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BIOMARKERS OF OBJECTIVE CRITERIA FOR SUBTLE COGNITIVE DECLINE IN PARKINSON'S DISEASE

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BIOMARKERS OF OBJECTIVE CRITERIA FOR SUBTLE COGNITIVE DECLINE IN PARKINSON'S DISEASE

A Thesis

Presented to the

Faculty of

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In Partial Fulfillment

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Master of Science

in

Clinical Counseling Psychology

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by

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ABSTRACT

Mild cognitive impairment in Parkinson's disease (PD-MCI) is the continuum from normal cognitive function to dementia. Recent studies suggest that objectively defined subtle cognitive decline (Obj-SCD), which uses non-traditional "process" neuropsychological scores, may be a better pathway to earlier detection of cognitive impairment. Obj-SCD has been defined as the stage where cognition is not impaired, but biomarkers are present or cognitive impairment is minimal but not sufficient to meet MCI or dementia criteria. We examined the longitudinal trajectories of neurodegenerative markers among individuals who are classified as cognitive normal (CN), Obj-SCD, and PD-MCI. Past literature has been inconsistent about the utility of subjective complaints to improve prediction of cognitive decline. Therefore, we investigated the associations between cerebrospinal fluid (CSF) markers with objective (i.e., neuropsychological process scores) and subjective markers as a second aim. Participants from the PPMI study (N=295) were classified as cognitively normal (CN), objectively defined subtle cognitive decline (Obj-SCD), or mild cognitive impairment in Parkinson's Disease (PD-MCI). Obj-SCD criteria was determined using three neuropsychological alternative/process scores. CSF was collected from participants via a lumbar puncture over 3 annual follow-ups. Samples were analyzed to detect tau (total tau), phosphorylated tau (p-tau), and amyloid beta (ab) using an enzyme-linked immunosorbent assay (ELISA). Tau and ab markers were examined as ratios: tau/ab, p-tau/ab and p-tau/tau. At baseline, 223 (76%)

individuals were classified as CN, 46 (16%) were classified as PD-MCI, and 26 (9%) were classified as Obj-SCD. Analyses failed to find any group differences in any of the CSF markers. Regarding aim 2, we found that subjective reports of cognitive difficulties, but not objective process scores, were significantly associated with worse biomarker outcomes (greater amounts of p-tau/ab and tau/ab). Although prior research has indicated that Obj-SCD is a risk factor for PD-MCI, Obj-SCD was not an intermediate group between CN and PD-MCI in CSF markers. Conversely, the association of subjective cognitive complaints with worse biomarker outcomes is consistent with previous findings that subjective complaints may have clinical utility in detecting cognitive decline.

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CHAPTER ONE:

INTRODUCTION

Neurodegenerative disorders (NDDs) are those which primarily affect individuals in their late adulthood. NDDs are characterized by persistent neuron loss which creates neurological deficits, behavioral changes, and functional and motor decline in the brain (Cummings, 2017). One of the most common neurological disorders is Parkinson's disease (PD) which involves the premature death of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc) (Katia & Lang, 2015). These neurons are important for voluntary movement regulation, goal-directed behaviors, and the learning of habits (Luo and Huang, 2016). Thus, dopaminergic neuron deficit leads to the presentation of the core motor symptoms of Parkinson's disease (i.e., rigidity, slowness, and tremor) (Armstrong and Okun, 2020).

The loss of dopamine neurons is one of the main pathological features of Parkinson's disease while another pathological hallmark is Lewy pathology. Lewy bodies (LBs) are composed of more than 90 proteins which are mainly made up of ubiquitin (i.e., a protein that helps regulate the process of other proteins in the body) and alpha-synuclein (Balestrino & Schapira, 2019). Alpha-synuclein is associated with presynaptic terminal function and the regulation of dopamine, but it tends to misfold and form intracellular inclusions. This cluster is formed from toxic oligomeric and proto-fibrillar forms which ultimately leads to neuronal degeneration (Winer, et al., 2018; Balestrino & Schapira, 2019).

Epidemiology

Parkinson’s disease affects individuals in their late adulthood (i.e., peeking between 85 to 89 years of age) but can be detected as early as 50 years of age (Armstrong and Okun, 2020). On average, the disease progresses over 15 years from the moment of diagnosis to death (Lees, Hardy, and Revesz, 2009). Armstrong and Okun (2020) also note that PD is most common in men, with a 1.4:1.0 male-to-female ratio. Additionally, it is believed that some of the PD sex differences may partly be due to estrogen being a neuroprotective factor in women (Smith and Dahodwala, 2014). Although Parkinson's disease is idiopathic, there are known genetic and environmental risk factors. Some of the genetic markers that are associated with mental deterioration in PD are apolipoprotein E (APOE), and catechol-O-methyltransferase (COMT) genotypes which are important for dopamine regulation, and microtubule-associated protein-tau (MAPT) which is responsible for tau regulation (Tropea et al., 2018). Kouli et al., (2018) highlighted the impact of environmental elements as risk factors for PD, such as cigarette smoking, caffeine, pesticides, herbicides, and heavy metals. Male sex, older age, motor severity, duration of the disease, depression, and psychosis have also been identified as greater risk factors for Parkinson's disease dementia (PDD). PDD is characterized by a severe cognitive decline that interferes with activities of daily living (Goldman and Litvan, 2011).

Although incidence rates have been found to vary across racial groups, research by Dahodwala et al. (2009) suggests that healthcare disparities may

perpetuate racial differences in patients with PD (e.g., African Americans are less likely to be diagnosed than Caucasians) and that biological differences could potentially contribute to some of these racial differences. Additionally, Dahodwala et al. found that African Americans in their study were twice as likely to be undiagnosed with PD when compared to white participants. The researchers also note that the racial disparities that exist within the healthcare system can be attributed to multiple factors such as clinician biases, stereotyping, access to care, and even legal policy (Dahodwala et al., 2009).

Motor Symptoms

Parkinson's disease is best represented by its cardinal motor features: akinesia, tremor, rigidity, and postural instability (Ha et al., 2013). Typically, individuals with PD first experience tremor symptoms which appear at rest and disappear upon action. Akinesia (i.e., loss of or delayed initiation of movement) bradykinesia (i.e., slowing of movement), and hypokinesia (i.e., the reduced amplitude of movement) are key impairments required for the diagnosis of PD. Akinesia and rigidity tend to be unilateral in PD patients. At the onset, most of these symptoms can often be confused with problems caused by a contralateral tumor or stroke as well as normal aging symptoms and/or depression. Postural instability, which typically isn't present at the onset of symptoms, is described as falls and difficulty with maintaining balance. Gait imbalance is also present in individuals with PD which is typically seen as shuffling steps (Ha, et al., 2013).

Akinesia is the key impairment required for the diagnosis of PD and is usually the blanket term for the other two impairments that occur in PD: bradykinesia (i.e., slowing of movement) and hypokinesia (i.e., the reduced amplitude of movement). Dystonia (i.e., involuntary contraction of the muscles) is also a common feature of PD when treatment either goes wrong or is lacking. Dystonia can occur throughout the entire body both in action and at rest. Dystonia rarely manifests on its own as a direct symptom of PD. Dystonic features can most commonly be observed in the legs or lower limbs as opposed to the upper limbs and neck which is an uncommon manifestation (Ha, et al., 2013).

