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Comparison and Review of DAT Scan, PET Scan, and α-synuclein In Relation to Parkinson's Disease

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ABSTRACT

In this article, the role of the Dopamine Active Transporter (DAT) scan, and Positron Emission Tomography (PET) scan along with the role of α-synuclein with regards to Parkinson's disease will be discussed. Furthermore, their applications and dependence as diagnostic techniques, as well as biomarkers, are also reviewed. In short, DAT-SPECT and PET scans can be used well to differentiate between Parkinson's and other Parkinsonian syndromes, but it takes experts with many years of experience to help with diagnosis. α-synuclein on the other hand may not serve as a good biomarker but it does have potential in therapeutic treatments. Furthermore, a few common diseases that are most often misdiagnosed with Parkinson's are also discussed. They include Multiple Sclerosis (MS) and Progressive Supranuclear Palsy. MS deals with the degeneration of the myelin sheath which PSP deals with the build-up of a certain protein in the brain called tau. In both cases, neuronal degeneration occurs, similar to what happens with respect to Parkinson's. Unfortunately, there is no current cure for Parkinson's, PSP, or MS. Lastly, this paper also reviews the author's future plans with regard to Parkinson's disease and other neurodegenerative diseases in general. There is a dire need for biomarkers and/or a concrete diagnostic technique that can detect Parkinson's earlier such that progression is either delayed or treatment is developed based on this.

Introduction

Parkinson's Disease, a mysterious neurodegenerative disease that does not have a cure yet, affects the substantia nigra and dopamine receptors in that brain area. Dopamine receptors start degenerating which causes early onset of motor symptoms such as resting tremor, bradykinesia, etc. This disease may even lead to cognitive impairment and, unfortunately, due to the lack of a cure, it leads to eventual death. The need for useful biomarkers to aid in diagnosis along with concrete diagnostic techniques such as neuroimaging scans will not only help in the treatment of the disease early on but may also lead to the development of a cure. Neuroimaging biomarkers such as DAT scans help with diagnosis, but they are not able to distinguish between various Parkinsonian syndromes.

