TITLE: Got the Jitters? Voice as symptom and treatment measure in Parkinson's Disease
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Parkinson's overview

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by the idiopathic loss of dopaminergic neurons, primarily in the substantia nigra. [1] PD is associated with dopamine deficiency and other derangements in other neuromediator systems, and accounts for a variety of motor and non-motor deficits. [2]

Almost 200 years ago, James Parkinson first described the disorder that bears his name, and 45 years ago the most effective therapy, levodopa, was introduced. Parkinson's disease affects over 1 million people in North America. Age is the single most consistent risk factor with genetic predisposition second. With aging of the general population, the prevalence of Parkinson's disease will increase steadily. Mortality of PD is two to five times higher than among age-matched controls, resulting in a marked reduction in life expectancy. In fact, neurodegenerative diseases (Parkinson's disease, motor neuron disease, and dementia) are projected to surpass cancer to become the second most common cause of death among the elderly by the year 2040. Therefore, Parkinson's disease greatly shortens life as well as causing debility during life. [3] Studies suggest that PD usually affects people after the age of 50 years old.

Only about 10% of all patients report symptoms before the age of 40 years of age. [4] However, PD is estimated to affect 1.6% of persons over the age of 65 years, [5] and prevalence in persons over 80 is 1 in 10. [3]

As a result, the statistics for the number of affected persons are expected to increase in proportion with the overall aging of the worldwide population as a whole.[6] In addition to the most characteristic motor symptoms such as resting tremor, bradykinesia, muscular rigidity, and postural instability, many patients with PD develop non-motor (non-dopaminergic) deficits such as disorders of mood, behavior, and cognition and a distinctive alteration of speech characterized as hypokinetic dysarthria.[7]

Etiology

Parkinson's disease is characterized by the progressive death of selected but heterogeneous populations of neurons (see powerpoint) including the neuromelanin-laden dopaminergic neurons of the pars compacta of the substantia nigra, selected catecholaminergic and serotoninergic brain-stem nuclei, the cholinergic nucleus basalis of Meynert, hypothalamic neurons, and small cortical neurons (particularly in the cingulate gyrus and entorhinal cortex), as well as the olfactory bulb, sympathetic ganglia, and parasympathetic neurons in the gut.[3]

Progression

The diagnosis of Parkinson's disease is made on the basis of clinical criteria. There is still no biologic marker that unequivocally confirms the diagnosis. [3] The Unified PD Rating Scale (UPDRS) is the most commonly used scale in the study of PD. It includes sections on Mentation/Behavior/Mood, Activities of Daily Living, a Motor Exam, and Complications of Therapy. Two scales are included in the UPDRS. The Modified Hoehn and Yahr Staging for severity of motor symptoms ranges from no evidence of disease to wheelchair or bedbound. The Schwab and England Activities of Daily Living Scale measures progression of disease from no interference with ADL to inability to perform ADL and lack of swallow, bladder or bowel function. [8] The decline usually takes several decades [4], and levodopa only appears to relieve the symptoms for around 5 years before the disease progress overwhelms its efficacy. There is some debate about when to start this medication.[3]

Voice analysis

Characteristics of speech

The ability to speak clearly involves a complex brain system that is not fully understood.[9] The ability to speak can be subdivided into several dimensions, including resonance, phonation, and articulation.[10]

Phonation

Phonation is the vibration of the vocal cords to create sound. [2] Phonation requires five conditions to be produced: the vocal folds must be approximated, there must be adequate respiratory expiration, the vocal folds must be flexible enough to vibrate, vocal fold length and tension must be under voluntary control, and the contour of the vocal folds must be favorable for

vibration. [10] Traditional measurement of sustained vowel phonation in PD includes measurement of the fundamental frequency or pitch of vocal oscillations (F0), extent of variation of voice range (jitter), the extent of variation of expiratory flow (shimmer), and the amplitude of noise relative to tonal components in the speech (NHR ratios). Another measure that has commonly been studied in PD is voice onset time (VOT), defined as the duration of time from articulatory release of a stop consonant to the onset of voicing for the following vowel. VOT can be categorized as a phonatory measure because its changes in PD are generally attributed to disruptions of phonation. [2]