Cognitive Symptoms

Cognitive symptoms in PD can range from mild cognitive disturbances to full-blown dementia. Clinical risk factors related to dementia (e.g., age, depression, olfactory loss, visual hallucinations, etc.) and the form and magnitude of brain pathology can dictate when patients will develop symptoms of cognitive impairment; however, all PD patients will eventually develop dementia (Aarsland and Bernadotte, 2015; Hely et. al., 2009). While some patients develop mild selective disturbances (e.g., memory and information processing) following the first few years after disease onset, others do not develop dementia until 20 or more years after onset (Aarsland and Bernadotte, 2015). Attention, memory, information processing, verbal fluency, and executive and visuospatial

functioning are all domains that are affected early on by PD and can be classified as dopamine-dependent (i.e., alleviated or exacerbated by dopamine replacement therapy) (McGregor and Nelson, 2019). Attention can be classified into three distinct categories: sustained, selective, and divided. Typically, individuals with PD can experience difficulties in all three areas of attention ranging from mild symptoms (e.g., forgetting grocery items) to major symptoms (e.g., easily distracted by mild stimuli, keeping up with conversations, etc.). Information processing and memory deficits can be observed as impairment in both short-term and long-term memory and difficulties with common tasks like paying bills and using the stove. Issues in verbal fluency or language can range from issues with finding words (e.g., the tip of the tongue phenomenon) to issues in producing language, poor articulation, and misnaming objects (Parkinson's Foundation, 2022). In PD patients, impairment in visuospatial functioning can be observed as disorientation and decreased mobility while impaired posture, balance, and gait are directly associated with impairments in executive functioning (Lally et al., 2020).

Impairments in attention, memory, information processing, verbal fluency, and executive and visuospatial functioning all pose issues for individuals living with PD which can be particularly observed in their activities of daily living (ADLs) (e.g., planning, remembering, organizing, etc.). Difficulties in ADLs are often intensified in individuals with PDD and further complicate individuals' ability to successfully carry out gainful employment and independent living (Mack &

Marsh, 2017). Additionally, deficits in episodic memory and visuospatial function are cognitive symptoms that can be deemed as dopamine independent. Illusions and hallucinations are also dopamine-independent non-motor symptoms and are typically present later in the development of the disease and could potentially be worsened by dopamine replacement therapy (McGregor and Nelson, 2019).

Mechanisms of Cognitive Impairment in PD

It is believed that a combination of alpha-synuclein, the development of comorbid Alzheimer's disease, and cerebrovascular factors are related to cognitive decline in PD (Winer, et al., 2018). Brain cells negatively affected by the accumulation of the alpha-synuclein protein contribute to both motor and non-motor symptoms. Alpha-synuclein gathers in the substantia nigra (region of the brainstem important for dopamine synthesis) and spreads from subcortical to cortical regions. Braak et al (2003) developed a six-stage model of hypothesized PD spread based on alpha-synuclein pathology which maps the clinical progression of PD. Deterioration first occurs at the olfactory bulb and dorsal vagal nucleus and progressively results in subcortical and cortical alpha-synuclein aggregation and degeneration toward later stages. At autopsy, PD patients in late stages show widespread pathology of alpha-synuclein in the brain compared to patients without dementia (Irwin and Hurtig, 2018).

Comorbid Alzheimer's Disease Pathology

Alzheimer's Disease (AD) is another neurodegenerative disorder characterized by dementia. AD pathology is attributed to the buildup of amyloid beta (Aβ) (i.e., a peptide that develops into toxic plaques in the brain) and neurofibrillary tangles (i.e., tau threads that tangle inside a cell and lead to deficits of neuronal networks) (Ewers et al., 2011). Cerebrospinal fluid biomarkers are the best way to follow the progression of AD. Specifically, t-tau, p-tau, and Aβ are the CSF biomarkers that are commonly used to distinguish individuals with normal cognition from those with AD (Tapiola et al., 2009). Although markers of t-tau, p-tau, and Aβ are traditionally associated with AD, there is also research suggesting they are important markers of cognitive impairment and disease severity in PD. Biomarkers of cognitive impairment in PD have been identified as higher cerebrospinal fluid (CSF) total tau (t-tau) and phosphorylated tau (p-tau) and lower amyloid beta 42 (Aβ42) (Tropea et al., 2018).

Cerebrospinal Fluid Biomarkers

Findings indicate that AD CSF biomarkers are also present at normal or lower levels when PD patients are examined. Hall et al. (2015) indicate that greater synaptic degeneration in PD can be associated with an increased release of alpha-synuclein[α-Syn]) into the interstitial fluid and CSF. Higher levels of p-tau can also be detected in the striatum of individuals with PD and PDD. Greater

levels of αSyn and p-tau have been associated with the progression of motor symptoms in PD. Decreased cognitive function in PD has been linked to increased αSyn and decreased Aβ42 in CSF. Hall et al. (2015) conducted a longitudinal study using PD patients without dementia. After the baseline assessments, researchers collected CSF and blood samples from PD participants who were also continuously examined for neurological, psychiatric, and cognitive changes. In comparison to the control group (i.e., neurologically healthy individuals), those with PD had significantly lower levels of αSyn, tau, and p-tau. Additionally, Hall et al. (2015) found associations between participants who had PD for a longer amount of time and who took the levodopa-equivalent daily dose (LEDD) (i.e., the total amount of each PD medication combined) with increased CSF levels of Aβ42. However, there were no significant correlations between PD duration or LEDD and tau, p-tau, or αSyn.

Schrag et al. (2017) analyzed cognitive performance in participants from the Parkinson's Progression Markers Initiative (PPMI) study using scores from the Montreal Cognitive Assessment (MoCA), demographic and clinical data, APOE status, and CSF biomarkers. Specifically, the predictive value of CSF biomarkers was assessed using the difference in MoCA scores across two years, 2 year follow-up MoCA scores, and cognitive impairment diagnosis (i.e., MCI classification or dementia). CSF ratio of Aβ42 to total tau was associated with a decrease in MoCA scores across time. Moreover, high accuracy of the prediction

of cognitive impairment at 2 years was found to be associated with Aβ42 among other variables (e.g., olfactory dysfunction, etc.) (Schrag et al., 2017).

Mild Cognitive Impairment and PDD

Mild cognitive impairment (MCI) refers to a transitional stage between individuals who are cognitively unimpaired to those with PDD. About 80% of individuals diagnosed with PD will develop PDD 15 to 20 years after onset (Hely et al., 2008). While PDD predominantly affects executive function, visuospatial function, and attention, it affects areas like language and declarative memory in later stages. Although MCI is commonly used to understand cognitive decline experienced by patients with Alzheimer's disease (AD), mild cognitive impairment in PD (PD-MCI) can also be understood as the continuum from normal cognitive function to dementia.

Furthermore, PD-MCI can affect both non-amnestic and amnestic phenotypes and their respective subtypes (i.e., amnestic single domain, amnestic multiple domains, non-amnestic single domain, and non-amnestic multiple domain). Amnestic MCI single domain refers to the presence of a single memory impairment while amnestic MCI multiple domain is the presence of memory impairment accompanied by a non-memory impairment. A single non-memory impairment refers to non-amnestic MCI single domain and two or more non-memory impairments refer to a non-amnestic MCI multiple domain. Impairment

within the non-amnestic single domain tends to be most prevalent therefore most frequently affecting the executive function domain (Goldman and Litvan, 2011).

