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Effects of Subthalamic Deep Brain Stimulation on Communication

Catherine C. Crowley, PhD, CCC-SLP[#]

School of Health Professions and Nursing, Long Island University, New York, USA

#Corresponding author: Catherine C. Crowley PhD, Chair/Assistant Professor, Communication Sciences and Disorders, School of Health Professions and Nursing, Long Island University, Brookville, New York 11548, USA

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Abstract

Background: Deep Brain Stimulation (DBS) of the subthalamic nucleus is an effective treatment for improvement of motor function in individuals with Parkinson disease. Although motor function improvement has been widely studied there are limited and inconsistent studies that assess the effects of DBS surgery on speech and language skills.

Aim: The purpose of this study was to assess the effects of DBS surgery on speech and language function.

Design: In this study voice and language skills were assessed pre-operatively, intra-operatively, and post-operatively, 3-6 months after the surgery and then again 2-4 years after the surgery.

Method: An acoustic analysis was completed to yield quantitative results of vocal function. A voice handicap index was administered to assess for self-perception of voice deficits. Additionally, lexical and semantic fluency naming skills were evaluated to determine the effects on language skills and in order to identify a microlesion effect.

Findings: Findings of this study revealed that the subthalamic nucleus plays a potential role in both voice and language function. Furthermore, self-perceived voiced deficits are more prominent following 2-4 years status post-surgery despite improvement in varied speech parameters. Additionally, the micro-lesion effect although present for motor skills is not a contributing factor for linguistic function, specifically for lexical and semantic naming skills.

Conclusion: The results of this study further support the need for more research regarding the effects of DBS surgery on communication. Findings of this study serve to facilitate patient counseling regarding expected outcomes of surgery and to improve speech and language skill following intervention with STN-DBS surgery

Introduction

Background

Parkinson Disease (PD) is a progressive neurological disorder resulting from a degeneration of dopamine neurons [1-3]. Its symptomatology is present as a function of a breakdown of the basal ganglia circuit. PD is initially treated pharmacologically; however, when this form of therapy is exhausted and relief from symptoms is no longer experienced, an alternative treatment is sought. This alternative may be Subthalamic Nucleus Deep Brain Stimulation Surgery (STN-DBS), but there is both a paucity and inconsistency in the research of the effects of surgery on overall communication skills.

Speech-language deficits are noted in approximately 75% of patients with Parkinson disease [4]. Speech skills are marked by a hypokinetic dysarthria, which manifests in all levels of speech, including respiration, phonation, resonance, and articulation. DBS surgery results in a reduction of some motor symptoms associated with PD. However, findings related to speech skills following surgery have been conflicting. “When comparing studies to evaluate the effects on speech of STN-DBS in individuals with PD, the one consistent finding appears to be variability” [5]. According to Narayana and his colleagues [6], one of the most common side effects of DBS surgery is diminished speech functioning. Reports of new or worsened dysarthria range from 5% to 61% of the patients who underwent this surgery. In general, most patients report reduced communicative competence due to compromised speech intelligibility following deep brain stimulation of the subthalamic nucleus, despite reported improvement in specific speech parameters [5].

Diminished verbal fluency is reportedly one of the most common side effects of DBS. However, little is known of the specific role of the Subthalamic Nucleus (STN) in the symptomatology of PD. The STN is suspected to have a role in the regulation of linguistic processes [7]. It is known that stimulation causes changes in the firing pattern of the STN, but it is not known what effect the changes have on language processes.

Furthermore, the non-motor disabilities associated with PD are said to have a greater impact on quality of life than the motor symptoms [8,9]. As a result, it is imperative for the complete understanding of the effects of DBS surgery to assess the self-perceived impact of the disease and its associated voice and language disorders.

Statement of the Problem

Deep brain stimulation surgery for the treatment of Parkinson disease symptoms results in alleviation of motor symptoms associated with the disease; however, the effects on speech and language symptoms remain ambivalent. Studies of vocal and language function following deep brain stimulation are limited, and findings within the current studies have been inconsistent. At present, there is no explanation for the inconsistent findings of the research. Participants in Ahleberg, Laakso, and Hartelius’ [5] study reported a paucity of information regarding possible side effects. A compromised understanding of the effects of STN-DBS on speech and language function can hinder clinical speech and language services provided to the patient with Parkinson disease.

Purpose of the Study

The purpose of the current study was to investigate the effects of subthalamic deep brain stimulation surgery on voice and language function, related to fluency naming, in patients with Parkinson disease. The present study aimed to examine severity of deficits prior to STN-DBS surgery and the improvement of skills post-surgery. Additionally, this study allows for more accurate prognosis of speech improvement 2-4 years post-surgery. This study also assesses for the presence of the Microlesion Effect (MLE) on language skills for semantic and lexical naming tasks. In order to do so, patients previously scheduled for the surgery were assessed four times: pre-operatively, intra-operatively, 3-6 months post-operatively, and 2-4 years post-operatively. An acoustic analysis and lexical and semantic fluency naming assessments were completed for this study. Self-perception of vocal function was also evaluated during this study.

Research Question

This study addressed the following research questions:

- What is the relationship between severity of deficits prior to STN-DBS surgery and improvement of skills post-surgery?
- Is there a difference in the psychosocial impact of the voice disorder pre-operatively and post-operatively?
- Does the subthalamic nucleus have a potential role in voice production as well as in lexical and semantic fluency naming skills?
- Is there a greater change in speech and language function of speech following 2-4 years post-surgery as compared to 3-6 months post-surgery?
- Is there a microlesion effect for lexical and semantic fluency naming?

Hypotheses

It is hypothesized that there will be a change in voice and language function following the STN-DBS surgery. A greater self-perceived deficit in voice function following the surgery is anticipated. Furthermore, it is hypothesized that greater deficits will be noted following a longer lapse between surgery date and assessment of function as compared to assessment 3-6 months post-surgery. Based on results from previous research of the microlesion effect on motor skills, it is anticipated that the participants will demonstrate a microlesion effect that adversely impacts lexical and semantic naming tasks.

Literature Review

Neurological Bases of Parkinson Disease

Parkinson Disease (PD) is a progressive degenerative neurological disease resulting from nigrostriatal dopamine deficiency [1-3]. PD was first described by James Parkinson in 1817 in which he noted symptoms of resting tremor, stooped posture, shuffling gait, and retropulsion calling the symptoms “shaking palsy” and dubbing the disease as “paralysis agitans”. Later added muscular rigidity, micrographia, sensory changes, and other features to the symptomatology and named the disease after James Parkinson [3]. Historically, PD has been defined by the cardinal motor features associated with the disease; however, PD is also associated with non-motor symptoms, such as cognitive-linguistic deficits. The term “parkinsonism” is used to refer to the clinical signs of the disease. It is often used synonymously with Parkinson disease; however, PD is a term used when the etiology of the parkinsonism symptoms is unknown [1]. In the interest of limiting variability, this review will limit its discussion to Parkinson disease.

Muscle activity of the body is a function of the motor system in the central and peripheral nervous systems. The motor system is responsible for normal reflexes, control of muscle tone and posture, and execution of volitional movements such as speech [1,2]. Volitional movement originates in the cerebral cortex with an intent to move. The desire to move is first turned into a planned pattern of muscle contractions in the cortical association areas. The association cortex is a region in the brain composed of four interconnected areas: the temporal association area, parietal association area, frontal association area, and occipital association area. These areas are said to “make sense” of the original sensory input [2]. At this point the planned pattern of muscle contractions is not refined and is an approximation of the intended movement. Subsequently, the motor impulses are sent to the basal ganglia and the cerebellum for refinement.

The basal ganglia, considered a part of, or synonymous with, the extrapyramidal system, regulate muscle tone, adjust associated automatic motor movements, and suppress movement extraneous to other motor activity [1]. The five nuclear masses of the basal ganglia are subcortical and consist of the caudate nucleus, putamen, globus pallidus, claustrum, and amygdaloid nucleus [10]. The caudate nucleus is a large c-shaped nucleus. The head of the caudate forms the lateral wall of the anterior horn of the lateral ventricle into which it bulges. The body lies laterally to the thalamus, and the tail extends posteriorly. The putamen is half-moon shaped and is the sensorimotor territory of the striatum. Depletion of the neurotransmitter dopamine, which is implicated in Parkinson disease, is most noted in the putamen [11]. Together with the caudate nucleus, this system is known as the striatum. The striatum receives input from the frontal cortex, thalamus, and the substantia nigra that manufactures dopamine. It also sends efferent fibers to the substantia nigra and the globus pallidus [1]. The striatum is paramount for the integration of desire to move and action [12]. The globus pallidus is medial to the putamen and is made up of external and internal components [11]. The basal ganglia’s major efferent pathways originate in the globus pallidus [1,2]. The efferent pathways, also known as the motor neurons, carry impulses away from the nervous system toward the muscles. The claustrum is a mass of gray matter that contributes to visceral functions such as muscles of respiration, digestion, swallowing, speech, and sensory integration. Lying in the rostromedial temporal lobe at the end of the temporal horn is the amygdaloid nucleus. It is functionally related to the limbic system, which aids in emotion, behavior, motivation, and long term memory [11]. The basal ganglia are composed of many interconnected circuits within the cortical and subcortical areas of the brain.

The basal ganglia nuclei synthesize five major neurotransmitters: dopamine, acetylcholine, γ -aminobutyric acid (GABA), substance P, and enkephalin. Neurotransmitters are chemicals that facilitate movement of signals from one neuron to another. Neurotransmitters have either an excitatory function to stimulate the electrochemical impulse that travels over the synaptic cleft from neuron to neuron or an inhibitory function that decreases the probability of an impulse to be transmitted to the adjoining neuron. A neuron will fire its electrochemical impulse when the excitation threshold is greater than the influence of the inhibitory neurotransmitter [2,11]. Dopamine is a neurotransmitter that serves to inhibit electrical impulses. It is secreted by the melanin-containing nerve cells in the substantia nigra and is released through the synaptic terminals of the striatum. As stated above, a reduction of dopamine has been linked to the features of motor deficits in PD. Acetylcholine has also been implicated in the pathophysiology of PD. Acetylcholine is an excitatory neurotransmitter. Dopamine and acetylcholine have been found to have opposing actions, that is, they have reciprocal inhibition, and an imbalance of the two neurotransmitters may have a role in the etiology of PD [1,12]. Acetylcholine is secreted by cells of the striatum and aids in the regulation of the thalamus and globus pallidus that refine motor movements.

The neurotransmitter GABA is also released by the efferent striatal cells [2]. This neurotransmitter inhibits the substantia nigra. Additionally, the GABA within the striatum participates in the metabolic activity of the basal ganglia [11]. Similar to dopamine, GABA is affected by acetylcholine and an imbalance of the two neurotransmitters can result in a dysfunction of muscle activity [12]. Motor programs are generated by activation of neurons of the basal ganglia by GABA, dopamine, and acetylcholine [13]. Substance P is also produced by striatal cells of the basal ganglia and serves as an inhibitor to regulate movement. Neural motor control is maintained by grading of excitatory and inhibitory neurotransmitters such as those produced by the basal ganglia. The substantia nigra is interconnected to the basal ganglia structure by way of the striatum. The striatum and the substantia nigra have a direct functional and anatomical relationship [2]. Dopaminergic neurons from the pars compacta region of the substantia nigra project to the caudate nucleus and inhibit the cholinergic striatal neurons. The cholinergic neurons then synapse on striatal GABA neurons. The GABA fibers project from the basal ganglia to the substantia nigra and back to the basal ganglia, thereby forming a circuit between the basal ganglia and the substantia nigra [11].

The basal ganglia circuit originates in the premotor, supplementary, and motor cortices. These areas then send output via direct and indirect pathways to the putamen, internal and external portions of the globus pallidus, and the substantia nigra that in turn have projections back to the cortical motor areas, via the thalamic nuclei. The direct and indirect pathways have an antagonistic effect; the direct pathways serve to aid in the execution of movement, whereas the indirect pathways role is to inhibit movements [13]. The speech mechanism is influenced by all levels of this circuit.

The basal ganglia can either promote or inhibit movement, depending on tonic dopamine and innervations of the striatum from the substantia nigra. However, when 60-80% of the dopamine-producing neurons of the substantia nigra are lost, the extrapyramidal system can no longer effectively promote movement, and the systems of PD appear [3]. Parkinson disease symptomatology is present as a result of loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies that are abnormal protein-rich aggregates, in the remaining neurons [14,15]. PD is a function of a breakdown of the basal ganglia circuit due to lack of dopamine resulting in an imbalance of the excitatory neurotransmitter acetylcholine and the inhibitory neurotransmitter dopamine [1]. When there is a depigmentation of the dopamine-producing cells, the system is in a state of disinhibition, as dopamine serves as an inhibitory neurotransmitter. When there is lack of inhibition the excitatory neurotransmitter does not have a grading system to regulate the neuron. As a result, the electrochemical impulse that travels from one neuron to the other is not controlled, and symptoms of Parkinson disease manifest.

There is a symbiotic relationship within the motor system where a breakdown in any aspect of the system will result in a neuropathology affecting muscle movement, including those involved in speech function. Parkinson disease is present as a result of a breakdown in the motor system due to a dopamine deficiency.

Etiology

The cause of Parkinson disease has not conclusively been identified to date. Initially, Parkinson discussed the possibility of chronic injury to the head as the cause of the disease. However, later studies found a reverse correlation between head injury and Parkinson disease. It was concluded that the motor deficits associated with PD, such as poor balance, resulted in head injuries and not that head injuries were a cause of the disease [16]. Currently it is believed that Parkinson disease is caused by an interaction of multiple factors including genetic predisposition, environmental toxins, and aging [17].

Familial history is reported in 15-20% of patients with PD [18]. Genealogical studies within these families have identified mutated genes; however these genes have not been identified in all PD patients. Berg and her colleagues [19] found that less than 10% percent of patients with PD had a genetic explanation. Historically, the Parkin gene on chromosome 6 and the Alpha-synuclein on chromosome 4 have been implicated in PD. The Parkin gene destroys defective or old proteins; therefore, a mutated Parkin gene allows for these defective proteins to multiply, and as a result, become toxic to the nerve cells. However, it has been found that some individuals with Parkin mutation present with clinical differences and as a result these patients may fall under a subcategory of PD or with a separate disease altogether [19]. The second gene, Alpha-synuclein, is found in Lewy bodies. The gene mutation involved in the production of Alpha-synuclein may start a biochemical sequence of events that eventually kills the nerve cells [18]. Additionally, LRRK2 gene mutation has been associated with motor neuron disease including PD [15,19]. LRRK2 consists of multiple protein to protein interaction domains. It is unknown if a breakdown within the protein to protein pathways may result in the symptomatology of PD [15]. This gene mutation has been found in approximately 0.5 to 1.0% of PD cases in western communities [20].

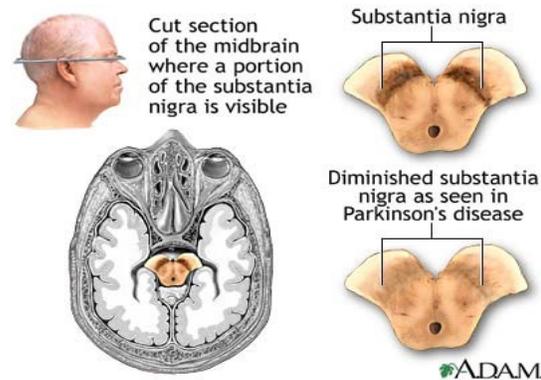
Environmental neurotoxins, use of well-water, exposure to pesticides and herbicides, and industrial chemicals have also been correlated with PD. Well-water consumption poses a greater risk for exposure to pesticides than consumption from public drinking water because of less stringent regulations and easier access for pesticides to reach the water. An epidemiological study by Gatto and her colleagues [21] found that consumption of well water contaminated with pesticides was associated with an elevated risk for PD. In this study residents exposed to well water contaminated with pesticides demonstrated a 70-90% greater risk for PD as compared to those not exposed to contaminated well water. Additionally, the pesticide rotenone, the herbicides paraquat [17,22], and the fungicide maneb were found to cause symptoms of PD in rodents [22]. Liew and colleagues [17] found that occupational exposures to pesticides in jobs related to farming increased the risk of developing PD. Furthermore, they found that direct exposure to pesticides further increased risk for PD as compared to indirect exposure. A study by Willis and her colleagues [23] identified a "Parkinson disease belt" in the Midwest and Northeast regions, which would suggest that byproducts of industrialization may also be a risk factor for Parkinson disease. In this study the prevalence of PD was 2-10 times greater in the Midwest and Northeast regions than in the Western and Southern regions of America. These regions demonstrate greater industrialization and in turn greater exposure to environmental toxins for those individuals living in these regions. Findings of this study further argue the point that environmental factors play a significant role in the etiology of Parkinson disease.

According to Hindle [24], “Aging is the largest single independent risk factor for the development of PD” (p. 157). Age-related damage to the somatic nervous system coupled with a breakdown of compensatory mechanisms of the nervous system lead to an increased prevalence and acceleration of PD with aging [24,25]. Buchman and colleagues [26] found that out of 750 elderly individuals without clinically defined PD 1/3 presented with neuronal loss within the substantia nigra and 10% demonstrated Lewy body pathology. The difference between dopamine degeneration in aging and dopamine degeneration in PD is the quantity of cell loss [25]. Age related changes within the substantia nigra are said to weaken the neurons and make individuals more susceptible to the disease process of PD [27]. Aging, environmental exposure, and genetic predisposition all play a role in the etiology of Parkinson disease. Further understanding of the etiology would aid in finding treatment possibilities and facilitate the diagnostic process. However, at this time no clear causation of the disease has been found.

Diagnosing PD

Historically, diagnoses of Parkinson disease was based on the presence of at least two out of three cardinal motor symptoms, which include resting tremors, bradykinesia, and rigidity. Postural instability is another cardinal feature of PD but is not considered for diagnosis, as it is typically a late-onset symptom and can be associated with many other neurological pathologies [28]. In addition to the clinical features, the patient must respond to levodopa therapy and be absent of markers suggestive of other diseases to be given the diagnosis of PD [19]. Recent studies have found biomarkers that may be able to aid in the diagnostic process of PD. The presence of the protein Alpha-synuclein and Lewy bodies has found to be correlated with the risk of PD and the progression of the disease. Biopsies of the stomach obtained several years prior to the onset of the motor features in PD patients found the presence of Alpha-synuclein and Lewy bodies [20]. Additionally, imaging markers have been identified to facilitate diagnosing PD. Preliminary studies of MRI imaging used to measure brain iron levels have found correlates of PD markers [20]. Furthermore, Single Photon Emission Computed Tomography (SPECT) has been able to identify loss of striatal dopamine neurons to facilitate the diagnosis of PD; however, this imaging testing is limited due to its inability to differentiate between various parkinsonian syndromes and its susceptibility to changes from the effects of dopaminergic medication [20]. Positron Emission Tomography (PET) scans using f-dopa as a radiotracer also allow for the assessment of dopamine metabolism. In order to measure pre-synaptic dopaminergic function f-dopa is used as the gold standard. Striatal uptake of f-dopa is decreased in PD and has an inverse relationship with the severity of motor signs and disease duration. Density of the dopaminergic terminals in the striatum and dopamine turnover affects the uptake of f-dopa. The compensatory mechanisms of unaffected dopaminergic receptors noted in the early stages of PD result in higher f-dopa values [29].

