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COGNITIVE DIFFERENCES IN PARKINSON'S DISEASE WITH AMYLOID POSITIVITY AND NEGATIVITY

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COGNITIVE DIFFERENCES IN PARKINSON'S DISEASE WITH AMYLOID POSITIVITY AND NEGATIVITY

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Kenya Luna

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ABSTRACT

In Parkinson's Disease (PD), research has shifted to investigate how biomarkers commonly seen in Alzheimer's Disease (AD), such as amyloid beta (AB), may be associated with cognitive functioning in PD. AB is considered a reliable biomarker for AD pathology, however in PD there is a lacking biomarker that can accurately reflect severity of cognitive impairment. AD research has shown an association between low AB and cognitive decline, but the data in PD has mixed results. Most studies that analyze cognitive decline and biomarkers do not use a cutoff level and the few that do have a threshold vary greatly in terms of the cutoff level. The purpose of this study was to determine if there were any cognitive differences between individuals who are amyloid positive in contrast to those that are amyloid negative. We also examined the association between amyloid beta levels and cognition amongst those individuals who are amyloid negative. This allowed us to determine if subclinical/threshold variability in amyloid was associated with cognition.

A secondary analysis using Parkinson's Progression Marker's Initiative (PPMI) data was run to analyze 929 newly diagnosed participants for longitudinally in both clinical and biological data including neuropsychiatric assessments, motor assessments, and cerebrospinal fluid yearly.

We used two thresholds to determine whether individuals are amyloid positive or negative; a <784 pg/mL cut-off (Abildgaard et al., 2023) and a <1100 pg/mL cutoff (Shaw et al., 2018).

Multilevel modeling (MLM) was conducted to examine group differences (amyloid positive vs amyloid negative) in longitudinal trajectory of cognitive functioning. We examined the longitudinal association between CSF amyloid markers and cognitive functioning among a subsample of amyloid negative PD participants also using MLM analyses.

There were no significant group differences or group X time interactions in any cognition domains.

Currently there is no consensus on determining toxic levels of amyloid beta (AB). The use of cutoff levels may aid in early clinical diagnosis and provide a more reliable measure of neurodegeneration, however finding an adequate cutoff level proves to be a challenge for researchers.

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CHAPTER ONE:

ETIOLOGY OF PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD) that affects more than 1 million Americans (Steward & Weiner, 2007; Elbaz et al., 2016). Although it is currently considered rare, PD rates are expected to rise to roughly nine million by 2030 (Dorsey et al., 2007). Despite studies confirming that men are more likely than women to be diagnosed with Parkinson's, the number of diagnoses is much higher as age increases regardless of gender (Marras et al., 2018). Age is the biggest risk factor for PD and our aging population is increasing, therefore incidence PD rates have been steadily increasing (Dorsey et al., 2018; Hirsch et al., 2016).

Etiology

James Parkinson was the first practitioner in the early 19th century to describe the motor symptoms of what we now know of as PD (Hawley et al., 2014, Elbaz et al., 2016). PD is often characterized by motor symptoms such as tremors, bradykinesia and rigidity but there are also several non-motor symptoms including cognitive decline that affect daily living. (Wirdefeldt et al., 2011; Ganqiang et al. 2017). Besides motor symptoms, mental and psychological

symptoms such as mood/apathy changes, gastrointestinal, attention, and memory are some of the most reported by PD individuals to heavily impact quality of life (Storch et al., 2015).

The symptoms seen in PD are believed to be caused by a loss of dopaminergic neurons in the basal ganglia, specifically for motor symptoms in a region known as substantia nigra pars compacta (Surmeier, 2018). The substantia nigra pars compacta is a subregion of the substantia nigra which is a part of the basal ganglia network responsible for motor control and learning (Bears et al., 2015). Non-motor symptoms, such as depression and cognitive impairment, are also affected by the loss of dopamine but it is believed to affect different areas of the brain. The abnormal levels of dopamine affect different networks of the brain including the limbic system (which includes the amygdala and thalamus) which are responsible for regulation in emotion and cognition (Hu et al., 2015). Currently, scientists are investigating what causes those dopamine neurons to die but there are several theories that suggest that a combination of genetics and environmental factors may be responsible.

Risk Factors

Our current understanding of the cause of PD is incomplete. However, many studies have reported a variety of risk factors including environmental, genetic and behavioral aspects. A study by Belvisi et al. (2020) found that family

history, exposure to toxic substances (including oils, metals and pesticides), physical activity and dyspepsia (recurring indigestion) were independently associated with PD. Another study by Ascherio & Schwarzschild (2016) included diseases as risks as well, such as cancer (specifically melanoma) and traumatic brain injury.

Genetics

While most PD cases are not linked to a single gene or a combination of gene mutations, some rare cases of PD are caused by genetic mutations. Mutations in the genes PARK2, PINK1 AND PARK7 cause autosomal recessive forms of early onset PD (meaning two copies of the abnormal gene are present), of which individuals rarely report dementia (Emre, 2015, Medline, 2022).

The most supported hypothesis of the cause of PD is the buildup of protein “alpha-synuclein” (Siddiqui et al., 2016). SNCA is the gene responsible for instructions for creating alpha synuclein, which in healthy individuals helps the communication between neurons specifically in the presynaptic terminals (Medline, 2022). When the instructions are incorrect, alpha synuclein misfolds which results in clumps to be formed, more commonly known as Lewy Bodies, which is a hallmark of Parkinsonism (Antonschmidt et al., 2022, The Cure Parkinson’s Trust, 2022, Rosborough et al., 2017). Alpha synuclein is thought to help regulate dopamine release and therefore disruptions may lead to issues with

voluntary and involuntary movements. Build-up of alpha synuclein in the brain leads to toxic clumps, which can disrupt normal brain function.

