HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 4 (2022)

Parkinson's Disease: An Overview on its Neurophysiological Effects and Potential Treatments

Santosha Pochiraju[1] and Mia Edgerton[2#]

[1]Adlai E. Stevenson High School, Lincolnshire, Illinois, USA
[2]Medical University of South Carolina, USA
[#]Advisor

ABSTRACT

Parkinson's disease is a progressive neurodegenerative disease characterized by tremors and bradykinesia (slowing of movement and speed) all due to the loss of dopamine levels in the brain. The loss of dopamine containing neurons in the brain becomes progressive and affects different parts of the brain. Dopamine is essential to the brain as dopamine enables neurons to communicate and control movement, which is lacking with Parkinson's Disease. In Parkinson's, the neurons are vulnerable to degeneration because of its extensive amount of energy with its vast systems of neurons. As Parkinson's currently has no cure, the vast majority of the Parkinson's Population is experiencing death at quick rates as short-term solutions are not able to become long term. This review article sheds light on the disease progress of Parkinson's, possible therapies with visual and auditory cueing at the main focus, and the studies effects on the treatment and scientific research progression on Parkinson's Disease.

Introduction

Parkinson's Disease (PD) is one of the most common neurodegenerative disorders in which more than 1% of the population is affected by this incurable disease by the age of 60. This disease is mainly due to the selective and significant loss of dopaminergic neurons in the substantia nigra **(1)**, which therefore becomes clinically characterized as a combination of bradykinesia (progressive hesitations or halts) and akinesia (loss of ability to move muscles voluntarily). Clinical manifestations include hypokinesia, marked postural instability, resting tremor, bradykinetic movements, and lagged facial expressions. These movement disorders become very harmful and difficult as age increases by compromising the individual's functions and inviting disabilities. In addition to the various motor instabilities, approximately 25% of those diagnosed who have no history of other underlying neurological disorders also suffer from cognitive deficits such as loss of attention, memory, and executive functions **(3)**. However, this 25 percent of newly diagnosed patients come from the fact that they enter the clinic after the disease has already reached a progressive stage, making PD undetectable without symptoms. This inevitable late action takes a large toll on treatment processes as the chances of catching Parkinson's Disease at its earliest stage is extremely rare. In a recent study, less than 10% of PD cases are associated with genetic mutations such as the mutation of alpha-synuclein (SCNA), while the other 90% of cases are idiopathic, meaning the cause of the disease is unknown **(11)**.

Numerous other studies have shown that the loss of cognitive functions are caused by the dysfunction of the caudate nucleus, which is responsible for the planning and execution of movement, learning, memory, and emotion. In PD, the dysfunction of the caudate nucleus suggests that dopamine is lacking where it is necessary to transfer information toward the motor-related functions, causing external disorders in patients with PD **(4)**. The caudate region of the brain is specifically involved in the deficits caused by PD, but this does not mean this is the only region being impacted. The caudate nucleus is merely one example of a brain region that is hypothesized to play a key role in Parkinson's Disease. Other brain regions will be explored through the course of this review paper. In America Parkinson's Disease: An overview on its neurophysiological effects and potential treatments researchers. From 1990 to 2015

the diagnosis of PD doubled to over 6 million **(5)**. Due to the inevitable cycle of aging, this number is projected to double again by 2040. In 1855 this neurodegenerative disease was classified as a rare disorder since only 22 out of 15 million people passed away from this disorder in England and Wales, contradicting the present skyrocketing rates. According to the Golden Burden of Disease study, from 1990-2015 the global PD rates have increased 118%, with PD being the number 1 fastest growing neurological disorder **(18)**. The underlying causes in these sudden increases within less than two centuries is widely debated. Current possibilities include increasing longevity and increased industrialization, leading to more diagnoses across the world **(5)**.

Several other studies across the world have also shown the growing prevalence in Parkinson's disease among adults. Specifically in China, as the aging population is growing (older than 65), China is projected to increase from 8.87% in 2010 to a significant 22.6% in 2040, **(2)** signaling a major health issue in the coming years, especially given PD's incurable stage. These statistics are just a few of the many recurring patterns of increased PD around the world. The fact that this once rare disorder is spreading across the world like a plague is quite alarming given that there is no cure to this disorder and so much more information is yet to be gathered. Therefore, this review will explore PD progression, neuropsychological effects, and potential therapies to mitigate the effects of PD.

Disease Progression

In order to begin a study of PD, the pathology behind it must be explained. The nervous system, the primary actor of PD, is composed of individual units called neurons which are responsible for the communication of information throughout the body. The chemical messengers that neurons use are called neurotransmitters which send information through millions of synapses (the space crossing between two neurons) **(6).** The main type of neurotransmitter that is most impacted in PD is dopamine that is produced by neurons in the substantia nigra. The loss of dopamine results in abnormal nerve firing patterns that as a result impair movement as one of their effects. By the time of diagnosis, people may have already lost a significant amount of dopamine producing cells, making this disease incurable **(3).** Perhaps the largest factor in PD is the degeneration of dopaminergic neurons that takes place throughout the CNS. In PD, the neurons are especially vulnerable to degeneration due to the amount of energy the brain requires, also because of pacemaker neurons. Pacemaker neurons constantly send nerve signals through extensive branching of the CNS as they are constantly discharging. Pacemaker neurons are also responsible for exerting control over neuronal circuit function by their intrinsic ability to generate bursts of rhythmic potential, involving high amounts of energy **(58)**. Because this takes an immense amount of energy, patients often experience postural instabilities as a result **(13)**. The extreme high energy demands of the dopaminergic neurons appear to project from the substantia nigra. This is because of the anatomical structure where substantial nigra neurons have branched axons and nerve fibers are not covered with a myelin sheath **(14,16)**. Statistically, these neurons are supposed to give rise to millions of synapses and a single action that potentially damages these neurons, creates increased energy requirements. This process is replicated in PD. The reduction of neuromelanin pigmentation, neuron loss, and formation of lewy bodies are all observed to be impacted in the substantia nigra **(7,15)**.