The Role of Subjective Complaints in MCI

In theory, the construct of PD-MCI has clinical utility because it may increase patients' quality of life by providing earlier interventions and treatment. PD-MCI can be seen as an antecedent to PDD and a risk factor for depression, lower life quality, and greater mortality rates (Jones et al., 2021). Previously, PD-MCI was recognized as the earliest stage of cognitive decline which represented the period between normal cognition and PD dementia (Goldman and Litvan, 2011). However, recent studies suggest a stage that precedes the onset of PD-MCI and can potentially allow for earlier detection of cognitive impairment. Subjective cognitive complaints (SCC) by PD patients have been found to predict both PD-MCI and PDD. However, it is likely that the clinical profile of PD patients such as depression and anosognosia (i.e., the lack of insight into one’s cognitive impairment) can reduce the accuracy of subjective self-report measures of cognition.

Studies from AD populations provide evidence that subjective reports may be problematic. Participants from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) were used to assess longitudinal change in the discrepancy between participant report and informant reporting on the Everyday Cognition questionnaire (ECog) across amnestic MCI, mixed MCI, and cluster-derived

normal (CDN)(i.e., MCI false positive group) subtypes and normal control (NC) participants (Edmonds et al., 2018). At baseline and two-year follow-up evaluations, participants were assessed for SCC using the ECog. Discrepancy scores between the participant report and informant report were then calculated. Researchers concluded that cognitive impairment is not predicted by self-report accounts of SCC based on findings where there was an increase of ECog discrepancy scores across time compared to CDN and NC groups whose performance was cognitively normal throughout the entirety of the study. Specifically, discrepancies between the scores of the MCI subtype participants indicate a gradual lack of awareness of cognitive deficits which is associated with AD CSF biomarkers (i.e., Aβ42, p-tau, and t-tau) (Edmonds et al., 2018).

Galtier et al (2019) conducted a long-term study to follow PD participants with subjective cognitive decline (SCD) as a risk factor for dementia. Differences in evaluating distinct cognitive domains versus only gathering memory complaint information as ways of assessing SCD were compared using a neuropsychological protocol (i.e., tests for each cognitive domain). Participants were classified as healthy controls (HC, N=20) or PD participants (N=43) with subclassifications of PD-SCD (i.e., PD patients with subjective cognitive decline), PD-MCI (i.e., PD patients with mild cognitive impairment) or PD-nSCD (i.e., PD patients without subjective cognitive decline). All participants were followed for an average of seven and a half years after the initial baseline assessment.

Attention was measured using the Digit span backward and Stroop color-word Test. Verbal fluency tasks and the Wisconsin Card Sorting Test (WCST) were administered to examine executive functioning. Memory was examined using the California Verbal Learning Test (CVLT) and the Spatial Recall Test. The Judgement of Line Orientation Test (JLOT, 15-item simplified version) and the Block design subtest (WAIS-III, 6 designs simplified version) served to examine visual function. Language was assessed using the Naming Test, a task of 20 pictorial visual stimuli representing actions. Results indicated that 30.2% of participants were classified as PD-SCD as indicated by the neuropsychological protocol whereas only 23.25% of participants met PD-SCD criteria when only focusing on memory complaints. The remaining 18.6% of patients were classified as PD-nSCD. The most frequent memory complaints were in the language and memory domains; however, no significant differences were found between HC groups and PD-SCD across any of the cognitive domain measures. Additionally, results demonstrated the language and memory domains to be good predictors of dementia based on discriminant function and logistic regression analyses. Moreover, follow-up assessments demonstrated clinically diagnosed dementia in PD-MCI (50%), PD-SCD (33.3%), and PD-nSCD (14.3%) (Galtier, et al., 2018). Overall, this study found that subjective complaints may have some utility in improving the prediction of cognitive decline and dementia. However, other researchers have found that subjective complaints are more strongly associated

with depressive symptoms, rather than cognitive impairment, which may limit its clinical utility as a marker of cognitive impairment (Edmonds et al., 2015).

Objective Criteria for Subtle Cognitive Decline (Obj-SCD)

Objective criteria/measures, rather than subjective complaints, may be a better pathway to understanding the preceding stages of PD-MCI (Jones et al., 2021). Specifically, objectively defined subtle cognitive decline (Obj-SCD) has been defined as the stage where cognition is not impaired, but biomarkers are present or cognitive impairment is minimal but not sufficient to meet MCI or dementia criteria (Edmonds et al., 2015). Research suggests that process scores (i.e., scores that measure an individual's attempt to complete a task on neuropsychological memory tests) serve as a method of identifying those who are at risk of developing cognitive impairment before being diagnosed with dementia or MCI (Jones et al., 2021).

Biomarker studies, among non-PD older adults, support the hypothesis that Obj-SCD may be a stage preceding MCI. An intermediate amount of amyloid and tau has been found in those with Objectively defined subtle cognitive decline (Obj-SCD) compared to those who were classified as cognitively normal or with MCI. The Obj-SCD participants tend to transition to MCI/AD faster than control groups by up to more than double the rate and display faster rates of amyloid accumulation and entorhinal cortex thinning (Thomas et al., 2018).

Moreover, the effectiveness of Obj-SCD criteria has been recently examined in PD patients. Jones and colleagues (2021) were the first to analyze Obj-SCD among individuals with PD opposed to previous studies that examined Obj-SCD in the AD population. Participants (N=483) were newly diagnosed PD patients classified as CN, Obj-SCD, PD-MCI, or PDD. Five different standard tests measured attention, processing speed, visuospatial functioning, verbal fluency, verbal learning, and verbal delayed recall. Learning slope, recognition of false positives, and IIV were computed as alternative/process scores to classify Obj-SCD (Jones et al., 2021).

Analyses revealed that Obj-SCD (i.e., impairment on 1 standard test/1 process score, or 2+ impaired process scores) was a risk factor for PD-MCI (i.e., impairment on ≥ 2/5 standard tests without functional impairment due to cognitive complaints) or PDD (i.e., impairment on ≥ 2/5 standard tests and subjective report of functional impairment due to cognitive complaints) when compared to the cognitively normal (CN) group (i.e., no indication of cognitive impairment on standard tests or process scores). Obj-SCD was also observed as an intermediate stage of cognitive and functional impairment relative to CN and PD-MCI groups. These findings demonstrate that Obj-SCD criteria can potentially identify individuals at risk for cognitive impairment that is not defined by PD-MCI criteria. However, Jones et al. (2021) suggest that further investigations (such as studies utilizing biomarkers of neurodegeneration) are needed to support the utility of Obj-SCD.

CHAPTER TWO:

METHODS

Aims:

The first aim of the present study is to examine the relationship between neurodegenerative markers (t-tau, p-tau, Aβ, α-Syn) and the cognitive status of participants (CN, Obj-SCD, PD-MCI). We predict that the Obj-SCD group will be an intermediate group between CN and PD-MCI in CSF markers. This is based on past finds from the Alzheimer's/aging population. Obj-SCD is an intermediate group between CN and MCI.

