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PREDICTORS OF DEPRESSION IN DIFFERENT SUBGROUPS OF PARKINSON'S DISEASE: A NEUROIMAGING STUDY

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A Thesis

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ABSTRACT

Parkinson's disease (PD) is one of the most debilitating neurodegenerative diseases in the world. PD is typically characterized by its motor symptoms which commonly include tremors, rigidity, postural instability, and repetitive or involuntary muscle movements. Some of the most common non-motor symptoms include cognitive impairment, personality changes, depression, and anxiety. Depression has shown to be a prominent symptom in individuals with PD which affects them at any point during disease progression. However, it has been suggested that depression is more common among individuals with early-onset PD compared to individuals with later onsets. Our first aim investigated depression rates among individuals newly diagnosed with young (< 49 years old), middle (50-69 years old), and late onset Parkinson's disease (> 70 years old). Our second aim investigated the neural correlates of depression among young (YOPD), middle (MOPD), and late onset PD (LOPD) individuals. The current study utilized data from the Parkinson's Progression Marker's Initiative (PPMI) database. The PPMI is a longitudinal multisite observational study to measure and identify biomarkers of Parkinson's disease progression. The overall sample consisted of 487 newly diagnosed PD patients who completed a questionnaire of depression at each annual follow-up for a period of five years (aim 1). A subsample of 133 participants underwent head MRI at baseline and first annual follow-up to investigate the neural correlates of depression (aim 2). Multilevel modeling (MLM) examined longitudinal group

differences in depression severity, and the association between depression and structural brain markers among age groups. Results for our first aim indicated a significant group X occasion interaction effect. More specifically, the LOPD group had higher depression scores overtime than the MOPD group in a model without medications. However, when medications were added in the model, these effects were no longer significant. Overall, this sample had an average score of 2.46 in the GDS-15 form suggesting that individuals were generally non-depressed. For our second aim, lower neuronal density in the frontal medial cortex was significantly associated with more depression in the MOPD group. Overall, our findings show that age of onset is significantly associated with depression severity between the LOPD and the MOPD groups. Furthermore, the frontal medial cortex significantly deteriorates over time as depression increases in the MOPD group.

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CHAPTER ONE

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder followed by Alzheimer's disease (National Institute of Aging [NIA], 2017). Nearly one million Americans are diagnosed with PD, which is expected to rise to 1.2 million by the year 2030, and more than 10 million people have PD worldwide (Marras et al., 2018; Parkinson's Foundation, 2021). The prevalence of PD exponentially increases as individuals age (Pringsheim et al., 2014). Interestingly, men are 1.5 times more likely than women to have PD (Parkinson's Foundation, 2020). PD typically begins at the age of 60, but symptoms can manifest earlier, and worsen over time (National Institute of Neurological Disorders and Stroke [NINDS], 2020). As disease progresses, motor, and cognitive symptoms exacerbate and could lead to death. There is no cure for PD, but specific-targeted drug treatments and therapies can be developed to alleviate the motor and non-motor symptoms.

Etiology

Parkinson's disease was first described as a neurological movement disorder by James Parkinson in the 1800s (Weintraub et al., 2008). Early studies of PD identified this disease as a distinct movement disorder. Movement dysfunctions in PD are attributed to the loss of dopaminergic neurons in the

substantia nigra (SN) pars compacta (Williams-Gray & Worth, 2016). Dopamine (DA) release mediates communication between the substantia nigra, the basal ganglia, and regions of the frontal cortex which are important for calibration of movement (Triarhou, 2000-2013). In Parkinson's disease, both nigral subpopulations, dorsal and ventral, are affected, but there is much more severe neuronal loss in the ventral SN region (Gibb & Lees, 1991). Interestingly, early symptoms of PD do not develop until there is a major reduction of dopamine in the striatum (Zhai et al., 2018). According to the National Health Service (2019) symptoms of PD begin appearing when about 80% of the neurons in the substantia nigra are lost. Additionally, cholinergic loss has been linked to PD severity, more specifically akinesia or inability to perform voluntary movement and gait deficits (Bohnen et al., 2013).

Abundant Lewy bodies are also found in PD patients, which are predominant in areas of neuronal loss such as the substantia nigra and locus coeruleus (Schultz-Schaeffer, 2010). Lewy bodies are mainly composed of the alpha-synuclein (SNCA) protein (abnormal protein deposits), and accumulation of these have been associated with neurotoxicity (Schulz-Schaeffer, 2010; Parkkinen et al., 2011). These protein deposits cause neurons to work less efficiently and eventually die. Furthermore, Lewy bodies can be formed in different brain regions affecting neurochemicals such as dopamine and norepinephrine which can lead to the motor and non-motor symptoms observed in PD (National Institute of Aging [NIH], 2017).

Risk Factors

Age

One of the strongest risk factors of PD is age. PD is a neurological disorder that rarely affects young adults; it begins in middle or late life. The development of medicine and treatment over the past decades have allowed populations to live longer, therefore, also increasing the occurrence of neurological disorders such as Alzheimer's disease, Parkinson's disease, and other types of dementia. As healthy individuals age, there is significant neuronal loss observed in multiple brain regions, but with extensive neuronal loss observed in the substantia nigra (SN) (Reeve et al., 2014). Several factors in the environment of the SN such as dopamine metabolism and oxidative stress, pace-making activity, or the handling of calcium in the SN for neuron excitability (important for maintenance of DA levels within the striatum), iron concentration changes, and neuromelanin accumulation, influence cell loss as individuals normally age (as reviewed in Reeve et al., 2014). Therefore, it is believed that the accumulation of these age-related changes weaken neurons in the substantia nigra, making it possible for the expression of PD symptoms (Reeve et al., 2014). Consequently, neurons in the substantia nigra predispose individuals to develop the motor and non-motor symptoms observed in PD.

Genetics

Genetics is another important risk factor of PD. According to the Parkinson's Foundation (2020) about 10% to 15% of PD cases are a cause of

genetics; however, environment, lifestyle, and other factors play a role in PD development. Recently discovered autosomal-dominant gene mutations associated with PD are Gly51Asp, and those found in the SNCA (Lesage et al., 2013; Kiely et al., 2013). The genes involved in an autosomal-recessive pattern are PARK7, PINK1, or PRKN (MedlinePlus, 2012). However, sporadic cases or those that appear with no family history of disorder, are the most common. Genes can play a major role in future PD cognitive decline and dementia (Morley et al., 2012).

Environment

Environment also plays a major role in the prevalence of PD. Studies reviewed by Palin et al., (2015) found an association between hydrocarbon exposure and the risk of developing PD. Interestingly, 13 review studies indicated that the risk of PD increases by 32% when individuals are exposed to hydrocarbon (Palin et al., 2015). Furthermore, other important environmental risk factors are exposure to pesticides, herbicides, and solvents, but not to fungicides (Pezzoli & Cereda, 2013; van der Mark et al., 2012). Paraquat (a herbicide), and rotenone (an insecticide) exposure have been most commonly associated with the development of PD, as these chemicals have shown to increase oxidative stress, and disrupt mitochondrial energy production (Mostafalou & Abdollahi, 2013; Dexter & Jenner, 2013). Furthermore, another type of pesticide called organochlorine (insecticide) has been associated with elevated amounts of dieldrin and beta-hexachlorocyclohexane, compounds associated with increased

oxidative stress and inflammation (as reviewed by Kamel, 2013). Other studies have further supported that exposure to pesticides has been associated with the development of idiopathic (cause is unknown) PD (Allen & Levy, 2013; Stykel et al., 2018).

Gender

Gender is also an important risk factor of PD. PD seems to occur 1.5x more in men than in women (Parkinson's Foundation, 2020). Some studies suggest that perhaps the typical "male lifestyle" such as more exposure to environmental toxins, or head trauma, account for these differences (Wooten et al., 2004). Regarding the onset of PD, some studies have shown that PD starts earlier in men with PD starting 2.1 years later in women (Haaxma et al., 2007). An important risk factor commonly observed in women is anemia (Savica et al., 2013). Moreover, women display later onset of motor symptoms, and they tend to be more tremor dominant, as opposed to other motor symptoms such as rigidity (Haaxma et al., 2007; Solla et al., 2012). Augustine et al. (2015) also found gender differences in cognitive impairment. Women in this study demonstrated better SCOPA-COG (Scales for Outcomes in Parkinson's Disease Cognition; a self-report measure of cognitive difficulties) and SDMT (Symbol Digit Modalities test; an objective measure of processing speed) performance than men (Solla et al., 2012). Moreover, women displayed higher and more severe symptoms of anxiety and more severe symptoms of depression leading to worse quality of life (Kovacs et al., 2016).

Substances

Substances such as alcohol intake, coffee drinking, and smoking have also been associated with PD. Alcohol intake, specifically beer, has been inversely associated with PD, meaning that it could prevent or slow down PD progression (Zhang et al., 2014). Beer contains purine, which may elevate plasma urate levels, and ultimately cause antioxidants which protect cells from damage; Therefore, purine has been associated with lower PD risk (Weisskopf et al., 2007). Coffee and smoking have also been negatively associated with PD. Interestingly, coffee reduces the risk of having PD by 33% and alcohol intake reduces it by 10% (Noyce et al., 2012). Of particular interest, a study found that A2A antagonists, caffeine being one of them, protect against neurodegeneration of dopaminergic neurons (Kachroo et al., 2010). The intake of vitamin B6 was also found to be negatively correlated with PD (Shen, 2015). Although these substances have been associated with risk reduction of PD, findings vary, and are unclear (Hernan et al., 2002; Costa et al., 2010; Hernan et al., 2003).

Motor Symptoms

Parkinson's disease is mainly known for its evident motor abnormalities such as slow movement, tremors, impaired posture/balance, stiffness, speech, and writing difficulties (American Parkinson's Disease Association [APDA], 2020). Younger people with PD may only notice one or two of the motor symptoms before they become worse (APDA, 2020).

According to the APDA (2020), tremors affect around 80% of individuals with PD. Tremors in PD are different from other types of tremors as they tend to appear when a person is at rest– a “resting tremor” (APDA, 2020). Furthermore, bradykinesia or slowness of movement is another important symptom of PD. Dystonia, or repetitive or involuntary muscle movements and vocal symptoms are also present. These are some of the primary motor symptoms observed in Parkinson’s disease and typically appear during the initial stages (APDA, 2021).

Non-Motor Symptoms

Dysfunctions of the basal ganglia have not only been associated with the movement abnormalities in PD, but also with non-motor symptoms such as depression, and cognitive impairment. Some studies using monkey models suggest that the basal ganglia is organized into three regions: sensorimotor, associative, and limbic (Parent & Hazrati, 1995). More specifically, the associative region comprises parts of the putamen, and caudate nucleus, and it receives projections from several association cortices in the frontal, temporal, and parietal lobes (Goldman & Nauta, 1977). The sensorimotor region receives information from cortical fibers from primary motor and somatosensory cortices (Liles & Updyke, 1985). Lastly, the limbic region receives projections from the limbic and paralimbic cortices, amygdala, and the hippocampus (Alheid & Heimer, 1988). These regions project to the subthalamic nucleus, and pallidosubthalamic, which have been associated with PD symptomatology, and

have been a target for surgery in PD (Karachi et al., 2005). Thus, these findings provide further support of the neural bases of the non-motor aspects of PD.

Non-motor symptoms in PD include disturbances in sense of smell, sleep problems, pain, psychosis, fatigue, weight loss, gastrointestinal issues, personality changes, cognitive impairment, depression, and anxiety (APDA, 2020). These symptoms are often overlooked since PD is mainly recognized and diagnosed based on the movement abnormalities, but the non-motor symptoms are significantly important for a patient's quality of life.