Alpha-synucleinopathies in PD

Alpha-synuclein is a major factor that is a part of dopamine in neurons and the pathology of Parkinson's disease. Alpha-synuclein is described to be the major constituent of Lewy bodies and a pathogenic mark of all synucleinopathies which includes Parkinson's disease. Before we move on to discuss the function of Lewy bodies in terms of alpha-synuclein, we must understand its proper function and structure as a whole. The current studies, however, have each shown various contrasting conclusions, leading to overall confusion in the role of alpha-synuclein. Some studies have tried to examine the structure in various environmental conditions like changes in pH, salt, lipid compositions, and modification of protein structure **(24,25,26)**. A current universal consensus suggests that alpha-synuclein functions to

promote membrane curvature which then contributes to synaptic trafficking and vesicle budding **(28,29)**. This serves as an important finding mainly because of the association of alpha-synuclein with presynaptic terminal SNARE complexes **(27)**, therefore suggesting a potential role of alpha-synuclein in modulating dopamine release, which we know as a major contributor to PD.

Lewy body pathology in PD

PD is also associated with the appearance of dopaminergic neuronal cytoplasmic inclusion called Lewy Bodies. Lewy bodies consist of large aggregation forms of alpha-synuclein which misfold and give rise to beta-sheet amyloid fibrils. When these Lewy bodies start forming, it blocks the production and transmission of dopamine, leading to the main movement issues of PD **(64)**. Specific research has shown that Lewy bodies from the substantia nigra of 6 patients were strongly immunoreactive for alpha-synuclein (the proteins in Lewy bodies). This data showcases the leading pathologic hallmark in biopsied patients which are not present in healthy individuals, indicating the impact of the duplication of autosomal dominant mutations in the SNCA **(23)**. Currently, research suggests that Lewy Bodies are found in about 10% of brains from normal elderly individuals over 65. These cases may represent the earliest stages of PD as Lewy bodies are known for the blockage of the transmission of dopamine. Lewy bodies are intracellular inclusions found in a range of neurodegenerative disorders such as Parkinson's and dementia. Specifically in PD, the mutations in the gene that codes for alpha synucleins, SNCA, can cause increased protein aggregation leading to neurodegeneration. However, the exact causal link between Lewy bodies and neuronal cell death is less certain. Lewy body pathology begins in the medulla and olfactory bulbs, which then progressively spread through six stages to involve the midbrain, amygdala, and the neocortex. The spread of these Lewy bodies have been shown to affect vulnerability of certain brain regions **(65)**. Those that are impacted earlier are susceptible to greater degeneration over the progression of PD. Overtime, we see that wherever there is neurodegeneration, there is the presence of Lew bodies in the brain.

Neurophysiological alterations in PD

PD is one of the largest diseases primarily attributed to the loss and dysfunction of dopaminergic neurons. To discuss the alterations in PD, we first must discuss the pivotal role of dopaminergic neurons in this specific disease. The primary role dopamine plays in the human body is the modulation of behavior and cognition, voluntary movement, motivation, sleep, mood, attention, and learning **(62)**. The high energy requirements of the substantia nigra make these neurons susceptible to degeneration. These energy demands are a function of their extensively branched anatomy and their large number of transmitter release sites. Therefore, these neurons have been said to be operating in a critical equilibrium where any stress may lead to decomposition and degeneration **(13)**. Degeneration is what primarily takes place in PD. Speaking of inflammation, excessive fat accumulation in the brain has induced inflammatory responses by promoting pro-inflammatory cytokine production in the CNS. This topic will be discussed further into the article The selective degeneration of these dopaminergic neurons in the substantia nigra does lead to PD, however the cause and origin for this cell loss is still unknown. The uncertainty of this loss makes therapies especially important as the only way to combat this disease is through early detection and long-term effective solutions.

Brain regions involved in PD development/progression

Although the substantia nigra is a brain region that is heavily involved in PD pathology, other brain regions such as the amygdala, hypothalamus, locus coeruleus, median rape nucleus, and basal ganglia also begin to deteriorate and destroy chemical pathways that regulate chemicals like norepinephrine, serotonin, and acetylcholine **(6).** It is reported that there are two types of subtypes of PD which will affect the basal ganglia in different manners: heterogeneous

phenotypes such as tremors and postural instability. The basal ganglia, which processes signals from the cortex and is responsible for accurate execution of voluntary movements, is proven to be the most affected brain area in PD as the lesion of the basal ganglia causes impairment in cognitive functions **(7)**.

Furthermore, In PD, the dopaminergic nigrostriatal pathway progressively degenerates as a result of PD. The dopaminergic projections to the sensorimotor striatum -contains neuronal activity related to movements which relate to preparation, initiation, and execution- are affected significantly stronger than those to the associative and limbic striatal regions in the basal ganglia, resulting in problems with movement in PD. The loss of dopamine in the striatal region is associated with a reduction in the density of dendritic spines in the striatum. This loss of dopamine SNc cells remains the best-known pathological aspect of PD **(10)**. Studies have shown that microstructural changes within the substantia nigra are severely affected in patients with postural instability compared to patients with tremor dominant phenotypes **(8,17)**. In PD patients, the loss of attenuation and also the length of the dendritic spines of medium sized neurons located in the striatum has also been reported in the substantia nigra. As a result, reduction in the volumes of the caudate nucleus and thalamus, which is observed in PD, is in fact an early sign of disease progression.