The second aim of the study is to investigate the associations between CSF markers with objective markers (e.g. process measures from neuropsychological tests) and subjective markers (e.g. self-report/informant report of subjective cognitive difficulties) of SCD. Past literature has been inconsistent about the utility of subjective markers to improve the prediction of cognitive decline. Therefore, we predict that CSF markers of neurodegeneration will be associated with objective neuropsychological process scores more than subjective cognitive complaints.

Methods

Data will be obtained from the Parkinson's Markers Initiative (PPMI). The PPMI is a longitudinal multisite study that includes newly diagnosed and

untreated individuals. The study received institutional review board approval from all study locations, and all participants provided informed consent. The present study is estimated to consist of a sample of 358 participants. All participants were followed for up to 3 years (first, second, and third year). Participants performed neuropsychological, mood, and subjective cognitive complaint testing yearly.

Neuropsychological Tests

Participants completed a series of neuropsychological tests at each visit. The following measures were used to assess attention (Letter-Number Sequencing task), processing speed (Symbol Digit Modalities Test [SDMT], verbal fluency (Animal Fluency), verbal learning, and verbal delayed recall (Hopkins Verbal Learning Test-Revised [HVLT-R]; Trials 1-3 and Delayed Recall), and visuospatial functioning (Judgement of Line Orientation [JOLO]). The neuropsychological tests' total scores were converted into z-scores and normed on demographic variables.

Obj-SCD criteria were determined using three neuropsychological alternative/process scores. Intraindividual variability (IIV) was computed using the standard deviation of the five neuropsychological scores (Letter-Number Sequencing, SDMT, JOLO, Animal fluency, HVLT-R Learning, and Delayed Recall). The learning slope (Trial 3 raw score minus Trial 1 raw score) and recognition of false positive errors were calculated using the HVLT-R (Jones et al., 2021). The PPMI sample of baseline non-PD control participants was used to

measure normative z-scores for learning slope, recognition of false-positive errors, and IIV (Wyman-Chick et al., 2018).

Cognitive Status

Participants were categorized among the following cognitive classifications: cognitively normal (CN), objectively defined subtle cognitive decline (Obj-SCD), or mild cognitive impairment in Parkinson's Disease (PD-MCI). Performance > 1.5 standard deviations (SD) below the mean on standard neuropsychological tests (Letter-Number Sequencing, SDMT, JOLO, Animal fluency, HVLT-R Learning, and Delayed Recall) and process scores were indicative of an impaired score for all cognitive status categories. Participants with impaired scores on ≤1 neuropsychological measure or process scores were classified as CN. Participants were classified as Obj-SCD if they had either a) impairments on one standard test and one process score; or b) had two or more impaired process scores. Participants with a cognitive status of PD-MCI were defined as those who exhibited impaired performance on at least two or more standard tests but without the endorsement of functional difficulties attributed to cognitive symptoms.

Subjective Cognitive Complaints

Participants and/or study partners indicated whether (i.e., yes or no answers) decline of cognitive functioning in the participants was observed. If the participant, study partner, or both parties endorsed a worsening of memory or

cognitive symptoms then MCI participants were classified as having a cognitive complaint.

Motor Severity

Motor severity was measured using the Unified Parkinson's Disease Rating Scale- part III (UPDRS-III). Higher scores of motor symptoms (e.g., rigidity, slowness, and tremor) on the UPDRS-III are indicative of greater motor severity.

CSF Markers

See the biologics manual ppmi.info.org for details on collection, shipment, storage, and standard operating procedures at each site. In brief, 15-20 mL of CSF was collected from participants via a lumbar puncture over 3 annual follow-ups. Samples were analyzed to detect tau (total tau), phosphorylated tau (p-tau), amyloid beta (ab), and alpha-synuclein (α-Syn) using an enzyme-linked immunosorbent assay (ELISA). The Elecsys electrochemiluminescence immunoassays on the cobas e 601 platform were used. Tau and ab markers were examined as ratios: tau/ab, p-tau/ab, and p-tau/tau. Ratios were log-transformed to reduce problematic skewness and kurtosis. Asyn was not transformed (skewness and kurtosis values were less than 2). The tau/ab and p-tau/ab ratios are markers of Alzheimer's disease pathologies, while Asyn was included as a marker of PD/Lewy body pathology.

Statistical Analyses

Aim 1 will examine group differences (CN, Obj-SCD, PD-MCI) in CSF makers (t-tau, p-tau, Aβ, α-Syn). Multilevel modeling (MLM) analyses will be conducted. Missing data will be handled with maximum likelihood estimates. The dependent variable will be the CSF markers analyzed as ratios (tau/ab, p-tau/ab, and p-tau/tau). A separate analysis will be conducted for each marker, for a total of 4 analyses. Independent variables will include cognitive classification (CN, Obj-SCD, PD-MCI), age, gender, education, and motor severity.

Aim 2 will examine the association between neuropsychological process scores (IIV, false positive, learning slope), subjective cognitive complaints, and in CSF makers (p-tau, t-tau, Aβ, α-Syn). The dependent variable will be the CSF markers analyzed as ratios (tau/ab, p-tau/ab, and p-tau/tau). A separate analysis will be conducted for each marker, for a total of 4 analyses. Independent variables will include process scores (IIV, false positive, learning slope), subjective cognitive complaints, age, gender, education, and motor severity.

CHAPTER THREE:

RESULTS

At baseline, 223 participants (76%) were classified as CN, 26 (8.8%) classified as Obj-SCD and 46 (15.6%) classified as PD-MCI. Baseline sample information can be found in Table 1. There were no significant differences across cognitive groups on age, education, motor severity, LEDD, or CSF markers. The PD-MCI group had significantly lower scores on the MOCA relative to the Obj-SCD and CN groups. This is expected due to the clinical profile of those with PD-MCI.

AIM 1: Examine the Relationship Between Neurodegenerative Markers and the Cognitive Status of Participants.

Multilevel modeling examined if there were differences across the three cognitive groups (CN, Obj-SCD, PD-MCI) in CSF makers analyzed as ratios (tau/ab, p-tau/ab, and p-tau/tau). Results failed to find statistically significant group differences in any of the markers: tau/ab p-tau/ab, and p-tau/tau CSF markers (Refer to Table 2). However, education was positively associated with the p-tau/tau CSF marker. Additionally, age was positively associated with tau/ab and p-tau/ab, such that older age was associated with greater amounts of tau/ab (β=.256, 95% CI [.162, .350], p<.001) and p-tau/ab in CSF (β=.261, 95% CI [.167, .354], p<.001). Moreover, older age (β=.166, 95% CI [.069, .264],

p<.001), and higher levels of educational attainment (measured in years) (β=.123, 95% CI [.026, .219], p<.013) were associated with higher amounts of p-tau/tau.

AIM 2: Investigate the Associations between CSF Markers with Objective Markers and Subjective Markers of SCD.

Multilevel modeling also examined the association between neuropsychological process scores (IIV, false positive, learning slope), subjective complaints, and CSF markers as ratios (See table 3). Analyses revealed that the age of participants was strongly associated with CSF markers such that higher amounts of tau/ab, p-tau/ab, and p-tau/tau in CSF were associated with older age (β=.242, 95% CI [.146, .337], p<.001, β=.240, 95% CI [.147, .334], p<.007, β=.137, 95% CI [.038, .235], p<.001) however neuropsychological process scores and subjective cognitive complaints were not associated with any of the CSF markers.