The major gross findings of PD confirmed during an autopsy are pallor of the substantia nigra and presence of single or multiple Lewy bodies within the pigmented neurons of the substantia nigra [29,30].



To date there is no singular diagnostic tool that can serve to accurately diagnose Parkinson disease or predict the disease progression over time. Diagnosis is based on the presence of clinical motor symptomatology. However, a more timely and accurate diagnosis could be made with the identification of biochemical and imaging markers.

Parkinson Disease Staging and Rating

Parkinson is a progressive disease; however, progression and duration of the stages of PD are highly variable from patient to patient. The stages of PD were developed by Margaret Hoehn and Melvin Yahr in the 1960s and has been identified as such:

Hoehn and Yahr Stages of Parkinson [31]

Stage 1: Unilateral features of Parkinson disease, including the major features of tremor, rigidity, and bradykinesia

Stage 2: Bilateral features mentioned above, along with possible speech abnormalities, decreased posture and abnormal gait

Stage 3: Worsening bilateral features of PD, along with balance difficulties. Patients are still able to function independently

Stage 4: Patients are unable to live alone or independently

Stage 5: Patients need wheelchair assistance and are unable to get out of bed

The United Parkinson's Disease Rating Scale (UPDRS) is also used to assess the progression of the disease. It was developed by Fahn, Marsden, Goldstein, and Calne [32]. The UPDRS assesses three areas: mentation, behavior, and mood; activities of daily living; and motor skills (See Appendix A).

Prevalence of Parkinson Disease

After Alzheimer disease, the second most common neurodegenerative disease is Parkinson disease [28,30]. The mean age of acquiring Parkinson disease is 60 years; however, 15% of PD patients are younger than 50 and 10% are 40 years or younger. There is a greater prevalence in men than women, with a mean prevalence sex ratio of 155 males to 100 females [23]. The highest prevalence rate is found in North America and Europe and the lowest in China, Nigeria, and Sardinia. It should be noted that the higher rate of prevalence may be influenced by availability of health care in more developed areas leading to increased life span. In North America, there are 1.2 million people diagnosed with PD; however, it is estimated that for every person diagnosed with PD there are at least two more who have the disease but have not yet been diagnosed. This is due to the long lapse of time between onset and diagnosis that is said to be on average 2.5 years [18,33]. Approximately 1.6% of the United States population receiving Medicare has Parkinson disease. There is a greater prevalence in Whites than in Blacks or Asians [23]. Additionally, because the prevalence of PD increases with age, 1% of those 60 years of age and older are diagnosed with PD and 4% of 80-year-olds or older individuals are afflicted with the disease. With the growth of the elderly population in the United States, it is expected that the PD population will double by the year 2030 [8]. The estimated direct medical cost per patient each year is estimated to be between \$10,043 and \$12,491, which is double that of individuals without PD [8]. This cost accounts for pharmacologic and surgical treatment and hospitalizations related to opportunistic infections or complications such as aspiration pneumonia and hip fractures.

Clinical Features

Motor Deficits: Parkinson disease is defined and diagnosed by its motor features [20]. The four cardinal features associated with Parkinson disease are resting tremor, bradykinesia/akinesia, rigidity, and postural instability. Resting tremor is a relatively early sign and the most common symptom of PD [34], affecting 75% of the PD population [35]. It is initially seen unilaterally, usually in the arm, progressing ipsilaterally to the leg, and then later in the disease the tremors are seen bilaterally. Although the tremors eventually become bilateral, there tends to be an asymmetry, in that the initially affected side continues to be more tremulous. Furthermore, as the disease progresses, the resting tremor can be seen in the face, lips, and/or chin. Initial characteristic tremors are a "pill rolling" movement of the fingers or a flexion/extension of the fingers or wrist. The tremors are rhythmic and occur at regular frequencies. The frequency of the tremors is typically 4-5 cycles per second with varying amplitude that increases with stress and fatigue [3,36]. The resting tremors occur intermittently and vary in severity, such that at times a patient may appear to have more rapid tremors and at other times less rapid. These tremors disappear with sleep and activity, as opposed to action tremors that are tremors noted during movements of the affected muscles. Although action tremors are not considered a cardinal feature of PD, they may also be present later in the progression of the disease [36]. The basal ganglia and cerebello-thalamo-cortical circuit have been associated with the tremors found in patients with PD [34].

Bradykinesia, the slowing of movement, and akinesia, the absence or failure of movement, are the second of the group of symptoms associated with PD. Early onset is confined to distal muscles, and is seen in micrographia, reduced dexterity, and impaired sequential movement of the fingers; with the progression of the disease all muscle groups can then be affected, including those required for speech and swallowing [37]. The manifestation of this symptom is seen in a slowness of movement, and start hesitation, where the patient has a difficult time initiating a movement, also called "Freezing" [1]. Additionally, there is paucity of movement, which is an inability to complete a movement or lack of movement at all. This is evident in masked facies and failure to swing the arms during walking. Bradykinesias are manifested due to difficulty initiating and executing the sequential motor acts necessary for movement [29,38]. A breakdown in the basal ganglia is implicated in the bradykinesia and akinesia of PD [2].

Rigidity is caused by an involuntary increase in muscle tone that can affect all muscle groups. This rigidity is elicited during passive movement and is either smooth (lead pipe) or ratchet-like (cogwheel). The cogwheel movement is thought to be associated with resting tremor. Upon examination of passive movement, the movement is noted as jerky with brief contractions throughout the movement [36]. Rigidity begins unilaterally and is typically found in the wrist, neck, or elbow. It can then progress bilaterally and eventually manifest itself in a stooped posture [37]. As was noted in resting tremor, there can be asymmetry in the rigidity of the muscles with noted increased deficits in the initial affected side. The rigidity varies during the day and is susceptible to mood, stress, and effects of medication. There are two theories that may explain rigidity. The first is an increased activity in the long-loop reflex pathway and the second, which is not mutually exclusive from the first, is abnormalities in spinal interneuron function because of altered input from descending tracts [29].

The fourth cardinal symptom of PD is postural instability, a late symptom, as compared to the first three symptoms [37]. It stems from a combination of deficits including changes in postural adjustment, the loss of postural reflexes, rigidity, and bradykinesia/akinesia. A PD patient is typically seen with a stooped posture with flexion of the neck and trunk. The patient tends to fall forward or backward due to a loss of ability to make rapid postural correction [2]. The postural instability may lead to a gait disturbance, which is often seen initially in reduction of arm swinging. Gait initiation and turning also becomes difficult for the PD patient. Once walking is initiated, loss of postural reflexes and a stooped posture combine to produce a festinating gait. In an effort to retain balance, the PD patient walks faster and faster in a shuffling manner as his legs try to catch up with the body's forward momentum. Freezing is also seen during walking, where by the patient stops and has difficulty re-initiating movement. Postural instability is the most common cause for falling in the PD population. Postural stability is regulated by the basal ganglia via neural connections with the extrapyramidal system, however a breakdown in the basal ganglia results in these symptoms associated with Parkinson disease [2]. Advanced dopaminergic loss results in a breakdown in the function of the basal ganglia and in turn results in the presence of the cardinal features of Parkinson disease. [20].

Non-Motor Deficits: Symptoms that are found in the Parkinson population but are not motor symptoms are called non-motor manifestations [9]. These non-motor deficits of Parkinson disease include autonomic dysfunction; as evidenced by constipation, due to reduced colonic motility; sweating; urinary frequency; dermatitis (chronic seborrhea); sexual dysfunction; and sleep disturbance [8,33]. Additionally, affective disturbance is noted, most predominantly depression that is seen in 38% of PD patients [3]. Sensory deficits, including loss of the sense of smell and consequently loss of the sense of taste, are also evident. PD patients additionally complain of sleep disturbance [33]. Sleep patterns change, as there is less nocturnal sleep and more daytime sleeping. Furthermore, ocular dysfunction has been reported, marked by limited up-gaze, a reduction of frequency of spontaneous eye blinking, and sustained glabellar reflex (Meyerson's sign) that is persistent eye blinking when the forehead is repeatedly tapped [8]. In a study by Barone and his colleagues [39], nearly all of the Parkinson disease participants presented with at least one non-motor deficit. Fatigue and anxiety were the most common deficits reported. Depression and anxiety were evident in the early stages of the disease.

Other non-motor manifestations include cognitive deficits, as characterized by subcortical dementia. Individuals with Parkinson disease demonstrate visuospatial impairment, attentional set-shifting difficulties, and poor executive function [40-42]. Deficits in executive functioning are marked by difficulty planning and carrying out complex goal directed tasks, as the PD patient's ability to plan, organize, and sequence are impaired. Dementia eventually occurs in 20-30% of patients with PD, making it the third most common cause of dementia in the elderly [29,42]. The dementia typical of PD is represented by bradyphrenia that is marked by latent response time and working memory impairment. Involvement of autonomic skills, depression, and psychosis were also associated with the presence of dementia in patients with PD [8].

Language Disturbance: Another non-motor deficit associated with PD is language disorder. Auditory comprehension of syntactically embedded information or late-stage syntactic processing may be compromised [43]. A mild -to- moderate deficit in language comprehension is present in 50 to 60% of those with PD in the early stages of the disease [44]. Expressive language skills may also be compromised. Verbal fluency is affected and less of what is said is considered informative. Speech productions are marked by reduced utterance length and syntactic complexity [44]. Word retrieval for confrontational naming tasks may also be impaired. The classical cortical areas for language function have been Wernicke's and Broca's; however, recent studies have found that language processing is also a function of the striatum. PET scans have noted activation of the basal ganglia during verbal processing tasks. Further evidence to support basal ganglia involvement in language processing was noted with improved receptive and expressive language skills following a regimen of dopamine antagonist medication in PD patients [45]. There is some thought that the presenting language deficits in PD are secondary to difficulties with cognition such as executive function, integration and inhibition, and not due to a breakdown in language function [46]. Friederici, et al. [43] hypothesized that reduced expression and comprehension of prosody found in PD patients may be due to their impaired emotional cognition.

There are non-dopaminergic pathways that are involved in Parkinson disease that result in the nonmotor symptoms of the disease that often manifest prior to the motor deficits [20,33]. Because the extranigral neuropathological changes occur prior to the degeneration of the dopaminergic neurons, non-motor deficits will present earlier than the motor deficits. The non-motor symptoms may precede the motor symptoms by years [14]. However, diagnosis is typically not made until the motor features are present in an individual. According to Kwan and Whitehall [47], Braak and Braak proposed a sequence of pathophysiological progression of Parkinson disease that is first seen in the dorsal motor nucleus of the vagus nerve and the olfactory nucleus, then the locus coeruleus found in the pons of the brainstem, and later on the substantia nigra pars compacta. The cortical area is affected at a later stage. Schrag and her colleagues [33] found disease progression to initiate with the autonomic system then progress to the limbic and somatomotor systems and later reach the midbrain and substantia nigra.

These non-motor disabilities are said to have a greater impact on quality of life than the motor symptoms [8,9]. They occur in approximately 80% of people with Parkinson disease [9]. A culmination of the actual neurodegenerative process, side effects of pharmaceutical therapy, and social factors are said to be the cause of the non-motor deficits found in PD. These non-motor deficits demonstrate that the neurodegenerative processes of PD affect areas of the brain further than the basal ganglia and involve neurotransmitters other than dopamine. As a result, non-motor deficits should be assessed and considered in the diagnostic phase of the disease. Because pathological abnormalities begin prior to nigrostriatal degeneration it is imperative to consider non-motor deficits in the diagnostic process.

Speech Deficits: Parkinson disease has been noted to affect speech function in approximately 75% of those people with the disease [4]. Speech function is marked by hypokinetic dysarthria, which manifests in all levels of speech, including respiration, resonance, phonation, articulation, and prosody. Historically the most common patient complaints are breathy, weak, monotonous voice; compromised pitch and loudness range; short rushes of speech; and imprecise articulation [1,2,4,48]. Deficits in speech production have been attributed to a reduced physiological support due to the clinical effects of Parkinson disease [49].

Parkinson disease affects respiratory support for both speech and non-speech tasks secondary to increased stiffness and weakness in the muscles involved in respiration due to the degeneration of dopaminergic neurons [46,50]. During vegetative breathing, Solomon and Hixon [50] found increased breathing rate in individuals with PD as compared to neuro-typical participants, which was attributed to decreased compliance of the chest wall. Studies of speech breathing found PD patients to have smaller rib cage volume [50]. Additionally, reduced subglottic air pressure, reduced peak air flow, reduced lung air volume expended per syllable, and reduced slope of declination in air flow were found in PD as compared to non-PD patients [51]. The pathophysiology of the respiratory disorders is said to be related to a dysfunction in the basal nuclei [52]. In addition to physiological changes in respiratory support, cognitive-linguistic deficits associated with PD play a role in compromised breath support for speech production. Reduced coordination of respiration and phonation is correlated with the complexity of the speaking task, such that greater cognitive demand required for speaking resulted in greater respiratory deficits [46].

Individuals with Parkinson disease may also present with a dysphonia noted in reduced vocal intensity, reduced pitch range, and compromised vocal quality. These dysphonic deficits tend to occur early in the disease process [53,54]. Vocal intensity is affected by poor breath support, reduced coordination of phonation and respiration, poor posture, glottal incompetence (bowing of the vocal folds), and overall compromised patient self-perception of speech production. Fox and Ramig [55], in their comparison of vocal sound pressure level in patients with idiopathic Parkinson disease and their neurologically healthy peers, found that the PD group produced speech at 2.00 to 4.00 dB SPL lower than the control group. Additionally, the Parkinson patient presents with limited intensity range [56]. Monotonous speech has been attributed to this population's compromised ability to regulate vocal intensity [57]. Hammer and Barlow [51] attributed the reduced vocal intensity found in the PD population to reduced subglottic respiratory drive and compromised adduction of the vocal folds during phonation.

Research has examined the perception of loudness in individuals with Parkinson disease. Ho and his colleagues [58] examined the self-regulation of speech volume in hypophonic subjects with Parkinson disease and age-gender matched groups. They investigated the ability of the patients to automatically regulate speech volume in response to background noise and instantaneous auditory feedback. The controls automatically spoke louder when there was competing noise and spoke quietly when hearing their own voice amplified. In contrast, the individuals with PD spoke quietly in general, and were less apt to increase or decrease their speech volume when appropriate. In this same study, the authors went further to investigate the response of individuals with PD to explicit cues to adjust speech volume. When provided with explicit cues, the patients were able to adjust their volume appropriately. As a result, the authors suggested that individuals with PD have difficulty responding to implicit cues needed for the scaling of speech volume, and therefore the hypophonia is in some part related to internal cueing. It can also be inferred that the hypophonia is not solely related to peripheral deficits such as muscle rigidity [37]. In another study, Ho and his colleagues [59] analyzed the performance of individuals with Parkinson disease when given the task of perceiving the loudness of self-generated speech. Findings of this study revealed that individuals with PD over-estimated the volume of their speech, which provides "Support for sensory anomalies in the perception of speech volume and in the sensorimotor integration involved in the appropriate scaling of speech volume".

Vocal quality in individuals with Parkinson disease is usually characterized as hoarse or breathy [48,60], which is related to incomplete vocal fold closure and/or asymmetry of vibratory pattern, as evidenced by compromised perturbation during acoustical assessment. The PD patient typically presents with greater jitter percentage than neurologically typical individuals [61]. Pitch range is also limited [56,57], which may play a role in the monotonous speech pattern noted, in conjunction with reduced dynamic range. Ikui and his colleagues [53] found narrower pitch ranges in PD patients as compared to the control, which was marked by reduced high registers in both males and females and increased low registers in males. They attributed the reduced pitch range to rigidity in the intrinsic laryngeal muscles required for pitch regulation. Sapir and colleagues [54] also found rigidity to be associated with pitch range deficits. Additionally, increased tone in the thyroarytenoid and cricothyroid muscles was found during rest, as noted by abnormal firing of motor units via electromyographic studies [62].

Hypernasality has also been identified in the some PD patients; however, the deficits tend to be mild [2]. Theodoros, Murdoch, & Thompson [63] found increased nasality during speech production, which they attributed to velopharyngeal dysfunction within the PD participants, as evidenced by instrumental and perceptual analysis. However, Logemann and colleagues [60] found that only 10% of the 200 patients studied presented with a resonance disorder, the least frequent perceptual feature of PD.

PD also affects articulatory precision, due to rigidity and bradykinesia associated with dopaminergic deficits of PD that tends to be characterized by an articulatory undershoot. As a result of the undershoot, a vowel formant centralization is evident, and so formants that are typically in the high frequencies tend to have lower frequencies and conversely those formants that have low frequencies now have higher frequencies [64]. Articulatory movements of the lips and tongue are marked by a reduction in speed of movement and/or reduced range of motion [65]. Logemann and colleagues [60] found that articulatory errors were most noted in stops, fricatives, and affricates. They also found that every PD participant in their study demonstrated misarticulation of the velar stops /k/ and /g/. The least frequent misarticulated phonemes were the alveolar stops /t/ and /d/. These authors concluded that the progression of articulation errors began with the posterior tongue, progressed to the anterior tongue and then to the labial articulators. Additionally, plosives were found to take the shape of fricative-like productions due to inadequate articulatory valving [1,49,66]. Solomon and Hixon [50] found that reduced oral pressure secondary to velopharyngeal valving deficits contributed to the imprecise articulation noted in PD. As with respiratory deficits, as stated above, articulatory imprecision becomes more prominent as the complexity of speaking tasks increases, suggestive of a cognitive component to the articulation deficits [44].