In addition to the nigrostriatal pathway, another brain region we see affected greatly by PD is the cerebellum, responsible for a wide range of functions and processes. Functional and morphological modulations in the cerebellum have been detected in relation to akinesia, tremor, gait disturbances, and some other non motor symptoms **(60)**. Due to the changes in the cerebellum, many research articles have shown that visual information relayed through this brain region can result in the bypass of defective basal ganglia circuits **(46)**, showcasing one of the potential solutions to gait disturbances. The occipital lobe, mainly responsible for processing and interpreting visual information is then activated through visual cues to promote activity in proper regions, leading to overall decreased gait variations **(61)**.

Brain volume alterations and its correlation with neuroinflammation in PD

A growing body of research has revealed there is a strong correlation between brain size and cognitive functions. In these complex areas of the brain, it has been reported that the volume of the frontal lobe, parietal lobe, insula, anterior cingulate cortex, basal ganglia, and thalamus has increased in PD patients. The loss of gray matter has also been reported **(7)** through VBM analysis that compares dyskinetic and non-dyskinetic groups which provided evidence on increased gray matter volume in the bilateral inferior frontal gyrus, which was more evident in patients with early-onset PD **(9)**. A study on the effect of the presence of active inflammatory lesions on brain volume has reported that with the increase in inflammation, the brain volume increased by an estimated mean of 1.2 cm cubed, simulating the similar processes that occur in neuroinflammation during PD.

Neuroinflammation specifically takes place usually in the ordinary aging brain, which occurs in the central nervous system due to molecules released from blood-derived immune cells. This inflammation is the body's initial response to an insult, acting as a mechanism in the brain and spinal cord to protect and re-establish the normal functions of the brain. An example includes aiding the recovery of injured neurons as a means of fighting against infection. As it may seem as though the functions of neuroinflammation are beneficial to the human brain, extreme or prolonged inflammation can be detrimental in terms of causing or further fueling neurodegenerative diseases **(4)**. Inflammatory reactions must be concluded to maintain the tissue structure and homeostasis in the brain. This includes eliminations of pathogens, dead cells, or other cellular debris. If neuroinflammation persists or the mechanisms involving the termination of inflammation are damaged, chronic inflation can arise and impact the average human brain **(11)**.

For example, the microglia is one of the major cells involved in the neuroinflammation of PD and inflammatory responses in the central nervous system. These cells constitute 5-10% of total brain cells and also 20% of the glial cell population in the brain **(12)**. Various studies across the board have proven the significance of the microglia and immune components of PD. The activation of microglia in the SNpc striatum is involved in various types of PD animal model studies. Further study of this has revealed higher levels of proinflammatory mediators in the midbrain of PD patients, indicating the role of inflammation as well. The protective role of M2 microglia in the process of polarization is important to note. M2 microglias role is to execute an anti-inflammatory effect and promote wound healing **(20)**. If

any aspect of the polarization of M2 microglia is suppressed, it immediately causes microglia overactivation and neuronal death as a result of aggravated dopamine in PD. An example of this concept would include Jmjd3, a protein essential for M2 microglia polarization, in the substantia nigra **(19)**. If this overactivation turns into a long-term condition the microglia in the PD brain increases the expression of proinflammatory cytokines which then results in the acceleration of high levels of dopamine degeneration, accelerating the progression of PD (**21**). A recent study on the treatment of experimental autoimmune neuritis disease emphasized the need to stop the toxic phase of M1 microglia polarization, which is associated with the production and release of multiple proinflammatory cytokines (20), by enhancing the beneficial effects of m2 microglia **(22)**.

Potential Therapies

Currently in the United States, the cost of treating PD is estimated to be around $14 billion with indirect costs of around $6.3 billion a year, all while there is still no permanent cure to PD **(6).** Although there are studies being done on finding clinical treatments, there is a lack of understanding on whether current treatment options prevent or improve PD development and progression, causing a severe burden on this population. Currently, most treatment options remain short term and to an extent, ineffective. Finding long term options through sensory and auditory cueing, which has been proved beneficial results, would alter the course of the PD community by giving patients access to a manageable life. Therefore, to battle the alterations presented by PD such as sensory-perceptual alterations, cueing provides a great tool to mitigate these effects. In the current field of research, evidence of altered auditory processing has been found to provide beneficial results These alterations range from disturbances in the processing of acoustic features, speech perception and sensitivity to affective and linguistic parody **(37, 38)**. The sensitivity of this motor input can be attributed as a defect because of the basal ganglia dysfunction in PD **(39)**. Therefore, auditory cues like music or augmented feedback have been used to prompt a motor response and control **(39)**. Because auditory and sensory alterations have been reported at relatively early stages of PD, it's important to understand whether further research into these types of cueing which can be used at that earlier stage, is truly beneficial or not. The reason why researchers and scientists have shifted to a more physical approach to PD is mainly because these sensory and auditory issues caused by such diseases are not correctly or efficiently controlled by levodopa **(39)**.

