut-brain axis, by acting as a central pathway to the brain, it’s here where there’s evidence of early asyn aggregation. Beginning where the vagus nerve innervates with the gastrointestinal tract and aggregates upward on the nerve towards the brain

(Fitzgerald et al., 2019). Yan and colleagues (2021) found disruption of the gut microbiome interacted with asyn misfolding and was associated with cognitive impairment as well as anxiety but not motor symptoms among their transgenic rhesus monkeys. MCI converters show a similar pattern of neurologic compromise.

When individuals convert from CN to MCI there has been noted neural atrophy among both AD (Long et al., 2018) and PD (Zhou et al., 2019 & Phongpreecha et al., 2020) patients associated with lower neurocognitive assessment scores compared to CN individuals. Zhou and colleagues (2019) utilized data from the PPMI for the first 4 years and utilized 126 individuals (34 healthy controls). They found both the right and left putamen and right and left caudate had differed between MCI converters and CN individuals but not MCI stable individuals. While including CSF markers in analyses, they did not find any differences across the groups. Phongpreecha and colleagues (2020) found among their sample no differences between MCI converters and MCI stable individuals but differences between MCI converters and CN individuals on neurocognitive measures. These studies both underscore the similarities between MCI converters and MCI stable individuals while also demonstrating that MCI converters have more atrophy and poorer performance on neurocognitive measures when compared to CN individuals.

Our findings further add to the existing literature by reinforcing how neurobiological correlates of impairment are associated with both MCI and CN-to-MCI conversion. Alpha synucleinopathies are associated with cognitive decline

and potential early onset of PD while brain atrophy and CSF markers are also associated with cognitive decline among MCI converters. The interaction of increases in asyn over time among MCI-stable individuals is further supported by previous findings in how sinister asyn aggregation can be; despite no differences at baseline between cognitive status groups. While the main effect of elevated p-tau/tau ratio among MCI converters is also supported by previous findings of brain atrophy (Zhou et al., 2019) and poorer performance on neurocognitive measures (Phongpreecha et al., 2020) among the PPMI cohort. While we did not find support for our hypothesis due to lack of findings among our MCI reverters but found significant findings among our MCI stable and converters.

Limitations

Our study presents a few limitations and a few other important considerations for future study designs. Practice effects have been demonstrated to increase MCI group sample size when adjusted for in models (Elman et al., 2018 & Sanderson-Cimino et al., 2022). While we covaried occasion in our models to account for practice effects, both Elman et al. (2018) and Sanderson-Cimino et al. (2022) outline alternative methodologies that may adequately improve adjusting for practice effects. In implementing their methodology for future studies, participants would be matched replacements to participants in the PPMI, and implementing the described bootstrapping technique, sample sizes could be improved to better reflect those who meet MCI criteria. Follow-up

studies should consider implementing this methodology to better account for practice effects. Future studies accounting for practice effects utilizing these techniques may also need to address group sizes, another potential limitation for our study.

Our PD-MCI group sizes [MCI reverters (22 participants), MCI-converters (35 participants), and MCI-stable (38 participants)] may also be a possible limiting factor. Our CN group containing 298 participants and our MCI groups containing a total of 95 participants make this an issue that needs to be addressed with equal group sizes. As a result of our small MCI subgroups, the generalizability of our sample is drawn into question. As noted in Table 1 the majority of our groups were Caucasian males, which represents most of the individuals reflected in the entire dataset of the PPMI. In accordance with other published studies there are notable differences in cognitive status group size and gender sample representation.

Chung and colleagues (2019) had a total of 196 participants across their MCI stable (118 participants, 60.2%) and their MCI reverter groups (78 participants, 39.7%). That is a 50.6% difference in the percentage of MCI stable participants and a 34.2% difference in MCI reverters between our sample and theirs. Whereas Thomas and colleagues (2019) had closer differences in their group sizes: 508 participants (51.8%) were CN and 90 participants (9.1%) were MCI reverters compared to our study (75.8% were CN and 5.5% were MCI reverters). However, Thomas and colleagues had more MCI stable individuals (38%) compared to our sample (9.6%). A similar pattern can be seen with Park

and Han concerning their MCI stable, with 779 participants (63.1%) and CN, with 413 participants (33.4%) group size compared to their MCI reverter group, with 42 participants (3.4%). In each of these studies, more reverters were detected among their sample compared to ours, emphasizing the need for an increased sample of MCI reverters.

With respect to gender size, Chung and colleagues (2019) had a greater representation of females among their sample with 94 (47%) compared our 121 (30.8%) with 19 female MCI reverters and 123 female MCI stable individuals. Thomas and colleagues had more females in their sample relatively similar to Chung and colleagues (2019) with 36 (40%) MCI reverters, 147 (47.9%) CN individuals, and 243 (38.8%) MCI stable individuals. Han and Park (2015) followed a similar pattern with 19 (45.2%) MCI reverters, 200 (48.4%) CN individuals, and 314 (40.4%) MCI stable individuals. None of these studies reported the ethnic demographics of their groups. Considerations for the future include adequately adjusting for practice effects, including subjective cognitive complaints, and length of data collection with biomarkers may strengthen future findings.

Subjective cognitive complaints (SCC) are frequently overlooked despite being necessary for screening and diagnosing MCI (Jones et al., 2022). Jones and colleagues (2022) demonstrated failure to include SCC as a diagnostic criterion, increases MCI diagnosis rates (16-19%) as opposed to whenits included, MCI rates are between 4-11%). Additionally, the authors included CSF biomarkers to demonstrate inclusion of SCC is associated with cognitive decline.

Their findings indicthat ate MCI with SCC was associated with higher levels of tau/Aβ and p-tau/Aβ compared to CN individuals and MCI without SCC. These findings support that SCC is important when diagnosing MCI as these individuals are at risk for cognitive decline evidenced through associations with CSF biomarkers. The implications of these results on MCI reverters underscore the importance of screening for SCC when diagnosing someone with MCI as MCI reverters may still be neurologically compromised. ‘

Participants included in the final analysis were missing 2 years of CSF data (3 years compared to the full 5 years of the study) which may have contributedthe to lack of findings. Jones and colleagues (2017) were able to conduct hazard ratios on their sample due to having 5 years of cognitive data from the PPMI. We utilized the same dataset to conduct our secondary analysis with the inclusion of CSF biomarkers as a follow-up to their study. Results may have differed over the course of the remaining annual follow-ups 3 and 4 (making a total of 5 years) had we not had any missing data. This could have further explained Jones and colleagues' results found in their 2017 study. Furthermore, future studies may want to consider additional markers of cognitive dysfunction and neurologic compromise among MCI reverters rather than these CSF markers in isolation.

Our study utilized asyn, Aβ, tau, and p-tau as CSF markers, asyn is a pathogenic hallmark in PD pathology whereas Aβ and tau can be observed in other pathologic diseases and disorders, such as AD. Focusing on other markers relevant to PD pathology, may yield more conclusive results. Nabizadeh and

colleagues (2023) investigated striatal dopamine uptake using DaT-SPECT (dopamine transporter- single-photon emission computed tomography) and how CSF biomarkers contribute to PD pathophysiology. They found that asyn was associated with decreased dopaminergic neurons evidenced by increased specific binding ratio scores in the caudate among PD patients. These findings not only further support the role the caudate may have in cognitive dysfunction (Shen et al., 2020; Hu et al., 2022; Kawabata et al., 2020; Sako et al., 2021) but demonstrates a link between reduced striatal dopamine as a function of aggregated asyn. Between the inclusion of practice effects, SCC, and other biomarkers, we may better evaluate MCI reversion.