The most prominent breakdown in speech production is evident in speech prosody [48,66]. Prosody is characterized by monoloudness, monopitch, reduced stress, short phrases, variable rate, and short rushes of speech [1,48]. The short rushes of speech, also called oral festination or palilalia, are most often apparent in advanced Parkinson disease [67]. The short rushes of speech are characterized by rapid productions of several words preceded and followed by brief pauses [2]. In a study by Moreau and his colleagues [68], oral festination was found in 45% of patients with PD [62]. Fluency of speech is also marked by inappropriate silences, most often evident at the beginning of a sentence [2]. Duffy [1] attributed the inappropriate silences to difficulty initiating movements.

Another deficit associated with prosody of individuals with PD is monotone speech that is attributed to limited pitch variability, intensity variability, and intonation [57,66]. Both the neurologically intact population and patients with PD demonstrated change in intonation patterns for productions of questions as compared to statements; however, the PD patient tends to have less of a variation in fundamental frequency [69]. Additionally, the PD patient presents with inappropriate use of intonation within syntactic boundaries, as marked by decreased use of falling contours in final boundaries and increased use of falling contours in non-final boundaries [70]

All of the subsystems of speech, including respiration, phonation, resonance, and articulation have a synergistic relationship. A breakdown in any of the subsystems may have a direct effect on another subsystem. Parkinson disease is known to hinder the adequate function of these subsystems and consequently impedes on overall communicative competence.

Speech Analysis Instrumentation: Standard practice of care in assessing voice disorders in the Parkinson population includes a perceptual and acoustic analysis of vocal function. The instrumentation used in the voice evaluation process varies a great deal, yielding differing results. This is especially true in the research of speech skills in individuals with Parkinson disease.

The auditory- perceptual judgment of the speech-language pathologist is critical in the diagnostic process of voice disorders. This perceptual judgment is used in discriminating between normal and abnormal voice function and to determine change in voice in a person in treatment to establish either improvement or deterioration in function. Furthermore, perceptual analysis of voice serves to rate the severity of the disorder and identify any abnormality in pitch, vocal intensity, vocal quality, and rate of speech. When assessing rate of speech, pitch, and vocal intensity, listener confidence and inter-judge agreement among speech-language pathologists are strong [71]. Additionally, greater listener reliability is noted when assessing rough and breathy vocal qualities [72]. However, there are limitations to the listener's perception of speech that may be more evident in the perception of disordered speech as compared to non-disordered speech [73]. "If reliability is defined as the stability of a measurement or detection process, then auditory-perceptual processing is not perfectly reliable and may be highly transient in some analysis that it performs on the speech signal" [71]. The human auditory system is geared to naturally process the speech signal as a whole entity, including its linguistic characteristics. For example, errors may occur due to auditory illusions as evidenced by phonemic restoration and verbal transformation. Phonemic restoration is noted when a listener perceives a speech sound that was in fact replaced by a non-speech sound. This is said to be due to the listener's preoccupation with making sense of the utterance and thereby failing to identify the incongruent sound. That is, semantic and syntactic knowledge prevails over perception of speech sounds. The verbal transformation effect is what occurs when the listener identifies a change in phonetic pattern within an unchanged repetitive stimulus [71]. Linguistic knowledge influences speech perception as the speech signal is typically analyzed as a whole entity and not by its acoustic characteristics [74].

Other variables that may affect the reliability and validity of the auditory-perceptual assessment of the voice include, but are not limited to, the way a stimulus is presented, effects of speaker characteristics, listener characteristics, and differences among rating scales. Furthermore, there is a lack of standardized language used to describe the vocal characteristics of the speaker [75]. Stimuli presented via audio-recordings yield a lower reliability than stimuli presented under live conditions. Additionally, isolated vowel stimuli are typically used for the analysis of voice, because it is easier to control for variables that are present in connected speech such as articulatory influences and prosody [76-79]. However, using isolated vowel productions may not be sufficient to determine a pathology, as it may result in an underestimation of a voice disorder. Speech productions are dynamic and require greater vocal control for adduction and abduction and overall vocal fold motility; therefore, assessment of connected speech would facilitate analysis of true vocal fold function and would reveal a vocal pathology more accurately than analysis of sustained phonation that is more static and less taxing on the vocal folds.

Additionally, sustained vowel productions are said to be more representative of singing than speaking [78]. Bele [80] found greater inter-rater reliability during the analysis of connected speech when compared to that of vowel productions. However, de Krom [79] found that analysis of connected speech was not more reliable or consistent for identifying breathiness and roughness than analysis of sustained phonation. Perceptual analysis of voice should include assessment of connected speech productions in addition to isolated vowel production in order to facilitate a comprehensive interpretation of variations in an individual's vocal characteristics.

Knowledge of a patient's history and physical appearance may also bias the clinician's assessment of the voice. Additionally, the listener's familiarity with the speaker and the listener's linguistic experience and background may also influence judgment of the patient's voice [71]. Kreiman, et al. [81] found that clinical training and experience resulted in greater inter-listener variation in the perception of vocal quality, which was attributed to the differing standards used to rate vocal quality. These different standards were most evident in expert listeners as compared to naïve listeners who had more homogeneous standards. The expert listeners are said to use their exposure and experience with varied voices during the perceptual analysis of voice, whereas the naïve listeners use their own internal standards as a reference to compare to the external stimuli heard [73]. One way to circumvent the variability of inter-rater reliability is with training in conjunction with the use of anchors. Anchors serve as a reference and replace the internal standard of the listener [82]. Experienced listeners who are trained and use voice samples to facilitate vocal quality rating demonstrated reduced inter-listener variability [72,73,83]. As a result of the shortcomings of the human auditory system in perceiving speech signals, further testing is required to assess vocal function. An acoustic analysis serves to identify vocal discrepancies due to anatomical and physiological changes in the vocal tract. Acoustic analysis tends to be the standard of care for a voice evaluation, because it is non-invasive and relatively less expensive than, for example, videostroboscopy or laryngoscopy. Doyle and Eadie [77] found that a combination of acoustic and perceptual analysis of voice productions results in a highly accurate identification of a dysphonia.

The identification of an individual's fundamental frequency is part of the acoustic analysis. Fundamental frequency is determined by the vibrating rate of the vocal folds that reflect the mass, tension, and length of the vocal folds. Fundamental frequency is the lowest frequency of the vocal fold tone produced [84,85] and determined by the number of vibratory cycles produced per second by the vocal folds [86]. According to Titze [87] fundamental frequency is imperative for acoustic measures to facilitate assessment of vocal fold function. Additionally, an acoustic analysis includes assessment of phonational range. Phonational range determines a person's ability to reach high and low registers and overall dynamic frequency. The physiological limits of a person's voice can be identified by the phonational range [74]. Furthermore, perturbation, or the variability in fundamental frequency from cycle-to-cycle, is used during acoustic analysis of vocal function. Frequency perturbation, also known as jitter, is a function of differences in mass, tension, and biomechanical characteristics of the vocal folds [84]. Additionally, neurogenic and aerodynamic function of the vocal folds play a role in the perturbation of a signal and anomalies in either system may result in increased jitter [74]. Perturbation allows the clinician to quantify the regularity of vocal fold vibration [88]. Perturbation is therefore used as part of an acoustic analysis, as it can serve to identify a variation or pathology in the vocal function, which may be related to compromised biomechanical, aerodynamic, or neurogenic function.

In addition to the analysis of frequency, acoustic analysis also assesses the amplitude of a signal to determine vocal fold dysfunction. Amplitude can be measured via Sound Pressure Levels (SPL). The average sound pressure of an utterance is measured to evaluate the strength of an acoustic signal. The synergistic relationship between the biomechanics of the vocal folds, aerodynamic function, subglottal pressure, and vocal tract status determines vocal intensity of a signal [74]. Vocal intensity is also affected by fundamental frequency, such that an increase in fundamental frequency tends to result in an increase in intensity and vice versa. Dynamic range, a measure of the difference between the highest and lowest achieved intensity, is also assessed during an acoustic analysis. Additionally, amplitude perturbation or shimmer is typically measured. Shimmer is the cycle-to-cycle changes of amplitude during phonation and deviance from the norm may be indicative of vocal hoarseness [74,84].

Although acoustic analysis tends to be part of the standard protocol for a voice evaluation, there are inherent limitations to this form of assessment. Acoustic analysis of vocal function is based on assumptions of signal periodicity, although the typical laryngeal signal is quasiperiodic [74,77]. In order for a signal to be periodic, it must be marked by constant and regular recurring waveforms [74]. A typical vocal signal is always marked by variable waveforms and that variability increases with vocal pathology; therefore, acoustic analysis of periodicity via perturbation may not be reliable [89,90]. Perturbation measures are restricted to quasi-periodic signals that are characteristic of a non-deviant voices but not of a vocal pathology. As a result, jitter and shimmer measures may be elevated and result in a false positive identification of deficits. Use of perturbation measures yields inconsistent results in differential diagnosis of pathological voices and normal voices [91]. Additionally, Brockmann and his colleagues [88] found that vocal intensity and vowel and gender differences between speakers had a significant impact on perturbation of frequency and amplitude. "The fact that measures of aperiodicity apparently cannot be reliably applied to signals that are even slightly aperiodic leads us to question their utility in analyzing vocal quality, especially in pathological voices" [92]. However, Werth and her colleagues [93] found that perturbation measures resulted in accurate classification of voice disorders 75-90% of the time. A significant correlation between perturbation measures and presence of a voice disorder assessed via laryngoscopy, stroboscopy, electroglottography, and voice profiles was found. Perturbation measures, such as jitter and shimmer, should be analyzed with caution, and clinicians should account for these variables during the assessment process.

In order to reduce the variability of a signal, a small segment that is judged to be most stable may be cut and used in the analysis of perturbation. Typically, the initial and final segments of the productions are the least stable and are eliminated [94]. However, there is no standard of practice to determine what segment of the utterance to isolate. Clinical judgment is often employed to identify a stable segment in the production, but this may result in inconsistencies and poor reliability. As a result, a standard rule must be developed [95]. In contrast, some studies found that eliminating the unstable parts of the signal may not represent the true dysphonia, which in turn may lead to an underestimation of the severity of the vocal pathology [96].

Nonlinear assessments of degree of voice abnormalities have also been employed to assess voice and identify a vocal pathology [87,93]. A nonlinear method of assessing voice facilitates the analysis of irregular activity that is consistent with pathological voice productions, because it is based on the idea that there is a random process that produced the signal, and thereby allows for the reconstruction and analysis of the production [97]. Nonlinear assessment is necessary because vocal fold vibration is not linear, as the interaction between the vocal folds and the vocal tract is not always linear [98]. The input and output of the vocal system are not proportionate to each other. Therefore, a nonlinear form of assessment must be employed. This dynamic assessment does not rely on the identification of cycle periods, as in perturbation measurement but instead describes the geometric properties of the signal [8,91,99]. Additionally, it is said to require shorter samples, a lower sampling rate, and have a greater response to noise [90]. Examples of nonlinear dynamic parameters include phase space reconstruction and correlation dimension (D_2). Phase space reconstruction is used when the strength of periodicity is measured by the difference between a plotted acoustic signal in real time and the same signal at a time delay. D_2 determines the number of degrees of freedom necessary to describe the signal using the phase space. There is a positive relationship between the amount of degrees of freedom and variability in a signal, such that as variability increases so does D_2 [100]. Nonlinear analysis should be used in conjunction with traditional acoustic analysis to allow for a more comprehensive evaluation and facilitate identification of vocal pathologies.

Standardization of the evaluation process is paramount for the acoustic analysis of voice. Technology has brought forth many computer applications for the analysis of voice that use digital signal processing techniques. However, there is no standardization among the systems, although most of the systems perform well [101]. The Kay Multi-Dimensional Voice Program (KayPentax Corporation) was found to be a valuable tool for the acoustic analysis of neurogenic speech disorders [102]. According to Smits, et al. [85], the Computerized Speech Lab (CSL; KayPentax Corporation) is the most cited computer software program in the study of voice. Felipe and her colleagues [86] reported that the CSL software program was the most accurate in measuring fundamental frequency for a sustained vowel. However, different acoustic analysis values differ in accordance to methodology and computerized software system being used for the analysis.

Another dimension in the voice evaluation process is the analysis of the psychosocial effects of voice disorders. The Voice Handicap Index (VHI) is a subjective patient questionnaire for self-analysis of vocal function and its psychosocial effects. The VHI is a 5-point scale developed to quantify the effects of voice disorders within 3 subscales; the functional subscale investigates the impact on activities of daily living, the emotional scale assesses the affective response to the voice disorder, and the physical subscale investigates the self-perceived vocal characteristics [103]. The VHI is a valuable tool in the assessment of voice disorders because it evaluates the patient's perception of her own vocal quality and perceived vocal demands both professionally and socially, which is an aspect of the vocal pathology not addressed during the standard perceptual and acoustic analysis of voice [104]. Identification of the psychosocial impact of a vocal pathology may aid in dictating the course of intervention, as a person with a low VHI score may not need intervention because the voice disorder may not hinder his or her quality of life. Guimaraes & Abberton [105] found that the VHI is sensitive to the presenting dysphonia. Those patients with a vocal pathology scored higher in the VHI than those with adequate voice. However Woisard and her colleagues [106] did not find any correlation between the scores yielded from the VHI and results from acoustic analysis. The VHI was not found to be a good predictor for acoustic measures. Therefore, the VHI should be used as a diagnostic tool in conjunction with perceptual and acoustic analysis.

The analysis of voice disorders is a highly variable process executed by speech-language pathologists. Despite the inherent limitations to the perceptual and acoustic analysis of voice, speech-language pathologists use these tools regularly for the evaluation and treatment of vocal pathology, as is present in individuals with Parkinson disease.

Speech Analysis in Individuals with Parkinson Disease: Acoustic characteristics of Parkinson disease typically include normal or faster-than-normal speaking rates, high mean fundamental frequency, reduced F2 extents and slopes, and decreased fundamental frequency variability [107]. Fundamental frequency for sustained /a/ is higher [108,109], whereas frequency variability is lower in the pharmaceutically treated and untreated PD population as compared to the neurologically intact population [110]. Cantor [57] found that neurologically intact individuals presented with a median fundamental frequency of 106 Hz, whereas the PD group had a median of 129 Hz. Fundamental frequency increases as clinical deficits increase [66]. Assessment of maximum phonational frequency range in the PD population tends to yield a reduced range, mostly noted for the low registers [57,74]. This reduced phonational range may attribute to the monotone voice that is often associated with PD speech. The PD patient presents with an average of 1.25 octaves, while the neurologically intact population average 1.84 octaves during a pitch variation task [49]. Additionally, there is a greater variability in voice onset time and increased spirantization, as evidenced during bilabial and velar alternating motion rates [111].

Increased frequency perturbation is also noted in the PD population both when untreated and when treated with medication [56,110]. The tremulous voice is marked by increased variation in amplitude and frequency as evidenced by increased jitter and shimmer [112]. However, as previously stated in this report, use of perturbation to analyze vocal pathology in a non-periodic production, as is characteristic of a PD voice, should be performed with caution. Use of non-linear dynamic measures results in the differential diagnosis of tremulous voices as compared to normal voices [112]. Rahn and his colleagues [61] found significantly increased correlation dimension (D_2) in the phonatory signal of individuals with PD when compared to the control group.

Reduced loudness also tends to be a common characteristic of PD. However, according to Cantor [57] vocal intensity of patients with PD during connected speech is comparable to that of neurologically intact individuals. Furthermore, difference between dynamic range of neurologically intact individuals and individuals with PD were not significant. In contrast, in a later study Cantor [49] found that patients with PD tend to average 4.4 dB less when using a self-perceived “loud” phonation. Additionally, PD patients with severe dysarthria are noted to have reduced variability of intensity [66]. The aberrant vocal intensity pattern apparent in the PD population is attributed to a problem in respiratory control and is variable in accordance with the severity of the disease [66].

Another perceptual characteristic of PD speech is increased rate of speech and shorter voiceless intervals that distinguishes PD from other dysarthrias [107]. The perceived accelerated speech is associated with articulatory undershoot [66]. As cited by Gentil and Pollak [66] found PD patients had reduced duration of phrases, reduced transitions between the phrases, and reduced duration of phonemes. The perceived increase in rate of speech may be a function of the production of imprecise consonants. However, Ackerman and Ziegler [113] and Cantor [57] found no statistically significant difference in rate of speech. In Cantor’s study the median rate of speech for the PD group was 172.6 words per minute while the control group’s mean rate was 177.6 words per minute. The only conclusion that can be made from these studies is that there is high variability of findings from studies that assess rate of speech in the PD population.

Physiological assessment of speech functions in the PD population yields a better understanding of overall function and deficits in this population. A comprehensive voice evaluation may include an endoscopic assessment, most likely a laryngeal stroboscopy. The stroboscopy assesses glottal closure and vibratory patterns. Most individuals with PD present with a bowed vocal fold configuration [114,115], but amplitude or mucosal wave is not affected [116]. However, Yuceturk and his colleagues [117] found decreased or absent mucosal wave and posterior or anterior glottal chink to be the most predominant feature identified via videolaryngostroboscopy. Ventricular fold and anterior-posterior approximation may be noted, which is judged to be related to hyperfunctionality as a compensatory mechanism for compromised true vocal fold approximation. Hypercontractility noted in the thyroarytenoid and cricothyroid muscles via laryngeal electromyography may also be related to rigidity associated with PD [118]. Furthermore, vocal tremor may also be present [116]. Stroboscopic findings vary according to the degree of severity of the PD. As the disease process progresses, the voice disorder is expected to worsen and symptomatology and signs would become more evident.

Physiological signs of PD may also be examined using laryngoscopic assessment. A study performed by Hanson and his colleagues [115] identified the most prominent laryngoscopic findings were bowed vocal folds, greater amplitude during vocal fold vibration, and laryngeal asymmetry of varying patterns. The patterns consisted of posterior position of the vocal process, posterior and lateral position of the apex of the arytenoids, and contracted ventricular folds.

Compromised respiratory function may play a contributory factor in the speech deficits associated with Parkinson disease. “Decreased loudness level, short phrases, abrupt interruptions of speech, and hurried generation of speech suggest inadequate respiratory support for normal speech production.” [66]. As a result, the pneumotactograph can be used to examine aerodynamic functioning, specifically air pressure and airflow. It is expected for a PD patient to present with increased airflow and decreased subglottic air pressure, due to poor glottic approximation during phonation. Additionally, reduced respiratory function for speech production may be due to rigidity or weakness in the muscles of respiration [46]. Non-instrumental assessment of breath support for phonation via a maximum phonation time task yields a significant difference between those with PD and those without neurological involvement [114]. Cantor [49] found that individuals without PD were able to sustain a phonation for an average of 20.6 seconds, where as those studied with PD sustained a phonation for an average of 9.5 seconds. Jimenez-Jimenez and his colleagues [110] found no significant difference in maximum phonation time between these two groups. Fox and Ramig [55] did not find statistically significant differences either. Those individuals studied with PD averaged a maximum phonation time between 5.74 seconds and 34.85 seconds and those individuals from the control group averaged between 8.47 seconds and 26.23 seconds. Once again findings correlated with degree of severity of the disease.