Sensory cueing and its implications for Freezing of Gait (FOG)

Recent reports have identified that sensory and auditory cueing shows effective utilization in the present and future for PD patients. Cueing is defined as a spatial stimulus that facilitates repetitive movement, which includes visual, tactile, or auditory rhythmic signals. Cueing proves to be a very effective therapy as it allows for the tuning of neuronal networks to external performance. In other words, cueing has been proved to enhance the timing and synchronization of movements, promoting decreased contractions at inappropriate times **(59)**. The biggest struggle with PD is the insufficient amount of research that proves long term therapies to mitigate or even cure extreme motor deficiencies. A patient loses all control over motor functioning, contributing to the inappropriate movement as described. This method, without a doubt, contrasts from the many traditional therapeutic practices we see such as deep brain stimulation, levodopa, stem cells, etc. However, this contrast does prove to be beneficial as external cueing provides a “template” to sculpt the new movement pattern. It allows the patient to utilize the existing motor pattern that is similar to the desired action, expediting the motor learning process.

The reason for using these types of cueing is because of the common symptom of freezing of gait (FOG) which is the condition of sudden, involuntary, and blocking of gait in advanced stages of Parkinson’s Disease. This symptom takes away a lot from a PD patient as it contributes to loss of function and independence within the movement of an individual. The freezing of gait normally appears in specific situations such as gait initiation, turning, passing narrow doorways, and shows up in movement of small steps, causing total akinesia **(44)**. Many neuroimages

suggest deficits that showcase an imbalance between the subcortical and cortical brain activations underlying the freezing episodes **(47)**. However, FOG has repeatedly been shown to correspond with the breakdown of an already strongly impaired gait. Patients who show a strongly impaired gait have shown symptoms of asymmetry and stride variability **(45)**. However, these variabilities are not observed in patients that are not suffering from FOG. It is important, though, to discuss implications of FOG as most PD patients do suffer from the imbalanced variability in gait.

To target impaired gaits, sensory cues have been identified as an essential tool to improve motor deficits. Previous reports have shown that using sensory cues can help relieve structural impairments in PD. Some studies use various sensory cues such as vibratory, auditory, and visual cues as their main focus. A study conducted on 7 PD patients suffering from FOG indicated that when cueing is applied after the onset of freezing, it can initiate a reduction of the average gait duration overall. The result of this study suggests that these cues may have helped patients to bypass defective basal ganglia circuits, which other neuroimaging methods have relieved a number of structural and functional impairments at the neurological level in patients with FOG **(47)**. Therefore, visual cues for example might be interpreted as helping patients reduce the load on the basal ganglia and allowing them to overcome freezing episodes quicker **(46)**. A study in 2012 on the improvement of motor imagery (MI) quality in patients with Parkinson's disease through external cueing has shown promising results. This experiment consisted of the investigation of whether the quality of motor imaging could be improved by external cueing. Patients with PD and 14 healthy control groups physically execute and visually imagine a goal-oriented task. They compared these results with the absence of cues. The research concluded that the presence of visual cues significantly reduced patients' bradykinesia and significantly increased the temporal isochrony between MI and execution. Additionally, the patients experienced the increased speed of both imagined hands movements and the patients' eye movements **(40)**.

The most accepted explanation for this would be the fact that these cues actually help patients compensate for movement deficits. External cueing can overcome these issues because it activates the premotor and parietal cortex and the cerebellum to bypass the basal ganglia **(42)**. The visual cues allow patients to gain a closed control mode in which they can adjust their movements based on the availability of visual information **(43)**. Another analysis on the upper-limb movements demonstrated that cued movement off-medication led to increased activity in the superior parietal lobe and inferior parietal cortex (IPC), indicating the increased motor and spatial awareness as a result of cueing **(47)**. The inferior parietal lobe, a portion of the cortex, is an anatomically heterogeneous region that is involved in sensory processing and known to be involved in oculomotor and attentional mechanisms and the adaptive recalibration of eye-hand coordination **(48)**. Given its functions, the increased activity of the IPC/IPL in PD patients suggests that the function of this cortex is enhanced, leading to positive effects with sensory cueing **(47)**.

In terms of targeting sensory aspects in the auditory region, we must look at the pathology behind the auditory region. Auditory cues, like music and variation in sound frequencies have also widely been known to be used successfully in the rehabilitation of motor functions with movement disorders like Parkinson's disease. It is said that this is because areas like the cerebellar-thalamocortical networks are typically involved in PD and since these areas are involved in perceiving rhythm **(49).** The activation in these regions through stimulated cues allows for these complex networks to be the cause of long-term motor improvements. However, before we explore the effects of auditory cues, let's take a look at the backgrounds of auditory cues and its involvement in different brain regions. The most success has been shown with the use of auditory sounds that mimic sounds of footsteps. Just like young kids who associate sounds with actions from early childhood, similar sounds such as footsteps enhance auditory skills **(52)**, this same natural technique could be used in PD patients. In an experiment recording the effect of footstep sounds on patients' motor improvements, found significant reduction of variability in gait. PD patients tried to imitate these actions and eventually recreated them **(51)**. The stimuli activate various brain regions we have discussed earlier in this paper such as the cerebellum, brainstem, and the sensorimotor cortex by instigating reorganization in the cortico-cerebellar circuits. Essentially, rhythmic cueing has been suggested to preserve neural centers involved in the perceiving externally cueing as goal directed movements. These great effects could easily help patients live a more normal life as they don't have to worry about situations of high stress like constraint of time and space, like escalators and traffic signals. With

improved gait, PD patients will be able to modify gait patterns all due to an "internal" attention towards control that comes from external cueing **(53)**.