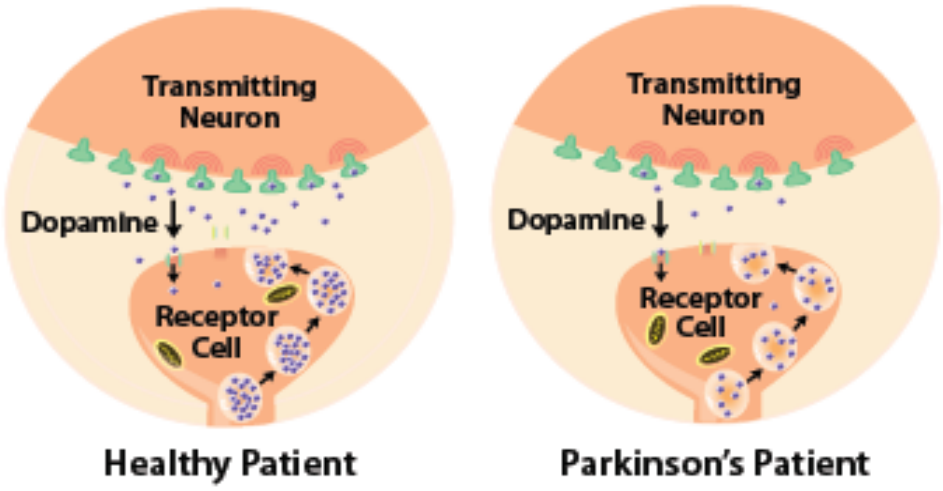
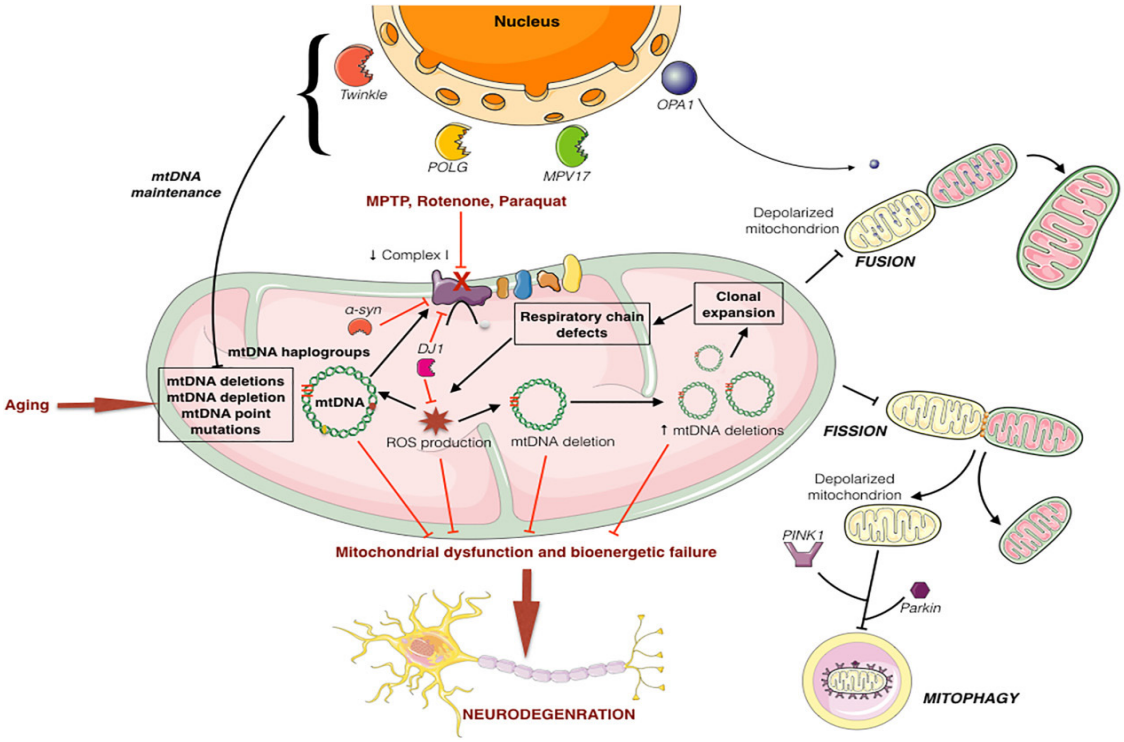


Figure 1: The diagram above illustrates the difference between dopamine being transmitted from one cell to another, in a healthy patient vs one with Parkinson's disease.

Cause of Parkinson's Disease

The cause of this disease varies as it can be due to environmental factors, genetic factors, and sometimes, a mix of both. Mutations in nearly 28 chromosomal loci have been implicated for genetic biomarkers of the disease. These loci include the PARK family, mutations in the SNCA gene, which codes for α-synuclein, glucocerebrosidase (GBA) gene, and the LRRK2 gene. Genetic mutations in LRRK2 and GBA genes are especially common in the Ashkenazi Jewish population. Relating to GBA, both heterozygotic and homozygotic mutations carriers have an increased risk of developing PD (Stefanis, 2012). According to various studies, if GBA does not function normally, it is sufficient to induce



α-synuclein accumulation and aggregation which can occur after lysosomal dysfunction (Stefanis, 2012). Other contradictory studies find that α-synuclein accumulation is a result only due to overexpression of GBA mutants, leading to a gain of a toxic function mechanism (Stefanis, 2012). There are almost 20 genes that have been identified, leading to Parkinson's disease. These genes, along with rural living and the use of well water for drinking may combine to result in protein aggregation (α-synuclein), mitochondrial dysfunction, oxidative stress, inflammation, and excitotoxicity, ultimately leading to neuronal degeneration.

Figure 2**:** The diagram above illustrates various ways for neurodegeneration.

