2023

Impact of speech rate and speaker-modulated vocal effort on laryngeal kinematics in people with Parkinson’s disease

BOSTON UNIVERSITY

SARGENT COLLEGE OF HEALTH AND REHABILITATION SCIENCES

Thesis

IMPACT OF SPEECH RATE AND SPEAKER-MODULATED VOCAL EFFORT ON LARYNGEAL KINEMATICS IN PEOPLE WITH PARKINSON'S DISEASE

by

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B.S., New York University, 2021

Submitted in partial fulfilment of the

requirements for the degree of

Master of Science

2023

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ACKNOWLEDGMENTS

Firstly, I would like to thank Dr. Cara Stepp, my thesis supervisor, for her guidance and support throughout the entire thesis process. Learning from someone as knowledgeable and insightful as you, in a lab that cares deeply about the research it conducts, has been an honor. I am grateful for your encouragement when I was overwhelmed and your thoughtful feedback that helped to hone my skills. I would also like to thank Hasini Weerathunge, for being such a dedicated mentor from the thesis' budding stages, to its final form. You consistently go above and beyond to support my growth with your patience, enlightenment, and encouragement. I cannot thank you enough for taking the time to guide me in times of doubt, even as you were completing your own dissertation. Both the speech research field and your future mentees are lucky to have you, and I cannot wait to see the other lives you will touch.

Additionally, I would like to thank the other members of my thesis committee, Rachael Kammer and Dr. Frank Guenther. From her warm check-ins as an advisor, to the wealth of knowledge she has as a professor, and the passion she has for PD, both in research and clinical practice, I have had the opportunity to learn from Rachael in many capacities both in and out of the classroom. Her kindness, and the functional lens she added to this thesis, have been invaluable. I am also thankful for the privilege to work with Dr. Guenther. The possibility of working with him was part of my initial motivation to join BU's MS-SLP program. I greatly appreciate the opportunity to learn from his expertise and vast knowledge in the neural bases of speech motor control within this thesis. Furthermore, I would like to thank Dr. Jennifer Vojtech, who collected and

curated all the data for this study, Manuel Diaz-Cadiz, who created the semi-automated algorithm used within the study, and Daniel Buckley, for scoping all of the participants involved.

Last, but certainly not least, I would like to thank my family and friends for their relentless support throughout this process. To my cohort, thank you for your friendship that has provided solace through the ups and downs of the program. To friends and loved ones who have supported me from back home, listening to my practice talks and repeated explanations, your understanding and belief mean the world to me. Finally, to Mummy, thank you for being my rock throughout this program and through the years. I would not have gotten this far without your love and support.

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ABSTRACT

Purpose: Communication difficulties in Parkinson's Disease (PD) are multifactorial. Observing cardinal motor symptoms may be insufficient in qualifying speech dysfunction in people with Parkinson's Disease (PwPD). This study aimed to use high-speed video (HSV) endoscopy to explore the use of three measures of laryngeal kinematics – spatiotemporal index, asymmetry index, and kinematic stiffness ratio – as a novel means of examining vocal motor control in PD, to better understand the pathophysiology of PwPD within the phonatory subsystem.

Method: 24 PwPD and 24 age- and sex-matched controls were trained to produce repetitions of a VCV target, /ifi/, while varying their speech rate and vocal effort during simultaneous HSV nasoendoscopic and acoustic recordings. Kinematic measures were calculated from HSV recordings during vocal fold adduction using both manual glottal angle tracking and a semi-automated algorithm. Six separate repeated measures analyses of variance (ANOVAs) were completed to determine the spatiotemporal index, asymmetry index and kinematic stiffness ratio, with main effects of group and condition (fast rate, regular rate, slow rate, mild effort, moderate effort, maximum effort). Alpha levels < .05 were considered statistically significant. Effect sizes of significant differences were calculated by using partial eta squared.

Results: The repeated ANOVAs showed a statistically significant effect of group on spatiotemporal index values across both rate ($p < .01$) and effort ($p < .05$) and on asymmetry index values across rate ($p < .01$). No statistically significant main effect of rate or effort or interaction effects between group × rate or group × effort were observed for all kinematic measures.

Conclusion: This study determined that spatiotemporal index, a measure of variability in movement, and asymmetry index, a measure of movement efficiency, are significantly higher for PwPD compared to controls. These findings are consistent with increased variability and reduced efficiency observed in other speech subsystems in PwPD. Further research is recommended to explore the use of laryngeal kinematics in characterizing the pathophysiology of the laryngeal subsystem in PwPD.