Future Directions

Considerations for future follow-up studies should consider the following: implementing adjustments for practice effects; including SCC criteria for detecting MCI; and expanding on the use of alternative/additional biomarkers to further investigate those with MCI reversion. The combined utilization of alternative methods for adjustments of practice effects and inclusion of SCC criteria would likely improve the sample by including a more accurate representation of those with MCI. This improvement could reduce potential errors associated with the sample of MCI reverters (excluding true MCI reverters and/or including non-MCI reverters). In addition to including this criterion, attempting to collect a large and diverse sample may also improve generalizability and allow

for further group-by-group analyses to be conducted. The expansion of the use of alternative/additional biomarkers may explain the underlying pathophysiology of MCI and MCI reversion that does not distinguish the two but may point to key differences, underscoring potential neurologic compromise among MCI and MCI reverters noted in previous studies.

Overall, our results replicate the findings of previous studies that have indicated that MCI is associated with greater cognitive decline than CN, as evidenced by CSF markers. MCI reverters may still be at risk of neurologic compromise and , requiring investigation into underlying neurobiological mechanisms.

APPENDIX A

TABLE 1. DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS

Table 1

Demographic and Clinical Baseline Characteristics

	CN-S (n= 298)		MCI-S (n= 38)		MCI-C (n= 35)		MCI-R (n= 22)			
	M	SD	M	SD	M	SD	M	SD	*p*	Contrasts
Age	61.61	9.83	62.96	8.63	60.92	1.65	62.67	8.34	.655	
% Male	64.1%	--	81.6%	--	54.3%	--	68.2%	--	.256	
% White	95.3%	--	84.2%	--	74.3%	--	95.5%	--	**<.001**	MCI-C, MCI-S < CN-S, MCI-R
Education (Years)	15.61	2.72	14.50	3.66	15.34	2.52	15.36	4.14	.169	
UPDRS Part III	20.09	8.70	22.92	10.26	22.20	8.35	25.41	6.94	**.012**	CN-S < MCI-R
t-tau/ab	.19	.09	.21	.09	.02	.00	.19	.084	.230	
p-tau/ab	.01	.01	.01	.01	.02	.00	.01	.00	.808	
p-tau/t-tau	.08	.00	.08	.00	.08	.00	.08	.00	.480	

	CN-S (n= 298)		MCI-S (n= 38)		MCI-C (n= 35)		MCI-R (n= 22)			
	M	SD	M	SD	M	SD	M	SD	*p*	Contrasts
asyn	1523.82	681.82	1306.78	482.12	1511.56	562.17	1445.28	529.60	.291	
HVLT Immediate Recall	25.57	4.84	18.45	3.44	23.51	3.70	19.91	2.68	**<.001**	CN-S > MCI-C, MCI-R, MCI-S; MCI-C > MCI-R, MCI-S
HVLT Delayed Recall	9.01	2.62	5.42	2.52	7.83	2.51	7.09	1.68	**<.001**	CN-S > MCI-C, MCI-R, MCI-S; MCI-C > MCI-S; MCI-R > MCI-S
LNS	11.04	2.58	8.00	2.90	10.22	2.14	9.72	2.27	**<.001**	CN-S > MCI-R, MCI-S; MCI-C > MCI-S; MCI-R > MCI-S
Animal Fluency	50.76	11.84	38.37	9.47	43.94	9.55	43.36	10.08	**<.001**	CN-S > MCI-C, MCI-R, MCI-S; MCI-C > MCI-S

	CN-S (n= 298)		MCI-S (n= 38)		MCI-C (n= 35)		MCI-R (n= 22)			
	M	SD	M	SD	M	SD	M	SD	*p*	Contrasts
SDMT	43.54	10.03	31.00	10.60	37.83	9.53	38.23	9.92	**<.001**	CN-S > MCI-C, MCI-R, MCI-S; MCI-C > MCI-S; MCI-R > MCI-S
JLO	13.26	1.90	11.45	2.89	11.69	2.49	12.14	2.37	**<.001**	CN-S > MCI-C, MCI-R, MCI-S

Cognitively normal stable (CN-S), mild cognitive impairment stable (MCI-S), mild cognitive impairment converter (MCI-C), and mild cognitive impairment reverter (MCI-R). M (mean) and SD (standard deviation) Unified Parkinson's Disease Rating Scale- Part III (UPDRS-III; motor severity). Geriatric Depression Scale (GDS). Epworth Sleepiness Scale (ESS). Total tau (t-tau), phosphorylated tau (p-tau),beta-amyloidd (ab), andalpha-synucleinn (asyn). Hopkins Verbal Learning Test (HVLT), Letter Number Sequencing (LNS), Symbol Digits Modalities Test (SDMT), and Benton Judgement of Line Orientation score (JLO).

APPENDIX B

TABLE 2. MLM PREDICTORS OF CSF BIOMARKERS

MLM: Predictors of tau/ab (*N* = 393)

	Estimate	SE	Sig.
MCI Stable vs. Cognitively Normal	.103	.147	.484
MCI Reverter vs Cognitively Normal	.058	.153	.706
MCI Converter vs Cognitively Normal	.001	.077	.980
MCI Stable vs Cognitively Normal x Occasion	-.019	.066	.771
MCI Reverter vs Cognitively Normal x Occasion	-.118	.073	.108
MCI Converter vs Cognitively Normal x Occasion	-.052	.065	.423
Gender			
Age	.262	.049	**< .001**
Education	.088	.051	.086
Occasion	.055	.019	**.004**
Motor Severity	-.037	.027	.177

SE = Standard error; Sig. = significance (significant p values shown in bold). Gender was coded as: 0 = male, 1 = female.

MLM: Predictors of p-tau/ab (*N* = 393)

	Estimate	SE	Sig.
MCI Stable vs. Cognitively Normal	.081	.147	.581
MCI Reverter vs Cognitively Normal	.037	.152	.805
MCI Converter vs Cognitively Normal	.032	.073	.661
MCI Stable vs Cognitively Normal x Occasion	-.039	.067	.556
MCI Reverter vs Cognitively Normal x Occasion	-.136	.071	.059
MCI Converter vs Cognitively Normal x Occasion	-.034	.061	.579
Gender			
Age	.267	.048	**< .001**
Education	.106	.050	**.033**
Occasion	.055	.019	**.004**
Motor Severity	-.049	.026	.066

SE = Standard error; Sig. = significance (significant p values shown in bold). Gender was coded as: 0 = male, 1 = female.

MLM: Predictors of p-tau/tau (*N* = 393)

	Estimate	SE	Sig.
MCI Stable vs. Cognitively Normal	-.087	.162	.591
MCI Reverter vs Cognitively Normal	-.238	.168	.157
MCI Converter vs Cognitively Normal	.177	.082	**.032**
MCI Stable vs Cognitively Normal x Occasion	-.112	.075	.139
MCI Reverter vs Cognitively Normal x Occasion	.021	.080	.788
MCI Converter vs Cognitively Normal x Occasion	.076	.069	.274
Gender			
Age	.179	.053	**< .001**
Education	.136	.054	**.013**
Occasion	-.014	.021	.499
Motor Severity	-.049	.030	.112

SE = Standard error; Sig. = significance (significant p values shown in bold). Gender was coded as: 0 = male, 1 = female.