Cognitive impairment (CI) is an important non-motor aspect of PD as it is associated with significant disability (Watson & Leverenz, 2010). Cognitive decline is evident in normal aging, but in PD it worsens as disease progresses. Cognitive impairments commonly involve dysfunction of several domains including executive functioning such as planning or organizing tasks, learning and memory, attention, and language (Williams-Gray & Worth, 2016). According to Litvan et al., (2012) mild cognitive impairment (MCI), a transitional state of gradual decline in cognitive abilities, predicts the development of PD dementia (PDD), which occurs in up to 80% of PD patients. Parkinson's disease dementia refers to severe decline in thinking and reasoning. More specifically, PDD involves deficits in recognition memory, visual perception, and more severe cognitive decline (Pagonabarraga & Kulisevsky, 2012).

Depression is another important non-motor symptom of Parkinson's disease. There is research suggesting that depression is more common in

individuals with PD compared to healthy elderly adults. According to Kirsch-Darrow et al., (2006) around 31% of individuals with PD will experience depression. Individuals with PD may experience sadness due to family distancing, losing friendships, or adapting to new changes; however, sadness greatly differs from depression. Depression is persistent and can last for weeks, months, even years.

Depression is defined as a mental illness that negatively impacts the way a person feels, thinks, and behaves (American Psychiatric Association [APA], 2021). It affects individuals in any population, regardless of age, gender, or ethnicity. According to the World Health Organization (WHO, 2021) more than 264 million people worldwide are affected by depression, and close to 800,000 individuals commit suicide every year. Depression symptoms vary from mild to severe, and can include difficulty thinking, loss of energy, feeling sad, and feeling worthless or guilty (APA, 2021). There are many causes of depression including brain changes, stressful life events, genetic vulnerability, abuse, medical problems, and medications (Harvard Health Publishing, 2009).

Neurobiological factors such as neuronal reduction or malfunction contribute to depression. Depression is not only influenced by the levels of these neurotransmitters in the brain (dopamine, norepinephrine, and serotonin), but also by nerve cell connections, nerve cell growth, and functioning of neuron circuitry (Racagni & Brunello, 1999). Reduction of an important neurotransmitter, serotonin, which is involved in mood, has been associated with depression (Tan

et al., 2011). Degeneration of the serotonin transmission system, specifically in the midbrain raphe nuclei, has been prominent in studies using Parkinson's disease rat models (Hou et al., 2012). Furthermore, the study by Remy et al., (2005) found that depressed PD patients had lower [11C]RTI-32 binding (an in vivo marker of dopamine and noradrenaline transporter binding) in many regions of the limbic system, including the anterior cingulate cortex, the thalamus, the amygdala, and the ventral striatum, but also the locus coeruleus, compared to non-depressed patients. These findings further support the idea that progression of PD is associated with degeneration of various regions associated with emotion.

Psychological factors that can influence the development of depression are negative thoughts and social isolation (APDA, 2020). Negative thoughts could be attributed to disease effects. For instance, an individual diagnosed with PD who has been excluded from family activities, or social gatherings due to their motor symptoms might be more vulnerable to depression (Saeedian et al., 2014). The study by Cheng et al., (2008) showed that low social support was associated with higher levels of depression. Furthermore, the stigma of having tremors, and slow movement might lead an individual with PD to isolate. The lack of family or social support, or loss of independence are also important factors that can lead to depression (Navarta-Sanchez et al., 2016). A review analysis by Reijnders et al. (2008) found that 35% of PD patients had significant depressive symptoms. Individuals with PD are more vulnerable to develop depression, anxiety

disorders, cognitive impairment, and psychosis (Rojo et al., 2003). Depression can develop at any point in PD, and symptoms can vary. Some studies suggest that depression symptoms vary based on age. However, in general, studies tend to be cross-sectional, and they typically have smaller sample sizes. Thus, it is relevant to examine longitudinal differences in depression rates at different ages of onset in Parkinson's disease.

CHAPTER TWO

AGE AT ONSET OF PARKINSON'S DISEASE

Young-onset Parkinson's Disease

Young onset Parkinson's disease (YOPD) or early onset PD (EOPD) is defined as being diagnosed with PD at any age between 21-40 years old (Mehanna & Jankovic, 2019). However, recent studies have proposed inconsistency/variability in these age ranges. According to Rana et al., (2012) early onset PD begins from ages 21 to 40 or less than 55 years old. However, other studies have suggested different cutoffs, and proposed three distinct subgroups: young onset, middle onset, and late onset PD (Mehanna et al., 2014; Kim et al., 2020). In this study, YOPD included individuals less than 49 years of age, middle onset included individuals between 50-69 years of age, and late onset included individuals older than 70 years of age (Mehanna et al., 2014).

YOPD individuals experience earlier motor complications such as dyskinesia and dystonia (Schrag & Schott, 2006). However, they have also shown to have less severe motor symptoms compared to older onsets (Post et al., 2008). YOPD has been associated with slower disease progression, but longer disease duration (compared to older groups), and less cognitive decline until later stages (Alves et al., 2005; Schrag et al., 1998). They are also less disabled compared to the middle and late onset PD groups, and typically have lower scores on the Hoehn and Yahr rating scale (scale used to measure severity of Parkinson's disease symptoms) (Post et al., 2008).

One of the most prevalent initial motor symptoms observed in YOPD patients is tremor. In the study by Mehanna et al., (2014), tremor was an important initial symptom in more than half (58.3%) of the YOPD group. Gait complaints and falls (15%), rigidity (21.7%), and bradykinesia (18.3%) were also important initial symptoms in this group (Mehanna et al., 2014). Seventy percent of YOPD patients also developed dyskinesia or impairment of voluntary movement (Mehanna et al., 2014). Regarding cognition, 26.7% of patients in this group developed dementia (Mehanna et al., 2014). According to Spica et al., (2013) YOPD individuals have a lower risk/prevalence of non-motor symptoms compared to the LOPD group. However, findings on the prevalence of non-motor symptoms in this PD subgroup are inconsistent.

Depression in Young Onset Parkinson's Disease

Depression is more frequent among individuals with YOPD (Mehanna et al., 2014). According to Mehanna et al., (2014) in this sample, depression was more evident in the YOPD group (48.3% of individuals expressed depressive symptoms) compared to the MOPD and LOPD (22.1% of individuals in the LOPD expressed depressive symptoms) groups. In a study conducted by Knipe et al., (2011) the YOPD group had worse quality of life and more depressive moods compared to the LOPD group. In this study, age of onset (YOPD) was a strong predictor of poorer scores of emotional well-being, even after adjustment of depression status (Knipe et al., 2011). Another study by Kasten et al., (2012) showed that the YOPD group had more suicidal ideation compared to the LOPD

group. Interestingly, the YOPD group displayed higher instances of panic attacks (24%), and social phobia (19%) compared to the LOPD group (Kasten et al., 2012). One of the most important risk factors of depression is age of onset, especially before the age of 55 (Santamaria et al., 1986; as reviewed in Calne et al., 2008). Disease duration and cognitive impairment were also highly associated with depression scores in the YOPD group (Starkstein et al., 1989).

The higher occurrence of depression among individuals with YOPD is likely multifactorial, but at least partially due to psychosocial factors. Employment is an important factor in YOPD individuals, as it has an effect on self-esteem, productivity, and financial aid (Schrag & Schott, 2006). Patients with YOPD may be unemployed or had to retire early due to their disability (Schrag & Schott, 2006). Banks and Lawrence (2006) found that symptom severity and lack of support in the workplace were main factors of early retirement among patients with YOPD. They might experience loss of independence when they are at their peak of productivity which might influence their self-esteem and might lead to depressive symptoms. Fereshtehnejad et al., (2014) explained how YOPD patients experience greater psychological features, especially depression, compared to LOPD patients. Thus, early retirement due to inability to perform efficiently might lead to or worsen existing depressive symptoms in YOPD individuals.

Other psychosocial factors such as role expectations significantly contribute to the development of depression in this group. Schrag et al., (2000)

suggest that older patients are more compatible/suitable with retirement and the physical symptoms associated with PD, whereas YOPD individuals struggle to adjust to these motor symptoms that interfere with their functional activities. Furthermore, according to the review by van Uem et al., (2016) poor health-related quality of life in Parkinson's disease patients was strongly associated with social role functioning. In the general social functioning role, PD patients often experience communication problems (e.g., voice problems) when socializing with others, which might lead to social withdrawal and isolation (Miller et al., 2006). In a social setting, PD individuals, especially YOPD, may feel an inability to have meaningful conversations with others or contribute relevant information.

Social support also plays a major role in the occurrence of depression in this group. According to Cheng et al., (2008) lower social support is associated with a higher risk of depression in PD. Family support is also an important component of well-being and motivation in PD. According to Navarta-Sanchez et al., (2016) Parkinson's disease patients who received support from their family felt more secure and motivated to continue their treatment.

YOPD individuals may also experience more family and marriage problems (Schrag & Schott, 2006). One of the main negative impacts on couple relationships is shifting relational roles. For instance, since one partner is unable to perform their daily activities, the other partner may have more responsibility, and as a couple, they may also engage in fewer activities together (Habermann, 1996). Some studies have found that reduced relationship satisfaction was

associated with higher levels of anxiety, and depression, especially in YOPD individuals (Wielinski et al., 2010; Ricciardi et al., 2015). Lower sexual satisfaction was also associated with lower marital satisfaction, especially in YOPD individuals, and those with worse motor symptoms (Bronner et al., 2014). On the other hand, Karlstedt et al., (2017) found that having a male care partner increased the positive quality of a relationship.

Stigmatization has also been associated with depression in this group. Research has shown that young age, and depression were significant predictors of self-perceived stigma in PD (Salazar et al., 2019). According to Schrag et al., (2003), YOPD is associated with greater disease burden, motor complications, unemployment due to disability, poor quality of life, stigmatization, and depression. Concerns about stigmatization can influence patients' perception of their condition and its treatment, and could lead to avoiding socialization (Verity et al., 2020). The study by Bhidayasiri et al., (2020) found that YOPD individuals rated slow movement, performing fine finger movements, stiffness, and muscle cramping as the most concerning symptoms of PD, which could relate to problems in social functioning, and stigmatization.

Loss of employment or early retirement, role expectations, low social support, family and marriage problems, and stigmatization are some of the factors that have shown to be strongly associated with depression in YOPD. However, there are other predictors that could also explain the occurrence of depression in this group.

Neurobiological Mechanisms in Young Onset Parkinson's Disease

Some studies have shown brain abnormalities in patients with YOPD. YOPD patients tend to have greater nigral cell loss than patients with LOPD (Gibb & Lees, 1988; as reviewed in Schrag & Schott, 2006). Other studies have found that the YOPD group experiences greater dopamine density loss, thus partly explaining slower disease progression in this group (de la Fuente-Fernandez et al., 2011). This group has also shown to have less dopamine transporter (DAT) density, low levels of cerebrospinal fluid (CSF) lactate, or CSF t-tau, and low levels of p-tau, which could further explain the early motor complications observed in this subgroup (Shih et al., 2007; Schirinzi et al., 2020).

Furthermore, in the study by Xuan et al., (2019) there were grey matter differences observed between the YOPD group and the middle-late onset PD (M-LOPD) group. In this study, YOPD patients had reduced grey matter density in the left putamen, inferior frontal gyrus, and insula (Xuan et al., 2019). Other studies have found more impairment in the putamen of YOPD compared to LOPD (Sheng et al., 2016). The putamen is a structure that is part of the basal ganglia and is involved in learning, motor control, cognitive functioning, and emotion (Ghandili & Munakomi, 2021). Interestingly, others have found greater dysfunction in the frontal gyrus, temporal pole, and temporal gyrus in YOPD (Yue et al., 2020). In summary, YOPD differs from MOPD and LOPD as they display greater nigral cell loss and dopamine density loss. YOPD individuals also have reduced grey matter densities in frontal subcortical regions. However, no studies

have examined if these neuroanatomical differences are associated with age-related differences in depression.