Jitter and Shimmer

The jitter and measures of period perturbation represent the variability of the speech fundamental frequency (pitch period) from one cycle to the next.[2] Jitter is one of the main measures for microinstability in vocal cord vibrations. It refers to a cycle-to-cycle, short-term perturbation in the fundamental frequency of the voice.[11]

The shimmer and measures of amplitude perturbation are derived from the sequence of maximum extent of the amplitude of the signal within each vocal cycle.[2] Shimmer is a cycle-to-cycle, short-term perturbation in amplitude of voice. It increases with poor and inconsistent contact between the vocal cord edges. [11]

Jitter and shimmer are used as measures to assess the micro-instability of vocal fold vibrations.[2] Stated another way, irregular vocal fold vibration causes random modulation of the source signal and affects the amplitude (shimmer) distribution of harmonics throughout the spectrum and its time period (jitter).[12]

Resonance

Resonance is the selective amplification of certain component frequencies using induction of vibrations in the chest, pharynx, and head. Vocal training maximizes resonance by learning to control the positions of the pharynx, tongue, jaw, and larynx. Additional control may involve the sound transmission through the nasopharynx as well.[10]

Characteristics of speech

Articulation

Articulation is the formation of consonants and vowels by controlling the lips, tongue, palate, and pharynx. This is coordinated with laryngeal stops and starts of phonation to form voiced and unvoiced sounds. [10] The most common method of evaluating articulatory skills is that of the diadochokinetic (DDK) task. Typically, the DDK task measures the subject's ability to repeat a consonant–vowel (C-V) combination with bilabial (both lips pursed: /pa/), alveolar (tongue against back of top teeth: /ta/), and velar (soft palate: /ka/) places of articulation, quickly, at a constant level and a rhythmic manner. Subjects are asked to repeat a combination of the three-syllable item, for example, /pa/-/ta/-/ka/, as fast and long as possible.[2]

Prosody

Prosody is another important characteristic of speech related to PD. Prosody is the variation in loudness, pitch, and timing accompanying natural speech. [13] Prosodic measures are usually determined from running speech and include measurement of fundamental frequency, intensity (relative loudness of speech), articulation rate, pause characteristics, and rhythm. [2]

Asthenia

Asthenia is the measure of strength of voice, or lack thereof. It is most often measured in relation to other vocal characteristics on the subjective GRBAS scale which stands for Grade of Dysphonia, Roughness, Breathiness, Asthenia, Strain. [14]

Dysarthria, the disorder vs the characteristics of speech

Dysarthria is not a single portion of speech. It is a characteristic speech alteration according to the motor dysfunction that creates it. Dysarthria describes the difficulties of speech quality and intelligibility caused by motor neuron dysfunction in different areas created by disturbances of respiration, laryngeal function, airflow direction, and articulation. For example, there are six major types of dysarthria: flaccid dysarthria associated with lower motor neuron impairment, spastic dysarthria associated with damaged upper motor neurons linked to the motor areas of the cerebral cortex, ataxic dysarthria primarily caused by cerebellar dysfunction, and hyperkinetic dysarthria and hypokinetic dysarthria, which are related to a disorders of the extrapyramidal system. [15] PD dysarthria is characterized as hypokinetic. [9]

Voice and speech changes in PD

Characteristic changes

PD characteristic vocal impairment is multifactorial. PD patients tend to speak in a soft, breathy monotone that they perceive as normal volume. The feedback mechanism of speech effort is deranged in PD, as well as the skeletal muscle bellows mechanism of chest wall and diaphragm. [10] Parkinsonian dysarthria can affect up to 90% of patients during the course of their disease.[16]

The primary disability of PD speech is related to phonatory impairment, with articulation being the second most affected speech characteristic, although patients with PD can have abnormalities related to all dimensions of speech. [2] For example, disturbance of prosody is another feature of PD speech. Prosody can be broken down into distinct subdimensions of speech rhythm and velocity, articulation rate and speech to pause ratio, speech intensity, and pitch variation. Reduction of fundamental frequency variability leads to the impression of monotonous ‘‘monopitch’’ intonation in PD speakers. [16] Studies show that as PD progresses, patients speak with decreasing pitch range. Changes in speech rate and pause characteristics have been found in people with PD in comparison to healthy controls (HC). Overall, patients with PD demonstrate production defects in all of these measurements, including reduced frequency and intensity variations, and differences in speech rate and pause characteristics in reading tasks. [2]