MLM: Predictors of asyn (*N* = 393)

	Estimate	SE	Sig.
MCI Stable vs. Cognitively Normal	-.182	.152	.233
MCI Reverter vs Cognitively Normal	-.311	.160	.052
MCI Converter vs Cognitively Normal	.036	.082	.658
MCI Stable vs Cognitively Normal x Occasion	.141	.064	**.030**
MCI Reverter vs Cognitively Normal x Occasion	.023	.073	.750
MCI Converter vs Cognitively Normal x Occasion	.109	.066	.101
Gender			
Age	.159	.051	**.002**
Education	-.007	.053	.892
Occasion	-.005	.019	.780
Motor Severity	-.014	.033	.662

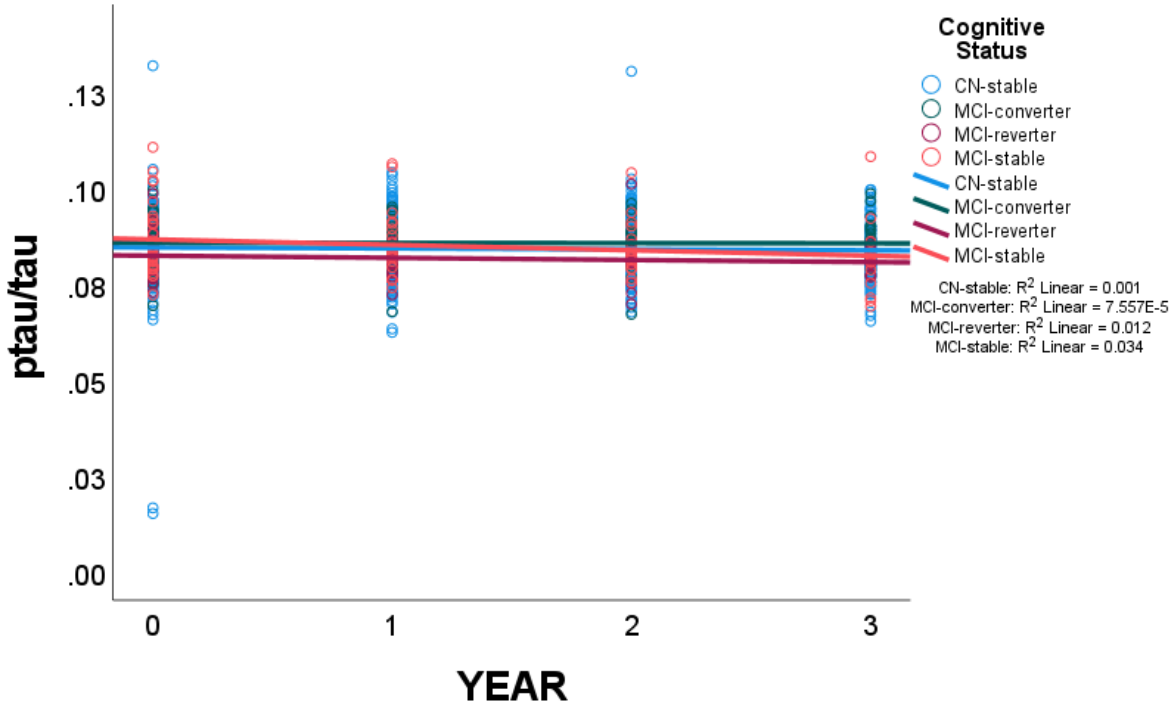
SE = Standard error; Sig. = significance (significant p values shown in bold). Gender was coded as: 0 = male, 1 = female.

APPENDIX C

FIGURE 1. MAIN EFFECT OF ELEVATED P-TAU/TAU RATIO AMONG MCI CONVERTERS

Figure 1.

Main Effect of Elevated P-Tau/Tau Ratio Among MCI Converters

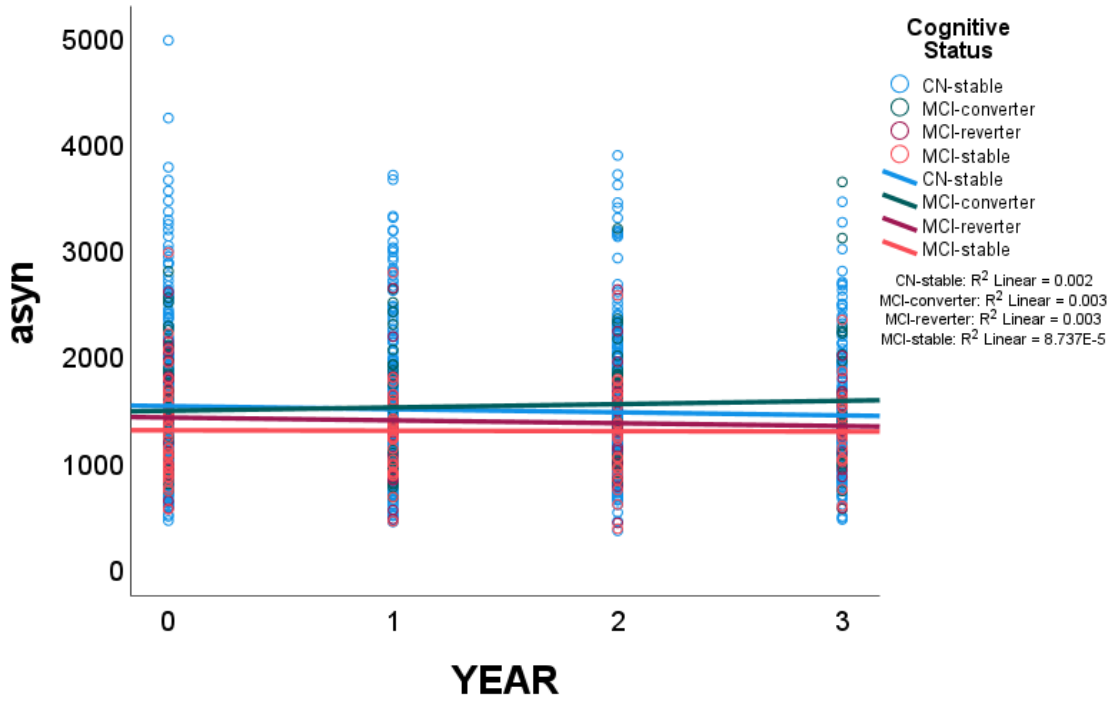


APPENDIX D

FIGURE 2. MCI STABLE COMPARED TO CN BY OCCASION IN ALPHA-SYNUCLEIN

Figure 2.