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, affecting 572 in 100,000 of people aged 45 years and older in North America (Marras et al., 2018). In addition to cardinal gross motor symptoms such as limb rigidity, resting tremor, bradykinesia, and postural instability, researchers estimate that up to 89% of people with Parkinson's disease (PwPD) present with communication issues (Ramig et al., 2008). These communication issues can be observed throughout the speech system, which consists of four subsystems — the respiratory system, the phonatory system, the articulatory system, and the resonatory system (Henderson et al., 2019; Jankovic, 2008; Kwan & Whitehill, 2011). As communication deficits in PD have critical detrimental effects on the quality of life of PwPD (Chu & Tan, 2019; Cruice, 2008; Duffy, 2005), an increasing body of research has been focused on better understanding the pathophysiology of PD within the speech system (Möbes et al., 2008; Rusz et al., 2015; Tang et al., 2010).

The clinical diagnosis of PD has been centered on the presence of cardinal motor symptoms, following the traditional belief that PD is associated with dopaminergic deficits from the loss of dopaminergic neurons in the substantia nigra pars compacta (Baker et al., 1998; Schapira et al., 2017; Skodda et al., 2013). Although the current methods for diagnosing PD are specific and sensitive to the presence of PD (Postuma et al., 2018), bradykinesia, rigidity, and rest tremor are generally only observable further along the disease's progression after 60–80% of striatal dopamine has been lost (Bernheimer et al., 1973). This means that a large proportion of PwPD only receive a

diagnosis when they are in later stages of the disease, suggesting that speech dysfunction, often observed several years before the onset of the motor symptoms typically associated with PD, is not identified promptly (Harel et al., 2004). Some argue that these early observations of speech dysfunction may be partially attributed to the complexity of the fine motor planning required in coordinating the sub-systems of respiration, voice, articulation, and resonance during speech, which may be more sensitive to slight changes in the basal ganglia circuitry (Harel et al., 2004). However, seminal research by Braak, Tredici, et al. (2003) found degeneration of brain circuits in the olfactory bulb and the lower brainstem likely occurs well before the onset of basal ganglia dysfunction (Braak et al., 2006; Braak et al., 2004; Braak, Rüb, et al., 2003; Braak, Tredici, et al., 2003), which implies that speech function could be affected by degeneration of brain circuits other than the basal ganglia. Thus, independent observation of the cardinal motor symptoms in the early diagnosis of PD may not result in a comprehensive evaluation when we are attempting to qualify speech dysfunction in PwPD.

The early onset of speech dysfunction is not the only indicator that speech is affected by factors other than the cardinal motor symptoms. Longitudinal studies have observed that PwPD on individually adjusted dopaminergic medication plans continue to have impairments in speech (articulation, fluency, voice, and prosody) features regardless of the stability of global motor impairment, suggesting additional differential non-motor contributors to speech motor control (Rusz et al., 2011; Rusz et al., 2013; Skodda et al., 2013). Speech is complex and the impact PD has on communication affects a PwPD's life participation and interpersonal relationships (Miller et al., 2006). Therefore, it is

critical to investigate the underlying pathophysiology of speech deficits in PwPD, to fill the gap in our understanding of the manifestation of PwPD in the various speech subsystems (Harel et al., 2004). Thus, researchers have been prompted to look into objective observation of pathophysiology of the phonatory subsystem more specifically to highlight potential characteristics in the various speech subsystems that may help differentiate PwPD from age- and sex- matched controls.

One of the most common manifestations of the communication issues in PD is hypokinetic dysarthria, which is characterized by hypophonia, monotonic speech, velopharyngeal incompetence, breathiness, and roughness (Darley et al., 1969; Ramig et al., 2008; Trail et al., 2005). In individuals with hypokinetic dysarthria, elevated levels of fundamental frequency (f_o) are often observed (Duffy, 2005), with PwPD presenting with increases in average f_o that are proportional to disease severity (Metter & Hanson, 1986). However, PwPD have increases in average f_o even when their f_o range is reduced (Bunton et al., 2001), which has been hypothesized to be attributed to a combination of damage to both dopaminergic systems and lower-level systems (Bowen et al., 2013). This is important as limitations in emotional prosody expressed through the use of varied speaking fundamental frequencies may have a negative impact on emotional communication in PwPD (Schröder et al., 2010). Other hypotheses as to what contributes to voice abnormalities in PwPD exist, including abnormalities in laryngeal physiology. Using telescopic cinelayrngoscopy, Hanson et al. (1984) documented vocal fold bowing in most PwPD, resulting in inadequate vocal fold adduction (i.e., the movement of the vocal folds towards the midline following phonation) and subsequently a weak and