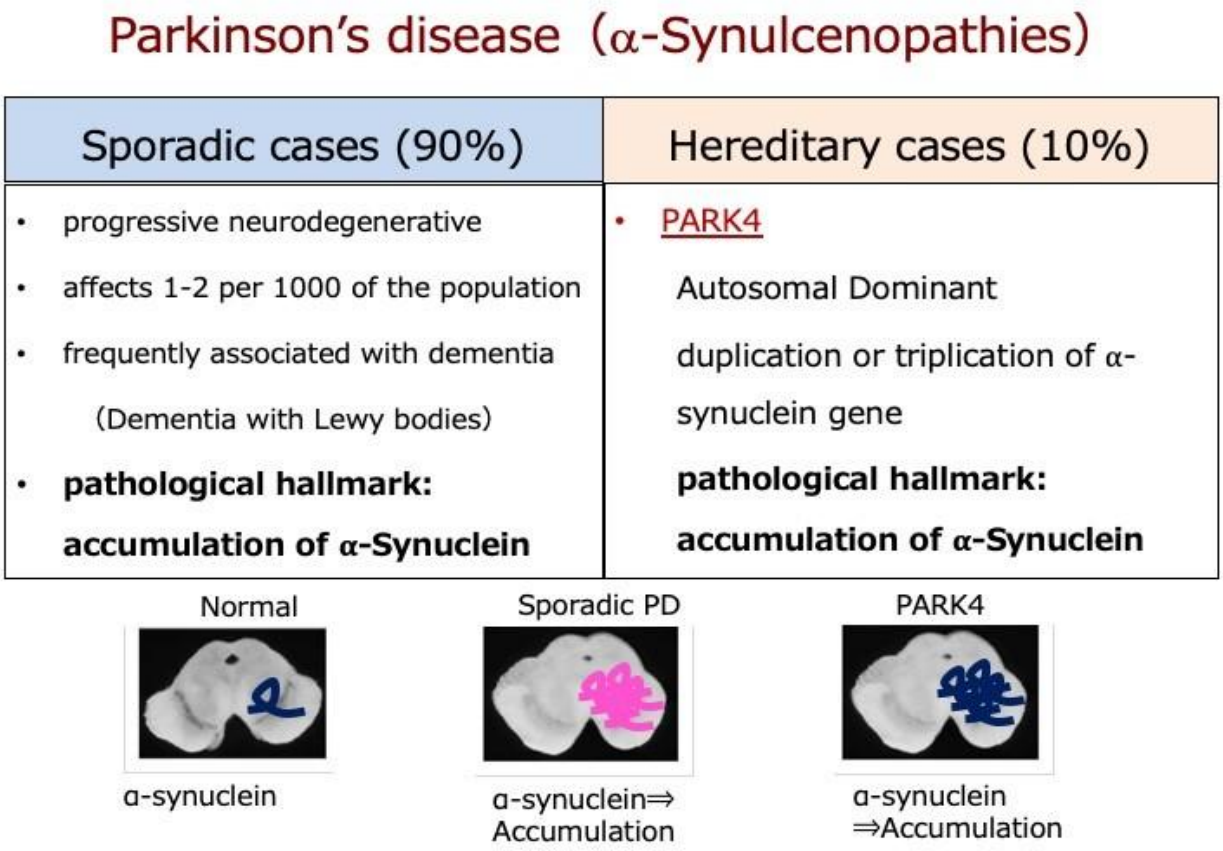


Figure 3**:** The diagram above illustrates the causes of sporadic and hereditary Parkinson's cases.