However, auditory cueing is highly dependent on the type of audio given. The sounds of footsteps, for example, produce continuous auditory information. On the other hand, noise from a metronome consists of sudden bursts of noise and periodic silence. Data concluded that continuous noise proved to reduce variability of gait at a much greater extent (50). However, regardless of what auditory measures are being displayed, we do see a common pattern among various research: the improvement in gait due to auditory cueing. Studies have shown that auditory information performs better than its counterparts. As a result, the auditory cortex has been reported to have perceived stimuli with shorter reaction times as compared to visual or sensory tactiles **(53)**. This is mainly because of the lower rhythm perceptual thresholds for the auditory cortex, rich neural connectivity, and better temporal precision. The rich connectivity to motor centers from the spinal cord that extends towards the cortical and subcortical structures allows strong cross-sensory impacts on motor execution **(53, 55)**. When auditory cueing is being presented, these various factors are enhanced and therefore improve motor performance in patients with deficits **(54)**.

Combination therapies in PD

Currently, the most common treatment includes the use of medicinal drugs to improve dopamine response, a major aspect of Parkinson's that we have previously discussed. Levodopa, for example, is absorbed by nerve cells in the brain and turned into a chemical dopamine, which is used to transmit messages between nerves and parts of the brain that controls movement. In Parkinson's disease, the site of the degeneration is in the substantia nigra, in which PD results in the disruption of the nigrostriatal pathway which decreases striatal dopamine levels (**30,33**). The function of this drug allows levodopa to convert to dopamine in the central nervous system. However, a downside of levodopa is the fact that it must be combined with other medications like benserazide or carbidopa in order to stop the levodopa from breaking down in the bloodstream before even reaching the brain. However, these treatments are very short term. Over the years, the effects become less impactful as more nerve cells in the brain are lost, there are fewer and fewer of them each year for the medicine to absorb **(31)**. To combat the growing ineffectiveness, the dose of this drug may have to be increased over time, leading to postural difficulties such as dyskinesias, or even situations where the person rapidly switches from being able to move to instantly being immobile. A clinical study on the effect of levodopa on the rate of progression of Parkinson disease in 2004 proved that subjects receiving the highest dose of Levodopa had significantly more dyskinesia, hypertonia, infection, and nausea. Levodopa on multiple occasions has proved it either accelerates the loss of nigrostriatal dopamine nerve terminals or its pharmacological effects modify the dopamine transporter (**32**). These types of medicines only allow for symptomatic relief rather than relief from the underlying pathology **(51)**. Either way, drugs like Levodopa have an uncertain long-term effect on the progression of Parkinson's disease.

Stem cell therapy treatments for PD patients

Furthermore, the fact that the regeneration of neurons is not possible gives rise to stem cell therapy. Stem cell therapy is beneficial in all aspects for replacing and repairing damaged dopamine-producing nerve cells within the brain. There are three types of stem cells: Embryonic, somatic, and pluripotent. Each type of stem cell varies in terms of the way they transform into many types of cells, how they repair functions of cells, and further mature cells. To treat the death of brain cells in PD, researchers use these various types of stem cells to introduce directly into the affected areas of your brain where they can transform into usable brain cells **(36)**. These brain cells could then take up the function of regulating dopamine levels and improve the symptoms of the disease. For example, iPSC became available to treat PD and in its first clinical trial in Japan **(35)**, it has shown improvements in movement and as well as non-motor symptoms like bladder control. iPSCs can be derived from a donor or derived from your own cells, which can reduce

the likelihood of your body rejecting them. However, as always, stem cell therapy is also a treatment and not a cure. As the disease is still present, the chance of PD destroying the newly impacted stem cells eventually is quite possible.

Conclusion

In this paper, we discussed the pathological aspects of PD. The loss of dopaminergic neurons in the substantia nigra is the main conductor behind all other pathological aspects impacted by PD. The various brain regions such as the caudate nucleus start to experience dysfunction such as loss of attention, memory, and cognitive functions. Other brain regions such as the sensorimotor striatum, which is responsible for neuronal activity relating to initiation and action are also significantly impacted by the loss of dopamine in the striatal region. Initially, PD was classified as a movement disorder, however after careful research the neuroinflammation, immune dysfunction, and its non-motor implications led to the conclusion of PD being a multi-system disorder, making treatment options even more limited **(63).**

With the ever-expanding statistics of the increase in Parkinson's Disease across the nation, it's important that our research guides us in the most effective route possible. Sensory and auditory cues do provide a significant amount of hope in many cases. For the most part, apart from the neurological standpoint of both methods of cueing, the economical contribution does prove to be cost effective. The use of rhythmic auditory tactics like smartphone-based metronomes and footsteps **(56)** are all methods that are cheap, viable, and easy to follow up. These therapies can be a useful rehabilitation tool in lower income countries who may not have the proper funding for higher level therapies or poor healthcare services **(54)**. Other therapies like stem cells can cost thousands for patients. Although proven to be successful to a certain degree, stem cells must be tested multiple times in many clinical trials just as sensory and auditory cueing. However, although Medicare does cover stem cell therapy, it doesn't cover treatments that aren't FDA approved like experimental treatments as a part of clinical trials **(57)**. Without the clinical setting, a patient could be experiencing the burden of paying anywhere from $5,000 to $50,000 **(58)**. Especially in low-income areas who may not have access to Medicare or other health insurances, this number could further skyrocket, leaving the majority of the population unwilling or unable to receive treatment. These statistics provide another data point to the beneficiary use of economical and effective rehabilitation techniques.

References

1. Samii A, Nutt JG, Ransom BR. 2004. Parkinson’s disease. Zenodo. 363(9423). doi:10.1016/s0140-6736(04)16305-8. https://zenodo.org/record/1259791#.XodMwWMzZhE.

2. Li J, Chen D, Song W, Chen K, Cao B, Huang R, Yang R, Shang H. 2014. Survey on general knowledge on Parkinson’s disease in patients with Parkinson’s disease and current clinical practice for Parkinson’s disease among general neurologists from Southwest China. Clinical Neurology and Neurosurgery. 118:16–20. doi:10.1016/j.clineuro.2013.12.009.