CHAPTER TWO:

SYMPTOMS OF PARKINSON'S DISEASE

Motor Symptoms

The four key motor symptoms seen in PD individuals are akinesia, tremor, rigidity, and postural instability (Jankovic et al., 2013). The severity of these motor symptoms eventually makes it difficult for individuals to complete tasks necessary for daily living. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most common clinical rating scale used by physicians to study the severity of motor impairments seen in PD patients. Prior to a formal diagnosis, individuals will notice begin to note subtle motor symptoms. A study by Schrag et al. (2014), found that 10 years prior to diagnosis, individuals have higher incidence of tremors and constipation than healthy controls and even at 2 years prior to diagnosis, individuals had higher incidence of tremors, shoulder pain/stiffness, balance impairments and rigidity than healthy controls. The modified Hoehn and Yahr scale (HY), a scale used to assess different stages of PD severity, now assesses the disease progression on unilateral and bilateral impairment (Goetz et al., 2004). Stage 1 is unilateral (impairment on only one side) whereas Stage 2 is bilateral (mild impairment on both sides). Stage 3 is mild to moderate bilateral impairment and Stage 4 and 5 are severe disabilities with Stage 5 being the most severe and individuals are not able to move without aid.

Non-motor Symptoms

Despite being recognized as a motor disorder, individuals with PD also show a variety of non-motor symptoms that range in functions and severity as the disease progresses. Some of these symptoms include neuropsychiatric dysfunction, sleep disorders, autonomic dysfunction, sensory symptoms and pain, and the most heavily researched cognitive dysfunction (Poewe, 2008). Many non-motor symptoms may precede motor symptoms by several years which in turn may significantly impact quality of life (Yu & Wu, 2022). Non-motor symptoms are extremely common, with almost 100% occurrence in PD populations (Pfeiffer, 2016; Kim et al., 2013).

Cognitive Impairment

Cognitive impairment is defined as confusion or memory loss that is progressively worsening over time, including trouble remembering or learning new things, concentrating or making decisions (CDC, 2009). Cognitive domains affected by PD may include memory and attention, frontal executive functioning, language, or visuospatial abilities (Langa and Levine, 2014; Watson and Leverenz, 2009). About 12-18% of older individuals are living with MCI (Alzheimer's Association, 2022). Although the data varies, 25-50% of individuals with PD will experience MCI (Weil et al., 2018).

Parkinson's Disease Mild Cognitive Impairment (PD-MCI) is defined as a transitional stage prior to receiving a formal diagnosis of Cognitive Impairment (CI) where individuals have a cognitive decline greater than what is expected for

normal aging, but it does not yet interfere with their daily living (Gauthier, 2006). PD-MCI is a topic researchers are acknowledging as critical for prevention of Parkinson's Disease Dementia (PDD) (Emre, 2015).

PDD is defined as impairment in both cognitive (attention, executive and visuo-spatial functions, memory and language) and behavioral (apathy, hallucinations, delusions, sleepiness and personality/mood changes) that severely impair daily living (Emre et al., 2007). About 80% of individuals with PD who survive for over 20 years after initial diagnosis will eventually develop PDD (Lim et al., 2019, Edison et al., 2013). Risk factors for PDD include old age, severity in motor symptoms (e.g. postural instability and gait difficulty), MCI, and hallucinations (e.g. visual) (Aarsland & Kurz, 2010; Mueller et al., 2013). Currently there are no treatments available for MCI, as this is a transitional stage, compared to the treatments geared towards PDD. However, development of treatments for MCI may slow down the progression to PDD and improve cognitive outcomes (Aarsland et al., 2021).

Mechanisms of Cognitive Impairment in PD

The loss of dopamine is a key component of PD but the dysregulation in other neurotransmitters such as acetylcholine, serotonin and noradrenaline have also been associated with the disease, specifically the pathology of PD-MCI (Matsumato, 2015, Lim et al., 2019). The cholinergic system, which is responsible for attention and higher processing cognitive functions, is affected as we grow older but dysfunctions in this system are exacerbated predominantly in

patients with AD and PD (Teipel et al., 2009; Matsumato, 2015). Cognitive impairment has been a topic of interest for researchers because not only is it not the predominant feature of PD, but it is also not a key overt symptom when diagnosing for the disease, so the deficits and its impact are not as obvious when newly diagnosed. Like clinicians in the field of AD, the concern is that the features of the disease are occurring years beforehand but are not able to be diagnosed or studied due to the lack of both proper testing scales and appropriate knowledge.

CHAPTER THREE:

BIOMARKERS OF COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

In PD, the alpha synuclein (a-syn) protein is the underlying pathophysiology of the dopaminergic loss, however recently researchers have investigated how other proteins may be associated with cognitive functioning (Recchia et al., 2004). In AD, amyloid beta (AB) is one of the three "state markers" of the disease that is reliable for AD pathology, however in PD there is a lacking "state marker" that can accurately reflect PD pathology especially in the early preclinical stages (Parnetti et al., 2013). Other neurodegenerative disorders such as Alzheimer's disease have shown an association with low amyloid beta in cerebrospinal fluid (CSF) to cognitive decline but the data in PD has mixed results (Lim et al., 2019). One study reported decreased AB levels among PD patients with gait and other motor symptoms suggesting that the biomarkers not only affect cognition but may worsen motor symptoms (Rochester et al., 2017).

The impact of the AB protein on individuals with Parkinson's has not yet been determined, but there are hypotheses that the toxic plaque build-up is somehow affecting cognitive functioning in PD individuals through a different pathway than their AD counterparts (Kim et al., 2019). In animal models, AB and a-syn have shown to have synergistic effects, however the direction of the relationship is still unknown (Lim et al., 2019). Most studies currently compare

how PD amyloid build-up differs from AD build up or healthy controls. There is currently no consensus on a specific cut off level for determining toxic levels of amyloid beta, with some researchers considering less than 600 ng/L in CSF to be considered significant while others are more sensitive and consider less than 250 pg/mL to be of importance (Irwin et al., 2020; Stav et al., 2015).