Because PD is a progressive disease, it is to be expected that there is a natural decline in skills with the progression of time. King, et al. [4], estimated an annual decline of 0.695 semi-tones for mean fundamental frequency and 0.856 semitone decline for maximum fundamental frequency range. Additionally, an annual decline of 0.439 seconds was identified for mean duration of sustained vowel phonation and 0.530 seconds for maximum duration of sustained phonation. Although time and progression of the disease significantly affects the vocal patterns of patients with PD, pharmacological therapy does not. No significant change in vocal function, as evidenced by fundamental frequency and jitter and shimmer measures, is noted as a result of levodopa therapy [108]. Elevated shimmer is noted in PD patients whether they are on levodopa medication or not [119]. Often PD is treated pharmacologically with levodopa. Levodopa is used to target PD symptoms such as rigidity and akinesia. However, little effect is noted in speech function with these medications. Therefore, it can be suggested that vocal pathology related to PD may be associated to non-dopaminergic mechanisms [114].

The analysis of voice disorders is a highly variable process executed by speech-language pathologists. The perceptual and acoustic analysis of voice is used for evaluation and treatment of individuals with Parkinson disease. However, there are inherent limitations to this process that subsequently result in compromised reliability and validity. Despite their limitations, speech-language pathologists use these tools as standard form of practice for both assessment and treatment of the Parkinson disease population.

Treatment

Pharmacological Therapy: Levodopa, a chemical form of dopamine, is said to be the “gold standard” for PD treatment [120,121]. Levodopa targets tremors; its effect on rigidity, bradykinesia, and postural instability is highly variable. Its side effects include nausea and vomiting; as a result, a chemical carbidopa has been added [122]. Additionally, the PD patient may experience orthostatic hypotension, a decrease in blood pressure when a person stands up; confusion associated with long term use; and hallucinations and delusions. Another side effect is motor fluctuations with “on” and “off” periods in between doses, evident with long term use of levodopa [111,121]. The patient may experience disabling akinesias and bradykinesias during the off period. Santos and her colleagues [108] reported that 50% of the patients treated with levodopa will develop on-off fluctuations. However, they found no significant difference in acoustic parameters, including fundamental frequency, jitter, shimmer, voice turbulence index, and harmonic noise proportion, within the off and on stages of PD. Furthermore, levodopa can sensitize dopamine receptors and cause dyskinesias that are dance-like involuntary movements and may involve the whole body [18,111]. According to Chen [8], approximately 25% of patients taking levodopa will develop dyskinesias after two and a half to three and a half years of taking the medication and 39% following four to six years of taking levodopa.

Dopamine agonists are also used in the treatment of PD. These medications mimic dopamine and directly stimulate post-synaptic striatal dopamine receptors [3,18,122]. The agonists are either used alone or in conjunction with levodopa/carbidopa medications. Often they are used in the early stages of PD prior to the initiation of levodopa to delay the use of levodopa and subsequently avoid the side effects of the levodopa [120]. However, following one to three years of use, the agonists will not work alone and other medications will need to be prescribed [3]. The side effects of dopamine agonists are nausea, vomiting, orthostatic hypotension, nightmares, hallucinations, leg edema, and constipation [18,120].

Research findings of the benefits of levodopa and dopamine agonists on speech deficits associated with PD have been discrepant [123]. Letter and his colleagues [124] found significant improvement in variation of pitch, variation of intensity, and overall intelligibility under the effects of levodopa. Sanabria and his colleagues [125] found increased fundamental frequency, decreased perturbation for jitter, and decreased vocal tremor with use of levodopa treatment, which they attributed to a decrease in laryngeal hypokinesia and rigidity. Jiang and his colleagues [126] also found improvement in vocal function as evidenced by reduced shimmer and vocal tremors and increased sound pressure level. However, Skodda, Visser, and Schlegel [127] and Larson, et al. [119] found no significant benefit of levodopa on vocal function. Additionally, no changes in maximum phonation time and articulation were noted with dopamine agonists [128]. Pharmacological therapy via dopamine agents improves symptoms related to the degeneration of the nigrostriatal system and subsequent depletion of dopamine, such as bradykinesia, rigidity, and tremors. However, the inconsistent response to pharmacological therapy of levodopa or dopamine agonists on speech impairments is suggestive of nondopaminergic pathways related to Parkinson disease. Therefore, therapy via dopamine agents may not serve to improve speech function and as a result, speech therapy should be employed to facilitate improved communicative function in individuals with PD [123,128].

Speech Therapy: Although the prevalence of speech deficits in the Parkinson population is high and compromised communicative competence is considered one of the most difficult aspects of PD [129], only 3-4% of the PD population receives speech therapy [123]. A 2002 published review by The Evidenced Based Medical Review for the Treatment of Parkinson’s Disease found that efficacious speech therapy should target loudness and prosody and be intensive. Furthermore, the Lee Silverman Voice Treatment (LSVT) demonstrated the greatest number of positive outcome measures when compared to other reviewed therapies [123,129]. The fundamental principles of LSVT is based on the effects on voice and articulatory function from the reduced amplitude of neural drive to the speech mechanism and compromised sensory self-perception of vocal effort and speech movement noted in PD [123,129]. LSVT is unique among therapy programs for dysarthria in that it uses increased intensity as a catalyst for improved overall speech production. As a result, LSVT focuses on loudness as a cue to increase effort and coordination across all speech mechanisms, including respiration, phonation, resonance, and articulation, while limiting cognitive demands on the PD patient. The final goal of therapy is generalization of increased vocal intensity during spontaneous speech production, which in turn results in overall increased communicative competence [129]. It is hypothesized that increased loudness facilitates speech motor output across the respiratory, laryngeal, and orofacial system [130]. Increased loudness as a therapy strategy is said to be effective because it uses a pre-existing, well-practiced movement organization. That is, using a louder voice is associated with a temporal and spatial organization that mimics the organization of spontaneous speech [130]. Furthermore, Dromey and colleagues [131] found an association between increased intensity after the LSVT program and an increase in F2 transition duration for diphthongs and an increase in F2 transition extent for both diphthongs and monothongs. Therefore, it is said that articulatory displacement increases with increased vocal intensity. Neel [132] proposed another reason why increased vocal intensity resulted in an improvement in overall speech intelligibility. She attributed the improvement to the increased audibility or signal-to-noise ratio.

The essential concepts of the LSVT program are as follows: (a) exclusive focus on voice (specifically vocal loudness), (b) stimulation of high-effort productions, (c) intensive delivery of treatment (4 individual sessions a week for 4 weeks, 16 sessions in one month), (d) enhancing sensory awareness of increased vocal loudness and effort (calibration), and (e) quantification of behaviors [133]. There are three main exercises or variables in LSVT; the first is maximum duration of sustained phonation. The patient is cued to sustain a loud “ah” sound for as long as possible. The only cue used is “loud”, which requires minimal cognitive effort by the patient. During this task, the patient is trained to improve respiratory-laryngeal coordination. The second variable maximizes fundamental frequency range, by sustaining a high and low pitch, which targets the presenting hypoprosody and hypophonia. The final variable assists the patient in carry-over and maintenance of louder voice into daily communication. The patient is given speech tasks in order to generalize a loud voice into communicative exchange. The tasks are in a hierarchical order from words up to conversation. Words and sentences produced loudly receive higher intelligibility ratings in the PD population [132].

Furthermore, LSVT is based on the premise that compromised perception of self-generated speech is due to an impaired ability to judge self-effort in relation to motor tasks [55]. Scaling loudness is part of everyday communication and routine for most people; however, individuals with PD have difficulty independently scaling the right amount of effort to produce adequate loudness [123]. As a result, a key component of LSVT is “calibration”, where the patient is taught to internalize the amount of effort needed to produce speech with adequate loudness. Acoustic measures via a Visipitch or sound level meter are used to quantify the results of therapy and as biofeedback for the patient.

Studies of the efficacy of LSVT found voice to be improved, as evidenced by increase vocal intensity, increased maximum phonation time, range of fundamental frequency, increased fundamental frequency variability during speech (reduce monotone speech), and a reduction in rate of speech [134]. Additionally, glottal closure improved as noted during videostroboscopy, and consequently vocal fold hyperfunctioning subsided [129].

Although LSVT does not directly target articulation, studies have found overall articulatory improvement following therapy, suggesting that vocal loudness training may stimulate increased amplitude and coordination of motor output to the orofacial system. Ramig and colleagues [123] found that a single treatment target may influence common control mechanisms that improve other motor behaviors not originally targeted. In a study by Sapir, et al. [135], articulation for vowel production of /i/, /u/, and /a/ improved both acoustically and perceptually. Additionally, formant transition duration and rate and extent of movement have improved as a function of LSVT.

PET studies in PD patients following the LSVT program revealed a reduction of cortical motor-premotor activation, resembling the functional patterns in healthy individuals. A shift from abnormally effortful premotor activation to a more automatic basal ganglia activation was noted [136]. PET imaging found improvement in basal ganglia, limbic system, prefrontal cortex, and right hemisphere function in those patients that underwent LSVT treatment [123].

In a study by Ramig and her colleagues [134] comparing two intensive therapy programs of respiration therapy versus LSVT, all participants were found to have improvement in vocal intensity, mean habitual fundamental frequency, fundamental frequency variability during reading, maximum phonation time, and utterance duration during reading. Improvement was reported in self and family ratings for both therapy programs. However, the patients who participated in the LSVT program made greater and more consistent changes in intensity and fundamental frequency variation. Only LSVT patients reported a significant reduction in the impact of PD on oral communication. Additionally, improved articulatory function was noted only in the LSVT participants. Therapy based on amplitude training as compared to rate training has been noted to be more effective. Overall, the LSVT program has been efficacious in the treatment of PD symptoms associated with speech, including hypophonia, hypoprosody, and reduced articulatory precision, when historically prognosis for improved speech and maintenance of skills were poor [123,129].

Parkinson disease is a multi-faceted progressive neurological disease, which manifests in both motor and non-motor functions. The effects of the disease are detrimental to an individual’s overall quality of life. With the progression of pharmacological therapy, surgical intervention, and behavioral therapy, treatment for this disease has improved exponentially; however, the cure for the symptomatology related to PD continues to elude science. For this reason, continued research in treatment for Parkinson disease is imperative. Further discussion of surgical intervention related to motor and nonmotor impairments related to Parkinson disease is found in the following section.

Surgical Treatment of Parkinson Disease

PD is initially treated pharmacologically; however, when this form of therapy is exhausted and relief from symptoms is no longer experienced, an alternative treatment is sought. This alternative may be surgery, but there are both a paucity and inconsistency on the research of the effects of surgery on overall speech production.

In the 1940s, surgery to treat the symptoms of Parkinson disease was pioneered by Russell Meyers. He was the first surgeon to target the extrapyramidal system in the treatment of PD [137]. At that time, the basal ganglia were located and ablated. Prior to 1947, the targeted areas were located by exposing regions of the brain and using surface landmarks. Spiegel and Wycis [18] then developed a crown-like stereotaxic frame that held the head in place and allowed regions inside the brain to be correlated with reference points on the frame.

Prior to the development of L-dopa, ablative surgery was the most common method of treatment for Parkinson disease. Once discovered, research and treatment then focused on the use of L-dopa; however, the inherent limitations of medicinal treatment served as a catalyst for new interest on surgical therapies. At present, research has returned its focus to surgery and, as a result, treatment through surgery is now sought. Currently, there are three forms of surgery: ablative, restorative, and stimulative.

Ablative Surgery: Ablative surgery refers to the destruction of affected areas of the brain. According to Lieberman and McCall [18], the area targeted in the surgery is the region of the brain that has been affected by PD, as evidenced by abnormal chemical or electrical discharge. The abnormal discharge results in static in that region, which impedes the overall harmonic function of the brain. Ablative surgery serves to destroy the region of the brain that is not functioning and, subsequently, eliminate the static and allow for normal brain function.

Thalamotomy: A thalamotomy is an example of ablative surgery, and was developed based on the idea that tremors are due to static in the loop from the cerebral cortex to the striatum, then to the globus pallidus, then to the ventral lateral thalamus, and then back to the cortex. Hassler and Riechert were the first surgeons to target the ventrolateral nucleus of the thalamus in 1954 [137]. Currently, this surgery is performed using a stereotaxic frame and an MRI or CT scan to locate the region. A small burr hole is made in the skull while the patient is under local anesthesia. A micro-electrode is then passed through the hole to the targeted area; the electrode is then heated, using radio frequency currents, to destroy small sections of the thalamus. The patient is awake during the surgery, to monitor the results of the ablation via observation of patient response. However, the full extent of the lesion is not known until several days or weeks have passed and swelling of the affected area has subsided. A thalamotomy is usually unilateral and contralateral to the affected limbs. This procedure is performed to address tremors and rigidity, not balance or bradykinesias. According to Fox and her colleagues [138], tremor suppression is reported in 93% of patients 5 years status post-thalamotomy. Therefore, the ideal candidate for a thalamotomy presents with unilateral tremors.

A bilateral thalamotomy is contraindicated, as it may cause problems with speech, cognition, and/or balance. Side effects from both unilateral and bilateral thalamotomies include dysarthria, as marked by hypophonia and articulatory imprecision, and aphasia; however, findings have been inconsistent. Permanent complications, including speech deficits, apraxia, or death occurred in 14-23% of patients [139]. Samra and his colleagues [140] found language deficits in 50% and speech deficits in 75% of the participants following bilateral thalamotomies. The posterior ventromedial thalamus has also been implicated in disfluencies, as evidenced by induced disfluencies via mechanical perturbation of the thalamus [141]. Furthermore, lesions that extend further than the sensorimotor regions of the thalamus have been found to cause aphasia in patients with PD. Side of lesion is a factor in the deficits caused by the surgery; left-sided thalamotomies result in more language deficits as compared to right-sided surgery [142]. In contrast, Hugdahl and Wester [143] did not find a negative effect of thalamotomy on cognitive-linguistic function. Nor did they find a laterality effect, such that there was no difference in the effects of thalamotomies when the lesion was on the right or left side of the brain. Furthermore, acoustic analysis of vocal production revealed increased vocal intensity and fundamental frequency in 7 patients following right-sided thalamotomy [144]. Speech deficits resulting from a thalamotomy are counterintuitive if we subscribe to the theory that dysarthria in PD is due to neuromuscular deficits such as rigidity. According to this theory, a thalamotomy should alleviate speech systems similarly to its alleviation of motor systems as related to PD. Based on the discrepant results of thalamotomies on speech and non-speech motor skills, it can be inferred that speech and non-speech skills are controlled by neural systems that are overlapping in some ways but distinct in others [10]. Changes in speech and language skills following thalamotomies are indicative of the critical role that the thalamus plays in the overall speech and language function. The motor cortex-ventrolateral thalamus modulation may have a great impact on the motor processes associated with 'speech' than the thalamic influences in general." [140]. Research on the effects of thalamotomies on speech and language skills is discrepant. Speech and language deficits have been inconsistently noted, and of those deficits some researchers have found a lateral effect of the dominant hemisphere. Furthermore, reports of the duration of thalamotomy-induced speech and language disorders have been controversial. Some studies have noted the disorders to be transient, whereas other studies have identified a more salient problem. The discrepancies in the findings have been attributed to size and site of lesion, differences in methodologies between studies, and overall function of the thalamus. Although the thalamus is a known contributor to speech and language function, the degree and exact role is still unknown.

Pallidotomy: Another ablative surgery is a pallidotomy, which is similar to the thalamotomy, except that the targeted region is the globus pallidus. Initially, the anterodorsal and medial part of the pallidum was targeted; however, due to poor results on tremor and hypokinesia alleviation, the target was then shifted to the posteroventral and lateral pallidum [137]. This procedure decreases dyskinesias, reduces tremors, and improves bradykinesias. Following pallidotomy surgery, 92% of patients experienced reduced rigidity and hypokinesias lasting up to six years, 81% of the patients had relief from tremors, and side effects from L-dopa therapy such as dyskinesias and muscle pain were reduced [145]. Samuel and colleagues [146] found the greatest effect on motor symptoms related to Parkinson disease was the reduction of contralateral dyskinesias that may enable the patient to take higher doses of L-dopa medication to further impede motor symptoms. By interrupting the outflow from the globus pallidus, the pathway that causes dyskinesias is inhibited, and there is a release of a brake that blocks the substantia nigra from producing dopamine. This procedure is done contralaterally to the affected limb. The ideal candidate is young, has no cognitive impairments, and demonstrates a good response to medication. Studies have found that younger patients, regardless of stage of disease, demonstrated greater motor improvements than older patients. Furthermore, pallidotomies yielded greater success in recovery of motor skills than conventional pharmacological therapy. Long-term success was most evident when the surgery targeted as much of the sensorimotor aspects of the pallidum as possible [147]. These authors also found ipsilateral improvement of motor skills. Increased metabolic activity in the primary motor, supplementary motor, and premotor cortical areas that receive projections from the thalamus was identified in patients who had pallidotomy surgery via Positron Emission Tomography (PET) studies [145].

Much like a thalamotomy, surgery is performed unilaterally to reduce the chance of increased hypophonia and the worsening of cognition and neuropsychiatric function. However, according to DeBie and his colleagues [148], greater improvement in motor skills was found with bilateral pallidotomies. Nonetheless, anteromedially placed unilateral pallidotomies may result in mild cognitive impairment that is usually transient. Studies have found mild phonemic fluency disturbance following left pallidotomies to be the most consistent side effect related to cognitive functioning. Deterioration of cognitive-linguistic function following pallidotomies demonstrates involvement of the globus pallidus in communication and in the disassociation of motor and nonmotor skills. "Pallidotomy may evoke excessive disinhibition of thalamocortical outputs and a consequent inability to temper superfluous cortical activity, also resulting in or perhaps exacerbating cognitive deficits" [149]. However, no significant changes are noted in voice function following pallidotomy surgery, as evidenced by acoustic analysis [150]. Findings related to the effects of pallidotomy on speech skills are inconsistent. Schulz and her colleagues [145] found that some of their participants demonstrated improved phonatory skills following unilateral pallidotomy; however, others did not. Despite the improvement noted in those patients, none ever achieved skills that were within normal limits for their age and gender. These authors did, however, find a positive correlation between severity of deficits and improved speech skills. Those patients with mild hypokinetic dysarthria prior to the surgery fared better than those with a moderate dysarthria. The differences in success of surgery for motor skills and non-motor skills further demonstrate that motor skills have different neurological characteristics than non-motor skills, despite the common affected area. Once again, research findings have not been consistent, which is due to the same reasons outlined following the analysis of thalamotomy surgery previously addressed.