Cognitive Status by Year and Change in Alpha Synuclein (asyn)

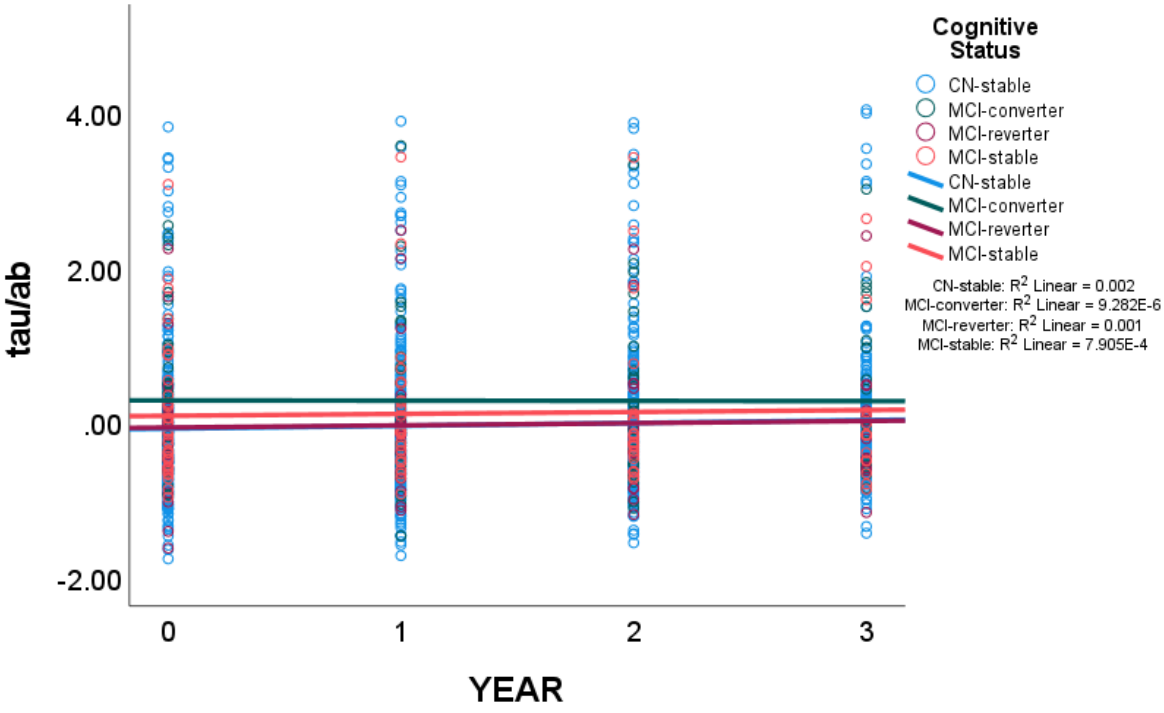


APPENDIX E

FIGURE 3. TAU/AB RATIO OVER TIME

Figure 3.

Cognitive Status by Year and No Change or Main Effect in tau/ab ratio

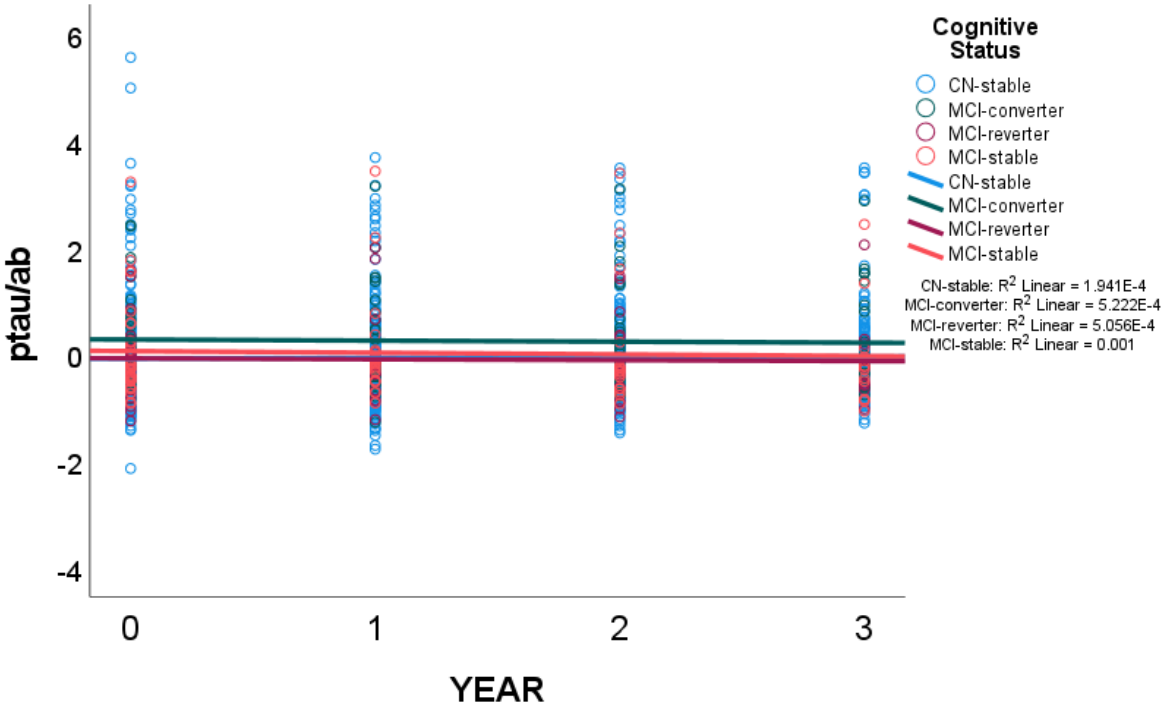


APPENDIX F

P-TAU/AB RATIO OVER TIME

Figure 4.

Cognitive Status by Year and No Change in p-tau/ab ratio



REFERENCES

Aarsland D., Andersen K., Larsen J.P., Lolk A., Nielsen H., Kragh-Sorensen P. (2001). Risk of dementia in Parkinson's disease: A community-based, prospective study. *Neurology*. 56:730–736. doi: 10.1212/WNL.56.6.730.

Aarsland, D., Batzu, L., Halliday, G.M. *et al.* (2021). Parkinson's disease-associated cognitive impairment. *Nature Review Disease Primers 7(*47). https://doi.org/10.1038/s41572-021-00280-3

Armstrong M.J., Okun M.S., Diagnosis and treatment of parkinson disease: A review. *Journal of the American Medical Association.* 2020;323(6):548–560. doi:10.1001/jama.2019.22360

Ascherio, A., & Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. *The Lancet Neurology*, 15(12), 1257-1272.

Bachhuber T, Katzmarski N, McCarter JF, Loreth D, Tahirovic S, Kamp F, Abou-Ajram C, Nuscher B, Serrano-Pozo A, Müller A, Prinz M, Steiner H, Hyman BT, Haass C, Meyer-Luehmann M. Inhibition of amyloid-β plaque formation by α-synuclein. *Nature Medicine*. 2015 Jul;21(7):802-7. doi: 10.1038/nm.3885. Epub 2015 Jun 22. PMID: 26099047.

Bäckström, D., Granåsen, G., Domellöf, M. E., Linder, J., Jakobson Mo, S., Riklund, K., Zetterberg, H., Blennow, K., & Forsgren, L. (2018). Early predictors of mortality in parkinsonism and Parkinson disease: A population-based study. *Neurology*, *91*(22), e2045–e2056. https://doi.org/10.1212/WNL.0000000000006576

Bäckström, D., Granåsen, G., Mo, S. J., Riklund, K., Trupp, M., Zetterberg, H., Blennow, K., Forsgren, L., & Domellöf, M. E. (2022). Prediction and early biomarkers of

cognitive decline in Parkinson disease and atypical parkinsonism: a population-based study. *Brain Communications*, *4*(2), fcac040. https://doi.org/10.1093/braincomms/fcac040

Bayram, E., Kaplan, N., Shan, G., & Caldwell, J. (2020). The longitudinal associations between cognition, mood and striatal dopaminergic binding in Parkinson's Disease. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *27*(4), 581–594. https://doi.org/10.1080/13825585.2019.1653445

Becker S, Bäumer A, Maetzler W, Nussbaum S, Timmers M, Van Nueten L, Salvadore G, Zaunbrecher D, Roeben B, Brockmann K, Streffer J, Berg D, Liepelt-Scarfone I. Assessment of cognitive-driven activity of daily living impairment in non-demented Parkinson's patients. (2020). *Journal of Neuropsychology*. (1):69-84. doi: 10.1111/jnp.12173. Epub 2018 Oct 15. PMID: 30320954.