Amyloid and Cognitive Impairment in PD

There is strong evidence that PD individuals with abnormal levels of biomarkers associated with cognitive decline, specifically AB1-42, have an increased risk for developing PDD. In a study with 341 newly diagnosed (about 6 months) PD patients enrolled in the Parkinson's Progression Marker Initiative (PPMI), individuals who had lower CSF AB1-42 showed cognitive impairment two years later, providing evidence that cognitive impairment may be starting in conjunction with the manifestation of motor symptoms or earlier (Terrelonge et al., 2016). Those with cognitive impairment had lower scores in at least two of the six cognitive tests which test domains of memory, visuospatial, working memory-executive function and attention-processing speed (Terrelonge et al., 2016). Lower CSF levels of AB1-42 correspond with higher levels of AB1-42 in the brain causing toxic buildup and accumulation (Sturchino et al., 2021).

Biomarkers AB, tau and cerebrovascular disease have all been correlated as a pathological substrate in the development of cognitive impairment (CI) (Lim et al., 2019). The protein tau is a hallmark of AD and has been shown to have elevated levels in CSF in those with MCI (Montine et al., 2010; Mattsson et al.,

2009). A longitudinal study with 423 newly diagnosed PD individuals found that CI was independently predicted by AB amyloid pathology (lower CSF AB1-42) (Caspell-Garcia et al., 2017). Another study with 27 PD individuals, found that baseline CSF AB42 levels were significantly lower in those who transitioned to PDD and subsequently developed worsened neuropsychology (Compta et al., 2013). One study saw no significant difference between their control group, PD-MCI group and PDD group when comparing their CSF AD biomarkers, including AB42/AB40, p-tau and tau (Bellomo et al., 2020). A large meta-analysis on PD concluded that a decrease of AB in CSF was a marker of cognitive decline in PD and further studies should focus on more precise measurements of each biomarker (Katayama et al., 2020).

CHAPTER FOUR:

PROPOSED STUDY

Most studies that analyze cognitive decline and CSF biomarkers do not use cutoff levels. The few that do include cutoff levels for each of the biomarkers have a threshold that varies greatly between studies. A PD study, using data from PPMI by Irwin et al. (2020) found a linear association between AB42 and longitudinal declines in certain cognitive tests (global cognition, working memory); they did not examine the association with cognition as a function of amyloid cutoff levels (i.e. amyloid positivity vs. amyloid negativity). Another PD study by Hall et al. (2015) used a broader cutoff level of 550 pg/mL or less to determine positivity and found that low levels of AB1-42 were associated with a worse performance on delayed memory recall. Several other studies are using cutoff levels however it is not explicitly stated or unclear what range of amyloid is determined to be “amyloid positivity” (Fiorenzato et al., 2018; Skogseth et al., 2015; Liu et al., 2015; Schrag et al., 2017). For this study, we will be using two cutoffs: Shaw’s (2018) cutoff of 1100 pg/mL, as it was deemed acceptable for use in similar populations as AD (in our case PD) and Abildgaard’s (2023) cutoff of 784 pg/mL which was deemed acceptable in AD populations.

Specific Aims

The purpose of this study was to determine if there were any cognitive differences between individuals who were amyloid positive in contrast to those that were amyloid negative. Therefore, we compared cognitive functioning in newly diagnosed PD individuals with low levels of amyloid beta (amyloid positive) and those with normal levels of amyloid beta (amyloid negative). Our first cutoff level had individuals with <784 pg/mL categorized as “amyloid positive” and individuals with >784 pg/mL categorized as “amyloid negative”. Our second cutoff level had individuals with <1100 pg/mL categorized as “amyloid positive” and individuals with >1100 pg/mL categorized as “amyloid negative”. Our first hypothesis was that PD individuals who were amyloid positive would experience worse cognitive functioning compared to PD individuals who were amyloid negative for both cutoff levels. Additionally, we are unaware of any studies investigating subclinical differences in amyloid beta among individuals with PD. Our second aim examined the association between amyloid beta levels and cognition amongst those individuals who were amyloid negative (i.e., less than 784pg/mL and less than 1100 pg/mL). This allowed us to examine if variability in subclinical amounts of amyloid was also associated with cognition (i.e. is any amount of amyloid associated with cognitive impairment). Our second hypothesis was that PD individuals who were amyloid negative with lower amounts of amyloid (i.e. closer to 784 and 1100) will experience worse cognitive

functioning compared to PD individuals who were amyloid negative with higher amounts of amyloid.

CHAPTER FIVE:

METHODS

Participants

This study utilized data retrieved from the Parkinson's Progression Marker's Initiative (PPMI). The PPMI study is a longitudinal study assessing both clinical and biological data including neuropsychiatric assessments, motor assessments, and cerebrospinal fluid yearly. The PPMI recruit participants from over 10 different sites worldwide including USA, Canada, multiple countries in Europe and the Middle East. These sites are supported by both public and private and non-profit partners, all of which are led by academic and industry scientists. A secondary analysis analyzed 929 newly diagnosed participants for the purpose of this study. Individuals received a formal diagnosis of Parkinson's Disease within the last 12 months. All participants were provided with informed consent and approval from the Institutional Review Board (IRB) at each site.

Measures and Procedures

Participants at each site completed a series of cognitive and neuropsychological assessments including Hopkins Verbal Learning Test (HVLT-II; trials 1–3 and delayed free recall) which assess verbal learning and verbal delayed recall, Letter-Number Sequencing (LNS) which assess attention and working memory, Judgment of Line Orientation (JOLO) which measures

visuospatial function, Animal Fluency which measures verbal fluency, Symbol Digit Modalities Test (SDMT) which assesses processing speed and the Montreal Cognitive Assessment (MOCA) which assess global cognitive functioning.