breathy vocal quality with reduced intensity (Duffy, 2005). Vocal fold bowing is generally caused by atrophy of the thyroarytenoid muscle (Tanaka et al., 1994). This suggests that weakness in musculature is one of the factors influencing restrictions in vocal fold movement. However, it has also been suggested that limitations in vocal fold movement may arise as a result of an improper balance between agonist and antagonist muscles of the larynx, resulting in the increased baseline levels of tension that are present in PwPD (Gallena et al., 2001).

An increased level of baseline laryngeal tension is one of the physiological characteristics that has been associated with hypokinetic dysarthria. This has been supported via research studies that demonstrate hypercontractility of the thyroarytenoid and cricothyroid muscles during vocal rest in PwPD (Duffy, 1995; Gallena et al., 2001; Zarzur et al., 2014; Zarzur et al., 2007). Despite our understanding that baseline laryngeal tension is increased in PwPD, there is no standardized objective measure of the direct impact of elevated tension on the performance of the phonatory subsystem (e.g., quantifying the movement of the vocal folds). Laryngeal function can be determined through the use of invasive methods such as needle electrode electromyography, that measures muscle activity levels. However, the lack of non-invasive methods reduces the accessibility of evaluation. Regardless, it has been proposed that laryngeal tension is one of the manifestations of the pathophysiology of the larynx in PwPD. Taken together with the other physiological changes observed in PwPD, the increase in laryngeal tension suggests an impairment in speech motor control, which could be determined by observing characteristics of vocal fold movement.

To ascertain what characteristics of vocal fold movement to observe, we must first understand speech motor control using pre-existing frameworks that illustrate how speech motor control works. Thereafter, we can begin to determine how these changes in motor control may manifest in laryngeal imaging. A widely accepted representation of speech motor control during the processes of speech acquisition and speech production is the Directions into Velocities of Articulators (DIVA) model (Tourville & Guenther, 2011). In this neural network model, it is suggested that when we are fine-tuning our speech motor systems, we use babbling to establish systematic mappings of early motor gestures and map relevant auditory and somatosensory feedback on top of our initial productions. Over time, the feedforward system becomes more robust and we create a generalized motor program for each motor target. Thereafter, during every instantiation of a motor program, we compare the actual auditory and somatosensory information we get to our expectations of what the movement should feel and sound like. If the feedback during the production is inconsistent with the target range of expectations we have for that motor program, we modify motor plans online to correct our movements for that production.

However, PwPD have demonstrated deficiencies in feedforward control (Abur et al., 2018; Abur et al., 2021; Mollaei et al., 2013), resulting in challenges in inhibiting extraneous movement (Disbrow et al., 2013). To compensate, many PwPD exhibit hyperactivity in their feedback systems (Huang et al., 2016; Yu et al., 2007). In behavioral studies using altered auditory feedback paradigms, PwPD have been observed to have reduced adaptive responses although they demonstrate relatively unimpaired

auditory motor control (Abur et al., 2018; Abur et al., 2021). Several studies have shown that PwPD have enhanced auditory feedback when controlling vocal f_o (i.e., the acoustic correlate of pitch; Chen et al., 2013; Liu et al., 2012). The feedback-based error corrections are integrated to current productions. However, the incorporation of these feedback-based error corrections to subsequent motor programs when feedback errors persist, seem to be impaired in PwPD (Chen et al., 2013; Liu et al., 2012; Mollaei et al., 2016; Mollaei et al., 2019).

Feedback based error-corrections for motor control may be particularly insufficient when we consider the short duration of movements in speech, which is a rapid, fine-motor activity. This remains the case even during slower movements of the vocal folds, such as adduction. The correction following auditory feedback has been observed to take between 100 – 120 ms to manifest (Burnett et al., 1998), whereas vocal fold adduction takes place between 104 – 227 ms on average (Dailey et al., 2005). Therefore, although the auditory feedback loop in PwPD remains largely intact, it may not be sufficient to modify real-time motor plans efficiently. Though auditory feedback corrections may occur in vocal productions with longer periods of vocal fold adduction, there are instances where auditory feedback alone will not be able to correct the vocal motor control for the necessary real-time modifications. With the ambiguity of the extent of auditory feedback integration in PwPD, it becomes important to quantify measurable changes in the voice through objective laryngeal assessments.