Bellomo, G., Paolini Paoletti, F., Chipi, E., Petricciuolo, M., Simoni, S., Tambasco, N., & Parnetti, L. (2020). A/T/(N) Profile in Cerebrospinal Fluid of Parkinson's Disease with/without Cognitive Impairment and Dementia with Lewy Bodies. *Diagnostics (Basel, Switzerland)*, *10*(12), 1015. https://doi.org/10.3390/diagnostics10121015

Benton, A. L., Hamsher, K. D., Varney, N. R., & Spreen, O. (1983). Judgment of line orientation. New York, NY: Oxford University Press.

Biundo, R., Weis, L., Fiorenzato, E., Pistonesi, F., Cagnin, A., Bertoldo, A., Anglani, M., Cecchin, D., & Antonini, A. (2021). The contribution of beta-amyloid to dementia in Lewy body diseases: a 1-year follow-up study. *Brain Communications*, *3*(3), fcab180. https://doi.org/10.1093/braincomms/fcab180

Brandt, J., & Benedict, R. H. B. (2001). Hopkins verbal learning test—revised, professional manual. Lutz, FL: Psychological Assessment Resources.

Brunnström, H. R., & Englund, E. M. (2009). Cause of death in patients with dementia disorders. *European Journal of Neurology*, *16*(4), 488–492. https://doi.org/10.1111/j.1468-1331.2008.02503.x

Buongiorno, M., Compta, Y., & Martí, M. J. (2011). Amyloid-β and τ biomarkers in Parkinson's disease-dementia. *Journal of the Neurological Sciences*, *310*(1-2), 25–30. https://doi.org/10.1016/j.jns.2011.06.046

Burré, J. (2015). The Synaptic Function of α-Synuclein. *Journal of Parkinson's Disease*, *5*(4), 699–713. https://doi.org/10.3233/JPD-150642

Chung, S. J., Park, Y.-H., Yoo, H. S., Lee, Y. H., Ye, B. S., Sohn, Y. H., Lee, J.-M., & Lee, P. H. (2019). Mild cognitive impairment reverters have a favorable cognitive prognosis and cortical integrity in Parkinson's disease. *Neurobiology of Aging*, *78*, 168–177. https://doi.org/10.1016/j.neurobiolaging.2019.02.023

Chung, S. J., Yoo, H. S., Oh, J. S., Kim, J. S., Ye, B. S., Sohn, Y. H., & Lee, P. H. (2018). Effect of striatal dopamine depletion on cognition in de novo Parkinson's disease. *Parkinsonism & Related Disorders*, *51*, 43–48. https://doi.org/10.1016/j.parkreldis.2018.02.048

Cipriani, S., Chen, X., & Schwarzschild, M. A. (2010). Urate: a novel biomarker of Parkinson's disease risk, diagnosis and prognosis. *Biomarkers in Medicine*, *4*(5), 701–712. https://doi.org/10.2217/bmm.10.94

Cohen T, Guo J, Hurtado D, Kwong L, Mills I, Trojanowski J, and others. 2011. The acetylation of tau inhibits its function and promotes pathological tau aggregation. *Nature Communications* 2:252.

Compta, Y., Martí, M. J., Ibarretxe-Bilbao, N., Junqué, C., Valldeoriola, F., Muñoz, E., Ezquerra, M., Ríos, J., & Tolosa, E. (2009). Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *24*(15), 2203–2210. https://doi.org/10.1002/mds.22594

Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or Impaired Cognitive Function in Parkinson’s Disease as a Function of Dopaminergic Medication and Task Demands. *Cerebral Cortex* 11, 1136–1143. https://doi.org/10.1093/cercor/11.12.1136

Dang, M., Yang, C., Chen, K., Lu, P., Li, H., Zhang, Z., & Beijing Aging Brain Rejuvenation Initiative, for the Alzheimer’s Disease Neuroimaging Initiative (2023). Hippocampus-centred grey matter covariance networks predict the development and reversion of mild cognitive impairment. *Alzheimer's Research & Therapy*, *15*(1), 27. https://doi.org/10.1186/s13195-023-01167-z

Diao J, Burre J, Vivona S, Cipriano DJ, Sharma M, Kyoung M, Sudhof TC, & Brunger AT (2013) Native alphasynynuclein induces clustering of synaptic-vesicle mimics via binding to phospholipids and synaptobrevin-2/VAMP2. Elife, 2,e00592.

Duff, K., Beglinger, L. J., Schultz, S. K., Moser, D. J., McCaffrey, R. J., Haase, R. F., Westervelt, H. J., Langbehn, D. R., Paulsen, J. S., & Huntington's Study Group (2007). Practice effects in the prediction of long-term cognitive outcome in three

patient samples: a novel prognostic index. *Archives of Clinical Neuropsychology: the Official Journal of the National Academy of Neuropsychologists*, *22*(1), 15–24. https://doi.org/10.1016/j.acn.2006.08.013

Dugger, B. N., & Dickson, D. W. (2017). Pathology of Neurodegenerative Diseases. *Cold Spring Harbor Perspectives in Biology*, *9*(7), a028035. https://doi.org/10.1101/cshperspect.a028035

Elman, J. A., Jak, A. J., Panizzon, M. S., Tu, X. M., Chen, T., Reynolds, C. A., Gustavson, D. E., Franz, C. E., Hatton, S. N., Jacobson, K. C., Toomey, R., McKenzie, R., Xian, H., Lyons, M. J., & Kremen, W. S. (2018). Underdiagnosis of mild cognitive impairment: A consequence of ignoring practice effects. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *10*, 372–381. https://doi.org/10.1016/j.dadm.2018.04.003

Emamzadeh F. N. (2016). Alphasynynuclein structure, functions, and interactions. *Journal of Research in Medical Sciences: the Official Journal of Isfahan University of Medical Sciences*, *21*, 29. https://doi.org/10.4103/1735-1995.181989

Fan, T. S., Liu, S. C., & Wu, R. M. (2021). Alpha-Synuclein and Cognitive Decline in Parkinson Disease. *Life (Basel, Switzerland)*, *11*(11), 1239. https://doi.org/10.3390/life11111239

Fitzgerald, E., Murphy, S., & Martinson, H. A. (2019). Alpha-Synuclein Pathology and the Role of the Microbiota in Parkinson's Disease. *Frontiers in Neuroscience*, *13*, 369. https://doi.org/10.3389/fnins.2019.00369

Galloway P, Bergeron C, Perry G. 1989. The presence of tau distinguishes Lewy bodies of diffuse Lewy body disease from those of idiopathic Parkinson disease. Neurosci Lett 100(1–3):6–10.

Goetz, C. G., Emre, M., & Dubois, B. (2009). Parkinson's disease dementia: Definitions, guidelines, and research perspectives in diagnosis. Annals of Neurology, 64(S2), S81–S92. doi:10.1002/ana.21455

Goetz, C. G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G. T., ... & Holloway, R. (2007). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Movement Disorders*, 22(1), 41-47.