For the biomarkers, a lumbar puncture was performed on participants to extract CSF during their annual visits. CSF samples were analyzed as ratios: total tau/amyloid beta, phosphorylated tau/amyloid beta and phosphorylated tau/total tau. For this study, we used two cut-off levels. One cut-off level was based on Abildgaard's (2023) cut-off of less than 784 pg/mL to determine amyloid positivity. Individuals who were Amyloid negative would be above 784 pg/mL. Our second cut-off level was based on Shaw's (2018) cut-off level of less than 1100 pg/mL to determine amyloid positivity. In this case, individuals who were amyloid negative would be above 1100 pg/mL.

Statistical Design

For aim 1, multilevel modeling (MLM) was conducted to examine group differences (amyloid positive vs amyloid negative) in longitudinal trajectory of cognitive functioning. The dependent variable was neuropsychological measures. A separate MLM was conducted for each cognitive and neuropsychological test, for a total of 7 analyses. The independent variables were the group individuals were categorized in, based on their amyloid beta values (amyloid positive vs amyloid negative), Unified Parkinson's Disease Rating Scale (UPDRS) score, age, education, and gender.

For aim 2, we examined the longitudinal association between CSF amyloid markers and cognitive functioning among a subsample of amyloid negative PD participants using the 784 and 1100 cutoffs levels based on Abildgaard and Shaw, respectively. Like aim 1, MLM analyses were conducted. The dependent variables were the cognitive and neuropsychological measures. A separate MLM was conducted for each test, for a total of 7 analyses. The independent variables were the CSF amyloid values, UPDRS, age, education, and gender.

CHAPTER SIX:

RESULTS

Aim 1: Group Differences in Longitudinal Trajectory of Cognitive Functioning

Cutoff Level of Amyloid Beta 784

The sample consisted of 382 individuals of which 65% identified as Male (see Table 1). The average age of the sample was 61.83 years old. The average years of education were 15.85. Multilevel modeling (MLM) examined group differences (amyloid positive vs amyloid negative) across the longitudinal trajectory of different neuropsychological measures based off a cutoff of less than 784 pg/mL. In the model with global cognitive functioning (assessed using the MOCA) as the dependent variable, there was no significant group by time interaction (see Table 3). This means there was no difference between the amyloid positive group and the amyloid negative group in cognitive functioning over time. Additionally, the main effect of the amyloid group was not significant. Worse global cognitive functioning was significantly associated with older age, less education and more severe motor symptoms (all p values < 0.05). Global cognitive functioning was not significantly associated with gender or time.

In the model with processing speed (assessed using the SDMT) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction ($\beta = 0.06$, $p = 0.10$). Additionally, the main effect of

the amyloid group was not significant (β= 0.08, p = 0.24). Worse processing speed was significantly associated with male gender, older age, less education, time (scores declined over time) and more severe motor symptoms (all p values < 0.05).

In the model with verbal fluency (assessed using the VLT) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative by time interaction (β= 0.04, p = 0.29). The main effect of the amyloid group was not significant (β= 0.00, p = 0.98). Worse verbal fluency was significantly associated with older age, less education and more severe motor symptoms (all p values < 0.05). Verbal fluency was not significantly associated with gender (β= 0.03, p = 0.71). Time was not significantly associated with scores, meaning scores did not change over time (β= -0.01, p = 0.46).

In the model with visual-spatial functioning (assessed using the BJLOT) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.03, p = 0.46). The main effect of the groups was not significant (β= 0.10, p = 0.17). Worse visual-spatial functioning was significantly associated with male gender, older age, less education and more severe motor symptoms (all p values < 0.05). Time was not significantly associated with visual-spatial functioning (β= 0.00, p = 0.99).

In the model with attention and working memory (assessed using the LNS) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.06, p = 0.10). The main effect of

the groups was not significant (β= -0.06, p = 0.40). Worse attention and working memory were significantly associated with older age, less education, and time (all p values < 0.05). LNS was not significantly associated with gender (β= 0.01, p = 0.91) or motor severity (β= -0.01, p = 0.69).

In the model with delayed verbal recall (assessed using the HVLT-D) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.01, p = 0.76). The main effect of the groups was not significant (β= 0.02, p = 0.82). Worse delayed verbal recall was significantly associated with male gender, older age and less education (all p values < 0.05). Delayed verbal recall was not significantly associated with motor severity (β= -0.02, p = 0.29) or time (β= 0.02, p = 0.25).

In the model with verbal learning (assessed using the HVLT-I) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.02, p = 0.68). The main effect of the groups was not significant (β= 0.04, p = 0.51). Worse HVLT-I was significantly associated with male gender, older age and less education (all p values < 0.05). Verbal learning was not significantly associated with motor severity (β= -0.03, p = 0.24) or time (β= 0.02, p = 0.31).

Cutoff level of Amyloid Beta 1100

The sample consisted of 547 individuals of which 62% identified as Male (see Table 2). The average age of the sample was 61.59. The average years of

education were 15.70. Multilevel modeling (MLM) examined group differences (amyloid positive vs amyloid negative) across the longitudinal trajectory of different neuropsychological measures based off a cutoff of less than 1100 pg/mL. In the model with global cognitive functioning (assessed using the MOCA) as the dependent variable, there was no significant group (amyloid positive vs amyloid negative) by time interaction (β= -0.02, p = 0.80). This means that amyloid positive group and the amyloid negative group did not differ in their cognitive functioning over time. Additionally, the main effect of the amyloid group was not significant (β= 0.13, p = 0.26). Worse global cognitive functioning was significantly associated with older age, less education and more severe motor symptoms (all p values < 0.05). Global cognitive functioning was not significantly associated with gender (β= 0.12, p = 0.07) or time (β= -0.01, p = 0.49).