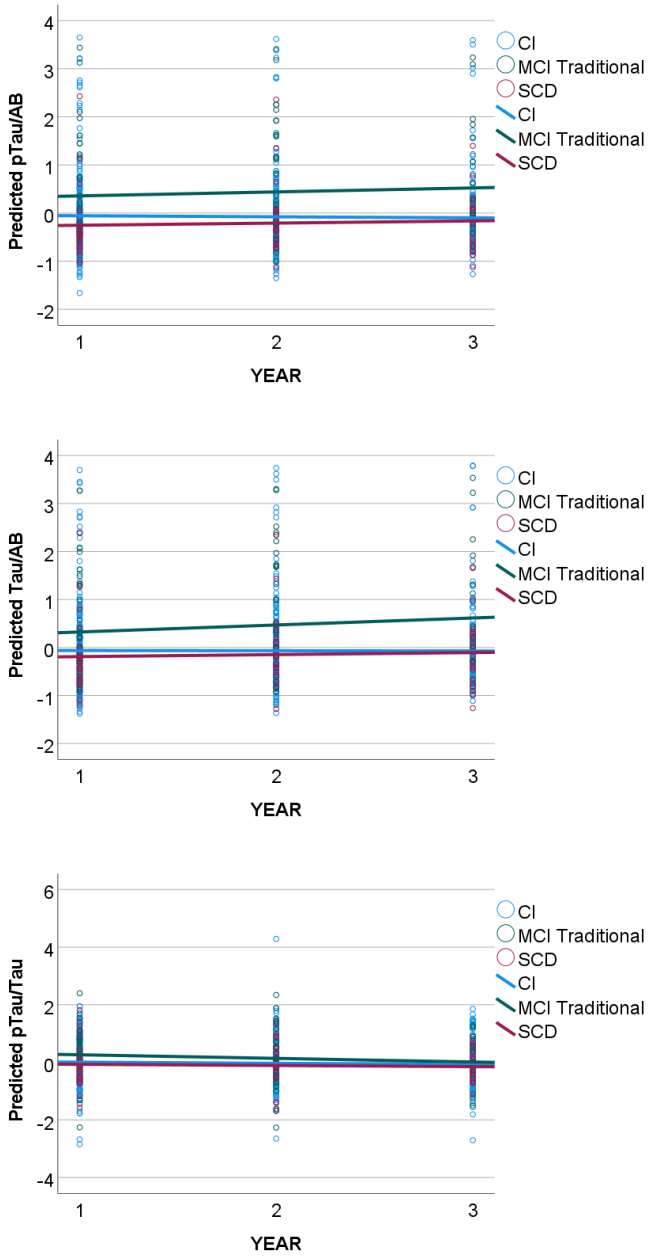

Figure 1. Differences in CSF Ratios Across Cognitive Groups.

Exploratory Aim: Subjective Cognitive Complaints (SCC) and Process Scores

As an exploratory aim, stepwise regressions were used to determine if SCC or objective markers (i.e., neuropsychological process scores) significantly predicted CSF markers analyzed as ratios (tau/ab, p-tau/ab, and p-tau/tau). Specifically, a stepwise approach was considered due to the potential for multi-collinearity among process scores and SCC, which could potentially reduce our ability to detect significance in models were variables are forced entered. A separate analysis was conducted for each marker, for a total of 3 analysis. Age and the Unified Parkinson's Disease Rating Scale motor scores were forced into the first block of each regression model. Secondly, scores from the three neuropsychological process scores measures (IIV, false positives, and learning slope) and subjective cognitive complaint measures were entered in stepwise fashion into the last block.

Results revelated that the overall model was significant [$F(1,752)=9.88$, $p<.001$, $R2=.103$]. Age and SCC significantly predicted the tau/ab CSF marker, whereas process scores and motor severity did not. Similarly, the overall model predicting p-tau/ab demonstrated good fit [$F(1,685)=26.674$, $p<.001$, $R2=.105$]. Age and SCC were the only significant predictors of the p-tau/ab marker. Lastly, age was a significant predictor of the p-tau/tau CSF marker; whereas subjective cognitive complaints, process scores, and motor severity did not significantly improve the model [$F(2,686)=8.763$, $p<.001$, $R2=.025$].

Table 1. Demographic and Clinical Information

N=358

	CN (n=223)		Obj-SCD (n=26)		PD-MCI (n=46)			
	M	SD	M	SD	M	SD	*p*	Contrast
Age	61.6	9.6	58.7	8.9	62.2	8.3	0.261	--
% Male	64.1%	--	76.9%	--	69.6%	--		--
% White	94.6%	--	96.2%	--	82.6%	--		--
Education	15.5	2.6	15.7	3.3	15.6	2.8	0.895	--
MDS-UPDRS III	24.11	10.6	28.1	12.4	25.15	9.8	0.209	--
LEDD	309	210	386	446	253	166	0.164	--
MOCA	27	2.3	26.4	2.1	24.2	3.2	<0.001	CN >Obj-SCD > PD-MCI
α-Syn	1449	606	1377	605	1400	564	.777	--
Tau/ab	.205	.11	.19	.08	.24	.13	.109	--
P-tau/ab	.020	.01	.01	.008	0.02	.01	.079	--
P-tau/tau	.083	.006	.083	.006	.086	.007	.123	--

CN = cognitively normal, Obj-SCD = objectively defined subtle cognitive decline, PD-MCI = mild cognitive impairment in Parkinson's Disease, MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale- Part III; LEDD = levodopa equivalent daily dose MOCA = Montreal Cognitive Assessment.

Table 2. Differences in CSF Markers and Cognitive Status of Participants.

	TAU/AB		P-TAU-AB		P-TAU-TAU	
Parameter	Unstandardized Estimate (95% CI)	p-value	Unstandardized Estimate (95% CI)	p-value	Unstandardized Estimate (95% CI)	p-value
Education	0.06 (-0.03 to 0.15)	0.208	0.08 (-0.01 to 0.17)	0.081	0.12 (0.02 to 0.22)	0.013
Motor Severity	-0.04 (-0.09 to -0.02)	0.198	-0.05 (-0.10 to 0.00)	0.091	-0.04 (-0.10 to 0.02)	0.166
Age	0.25 (0.16 to 0.35)	**< 0.001**	0.26 (0.17 to 0.35)	**<0.001**	0.17 (0.07 to 0.26)	**<0.001**
Gender	-0.04 (-0.24 to 0.15)	0.674	-0.02 (-0.22 to 0.17)	0.836	0.02 (-0.17 to 0.23)	0.803
CN vs Obj-SCD	0.06 (-0.08 to 0.20)	0.392	0.08 (-0.06 to 0.21)	0.267	-0.11 (-0.26 to 0.05)	0.174
PD-MCI vs Obj-SCD	0.12 (-0.05 to 0.29)	0.160	0.13 (-0.02 to 0.29)	0.094	-0.01 (-0.18 to 0.17)	0.956

CN = cognitively normal, Obj-SCD = objectively defined subtle cognitive decline, PD-MCI = mild cognitive impairment in Parkinson's Disease.