Goldman, J. G., Aggarwal, N. T., & Schroeder, C. D. (2015). Mild cognitive impairment: An update in parkinson's disease and lessons learned from alzheimer's disease. *Neurodegenerative Disease Management*, *5*(5), 425–443. https://doi.org/10.2217/nmt.15.34

Golomb, J., Kluger, A., Ferris, S.H. (2004). Mild cognitive impairment: Historical development and summary of research. *Dialogues in Clinical Neuroscience*, *6*(4), 351–367. https://doi.org/10.31887/DCNS.2004.6.4/jgolomb

Haber S. N. (2014). The place of dopamine in the cortico-basal ganglia circuit. *Neuroscience*, *282*, 248–257. https://doi.org/10.1016/j.neuroscience.2014.10.008

Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2004). Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. Lutz, FL: Psychological Assessment Resources.

Hu, Q., Wang, Q., Li, Y., Xie, Z., Lin, X., Huang, G., Zhan, L., Jia, X., & Zhao, X. (2022). Intrinsic brain activity alterations in patients with mild cognitive impairment-to-normal reversion: A resting-state functional magnetic resonance imaging study from voxel to whole-brain level. *Frontiers in Aging Neuroscience*, *13*, 788765. https://doi.org/10.3389/fnagi.2021.788765

Indiana University PPMI Biorepository (2020, June 10). *PPMI biologics manual: PPMI biospecimen collection, processing, and shipment manual.* PPMI. PPMI Biologics Manual V9.pdf (ppmi-info.org)

Jellinger, K. A., & Korczyn, A. D. (2018). Are dementia with lewy bodies and parkinson's disease dementia the same disease*? BMC Medicine, 16(1).* doi:10.1186/s12916-018-1016-8

Jones, J. D., Kuhn, T. P., & Szymkowicz, S. M. (2017). Reverters from PD-MCI to cognitively intact are at risk for future cognitive impairment: Analysis of the PPMI cohort. *Parkinsonism & Related Disorders*, *47*, 3–7. https://doi.org/10.1016/j.parkreldis.2017.12.006

Jones, J. D., Kurniadi, N. E., Kuhn, T. P., Szymkowicz, S. M., Bunch, J., & Rahmani, E. (2019). Depressive symptoms precede cognitive impairment in de novo Parkinson's disease patients: Analysis of the PPMI cohort. *Neuropsychology, 33*(8), 1111–1120. https://doi.org/10.1037/neu0000583

Jones, J. D., Rivas, R., Luna, K., Ryczek, C. A., & Thomas, K. R. (2023). Subjective cognitive complaints are important in PD-MCI criteria: Associations with CSF markers and cognitive decline. *Parkinsonism & Related Disorders*, *106*, 105221. https://doi.org/10.1016/j.parkreldis.2022.11.013

Kawabata, K., Watanabe, H., Bagarinao, E., Ohdake, R., Hara, K., Ogura, A., Masuda, M., Kato, T., Tsuboi, T., Maesawa, S., Katsuno, M., & Sobue, G. (2020). Cerebello-basal ganglia connectivity fingerprints related to motor/cognitive performance in Parkinson's disease. *Parkinsonism & Related Disorders*, *80*, 21–27. https://doi.org/10.1016/j.parkreldis.2020.09.005

Klein, C., & Westenberger, A. (2012). Genetics of Parkinson's Disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(1), a008888–a008888.

Koepsell, T. D., & Monsell, S. E. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. *Neurology*, *79*(15), 1591–1598. https://doi.org/10.1212/WNL.0b013e31826e26b7

Larsen K. E., Schmitz Y., Troyer M.D., Mosharov E., Dietrich P., Quazi A.Z., Savalle M., Nemani V., Chaudhry F.A., Edwards R.H., Stefanis L., & Sulzer D. (2006) Alphasynynuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. *Journal of Neuroscience*, 26, 11915-11922.

Lau A, Tymianski M. Glutamate receptors, neurotoxicity and neurodegeneration. Pflugers Arch. 2010 Jul;460(2):525-42. doi: 10.1007/s00424-010-0809-1. Epub 2010 Mar 14. PMID: 20229265.

Lin, C. H., Yang, S. Y., Horng, H. E., Yang, C. C., Chieh, J. J., Chen, H. H., Liu, B. H., & Chiu, M. J. (2017). Plasma α-synuclein predicts cognitive decline in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *88*(10), 818–824. https://doi.org/10.1136/jnnp-2016-314857

Liu S., Ninan I., Antonova I., Battaglia F., Trinchese F., Narasanna A., Kolodilov N., Dauer W., Hawkins R.D., & Arancio O. (2004) alpha synuclein produces a long-lasting increase in neurotransmitter release. *EMBO Journal*, 23,4506-4516.

Long, X., Jiang, C., & Zhang, L. (2018). Morphological Biomarker Differentiating MCI Converters from Nonconverters: Longitudinal Evidence Based on Hemispheric Asymmetry. *Behavioural Neurology*, *2018*, 3954101. https://doi.org/10.1155/2018/3954101

Lu, J., Li, X., Wang, Q., & Pei, G. (2017). Dopamine D2 receptor and β-arrestin 2 mediate Amyloid-β elevation induced by anti-parkinson's disease drugs, levodopa and piribedil, in neuronal cells. *PloS One*, *12*(3), e0173240. https://doi.org/10.1371/journal.pone.0173240

MacDonald, P.A., MacDonald, A.A., Seergobin, K.N., Tamjeedi, R., Ganjavi, H., Provost, J.-S., Monchi, O., 2011. The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson’s disease: support from functional MRI. *Brain* 134, 1447–1463. https://doi.org/10.1093/brain/awr075

Marino B. LB., de Souza L.R., Sousa K.P.A., Ferreira J.V., Padilha E.C., da Silva C.H.T.P., Taft C.A., Hage-Melim L.I.S. (2020). Parkinson's Disease: A Review from Pathophysiology to Treatment. *Mini Review Medical Chemistry* ;20(9):754-767. doi: 10.2174/1389557519666191104110908. PMID: 31686637.

Masliah E., Rockenstein E., Veinbergs I., Mallory M., Hashimoto M., Takeda A., Sagara Y., Sisk A., & Mucke L. (2000) Dopaminergic loss and inclusion body formation in alphasynynuclein mice: Implications for neurodegenerative disorders. *Science*, 287, 1265-1269.

Martin E.D., Gonzalez-Garcia C., Milan M., Farinas I., & Cena V. (2004) Stressor-related impairment of synaptic transmission in hippocampal slices from alphasynynuclein knockout mice. *European Journal of Neuroscience*, 20, 3085-3091.

Martínez-Horta, S., & Kulisevsky, J. (2011). Is all cognitive impairment in Parkinson's disease "mild cognitive impairment"? *Journal of Neural Transmission, 118*, 1185-1190.

Meder, D., Herz, D. M., Rowe, J. B., Lehéricy, S., & Siebner, H. R. (2018). *The role of dopamine in the brain - Lessons learned from Parkinson's disease. NeuroImage.* doi:10.1016/j.neuroimage.2018.11.021

Mery, V. P., Gros, P., Lafontaine, A. L., Robinson, A., Benedetti, A., Kimoff, R. J., & Kaminska, M. (2017). Reduced cognitive function in patients with Parkinson disease and obstructive sleep apnea. *Neurology*, *88*(12), 1120–1128. https://doi.org/10.1212/WNL.0000000000003738

Mironova, Y.S.; Zhukova, I.A.; Zhukova, N.G.; Alifirova, V.M.; Izhboldina, O.P.; Latypova, A.V. Parkinson's disease and glutamate excitotoxicity. *Zh Nevrol. Psikhiatrii. Imeni S. S. Korsakova,* 2018, *118*(6. Vyp. 2), 50-54.