3. Varalta V, Picelli A, Fonte C, Amato S, Melotti C, Zatezalo V, Saltuari L, Smania N. 2015. Relationship between Cognitive Performance and Motor Dysfunction in Patients with Parkinson’s Disease: A Pilot Cross-Sectional Study. BioMed Research International. 2015:1–6. doi:10.1155/2015/365959.

4. 2022 Dec 1. Peripheral inflammation and neurodegeneration; a potential for therapeutic intervention in Alzheimer’s disease (AD), Parkinson’s disease (PD) and amyotrophic lateral sclerosis (ALS). ProQuest. doi:10.1186/s41984-022-00150-4. [accessed 2022 Sep 4].

5. Dorsey ER, Sherer T, Okun MS, Bloem BR. 2018. The Emerging Evidence of the Parkinson Pandemic. Brundin P, Langston JW, Bloem BR, editors. Journal of Parkinson's Disease. 8(s1):S3–S8. doi:10.3233/jpd-181474.

6. Parkinson's Disease: Challenges, Progress, and Promise | National Institute of Neurological Disorders and Stroke. wwwnindsnihgov. https://www.ninds.nih.gov/health-information/patient-caregiver-education/hope-through-research/parkinsons-disease/parkinsons-disease-challenges-progress-and-promise.

7. Prakash K, Bannur B, Chavan M, Saniya K, Sailesh K, Rajagopalan A. 2016. Neuroanatomical changes in Parkinson′s disease in relation to cognition: An update. Journal of Advanced Pharmaceutical Technology & Research. 7(4):123. doi:10.4103/2231-4040.191416. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052937/.

8. Nagae LM, Honce JM, Tanabe J, Shelton E, Sillau SH, Berman BD. 2016. Microstructural Changes within the Basal Ganglia Differ between Parkinson Disease Subtypes. Frontiers in Neuroanatomy. 10. doi:10.3389/fnana.2016.00017.

9. Cerasa A, Messina D, Pugliese P, Morelli M, Lanza P, Salsone M, Novellino F, Nicoletti G, Arabia G, Quattrone A. 2011. Increased prefrontal volume in PD with levodopa-induced dyskinesias: A voxel-based morphometry study. Movement Disorders. 26(5):807–812. doi:10.1002/mds.23660.

10. Galvan A, Devergnas A, Wichmann T. 2015. Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state. Frontiers in Neuroanatomy. 9. doi:10.3389/fnana.2015.00005.

11. Troncoso-Escudero P, Parra A, Nassif M, Vidal RL. 2018. Outside in: Unraveling the Role of Neuroinflammation in the Progression of Parkinson's Disease. Frontiers in Neurology. 9. doi:10.3389/fneur.2018.00860.

12. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol. (2018) 18:225–42. doi: 10.1038/nri.2017.125

13. Mamelak M. 2018. Parkinson's Disease, the Dopaminergic Neuron and Gammahydroxybutyrate. Neurology and Therapy. 7(1):5–11. doi:10.1007/s40120-018-0091-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5990513/.

14. Surmeier DJ, Obeso JA, Halliday GM. 2017. Selective neuronal vulnerability in Parkinson disease. Nature Reviews Neuroscience. 18(2):101–113. doi:10.1038/nrn.2016.178. https://www.nature.com/articles/nrn.2016.178.

15. Fathi M, Vakili K, Yaghoobpoor S, Qadirifard MS, Kosari M, Naghsh N, Asgari taei A, Klegeris A, Dehghani M, Bahrami A, et al. 2022. Pre-clinical Studies Identifying Molecular Pathways of Neuroinflammation in Parkinson's Disease: A Systematic Review. Frontiers in Aging Neuroscience. 14:855776. doi:10.3389/fnagi.2022.855776. [accessed 2022 Nov 9]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9327618/.

16. Bolam JP, Pissadaki EK. 2012. Living on the edge with too many mouths to feed: Why dopamine neurons die. Movement Disorders. 27(12):1478–1483. doi:10.1002/mds.25135.

17. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, et al. 1990. Variable expression of Parkinson's disease: A base-line analysis of the DAT ATOP cohort. Neurology. 40(10):1529–1529. doi:10.1212/wnl.40.10.1529. https://physionet.org/files/inipdmsa/1.0/References/Jankovic-J_Variable-expression-of-Parkinsons-disease-a-base-line-analysis-of-the-DATATOP-cohort.pdf.

18. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, Abyu GY, Ahmed MB, Aichour AN, Aichour I, et al. 2017. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Neurology. 16(11):877–897. doi:10.1016/s1474-4422(17)30299-5. https://www.sciencedirect.com/science/article/pii/S1474442217302995.

19. Wang Q, Liu Y, Zhou J. 2015. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Translational Neurodegeneration. 4(1). doi:10.1186/s40035-015-0042-0. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4603346/.

20. Tang Y, Li T, Li J, Yang J, Liu H, Zhang XJ, Le W. 2013. Jmjd3 is essential for the epigenetic modulation of microglia phenotypes in the immune pathogenesis of Parkinson's disease. Cell Death & Differentiation. 21(3):369–380. doi:10.1038/cdd.2013.159.

21. Polazzi E, Contestabile A. 2002. Reciprocal Interactions Between Microglia and Neurons: From Survival to Neuropathology. Reviews in the Neurosciences. 13(3). doi:10.1515/revneuro.2002.13.3.221.