Studies show that brain changes in hypokinetic dysarthria do not parallel those of limb movements and it has been postulated that pathophysiology of PD dysarthria is, at least in part, different from that of limb dysfunction. [7]

One study of early PD patients not taking medications compared to HC measured the voice functions jitter and shimmer and their variants, and noise to harmonics ratios (NHR) using sustained vowel phonation. These ratios compare the amplitude of noise relative to tonal components in the speech. The only measurement of phonation that did not show statistical significances between the PD and HC group was pitch variations. This can be caused by the fact that people with early stages of PD don't necessarily show impaired control of stationary voice pitch during sustained phonation. Otherwise, significant differences were found in all measurements of phonation. For example, more signal noise addition measured by NHR can indicate incomplete vocal fold closure and unsynchronized vocal fold oscillations. Turbulent airflow through the vocal fold can increase the noise in speech. Clinical changes in voice such as hoarseness, hypophony, and tremolo are linked to the significant differences in measurements of all types of shimmers and jitters, and NHR. [2]

Another study evaluated voice parameters compared to UPDRS scores. They found roughness, breathiness, and asthenia were increased in patients with PD compared with healthy controls. For both males and females with PD, breathiness and asthenia values were higher. Males with PD also showed an increase in roughness. The study also evaluated jitter, shimmer, harmonics ratios, and DDK tasks. On videostroboscopy examination, non-closure glottic pattern was found to be more frequent in the PD group. The authors concluded that although it is well known that pathophysiological changes in PD affect the voice, they only found a few significant correlations between the UPDRS and traditional voice parameters. [14] To that end, significant work has been done to develop advanced mathematical algorithms that appply to nontraditional but mathematically significant parameters of vocal qualities.

In addition, abnormalities in the auditory system and deranged auditory-motor integration in PD may contribute both to disturbances of self-perception of voice and thereby speech production in these patients. Although pharmacological and surgical treatments are effective in treating motor symptoms of PD, the gains are not as significant for speech as they are for limb symptoms. The results of studies of pharmaceutical or surgical improvements of speech disabilities are variable. [7]

One interesting study found differences in PD speech between spontaneous speech and reading from a text. "Poor coordination of speech gestures in hypokinetic dysarthria may be attributable to impaired motor planning as well as defective ongoing monitoring. Speech disorders in basal ganglia disease may arise in part from deficient execution and maintenance of an appropriate internal model of the action plan. Contemporary models of the basal ganglia are consistent with the notion that specific vocal tasks might be expected to place different demands on processing and, therefore, might be differentially affected by disease. The study reported here arises from clinical observations as well as previous reports that compromise to basal ganglia competence affects articulatory and phonatory success for spontaneous and repeated speech quite differently. One of the important differences between these two speech modes may well be that although spontaneous speech requires the generation of an internal motor plan followed by

initiation, execution, and monitoring, an external template is provided for repeated speech, thus reducing the burden on motor speech control throughout the process." [9]

In a study that mapped PD speech characteristics to the UPDRS disability scale, they found that speaking rate related features noted most often in a reading task, which is less constrained than DDK or sustained vowel speech, could accurately predict the motor sub-scale score within about 5 points. [12]

On the other hand, in a 5 year longitudinal study of PD patients' speech characteristics, " we were able to demonstrate a special pattern of speech rate in Parkinson's disease characterized by an articulatory acceleration in the early stages and slowing during disease progression, especially in male patients with PD. Furthermore, fundamental frequency variability showed a worsening over time, at least in female patients with PD. As motor performance according to UPDRS motor score was stable over time, the changes of prosody obviously are independent from global motor function. Therefore, progression of Parkinsonian dysprosody could be the result of an escalation of axial dysfunction too subtle to be mirrored by global UPDRS motor score. Alternatively, alterations of speech parameters could be completely independent from motor performance maybe based upon non-dopaminergic mechanisms, as it is supported by the lack of an unequivocal evidence of speech amelioration under short-time L-dopa administration."[17]