Present-day voice evaluations consist of a client history, patient-reported outcomes, acoustic measures, aerodynamic measures, laryngeal endoscopic imaging, and

auditory-perceptual measures (Patel et al., 2018; Roy et al., 2013). Of these measures, auditory-perceptual measures such as the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) and the grade, roughness, breathiness, asthenia, strain scale (GRBAS) remain the gold standard in determination of voice dysfunction. These measures are limited in terms of inter-rater reliability, as auditory perceptions are often subjective (De Bodt et al., 1997; Karnell et al., 2007; Zraick et al., 2011). Presently, there is no quantitative measure of laryngeal function that can characterize the manifestation PD pathophysiology in the phonatory subsystem that has been widely accepted, as current quantitative evaluation methods (i.e., high speed video (HSV) rigid and nasoendoscopy) are time-consuming and not readily available (Lohscheller et al., 2007; Mehta et al., 2011; Qiu et al., 2003; Yuling et al., 2006). Objective measures of laryngeal function can potentially aid in the process of characterizing vocal function but remain less investigated and validated at the moment.

Direct observation of the laryngeal structures using instrumentation is a burgeoning area of research. However, quantifying laryngeal kinematics has traditionally required invasive instrumentation at higher speeds. Customarily, HSV endoscopy has only been used for rigid endoscopy (Patel et al., 2011). Although rigid endoscopy provides a clearer picture of the laryngeal structures compared to flexible nasal endoscopy; tongue movement is restricted during rigid endoscopy and production targets are limited to vowels and breathing, which are unnatural and dissimilar from typical speech (Woo & Baxter, 2017). In comparison, the relatively less restrictive flexible endoscopy has only been used with a 30-frames per second (fps) sampling rate. These

low sampling rates limit the temporal resolution for observation of the vocal folds, which typically vibrate between 145 – 275 times per second in women and 80 – 165 times per second in men on average during conversational speech (Davies & Goldberg, 2006). Even slower aspects of laryngeal kinematics such as vocal fold adduction (i.e., the movement of the vocal folds towards the midline) have movement times of 104 – 227 ms on average, meaning that a sampling rate of 30-fps will only provide between 3.1 – 6.8 frames for each adductory movement, far too little to provide reliable information on vocal fold movement (Dailey et al., 2005).

However, HSV is an option for flexible endoscopy as well. The incorporation of HSV in flexible endoscopy makes it possible to observe vocal fold adduction at resolutions of up to 8000 fps. The use of HSV with flexible endoscopy has therefore provided an additional method for observation of vocal fold adduction. Nonetheless, instrumental measures of vocal fold movement have their limitations. Much like the gold standard of voice evaluation, endoscopy is often conducted by an examiner who evaluates vocal fold vibratory characteristics such as regularity, amplitude, the mucosal wave, right and left phase symmetry, vertical level, glottal closure patterns, and glottal closure duration (Patel et al., 2018). Consequently, there may be inconsistencies in the qualitative descriptions of vocal fold movement provided by each examiner. Therefore, observation of vocal fold movement should involve a more objective analysis of the images captured by HSV to ensure better rates of inter-rater reliability and objective determinants of changes in vocal fold movement.

To determine relevant measures that could be used as objective measures following instrumental measures, we looked at kinematic measures that were applied in other domains of speech kinematics. One objective measure that had previously been used to observe inconsistency in movement is a spatiotemporal index (STI), which quantifies the extent that repetitions of a motor movement need to be adjusted to converge onto a predetermined movement template. Using STI, it is possible to determine whether auditory feedback has a significant effect on vocal fold movement in PwPD, as a higher STI would reflect greater inconsistency as a result of the changes in vocal fold movement caused by the integration of feedback. STI was initially used by Smith et al. (1995) to observe the variability of articulatory movement. In a study on articulation in PwPD that have employed STI, they found that slow rates of speech produced elevated STI whereas increased loudness lowers STI (Kleinow et al., 2001). The authors suggest that since slow rates of speech give more time for auditory feedback, there is more variability in the movement of the vocal folds. This study also observed that increased loudness lowers STI, which was attributed to inducing simpler movements closer to habitual speech targets (Dromey, 2000). STI has since been applied to observe the variability of acoustic signals in PwPD compared to age- and sex-matched controls (Anderson et al., 2008). In the aforementioned study, the acoustic signals produced by PwPD were observed to have differential spatial variability but comparable temporal variability in comparison to controls. However, no research so far has looked at the STI of vocal fold movements in PwPD. Therefore, we hope to use STI as an objective measure of analysis for the HSV imaging of laryngeal kinematics.