For example, according to Frontiers in Aging Neuroscience, in post-mortem studies, an enzyme called peroxisome proliferator-activated receptor-gamma coactivator-1 α or PGC-1α coordinates the expression levels of many genes needed for mitochondrial biogenesis and electron transport chain activity. The expression of PGC-1α was reported to be decreased in [the] substantia nigra of PD patients, which could be partially attributed to increased cytosine methylation at the promoter region of the PGC-1α gene. PGC-1α regulated nuclear-genes encoding mitochondrial proteins were also downregulated in substantia nigra of the PD brain (Ganguly et al., 2021).
In addition, the accumulation of transition metals like iron and copper, oxidative damage markers of phospholipids, proteins, and DNA, depletion of reduced glutathione (GSH) and increased activity of glutathione degradative enzyme, and elevated levels of peroxiredoxins were reported in substantia nigra of post-mortem PD brains (Ganguly et al., 2021). Reactive oxygen species (ROS)—which can damage mitochondrial DNA or the ETC components, causing a

further increase in ROS production—is increased when the iron is accumulated in the substantia nigra (Ganguly et al., 2021).

ROS has an important implication on the proteasomal pathway relating to protein degradation. However, 19S regulatory units and 20S proteasomal catalytic units could occur due to high levels of oxidative stress inactivation of ubiquitinating enzymes. This leads us to conclude that an increase in ROS could lead to intra-neuronal accumulation of proteins such as α-synuclein, which is later on cleared from the cell in an important way by the proteasomal pathway. Furthermore, relating to oxidative damage in Parkinson's: dopamine oxidation does produce ROS and very reactive quinones which in turn can form conjugates with proteins via thiol residues, resulting in an inactivation of function which in turn could have important applications in Parkinson's diagnosis (Ganguly et al., 2021).

Neuroimaging Technique: Dopamine Active Transporter Scan (DAT Scan)

Dopamine Active Transporter Scan or DAT scan is a neuroimaging scan that helps identify and assess how well the dopamine neurons are doing. A special radioactive chemical called Ioflupane I-123 is injected intravenously. This chemical crosses the blood-brain barrier and is attached to the presynaptic dopamine transporter in the striatum. Usually, around 3-4 hours are required for the chemical to spread all over the body. Then, using gamma imaging, gamma rays are picked up from a single-photon emission computerized tomography camera or SPECT camera. Scans are then taken indicating the location and concentration in both three-dimensional and cross-sectional views.