Neurochemical pathways involved in speech production

One study of PD versus HC using functional MRI during a reading task found increased strength of functional connectivity in PD as compared with healthy controls, specifically in the right striatum. The connectivity strength in the putamen positively correlated with speech intonation. The putamen is a central constituent of the dopaminergic nigrostriatal pathway which is known to be degenerated in PD, and part of the motor circuit which is connected through the ventral thalamus to the supplementary motor area. The motor circuit might enable more precise voluntary control over the laryngeal, respiratory and articulatory activity during voiced speech. In PD, the enhanced connectivity strength between periaqueductal gray matter and putamen might reflect either successful compensatory changes in PD involved due to the dysfunction of the nigrostriatal circuitry or direct effects of dopaminergic therapy or combination of both.[7]

Another study investigated correlations between speech velocity and walking velocity. The decrease in PD patients' walking velocity results from a decrease in step length. Their speech velocity decrease during a reading task is a result of increased interpause speech duration. These akinetic parameters are strongly correlated and regulated by the dopaminergic basal ganglia loop. However, walking cadence and speech index of rhythmicity, which are the rhythmic gait and speech parameters, seem to be regulated by different non-dopaminergic structures. Furthermore, the structure that controls speech seems to undergo degradation during the course of PD prior to the one that controls gait.[18]

Treatment efficacy of PD as measured by voice and speech changes

Acoustical voice analyses and measurements might provide useful biomarkers for the diagnosis of PD in the early stage of the disease, for possible remote monitoring of patients, but

above all, for providing important feedback in voice treatment for clinicians or patients themselves.[2]

However, the significant influence of task on motor speech measures, as discussed earlier, has implications for the study of motor speech. The task used to measure voice derangements must be taken into account to describe motor speech processes, and to understand and perhaps separate the effects of brain dysfunction on articulation and voice. [9]

- Voice therapy

A targeted voice therapy called Lee Silverman Voice Treatment (LSVT) has been shown in several studies to be effective for the treatment of hypokinetic dysarthria. It targets increased amplitude of motor output during speech production by training increased vocal effort and loudness, while also training individuals to monitor their own vocal output.[19] It has been shown to yield statistically significant therapeutic effects on speech disorders in individuals with mild to moderate PD. These effects have been proven to last more than 2 years. Initial data also suggest this voice behavioral therapy can improve swallowing, articulation, communicative gestures, facial expression, and neural functioning as well. [20] Further development has been directed at computer-based LSVT/LOUD training which delivers comparable results. [21]

A 2010 literature review on behavioral training (such as LSVT) for Parkinsonian voice and swallow deficits had three conclusions. The first is that targeted training can create lasting changes in voice behavior. The second finding was that targeted training to systems that share similar muscles and nerves to voice and swallowing may improve voice and swallowing to some degree. Finally, little evidence exists regarding cranial sensorimotor interventions for Parkinson disease. [22]

- Levodopa

Some authors described an initial improvement in fundamental frequency (F0) range in PD patients after L-dopa administration followed by further decline over the course of the disease, supporting the hypothesis that laryngeal (skeletal) muscle hypokinesia is the major mechanism of F0 range reduction. However, follow up studies failed to demonstrate a consistent correlation between F0 range and disease severity, a predictable response to dopaminergic therapy, or a correlation between monopitch speech and general motor symptoms in PD. These discrepancies might be explained by small sample sizes and by the wide variability of dysprosody intensity in individual PD patients. [16]

"Traditionally, speech disorders in PD have been attributed to dopamine deficiency and muscle rigidity. Recent studies of dysarthria in PD provide some support for this attribution, as there is evidence for improved speech functioning with levodopa treatment. The improvement is in respiratory function, prosodic pitch and loudness variation, and speech intelligibility. There is also electromyographic evidence for hypertonicity of laryngeal muscles at rest in individuals with PD. However, recent reviews indicate that the majority of other studies have failed to find a causal relationship between dopamine and speech, or rigidity and speech, or a positive impact of dopamine therapy on functional speech intelligibility in individuals with PD; moreover, there is evidence to suggest other etiologies for speech problems in PD, such as deficits in internal

cueing, scaling movement force and amplitude, sensorimotor gating, self-perception of voice, and self-regulation of vocal output."[20,23]