Middle Onset Parkinson's Disease

Middle onset PD (MOPD) consists of individuals with disease onset of 50-69 years of age (Mehanna et al., 2014). According to Mehanna et al., (2014), 36.1% of individuals in this group developed dementia. Dyskinesia developed in 34.1% of patients in this group (Mehanna et al., 2014). Rigidity (54%) and tremor (46%) have also shown to be initial motor symptoms in MOPD individuals (Stella et al., 2008). In a study with MOPD patients, it was shown that depression was a significant predictor of disability and low quality of life in PD (Menon et al., 2015). The study conducted by Pellicano et al., (2015) found that body side of onset of motor symptoms (left versus right) has a slight impact on depressive symptoms and anxiety. Results from this study suggest that left-sided PD patients may slightly suffer more depressive symptoms compared to the right-sided PD patients (Pellicano et al., 2015). It is explained that this is due to the right hemisphere's responsibility in processing negative thoughts/emotions.

Depression in Middle Onset Parkinson's Disease

According to Post et al., (2008) individuals in this intermediate group experienced more anxiety, and depressive symptoms, and had low perceived quality of life scores, compared to the older group (LOPD). Depressive symptoms were reported in 35.1% of this group (Mehanna et al., 2014). Furthermore, another study by Stella et al., (2008) found that 54% of MOPD patients showed

depressive symptoms. Greater UPDRS scores (scale to assess motor symptom severity) were also highly associated with more depression (Stella et al., 2008). Other studies have shown similar rates of depression symptoms in MOPD individuals, typically ranging from 20% to 40% (Rojo et al., 2003; Slaughter et al., 2001).

Regarding the neural mechanisms of depression, the M-LOPD group had reduced grey matter density in the left cerebellum posterior lobe, left occipital lobe, and right supplementary motor area (Xuan et al., 2019). Another study found decreased grey matter density in the left inferior orbitofrontal gyrus, bilateral rectal gyrus, and right superior temporal pole of depressed PD patients compared to non-depressed PD patients (Feldmann et al., 2008). Moreover, there was a negative correlation between depression severity and gray matter density of the right medial temporal gyrus, right parahippocampal gyrus, medial and anterior cingular cortex, and right cerebellum (Feldmann et al., 2008). Another study found lower activation in the medial prefrontal cortex and left mediodorsal (MD) of depressed MOPD patients (Cardoso et al., 2009). There was also increased volume of MD thalamic nuclei in this depressed group, which could be explained by major input coming from the amygdala, basal ganglia, and hypothalamus, as they have an important role in emotion (Cardoso et al., 2009). According to Huang et al., (2015) PD depressed patients showed increased amygdala metabolism. Regarding white matter loss, the PD depressed group had more severe white matter loss in the right frontal lobe, including the anterior

cingulate bundle, and the inferior orbito-frontal region (Petrovic et al., 2012). These studies have supported the idea that as PD progresses, more brain regions become affected.

Late Onset Parkinson's Disease

Late onset PD (LOPD) includes individuals who are diagnosed with Parkinson's disease after the age of 70 (Mehanna et al., 2014). This late onset group shows more motor impairments, and higher rates of disease progression (Post et al., 2008). In this late onset group tremors were an important initial symptom (70.1%), followed by gait complaints (22.5%), and bradykinesia (18.6%) (Mehanna et al., 2014). Depressive symptoms were reported in 22.1% of patients in this group. According to Mehanna et al., (2014) 34.2% developed dementia. Dyskinesia developed in 13% of these patients (Mehanna et al., 2014). Bradykinesia, resting tremor, and postural instability scores were more severe in older onset subgroups (50-59, 60-69, > 70 years of age) compared to the YOPD group. Furthermore, in terms of non-motor symptoms, individuals with an older age at onset had higher impairment in cognitive functioning (Pagano et al., 2016; Kim et al., 2020).

Depression in Late Onset Parkinson's Disease

According to Starkstein et al., (1989) depression scores in this group were highly associated with impairment in activities of daily living (ADL) such as cooking, bathing, or managing medications. Individuals with typical PD onset experience a decrease in their ADL abilities, and quality of life compared to

healthy older adults (Hariz & Forsgren, 2011). In the study conducted by Starkstein et al., (1990), they found that there was a significant correlation between depression and physical disability. They also found that longer duration of PD and greater frequency of history of depression before onset of PD were highly correlated with depression (Starkstein et al., 1990). However, other studies have suggested that depression is presented before PD motor symptoms (Taylor et al., 1986).

Research on age differences in quality of life (QoL) inform the literature on depression in YOPD and LOPD. Although QoL can be separate from depression, several studies have indicated that depression, and other non-motor symptoms, moderately correlate with QoL (Schrag et al., 2000; Kuopio et al., 2000). Research has indicated that individuals with Parkinson's disease have lower quality of life scores compared to healthy controls. More specifically, there are differences observed in YOPD and LOPD groups. According to Kasten et al., (2012) the YOPD group were most unhappy with their ability to work, whereas the LOPD had more difficulties with mobility. According to this same study, the LOPD group were less satisfied with their ability to perform their daily activities, capacity for work, and felt that physical pain prevented them from doing what they needed to do compared to the YOPD group (Kasten et al., 2012).

Freezing of gait (FOG) is a common motor symptom in Parkinson's disease and is mainly observed in the most advanced stages (Giladi et al., 2001; as reviewed in Moore et al., 2007). FOG is characterized by the inability to move

the feet forward and is one of the most impairing symptoms of PD (Heremans et al., 2013). Since FOG tends to occur at unexpected events, such as social gatherings, or professional events, it can be very unpleasant or embarrassing for the individual and can prevent future social interactions possibly leading to depression. Previous studies have associated FOG with depression, stress, and anxiety (Giladi et al., 2006). Furthermore, FOG has also been directly associated with QoL. The study by Moore et al., (2007) found that FOG has an important impact on QoL in PD patients. More specifically, they found a strong association between FOG and the QoL dimensions of emotion, cognition, and communication (Moore et al., 2007). Overall, FOG is a motor complication that is mostly seen in LOPD and may contribute to depression as it has an impact on an individual's social life.

Maladaptive coping strategies are also determinants of depression and anxiety in PD patients. According to Garlovsky et al., (2016) previous studies have reported that wishful thinking, emotion-focused, and avoidant coping strategies were highly related to depression and anxiety. Furthermore, in the study by Hurt et al., (2011) more emotion-focused coping was related to an increase in anxiety and depression (as reviewed by Garlovsky et al., 2016). According to other studies, increased illness identity or knowing more about their PD symptoms and disease have been associated with increased anxiety and depression (Evans & Norman, 2009). Although maladaptive coping strategies

could be developed at any point during PD, and at any age of onset, they could partly explain depressive symptoms in this late-onset group.

In another study conducted by Kim et al., (2020) the late onset group showed greater anxiety and depression compared to the middle onset PD group. More specifically, the LOPD group had more rapid progression of cognitive decline, anxiety, and depression compared to the MOPD patients (Kim et al., 2020). Advancing age is a major risk factor of PD, therefore, an increase in LOPD cases is expected (Mercado et al., 2017).

However, age at onset of PD regarding depression and anxiety has been inconsistent (Pagano et al., 2016; Mehanna et al., 2014; Schrag et al., 2003; Spica et al., 2013). Differences in results could be due to study designs and different cut-off values for different ages at onset.

Neurobiological Mechanisms in Older PD Individuals

At later stages of disease, cortical deposition (e.g., Lewy bodies) play a major role in the development of neuropsychiatric disorders such as anxiety and depression (Mendonca et al., 2017). The study conducted by Frisina et al., (2009) found that depression in older PD individuals (average age = 82 years old) was related to neuropathology in the brainstem, more specifically areas where catecholamine systems (norepinephrine, dopamine) are found. Depression symptoms may be due to catecholamine dysfunction, as by this stage many brain regions and systems are already severely affected by PD.

However, these studies only focused on depression in older PD individuals and did not discuss how age at onset (e.g., LOPD) was related.

Decreased levels of serotonin in the central nervous system (CNS) have been significantly associated with depression in Parkinson's disease (Mayeux et al., 1984). Interestingly, the study by Myslobodsky et al., (2001) showed that patients who underwent subthalamic nucleus deep brain stimulation had increased suicidal rates. Suicidal behavior has been associated with disturbances in serotonin neuroregulation, and dysfunctions in the hypothalamic-pituitary adrenal axis (Kostic et al., 1996; as reviewed in Kostic et al., 2010). Similarly, these studies focused on older PD individuals and depression, but age at onset was not considered.

Pagano et al., (2016) describe that later onset of PD is associated with greater dopaminergic dysfunction on DaTSCAN, reduction of CSF alpha-synuclein, and total tau, which could explain that greater accumulation of these are found in healthy neurons. Furthermore, Matsui et al., (2007) found reduced white matter integrity in the anterior cingulate cortex of depressed PD patients. Reduction of FA values indicate histological abnormality (Matsui et al., 2007). Another study by Huang et al., (2014) found reduced integrity in left uncinate fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, forceps minor, and the inferior longitudinal fasciculus in depressed PD patients.

To the best of our knowledge, not many studies have investigated the neural correlates of depression in LOPD. Many of the current literature focuses

on depression in PD at any stage or they provide possible explanations of depression occurrence in older PD groups. Therefore, it is concluded that as individuals age and as disease progresses, there is severe neurodegeneration potentially explaining the neuropsychiatric symptoms in PD.

Summary of Literature

Overall, these studies provide preliminary evidence in how depression severity is dependent on age at onset. Young-onset PD individuals tend to experience more depression symptoms compared to middle- and late-onset PD. This is partially due to psychosocial factors such as unemployment, low social support, stigmatization, and role expectations. Additionally, there may be neuroanatomical differences that contribute to differences in depression rates. YOPD tend to experience more compromise in frontal subcortical brain regions, whereas LOPD show more degeneration in temporal regions. However, studies examining depression as a function of age have been primarily cross-sectional and with limited sample sizes (sample sizes range from 34 to 105). Additionally, we are unaware of any studies examining neural correlates of depression as a function of age.

Present Study

The proposed thesis seeks to increase our understanding of the occurrence and neural correlates of depression across the spectrum of young,

middle, and late onset Parkinson's disease. The overall hypothesis is that rates and neural correlates of depression will differ across the age spectrum.

Specific Aims

Aim 1: Investigate the longitudinal occurrence of depression among individuals newly diagnosed with young (< 49 years old), middle (50-69 years old), and late onset Parkinson's disease (> 70 years old).

Hypothesis Aim 1: We predict that the young-onset PD group will experience higher depression rates compared to the middle-, and late-onset groups.

Rationale for Hypothesis: Previous studies on PD patients have indicated that depression is most common among YOPD individuals compared to later onset groups (Mehanna et al., 2014; Knipe et al., 2011; Kasten et al., 2012). YOPD individuals are at their peak of productivity, thus are most affected by the disabling motor and non-motor symptoms of this disease. In contrast with previous studies that have utilized smaller sample sizes (typically ranging from eight to forty participants) and cross-sectional studies, this study seeks to examine longitudinal differences in YOPD, MOPD, and LOPD across the five years of diagnosis.

Aim 2: Investigate the neural correlates of depression among young, middle, and late onset PD patients.

Hypothesis Aim 2: Depression will be associated with lower neuronal density in important frontal subcortical regions of YOPD individuals.

Rationale for Hypothesis: There have been differences in the biological mechanisms contributing to depressive symptoms in different PD subgroups (YOPD, MOPD, LOPD) (Xuan et al., 2019; Feldmann et al., 2008; Huang et al., 2014). YOPD individuals tend to show greater neuronal reduction in frontal subcortical areas, whereas later onset groups tend to show more loss in temporal regions (Yue et al., 2020).