Table 3 Associations Between CSF Markers with Objective Markers and Subjective Markers of SCD

	TAU/AB		P-TAU-AB		P-TAU-TAU	
Parameter	Unstandardized Estimate (95% CI)	p-value	Unstandardized Estimate (95% CI)	p-value	Unstandardized Estimate (95% CI)	p-value
Education	0.08 (-0.15 to 0.17)	0.100	0.08 (-0.01 to 0.17)	0.100	0.12 (0.02 to 0.22)	0.014
Motor Severity	-0.03 (-0.10 to -0.03)	0.281	-0.03 (-0.09 to 0.02)	0.281	-0.04 (-0.11 to 0.02)	0.217
Age	0.24 (0.14 to 0.33)	**< 0.001**	0.24 (0.14 to 0.34)	**<0.001**	0.14 (0.04 to 0.23)	0.007
Gender	-0.04 (-0.25 to 0.16)	0.664	-0.04 (-0.25 to 0.16)	0.664	0.01 (-0.19 to 0.22)	0.896
IIV	-0.00 (-0.06 to 0.06)	0.934	-0.00 (-0.06 to 0.05)	0.934	-0.00 (-0.07 to 0.06)	0.906
False Positives	-0.01 (-0.06 to 0.04)	0.000	-0.01 (-0.05 to 0.04)	0.667	-0.00 (-0.05 to 0.05)	0.870
Learning Slope	0.03 (-0.02 to 0.08)	0.206	-0.89 (-0.02 to 0.08)	0.206	0.00 (-0.19 to 0.13)	0.719
SCC	-0.09(-0.22 to 0.04)	0.194	-0.10 (-0.24 to 0.03)	.124	-0.03(-0.19 to 0.13)	.719

IIV = Intraindividual variability
SCC= Subjective cognitive complaints

CHAPTER FOUR:

DISCUSSION

One of the known risk factors of cognitive decline among those with Parkison's disease includes the development of comorbid Alzheimer's disease (Winer, et al., 2018). Past biomarker studies among individuals who are cognitively normal in the Alzheimer's Disease Neuroimaging Initiative (ADNI) suggest that Obj-SCD is a stage of cognitive decline that precedes MCI (Thomas et al., 2018). Based on this premise, the present study aimed to examine the relationship between neurodegenerative markers and the cognitive status of participants. We predicted that the Obj-SCD group would serve as an intermediate group between those who are cognitively normal (CN) and those with mild cognitive impairment in Parkinson's disease (PD-MCI). The second aim of the study was to investigate the associations between CSF markers with objective markers (e.g., process scores) and subjective markers (e.g., subjective cognitive complaints [SCC]) of subtle cognitive decline (SCD). The utility of subjective markers to improve the prediction of cognitive decline has been inconsistent in previous studies. Therefore, we predicted that CSF markers of neurodegeneration would be associated with objective neuropsychological process scores more than subjective cognitive complaints.

For the first aim of this study, analyses did not reveal statistically significant group differences in any of the CSF markers. A past study utilizing the Parkinson's Progression Markers Initiative (PPMI), provided support that Obj-

SCD serves as an intermediate group between those who are cognitively normal and those with PD-MCI or PDD (Jones et al., 2021). Specifically, the researchers found that individuals classified as Obj-SCD at baseline were at greater risk for developing PD-MCI or PDD within 5 years relative to the control group. Jones and colleagues (2021) were the first researchers to analyze Obj-SCD within a PD population, and the present study may be one of the first studies to analyze Obj-SCD within the context of CSF biomarkers.

Moreover, the clinical utility of Obj-SCD within the context of AD has been suggested as a sensitive and noninvasive predictor of neurodegeneration prior to frank cognitive impairment associated with MCI (Thomas et al., 2018). Specifically, higher rates of progression to dementia in early subtle cognitive decline (E-SCD) and late subtle cognitive decline (L-SCD) groups compared to the normal control group suggest that process scores hold the same clinical utility as total test scores during the preclinical stage of AD. Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cognitively normal participants from were classified as early SCD (E-SCD) if they scored >1 SD below the norm-adjusted mean on 2 process scores or on 1 process score plus 1 NP total score. Those who met existing SCD criteria of >1 SD below norm-adjusted mean on 2 NP total scores in different domains were classified as late SCD (L-SCD). Thomas and colleagues (2018) found that the E-SCD and L-SCD groups had a risk of progression to MCI that was 2.60 and 3.44 times greater than the cognitively normal group over 5 years. Additionally, there were

significant group differences in the proportion of positive markers for Aβ42, t-tau/ Aβ, and p-tau/ Aβ with greater biomarker positivity in the E-SCD, L-SCD, and MCI groups compared to the control group. There was also greater biomarker positivity in the MCI group compared to both SCD groups. Thomas et al (2018) findings suggest that the early, preclinical changes in cognition in the E-SCD and L-SCD groups coincide with AD biomarker changes. Relative to PD biomarker changes, the findings of the present study revealed that the Obj-SCD group was not found to be an intermediate group between CN and PD-MCI participants. Despite previous findings indicating that Obj-SCD served as an intermediate level of cognitive and functional impairment between those with normal cognition and those with PD-MCI (Jones et al., 2021), Obj-SCD may not be a useful indicator of those at risk for cognitive impairment who are not detected by PD-MCI criteria when examining CSF biomarkers.

For the second aim of the study, findings revealed that neuropsychological process scores and subjective cognitive complaints were not associated with any of the CSF markers. Previously, Thomas and colleagues (2018) demonstrated support for the idea that process scores may be integrated into the SCD criteria that allow for improved sensitivity and earlier identification of CN individuals at risk for cognitive decline prior to neuropsychological total scores. The process scores that were examined (learning slope, recognition, false positives, and IIV) have previously shown to predict progression from normal cognition to MCI in the preclinical pathogenesis of AD. Thomas et al., (2018) also found support for AD

biomarker changes (i.e., Aβ42, p-tau/ab, and t-tau/ab ratio) coinciding with early preclinical cognitive changes in E-SCD and late L-SCD groups. The present study analyzed tau/ab, p-tau/ab, and p-tau/tau CSF as ratios based on the premise that AD CSF biomarkers are also present at normal or lower levels when PD patients are examined (Tropea et al., 2018). Despite the previously established AD and PD comorbidity, our findings suggest that the CSF markers of cognitive decline in AD may not be significant markers of cognitive decline in PD when attempting to capture a stage between normal cognition and PD-MCI. However, the current study only analyzed CSF data within the first 3 years of PD progression in newly diagnosed participants. It is likely that CSF changes may have not been significant due to not having data that is representative of participants who have greater disease severity.