- Deep brain stimulation

Deep brain stimulation of the subthalamic nucleus (DBS-STN) can dramatically improve global motor functions of the limbs and reduce tremor, but its effects on speech are variable. While several studies have reported speech problems as side effects after implantation, some studies have noted no changes in speech, and others actually note improvement. The reasons for these diverse outcomes are not clear, but they are likely related to factors such as stimulating electrode lesions, stimulus settings, neuroanatomical and neurophysiological and disease pattern differences among patients, and the surgeon's skills. [20]

Many studies have evaluated the differences in speech with DBS-STN. One study experimented with changing the DBS settings away from optimal motor control and found different settings can positively affect speech characteristics. However, the improvement or deterioration is determined not only on the basis of the parameter setting but also on the individuals' relative disability at baseline. This study also notes differences within an individual in the effects of stimulation on the two speech subsystems. These findings should temper global statements about the effect of neurostimulatory implants on Parkinsonian patients. They also emphasize how important careful consideration of individual differences may have on the effect of deep brain stimulation on different speech subsystems. [24]

Another study had similar findings. The effects of STN-DBS on respiratory and laryngeal control were not uniform across participants and did not correlate with changes in limb-related function. High-frequency settings on the stimulator frequently created respiratory over-drive and excessive vocal fold closure. This finding suggests that speech may benefit more from low-frequency stimulation than high-frequency stimulation. The authors emphasize the importance of accounting for significant differences between speech and limb function, and between high- versus low-frequency stimulation when adjusting the parameters for individuals with PD. [25]

Electrical stimulation of the subthalamic nucleus to treat PD provides a reversible and adjustable means of modifying the activity of the basal ganglia. Even though it has proven efficacy in the motor system, it often has no or detrimental effect on speech. Levadopa therapy, which has a variable effect on motor activation, behaves in a similar manner in that gains from pharmacological intervention are not as significant for speech as they are for limb function. These facts point out differences in the relationship between speech and nonspeech motor control in PD and, in general, underline the complex nature of cortical–subcortical interactions during speech. DBS may affect different components of motor speech processes in different or even opposite ways. Because of the inherent differences noted in previous studies of PD speech depending on the task undertaken, it is more difficult to compare nonuniform effects of DBS on elements of motor speech. [9]

"Compounding the difficulties in understanding the breakdown of a complex control system in PD and its alteration with DBS is evidence that the progression of PD is the result of neuropathology that progresses by encroaching on a series of brain structures based on their

neurobiological properties rather than simply increased destruction in a restricted neuroanatomical region. This raises the possibility that different aspects of motor speech control in PD are associated with changes in different neurotransmitter systems."[9]

Progress towards earlier diagnosis and treatment with speech assessment

Studies report that approximately 70%–90% of patients with PD show some form of vocal impairment, and this deficiency may also be one of the earliest indicators of the disease, in addition to one of the most difficult aspects.[2] For most elderly people with Parkinson's disease, frequent physical visits to the clinic for diagnosis, monitoring, and treatment are difficult. [26] Another problem is recruiting patients into clinical PD trials when assessment scales such as the UPRDS must be administered in person and usually take at least 15 minutes to perform. [8] A test that could be administered quickly and remotely would likely increase clinical trial participation and could improve disease management. [26]

Research being conducted to link vocal parameters with motor scores has gained ground by defining certain nontraditional vocal characteristics more frequently observed in PD patients than HC patients. Mathematical analysis of voice patterns in more than 6000 laboratory recorded voice samples of 42 PD patients has delineated a small number of these interrelated inherent PD characteristics and shown reliable prediction of the UPDRS with limited bias, simply from the strength of the nonlinear vocal patterns. In fact, the algorithms have predicted disease severity with less standard deviation than the inherent error in the subjective UPDRS score. [27, 28] This research has been expanded to include 10,000 voice samples from around the world from mobile phones to evaluate the reliability of the algorithms under nonideal (i.e. real life) conditions. Please see www.parkinsonsvoice.org for more information on this project.

Conclusions

PD is debilitating and increasing in frequency. The etiology of parkinsonian dysprosody is not purely dopaminergic, and therefore traditional treatments for motor defects do not consistently address speech problems. Voice therapy can be very helpful, especially for mild to moderate cases of PD.

Speech assessment appears to be a powerful tool for diagnosis and treatment, but further development is required before it will be widely available.

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