CHAPTER THREE

METHOD

Participants and Study Design

The current study utilized data from the Parkinson's Progression Marker's Initiative (PPMI) database. The PPMI is a longitudinal multisite observational study to measure and identify biomarkers of Parkinson's disease progression. Participants provided written informed consent, and the institutional review board approved this study. There were approximately 487 participants newly diagnosed with Parkinson's disease who completed a questionnaire of depression at each annual follow up (five annual follow-ups). Aim two utilized a subsample of approximately 133 individuals (only 133 individuals had neuroimaging data) that underwent head MRI at baseline and first annual follow-up.

Age Groups

Age groups will be classified based on past studies. YOPD will include individuals under the age of 49 years old, MOPD will include individuals between the ages of 50 and 69 years old, and LOPD will include individuals over the age of 70.

Measures

Depression. The Geriatric Depression Scale, short form (GDS) was used to measure depressive symptoms in PD patients. The GDS is a self-report measure of depression in older adults and has shown to be a reliable measure in

PD, as it measures depression across a range of PD severity (Schrag et al., 2007). Unlike other questionnaires, the GDS primarily assesses the emotional or behavioral symptoms of depression, as opposed to somatic symptoms of depression that may be confounded by the motor symptoms experienced by individuals with PD. Some questions included in the GDS were, “Have you dropped many of your activities and interests?” and “Do you feel that your situation is hopeless?” Participants were administered the GDS at baseline, and at each annual follow-up.

Severity of Motor Symptoms. The Unified Parkinson’s Disease Rating Scale (UPDRS) assessed severity of motor symptoms (Goetz et al., 2008). More specifically, part III (Motor Examination) of the scale measures motor symptom severity, with higher scores indicating greater severity of motor symptoms. The motor examination section assesses speech, facial expression, tremor, rigidity, posture, gait, and bradykinesia (Goetz et al., 2008).

Levodopa Equivalent Dose (LED). Since some patients are in certain brands of dopaminergic medication, whereas others are in other brands, and these differences might be meaningful, conversion factors were utilized to produce a total daily levodopa equivalent dose (LED).

MRI Analyses

Participants underwent neuroimaging at baseline and at a one-year follow-up. MRI parameters can be found at http://www.ppmi-info.org/wp-content/uploads/2010/07/Imaging-Manual.pdf. Briefly, parameters were repetition

time 5–11 ms; echo time 2–6 ms; slice thickness 1–1.5 mm; inter slice gap 0 mm; voxel size 1*1*1.2 mm; matrix 256 * minimum 160. MR images were visually inspected, and quality controlled before further processing. FreeSurfer (http://surfer.nmr.mgh.harvard.edu) was used to reconstruct and sement T1-weighted images. This involved standard FreeSurfer preprocessing procedures, which resulted in automated parcellation of cortical surfaces and subcortical structures defined by the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006; Fischl et al., 2004) and extraction of regional volume and cortical thickness (Fischl and Dale, 2000). The regions analyzed are listed in Table 1.

Statistical Analyses

Aim 1. We investigated the longitudinal occurrence of depression among individuals newly diagnosed with young, middle, and late onset Parkinson's disease. Regarding descriptive statistics, the average GDS score for each age group (young, middle, and late onset PD) was reported at each annual assessment. Additionally, the percent of individuals experiencing significant clinical symptoms of depression (GDS ≥ 5) for each age group was reported.

Multilevel modeling (MLM) examined longitudinal group differences in depression severity. GDS total scores were entered as the dependent variable. Independent variables included gender, education, UPDRS scores, age group, occasion, and an age group by occasion interaction. The interaction term

examined if certain age groups were more/less likely to experience longitudinal changes in depression.

Aim 2. Investigated the neural correlates of depression among young, middle, and late onset PD patients. MLM examined the association between depression and structural brain markers among age groups. GDS total scores were entered as the dependent variable. Independent variables included gender, education, UPDRS scores, age group, occasion, MRI region volume and their associated interaction terms. Models were repeated for each MRI region (a total of 53 regions).

CHAPTER FOUR

RESULTS

From the 487 participants, the majority identified as male (65.1%), and Caucasian (94.9%). In terms of age at onset, the majority were in the MOPD group (66.5%). Other demographic characteristics are summarized in Table 2. Our first aim sought to investigate the longitudinal occurrence of depression among individuals newly diagnosed with young, middle, and late onset Parkinson's disease. In the model with no medications (anti-depressants and Levodopa), there was a significant group X occasion interaction effect. Specifically, the LOPD group indicated higher depression scores overtime when compared to the MOPD group (see Table 3). There were no longitudinal differences in depression between the YOPD group when compared to the LOPD group (see Table 3). There is no main effect of group; meaning the YOPD and MOPD groups did not differ from the LOPD group in depression scores (see Table 3). Regarding motor symptoms, higher severity of motor symptoms was indicative of higher depression scores (see Table 3). Furthermore, there was a significant effect of occasion, meaning individuals became more depressed the longer they have been on the study. Gender was not a significant predictor (see Table 3). Overall, our results showed that the average score for the GDS-15 short form was 2.46. Scores that are greater or equal than 5 suggest depression. This suggests that our group was generally non-depressed. In this model, we are

explaining 6% of the variance between participants, and 20.7% within participants.

In the model with medications (anti-depressants and Levodopa), results indicated the group X occasion interaction effects were no longer significant. Individuals in the LOPD group did not significantly differ in depression severity over time when compared to the MOPD, neither does the LOPD group when compared to the YOPD group after controlling for Levodopa and use of anti-depressant medications (see Table 4). The main effect of group was not significant either (see Table 4). Gender was not significant. The use of Levodopa was not significant; however, more severe depressive scores were predicted by antidepressant use, and more severe motor symptoms (see Table 4).

Our second aim sought to investigate the neural correlates of depression among young, middle, and late onset PD patients. Results for our second aim demonstrated a negative association between brain volume in the frontal medial cortex and depression severity. More specifically smaller volumes in the frontal medial cortex were associated with more depression but only in the MOPD group (see Table 5). On the other hand, there was a positive trend between brain volume and depression severity in the YOPD and LOPD groups (see Figure 1). Other brain regions were not significant after adjusting for multiple comparisons ($p > .05$).

CHAPTER FIVE

DISCUSSION

Our results indicated that the LOPD group displayed more severe depression than the MOPD group overtime; however, there were no longitudinal differences in depression severity between the LOPD and YOPD groups. Furthermore, smaller volumes in the frontal medial cortex were associated with higher depression severity, but only in the MOPD group.

Past studies have found significant differences between depression and age at onset in PD individuals. Thus, we hypothesized that individuals with YOPD would experience higher depression severity than individuals with LOPD. However, our findings showed that there were no differences in depression between these groups. These inconsistencies might be explained by different research study designs. Other studies have been cross-sectional and have not examined these differences over time (Schrag et al., 2003; Mehanna et al., 2014). Furthermore, our study had relatively less individuals in the YOPD (13.3%) and LOPD (66.5%) groups compared to the MOPD sample (66.5%). Previous studies that have found differences in depression between YOPD individuals, and LOPD tend to have more individuals in these groups. For instance, the study by Knipe et al., (2011) had 90 individuals in the YOPD group, and 336 in the LOPD, whereas in our study, we only had 65 individuals in the YOPD group and 98 in the LOPD group. Thus, given that larger sample sizes have an impact on significance, perhaps having more individuals in these groups

could have led to significant differences in depression. Furthermore, our sample was largely non-depressed given they had an average score of 2.46 on the GDS scale. A score of less than or equal to 5 indicates minimal depressive symptoms, whereas scores ≥ 5 indicate mild or severe depression (Yesavage et al., 1983). Having a non-depressed sample gave us a restricted range or less variability of depression severity across these groups.

There have been other studies that have found no differences in depression between YOPD and typical-onset PD (Kim et al., 2020). The study by Kim et al., (2020) found differences in depression between the YOPD group and MOPD group, but only at baseline; they did not differ overtime. They suggest that these baseline differences may not be disease-specific but instead related to psychosocial factors such as stigma and loss of normal functioning (Kim et al., 2020). Other studies also have not found a relationship between depression and age of PD onset (Riedel et al., 2010; Borek et al., 2006).

Regarding differences between the LOPD and MOPD groups, LOPD individuals became more depressed overtime compared to MOPD individuals. This finding may partially support our hypothesis that age is associated with depression. Although it was in the alternate direction that we anticipated, there is a precedent for age being a risk factor for depression. Raket et al., (2022) found that in PD, higher age at onset was associated with more severe course of disease. More specifically, they found that later onset of PD was related to more non-motor symptoms, including depression, and the appearance of more

symptoms over time (Raket et al., 2022). Furthermore, later onset was also related to worse health-related quality of life scores (Raket et al., 2022). Quality of life has been associated with depression in PD. Schrag et al., (2000) found that individuals with higher depression levels had worse quality of life scores. Other studies have further supported that depression and worse quality of life in PD are strongly related (Findley & Global Parkinson's Disease Steering Committee, 1999).

Disability and higher motor impairments also have been related to depression in old onset PD. Post et al., (2008) found that older onset PD groups have more rates of disease progression and motor impairment compared to younger onsets. Furthermore, increasing age at onset was associated with higher levels of disability, and lower perceived quality of life (Post et al., 2008). Disability leads to an impairment in activities of daily living which commonly include bathing, eating, and taking medications. Furthermore, a decrease in activities of daily living have been associated with worse perceived quality of life (Hariz & Forsgren, 2011). Therefore, higher motor impairments, disability, and perceived quality of life in late-onset PD group lead to more depression compared to younger onsets.

Further supporting our findings, the study by Kim et al., (2020) found that LOPD individuals had a faster progression of cognitive impairment, depression, and anxiety compared to the MOPD group. In this study, the LOPD group also had a faster progression of motor severity (Kim et al., 2020). It is suggested that

the aging process and its contribution to the neurodegeneration in PD may be explaining depression in this LOPD group (Hindle, 2010).

Regarding the effect of medication, findings show that when medications (anti-depressants) are added in the model, there are no differences observed between these groups. An explanation for this could be the positive association between anti-depressant use and depression. More specifically, higher use of anti-depressants is associated with more depressive symptoms. This may not be surprising considering that individuals without depression have no (or at least minimal) clinical reason to be taking anti-depressants. When anti-depressants are added in the model it may be reducing systematic variance in depression that we seek to address in this study.

For our second aim, we found smaller volumes in the frontal medial cortex were associated with more severe depression in our MOPD group (see Figure 1). The frontal medial cortex plays an important role in decision-making and guidance of emotional related behavior (Ongur & Price, 2000). Past studies have shown that functional and structural abnormalities in the frontal medial cortex have been observed in patients with major depressive disorder (Kanner, 2004; Davidson et al., 2003). Thus, consistent with previous research, it is not surprising that lower volumes in this region are associated with more depression. Interestingly, we did not observe similar findings in the YOPD and LOPD groups. This could be explained by depression being influenced by psychosocial stress (e.g., early retirement) experienced by the YOPD group rather than neurologic

effects. In regard to the neural basis of depression in LOPD, we did not find an association between any brain region and depression in this group. A reasonable explanation for this is differences in techniques/scanners. Previous studies have found heterogenous findings regarding the neurobiology of depression in Parkinson's disease and older adults (Kano et al., 2011). For example, the study by Remy et al., (2005) suggested that depression may be associated with the loss of dopamine and noradrenaline in the nervous system. Therefore, since PD is primarily defined by the loss of dopaminergic neurons, it is not surprising that depression is also present. Furthermore, other studies have found lower cerebral spinal fluid levels of homovanillic acid (a catecholamine metabolite associated with dopamine levels) in depressed individuals (Roy et al., 1985). The study by Pagano et al., (2016) used DaTSCAN imaging, which shows loss of dopaminergic neurons, and found group differences in depression. On the other hand, the study by Huang (2014) used diffusion tensor imaging and found reductions in certain brain regions of depressed PD patients. Therefore, differences in techniques/scanners could lead to inconsistent findings.