Since neither objective process scores nor SCC were associated with any marker in aim 2, we conducted an exploratory aim that could potentially increase sensitivity by reducing multicollinearity. Results revealed that subjective cognitive complaints were significant across the tau/ab and p-tau/ab CSF markers, but not the p-tau/tau CSF marker. These results are consistent with findings that SCC by PD patients are useful in predicting PD-MCI and PDD. Jones et al (2022) examined how incorporating SCC would affect the occurrence of PD-MCI and if the inclusion of SCC would be associated with faster cognitive decline and CSF markers (i.e., alpha-synuclein, amyloid beta, total tau, and phosphorylated tau.) Participants were classified as cognitively normal (CN), PD-MCI with subjective

cognitive complaints (PD-MCI + SCC) and PD-MCI without subjective cognitive complaints (PD-MCI –SCC). Results showed that PD-MCI + SCC experienced greater cognitive decline and had significantly higher levels of tau/ab and p-tau/ab compared to the other groups. This suggests that classifying PD-MCI only using neuropsychological criteria and excluding SCC may lead to greater incidences of PD-MCI. Jones et al (2023) suggested that inclusions of SCC in PD-MCI criteria in newly diagnosed PD participants may strengthen the ability to detect individuals at risk for future cognitive decline. The researchers also acknowledged that the cognitive decline could be related to AD changes rather than worse PD pathology.

However, there are inconsistencies in the literature regarding SCC as a meaningful predictor of PD-MCI. Erro et al (2014) did a longitudinal study on newly diagnosed, untreated PD patients with symptoms onset less than 2 years to evaluate whether subjective memory complaints would predict development of MCI over a 2-year follow-up evaluation. Results did not find any association between subjective complaints and presence of MCI at baseline. Similarly, Lehrner et al (2014) examined the prevalence of subjective memory complaints and depressive symptoms and their relation to cognitive functioning in 104 PD patients and 248 controls. Despite finding a significant correlation between subjective cognitive complaints and depressive symptoms, Lehrner et al (2014) did not find any correlations between subjective cognitive complaints and participants' performance on neuropsychological tests. Dupoy et al (2018)

developed a tool to assess SCC within PD by having group of experts in movements disorders and neurocognition create an easy-to-use tool based on a visual analogue scale (VAS) for five cognitive domains: memory, executive functions, spatial orientation, attention, and language. PD patients with disease duration of less than 5 years underwent neuropsychological testing and SCC was assessed twice within a 1 month interval. Dupoy et al (2018) found significant correlations across three cognitive domains (i.e., executive functions, language, and attention) and SCCs for those with PD. However, results failed to find a relationship between SCC and neuropsychological testing.

Limitations to our study include the sample consisting of participants who are mostly cognitively healthy and highly functioning (62%), whereas less than 7% of the participants met the criteria for Obj-SCD and less than 12% of participants met the criteria for PD-MCI. Participants were also predominantly White across the three cognitive groups (CN= 94.6%, Obj-SCD= 92.2%, PD-MCI= 82.6%). It would be important to acquire data that is equally representative of races other than White to reduce racial, ethnic, and other social disparities to better meet the needs of individuals with PD. As previously discussed, PPMI participants are comprised of individuals who are newly diagnosed with PD and therefore do not represent individuals who are in later stages of the disease progression. Future research studies should aim to analyze data that includes participants who are more advanced in disease severity and are therefore more likely to experience cognitive impairments.

Moreover, the present study included CSF marker PPMI data that was collected across 3 years. It is possible that having access to CSF data over a longer period would yield different results. A study that examined α-Syn CSF among unmedicated PD patients who participated in the deprenyl and tocopherol antioxidative therapy of Parkinson ism (DATATOP) study with 8 years of follow-up suggests that the predictive value of CSF α-Syn in cognitive decline may not be significant within a 3 year period. Stewart et al (2014) collected CSF at the beginning of phase 1 (i.e., before levodopa therapy) and phase 2 (i.e., during levodopa therapy) as they examined motor and cognitive function. It was found that CSF α-Syn levels significantly predicted the progression of cognitive decline over the phase 2 follow-up period, but not over phase 1. Cognitive scores tended to remain the same or increase during Phase 1 but decline over Phase 2. Specifically, it was indicated that participants with higher α-Syn levels in CSF showed a faster decline in cognitive performance. Furthermore, the researchers suggested that the more significant correlation between α-Syn and cognitive decline during phase 2 is likely because of a longer follow-up and disease progression rather than a consequence of the dopamine replacement therapy (Stewart et al., 2014).

Based on the findings from this study, it is unclear that the use of neuropsychological process scores (i.e., learning slope, false positive errors, and intraindividual variability) may serve to capture neurologic compromise and classify individuals with Obj-SCD before meeting criteria for MCI relative to CSF

markers. The clinical utility of subjective cognitive complaints and their association to objective criteria for cognitive impairment remains unclear. While the lack of support for SCC may be related to the clinical profile of individuals who are at risk for cognitive decline (e.g., anosognosia and depression), inconsistencies throughout the literature may be due to different methodologies used across studies. For example, Erro et al (2014) and Lehrner et al (2014) assessed subjective cognitive complaints as memory complaints whereas Dupoy et al (2018) assessed subjective cognitive complaints. Additionally, future studies looking to examine biomarkers of cognitive decline in PD may benefit by including CSF data that is captured throughout longer time points to effectively rule out whether CSF data can be used to capture cognitive decline in PD before an individual meets the criteria for PD-MCI. Continuing to investigate and establish biomarkers of cognitive decline within PD is important so that individuals may become aware of future cognitive impairments that may follow their PD diagnosis. Having established biomarkers would also allow PD patients to seek out the appropriate resources to increase their quality of life despite the presence of the disease. Therefore, more work is needed to develop consistent methodologies for SCC and to establish the clinical utility of Obj-SCD in PD.

REFERENCES

Aarsland, D., & Bernadotte, A. (2015). Epidemiology of dementia associated with Parkinson's disease. In *Cognitive Impairment and Dementia in Parkinson's Disease.* Oxford University Press. https://doi.org/10.1093/med/9780199681648.003.0002

Armstrong, M. J., & Okun, M. S. (2020). Diagnosis and treatment of Parkinson disease: A Review. JAMA: *The Journal of the American Medical Association*, 323(6), 548–560. https://doi.org/10.1001/jama.2019.22360

Balestrino, R., & Schapira, A. H. V. (2020). Parkinson disease. *European Journal of Neurology*, 27(1), 27–42. https://doi.org/10.1111/ene.14108

Braak, H., Tredici, K. D., Rüb, Udo, R., Rob, A.I., Ernst, N.H.J.S., Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, 24(2), 197–211. https://doi.org/10.1016/S0197-4580(02)00065-9

(n.d.). Cognitive Changes. Parkinson's Foundation. Retrieved January 14, 2022, from https://www.parkinson.org/understanding-parkinsons/non-movement-symptoms/cognitive

Cummings, J. L., & Pillai, J. A. (2016). Neurodegenerative diseases: evolving unifying principles. In *Neurodegenerative Diseases*. Oxford University Press, Incorporated.