An additional measure of the impact of the feedback system on vocal fold movement is the Asymmetry Index (AI) of the velocity profile of the vocal folds during laryngeal imaging. Though a bell-shaped curve of the velocity profile is expected to produce the most efficient movement of the vocal folds, the anticipated impact of feedback during different rate and effort conditions on the vocal fold movement in PwPD may cause a skew in the velocity profile, resulting in an asymmetrical vocal fold velocity profile. Therefore, AI could be considered as a supplementary measure of the effects of feedback on the variability of velocity profile of vocal folds in PwPD.

In an attempt to create alternative objective measures of muscle tension in the intrinsic laryngeal muscles, researchers have designed indirect measures such as a kinematic stiffness ratio (KS). Originally developed as a correlate of muscle tension in limb kinematics, KS measures the ratio of a movement's maximum velocity to its movement extent (Cooke, 1980). However, the application of KS has since been extended as an estimate of muscle tension in laryngeal kinematics (Stepp et al., 2010). KS have been applied using a virtual trajectory model to determine if laryngeal kinematics can be used to determine the efficacy of calculating the tension through indirect measures (Stepp et al., 2010). The researchers found that there were strong positive correlations between kinematic stiffness and muscle tension when mimicking intrinsic muscle activation of the thyroarytenoid muscles, lateral cricoarytenoid muscles, and the posterior cricoarytenoid muscles — intrinsic laryngeal muscles that are important during voicing. The correlation suggests that KS is a possible measure for estimation of laryngeal tension.

Given the three proposed measures (STI, AI, KS) of the impact of the atypical feedforward and feedback systems in PwPD on vocal fold movement, we need to consider the conditions that may result in variations in each measure. One aspect we can consider is speech rate. As previously mentioned, hyperactivity of the feedback system is commonly observed in PwPD. This phenomenon may be particularly exacerbated in slow rates of speech. Slow rates of speech give more time for auditory feedback. Therefore, as observed in studies of articulatory movement and acoustic signal variation (Anderson et al., 2008; Kleinow et al., 2001), adjustments for vocal motor control of the vocal folds may be made during the vocal fold adduction that further increase variability in the movement of the vocal folds. These adjustments may be reflected by increases in STI and AI and decreases in KS. Therefore, we should consider the effect of rate on the consistency and stiffness of vocal fold movement.

The other condition that may be differentially affected by feedforward and feedback is vocal effort. Vocal effort is the self-perceived effort of an individual when they speak. For PwPD, it is particularly important to consider the impact of vocal effort as it is one of the focus areas in the most effective treatment methods for PwPD, such as the Lee Silverman Voice Treatment (Sapir et al., 2007; Yuan et al., 2020). Given the increased laryngeal tension in PwPD at baseline, we expect a higher baseline level of tension at a regular effort condition, as reflected by increases in KS. The increased baseline levels of tension may invite us to extrapolate this to other levels of vocal effort. However, varying vocal effort may not inherent be reflected in an increase in laryngeal tension, as vocal effort has been shown to significantly correlate with extrinsic

musculature rather than intrinsic (McKenna et al., 2019). Therefore, it is worthwhile to explore whether varying levels of vocal effort will increase KS and stabilize vocal fold movements as measured by STI and AI.