Some of the limitations in our study were that participants were predominantly Caucasian males; potentially limiting generalizability to other diverse populations. Another limitation was that there was an unequal number of participants in each age group. There were more participants in the MOPD group than the YOPD and LOPD groups. Other studies that have found significant differences between age of onset and depression in PD have had slightly more

participants in the YOPD and LOPD groups (Knipe et al., 2011). et al., 2003). Furthermore, our sample is highly functioning/largely non-depressed which gave us a restricted range.

Future studies could expand more on these findings by using a more diverse sample, and fairly similar number of individuals in each age-at-onset group. Overall, our findings show that there are significant group differences in depression overtime between the LOPD and MOPD groups, and that the frontal medial cortex plays an important role in depression severity in our MOPD group. Due to the amount of limited research in depression in Parkinson's disease this study further expands on the literature by demonstrating significant differences in depression (and structural differences) overtime between groups. Given that the LOPD group becomes more depressed overtime compared to a younger onset group, better treatments and drug therapies could be developed to treat depression.

APPENDIX A

TABLE 1. CORTICAL AND SUBCORTOCAL REGIONS ANALYZED

Table 1

Cortical and Subcortical Regions Analyzed

Cortical			
Frontal Pole	Temporal Occipital Middle Temporal Gyrus	Inferior Lateral Occipital Cortex	Lingual Gyrus
Insula cortex	Anterior Inferior Temporal Gyrus	Intracalcerine Cortex	Anterior Fusiform Gyrus
Supramarginal Frontal Gyrus	Posterior Inferior Temporal Gyrus	Supplementary Motor Cortex	Posterior Fusiform Gyrus
Middle Frontal Gyrus	Temporal Occipital Inferior Temporal Gyrus	Subcallosal Cortex	Temporal Occipital Fusiform Gyrus
Pars Triangularis	Posterior Central Gyrus	Paracingulate Cortex	Occipital Fusiform Gyrus
Pars Opercularis	Superior Parietal Lobule	Anterior Cingulate Gyrus	Frontal Operculum Cortex
Precentral Gyrus	Anterior Supramarginal Gyrus	Posterior Cingulate Gyrus	Central Operculum Cortex
Temporal Pole	Posterior Supramarginal Gyrus	Precuneus Cortex	Parietal Operculum Cortex
Anterior Superior Temporal Gyrus	Angular Gyrus	Cuneal Cortex	Planum Temporale
Posterior Superior Temporal Gyrus	Superior Lateral Occipital Cortex	Frontal Orbital Cortex	Heschls Gyrus
Anterior Middle Temporal Gyrus	Frontal Medial Cortex	Anterior Parahippocampal Gyrus	Supracalcerine Cortex
Posterior Middle Temporal Gyrus		Posterior Parahippocampal Gyrus	Occipital Pole

Subcortical			
Brain stem	Bilateral Amygdala	Bilateral Caudate	Bilateral Cerebral Cortex
Bilateral Accumbens	Bilateral Cerebral White Matter	Bilateral Hippocampus	Bilateral Lateral Ventricle
Bilateral Pallidum	Cerebrospinal Fluid	Bilateral Thalamus	White Matter
Bilateral Putamen		Grey Matter	

APPENDIX B

TABLE 2. BASELINE CHARACTERISTICS

Table 2

Baseline characteristics

	Mean	SD	IQR
% YOPD	13.3%	--	---
% MOPD	66.5%		
% LOPD	20.1%		
Education	15.48	3.118	5-26
% Male	65.1%	--	--
% Caucasian	94.9%	--	--
Motor Severity	20.03	9.195	2-51
GDS	2.46	2.647	0-15

Note. *N* = 487. SD = Standard deviation; IQR = Inter-Quartile Range; GDS = Geriatric Depression Scale scores.

APPENDIX C

TABLE 3. MLM PREDICTORS OF DEPRESSION (MODEL WITHOUT MEDICATIONS)

Table 3

MLM: Predictors of Depression (model without medications) (*N* = 487).

	Estimate	SE	Sig.
YOPD vs. LOPD	-.005800	.136602	.966
MOPD vs. LOPD	-.105574	.099363	.289
LOPD vs. YOPD X Occasion	-.115182	.064316	.074
LOPD vs. MOPD X Occasion	-.127861	.047551	**.007**
Gender	.050458	.080372	.530
Occasion	.116297	.042612	**.007**
Motor severity	.173693	.029164	**<.001**
Model Fit			
*Δ -2LL	187		<.001
*Δ AIC	169		<.001
*Δ BIC	117		<.001
Between-Person Pseudo r^2	0.062		
Within-Person Pseudo r^2	0.207		

SE = Standard error; Sig. = Significance (significant p values shown in bold). LL = Log Likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion. Gender was coded as: 0 = male, 1 = female. *Change in model indices relative to a null model with no predictors.

APPENDIX D

TABLE 4. PREDICTORS OF DEPRESSION (MODEL WITH MEDICATIONS)

Table 4

MLM: Predictors of Depression (model with medications) (N = 487).

	Estimate	SE	Sig.
Age YOPD vs LOPD	-.198755	.150982	.189
Age MOPD vs LOPD	-.199472	.108721	.067
LOPD vs YOPD x Occasion	-.015220	.098364	.877
LOPD vs MOPD x Occasion	-.061282	.073368	.404
Gender	.027321	.090235	.303
Occasion	.062650	.065543	.340
Motor severity	.153299	.033916	**<.001**
Anti-depressants	-.615316	.085773	**<.001**
Levodopa	.000064	.000052	.219
Model Fit			
*Δ -2LL	2120		<.001
*Δ AIC	2098		<.001
*Δ BIC	2041		<.001
Between-Person Pseudo r^2	0.088		
Within-Person Pseudo r^2	0.239		

SE = Standard error; Sig. = Significance (significant p values shown in bold). LL = Log Likelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Gender was coded as: 0 = male, 1 = female.

APPENDIX E

TABLE 5. NEURAL CORRELATES OF DEPRESSION

Table 5

Neural Correlates of Depression (N = 487).

	Estimate	SE	Sig.
YOPD X Frontal Medial Ctx.	.055760	.171358	.909
MOPD X Frontal Medial Ctx.	-.384810	.137498	**.038**

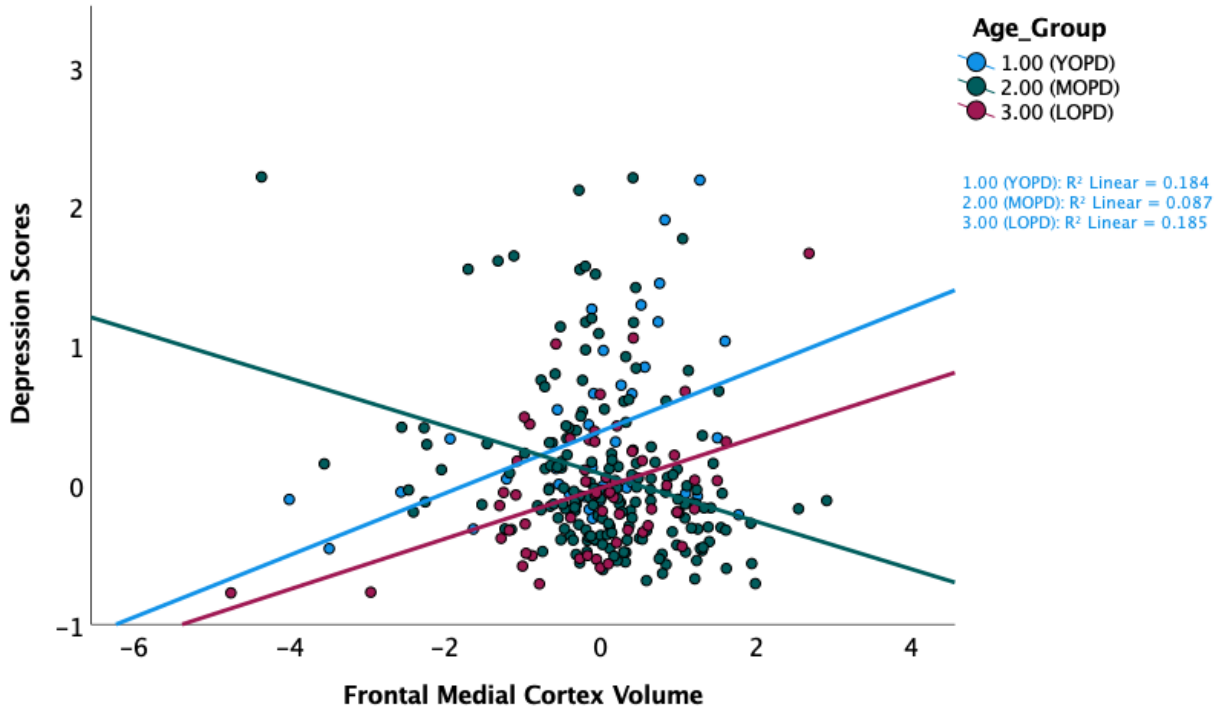
Note. SE = Standard error; Sig. = Significance

APPENDIX F

FIGURE 1. NEURAL CORRELATES OF DEPRESSION

Figure 1

Neural Correlates of Depression in YOPD, MOPD, and LOPD



Note. Each regression line represents our groups. The MOPD group displayed higher scores in depression severity which were significantly associated with lower frontal medial cortex volumes.

REFERENCES

Alheid, G.F., & Heimer, L. (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: The striatopallidal amygdaloid, and corticopetal components of substantia innominate. *Neuroscience, 27*(1), 1-39. https://doi.org/10.1016/0306-4522(88)90217-5

Allen, M.T., Levy, L.S. (2013). Parkinson's disease and pesticide exposure—a new assessment. *Critical Reviews in Toxicology, 43*(6), 515-534. https://doi.org/10.3109/10408444.2013.798719

Alves, G., Wentzel-Larsen, T., Aarsland, D., Larsen, J.P. (2005). Progression of motor impairment and disability in Parkinson's disease. *Neurology, 65*(9), 1436-1441. https://doi.org/10.1212/01.wnl.0000183359.50822.f2

American Parkinson's Disease Association. (2019-2021). What is Parkinson's disease? https://www.apdaparkinson.org/what-is-parkinsons/

American Psychiatric Association. (2021). What is Depression? https://www.psychiatry.org/patients-families/depression/what-is-depression

American Psychological Association. (2021). Depression. https://www.apa.org/topics/depression

Arnold, B., Cassady, S.J., VanLaar, V.S., Berman, S.B. (2011). Integrating multiple aspects of mitochondrial dynamics in neurons: Age-related

differences and dynamic changes in a chronic rotenone model. *Neurobiology of Disease, 41*(1), 189-200. https://doi.org/10.1016/j.nbd.2010.09.006

Augustine, E.F., Perez, A., Dhall, R., Umeh, C.C., Videnovic, A., Cambi, F., Willis, A.M., Elm, J.J., Zweig, R.M., Shulman, L.M., Nance, M.A., Bainbridge, J., Suchowersky, O. (2015). Sex differences in clinical features of early, treated Parkinson's disease. *PLOS One*. https://doi.org/10.1371/journal.pone.0133002

Banks, P., & Lawrence, M. (2006). The disability discrimination act, a necessary, but not sufficient safeguard for people with progressive conditions in the workplace? The experiences of younger people with Parkinson's disease. *Disability and Rehabilitation, 28*(1), 13-24. https://doi.org/10.1080/09638280500165120

Bhidayasiri, R., Boonmongkol, T., Thongchuam, Y., Phumphid, S., Kantachadvanich, N., Panyakaew, P., Jagota, P., Plengsri, R., Chokpatcharavate, M., Phokaewvarangkul, O. (2020). Impact of disease stage and age at Parkinson's disease onset on patients' primary concerns: Insights for targeted management. *PLOS ONE, 16*(6). https://doi.org/10.1371/journal.pone.0243051