Modreanu, R., Cerquera, S. C., Martí, M. J., Ríos, J., Sánchez-Gómez, A., Cámara, A., Fernández, M., & Compta, Y. (2017). Cross-sectional and longitudinal associations of motor fluctuations and non-motor predominance with cerebrospinal τ and Aβ as well as dementia-risk in Parkinson's disease. *Journal of the Neurological Sciences*, *373*, 223–229. https://doi-org.libproxy.lib.csusb.edu/10.1016/j.jns.2016.12.064

Montine, T. J., Shi, M., Quinn, J. F., Peskind, E. R., Craft, S., Ginghina, C., Chung, K. A., Kim, H., Galasko, D. R., Jankovic, J., Zabetian, C. P., Leverenz, J. B., & Zhang, J. (2010). CSF Aβ(42) and tau in Parkinson's disease with cognitive impairment. *Movement Disorders: Official Journal of the Movement Disorder Society*, *25*(15), 2682–2685. https://doi.org/10.1002/mds.23287

Moradi, K., Faghani, S., Abdolalizadeh, A., Khomeijani-Farahani, M., Ashraf-Ganjouei, A., & Alzheimer's Disease Neuroimaging Initiative (2021). Biological Features of Reversion from Mild Cognitive Impairment to Normal Cognition: A Study of Cerebrospinal Fluid Markers and Brain Volume. *Journal of Alzheimer's disease Reports*, *5*(1), 179–186. https://doi.org/10.3233/ADR-200229

Nabizadeh, F., Pirahesh, K. & Ramezannezhad, E. Longitudinal striatal dopamine transporter binding and cerebrospinal fluid alpha-synuclein, amyloid beta, total tau, and phosphorylated tau in Parkinson's disease. *Neurological Science* 44, 573–585 (2023). https://doi.org/10.1007/s10072-022-06440-x

Nazem, S., Siderowf, A. D., Duda, J. E., Brown, G. K., Ten Have, T., Stern, M. B., & Weintraub, D. (2008). Suicidal and death ideation in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *23*(11), 1573–1579. https://doi.org/10.1002/mds.22130

Nemani V.M., Lu W., Berge V., Nakamura K., Onoa B., Lee M.K., Chaudhry F.A., Nicoll R.A., & Edwards R.H. (2010). Increased expression of alphasynynuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. *Neuron*, 65, 66-79.

Noyce, A. J., Bestwick, J. P., Silveira, M. L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Annals of Neurology*, *72*(6), 893–901. https://doi-org.libproxy.lib.csusb.edu/10.1002/ana.23687

Palmeri, R., Buono, V. L., Bonanno, L., Allone, C., Drago, N., Sorbera, C., Cimino, V., di Lorenzo, G., Bramanti, A., & Marino, S. (2020). Impaired recognition of facial emotion in patients with Parkinson disease under dopamine therapy. *Journal of Geriatric Psychiatry and Neurology*, *33*(5), 265–271. https://doi-org.libproxy.lib.csusb.edu/10.1177/0891988719882094

Park M.H. & Han C. (2015). Is there an MCI reversion to cognitively normal? Analysis of alzheimer's disease biomarkers profiles. *International Psychogeriatrics*. 2015 Mar;27(3):429-37. doi: 10.1017/S1041610214002129. Epub 2014 Sep 26. PMID: 25255915.

Petersen R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x

Pedersen, Kenn Freddy; Larsen, Jan Petter; Tysnes, Ole-Bjørn; Alves, Guido (2017). Natural course of mild cognitive impairment in Parkinson disease*. Neurology, 88*(8)*, 767–774.* doi:10.1212/WNL.0000000000003634

Phongpreecha, T., Cholerton, B., Mata, I. F., Zabetian, C. P., Poston, K. L., Aghaeepour, N., Tian, L., Quinn, J. F., Chung, K. A., Hiller, A. L., Hu, S. C., Edwards, K. L., & Montine, T. J. (2020). Multivariate prediction of dementia in

Parkinson's disease. *NPJ Parkinson's Disease*, *6*, 20. https://doi.org/10.1038/s41531-020-00121-2

Pîrşcoveanu D.F.V., Pirici I., Tudorică V., Bălşeanu T.A., Albu V.C., Bondari S., Bumbea A.M., Pîrşcoveanu M. (2017). Tau protein in neurodegenerative diseases - a review. *Romanian Journal of Morphology Embryology*. 58(4):1141-1150. PMID: 29556602.

Postuma R.B., Aarsland D., Barone P., Burn D.J., Hawkes C.H., Oertel W., et al. Identifying prodromal Parkinson's disease: Pre-motor disorders in Parkinson's disease. *Movement Disorders*. 2012 Apr 15;27(5):617–26.

Przedborski S. (2008) Neurodegeneration. In: Gendelman H.E., Ikezu T. (eds) Neuroimmune Pharmacology. Springer, Boston, MA. https://doi.org/10.1007/978-0-387-72573-4_17.

Ravdin, L. D., & Katzen, H. L. (Eds.). (2013). *Handbook on the Neuropsychology of Aging and Dementia*. Springer New York. https://doi.org/10.1007/978-1-4614-3106-0

Riedel M, Goldbaum O, Richter-Landsberg C (2009) Alphasynynuclein promotes the recruitment of tau to protein inclusions in oligodendroglial cells: effects of oxidative and proteolytic stress. *Journal of Molecular Neuroscience,* 39:226–234. doi:10.1007/s12031-009-9190-y

Riedel O., Klotsche J., Spottke A., et al. (2010) Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease. *Journal of Neurology*. 257(7):1073–1082. doi: 10.1007/s00415-010-5465-z.

Roberts, R. O., Knopman, D. S., Mielke, M. M., Cha, R. H., Pankratz, V. S., Christianson, T. J. H., Geda, Y. E., Boeve, B. F., Ivnik, R. J., Tangalos, E. G., Rocca, W. A., & Petersen, R. C. (2014). Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology*, *82*(4), 317–325. https://doi.org/10.1212/WNL.0000000000000055

Sako, W., Abe, T., Matsumoto, Y., Nakamura, K., Haji, S., Osaki, Y., Harada, M., & Izumi, Y. (2021). The Cerebellum Is a Common Key for Visuospatial Execution and Attention in Parkinson's Disease. *Diagnostics (Basel, Switzerland)*, *11*(6), 1042. https://doi.org/10.3390/diagnostics11061042

Sanderson-Cimino, M., Elman, J. A., Tu, X. M., Gross, A. L., Panizzon, M. S., Gustavson, D. E., Bondi, M. W., Edmonds, E. C., Eglit, G. M. L., Eppig, J. S., Franz, C. E., Jak, A. J., Lyons, M. J., Thomas, K. R., Williams, M. E., Kremen, W. S., & Alzheimer's Disease Neuroimaging Initiative (2022). Cognitive practice effects delay diagnosis of MCI: Implications for clinical trials. *Alzheimer's & Dementia (New York, N. Y.)*, *8*(1), e12228. https://doi.org/10.1002/trc2.12228

Sanderson-Cimino, M., Elman, J. A., Tu, X. M., Gross, A. L., Panizzon, M. S., Gustavson, D. E., Bondi, M. W., Edmonds, E. C., Eppig, J. S., Franz, C. E., Jak, A. J., Lyons, M. J., Thomas, K. R., Williams, M. E., & Kremen, W. S. (2022). Practice Effects in Mild Cognitive Impairment Increase Reversion Rates and Delay Detection of New Impairments. *Frontiers in Aging Neuroscience*, *14*, 847315. https://doi.org/10.3389/fnagi.2022.847315

Saredakis, D., Collins-Praino, L., Gutteridge, D., Stephan, B. C., & Keage, H. A. D. (2019). Conversion to MCI and dementia in Parkinson’s disease: a systematic

review and meta-analysis. *Parkinsonism & Related Disorders*. doi:10.1016/j.parkreldis.2019.04.020

Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: A case-control study. *Lancet Neurology*. 2015 (1):57–64.