In this study, we aimed to explore the use of measures of laryngeal kinematics as a possible novel means of exploring vocal motor control in PD. We examined three overarching measures: STI, AI, and KS as measures of vocal motor control. We examined the changes in these measures of laryngeal kinematics under varied rates and differing levels of speaker-modulated vocal effort of vowel-consonant-vowel (VCV) productions in PwPD compared to neurotypical age- and sex-matched controls. When examining the effect of the rate conditions of STI, we hypothesized that PwPD would exhibit: (1a) greater STI in their vocal fold movements than their control counterparts at each condition, (1b) greater decreases in STI as rate increases, and (1c) smaller decreases in STI as effort increases, compared to controls. We hypothesized that AI would mirror STI, with PwPD exhibiting (2a) a greater AI at all rates and effort conditions, (2b) larger differences in AI between slow and fast rates, and (2c) smaller differences in AI across effort conditions in comparison to controls. Finally, when examining the effects of the rate and effort conditions on KS, we hypothesized that PwPD would exhibit (3a) a greater KS across all rate and effort conditions, (3b) smaller differences in KS between slow and fast speech production rates and (3c) comparable differences in KS across effort conditions compared to controls. To test the hypothesis 3c, we tested the alternative hypothesis, that changing effort conditions will result in significant differences across effort conditions. The outcomes of this exploratory study aimed to provide preliminary

insight on whether vocal motor control can be quantified through objective measures of laryngeal kinematics that can guide robust and targeted clinical intervention in future.

Methods

Participants

This study contains a reanalysis of data that are published elsewhere (Vojtech et al., 2021). Twenty-three cisgender PwPD (six female, 17 male) and one transgender PwPD (one female) individuals with a mean age of 62.8 years (standard deviation = 9.6 years, range: 43 – 75 years) and twenty-four age- and sex- matched control speakers with typical voices with a mean age of 63.8 years (standard deviation = 10.2 years, range = 41 – 81 years) were recruited as participants in the study. The participants were age- and sex-matched to minimize any effects of sex (at birth) and age on vocal fold movement. The PwPD were diagnosed by a neurologist as having idiopathic PD. See Table 1 for more information on disease severity and diagnosis history. All participants were native speakers of American English and had no prior conditions affecting voice function, including but not limited to neurological or voice disorders and respiratory conditions (i.e., other than idiopathic PD for the PwPD). Furthermore, no participants had any history of speech and language disorders (i.e., other than speech or voice therapy recommended as treatment for PD for the PwPD). All participants were screened with an auditory-perceptual assessment and preliminary endoscopic imaging via a flexible endoscope performed by a certified speech-language pathologist (SLP) with a specialization in voice. Additionally, all PwPD proceeded with their typical medication schedules relevant to PD (detailed in Table 1) and deep brain stimulation devices used by

five of the participants were asked to be turned off during data collection. The overall severity of dysphonia for each participant was determined by a voice-specializing SLP through the use of the CAPE-V (Kempster et al., 2009), a 100-mm visual analog scale. The SLP was blinded to the date, sampling time, and diagnosis of the participants. PwPD also completed the first two parts of the Movement Disorder Society–Sponsored Revision of the Unified Parkinson' Disease Rating Scale (MDS-UPDRS; Goetz et al., 2008) and a trained clinician conducted Part III, the motor examination, to establish motor severity during the time of the study.

In addition, all participants had to undergo a hearing screening. All except six participants passed a hearing screening of pulsed pure tones (Burk & Wiley, 2004) at frequencies of 125, 250, 500, 1000, 2000, and 4000 Hz under 40 dB in at least one ear. Four participants with PD passed at all frequencies below 4000 Hz, but of the four, two had a threshold of 45 dB HL (PwPD19, and PwPD23 in Table 1) at 4000 Hz, while two had a threshold of 50 dB HL (PwPD13 and PwPD18). Of the two remaining participants, one (PwPD16) passed all frequencies except 2000 Hz, where they had a threshold of 45 dB HL, while the other (PwPD12) wore hearing aids throughout the course of the study and demonstrated thresholds of 45 dB HL at 125 Hz and 250 Hz. For all participants, informed written consent, in compliance with the Boston University Institutional Review Board, was obtained prior to participation.

Table 1.