Bohnen, N., Frey, K.A., Studenski, S., Kotagal, V., Koeppe, R.A., Scott, P.J., Albin, R.L., Muller, M.L. (2013). Gait speed in Parkinson's disease

correlates with cholinergic degeneration. *Neurology, 81*(18), 1611-1616. https://doi.org/10.1212/WNL.0b013e3182a9f558

Bronner, G., Cohen, O.S., Yahalom, G., Kozlova, E., Orlev, Y., Molshatzki, N., Strauss, H., Hassin-Baer, S. (2014). Correlates of quality of sexual life in male and female patients with Parkinson's disease and their partners. *Parkinsonism & Related Disorders*, *20*(10), 1085-1088. https://doi.org/10.1016/j.parkreldis.2014.07.003

Borek, L.L., Amick, M.M., Friedman, J.H. (2014). Non-motor aspects of Parkinson's disease. *CNS Spectrums, 11*(7), 541-554. https://doi.org/10.1017/s1092852900013560

Calne, S.M., Lidstone, S.C., Kumar, A. (2008). Psychosocial issues in young-onset Parkinson's disease: current research and challenges. *Parkinsonism & Related Disorders, 14*(2), 143-150. https://doi.org/10.1016/j.parkreldis.2007.07.012

Cardoso, E.F., Maia, F.M., Fregni, F., Myczkowski, M.L., Melo, L.M., Sato, J.R., Marcolin, M.A., Rigonatti, S.P., Cruz, A.C., Barbosa, E.R., Amaro, E. (2009). Depression in Parkinson's disease: Convergence from voxel-based morphometry and functional magnetic resonance imaging in limbic thalamus. *NeuroImage, 47*(2), 467-472. https://doi.org/10.1016/j.neuroimage.2009.04.059

Cheng, Y., Liu, C., Mao, C., Qian, J., Liu, K., Ke, G. (2008). Social support plays a role in depression in Parkinson's disease: A cross-section study in a Chinese cohort. *Parkinsonism and Related Disorders, 14*(1), 43-45. https://doi.org/10.1016/j.parkreldis.2007.05.011

Costa, J., Lunet, N., Santos, C., Santos, J., Vaz-Carneiro, A. (2010). Caffeine Exposure and the risk of Parkinson's disease: A systematic review and meta-analysis of observational studies. *Journal of Alzheimer's disease, 1*(1), 221-238. https://doi.org/10.3233/JAD-2010-091525.

de la Fuente-Fernandez, R., Schulzer, M., Kuramoto, L., Cragg, J., Ramachandiran, N., Au, W.L., Mak, E., Mckenzie, J., McCormick, S., Sossi, V., Ruth, T.J., Lee, C.S., Calne, D.B., Stoessl, J. (2010). Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. *Annals of Neurology, 69*(5), 803-810. https://doi.org/10.1002/ana.22284

Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H. (2003). The neural substrates of affective processing in depressed patients treated with Venlafaxine. *The American Journal of Psychiatry, 160*, 64-75. https://doi.org/10.1176/appi.ajp.160.1.64

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest.

NeuroImage, 31(3), 968-980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dexter, D.T., & Jenner, P. (2013). Parkinson disease: from pathology to molecular disease mechanisms. *Free Radical Biology & Medicine, 62*, 132-144. https://doi.org/10.1016/j.freeradbiomed.2013.01.018

Evans, D., & Norman, P. (2009). Illness representations, coping and psychological adjustment to Parkinson's disease. *Psychology & Health, 24*(10), 1181-1196. https://doi.org/10.1080/08870440802398188

Feldmann, A., Illes, Z., Kosztolanyi, P., Illes, E., Mike, A., Kover, F., Balas, I., Kovacs, N., Nagy, F. (2008). Morphometric changes of gray matter in Parkinson's disease with depression: A voxel-based morphometry study. *Movement Disorders, 23*(1), 42-46. https://doi.org/10.1002/mds.21765

Fereshtehnejad, S.M., Hadizadeh, H., Farhadi, F., Shahidi, G.A., Delbari, A., Lokk, J. (2014). Comparison of the psychological symptoms and disease-specific quality of life between early-and typical-onset Parkinson's disease patients. *Parkinson's Disease*, 2014, 1-7. https://doi.org/10.1155/2014/819260

Fischl, B., & Dale, A.M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *PNAS, 97*(20), 11050-11055. https://doi.org/10.1073/pnas.200033797

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14*(1), 11-22. https://doi.org/10.1093/cercor/bhg087

Frisina, P.G., Haroutunian, V., Libow, L.S. (2009). The neuropathological basis for depression in Parkinson's disease. *Parkinsonism & Related Disorders, 15*(2), 144-148. https://doi.org/10.1016/j.parkreldis.2008.04.038

Gareri, P., De Fazio, P., De Sarro, G. (2002). Neuropharmacology of depression in aging and age-related disease. *Ageing Research Reviews, 1*(1), 113-134. https://doi.org/10.1016/S0047-6374(01)00370-0

Garlovsky, J.K., Overton, P.G., Simpson, J. (2016). Psychological predictors of anxiety and depression in Parkinson's disease: A systematic review. *Journal of Clinical Psychology, 72*(10), 979-998. https://doi.org/10.1002/jclp.22308

Ghandili, M., & Munakomi, S. (2021). Neuroanatomy, Putamen. *StatPearls Publishing*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542170/

Gibb, W.R., Lees, A.J. (1991). Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in

Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 54*(5), 388-396. https://doi.org/10.1136/jnnp.54.5.388

Giladi, N., & Hausdorff, J.M. (2006). The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. *Journal of the Neurological Sciences, 248*(1-2), 173-176. https://doi.org/10.1016/j.jns.2006.05.015

Global Parkinson's Disease Survery (GPDS) Steering Committee. (2002). Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Movement Disorders, 17*(1), 60-67. https://doi.org/10.1002/mds.10010

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Scharg, A., Teresi, J.A., van Hilten, J.J., LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorder, 23*(15), 2129-2170. https://doi.org/10.1002/mds.22340

Goldman, P.S., & Nauta, W.J. (1977). An intricately patterned prefronto-caudate projection in the rhesus monkey. The Journal of Comparative Neurology, 171(3), 369-385. https://doi.org/10.1002/cne.901710305

Haaxma, C.A., Bloem, B.R., Borm, G.F., Oyen, W.J., Leenders, K.L., Eshuis, S., Booij, J., Dluzen, D.E., Horstink, M.W. (2007). Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(8), 819-824. https://doi.org/10.1136/jnnp.2006.103788

Habermann, B. (1996). Day-to-day demands of Parkinson's disease. *Western Journal of Nursing Research, 18*(4), 397-413. https://doi.org/10.1177/019394599601800403

Hariz, G.M., & Forsgren, L. (2011). Activities of daily living and quality of life in persons with newly diagnosed Parkinson's disease according to subtype of disease, and in comparison to healthy controls. *Acta Neurologica Scandinavica, 123(*1), 20-27. https://doi.org/10.1111/j.1600-0404.2010.01344.x

Harvard Health Publishing. (2019). What causes depression? https://www.health.harvard.edu/mind-and-mood/what-causes-depression

Heremans, E., Nieuwboer, A., Vercruysse, S. (2013). Freezing of gait in Parkinson's disease: Where are we now? *Current Neurology and Neuroscience Reports, 13*(350), 1-9. https://doi.org/10.1007/s11910-013-0350-7

Hernan, M.A., Chen, H., Schwarzschild, M.A., Ascherio, A. (2003). Alcohol consumption and the incidence of Parkinson's disease. *Annals of Neurology, 54*(2), 170-175. https://doi.org/10.1002/ana.10611

Hernan, M.A., Takkouche, B., Caamano-Isorna, F., Gestal-Otero, J.J. (2002). A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Annals of Neurology, 52*(3), 276-284. https://doi.org/10.1002/ana.10277

Hindle, J.V. (2010). Ageing, neurodegeneration and Parkinson's disease. *Age Ageing, 39*(2), 156-161. https://doi.org/10.1093/ageing/afp223

Hou, C., Xue, L., Feng, J., Wang, Y., Chen, L., Wang, T., Zhang, Q.J., Liu, J. (2012). Unilateral lesion of the nigrostriatal pathway decreases the response of GABA interneurons in the dorsal raphe nucleus to 5-HT1A receptor stimulation in the rat. *Neurochemistry International, 61*(8), 1344-1356. https://doi.org/10.1016/j.neuint.2012.09.012

Huang, P., Xu, X., Gu, Q., Xuan, M., Yu, X., Luo, W., Zhang, M. (2014). Disrupted white matter integrity in depressed versus non-depressed Parkinson's disease patients: A tract-based spatial statistics study. *Journal of the Neurological Sciences, 346*(1-2), 145-148. https://doi.org/10.1016/j.jns.2014.08.011

Huang, P., Xuan, M., Gu, Q., Yu, X., Xu, X., Luo, W., Zhang, M. (2015). Abnormal amygdala function in Parkinson's disease patients and its

relationship to depression. *Journal of Affective Disorders, 183*(1), 263-268. https://doi.org/10.1016/j.jad.2015.05.029

Kachroo, A., Irizarry, M.C., Schwarzschild, M.A. (2010). Caffeine protects against combined paraquat and maneb-induced dopaminergic neuron degeneration. *Experimental Neurology, 223*(2), 657-661. https://doi.org/10.1016/j.expneurol.2010.02.007

Kamel, F. (2013). Paths from pesticides to Parkinson's. *Science, 341*(6147), 722-723. https://doi.org/10.1126/science.1243619

Kanner, A.M. (2004). Structural MRI changes of the brain in depression. *Clinical EEG and Neuroscience, 35(*1), 46-52. https://doi.org/10.1177/155005940403500111

Karachi, C., Yelnik, J., Tande, D., Tremblay, L., Hirsch, E.C., Francois, C. (2005). The pallidosubthalamic projection: an anatomical substrate for nonmotor functions of the subthalamic nucleus in primates. *Movement Disorders, 20*(2), 172-180. https://doi.org/10.1002/mds.20302

Karlstedt, M., Fereshtehnejad, S.M., Aarsland, D., Lokk, J. (2017). Determinants of dyadic relationships and its psychosocial impact in patients with Parkinson's disease and their spouses. *Parkinson's Disease*,1-9. https://doi.org/10.1155/2017/4697052

Kasten, M., Kertelge, L., Tadic, V., Bruggemann, N., Schmidt, A., van der Vegt, J., Siebner, H., Buhmann, C., Lencer, R., Kumar, K.R., Lohmann, K.,

Hagenah, J., Klein, C. (2012). Depression and quality of life in monogenic compared to idiopathic, early-onset Parkinson's disease. *Movement Disorders, 27(*6), 754-759. https://doi.org/10.1002/mds.24999

Kiely, A.P., Asi, Y.T., Kara, E., Limousin, P., Ling, H., Lewis, P., Proukakis, C., Quinn, N., Lees, A.J., Hardy, J., Revesz, T., Houlden, H., Holton, J.L. (2013). a-Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy? *Acta Neuropathologica, 125,* 753-769. https://doi.org/10.1007/s00401-013-1096-7

Kim, R., Shin, J.H., Park, S., Kim, H.J., Jeon, B. (2020). Longitudinal evolution of non-motor symptoms according to age at onset in early Parkinson's disease. *Journal of the Neurological Sciences, 418*, 117-157. https://doi.org/10.1016/j.jns.2020.117157

Kirsch-Darrow, L., Fernandez, H.H., Marsiske, M., Okun, M.S., Bowers, D. (2006). Dissociating apathy and depression in Parkinson's disease. *Neurology, 67*(1), 33-38. https://doi.org/10.1212/01.wnl.0000230572.07791.22