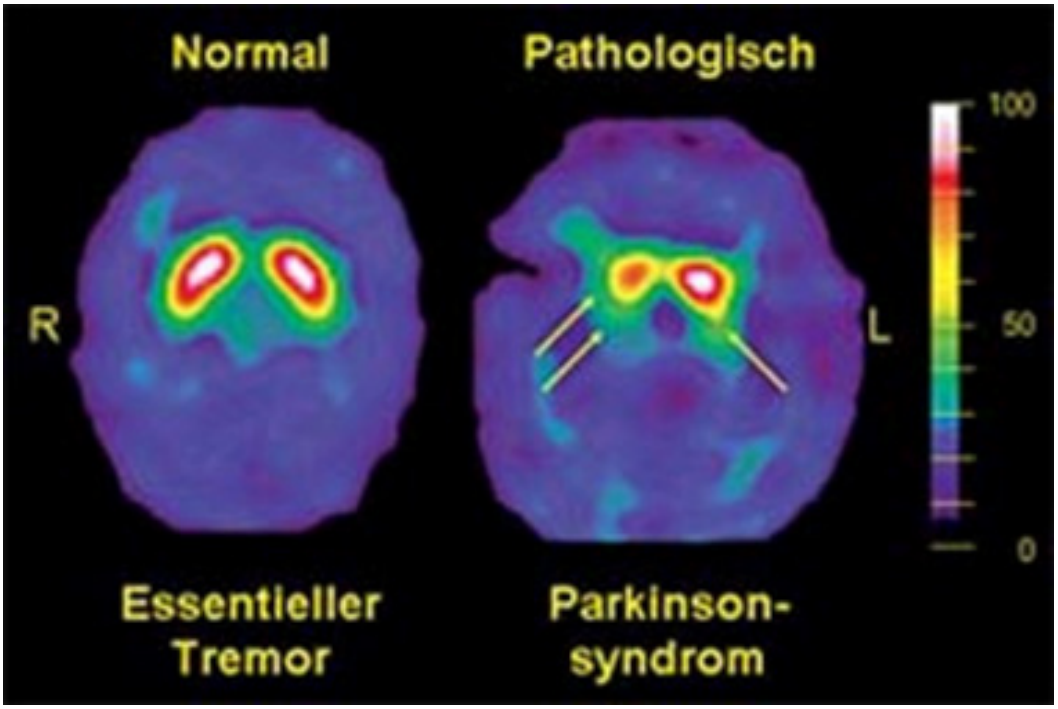


Figure 4: The diagram above illustrates the difference between an essentially tremor and Parkinson syndrome using a DAT scan

Despite what may seem like an accurate test, DAT scans are usually used to differentiate between Parkinson's disease and other Parkinsonian disorders, after one has experienced symptoms common to both such as tremors. Even after the scan, it takes an expert with years of experience to accurately diagnose Parkinson's disease. Furthermore, clinical diagnosis is accurate in 65 to 94% of patients compared to the final pathological diagnosis. As mentioned above, this

accuracy increases with the duration of symptoms present. More studies are needed to determine the actual accuracy of the DAT SPECT imaging technique.

Neuroimaging Technique: Positron Emission Tomography (PET Scan)

The Positron Emission Tomography or PET scan is a neuroimaging technique that detects the amount of glucose that has been up taken by cells. Since Parkinson's disease affects dopamine uptake in the basal ganglia, the substantia nigra, and surrounding parts, this test can help determine the severity and may act as a diagnosis method for Parkinson's disease. This test, similar to the Dopamine Transporter (DAT) scan, is also used to differentiate between Parkinson's disease and other similar Parkinsonian syndromes.

The way it works is that a patient is first injected with a radioactive form of glucose called 2-fluoro-2-deoxy-D-glucose. The patient's cells uptake the glucose from this and radioactivity is given off, as a result. Finally, the patient is moved into a ring of detectors which ultimately intercepts the radioactive glucose, indicating the amount of glucose that has been up taken in parts of the body (in this case the brain) and the location of the uptake.