In the model with processing speed (assessed using the SDMT) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.02, p = 0.75). Additionally, the main effect of the amyloid group was not significant (β= 0.06, p = 0.61). Worse processing speed was significantly associated with male gender, older age, less education, time (scores declined over time) and more severe motor symptoms (all p values < 0.05).

In the model with verbal fluency (assessed using the VLT) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.14, p = 0.09). The main effect of the

amyloid group was not significant (β= 0.17, p = 0.18). Worse verbal fluency was significantly associated with older age, less education and more severe motor symptoms (all p values < 0.05). Verbal fluency was not significantly associated with gender (β= 0.03, p = 0.68) or time (β= -0.01, p = 0.63).

In the model with visual-spatial functioning (assessed using the BJLOT) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.07, p = 0.39). The main effect of the amyloid group was not significant (β= 0.12, p = 0.32). Worse visual-spatial functioning was significantly associated with male gender, older age, less education and more severe motor symptoms (all p values < 0.05). Time was not significantly associated with visual-spatial functioning scores (β= 0.01, p = 0.74).

In the model with attention and working memory (assessed using the LNS) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.07, p = 0.36). The main effect of the groups was not significant (β= 0.09, p = 0.44). Worse attention and working memory were significantly associated with older age, less education and time (all p values < 0.05). Attention and working memory were not significantly associated with gender (β= 0.00, p = 0.96) or motor severity (β= -0.01, p = 0.61).

In the model with delayed verbal recall (assessed using the HVLT-D) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β=- 0.03, p = 0.73). The main effect of the groups was not significant (β= 0.02, p = 0.86). Worse delayed verbal recall was

significantly associated with male gender, older age and less education (all p values < 0.05). Delayed verbal recall was not significantly associated with motor severity (β= -0.02, p = 0.28) or time (β= 0.03, p = 0.10).

In the model with verbal learning (assessed using the HVLT-I) as the dependent variable, there was not a significant group (amyloid positive vs amyloid negative) by time interaction (β= 0.02, p = 0.80). The main effect of the groups was not significant (β= 0.15, p = 0.19). Worse verbal learning was significantly associated with male gender, older age and less education (all p values < 0.05). Verbal learning was not significantly associated with motor severity (β= -0.03, p = 0.24) or time (β= 0.03, p = 0.15).

Aim 2: Association between amyloid beta levels and cognition amongst those individuals who are amyloid negative

Cutoff level of Amyloid Beta 784

Multilevel modeling (MLM) examined the longitudinal association between CSF amyloid markers and cognitive functioning among only amyloid negative PD participants using the less than 784 cutoff level. In the model with global cognitive functioning (assessed using the MOCA) as the dependent variable, there was a significant group by time interaction (see Table 4). Specifically, individuals with greater amounts of subthreshold amyloid experienced improvements in cognitive functioning over time. Additionally, the main effect of the amyloid negative group was not significant. Worse global cognitive functioning was significantly associated with older age, less education and more

severe motor symptoms (all p values < 0.05). Global cognitive functioning was not significantly associated with gender or time.

In the model with processing speed (assessed using the SDMT) as the dependent variable, there was no significant group by time interaction (β= -0.00, p = 0.96). Additionally, the main effect of the amyloid group was not significant (β= 0.00, p = 0.96). Worse processing speed was significantly associated with gender, older age, less education, time (scores declined over time) and more severe motor symptoms (all p values < 0.05).

In the model with verbal fluency (assessed using the VLT) as the dependent variable, there was no significant group by time interaction (β= -0.02, p = 0.42). The main effect of the amyloid group was not significant (β= -0.02, p = 0.36). Worse verbal fluency was significantly associated with older age, less education, and motor severity (all p values < 0.05). Verbal fluency was not significantly associated with gender (β= 0.00, p = 0.98) or time (β= -0.02, p = 0.43).

In the model with visual-spatial functioning (assessed using the BJLOT) as the dependent variable, there was no significant group by time interaction (β= 0.02, p = 0.43). The main effect of the amyloid group was not significant (β= 0.02, p = 0.43). Worse visual-spatial functioning was significantly associated with male gender, older age, less education and more severe motor symptoms (all p values < 0.05). Time was not significantly associated with visual-spatial functioning scores (β= 0.00, p = 0.91).

In the model with attention and working memory (assessed using the LNS) as the dependent variable, there was no significant group by time interaction (β= 0.00, p = 0.73). The main effect of the groups was not significant (β= 0.04, p = 0.16). Worse attention and working memory were significantly associated with older age, less education and time (all p values < 0.05). Attention and working memory were not significantly associated with gender (β= 0.12, p = 0.15) or motor severity (β= 0.00, p = 0.99).

In the model with delayed verbal recall (assessed using the HVLT-D) as the dependent variable, there was no significant group by time interaction (β= 0.03, p = 0.18). The main effect of the groups was not significant (β= -0.01, p = 0.62). Worse delayed verbal recall was significantly associated with male gender, older age and less education (all p values < 0.05). Delayed verbal recall was not significantly associated with motor severity (β= -0.02, p = 0.36) or time (β= 0.03, p = 0.16).

In the model with verbal learning (assessed using the HVLT-I) as the dependent variable, there was no significant group by time interaction (β= -0.04, p = 0.18). The main effect of the groups was not significant (β= 0.03, p = 0.34). Worse verbal learning was significantly associated with male gender, older age and less education (all p values < 0.05). Verbal learning was not significantly associated with motor severity (β= -0.01, p = 0.90) or time (β= 0.04, p = 0.19).