Knipe, M.D., Wickremaratchi, M.M., Wyatt-Haines, E., Morris, H.R., Ben-Shlomo, Y. (2011). Quality of life in young-compared with late-onset Parkinson's disease. *Movement Disorders, 26*(11), 2011-2018. https://doi.org/10.1002/mds.23763

Kostic, V.S., Agosta, F., Petrovic, I., Galantucci, S., Spica, V., Jecmenica-Lukic, M., Filippi, M. (2010). Regional patterns of brain tissue loss associated with depression in Parkinson's disease. *Neurology, 75*(10), 857-863. https://doi.org/10.1212/WNL.0b013e3181f11c1d

Kovacs, M., Makkos, A., Weintraut, R., Karadi, K., Janszky, J., Kovacs, N. (2017). Prevalence of anxiety among Hungarian subjects with Parkinson's disease. *Behavioural Neurology*. https://doi.org/10.1155/2017/1470149

Kuopio, A.M., Marttila, R.J., Helenius, H., Toivonen, M., Rinne, U.K. (2020). The quality of life in Parkinson's disease. *Movement Disorders, 15*(2), 216-233. https://doi.org/10.1002/1531-8257(200003)15;2<216::AID-MDS1003>3.0.CO;2-%23

Lesage, S., Anheim, M., Letournel, F., Bousset, L., Honore, A., Rozas, N., Pieri, L., Madiona, K., Durr, A., Melki R., Verny, C., Brice, A. (2013). G51D α-synuclein mutation causes a novel Parkinsonian–pyramidal syndrome. *Annals of Neurology, 73*(4), 459-471. https://doi.org/10.1002/ana.23894

Liles, S.L., Updyke, B.V. (1985). Projection of the digit and wrist area of precentral gyrus to the putamen: Relation between topography and physiological properties of neurons in the putamen. *Brain Research, 339*(2), 245-255. https://doi.org/10.1016/0006-8993(85)90089-7

Litvan, I., Goldman, J.G., Troster, A.I., Schmand, B.A., Weintraub, D., Petersen, R.C., Mollenhauer, B., Adler, C.H., Marder, K., Williams-Gray, C.H.,

Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M.C., Burn, D.J., Barker, R.A., Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement disorder society task force guidelines. *Movement Disorder, 27*(3), 349-356. https://doi.org/10.1002/mds.24893

Matsui, H., Nishinaka, K., Oda, M., Niikawa, H., Komatsu, K., Kubori, T., Udaka, F. (2007). Depression in Parkinson's disease. *Journal of Neurology, 254*, 1170. https://doi.org/10.1007/s00415-006-0236-6

Marras, C., Beck, J.C., Bower, J.H., Roberts, E., Ritz, B., Ross, G.W., Abbott, R.D., Savica, R., Van Den Eeden, S.K., Wilis, A.W., CM Tanner on behalf of the Parkinson's Foundation P4 Group. (2018). Prevalence of Parkinson's disease across North America. *NPJ Parkinson's Disease, 4*(21). https://doi.org/10.1038/s41531-018-0058-0

Mayeux, R., Stern, Y., Cote, L., Williams, J.B. (1984). Altered serotonin metabolism in depressed patients with Parkinson's disease. *Neurology, 34*(5), 642. https://doi.org/10.1212/WNL.34.5.642

Medline Plus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2017 February 1; cited 2020]. Parkinson's disease; [updated 2020 August 18; reviewed 2012 May 1; cited 2021 May 27]. Available from https://medlineplus.gov/heartattack.html.

Mehanna, R., & Jankovic, J. (2019). Young-onset Parkinson's disease: Its unique features and their impact on quality of life. *Parkinsonism & Related Disorders, 65*, 39-48. https://doi.org/10.1016/j.parkreldis.2019.06.001

Mehanna, R., Moore, S., Hou, J.G., Sarwar, A.I., Lai, E.C. (2014). Comparing clinical features of young onset, middle onset and late onset Parkinson's disease. *Parkinsonism & Related Disorders, 20*(5), 530-534. https://doi.org/10.1016/j.parkreldis.2014.02.013

Mendonca, M.D., Lampreia, T., Miguel, R., Caetano, A., Barbosa, R., Bugalho, P. (2017). Motor and non-motor symptoms in old-age onset Parkinson's disease patients. *Journal of Neural Transmission, 124*, 863-867. https://doi.org/10.1007/s00702-017-1711-1

Menon, B., Nayar, R., Kumar, S., Cherkil, S., Venkatachalam, A., Surendran, K., Deepak, K.S. (2015). Parkinson's disease, depression, and quality-of-life. *Indian Journal of Psychological Medicine, 37*(2), 144-148. https://doi.org/10.4103/0253-7176.155611

Mercado, N.M., Collier, T.J., Sortwell, C.E., Steece-Collier, K. (2017). BDNF in the aged brain: Translational implications for Parkinson's disease. *Austin Neurology & Neurosciences, 2*(2), 1021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5929154/

Miller, N., Noble, E., Jones, D., Burn, D. (2006). Life with communication changes in Parkinson's disease. *Age and Ageing, 35*(3), 235-239. https://doi.org/10.1093/ageing/afj053

Moore, O., Peretz, C., Giladi, N. (2007). Freezing of gait affects quality of life of peoples with Parkinson's disease beyond its relationship with mobility and gait. *Movement Disorders, 22*(15), 2192-2195. https://doi.org/10.1002/mds.21659

Morley, J.F., Xie, S.X., Hurtig, H.I., Stern, M.B., Colcher, A., Horn, S., Dahodwala, N., Duda, J.E., Weintraub, D., Chen-Plotkin, A.S., Deerlin, V.V., Falcone, D., Siderowf, A. (2012). Genetic influences on cognitive decline in Parkinson's disease. *Movement Disorders, 27*(4), 512-518. https://doi.org/10.1002/mds.24946

Mostafalou, S., & Abdollahi, M. (2013). Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicology and Applied Pharmacology, 268*(2), 157-177. https://doi.org/10.1016/j.taap.2013.01.025

Myslobodsky, M., Lalonde, F.M., Hicks, L. (2001). Are patients with Parkinson's disease suicidal? *Journal of Geriatric Psychiatry and Neurology, 14*(3), 120-124. https://doi.org/10.1177/089198870101400304

Navarta-Sanchez, M.V., Garcia, J.M., Riverol, M., Sesma, M.E., Ayesa, S.D., Bravo., S.A., Civera, N.C., Portillo, M.C. (2016). Factors influencing

psychosocial adjustment and quality of life in Parkinson's patients and informal caregivers. *Quality of Life Research, 25*, 1959-1968. https://doi.org/10.1007/s11136-015-1220-3

National Health Services. (2019, April 30). *Parkinson's disease*. https://www.nhs.uk/conditions/parkinsons-disease/

National Institute of Aging. (2017, May 16). *Parkinson's disease*. https://www.nia.nih.gov/health/parkinsons-disease

National Institute of Neurological Disorders and Stroke. (2020, April 29). Parkinson's disease information page. https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page

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

Nuti, A., Ceravolo, R., Piccinni, A., Dell'Agnello, G., Bellini, G., Gambaccini, G., Rossi, C., Logi, C., Dell'Osso, L., Bonuccelli, U. (2004). Psychiatric comorbidity in a population of Parkinson's disease patients. *European Journal of Neurology, 11*(5), 315-320. https://doi.org/10.1111/j.1468-1331.2004.00781

Ongur, D., & Price, J.L. (2000). The organization of networks within the orbital and medial frontal cortex of rats, monkeys and humans. *Cerebral Cortex, 10*(3), 206-219. https://doi.org/10.1093/cercor/10.3.206

Pagano, G., Ferrara, N., Brooks, D.J., Pavese, N. (2016). Age at onset and Parkinson's disease phenotype. *Neurology, 86*(15), 1400-1407. https://doi.org/10.1212/WNL.0000000000002461

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

Palin, O., Herd, C., Morrison, K.E., Jagielski, A.C., Wheatley, K., Thomas, N., Clarke, C.E. (2015). Systematic review and meta-analysis of hydrocarbon exposure and the risk of Parkinson's disease. *Parkinsonism & Related Disorders, 21*(3), 243-248. https://doi.org/10.1016/j.parkreldis.2014.12.017

Parent, A., & Hazrati, L. (1995). Functional anatomy of the basal ganglia 1: the cortico-basal ganglia-thalamo-cortical loop. *Brain Research Reviews, 20*, 91-127. https://doi.org/10.1016/0165-0173(94)00007-C76.

Parkinson's Foundation. (2020). *Understanding Parkinson's*. https://www.parkinson.org/Understanding-Parkinsons/Statistics

Parkinson's Progression Markers Initiative. (2010, June 9). *PPMI imaging technical operations manual*. http://www.ppmi-info.org/wp-content/uploads/2010/07/Imaging Manual.pdf

Parkkinen, L., O'Sullivan, S.S., Kuoppamaki, M., Collins, C., Kallis, C., Holton, J.L., Williams, D.R., Revesz, T., Lees, A.J. (2011). Does levodopa accelerate the pathologic process in Parkinson disease brain? *Neurology, 77*(15), 1420-1426. https://doi.org/10.1212/WNL.0b013e318232ab4c

Pellicano, C., Assogna, F., Cravello, L., Langella, R., Caltagirone, C., Spalletta, G., Pontieri, F.E. (2015). Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients. *Parkinsonism & Related Disorders, 21*(9), 1096-1100. https://doi.org/10.1016/j.parkreldis.2015.07.002

Petrovic, I.N., Stefanova, E., Kozic, D., Semnic, R., Markovic, V., Daragasevic, N.T., Kostic, V.S. (2012). White matter lesions and depression in patients with Parkinson's disease. *Journal of the Neurological Sciences, 322*(1-2), 132-136. https://doi.org/10.1016/j.jns.2012.07.021

Pezzoli, G., & Cereda, E. (2013). Exposure to pesticides or solvents and risk of Parkinson disease. *Neurology, 80*(22), 2035-2041. https://doi.org/10.1212/WNL.0b013e318294b3c8

Post, B., Speelman, J.D., de Haan, R.J. (2008). Clinical heterogeneity in newly diagnosed Parkinson's disease. *Journal of Neurology, 255*, 716-722. https://doi.org/10.1007/s00415-008-0782-1

Pringsheim, T., Jette, N., Frolkies, A., Steeves, T.D.L. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583-1590. https://doi.org/10.1002/mds.25945

Racagni, G., Brunello, N. (1999). Physiology to functionality: the brain and neurotransmitter activity. *International Clinical Psychopharmacology, 14(*1), 3-7. https://doi.org/10.1097/00004850-199905001-00002

Raket, L.L., Astrom, D.O., Norlin, J.M., Kellerborg, K., Martinez-Martin, P., Odin, P. (2022). Impact of age at onset on symptom profiles, treatment characteristics and health-related quality of life in Parkinson's disease. *Scientific Report, 12*, 526. https://doi.org/10.1038/s41598-021-04356-8

Rana, A.Q., Siddiqui, I., Yousuf, M.S. (2012). Challenges in diagnosis of young onset Parkinson's disease. *Journal of the Neurological Sciences, 323*(1-2), 113-116. https://doi.org/10.1016/j.jns.2012.08.029

Reeve, A., Simcox, E., Turnbull, D. (2014). Ageing and Parkinson's disease: Why is advancing age the biggest risk factor? *Ageing Research Reviews, 14*, 19-30. https://doi.org/10.1016/j.arr.2014.01.004

Reijnders, J.S., Ehrt, U., Weber, W.E., Aarsland, D., Leentjens, A.F. (2008). A systematic review of the prevalence studies of depression in Parkinson's disease. *Movement Disorder, 23*(2), 183-189. https://doi.org/10.1002/mds.21803

Remy, P., Doder, M., Lees, A., Turjanski, N., Brooks, D. (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain, 128*(6), 1314-1322. https://doi.org/10.1093/brain/awh445