22. Zhang Z, Zhang Z-Y, Schluesener HJ. 2009. Compound A, a Plant Origin Ligand of Glucocorticoid Receptors, Increases Regulatory T Cells and M2 Macrophages to Attenuate Experimental Autoimmune Neuritis with Reduced Side Effects. The Journal of Immunology. 183(5):3081–3091. doi:10.4049/jimmunol.0901088. [accessed 2022 Nov 9]. https://www.jimmunol.org/content/183/5/3081.

23. Goedert M, Jakes R, Spillantini MG. 2017. The Synucleinopathies: Twenty Years On. Journal of Parkinson's Disease. 7(s1): S51–S69. doi:10.3233/jpd-179005.

24. Meade RM, Fairlie DP, Mason JM. 2019. Alpha-synuclein structure and Parkinson's disease – lessons and emerging principles. Molecular Neurodegeneration. 14(1). doi:10.1186/s13024-019-0329-1.

25. Theillet F-X, Binolfi A, Bekei B, Martorana A, Rose HM, Stuiver M, Verzini S, Lorenz D, van Rossum M, Goldfarb D, et al. 2016. Structural disorder of monomeric α-synuclein persists in mammalian cells. Nature. 530(7588):45–50. doi:10.1038/nature16531.

26. Giasson BI. 2000. Oxidative Damage Linked to Neurodegeneration by Selective alpha -Synuclein Nitration in Synucleinopathy Lesions. Science. 290(5493):985–989. doi:10.1126/science.290.5493.985.

27. Burre J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Sudhof TC. 2010. -Synuclein Promotes SNARE-Complex Assembly in Vivo and in Vitro. Science. 329(5999):1663–1667. doi:10.1126/science.1195227.

28. Chandra S, Chen X, Rizo J, Jahn R, Südhof TC. 2003. A Broken α-Helix in Folded α-Synuclein. Journal of Biological Chemistry. 278(17):15313–15318. doi:10.1074/jbc.m213128200.

29. Varkey J, Isas JM, Mizuno N, Jensen MB, Bhatia VK, Jao CC, Petrlova J, Voss JC, Stamou DG, Steven AC, et al. 2010. Membrane curvature induction and tubulation are common features of synucleins and apolipoproteins. The Journal of Biological Chemistry. 285(42):32486–32493. doi:10.1074/jbc.M110.139576. [accessed 2021 Mar 23]. https://pubmed.ncbi.nlm.nih.gov/20693280/.

30. Gandhi KR, Abdolreza Saadabadi. 2018 Oct 27. Levodopa (L-Dopa). Nihgov. https://www.ncbi.nlm.nih.gov/books/NBK482140/.

31. Parkinson's disease - Treatment. 2017 Oct 23. nhsuk. https://www.nhs.uk/conditions/parkinsons-disease/treatment/#:~:text=your%20needs%20change.-.

32. The Parkinson Study Group. 2004. Levodopa and the Progression of Parkinson's Disease. New England Journal of Medicine. 351(24):2498–2508. doi:10.1056/nejmoa033447. https://www.nejm.org/doi/full/10.1056/NEJMoa033447.

33. Cona L. 2022 Jan 26. Stem Cell Therapy for Parkinson's Disease in 2020. wwwdvcstemcom. https://www.dvcstem.com/post/stem-cell-therapy-for-parkinsons.

34. Gravitz L. 2021. The promise and potential of stem cells in Parkinson's disease. Nature. 597(7878):S8–S10. doi:10.1038/d41586-021-02622-3. https://www.nature.com/articles/d41586-021-02622-3.

35. Stoddard-Bennett T, Reijo Pera R. 2019. Treatment of Parkinson's Disease through Personalized Medicine and Induced Pluripotent Stem Cells. Cells. 8(1):26. doi:10.3390/cells8010026. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357081/.

36. Stem Cell Therapy for Parkinson's: Current Developments. 2022 Aug 1. Healthline. https://www.healthline.com/health/parkinsons/stem-cell-therapy-for-parkinsons.

37. Troche J, Troche MS, Berkowitz R, Grossman M, Reilly J. 2012. Tone Discrimination as a Window Into Acoustic Perceptual Deficits in Parkinson's Disease. American Journal of Speech-Language Pathology. 21(3):258–263. doi:10.1044/1058-0360(2012/11-0007).

38. De Groote E, De Keyser K, Santens P, Talsma D, Bockstael A, Botteldooren D, De Letter M. 2020. Future Perspectives on the Relevance of Auditory Markers in Prodromal Parkinson's Disease. Frontiers in Neurology. 11. doi:10.3389/fneur.2020.00689.

39. Nieuwboer A. 2015. Cueing effects in Parkinson's disease: Benefits and drawbacks. Annals of Physical and Rehabilitation Medicine. 58:e70–e71. doi:10.1016/j.rehab.2015.07.173.

40. Heremans E, Nieuwboer A, Feys P, Vercruysse S, Vandenberghe W, Sharma N, Helsen WF. 2011. External Cueing Improves Motor Imagery Quality in Patients With Parkinson Disease. Neurorehabilitation and Neural Repair. 26(1):27–35. doi:10.1177/1545968311411055.

41. Rubinstein TC, Giladi N, Hausdorff JM. 2002. The power of cueing to circumvent dopamine deficits: A review of physical therapy treatment of gait disturbances in Parkinson's disease. Movement Disorders. 17(6):1148–1160. doi:10.1002/mds.10259. https://pubmed.ncbi.nlm.nih.gov/12465051/.

42. Lim I, van Wegen E, de Goede C, Deutekom M, Nieuwboer A, Willems A, Jones D, Rochester L, Kwakkel G. 2005. Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. Clinical rehabilitation. 19(7):695–713. doi:10.1191/0269215505cr906oa. https://www.ncbi.nlm.nih.gov/pubmed/16250189?dopt=Abstract.