Scorza, F. A., Guimarães-Marques, M., Nejm, M., de Almeida, A., Scorza, C. A., Fiorini, A. C., & Finsterer, J. (2022). Sudden unexpected death in Parkinson's disease: Insights from clinical practice. *Clinics (Sao Paulo, Brazil)*, *77*, 100001. https://doi.org/10.1016/j.clinsp.2021.100001

Shen, B., Pan, Y., Jiang, X., Wu, Z., Zhu, J., Dong, J., Zhang, W., Xu, P., Dai, Y., Gao, Y., Xiao, C., & Zhang, L. (2020). Altered putamen and cerebellum connectivity among different subtypes of Parkinson's disease. *CNS neuroscience & Therapeutics*, *26*(2), 207–214. https://doi.org/10.1111/cns.13259

Shimada, H., Doi, T., Lee, S., & Makizako, H. (2019). Reversible predictors of reversion from mild cognitive impairment to normal cognition: a 4-year longitudinal study. *Alzheimer's Research & Therapy*, *11*(1), 24. https://doi.org/10.1186/s13195-019-0480-5

Smith, A. (1982). Symbol digit modalities test (SDMT) manual. Los Angeles, CA: Western Psychological Services.

Spies, P. E., Verbeek, M. M., van Groen, T., & Claassen, J. A. (2012). Reviewing reasons for the decreased CSF Abeta42 concentration in Alzheimer disease. *Frontiers in Bioscience (Landmark edition)*, *17*(6), 2024–2034. https://doi.org/10.2741/4035

Stoker, T. B., Greenland, J. C., & John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK (Eds.). (2018). *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018

Teravskis, P. J., Ashe, K. H., & Liao, D. (2020). The Accumulation of Tau in Postsynaptic Structures: A Common Feature in Multiple Neurodegenerative Diseases? *The Neuroscientist*, *26*(5–6), 503–520. https://doi.org/10.1177/1073858420916696

Thomas, K. R., Edmonds, E. C., Eppig, J. S., Wong, C. G., Weigand, A. J., Bangen, K. J., Jak, A. J., Delano-Wood, L., Galasko, D. R., Salmon, D. P., Edland, S. D., Bondi, M. W., & Alzheimer's Disease Neuroimaging Initiative (2019). MCI-to-normal reversion using neuropsychological criteria in the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*, *15*(10), 1322–1332. https://doi.org/10.1016/j.jalz.2019.06.4948

Thomas, K.R., Eppig, J.S., Weigand, A.J., Edmonds, E.C., Wong, C.G., Jak, A.J., Delano-Wood, L., Galasko, D.R., Salmon, D.P., Edland, S.D. & Bondi, M.W. (2019). Artifically low mild cognitive impairment to normal reversion rate in alzheimer's disease neuroimaging initiative. *Alzheimer's & Dementia* 15.

Tomaazewski, S., Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., & DeCarli, C. (2009). Progression of Mild Cognitive Impairment to Dementia in Clinic- vs Community-Based Cohorts. *Archives of Neurology*, *66*(9). https://doi.org/10.1001/archneurol.2009.106

Vermunt, L., van Paasen, A. J. L., Teunissen, C. E., Scheltens, P., Visser, P. J., Tijms, B. M., & for the Alzheimer's Disease Neuroimaging Initiative. (2019). Alzheimer disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal. *Neurology*, *92*(23), e2699–e2705. https://doi.org/10.1212/WNL.0000000000007609

Wallin, A., Göthlin, M., Gustavsson, M., Zetterberg, H., Eckerström, C., Blennow, K., Edman, A., Lind, K., Nordlund, A., & Rolstad, S. (2011). Progression from mild to pronounced MCI is not associated with cerebrospinal fluid biomarker deviations. *Dementia and Geriatric Cognitive Disorders*, *32*(3), 193–197. https://doi.org/10.1159/000333034

Wechsler, D. (2008). Wechsler adult intelligence scale—fourth edition (WAIS–IV). San Antonio, TX: The Psychological Corporation.

Weil, R.S., Costantini, A.A. & Schrag, A.E. (2018). Mild Cognitive Impairment in Parkinson's Disease—What Is It? *Current Neurology Neuroscience Reports* 18(*17*). https://doi.org/10.1007/s11910-018-0823-9

Wu, T.H., Lu, Y.N., Chuang, C.L., Wu, C.L., Chiang, A.S., Krantz, D.E,, et al. (2013). Loss of vesicular dopamine release precedes tauopathy in degenerative dopaminergic neurons in a Drosophila model expressing human tau. *Acta Neuropathology.* 125:711–725.

Wyman-Chick, K. A., Martin, P. K., Minár, M., Menéndez-González, M., Erickson, L. O., Álvarez-Avellón, T., & Schroeder, R. W. (2018). Neuropsychological test performance in parkinsonism without dopaminergic deficiency on [123I]-FP-CIT

SPECT imaging. *Journal of the International Neuropsychological Society*, *24*(6), 646–651. https://doi-org.libproxy.lib.csusb.edu/10.1017/S1355617718000164

Xia R, Mao ZH. Progression of motor symptoms in Parkinson's disease. *Neuroscience Bulletin*. 2012 Feb;28(1):39-48. doi: 10.1007/s12264-012-1050-z. PMID: 22233888; PMCID: PMC5560285.

Yan, Y., Ren, S., Duan, Y., Lu, C., Niu, Y., Wang, Z., Inglis, B., Ji, W., Zheng, Y., & Si, W. (2021). Gut microbiota and metabolites of α-synuclein transgenic monkey models with early stage of Parkinson's disease. *NPJ Biofilms and Microbiomes*, *7*(1), 69. https://doi.org/10.1038/s41522-021-00242-3

Zanetti, O., Solerte, S. B., & Cantoni, F. (2009). Life expectancy in Alzheimer's disease (AD). *Archives of Gerontology and Geriatrics*, *49 Suppl 1*, 237–243. https://doi.org/10.1016/j.archger.2009.09.035

Zhang X, Gao F, Wang D, Li C, Fu Y, He W, Zhang J. Tau Pathology in Parkinson's Disease. *Frontiers Neurology*. 2018 Oct 2;9:809. doi: 10.3389/fneur.2018.00809. PMID: 30333786; PMCID: PMC6176019.

Zhou, C., Guan, X. J., Guo, T., Zeng, Q. L., Gao, T., Huang, P. Y., Xuan, M., Gu, Q. Q., Xu, X. J., & Zhang, M. M. (2020). Progressive brain atrophy in Parkinson's disease patients who convert to mild cognitive impairment. *CNS Neuroscience & Therapeutics*, *26*(1), 117–125. https://doi.org/10.1111/cns.13188