Dahodwala, N., Siderowf, A., Xie, M., Noll, E., Stern, M., & Mandell, D. S. (2009). Racial differences in the diagnosis of Parkinson's disease. *Movement Disorders*, 24(8), 1200–1205. https://doi.org/10.1002/mds.22557

Dupouy, J., Ory-Magne, F., Mekies, C., Rousseau, V., Puel, M., Rerat, K., Pariente, J., Brefel-Courbon, C., Andrieu, P., Angibaud, G., Aranda, A., Attané, F., Azais, C., Balague, J. P., Benazet, M., Beziaud, A. ., Boulesteix, M., Boulloche, N., Carel, C., … Vidry, E. (2018). Cognitive complaint in early Parkinson's disease: A pilot study. *Acta Neurologica Scandinavica*, 137(1), 59–66. https://doi.org/10.1111/ane.12808

Edmonds, E. C., Delano-Wood, L., Galasko, D. R., Salmon, D. P., & Bondi, M. W. (2015). Subtle cognitive decline and biomarker staging in preclinical alzheimer's disease. *Journal of Alzheimer's Disease*, 47(1), 231–242. https://doi.org/10.3233/JAD-150128

Erro, R., Santangelo, G., Barone, P., Picillo, M., Amboni, M., Longo, K., Giordano, F., Moccia, M., Allocca, R., Pellecchia, M. T., & Vitale, C. (2014). Do subjective memory complaints herald the onset of mild cognitive impairment in Parkinson disease? *Journal of Geriatric Psychiatry and Neurology*, 27(4), 276–281. https://doi.org/10.1177/0891988714532015

Ewers, M., Sperling, R. A., Klunk, W. E., Weiner, M. W., & Hampel, H. (2011). Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends in Neurosciences* (Regular Ed.), 34(8), 430–442. https://doi.org/10.1016/j.tins.2011.05.005

Galtier, I., Nieto, A., Lorenzo, J. N., & Barroso, J. (2019). Subjective cognitive decline and progression to dementia in Parkinson's disease: a long-term follow-up study. *Journal of Neurology*, 266(3), 745–754. https://doi.org/10.1007/s00415-019-09197-0

Goldman, J. G., & Litvan, I. (2011). Mild cognitive impairment in Parkinson's disease. *Minerva Medica*, 102(6), 441

Hall, S., Surova, Y., Öhrfelt, A., Zetterberg, H., Lindqvist, D., & Hansson, O. (2015). CSF biomarkers and clinical progression of Parkinson disease. *Neurology*, 84(1), 57–63. https://doi.org/10.1212/WNL.0000000000001098

Hely, M. A., Reid, W. G. J., Adena, M. A., Halliday, G. M., & Morris, J. G. L. (2008). The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders*, 23(6), 837–844. https://doi.org/10.1002/mds.21956

Irwin, D. J., & Hurtig, H. I. (2018). The contribution of tau, amyloid-beta and alpha-synuclein pathology to dementia in Lewy body disorders. *Journal of Alzheimer's Disease and Parkinsonism*, 8(4). https://doi.org/10.4172/2161-0460.1000444

Ha, A.D., Kim, S.D., & Fund, V.S.C. (2013). Motor features of Parkinson's disease. In J. Jankovic (Ed.), *Clinical insights: Parkinson's disease: diagnosis, motor symptoms and non-motor feature* (pp.21-33). Future Medicine Ltd.

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, 105221–105221. https://doi.org/10.1016/j.parkreldis.2022.11.013

Jones, J. D., Uribe, C., Bunch, J., & Thomas, K. R. (2021). Beyond PD-MCI: objectively defined subtle cognitive decline predicts future cognitive and functional changes. *Journal of Neurology*, 268(1), 337–345. https://doi.org/10.1007/s00415-020-10163-4

Kouli, A., Torsney, K.M., & Kuan, W. (2018). Parkinson's disease: etiology, neuropathology, and pathogenesis. In T.B., Stoker & J.C. (Eds.), *Parkinson's Disease Pathogenesis and Clinical Aspects*

Lally, H., Hart, A. R., Bay, A. A., Kim, C., Wolf, S. L., & Hackney, M. E. (2020). Association between motor subtype and visuospatial and executive function in mild-moderate Parkinson disease. *Archives of Physical Medicine and Rehabilitation*, 101(9), 1580–1589. https://doi.org/10.1016/j.apmr.2020.05.018

Lees, A. J., Hardy, J., & Revesz, T. (2009). Parkinson's disease. *The Lancet (British Edition)*, 373(9680), 2055–. https://doi.org/10.1016/S0140-6736(09)60492-X

Lehrner, J., Moser, D., Klug, S., Gleiß, A., Auff, E., Dal-Bianco, P., & Pusswald, G. (2014). Subjective memory complaints, depressive symptoms and cognition in patients attending a memory outpatient clinic. *International Psychogeriatrics*, 26(3), 463–473. https://doi.org/10.1017/S1041610213002263

Luo, S. X., & Huang, E. J. (2016). Dopaminergic neurons and brain reward pathways: from neurogenesis to circuit assembly. *The American Journal of Pathology*, 186(3), 478–488. https://doi.org/10.1016/j.ajpath.2015.09.023

Mack, J., & Marsh, L. (2017). Parkinson's disease: cognitive impairment. *Focus (American Psychiatric Publishing)*, 15(1), 42–54. https://doi.org/10.1176/appi.focus.20160043

McGregor, M. M., & Nelson, A. B. (2019). Circuit mechanisms of Parkinson's disease. *Neuron (Cambridge, Mass.)*, 101(6), 1042–1056. https://doi.org/10.1016/j.neuron.2019.03.004

Schrag, A., Siddiqui, U. F., Anastasiou, Z., Weintraub, D., & Schott, J. M. (2017). Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. *Lancet Neurology*, 16(1), 66–75. https://doi.org/10.1016/S1474-4422(16)30328-3

Smith, K. M., & Dahodwala, N. (2014). Sex differences in Parkinson's disease and other movement disorders. *Experimental Neurology*, 259, 44–56. https://doi.org/10.1016/j.expneurol.2014.03.010

Stewart, T., Liu, C., Ginghina, C., Cain, K. C., Auinger, P., Cholerton, B., Shi, M., & Zhang, J. (2014). Cerebrospinal fluid α-synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort. *The American Journal of Pathology*, 184(4), 966–975. https://doi.org/10.1016/j.ajpath.2013.12.007

Tapiola, T., Alafuzoff, I., Herukka, S.-K., Parkkinen, L., Hartikainen, P., Soininen, H., & Pirttilä, T. (2009). Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Archives of Neurology (Chicago)*, 66(3), 382–389. https://doi.org/10.1001/archneurol.2008.596

Thomas, K. R., Edmonds, E. C., Eppig, J., Salmon, D. P., & Bondi, M. W. (2018). Using neuropsychological process scores to identify subtle cognitive decline and predict progression to mild cognitive impairment. *Journal of Alzheimer's Disease,* 64(1), 195–204. https://doi.org/10.3233/JAD-180229

Tropea, T. F., Xie, S. X., Rick, J., Chahine, L. M., Dahodwala, N., Doshi, J., Davatzikos, C., Shaw, L. M., Van Deerlin, V., Trojanowski, J. Q., Weintraub, D., & Chen-Plotkin, A. S. (2018). APOE, thought disorder, and SPARE-AD predict cognitive decline in established Parkinson's disease. *Movement Disorders*, 33(2), 289–297. https://doi.org/10.1002/mds.27204

Winer, J. R., Maass, A., Pressman, P., Stiver, J., Schonhaut, D. R., Baker, S. L., Kramer, J., Rabinovici, G. D., & Jagust, W. J. (2018). Associations between tau, β-amyloid, and cognition in Parkinson disease. *JAMA Neurology*, 75(2), 227–235. https://doi.org/10.1001/jamaneurol.2017.3713