43. Verschueren SM, Swinnen SP, Dom R, De Weerdt W. 1997. Interlimb coordination in patients with Parkinson's disease: motor learning deficits and the importance of augmented information feedback. Experimental Brain Research. 113(3):497–508. doi:10.1007/pl00005602. https://pubmed.ncbi.nlm.nih.gov/9108216/.

44. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. 2003. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. European Journal of Neurology. 10(4):391–398. doi:10.1046/j.1468-1331.2003.00611.x.

45. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. 2001. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Movement Disorders. 16(6):1066–1075. doi:10.1002/mds.1206.

46. Velik, Rosemarie, et al. "Effect of Sensory Cues Applied at the Onset of Freezing Episodes in Parkinson's Disease Patients." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, vol. 6, no. 8, Aug. 2012, pp. 57–62.

47. Clower DM, West RA, Lynch JC, Strick PL. 2001. The Inferior Parietal Lobule Is the Target of Output from the Superior Colliculus, Hippocampus, and Cerebellum. The Journal of Neuroscience. 21(16):6283–6291. doi:10.1523/jneurosci.21-16-06283.2001.

48. Dalla Bella S. 2015. Using music to improve mobility in Parkinson's disease: Effects beyond gait? Annals of Physical and Rehabilitation Medicine. 58:e71. doi:10.1016/j.rehab.2015.07.174.

49. Young WR, Shreve L, Quinn EJ, Craig C, Bronte-Stewart H. 2016. Auditory cueing in Parkinson's patients with freezing of gait. What matters most: Action-relevance or cue-continuity? Neuropsychologia. 87:54–62. doi:10.1016/j.neuropsychologia.2016.04.034.

50. Young WR, Rodger MWM, Craig CM. 2014. Auditory observation of stepping actions can cue both spatial and temporal components of gait in Parkinson′s disease patients. Neuropsychologia. 57:140–153. doi:10.1016/j.neuropsychologia.2014.03.009.

51. Ghai S, Ghai I, Schmitz G, Effenberg AO. 2018. Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis. Scientific Reports. 8(1). doi:10.1038/s41598-017-16232-5. https://www.nature.com/articles/s41598-017-16232-5.

52. Kraus N, Slater J, Thompson EC, Hornickel J, Strait DL, Nicol T, White-Schwoch T. 2014. Auditory learning through active engagement with sound: biological impact of community music lessons in at-risk children. Frontiers in Neuroscience. 8. doi:10.3389/fnins.2014.00351.

53. Ghai S, Ghai I, Effenberg AO. 2018. Effect of Rhythmic Auditory Cueing on Aging Gait: A Systematic Review and Meta-Analysis. Aging and disease. 9(5):901. doi:10.14336/ad.2017.1031. [accessed 2019 Oct 16]. http://www.aginganddisease.org/EN/abstract/abstract147691.shtml.

54. Ermolaeva VYu, Borgest AN. 1980. Intercortical connections of the auditory areas with the motor area. Neuroscience and Behavioral Physiology. 10(3):210–215. doi:10.1007/bf01182212.

55. Rosenthal L, Sweeney D, Cunnington A-L, Quinlan LR, ÓLaighin G. 2018. Sensory Electrical Stimulation Cueing May Reduce Freezing of Gait Episodes in Parkinson's Disease. Journal of Healthcare Engineering. 2018:1–6. doi:10.1155/2018/4684925.

56. Does Medicare Cover Stem Cell Therapy? Verywell Health. https://www.verywellhealth.com/does-medicare-cover-stem-cell-therapy-5206838.

57. Cona LA. 2021 Jun 17. The Cost of Stem Cell Therapy in 2020. wwwdvcstemcom. https://www.dvcstem.com/post/stem-cell-therapy-cost-2020.

58. Klimovich A, Giacomello S, Björklund Å, Faure L, Kaucka M, Giez C, Murillo-Rincon AP, Matt A-S, Willoweit-Ohl D, Crupi G, et al. 2020. Prototypical pacemaker neurons interact with the resident microbiota. Proceedings of the National Academy of Sciences. 117(30):17854–17863. doi:10.1073/pnas.1920469117.

59. Geierman DB. 2022 Jan 30. Playing With Processing: External Cues and Motor Performance. Barbell Rehab. [accessed 2022 Nov 26]. https://barbellrehab.com/external-cues-motor-performance/#:~:text=Well%2C%20research%20shows%20that%20external.

60. Wu T, Hallett M. 2013. The cerebellum in Parkinson's disease. Brain. 136(3):696–709. doi:10.1093/brain/aws360.

61. Sukel K. 2019 Aug 25. Neuroanatomy: The Basics. Dana Foundation. https://dana.org/article/neuroanatomy-the-basics/.

62. Calabresi P., Picconi B., Tozzi A., Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences.* 2007;30(5):211–219. doi: 10.1016/j.tins.2007.03.001.

63. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. 2022 Mar 4. Inflammation and immune dysfunction in Parkinson disease. Nature Reviews Immunology.:1–17. doi:10.1038/s41577-022-00684-6. https://www.nature.com/articles/s41577-022-00684-6#Sec2.

64. Lewy Body Dementia (LBD). 2022. wwwhopkinsmedicineorg. https://www.hopkinsmedicine.org/health/conditions-and-diseases/dementia/dementia-with-lewy-bodies.

65. Lewy Body - an overview | ScienceDirect Topics. wwwsciencedirectcom. https://www.sciencedirect.com/topics/neuroscience/lewy-body.