Restorative Therapy/Transplantation Surgery

A second surgical option is restorative surgery or transplantation surgery. This surgery involves the transfer or implantation of dopamine producing cells into the striatum. Transplantation attempts to reestablish dopamine levels while "setting back the PD clock" [18]. Fetal dopamine neurons were first transplanted in rodents in 1979, which led to further experimental transplants in non-human primates. Motor skills improved in these primates who were afflicted with PD and received transplantations. Success in these studies resulted in transplantation of fetal cells and stem cells for the treatment of Parkinson disease. Research on the effects of transplantation found less need for L-dopa therapy, reduced dyskinesias, and fewer on-off fluctuations [151]. Transplantation is usually performed bilaterally, while the patient is under general anesthesia. The cells are implanted in the striatum, and not the substantia nigra, because it is easier and safer to locate. Because of this, the procedure cannot impart the characteristics of the lost nigral cells exactly. Another contraindication is that transplantation requires at least 1.6 million cells to make up for the 60% lost to PD and the 80-90% of cells that die during transplantation. There are only 400,000 cells in each embryo; therefore, surgery would require 3-4 embryos. A study of voice and speech function following fetal dopamine transplant in 5 PD patients found no remarkable changes pre- to post-operation [152]. Other studies have found the development of dyskinesias in patients who underwent fetal transplantations. These dyskinesias are typical side effects of dopaminergic medication; however, the participants in the above-stated studies were not taking dopaminergic drugs [138]. Politis [153] also found these graft-induced dyskinesias in patients' status post- transplantation of fetal tissue. Further research is needed before transplantation surgery can be considered for consistent use as a treatment for Parkinson disease.

Deep Brain Stimulation

History of Deep Brain Stimulation: The alternative to ablative and restorative surgery is stimulation surgery, or deep brain stimulation (DBS). This surgery was pioneered by Fritsch and Hitzig's description of the motor cortex's localized electrical excitability. In 1874, Bartholow reported on the first human cortical stimulation. Early benefits from stimulation were noted during intra-operative stimulation that was used to aid in the identification of deep brain structures. It was noted that there was a reduction of tremors following high-frequency stimulation of the ventrolateral thalamus in the 1960s. These changes led to Sem-Jacobsen's [154] development of a method to implant a bundle of electrodes deep in the brain. The electrodes were left in place for weeks, and trials of stimulation were given to assess the ideal target area for subsequent lesions. In the 1970s chronic stimulation was used to relieve pain, movement disorders, and epilepsy. During that time electrical stimulation was delivered transcutaneously to electrodes placed on the surface of the cerebellar cortex to treat cerebral palsy. Implantable pacemakers were coupled with deep brain electrodes for long-term deep brain stimulation in the 1990s [154]. DBS surgery was FDA approved for the treatment of PD in 2002.

Deep brain stimulation to the Ventral Intermediate Nucleus of the Thalamus (VIM) was first used to treat essential tremor. The success rate was over 80% for the reduction of tremors status post-VIM DBS. DBS was then extended to treat patients with Parkinson disease. Originally the targeted area was the VIM because of the success of DBS in reduction of tremors; however, little change was noted in treatment of other clinical symptoms, such as rigidity, dyskinesias, and bradykinesias. The regions targeted by DBS were then extended to the Globus Pallidus Pars Interna (GPi), and Subthalamic Nucleus (STN). GPi stimulation resulted in a more global diminution of symptoms, including painful cramps. Studies, however, did not demonstrate a reduction of medication needed to treat the overall PD symptoms. STN-DBS then became more widely used as it has shown greater improvement in off-medication motor skills, as evidenced by diminished bradykinesia, rigidity, tremor, gait disturbance, and allows for a reduction of dopaminergic medication [154]. As of 2006, more than 35,000 Parkinson patients have undergone STN-DBS surgery worldwide [6]. DBS surgery has been extended to treat Tourette syndrome, dystonia, pain, depression, and obsessive compulsive disorders. Clinical benefits from STN-DBS when patients are off medication are noted for approximately four years following surgery. However, motor skills while on medication significantly diminished at the four-year marker status post-surgery [155]. Success has been mostly noted in patients who report benefit from dopaminergic medication; however, the effects do not last for a long period of time and are hindered by the side effects of the medication [154].

Description of Deep Brain Surgery Procedures: Deep brain stimulation surgery is a three-step process. The first step is the implantation of a microelectrode or a lead into the brain while the patient is awake. The patient does not feel pain while the electrode is advanced through the brain, as the brain does not generate pain signals. The microelectrode is a thin quadropolar electrode, in which the polarity, amplitude, pulse width, and frequency can be changed to optimize the benefits of this treatment. Correct placement of the electrode is determined by MRI and/or CT images. Placement is then more accurately defined by Doppler findings and recordings of electrical impulses from individual neurons [156]. Additionally, the patient's brain functions are assessed to aid in the placement of the electrode during this process. The second step in DBS surgery involves passing the "extension", an insulated wire, from the head, behind the ear, down the side of the neck, to the "Implanted Pulse Generator" (IPG). The IPG is placed subcutaneously below the clavicle. The IPG is a battery-powered neurostimulator, which sends electrical pulses to the brain. The final step of the process involves the mapping of the device. The neurosurgeon adjusts the polarity, amplitude, pulse width, and frequency, in order to optimize the efficacy of the device while reducing potential side effects. A magnet is used to adjust the parameters of the device, which is then given to the patient to allow for the device to be turned on or off by the patient (Figure 1).

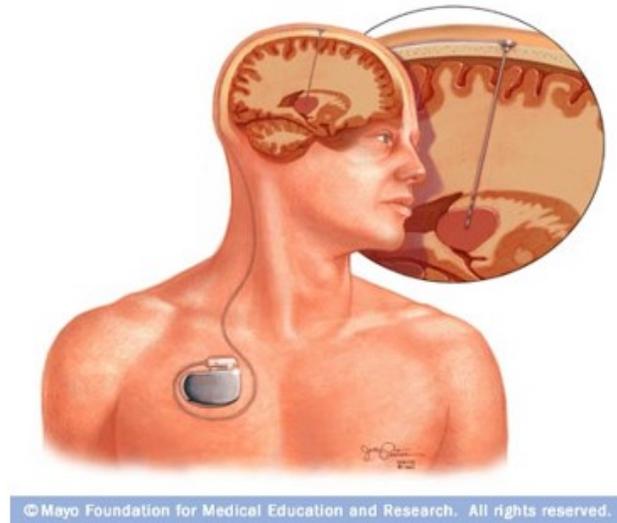


Figure 1: Deep Brain Stimulation Device.

Unilateral or bilateral stimulators are used to target electrical signals to the STN during DBS surgery. It is believed that the electrical stimulation disrupts brain signaling involved in motor and vocal symptoms associated with [157]. The nervous system operates by electrical impulses, generated by neurons, called action potential. Information is electrically encoded via the sequences of action potential. Electrical impulses travel through an axon and reach the next axon through a synapse. The electrical impulse changes to a chemical neurotransmitter pulse that travels across the junction between the neurons onto the next neuron. Once the neurotransmitter reaches the next neuron, electrical changes begin. These are called postsynaptic potentials. There are both inhibitory and excitatory neurotransmitters. An action potential is generated when the difference between the inhibitory and excitatory postsynaptic potential results in the electrical state being less negative than the threshold needed for generation of an action potential. Typically, the action potential travels away from the cell body of the neuron, a process called orthodromic conduction. Antidromic conduction occurs when the impulse travels in the opposite direction. The action potential can also travel in both directions if the axon is affected by the electrical stimulation generated by DBS [156]. The electrode placed in the brain for deep brain stimulation surgery generates a blocking or inhibiting counter-current in order to eliminate or negate the static caused by the abnormal discharges. It should be noted that new DBS technology with directional leads is currently being studied, however data for these new leads was not available at the time of this study.

Subthalamic Nucleus DBS: The subthalamic nucleus is essential to the successful function of the basal ganglia, whose role is to control background movement and initiate various movement patterns. The subthalamic nucleus is a lentiform structure and is located on the inner surface of the internal capsule. Fibers that connect to the thalamus pass through the STN. The function of the STN is to control striated muscles via input from the globus pallidus and the motor cortex. Bilateral lesions in this area result in ballism, which is a violent, uncontrolled flailing of the arms and legs. A unilateral insult to the STN would result in hemiballism of the contralateral side [158]. The subthalamic nucleus is also implicated in parkinsonian motor symptoms in nonhuman primates. Abnormal STN activity, marked by increased irregular and bursting neuronal firing patterns, is noted in primates that were injected with a neurotoxin that causes PD motor symptoms by destroying dopaminergic neurons. Preliminary studies demonstrate increased firing rates of STN neurons in advanced stage PD as compared to that of early stage PD, indicative of subthalamic involvement in Parkinson disease [159]. Additionally, there is a "potential role for the STN in the mediation of linguistic processes, presumably by way of excitatory projections to primary basal ganglia output nuclei responsible for the regulation of thalamocortical activity" [7]. However, the role of the subthalamus in the symptomatology of Parkinson disease has not yet been completely determined (Figure 2).

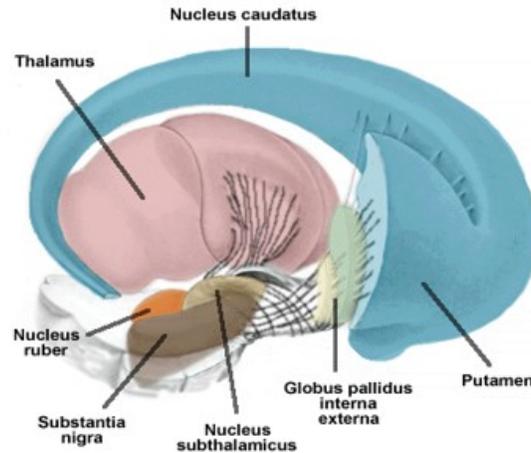


Figure 2: Subthalamic Nucleus.

DBS to the subthalamic nucleus was said to be effective, because it mimicked a lesion to the STN, which in turn inactivated it to hinder the motor symptoms of PD. The lesion was thought to inhibit the surrounding neurons via direct inhibition or activation of inhibitory presynaptic afferent terminals [160]; as cited by Carlson, et al. [161]. However, Carlson and his colleagues [161] did not find significant inhibition of the surrounding neuron of the STN. Inhibition was noted, but it was short term and did not have a lasting effect on firing rates. No difference was found between firing rate immediately after stimulation and firing rate before stimulation. Stimulation did cause a change in the firing pattern; prior to stimulation the pattern was more tonic or bursting, which changed to a random pattern following stimulation. These findings suggest that DBS serves to hinder abnormal oscillations for motor output in the basal ganglia by activating surrounding myelinated fibers. According to these authors, “activation of STN efferent and/or surrounding white matter results in a regular, high-frequency neuronal signal that normalizes pathological activity” (p. 966). It can be concluded that the effects of STN-DBS is a consequence of changes to the cortex, not at the site of the electrode, which is the STN. This is evidenced by a suppression of beta waves in the Electroencephalography (EEG) for cortical activity, which disrupts the rhythmic activity on the cortex and reduces the clinical effect of PD [13]. The effects of STN-DBS may also be attributed to an interference with neural signals, desynchronization of abnormal oscillations, inhibition, excitation, or modulation of neurotransmitter and hormonal signal. Additionally, high frequency STN stimulation resulted in increased Global Cerebral Blood Flow (gCBF) as noted using Positron Emission Tomography (PET). The increased gCBF may be due directly to the stimulation of the STN or an indirect effect on neighboring tissue. An increase in gCBF is also seen with dopaminergic medication, suggestive of similar effects of pharmacological therapy and surgical therapy on motor symptoms [162].

Effects of STN Deep Brain Stimulation on Speech and Other Non-Motor Functions

Deep brain stimulation surgery results in a reduction of motor symptoms associated with PD, a reduction of dyskinesias related to L-dopa medication, diminished “off” times, and an overall improvement in quality of life. This surgical therapy has demonstrated greater success than traditional pharmacological therapy and ablative surgery. A meta-analysis of 22 studies of STN-DBS found improvement on the Unified Parkinson’s Disease Rating Scales (UDRS) of greater than 50% and a 69% reduction of dyskinesias as cited by Narayana, et al. [6]. Additionally, reports of depression decreased and performance of activities of daily living improved following STN-DBS [163]. However, significant side effects of surgery have also been reported, which include brain hemorrhage, temporary tingling of the face or limbs, infection at the site of lesion, and reduced cognition. Additionally, speech deficits have been reported following DBS surgery. Deterioration in speech skills has been attributed to diffusion of the effects of stimulation of corticobulbar fibers of the corticonucleus. However, findings related to speech skills following surgery have been conflicting. There are studies that describe an improvement in overall speech functioning, whereas other research has found either no change in skills or an actual decline in speech skills following DBS surgery. According to Narayana and his colleagues [6], one of the most common side effects of DBS surgery is diminished speech functioning. Reports of new or worsened dysarthria range from 5% to 61% of the patients who underwent this surgery.

Voice: Hypokinetic dysarthria related to Parkinson disease is characterized by deficits in all levels of speech. Voice function is marked by reduced vocal intensity, compromised vocal quality, and diminished dynamic and pitch range. Inconsistent changes in voice function following STN-DBS have been reported. Some studies reported a benefit in vocal function, as evidenced by improved harmonics to noise ratio during conversation [164]. Furthermore, perturbation analysis of the voice demonstrated an overall improvement. Patients who had DBS surgery presented with lower jitter and shimmer and higher signal-to-noise ratios when the device was in the on-position as compared to when the device was off. This noted improvement was evident whether the patients had taken their regular dose of levodopa or not [157,165]. Furthermore, Moreau and her colleagues [68] and Gentil and her colleagues [160] found increased maximum phonation time and vocal intensity when the stimulation was set at a low frequency. This was attributed to increased coordination of respiration and phonation. However, in other studies patients did not present with improved perturbation results [166]. Overall vocal intensity for sustained phonation increased in patients one year status post-bilateral STN-DBS [167].

Respiration: The effects of Parkinson disease are also noted in the coordination of respiration and phonation and in compromised respiratory driving pressure, resulting in reduced vocal intensity. Current research on the effects of DBS on respiratory function related to speech found inconsistent results. Some patients were noted to have improved aerodynamic measures of respiratory and laryngeal control, whereas others had reduced function [168].

Resonance: Hypernasality due to velopharyngeal incompetence is another speech parameter that is affected by Parkinson disease. Studies of STN-DBS on velopharyngeal closure are limited. However, one study found a general mild increase in intraoral pressure and velopharyngeal closure during production of a non-nasal CV utterance. There was a positive correlation between low frequency stimulation and improved velopharyngeal function. Furthermore, a hemispheric effect was noted, as evidenced by greater change of intraoral pressure in right STN-DBS and greater change in velopharyngeal closure in left STN-DBS [169].

Fluency: In a study by Walker and his colleagues [170], an improvement in an acquired disfluency disorder was noted following left hemisphere DBS surgery when the device was on. When all of the results from the three tested sessions were combined, 10% of the syllables were affected when the DBS was off, whereas only 1% was affected when the DBS was on. During all three conditions tested, a significant improvement in stuttering when the DBS was on was noted. The improvement was relatively independent of the medication. The patient in this single-subject experiment presented with a greater number of blocks, as compared to repetitions and prolongations that exhibited the greatest amount of improvement with the DBS on. However, Sidtis and her colleagues [164] found little improvement with the DBS in the on position when disfluencies were measured during conversation. In contrast, Toft and Dietrichs [171] found both aggravation and reoccurrence of disfluencies marked by difficulty initiating speech, blocking, and initial phoneme repetitions in the participants of their study. New onset of stuttering and a reemergence of childhood stuttering has been reported as a result of advanced Parkinson disease. Disfluencies are marked by syllable, word, and phrase repetitions. This suggests that subcortical structures, including the subthalamic nucleus, may play a role in the rapid integration of motor commands and language skills needed for fluent speech production. However, the results of STN-DBS on fluency of speech continue to be questionable. Further research is indicated for STN-DBS to be used in the treatment of fluency disorders.

Prosody: The most prominent breakdown in speech production is evident in speech prosody [48,66]. Deficits in prosody are marked by reduced pitch and intensity variation, increased rate of speech, and aberrant pausing within utterances. Overall rhythm and timing of speech are impaired, much as seen in gait festinations. Walking and speaking deficits are due to the Parkinson patient's difficulty modulating velocity in both speech and gait. Limited improvement has been noted in prosodic skills following STN-DBS, which may be attributed to the fact that rhythm of speech production is not a function of dopaminergic structures [172,173]. In addition to the compromised prosody in speech production, patients with PD often present with an impaired ability to perceive emotional prosody in speech. Prior research has demonstrated a reduction of decoding of facial affect following STN-DBS surgery. Additionally, Bruck and her colleagues [174] identified compromised decoding of emotional prosody, which was attributed to an overall cognitive deficit, specifically in executive function. These same authors also found deterioration of emotional decoding skills following STN-DBS treatment.

Speech Intelligibility/Communicative Competence: In general, most patients report reduced communicative competence due to compromised speech intelligibility following deep brain stimulation of the subthalamic nucleus, despite reported improvement in specific speech parameters [5]. Therefore, it can be concluded that communication as a whole is influenced by many speech subsystems that need to work synergistically. However, deficits in one area of speech do not necessarily completely impede communication.

Language: The role of the subthalamic nucleus in mediation of linguistic processes is questioned via studies of language skills following deep brain stimulation. The basal ganglia has been found to play a role in the implicit and explicit development of grammar during early childhood. Additionally, it plays a role in processing of grammar through out adulthood [179]. Once again, research findings are discrepant. Diminished verbal fluency is reportedly one of the most common side effects of DBS; however, some studies were not able to replicate these findings. Verbal fluency skills were noted to be susceptible to the effects of rate of stimulation in the DBS surgery. Those patients that had low frequency stimulation presented with improved word fluency skills; however, higher stimulation resulted in either no change or a reduction in skills [166]. Furthermore, Whelan and her colleagues [7] identified improved high level linguistic skills for generation of novel responses in describing multiple definitions of words following DBS surgery. Morphosyntactic skills also improved for story generation following bilateral STN-DBS. This improvement was attributed to a restoration of equilibrium within the basal ganglia and between the connection from the basal ganglia and the frontal cortex [176].