Cutoff level of Amyloid Beta 1100

Multilevel modeling (MLM) examined the longitudinal association between CSF amyloid markers and cognitive functioning among only amyloid negative PD participants using the less than 1100 cutoff level. In the model with global cognitive functioning (assessed using the MOCA) as the dependent variable, there was no significant group by time interaction (β= -0.01, p = 0.50). Additionally, the main effect of the amyloid negative group was not significant (β= 0.02, p = 0.43). Worse global cognitive functioning was significantly associated with older age, less education and more severe motor symptoms (all p values < 0.05). Global cognitive functioning was not significantly associated with gender or time.

In the model with processing speed (assessed using the SDMT) as the dependent variable, there was no significant group by time interaction (β= -0.00, p = 0.78). Additionally, the main effect of the amyloid group was not significant (β= 0.01, p = 0.65). Worse processing speed was significantly associated with gender, older age, less education, time (scores declined over time) and more severe motor symptoms (all p values < 0.05).

In the model with verbal fluency (assessed using the VLT) as the dependent variable, there was no significant group by time interaction (β= -0.01, p = 0.62). The main effect of the amyloid group was not significant (β= -0.01, p = 0.49). Worse verbal fluency was significantly associated with older age, less education, and motor severity (all p values < 0.05). Verbal fluency was not

significantly associated with gender (β= 0.03, p = 0.71) or time (β= -0.00, p = 0.86).

In the model with visual-spatial functioning (assessed using the BJLOT) as the dependent variable, there was no significant group by time interaction (β= 0.01, p = 0.55). The main effect of the amyloid group was not significant (β= 0.02, p = 0.25). Worse visual-spatial functioning was significantly associated with male gender, older age, less education and more severe motor symptoms (all p values < 0.05). Time was not significantly associated with visual-spatial functioning scores (β= 0.01, p = 0.58).

In the model with attention and working memory (assessed using the LNS) as the dependent variable, there was no significant group by time interaction (β= 0.02, p = 0.28). The main effect of the groups was not significant (β= 0.04, p = 0.10). Worse attention and working memory were significantly associated with older age, less education and time (all p values < 0.05). Attention and working memory were not significantly associated with gender (β= 0.01, p = 0.93) or motor severity (β= -0.01, p = 0.67).

In the model with delayed verbal recall (assessed using the HVLT-D) as the dependent variable, there was no significant group by time interaction (β= 0.01, p = 0.66). The main effect of the groups was not significant (β= -0.00, p = 0.84). Worse delayed verbal recall was significantly associated with male gender, older age and less education (all p values < 0.05). Delayed verbal recall was not

significantly associated with motor severity (β= -0.02, p = 0.30) or time (β= 0.03, p = 0.09).

In the model with verbal learning (assessed using the HVLT-I) as the dependent variable, there was no significant group by time interaction (β= -0.01, p = 0.52). The main effect of the groups was not significant (β= 0.02, p = 0.30). Worse verbal learning was significantly associated with male gender, older age and less education (all p values < 0.05). Verbal learning was not significantly associated with motor severity (β= -0.02, p = 0.27) or time (β= 0.03, p = 0.14).

CHAPTER SEVEN:

DISCUSSION

The purpose of this study was to determine if there are any cognitive differences between individuals who are amyloid positive in contrast to those that are amyloid negative. There were no significant differences in cognitive test performance between individuals who were considered amyloid positive in contrast to those who were amyloid negative. Additionally, there were no significant associations in subclinical amounts of amyloid among amyloid negative individuals and cognitive functioning. Despite our hypothesis not being supported, our results still showcase similar trends seen in aging adults.

Inconsistencies with older aging adults (non-PD)

The results from our study are not consistent with the trend seen in older adults who are otherwise clinically cognitively intact. Most older adults show a downward trend of amyloid beta in CSF as they age, however our study found no significant differences in cognition because of amyloid concentration in both PD groups (amyloid positive and amyloid negative). Roughly 30% of cognitively normal adults show abnormal AB pathology (Guo et al., 2020). One study found that higher concentrations of amyloid in Pittsburgh Compound-B (PIB) scans (i.e. abnormal AB levels) was associated with decline in episodic memory and language over a span of 18 months (Ellis et al., 2013). Additionally, one study concluded that AB+ participants had scored lower on cognitive tests of memory

particularly after the age of 70 (Jansen et al., 2018). Even after taking into consideration other variables such as age, sex, educational level and hippocampal volume, cognitively normal adults with abnormal levels of AB performed worse on cognitive measures (Peterson 2016). Studies have shown that the ratio of AB with other biomarkers may be helpful in determining the risk of developing cognitive impairment in individuals who are otherwise cognitively healthy at baseline (Fagan et al., 2009; Hannson et al., 2006). In cognitively intact individuals, AB deposition was associated with gray matter volume; however, it is unclear whether the loss in volume is mediated by other structure loss (Oh et al., 2011). Svenningsson's (2019) study found that again, even after controlling for age, sex and education, AB was the only biomarker associated with memory (delayed recall) in cognitively healthy older adults. Vila-Castellar's (2020) study found that increased AB burden was significantly associated with memory (associative, immediate and delayed) in a cohort with genetic mutations associated with AD and controlled matches. Although the literature on AB in AD and its implications on cognition are still not conclusive, there are several years' worth of work published whereas the implications of AB in exclusively PD (i.e. not including other Parkinsonism like Lewy Body Dementia), there is a very limited notion.

One review found four studies indicating that older adults with depression had lower CSF AB levels compared to those without depression, following similar pathology to those with AD (Harrington et al., 2015). However, the previously

mentioned review failed to specify amyloid beta levels and whether populations had different cutoff levels to determine “low levels", therefore the findings may vary drastically within studies. Despite our findings, amyloid buildup is still associated with cognitive impairment in older adults.