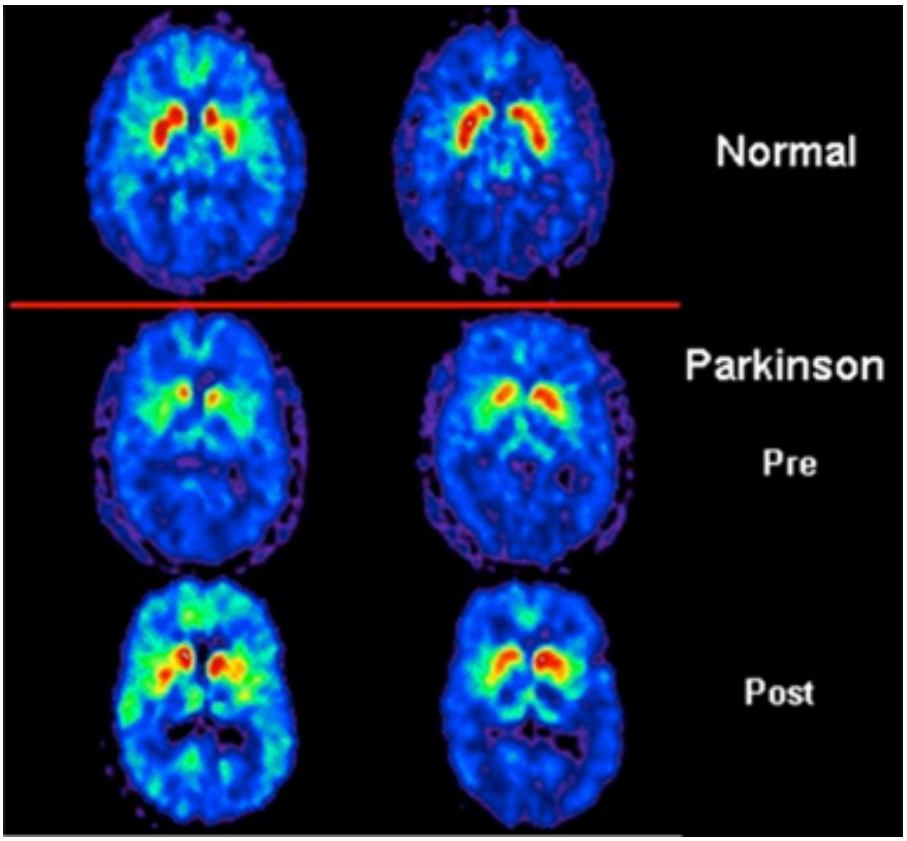


Figure 5: The diagram above illustrates a brain in three different stages: One is a normal brain, one before the diagnosis of Parkinson's disease, and one after diagnosis of Parkinson's disease.

Although the diagnosis of Parkinson's disease may not be guaranteed with PET scans, they do have implications in restorative therapy. It can be used to evaluate the efficacy of a therapy and monitor improvements (or declines) longitudinally (Loane & Politis, 2011). However, there are many gaps in our knowledge still remaining, which could be closed by using PET imaging techniques. Future PET studies should focus on understanding the role of non-DA neurotransmitter systems in not only the pathogenesis of the PD motor disease and arising medication-related

complications, but also the non-motor features, such as addiction and compulsion as they greatly impact the quality of life of PD patients (Loane & Politis, 2011).

α-synuclein in Parkinson's Disease

α-synuclein, a protein found in Lewy bodies, is a key player in Parkinson's pathogenesis. This protein's expression levels are modulated in conditions that alter plasticity or confer injury leading to a conclusion that it may be a modulator of synaptic transmission. The main function of α-synuclein appears to be to control neurotransmitter release, through effects on the SNARE complex (Stefanis, 2012). It is believed that this protein not only allows Parkinson's to spread through the brain but also initiates the start of this disease. The process of α-synuclein, starting from the "natively unfolded protein and culminating in the mature fibril formation, is collectively termed α-synuclein aggregation (Stefanis, 2012). It becomes dangerous when it becomes a mature fibril.

In detail, possible scenarios where α-synuclein could lead to neurodegeneration are as follows: α-synuclein oligomers could form pores on cell membranes or can also change the properties of voltage-gated receptors, resulting in excess calcium influx. Similarly, through other related porelike mechanisms, oligomeric α-synuclein can also attack synaptic vesicles causing neurotransmitters to leak in the cytosol. With respect to dopamine vesicles, this could mean excess dopamine in the cytosol, leading to stress-induced death. Excess intracellular calcium had amplified dopamine in the cytosol. Both this and AS had been required for death induced by too much dopamine, which further created a possible scenario where α-synuclein, dopamine in the cytosol, and intracellular calcium would interact with each other causing neurodegeneration, at last (Stefanis, 2012).

In simpler terms, the buildup of these proteins causes aggregates which eventually leads to the degeneration of neurons. This loss of neurons leads to a significant drop in dopamine levels in the substantia nigra. In many cases, mutations in α-synuclein, a misfolded version, or accumulation of α-synuclein tend to damage the brain. In this case, it leads to Parkinson's disease symptoms. When cells get overloaded with α-synuclein, they "pump" it to nearby cells which is supposedly how Parkinson's disease spreads.

As for the usefulness of an α-synuclein biomarker, it may not be the best. However, it does have promising therapeutic targets in Parkinson's disease and other similar diseases where the protein is involved.

Diseases Parkinson's is Commonly Misdiagnosed With

Oftentimes, the reason Parkinson's is misdiagnosed is that many of the symptoms overlap with other diseases such as multiple sclerosis, progressive supranuclear palsy, and essential tremor, to name a few. Here, I will briefly go over a few key differences between the three diseases mentioned above:

Multiple Sclerosis vs. Parkinson's Disease

Firstly, Parkinson's affects patients who are usually aged 60 or older whereas Multiple Sclerosis typically affects patients aged between 20 and 50. It also has a few key symptoms that do not overlap with Parkinson's disease such as double vision, dizziness, tingling sensations in the body, hearing loss, seizures, among others. Parkinson's disease also varies with unique symptoms such as bradykinesia, poor posture, loss of control over basic movements, dragging of feet, etc.