Motor Skills Vs Speech Skills Following STN-DBS

Farrell, et al. [177] performed a perceptual analysis of speech following pallidotomy, thalamotomy, and DBS. The hypothesis was based on the observation that speech impairments due to PD were related to rigidity and akinesia. Therefore, if surgery targeted these symptoms, then speech should improve as a result of surgery. However, what was found was that there was overall no significant change in speech production. One theory for the lack of improvement was that limb and speech motor systems are different in their organization and control and may be different in neural innervations, organization, and motor planning. Neural innervations are different in that, in limb movement, corticospinal fibers are organized to provide unilateral innervations to the spinal nuclei.

However, innervations are bilateral for laryngeal and supralaryngeal movement. Furthermore, limb and speech structures are organized differently, as marked by the distinct agonist-antagonist muscle relation of the limb skeletal muscles, not seen in the speech mechanism. Another theory for the findings of this study is that speech, postural and gait impairment may be mediated by other neurotransmitter systems, in addition to dopamine. Speech is not a dopaminergic system; therefore, dopamine medication has minimal effect on speech.

Rationale for Inconsistencies in Research

Current research related to the effects of DBS on speech has led to discrepant findings, which has been attributed to various factors. Such variables include differences in methodology between studies, differences related to the disease itself, and differences in surgical features; for example, loci of electrode and amplitude and frequency of the stimulation. “When comparing studies to evaluate the effects on speech of STN-DBS in individuals with PD, the one consistent finding appears to be variability” [5]. Loci of the placement of the STN-DBS have been noted to play a role in the effects of the surgery on motor speech symptoms associated with PD. Studies have found that when the site of the STN-DBS is on the left hemisphere of the brain, there is a reduction in articulatory precision and syllable rate. However, if the DBS is in the right hemisphere, then there is an improvement or no change at all in speech function. This is said to be attributed to the speech and language dominance of the left hemisphere [6,178]. A study by Solomon and her colleagues [50] assessed the effects of GPi DBS surgery on speech in three cases of severe PD. The hypothesis was that speech should improve, based on the same reason other motor systems improve following DBS. However, the results were inconsistent. Unilateral right DBS surgery yielded improved word intelligibility and an elimination of painful facial-mandibular dystonia in one patient. Increased hypophonia was, however, noted following bilateral DBS in a second patient, and in a third patient onset of disfluencies was noted. The inconsistent findings of these three cases were attributed to the different areas of electrode placement, albeit a small difference. Speech skills are more susceptible to deterioration due to STN-DBS when the electrodes are placed medial and/or posterior to the center of the subthalamic nucleus [179,180].

The effects of DBS are task specific. As a result, it can be concluded that DBS influences motor speech production in varying ways, depending on the demands on the speech and language regions of the brain. Therefore, “efforts to understand the effects of DBS on motor speech competence must carefully consider task demands when evaluation and treatment are undertaken.” [164]. Methodology of each study must be considered carefully when comparing results of studies. Furthermore, Tripoliti and his colleagues [180] found that variables related to the PD served as predictors for speech success following STN-DBS. Patients with more significant symptoms on medication demonstrated a greater deterioration of speech symptoms.

Factors related to the DBS stimulation may explain the variability in findings related to the effects of speech following surgery. In a study by Tornqvist, et al. [181], DBS was found to impair the intelligibility of speech in some patients, which was said to be related to the settings of the electrical parameters. High amplitude and high frequency resulted in a greater risk of impaired speech following DBS, marked by respiratory over drive and hyperadduction of the vocal folds. Low-frequency stimulation is said to improve speech outcomes following DBS [168,180].

The current surgical approaches for the treatment of Parkinson disease symptoms have demonstrated their ability to alleviate motor symptoms; however, the effects on speech symptoms remain ambivalent. “Improvement in motor function and mobility following STN stimulation may not be sufficient alone to improve the overall disability of a patient in whom cognitive decline and speech problems are present preoperatively” [167]. Studies of vocal function following deep brain stimulation are limited and findings within the current studies have been inconsistent. The explanation for the inconsistent findings of the research thus far continues to be unknown. Some researchers hypothesize that variations may be due to the speech task or location of the device. Currently, the PD patient and the SLP cannot be certain of speech effects following this type of surgery and, therefore, consent for surgery is based on uncertainties. Participants in Ahleberg, Laakso, and Hartelius’ [5] study reported a paucity of information regarding possible side effects. It is our job as speech-language pathologists to counsel these patients on possible effects on specific speech parameters and overall communicative function.

Micro-lesion Effect of DBS

Deep Brain Stimulation (DBS) surgery has been established as a treatment for the symptomatology of Parkinson Disease (PD) when pharmacological treatment is no longer effective. DBS surgery involves the implantation of a microelectrode and a macrostimulation electrode to facilitate adequate DBS placement in the targeted area. Electrical currents are then sent to the electrodes from an external generator, which in turn stimulate the surrounding tissue and result in relief of PD symptoms. However, it has been found that implanted patients demonstrate an improvement in motor and non-motor function prior to the onset of electrical stimulation. In order to have a better understanding of DBS surgery, it is paramount to distinguish the effects of surgery itself from that produced by the stimulation of the subthalamic nucleus.

The Microlesion Effect (MLE) is evident when implantation of the electrode for deep brain stimulation produces a transient improvement in clinical function prior to initiation of the electrical stimulation [182-184]. The MLE is present when the DBS electrode is placed either in the Subthalamic Nucleus (STN), the internal segment of the Globus Pallidus (GPi) [185] or the Ventralis Intermedius Nucleus (VIM) during deep brain stimulation surgery [186]. Greater motor improvement is noted when the electrode is placed in the STN as compared to the GPi. It is hypothesized that the STN is more susceptible to the MLE because it is smaller in size than the GPi [187,188].

The MLE occurs as a result of several factors [189]. It is theorized that there is a disruption of cells and/or fibers that neighbor the surgical tracks that affect the subthalamic nucleus [187,190] and thereby reduces the abnormal basal ganglia function that is evident with Parkinson disease [182]. This microlesion effect mimics the ablative lesion surgeries, such as pallidotomies and subthalamotomies with the exception that these ablative surgeries cannot be reversed and the MLE is instead transient [182]. It is further postulated that in addition to the disruption of brain tissue, there is edema of the brain matter that surrounds the electrode and causes the MLE [182,189,191]. Edema near the electrode placement was found in 92% of implanted patients and had a positive correlation with improvement in function; as the edema resolved, clinical function declined [189]. Additionally, Holiga and colleagues [182] found that the brainstem serves as a “compensatory hub” to support the affected motor networks and maintains baseline motor function during the microlesion effect phase. The brainstem does this by increasing connectivity to the cerebellum. These findings support the role of the brainstem and cerebellum in PD and STN DBS. In addition, the MLE may be due to a biochemical response [188]. There is leakage of neurotransmitters that influence the surrounding unaffected neurons [182,189]. The neurotransmitters involved are the Gama-Aminobutyric Acid (GABA) that serves as an inhibitory substance and glutamate that serves as an excitatory mediator [189]. Furthermore, animal studies have demonstrated an increase in the neurotransmitter levels of adenosine and glutamate following electrode implantation [188].

The trajectory of the electrode placement may further play a role in the MLE, as there are tissue changes that occur through the surgical trajectory [190]. In STN DBS surgery, the surgical trajectory intersects the thalamus unilaterally and/or bilaterally. Additionally, most patients have surgical intersection of the lateral ventricles and the caudate [192]. Although trajectories used to reach the STN varies from surgeon to surgeon, most surgical tracks have lateral and antero-posterior cortical entry angles. Prior to reaching the STN, the electrode travels through the dorsolateral prefrontal cortex, thalamus pars reticularis or ventral anterior, through the white matter of the thalamic fasciculus, the anterior limb of the internal capsule, the zone incerta, and the lenticular fasciculus [193]. The surgical trajectory is found to cause a collision between the reciprocal connections between the STN and GPi and the ansa lenticularis [188]. Pourfar and colleagues [194] found that the number of electrode trajectories correlated with the network effects noted in PET findings, suggestive of the role of procedural variations on the MLE.

In addition to clinical findings, neuroimaging studies demonstrate the presence of a MLE following surgery. PET studies have identified that the regional metabolism of the affected areas, such as the STN, globus pallidus, and ventral thalamus, are altered during surgery [194,195]. The regions that demonstrated greater metabolic activity were those associated with STN activity [194]. Following electrode placement, there is reduced metabolism in the ventral thalamus and increased metabolism in the sensorimotor cortex and cerebellum, as evidenced by PET studies [183]. Furthermore, fMRI studies have demonstrated generally lowered activation in the cerebral motor network during simple finger movement following the placement of the electrode and prior to stimulation [189].

The microlesion effect has been identified in approximately 21% of patients with Parkinson disease who have been implanted [195]. In contrast, Sitburana, Almaguer, and Ondo [186] found that 75% of their patients experienced the MLE effect. The MLE is at its peak at 38.5 hours following surgery when observed within the range of 24 to 72 hours post insertion of the electrode [185]. The benefits from this effect diminish with time due to healing of the damaged brain tissue cause by the electrode placement [188]. The MLE has been found to last from one to three weeks, which may be indicative of widespread depolarization and synaptic modulation within the basal ganglia, in addition to the acute effects of microhemorrhage and edema that is expected to last only a few days [185]. Jech and colleagues [189] found the improvements in function associated with MLE disappeared one month post- surgery. Mann and colleagues [187], however, found the MLE lasted 4 to 6 months, thereby noting the therapeutic benefit of the MLE. The variation found in the duration of the MLE may be attributed to differing surgical techniques and unique patient situations [184]. The surgical technique determines the size of the microlesion and the number of microelectrodes that pass through the targeted region that may affect the amount of improvement received from the MLE [189].

Patient specific factors play a role on the level of improvement received from MLE. Younger patients who had a better response to levodopa therapy and had more severe dyskinesias demonstrated greater improvement in function from electrode placement [188]. Morishita and colleagues [184] hypothesized that a long- lasting effect of the MLE may be secondary to a reorganization of the neuronal circuitry of the basal ganglia from chronic DBS. DBS is said to cause neuroplasticity as evidenced from post- mortem studies.

The microlesion effect has been considered as a predictor for the long-term benefit of deep brain stimulation in PD patients [185,188,190]. There is a noted correlation between the amount of MLE and the motor benefits of DBS; however, a lack of a MLE does not hinder the benefits of DBS surgery on motor skills [185]. Tykocki and colleagues [188] found that patients who demonstrated the most benefit from DBS surgery had at least a 40% degree of improvement in motor function with the MLE alone. In addition to the magnitude of the MLE, there is a positive correlation between duration of MLE and degree of improvement from DBS surgery [188]. In contrast, Jech and colleagues [189] found no impact on long-term response to STN DBS. Furthermore, no correlation between MLE and long-term presence of activation tremor was found [186].

Microlesion Effect in Motor Deficits: The microlesion effect has been noted to affect all of the cardinal features of PD, including tremor, rigidity, and bradykinesia [187,190], as noted by a reduction in scores of the Unified Parkinson Disease Rating Scale (UPDRS) [182]. The UPDRS is used to determine the effects of the MLE on motor skills. Jech and colleagues [189] found a 24% reduction in UPDRS scores one day post-operative and a 33% reduction three days post-operative. Greater improvement was noted in rigidity and akinesia; however, improvement was also noted in gait and postural stability. An improvement in the bradykinesia associated with PD was also noted, as evidenced by an increase of speed in proximal and distal movements. Proximal arm movements are slightly faster than distal movements following the MLE [191]. In addition to the noted improvement within the cardinal features, there is a MLE in off-period dystonia [191,196] that is evident 6 months following surgery [190]. The MLE has also been noted in unilateral DBS surgery for essential tremor immediately following surgery and 6 months post surgery [184,186].

Microlesion Effects in Non-Motor Deficits: Both the motor and nonmotor deficits associated with PD are affected by the MLE [183]. For example, the limbic system is influenced by this effect, such that acute psychosis has been reported following the implantation of the stimulator but prior to its activation [195]. Aiello and her colleagues [195] found that the microlesion effect also extends to emotion recognition in facial expressions. Patients with PD historically have difficulty discriminating and recognizing facial expression, most evident with the recognition of disgust. Following DBS surgery but prior to turning the stimulation on, the participating patients were found to recover their ability to recognize disgust; however, recognition of sadness worsened. Following 2 to 6 months of stimulation, poor recognition of disgust was once again prominent, consistent with baseline skills prior to surgery. Furthermore, a case report by Rozanski and colleagues [196] identified acute paranoid psychosis as a MLE. It was hypothesized that the acute psychosis was due to involvement of dopaminergic mesolimbic fiber bundles adjacent to the GPi, which was affected by the electrode placement and not the DBS itself. This is consistent with the finding of excessive dopamine in the mesolimbic pathway in schizophrenia.

A cognitive microlesion effect has also been identified in PD patients following STN-DBS. A decline in verbal fluency and frontal executive function has been associated with a MLE [197,198] of DBS in the STN and globus pallidus [193]. The decline in fluency naming skills is transient, and skills improve within 6 months from onset [198]. The decline in phonemic verbal fluency from the MLE may be predictive of long-term phonemic verbal fluency deficits [197]. It is hypothesized that the MLE is noted more in phonemic verbal fluency in comparison to semantic verbal fluency, because word retrieval skills that are constrained by phonology are supported by the frontal regions of the cortex and are affected by the trajectory of the electrodes that pass through the dorsal lateral prefrontal cortex [197]. However, Le Goff and colleagues [193] found no correlation between lead trajectories and phonemic verbal fluency decline. They did find a positive correlation between semantic verbal fluency and electrode trajectory that was to the left with a more anterior cortical entry point. Less of semantic verbal fluency decline was evident when the trajectory passes through the left thalamus. Witt and colleagues [199] found that there was a greater risk for cognitive decline when the electrode passed through the head of the caudate nucleus. The number of microelectrode passes, however, does not affect verbal fluency deficits noted from the MLE [193,200]. A decline in function is not only related to the neurophysiological and biochemical changes associated with electrode placement as discussed above, it can also be associated with a reduction in dopaminergic treatment. Verbal fluency skills have been susceptible to dopamine pharmacological therapy, such that an improvement is noted with this medication. As a result it can be assumed that a decline or elimination of dopamine therapy would result in a decline in fluency naming skills [198]. The microlesion effect demonstrates that DBS surgery provides benefits for patients with PD that is independent of stimulation [194]. The MLE as it can serve to facilitate adequate DBS electrode placement and improve on timing and amount of electrode stimulation required to optimize the benefits of the surgery. As an improvement is noted with the simple placement of the probe, the MLE can be indicative of adequate placement of the electrode during surgery [182,190]. The MLE may influence the decisions on the final placement of the DBS electrode [184]. The MLE can also provide greater understanding of the pathophysiological effects of PD.

Methods

Participants

Five English-speaking patients were recruited from the Northwell Health's Movement Disorders Center of the Neuroscience Institute. Patients who were previously scheduled for subthalamic deep brain stimulation surgery were asked to participate in this study during their pre-operative work-up with the treating neurologist. All participants had a medical diagnosis of idiopathic Parkinson Disease (PD) and underwent Subthalamic Nucleus Deep Brain Stimulation Surgery (STN-DBS) for the treatment of the presenting PD. There were four men and one woman who participated. They represented diverse ethnicities and varying levels of socio-economic status. There were two African American patients and three Caucasians patients. The age of the patients ranged from 41 years to 75 years and averaged 54.4 years. The patients fell within the specifications of the Modified Hoehn and Yahr's Stage 3 of PD (see (Table 1) for demographics). These specifications include worsening bilateral features of PD, along with balance difficulties; however, patients are still able to function independently [31]. As PD progresses at varying rates, the time of onset was not a critical factor; instead uniformity was based on placement of PD stages on the Modified Hoehn and Yahr [31] rating scale. These patients were on a consistent regimen of pharmacological treatment, including L-Dopa, Dopa-agonists, MAO-inhibitors, or any combination of the three medications, for at least three months. The patients were assessed in the "on-phase", between one and three hours following PO intake of the prescribed medication for the pre- and post-operative testing. However, during the intra-operative testing the patients were not under the effects of any medication. Parkinson medications were discontinued under the direction of the neurosurgeon at least 12 hours prior to the surgery. The participants had no other Neurological medical history nor had they participated in prior speech treatment.

Variables Participants (n=5)
Gender Male 4 Female 1
Age (in years) Mean 54.4 Range 41-75
Race Non-Hispanic White 3 African American 2
Site of DBS Unilateral STN(left side) 3 Bilateral STN 2
Modified Hoehn & Yahr Staging [31] (range 1-5) 3

Table 1: Demographic Information for Study Participants.

Procedure

Speech and language testing for this study was completed in four visits during a course of two to four years. The first visit was performed following the participant's pre-operative appointment with the neurologist. The second visit was conducted intra-operatively. The third visit took place three to six months after surgery and the final visit took place two to four years following the pre-operative appointment.

During the pre- and two post-operative testing sessions, an acoustic analysis was performed using Visi-Pitch IV Model 3950 from PENTAX. Acoustic analysis yields objective measures in order to quantify voice patterns and assist in determining a vocal pathology. The participants were asked to don a headset with an attached microphone to control for microphone-to-mouth distance. They were then asked to sustain phonation in their natural pitch, in their highest pitch, and lastly in their lowest pitch. The voice sample was audio recorded using a SONY® digital voice recorder. The data was then converted to sound waves with the SONY Sound Forge Audio Studio and then uploaded onto the Visi-Pitch IV program for analysis. This procedure was followed for testing of all of the participants with the exception of one time during the second post-operative assessment of one of the participants when the voice sample was audio recorded using the application TapeACall®; all other procedures as stated above were followed. An analysis of fundamental frequency, pitch range, perturbation, and vocal intensity was completed using the Visi-Pitch IV program. Each task was repeated three times and an average of the scores was obtained.

The participants were also asked to read the "Rainbow Passage" that consists of a total of one hundred words and is phonetically balanced. Once again the data was audio recorded, converted into sound waves, and analyzed using the Visi-Pitch IV program. This speech sample yielded acoustic measures for fundamental frequency and intensity for this task.