Inconsistencies with Parkinson’s Disease

Throughout studies with PD individuals, there has been consistent evidence that CSF AB levels are reduced compared to healthy controls, however interpretations of these kinds of studies should be used cautiously because they typically do not dichotomize their participants into amyloid positive and negative groups (Lim et al., 2019). One study found that although there was no association between CSF AB (AB cutoff of ≤192) and baseline cognitive status in PD patients, but there was a strong association in decline in cognitive function (measured by the Mattis Dementia Rating Scale) over time (Siderowf et al., 2010). A more recent study also using PPMI, utilized a cutoff of 683.45 pg/mL and found that PD patients with low CSF AB (<683.45) at baseline declined faster in cognitive performance (specifically in MOCA and HVLT-delayed) than their counterparts with high CSF AB (>683.45) (Baek et al., 2021). From review of Baek et al., 2021, it is unclear where the cutoff of 683 came from despite citing Irwin et al., 2020, who cited Shaw et al., 2019 who’s cutoff was 1100, as cited in our methods section. Future studies are needed to validate the 683 cut off. Myers' (2022) study found that the baseline presence of amyloid (whether in CSF, PET or APOE gene) predicted longitudinal cognitive decline (in tests of

memory) in a PD population. Given that our study used de-novo PD participants, amyloid differences may be too subtle for detection in CSF, particularly during the earlier stages of the disease. A follow up longitudinal study may be beneficial to compare the decline seen in the later stages of the disease.

Cutoff may still be relevant with Parkinson's Disease

In AD populations, the biological marker AB, tau, and its ratio AB/tau are successful in determining poorer cognitive functioning. One study found that their data-driven cutoff level of 680 pg/mL better predicted future AD dementia than previous clinically determined cut-offs (Bertens et al., 2017). Another study found that a CSF AB42 level of <647 pg/mL meant a higher probability of abnormal amyloid PET scan, showing that CSF had a 90% accuracy compared to the traditionally used PET scan (i.e. potentially used interchangeably) (Palmqvist et al., 2015). Laboratories typically have a cutoff level to determine amyloid positivity, however this varies within laboratories and countries. One study found that AB variability in cutoff level is considerably greater than other biomarkers, such as t-tau and p-tau, with a median of 500 pg/mL but a wide range of 300-849 pg/mL (in comparison to median 367 and range of 195-400 pg/mL and median 60, 40-85, respectively) (Hort et al., 2009). Even within clinical laboratories, there is often variability in CSF analysis, particularly greater variability with AB, which may cause a change in AD classification (Vos et al., 2014; Verwey et al., 2009). Because we have seen success in AD populations, it is critical to determine an accurate cutoff level for PD populations to improve detection of AB abnormalities.

The sooner abnormalities are detected, the sooner we may be able to respond with interventions for severe cognitive decline as seen in PDD. However, this proves to be difficult given that there is not a conclusive CSF cutoff for AD in the first place, the disease that is primarily affected by AB.

The specific cutoff numbers used in this study were based on AD cutoffs used (Abildgaard (2023) and Shaw (2018)). They may not be particularly useful in our specific sample with newly diagnosed PD individuals. These numbers may not be useful because of the sample population (PD vs AD or newly PD vs PD) or the sensitivity of the test (Elecsys Ab vs ELISA Innotest β-amyloid). However, other studies have found worse cognitive performance on the MOCA within older PD populations using lower cutoff values than our study (<300 pg/mL) (Lerche et al., 2019).

CSF vs PET

Amyloid beta can be analyzed through different techniques including neuroimaging and biological measures. Positron emission tomography (PET) scans, specifically the Pittsburgh Compound-B (PIB) is known to have high accuracy in detecting amyloid buildup however there are other PET scan techniques used including F-FDG that can assess different stages of AD progression (Lowe et al., 2009; Klunk et al., 2004). Biological measures, including CSF and blood plasma, may work just as accurately in detecting amyloid changes (Schindler et al., 2019). All three types of measurements of amyloid mentioned are equally accurate in detecting changes in amyloid when

the variable is dichotomous, as was used in this study (Wisch et al., 2023). It is worth considering PET imaging as an alternative to CSF in measuring amyloid build up and differentiating, particularly our AB positive group. In Guo's (2020) study, AB- individuals showed worsening in CSF earlier on than in PET imaging, hinting at earlier detection of abnormal changes in CSF may be more useful particularly in our sample which was de-novo PD individuals.

PD x Biomarkers

Most of the literature uses AB as a continuous measure; however, we dichotomized AB in efforts of establishing a clearer cutoff level. Some studies that use continuous variables find no association between AB in PD and cognition while others find the opposite to be true (Melzer, 2019; Irwin et al., 2020). Dichotomized AB variables typically find no associations between cognition and AB in PD (Tufekcioglu et al., 2023).

Although studies have shown an association between AB and PD, it may be that AB exclusively does not affect cognition rather the interaction between other biological and environmental factors and AB buildup may be resulting in cognitive deficits. Some studies found no association between AB and cognition in PD but did find associations with tau, so it may be worthwhile to investigate the relationship between both biomarkers and cognition in our target population (Winer et al., 2018, Lim et al., 2019).

Limitations & Future Directions

One limitation to our study is that our population is “de novo” participants meaning they are newly diagnosed (<12 months). As a result, our population is relatively cognitively intact. Future studies may be interested in investigating individuals who transition into different severities of cognitive impairment (i.e. diagnosed with MCI or dementia). Researchers may find it beneficial to study the transition longitudinally, particularly in PD because the disease worsens over time. Newly diagnosed participants also tend to be “drug-naive”, meaning they are not currently on medications for PD such as carbidopa-levodopa. Future research may find it beneficial to investigate the interaction between different medications and its effects on amyloid buildup which in turn affect cognitive performance.