Ricciardi, L., Pomponi, M., Demartini, B., Ricciardi, D., Morabito, B., Bernabei, R., Bentivoglio, A.R. (2015). Emotional awareness, relationship quality, and satisfaction in patients with Parkinson's disease and their spousal caregivers. *The Journal of Nervous and Mental Disease, 203*(8), 646-649. https://doi.org/10.1097/NMD.0000000000000342

Riedel, O., Klotsche, J., Spottke, A., Deuschl, G., Forstl, H., Henn, F., Heuser, I., Oertel, W., Reichmann, H., Riederer, P., Trenkwalder, C., Dodel, R., Wittchen, H.U. (2010). Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,440 outpatients with Parkinson's disease. *Journal of Neurology, 257*, 1073-1082. https://.org/10.1007/s00415-010-5465-z

Rojo, A., Aguilar, M., Garolera, M.T., Cubo, E., Navas, I., Quintana, S. (2003). Depression in Parkinson's disease: clinical correlates and outcome. *Parkinsonism & Related Disorders, 10*(1), 23-28. https://doi.org/10.1016/S1353-8020(03)00067-1

Roy, A., Pickar, D., Linnoila, M., Doran, A.R., Ninan, P., Paul, S.M. (1985). Cerebrospinal fluid monoamine and monoamine metabolite concentrations

in melancholia. *Psychiatry Research, 15*(4), 281-292. https://doi.org/10.1016/0165-1781(85)90065-4

Saeedian, R.G., Nagyova, I., Krokavcova, M., Skorvanek, M., Rosenberger, J., Gdovinova, Z., Groothoff, J.W., van Dijk, J.P. (2014). The role of social support in anxiety and depression among Parkinson's disease patients. *Disability and Rehabilitation, 36*(24), 2044-2049. https://doi.org/10.3109/09638288.2014.886727

Salazar, R.D., Weizenbaum, E., Ellis, T.D., Earhart, G.M., Ford, M.P., Dibble, L.E., Cronin- Golomb, A. (2019). Predictors of self-perceived stigma in Parkinson's disease. *Parkinsonism & Related Disorders, 60*, 76-80. https://doi.org/10.1016/j.parkreldis.2018.09.028Get

Savica, R., Grossardt, B.R., Bower, J.H., Ahlskog, J.E., Rocca, W.A. (2013). Risk factors for Parkinson's disease may differ in men and women: an exploratory study. *Hormones and Behavior, 63*(2), 308-314. https://doi.org/10.1016/j.yhbeh.2012.05.013

Schirinzi, T., Lazzaro, G.D., Sancesario, G.M., Summa, S., Petrucci, S., Colona, V.L., Bernardini, S., Pierantozzi, M., Stefani, A., Mercuri, N. B., Pisani, A. (2020). Young-onset and late-onset Parkinson's disease exhibit a different profile of fluid biomarkers and clinical features. *Neurobiology of Aging, 90*, 119-124. https://doi.org/10.1016/j.neurobiolaging.2020.02.012

Schrag, A., Barone, P., Brown, R.G., Leentjens, A.F., McDonald, W.M., Starkstein, S., Weintraub, D., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T., Goetz, C.G. (2007). Depression rating scales in Parkinson's disease: Critique and recommendations. *Movement Disorders, 22*(8), 1077-1092. https://doi.org/10.1002/mds.21333

Schrag, A., Ben-Shlomo, Y., Brown, R., Marsden, D., Quinn, N. (1998). Young-onset Parkinson's disease revisited—clinical features, natural history, and mortality. *Movement Disorders, 13*(6), 885-894. https://doi.org/10.1002/mds.870130605

Schrag, A., Hovris, A., Morley, D., Quinn, N., Jahanshahi, M. (2003). Young- versus older- onset Parkinson's disease: Impact of disease and psychosocial consequences. *Movement Disorders, 18*(11), 1250-1256. https://doi.org/10.1002/mds.10527

Schrag, A., Jahanshahi, M., Quinn, N. (2000). What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery, and Psychiatry, 69*(3), 308-312. http://dx.doi.org/10.1136/jnnp.69.3.308

Schrag, A., Schott, J.M. (2006). Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. *The Lancet Neurology, 5*(4), 355-363. https://doi.org/10.1016/S1474-4422(06)70411-2Get

Schulz-Schaeffer, W.J. (2010). The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease, and

Parkinson's disease dementia. *Acta Neuropathologica, 120*, 131-143. https://doi.org/10.1007/s00401-010-0711-0

Shen, L. (2015). Associations between B vitamins and Parkinson's disease. *Nutrients, 7*(9), 7197-7208. https://doi.org/10.3390/nu7095333

Sheng, K., Fang, W., Zhu, Y., Shuai, G., Zou, D., Su, M., Han, Y., Cheng, O. (2016). Different alterations of cerebral regional homogeneity in early-onset and late-onset Parkinson's disease. *Frontiers in Aging Neuroscience, 8*, 165. https://doi.org/10.3389/fnagi.2016.00165

Shih, M.C., Franco de Andrade, L.A., Amaro, E., Felicio, A.C., Ferraz, H.B., Wagner, J., Hoexter, M.Q., Lin, L.F., Fu, Y.K., Mari, J.J., Tufik, S., Bressan, R.A. (2007). Higher nigrostriatal dopamine neuron loss in early than late onset Parkinson's disease? —A [99mTc]-TRODAT-1 SPECT study. *Movement Disorders, 22*(6), 863-866. https://doi.org/10.1002/mds.21315

Slaughter, J.R., Slaughter, K.A., Nichols, D., Holmes, S.E., Martens, M.P. (2001). Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13*(2), 187-196. https://doi.org/10.1176/appi.neuropsych.13.2.187

Solla, P., Cannas, A., Ibba, F.C., Loi, F., Corona, M., Orofino, G., Marrosu, M.G., Marrosu, F. (2012). Gender differences in motor and non-motor symptoms

among Sardinian patients with Parkinson's disease. *Journal of the Neurological Sciences, 323*(1-2), 33-39. https://doi.org/10.1016/j.jns.2012.07.026

Spica, V., Pekmezovic, T., Svetel, M., Kostic, V.S. (2013). Prevalence of non-motor symptoms in young-onset versus late-onset Parkinson's disease. *Journal of Neurology, 260*, 131-137. https://doi.org/10.1007/s00415-012-6600-9

Starkstein, S.E., Berthier, M.L., Bolduc, P.L., Preziosi, T.J., Robinson, R.G. (1989). Depression in patients with early versus late onset of Parkinson's disease. *Neurology, 39*(11), 1441. https://doi.org/10.1212/WNL.39.11.1441

Starkstein, S.E., Preziosi, T.J., Bolduc, P.L., Robinson, R.G. (1990). Depression in Parkinson's disease. *The Journal of Nervous and Mental Disease, 178*(1), 27-31. https://doi.org/10.1097/00005053-199001000-00005

Stella, F., Banzato, C.E., Quagliato, E.M., Viana, M.A. (2008). Depression in patients with Parkinson's disease: Impact on functioning. *Journal of the Neurological Sciences, 272*(1-2), 158-163. https://doi.org/10.1016/j.jns.2008.05.018

Stykel, M.G., Humphries, K., Kirby, M.P., Czaniecki, C., Wang, T., Ryan, T., Bamm, V., Ryan, S.D. (2018). Nitration of microtubules blocks axonal mitochondrial transport in a human pluripotent stem cell model of

Parkinson's disease. *FASEB Journal, 32*(10), 5350-5364. https://doi.org/10.1096/fj.201700759RR

Tan, S.K.H., Hartung, H., Sharp, T., Temel, Y. (2011). Serotonin-dependent depression in Parkinson's disease: A role for the subthalamic nucleus? *Neuropharmacology, 61*(3), 387-399. https://doi.org/10.1016/j.neuropharm.2011.01.006

Taylor, A.E., Saint-Cyr, J.A., Lang, A.E., Kenny, F.T. (1986). Parkinson's disease and depression: A critical re-evaluation. *Brain, 109*(2), 279-292. https://doi.org/10.1093/brain/109.2.279

Triarhou, L.C. (2000-2013). Dopamine and Parkinson's disease. Madame Curie Bioscience Database [internet]. https://www.ncbi.nlm.nih.gov/books/NBK6271/

van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., Vermeulen, R. (2012). Is pesticide use related to Parkinson Disease? Some clues to heterogeneity in study results. *Environmental Health Perspectives, 120*(3), 340-347. https://doi.org/10.1289/ehp.1103881

van Uem, J.M., Marinus, J., Canning, C., van Lummel, R., Dodel, R., Liepelt-Scarfone, I., Berg, D., Morris, M.E., Maetzler, W. (2016). Health-related quality of life in patients with Parkinson's disease—A systematic review based on the ICF model. *Neuroscience & Behavioral Reviews, 61*, 26-34. https://doi.org/10.1016/j.neubiorev.2015.11.014

Verity, D., Eccles, F.J., Boland, A., Simpson, J. (2020). Does perceived control mediate the relationship between stigma and well-being for individuals with Parkinson's disease? *Journal of the Neurological Sciences, 414*, 1-6. https://doi.org/10.1016/j.jns.2020.116841

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

Weintraub, D., Comella, C.L., Horn, S. (2008). Parkinson's disease—Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. *The American Journal of Managed Care,14*(2), 40-48. https://pubmed.ncbi.nlm.nih.gov/18402507/

Weisskopf, M.G., Reilly, E.O., Chen, H., Schwarzschild, M.A., Ascherio, A. (2007). Plasma urate and risk of Parkinson's disease. *American Journal of Epidemiology, 166*(5), 561-567. https://doi.org/10.1093/aje/kwm127

Wielinski, C.L., Varpness, S.C., Erickson-Davis, C., Paraschos, A.J., Parashos, S.A. (2010). Sexual and relationship satisfaction among persons with young-onset Parkinson's disease. *The Journal of Sexual Medicine, 7*(4), 1438-1444. https://doi.org/10.1111/j.1743-6109.2009.01408.x

Williams-Gray, C.H., Worth, P.F. (2016). Parkinson's disease. *Medicine, 44*(9), 542-546. https://doi.org/10.1016/j.mpmed.2016.06.001

Wooten, G.F., Currie, L.J., Bovbjerg, V.E., Lee, J.K., Patrie, J. (2004). Are men at greater risk for Parkinson's disease than women? J*ournal of Neurology, Neurosurgery, and Psychiatry, 75*(4), 637-639. https://doi.org/10.1136/jnnp.2003.020982

World Health Organization. (2021). *Depression*. https://www.who.int/health-topics/depression#tab=tab_1

Xuan, M., Guan, X., Huang, P., Shen, Z., Gu, Q., Yu, X., Xu, X., Luo, W., Zhang, M. (2019). Different patterns of grey matter density in early-and middle-late-onset Parkinson's disease: a voxel-based morphometry study. *Brain Imaging and Behavior, 13*, 172-179. https://doi.org/10.1007/s11682-017-9745-4

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17*(1), 37-49. https://doi.org/10.1016/0022-3956(82)90033-4

Yue, Y., Jiang, Y., Shen, T., Pu, J., Lai, H.Y., Zhang, B. (2020). ALFF and ReHo mapping reveals different functional patterns in early-and late-onset Parkinson's disease. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2020.00141

Zhai, S., Tanimura, A., Graves, S.M., Shen, W., Surmeier, D.J. (2018). Striatal synapses, circuits, and Parkinson's disease. *Current Opinion in Neurobiology, 48*, 9-16. https://doi.org/10.1016/j.conb.2017.08.004

Zhang, D., Jiang, H., Xie, J. (2014). Alcohol intake and risk of Parkinson's disease: A meta-analysis of observational studies. *Movement Disorders, 29(*6), 819-822. https://doi.org/10.1002/mds.25863