Language skills related to fluency naming for semantic and lexical categories were also examined. This task required the participants to name as many animals as they could think of in one minute and then as many things that begin with the letter "r" in one minute. Counts were audio recorded and then tallied. Any non-words that were produced were not included in the total. Further, both a lenient count (including proper nouns) and a strict count (not including them) were examined. Lastly, this study analyzed the psychosocial impact of the voice disorder pre- and post-operatively via the Voice Handicap Index (VHI), a patient questionnaire for self-analysis of vocal function. The VHI is a 5-point scale developed to quantify the effects of voice disorders within 3 subscales; the functional subscale investigates the impact on activities of daily living, the emotional scale assesses the affective response to the voice disorder, and the physical subscale investigates the self-perceived vocal characteristics [103]. The participants were asked to complete the questionnaire and the scores were then obtained.

The above stated tasks were completed pre-operatively and during the two post-operative assessments. Pre-operative testing is imperative to account for the effects of micro-lesions associated with multiple microelectrode insertions and DBS lead placement. Post-surgical testing was completed with the device on and medications "on-phase," as this study did not investigate the effects of medication but instead investigated speech function that was exemplary of the participants' typical daily status. It should be noted that variation in medication from the time of pre-operative testing and post-operative testing represents a delimitation of the study.

During the intraoperative testing the fluency naming task was performed to provide information regarding the role of the subthalamic nucleus on this language process and the effects of the micro-lesion from the lead placement. The patient's brain functions were assessed by the surgeon to aid in the placement of the electrode during the operative procedure. The fluency naming task performed for this study was part of this evaluation processes. This task was completed 3 times throughout the operation. The first time was prior to the surgeon inserting the lead into the brain. The second time the fluency naming test was administered was with the lead placed in the subthalamic nucleus without the stimulation on. The final time the task was completed was with the macro-lead in place and the DBS on. Once again, the participants' responses were audio recorded and then tallied. The same restrictions regarding non-words were applied during this set of testing. Two participants were seen twice intra-operatively as placement of the leads in the left and right hemispheres of the brain where done during two separate surgeries.

Results

Acoustic

Analysis

Maximum Phonation Time: (Figure 3) contains the graphical interpretation of the average maximum phonation time in seconds of the participants pre-operatively and post operatively, both 3-6 months and 2-4 years after the DBS surgery. Findings demonstrated a reduction of maximum phonation time for all participants in the initial post-operative testing as compared to the pre-operative scores. The participant who presented with highest baseline maximum phonation time of 17 seconds demonstrated the greatest amount of decrease, a difference of 7 seconds as compared to an average difference of 2 seconds from the other participants, following the surgery. The participants all increased their maximum phonation times given a greater amount of time after the surgery, with the exception of one. Furthermore, three of those participants reached or exceeded their baseline scores (Table 2).

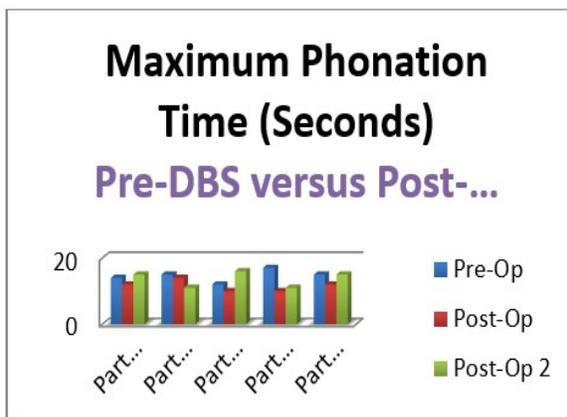


Figure 3: Maximum Phonation Time Results for Pre- and Post-Operative Testing.

Participant	Pre-Op	Post-Op	Post-Post-OP
1	14	12	15
2	15	14	11
3	12	10	16
4	17	10	11
5	15	12	15

Table 2: Maximum Phonation Time (seconds).

Fundamental Frequency: During sustained phonation, 4 out of the 5 participants demonstrated reduced fundamental frequency following the surgery, as noted in (Figure 4). The only participant that did not demonstrate a reduction of fundamental frequency had an increase in results of one hertz. The long-term post-operative testing yielded scores that demonstrated an increase on the average fundamental frequency compared to the short-term post-operative testing of each participant except one. However, 3 of those 4 participants never exceeded their fundamental frequency at baseline. (Figure 5) is a graphical representation of the fundamental frequency for a reading task of the participants pre-operatively and post-operatively, both 3-6 months and 2-4 years after the DBS surgery. These scores demonstrate greater inconsistency between the participants relative to fundamental frequency for sustained phonation. Three out of the 5 participants had a lower fundamental frequency when comparing short-term post-operative testing to baseline results. However, most of the participants (4 out of 5) had increased fundamental frequency following an extended amount of time after the surgery as compared to 3 to 6 months after surgery, but only two exceeded their baseline results (Table 3,4).

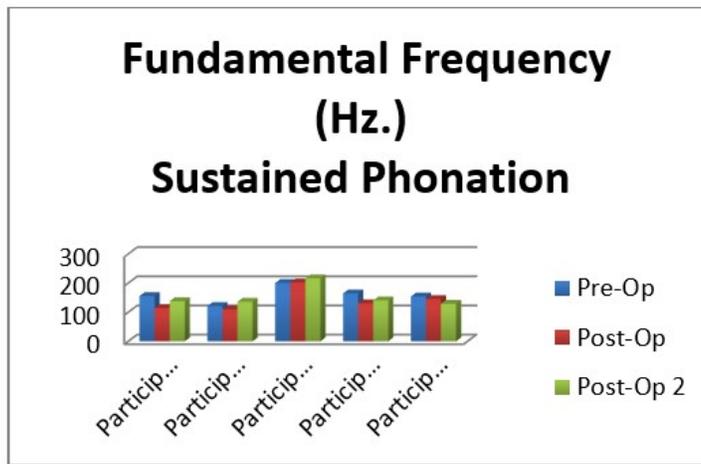


Figure 4: Fundamental Frequency for Sustained Phonation for Pre- and Post-Operative Testing.

Participants	Pre-Op	Post-Op	Post-Post-Op
1	155.44	114.16	137.78
2	121.23	109.41	136.03
3	200.42	201.93	216.18
4	164.28	130.47	140.26
5	153.97	144.93	128.7

Table 3: Fundamental Frequency for Sustained Phonation (Hz.).

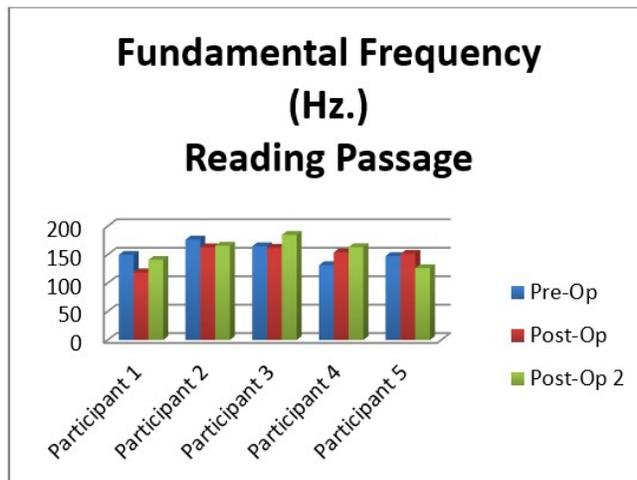


Figure 5: Fundamental Frequency for Reading Passage for Pre- and Post-Operative Testing.

Patient	Pre-Op	Post-Op	Post-Post-Op
1	149.67	118.7	140.55
2	176.32	162.64	165.56
3	164.68	161.96	184.5
4	131.36	153.81	162.96
5	147.52	151.08	126.26

Table 4: Fundamental Frequency for Reading Passage (Hz.).

Vocal Intensity: (Figure 6) contains the graphical representation of the average vocal intensity in Decibels (dB) of sustained phonation tasks pre-operatively, 3-6 months post-operatively, and 2-4 years post-operatively. Results yielded increased intensity in 4 out of the 5 participants when comparing initial post-operative results to baseline results. The one participant that did not demonstrate an increase in vocal intensity had a reduction of intensity of .72 dB. Most of the participants' vocal intensity, with the exception of one, was less than the initial post-operative testing when assessed again 2-4 years later. Three of those 4 participants had a lower vocal intensity 2-4 years later as compared to their initial baseline scores. The one participant that did not have a lower vocal intensity demonstrated a difference of 1 dB from the baseline results.

Contrary to the results of vocal intensity for sustained phonation tasks, all but one of the participants had lower vocal intensity scores during the post-operative testing as compared to baseline during paragraph reading (Figure 7). When comparing initial post-operative results to delayed post-operative results, it is noted that 4 out of the 5 participants had reduced vocal intensity during the delayed post-operative testing. One of the 5 participants demonstrated vocal intensity that was higher than baseline when comparing delayed post-operative findings to baseline findings (Table 5,6).

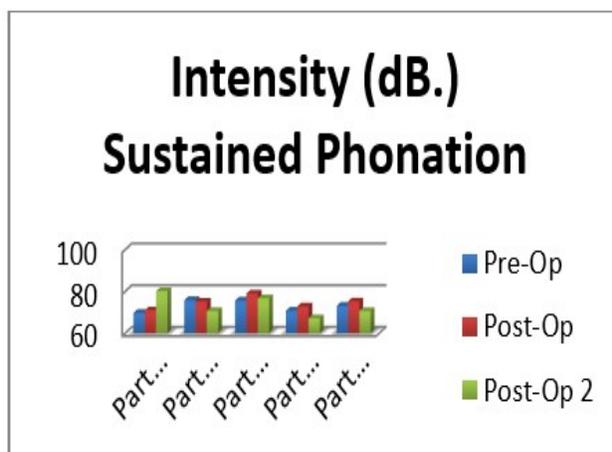


Figure 6: Vocal Intensity for sustained phonation for pre- and post-operative testing.

Participant	Pre-Op	Post-Op	Post-Post-Op
1	69.84	71.01	80.22
2	75.93	75.21	70.74
3	75.74	79.13	76.74
4	70.86	72.9	67.25
5	73.18	75.28	70.73

Table 5: Intensity for Sustained Phonation (dB.).

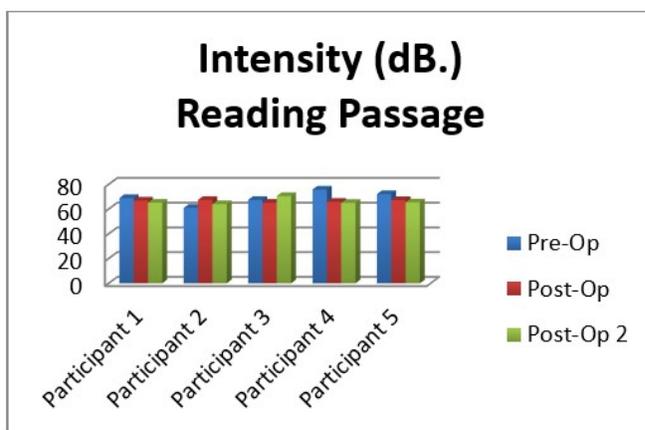


Figure 7: Vocal Intensity for reading for pre- and post-operative testing

Participants	Pre-Op	Post-Op	Post-Post-Op
1	68.91	66.91	65.2
2	61.01	67.47	63.97
3	67.42	65.16	70.57
4	75.83	65.92	65.02
5	72.1	67.28	65.43

Table 6: Intensity for Reading Passage (dB.).

Perturbation: Frequency perturbation, also known as jitter, is the variability in fundamental frequency from cycle to cycle. (Figure 8) is a graphical representation of the average jitter found during sustained phonation tasks during pre-operative testing and both post-operative testings. Most of the participants (4 out of 5) demonstrated a decrease in jitter when comparing initial post-operative testing with baseline testing. Of those four participants, all jitter results were noted to go up during the 2-4 year post-operative testing; however, only two exceeded the baseline scores (Table 7).

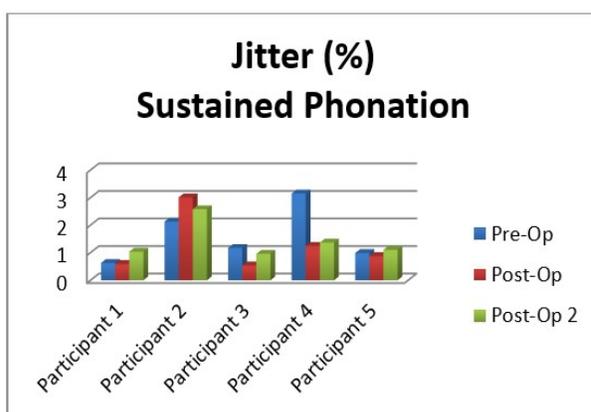


Figure 8: Jitter for sustained phonation.

Participants	Pre-Op	Post-Op	Post-Post-Op
1	0.63	0.59	1.04
2	2.13	3.01	2.58
3	1.17	0.54	0.96
4	3.15	1.25	1.37
5	0.99	0.88	1.1

Table 7: Jitter for Sustained Phonation (%).

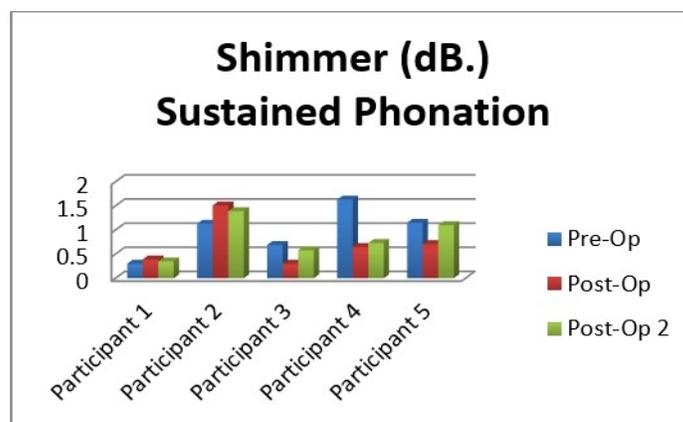


Figure 9: Shimmer for sustained phonation.

Participants	Pre-Op	Post-Op	Post-Post-Op
1			
2	1.13	1.51	1.39
3	0.69	0.3	0.58
4	1.63	0.65	0.73
5	1.15	0.71	1.1

Table 8: Shimmer for Sustained Phonation (dB.).

Phonation Range: (Figure 10) contains graphical representations of the participants' phonational range. The scores demonstrate the difference between the average highest pitch (frequency) obtained during sustained phonation to that of the average lowest pitch obtained. All participants demonstrated reduced phonation range when comparing initial post-operative testing to baseline testing. However, all of the participants were noted to have increased range during the delayed post-operative testing. Two of the participants exceeded their baseline scores during the delayed post-operative testing (Table 9).

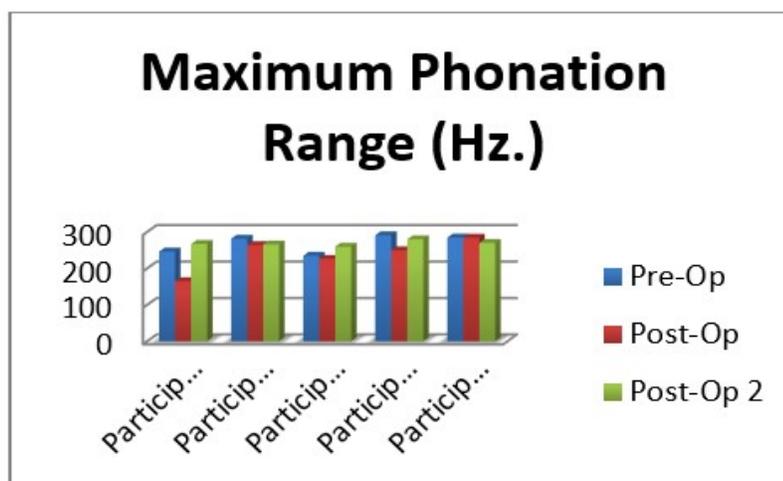


Figure 10: Phonation range - Difference between highest and lowest pitch during sustained phonation.

Participant	Pre-Op	Post-Op	Post-Post-Op
1			
2	281.4	264.13	265.32
3	234.79	226.25	259.59
4	290.92	249.61	279.92
5	284.54	284.29	269.99

Table 9: Maximum Phonation Range (Hz.).

Voice Handicap Index: The Voice Handicap Index (VHI) is a subjective patient questionnaire for self-analysis of vocal function and its psychosocial effects. A higher number denotes perception of increased deficits. Pre-operative results demonstrate a range of self-perceived deficits from mild to severe within the participants. However, following 2-4 years post-operatively the range of self-perceived deficits was from moderate to severe. All of the participants reported an increase in handicap in vocal function when comparing baseline scores to the delayed post-operative scores. Comparison of 3-6 month post-operative scores and 2-4 year post-operative scores demonstrates a decrease in self-perceived deficits in all of the participants except one (Figure 11). Greater variability was noted when comparing baseline scores to initial post-operative scores; 3 out of 5 participants reported a reduction in self-perceived deficits (Table 10).

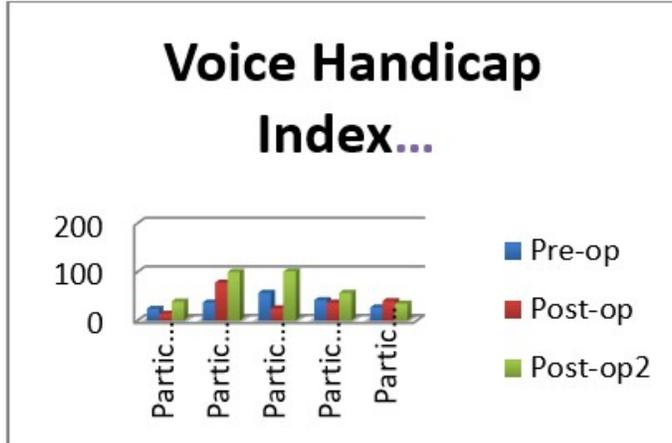


Figure 11: Voice Handicap Index.

Participants	Pre-op	Post-op	Difference	Post-op 2	Difference
1	24 (Mild)	14 (Mild)	Less handicap	39 (Moderate)	More
2	37 (Mild)	78 (Severe)	More handicap	100 (Severe)	More
3	57 (Severe)	25 (Mild)	Less handicap	101 (Severe)	More
4	42 (Moderate)	37 (Moderate)	Less handicap	57 (Moderate)	Less
5	27 (Mild)	40 (Moderate)	More handicap	35 (Moderate)	Less

Table 10: Voice Handicap Index (VHI).