Our study was only interested in the interaction between AB and cognition; however, it is worth mentioning that the interaction of AB and other biomarkers may be more sensitive at detecting differences in cognitive performance. Our study did not include AB as a ratio of other biomarkers (i.e. AB/tau or AB/p-tau) that are associated with AD. One study found that the ratio of biomarkers tau/AB was associated with poorer memory and executive function in PD patients but not AB alone (Liu et al., 2015). Future studies may consider how the ratios of these biomarkers may better detect cognitive decline. It may be useful to also consider AD pathology (i.e. APOE risk) to determine whether pathology of one disease aggregates the other. Studies that include both APOE genotype and

amyloid build up in PD patients find that participants have greater decline in cognitive performance than their counterparts with normal amyloid (Jo et al., 2021; Shahid et al., 2019).

Future studies may consider different cutoff points/numbers to investigate whether lower numbers of AB are associated with poorer cognitive performance in CSF. However, our cutoff levels were selected after thorough review of amyloid cutoffs particularly in a PD population where a more conservative cutoff is appropriate (Weinshel et al., 2022).

A follow up Receiver operating characteristics (ROC) analysis may be useful in discriminating those with amyloid positivity and negativity and creating a clear dichotomous scale rather than a continuous scale seen in amyloid studies. One study conducted a ROC analysis that showed decreased AB could support in distinguishing PD patients with dementia from nondemented PD patients (Mizutani et al., 2023).

Conclusions

In this study, we found no association between amyloid positivity and cognition in a PD population. This lack of finding may be attributed to our demographics which were de novo PD patients. Although AB is known to be associated with poorer cognition in an AD population, this may not be the case for our PD population due to our cutoff levels. Future studies should focus on identifying a more refined cutoff level to determine amyloid positivity in PD populations (in CSF) but before identifying a cutoff point, more studies should be

conducted on cognition and biomarkers in a PD population. There are a plethora of studies investigating the relationship between AD and biomarkers but not for PD. To investigate the relationship between PD and AB and its implications on cognition, we must first determine if there is a relationship at all.

APPENDIX A:

TABLE 1. DEMOGRAPHICS FOR AMYLOID BETA 784

Table 1. *Demographics for Amyloid Beta 784*

Variable	Amyloid Positive (N=382)	Amyloid Negative (N=228)	p-value
Age	61.83 (9.73)	61.53 (9.36)	.71
Education	15.85 (3.41)	15.22 (3.70)	**.03**
Sex	65% Male	55% Male	**.02**
UPDRS	19.48 (9.41)	20.95 (9.03)	.06
HVLT Immediate	24.47 (5.02)	24.47 (4.98)	1.0
HVLT Delayed	8.35 (2.65)	8.33 (2.75)	.94
Letter-Number Sequencing	10.49 (2.73)	10.11 (2.85)	.10
Judgment of Line	12.45 (2.38)	12.35 (2.69)	.65
Animal Fluency	21.02 (5.34)	20.68(6.02)	.46
Symbol Digit Modality	41.07 (10.79)	40.40 (9.65)	.44
MOCA	26.88 (2.47)	26.81 (2.81)	.75

Note. Mean (SD)

APPENDIX B:

TABLE 2. DEMOGRAPHICS FOR AMYLOID BETA 1100

Table 2. *Demographics for Amyloid Beta 1100*

Variable	Amyloid Positive (N=547)	Amyloid Negative (N=63)	p-value
Age	61.59 (9.67)	62.84 (8.84)	.33
Education	15.70 (3.45)	14.84 (4.11)	.07
Sex	62% Male	55% Male	.31
UPDRS	19.98 (9.39)	20.47 (8.44)	.69
HVLT Immediate	24.47 (4.99)	24.46 (5.15)	.99
HVLT Delayed	8.37 (2.70)	8.13 (2.62)	.50
Letter-Number Sequencing	10.34(2.74)	10.41 (3.11)	.85
Judgment of Line	12.42 (2.46)	12.37 (2.83)	.89
Animal Fluency	20.97 (5.70)	20.24 (4.60)	.33
Symbol Digit Modality	40.97 (10.46)	39.51 (9.57)	.30
MOCA	26.82 (2.64)	27.15 (2.22)	.35

Note. Mean (SD)

APPENDIX C:

TABLE 3. GLOBAL COGNITION IN AMYLOID POSITIVE AND NEGATIVE INDIVIDUALS

Table 3. *Global Cognition in Amyloid Positive and Negative Individuals*

Parameter	Standardized Estimate	95% CI	p-value
Amyloid X Year	0.02	-0.06 to 0.10	0.604
Amyloid + vs. Amyloid -	-0.03	-0.16 to 0.11	0.703
Year	-0.02	-0.06 to 0.02	0.340
Age at Baseline	-0.25	-0.31 to -0.19	**<0.001**
Sex	0.13	-0.00 to 0.26	0.06
MDS-UPDRS III	-0.08	-0.13 to -0.02	**0.005**
Education	0.12	0.05 to 0.18	**< 0.001**

Dependent Variable = Montreal Cognitive Assessment. Amyloid negativity was based on a 784 cut-off level. MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale – Part III

APPENDIX D:

TABLE 4. GLOBAL COGNITION IN AMYLOID NEGATIVE INDIVIDUALS

Table 4. *Global Cognition in Amyloid Negative Individuals*

Parameter	Standardized Estimate	95% CI	p-value
Amyloid X Year	-0.07	-0.12 to -0.01	**0.014**
Amyloid	-0.00	-0.07 to 0.06	0.926
Year	0.00	-0.05 to 0.06	0.845
Age at Baseline	-0.13	-0.25 to -0.02	**0.022**
Sex	-0.01	-0.25 to -0.22	0.920
MDS-UPDRS III	-0.10	-0.20 to -0.00	**0.042**
Education	0.21	0.10 to 0.32	< **0.001**

Dependent Variable = Montreal Cognitive Assessment. Amyloid negativity was based on a 784-cut-off level. MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale – Part III

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