From the molecular perspective, in MS, the myelin sheath covering around nerve fibers is attacked by the body's immune system leaving scarred tissues or lesions, disrupting electrical impulses in much of the body. In Parkinson's, however, there is a loss of dopamine receptors and hence a loss of dopamine in the substantia nigra and neighboring parts of the brain leading to a lack of control over voluntary movement and other such symptoms.

Progressive Supranuclear Palsy vs. Parkinson's Disease

A few common differences between Progressive Supranuclear Palsy and Parkinson's Disease: people with PSP usually stand straight or tilt their heads backward (termed axial rigidity), while Parkinson's disease patients usually bend forward. Additionally, from a molecular perspective, PSP shows the accumulation of the *tau* protein in affected brain cells while PD patients show accumulation of α-synuclein. Other symptom differences include tremor, which is rare in PSP but quite common in PD. Also, eye movements are abnormal in PSP but quite normal in PD patients.

Future

I am passionate about this topic and hope to continue researching Parkinson's and other neurodegenerative diseases—especially ones where little is known. Neurodegenerative diseases, in general, are troublesome for patients and I hope to reduce the number of people they impact. I plan to continue researching this disease until I am able to find a concrete biomarker or technique for diagnosis.

Discussion

My hope is to find a key characteristic—be it with respect to a certain symptom or even to the cellular or molecular level—that can help differentiate Parkinson's disease from any other similar neurodegenerative disease. Based on this differentiation, I hope to create a diagnostic technique that is accurate 100% of the time.

Conclusion

As of right now, there is no diagnosis for Parkinson's disease that works 100% of the time. As mentioned above, neuroimaging scans such as the Dopamine Transporter (DAT) scan or positron emission tomography (PET) scan can only do so much in diagnosis. An expert with years of experience is needed to diagnose Parkinson's disease. Furthermore, there are many other neurodegenerative diseases that I briefly touched upon, including progressive supranuclear palsy that have symptoms and neurodegenerative progressions similar to Parkinson's. Unfortunately, Parkinson's affects more than 10 million people worldwide. Individuals are also more likely to get Parkinson's as age increases. An estimated four percent of people with Parkinson's disease are diagnosed before age 50, which I think is unfortunately quite late in life. Not only does it affect patients and worsen neurons in the brain, but it also has a huge toll on the economy, both on the micro and macro level. The combined direct and indirect cost of Parkinson's including treatment, social security payments, and lost income, is estimated to be nearly $52 billion a year, just in the United States (Marras et al., 2018). Medications cost an average of $2,500 a year and therapeutic surgery can cost up to $100,000 per person (Marras et al., 2018). The earlier the diagnosis, as with many diseases, the better the patient fares in the long run. Furthermore, since this disease has no cure yet, doctors will be able to treat the patient earlier and at the very Least be able to help delay progression.

Neuroimaging Technique/protein	Strength	Weakness
Dopamine active transporter (DAT) Scan	This scan can differentiate Parkinson's disease from other Parkinsonian syndromes.	It takes an expert to differentiate and this technique cannot diagnose early on with precision.
Positron Emission Tomography (PET) Scan	Similar to DAT scan but also has important implications in therapy or evaluation of therapies for the treatment of PD.	Similar to DAT scan but also diagnosis is not as good as DAT scan. More studies need to be done to determine precision and potential for diagnosis.
α-synuclein	Function is slightly known but still needs to be fully discovered. We know it plays an important role in pathogenesis and does have important implications as a therapeutic target (for the development of drugs, etc.)	It cannot be used as a suitable biomarker.

Figure 6: Summary of factors relating to Parkinson's Disease; created by Pranav VK

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