Fluency Naming

(Figure 12) represents lexical naming skills for fluency naming tasks pre-operatively, intra-operatively and short term and long term post-operatively of left sided DBS surgery. Intra-operative testing included assessment of skills prior to insertion of the DBS probe, following the insertion of the probe sans stimulation, and following insertion of the probe with stimulation. Comparison of lexical fluency naming skills before the surgery and shortly after the surgery yielded an increase in skills following the surgery for all participants except one. However, all of the participants were noted to have a reduction in skills after 2-4 years post-surgery in comparison to short-term post-surgery findings. Despite a reduction in skills during this time, 3 of the 5 participants' lexical fluency naming skills were higher than what was found at baseline. Intra-operative findings represent skills sans medication. Furthermore, pre-inserted findings represent skills that are absent of the influence of medication or stimulation from the surgery. All of the participants demonstrated a reduction of skills from baseline to the pre-insertion testing. For 3 out of the 5 participants, lexical fluency naming skills continued to decline once the DBS probe was inserted. However, all 3 in this group demonstrated an increase in skills once the DBS was turned on. Despite this increase, none of those participants exceeded baseline lexical fluency naming skills. When comparing lexical fluency naming skills intra-operatively with the DBS in place and on without medication to 3-6 months after the surgery with DBS in place and on and medicated, all of the participants showed an increase in skills (Table 11).

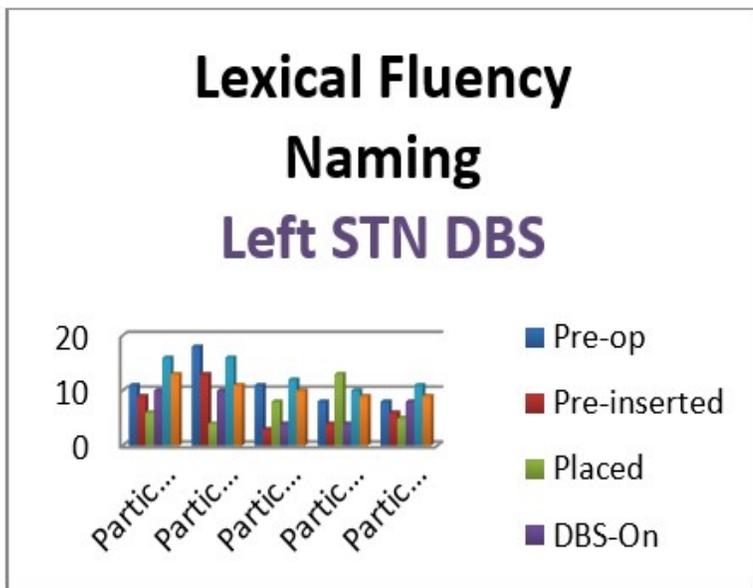


Figure 12: Lexical fluency naming for left STN DBS.

23Participants	Pre-op	Pre-insert	Placed	DBS-On	Post-op	Post-op 2
1	11	9	6	10	16	13
2	18	13	4	10	16	11
3	11	3	8	4	12	10
4	8	4	13	4	10	9
5	8	6	5	8	11	9

Table 11: Fluency naming: Lexical L STN DBS.

Fluency naming skills were also assessed given semantic categories. The findings of this testing is noted in (Figure 13). Similar to the lexical naming assessment, all of the participants except one demonstrated an increase in skills when comparing pre- and short-term post-operative results. Also consistent with the lexical findings, all of the participants' skills were noted to decrease following the greater lapse of time after surgery. Despite the reduction in skills, 3 out of the 5 participants' semantic naming skills exceeded their baseline results. However, all participants demonstrated a decrease in function intra-operatively as compared to pre-operative and post-operative findings. All of the participants demonstrated a reduction of skills from baseline to the pre-insertion testing with the exception of one. When comparing pre-insertion skills to insertion of DBS sans device being on, 3 out of the 5 participants demonstrated a decline in skills. Once the DBS was turned on, 4 out of the 5 participants either stayed the same or continued to decline, which differs from the lexical naming findings. However, as was noted with the lexical fluency naming assessment, when comparing skills intra-operatively with the DBS in place and on to 3-6 months after the surgery with DBS in place, on and medicated, all of the participants showed an increase in skills (Table 12).

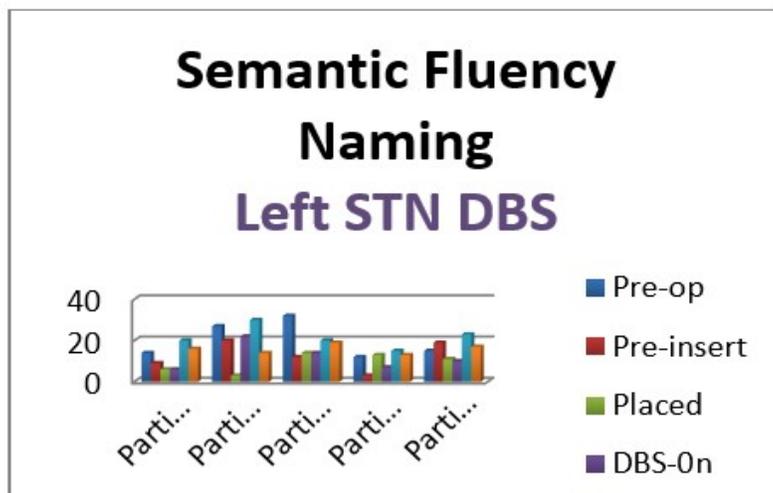


Figure 13: Semantic fluency naming for left STN DBS.

Participants	Pre-op	Pre-insert	Placed	DBS-On	Post-op	Post-op 2
1	14	9	6	6	20	16
2	27	20	3	22	30	14
3	32	12	1	14	20	19
4	12	3	13	7	15	13
5	15	19	11	10	23	17

Table 12: Fluency naming: Semantic L STN DBS.

Two of the participants were assessed during DBS surgery on the right and left side of the brain. (Figure 14) is a graphical representation of the comparison of lexical naming scores presented with left- sided DBS and right-sided DBS surgery. Participant 1 demonstrated a reduction in skills when the left DBS was in place and on during the surgery as compared to no change with placement on the right side. This same participant demonstrated an increase in skills that surpassed baseline skills when the DBS was turned on during right sided intra-operative testing that was not evident with left sided placement. Participant 3 demonstrated skills that equaled baseline skills on the right side but not the left side.

As noted in (Figure 15), semantic naming skills were also assessed during left and right-sided placement of the DBS. Both participants' scores reflected a decrease in skills from baseline to pre-insertion bilaterally. When comparing pre-insertion findings to that of when the DBS probe was placed, there was an increase in scores and then a greater increase when the DBS was turned on for both participants during right sided surgery; this was not evident during left sided surgery when only one of the participants demonstrated a consistent increase in skills (Table 13,14).

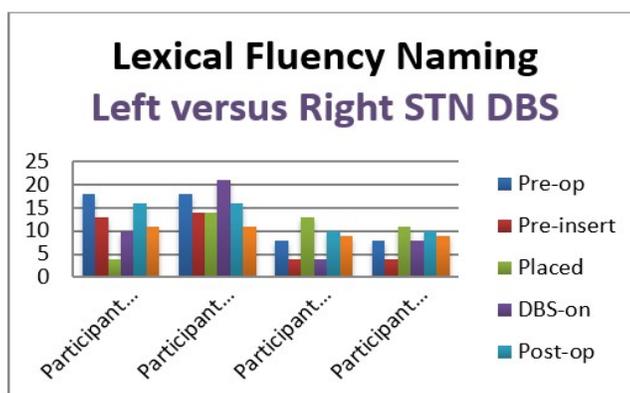


Figure 14: Lexical fluency naming for left and right STN DBS.

Participants	Pre-op	Pre-insert	Placed	DBS-On	Post-op	Post-op 2
1 left	18	13	4	10	16	11
1 right	18	14	1	21	16	11
3 left	8	4	13	4	10	9
3 right	8	4	11	8	10	9

Table 13: Fluency Naming: Lexical L STN DBS versus R STN DBS.

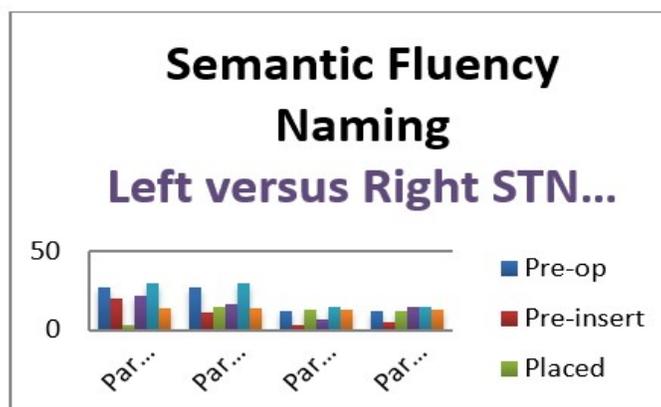


Figure 15: Semantic fluency naming for left and right STN DBS.

Participants	Pre-op	Pre-insert	Placed	DBS-On	Post-op	Post-op 2
1 left	27	20	3	22	30	14
1right	27	11	15	16	30	14
3 left	12	3	13	7	15	13
3 right	12	5	12	15	15	13

Table 14: Fluency Naming: Semantic L STN DBS versus R STN DBS.

Discussion

Summary

The intent of this study was to determine the effects of deep brain stimulation in the subthalamic nucleus on vocal function and language skills, specifically regarding fluency naming tasks, in patients with idiopathic Parkinson disease. Vocal function was assessed via an acoustic analysis of voice and speech samples. Self-perception of vocal function was also evaluated during this study. The present study aimed to examine severity of deficits prior to STN-DBS surgery and improvement of skills post-surgery. Additionally, this study allows for examination of prognosis of speech improvement following 2-4 years post-surgery. This study also assesses for the presence of the Microlesion Effect (MLE) on language skills for semantic and lexical naming tasks.

The MLE is a transient improvement in clinical function as a result of the implantation of the electrode prior to initiation of the stimulation [182,183,184]. Sitburana and colleagues [186] found that 75% of their patients experienced the microlesion effect. The MLE results in benefits to tremor, rigidity, and bradykinesia [187,190]. In contrast to the benefits noted on motor function, prior research has found a decline in verbal naming skills as a result of the microlesion [197,198]. Similar to those findings, 60% of the participants in this study did not present with a positive MLE effect; instead a decline was noted for both lexical and semantic fluency naming skills in three of the five participants. Of those participants that demonstrated a decline in function, all of them improved once the stimulation was on when testing for lexical fluency naming. In contrast, only one of the participants demonstrated improvement in semantic naming skills with the stimulation. It can be suggested as a result of these findings that lexical fluency naming skills, and not semantic naming skills, may be susceptible to the benefits of DBS stimulation alone sans medication.

Borden and colleagues [197] found a greater MLE in phonemic verbal fluency in comparison to semantic verbal fluency, which was associated with the trajectory of the electrode placement. In this study, a greater decline in fluency naming was noted for semantic naming tasks at an average loss of 9 words per minute as compared to a 4 words per minute loss for the lexical naming task. A decline in function cannot only be associated with surgical trajectory but it may also be attributed to a decline in dopamine pharmacological therapy. Because verbal fluency skills have been susceptible to dopamine therapy, a decline in this medication may in turn result in a decline in function [198].

A decline in fluency naming skills in the present study was noted when comparing pre-operative testing to intra-operative testing prior to insertion of the electrode, which may be associated to the absence of dopaminergic therapy as medication was suspended 24 hours prior to the surgery. However, the decline in function cannot be completely attributed to the lack of medication as fluency naming skills further declined in most of the participants once the electrode was placed, demonstrating a negative effect of electrode placement beyond that of lack of medication alone. The benefit of medication can be further evidenced as all of the participants demonstrated improved lexical and semantic naming skills during post-operative testing when the patients received the benefit of both stimulation and medication, as compared to intra-operatively when the electrode was in place and turned on.

Loci of the placement of the DBS electrode has also been associated with discrepancy in the findings of the effects of DBS on language skills, where placement in the left hemisphere of the brain resulted in greater deficits in function as compared to right hemisphere placement. This has been associated with speech and language dominance of the left hemisphere of the brain [6,178]. Findings of the present study is consistent with the above- stated findings as evidenced by a decline in lexical fluency naming skills with left hemisphere placement, which was not evident with right hemisphere placement, as was noted when the DBS was placed and turned on intra-operatively. Furthermore, lexical fluency naming skills either equaled or surpassed baseline function when the DBS was turned on during right intra-operative testing that was not evident with left hemisphere placement. There was greater inconsistency noted when comparing left and right electrode placement for semantic fluency naming skills, as compared to lexical fluency naming.

The MLE may play a role in predicting the long-term benefits of DBS [185,188,190]. As most of the participants in the present study demonstrated a negative effect from the microlesion, the MLE cannot serve as a predictor in the long-term benefit of DBS on language function. Of the participants in this study that demonstrated a decline in fluency naming skills, two demonstrated improved lexical and semantic fluency naming skills when comparing pre-operative findings to short-term and long-term post-operative findings.

The present investigation is one of the only comprehensive studies that evaluate the microlesion effect intra-operatively, allowing for immediate identification of a microlesion effect. The intra-operative assessment facilitates the investigation of the MLE following insertion of the electrode absent of the benefits of medication, stimulation, and recovery time. Jech and colleagues [189] found that 92% of their implanted patients had edema near the site of placement, and as the edema resolved, so did the MLE. In the present study the patients are assessed immediately following insertion, thereby eliminating the factor of edema resolution.

The present investigation is consistent with Whelan and colleagues' [7] study that demonstrated a potential role of the subthalamic nucleus in linguistic function. Specifically, lexical and semantic fluency naming skills may be in some part mediated by the subthalamic nucleus, as evidenced by the present findings.

In addition to the likely linguistic role of the Subthalamic Nucleus (STN), voice skills were also noted to be affected by stimulation to the STN via DBS surgery. In previous studies, inconsistent changes in voice function following STN-DBS have been reported. Findings from the present study demonstrated a reduction in perturbation for both jitter and shimmer in most of the participants. This is consistent with prior studies that found a reduction in jitter and shimmer when the device was on, as compared to when the device was off [157,165]. Additionally, maximum phonation time and vocal intensity for sustained phonation were also noted to improve with STN-DBS surgery.

These findings are consistent with that of Moreau and colleagues [68] and Gentil and colleagues [160]. However, the improvement in maximum phonation time was noted in the post-operative testing following 2-4 years; findings following 3-6 months post-surgery yielded a reduction in maximum phonation time as compared to baseline. In contrast, the increase in vocal intensity was noted 3-6 months post-operatively, with a decline in function in the delayed post-operative testing. These results may be related to an improvement in vocal function for sustained phonation from DBS surgery. However, despite reported improvement in specific speech parameters, most patients report reduced speech intelligibility following STN-DBS [5]. This can be supported by finding from the present study where vocal intensity for sustained phonation was noted to improve; however, most of these same participants demonstrated a reduction in vocal intensity for speech production, which may impact overall speech intelligibility.

Further support of perceived reduction in overall communicative skills despite improvement in specific speech parameters is evident from analysis of the Voice Handicap Index results. Most of the participants reported an increase in self-perceived voice handicap following 2-4 years post-operatively. This increase in perceived deficits well after surgery supports Rodriguez-Oroz and colleagues' [155] findings that motor skills while on medication significantly diminished at the four-year marker.

Prosody of speech is the most prominent breakdown in speech production for individuals with PD [48,66]. However, limited improvement has been noted in prosodic skills after STN-DBS surgery, presumably because rhythm of speech production is not a function of dopaminergic structures [172,173]. However, in the present study all of the participants demonstrated reduced phonation range, which in turn may impact inflection for prosody of speech.

In summary, findings of the present investigation are similar to previous studies of the effects of deep brain stimulation surgery of the STN on speech and language function, such that variability in the findings continues to be a factor. However, it can be concluded that the STN plays a role in both voice and language function. Furthermore, self-perceived voiced deficits are more prominent following 2-4 years status post-surgery despite improvement in varied speech parameters. Additionally, the micro-lesion effect, although present for motor skills, is not a contributing factor for linguistic function, specifically for lexical and semantic naming skills. The results of this study further support the need for more research regarding the effects of DBS surgery on communication.

Limitations of the Study

Limitations of this study include the small sample size of five participants, which does not allow for statistical generalization to the idiopathic Parkinson disease population. The sample size allows for identification of trends resulting from STN-DBS; however, because of the sample size any outliers cannot be identified. Although there was ethnic diversity within the participants, the diversity was limited to African American and Caucasian patients and not a comprehensive representation of all ethnicities that may receive the STN-DBS surgery. Once again, this is due to the limitation of a small sample size. Furthermore, variation in medication from the time of pre-operative testing and post-operative testing represents a delimitation in the study. Post-surgical testing was completed with the device on and medications "on-phase," as this study did not investigate the effects of medication, but instead investigated speech function that is exemplary of the participant's typical daily status. However, variability in type of medication and change in doses of medication from the time prior to the DBS surgery to following the surgery may affect the status of speech and language skills in each of the participants. Therefore, the change in skills that were identified following the surgery in this study may partially be attributed to the influence of medication variability.

Suggestions for Future Research

This study was a single center study. Future research of the effects of STN-DBS should incorporate a multicenter design, which would allow for a larger sample size. The larger sample size might yield results that could be statistically generalized to the PD population receiving this surgery. A multicenter replication of this study would also allow for analysis of the effects of differing surgical techniques such as loci and trajectory of the implantation. Future research should also analyze the effects of changes in programming of the device on speech and voice skills such as frequency and amplitude. Speech and language skills should be analyzed and compared to baseline with various settings to allow for analysis of optimal benefit of the DBS surgery. At this time, the patient is able to vary the parameters of the settings independently. With greater knowledge of optimal settings for communication, the patient can be educated on parameter settings that would better facilitate communication skills. The speech-language pathologist can also incorporate setting adjustments within the treatment plan for improved intervention.

Clinical Implications of the Study

Deep brain stimulation surgery in the subthalamic nucleus has yielded great benefit in motor skills of people with Parkinson disease; however, the benefits to non-motor skills such as speech and language have been more elusive. Past studies have resulted in variable findings with no clear identification of the role of the subthalamic nucleus in communicative skills. This current study adds to the literature on the role of the STN in voice and language skills. Additionally, the microlesion effect identified for motor skills in past research was not present for language skills in this study. Based on these results, the speech-language pathologist can better serve the PD patient for pre-operative counseling regarding potential results for the STN-DBS surgery. Additionally, the SLP can modify the intervention program to facilitate optimal results following the DBS surgery.

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Dedication

To my brother, Nestor, who although may not be here in body will always be here in spirit. You always epitomized the idea that life is about the journey and not the destination. Thank you for helping me throughout this journey. You demonstrated the true definition of strength and determination. Mostly, thank you for helping me accept what is and to continue despite of. This dissertation is very much because of you.

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