Participant Information for PwPD

Speaker	Age	Sex (at birth)	Years since dx	MDS-UPDRS PIII	Medication	DBS	CAPE-V
PwPD01	60	M	7	54	Levodopa/Carbidopa Drugs Dopamine Agonist	Y	30.1
PwPD02	49	M	7	47	Anticholinergic drugs	N	5.8
PwPD03	62	F	9	49	Levodopa/Carbidopa Drugs Dopamine Agonist	N	5.6
PwPD04	45	M	10	51	Levodopa/Carbidopa Drugs	Y	10.4
PwPD05	70	F	6	77	Levodopa/Carbidopa Drugs Glutamate Agonist	Y	14.7
PwPD06	50	M	0	17	Dopamine Degradation Reduction	N	7.1
PwPD07	55	M	21	49	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction Dopamine Reuptake Inhibitor	N	18.4
PwPD08	62	M	3	50	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction Dopamine Agonist	N	10.0
PwPD09	74	F	24	59	Levodopa/Carbidopa Drugs Glutamate Agonist	N	30.6
PwPD10	73	M	9	19	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction	N	33.6
PwPD11	67	M	4	63	Levodopa/Carbidopa Drugs	N	6.4
PwPD12	67	M	2	38	Levodopa/Carbidopa Drugs	N	19.4
PwPD13	62	M	13	47	Levodopa/Carbidopa Drugs Dopamine Agonist Glutamate Agonist	Y	27.9
PwPD14	59	M	2	23	Levodopa/Carbidopa Drugs Dopamine Agonist	N	4.0
PwPD15	73	M	3	23	Levodopa/Carbidopa Drugs	N	6.8
PwPD16	68	M	6	38	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction Dopamine Agonist	N	5.0
PwPD17	72	M	7	81	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction	N	45.0
PwPD18	73	F	8	52	Dopamine Degradation Reduction	N	33.3
PwPD19	75	M	1.5	68	Levodopa/Carbidopa Drugs	N	22.1
PwPD20	65	F	10	48	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction	N	15.4
PwPD21	68	M	1	52	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction	N	8.5
PwPD22	43	M	5	91	Glutamate Agonist	N	35.8
PwPD23	65	M	1	35	Levodopa/Carbidopa Drugs	N	28.3
PwPD24	51	F	5	13	Levodopa/Carbidopa Drugs Dopamine Degradation Reduction	N	9.7

Note. Age (in years), sex assigned at birth (F = female, M = male), years since diagnosis (dx), Movement Disorder Society–Sponsored Revision of the Unified Parkinson's disease rating scale (MDS-UPDRS) Part III motor scores (< 33 indicates mild impairment, and > 59 indicates severe impairment), Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) ratings for overall severity (0 indicates no audible symptoms, 100 indicates maximum severity)

Procedure

Participant Training

Participants were trained by an investigator on vocal tasks before data collection to reduce the duration of the nasoendoscopy examination and to get used to the production of the target utterance under varying conditions. During the training period, following a verbal model produced by the investigator, participants were instructed to produce eight repetitions of the VCV target, /ifi/, by producing four consecutive utterances, taking a breath, then producing the remaining four utterances, while seated. The consonant /f/ was chosen as it limits individual variability among a speaker's utterances in comparison to other voiceless consonants (Lien et al., 2014); the vowel /i/ was chosen to keep the pharynx open and provide a view that was minimally impeded during nasoendoscopy (Boone & McFarlane, 1993). Additionally, participants were requested to use their typical pitch, volume, and rate of speech and refrain from varying intonation unless instructed otherwise.

Thereafter, the participants were instructed to produce the eight repetitions under six different conditions — three with varying speech rates and three under varying effort conditions. The different rates of the utterances were regulated by the use of a metronome (McKenna et al., 2016). The slow, regular and fast rates corresponded to rates of 50 beats per minute (BPM), 65 BPM, and 80 BPM respectively. The different speaker-modulated vocal effort conditions (mild, moderate, maximum) were elicited as follows: participants were instructed to use "mildly more effort in your normal speaking voice" for the mild condition, "more effort than mild" for the moderate condition, and "as much effort as you

can while still having a voice" for the maximum condition (Groll et al., 2020; Vojtech et al., 2021).

Experimental Setup

After participants were trained, a nasoendoscopy was conducted. Participants were not provided with numbing agents to prevent changes to laryngeal function (Dworkin et al., 2000). However, Afrin, a nasal decongestant, was presented as an option to participants before insertion of the endoscope to keep discomfort to a minimum. Thereafter, participants were seated and a flexible endoscope (Pentax, Model FNL-10RP3, 3.5-mm) was fed through the inferior nasal turbinate into the hypopharynx for vocal fold visualization. A pediatric endoscope (Pentax, Model FNL-7RP3, 2.4-mm) was used in instances in which discomfort was observed or nasal anatomical differences made it hard to pass the adult endoscope through to the hypopharynx. The flexible endoscope was attached to a camera (FASTCAM Mini AX100; Model 540K-C-16GB; 256×256 pixels) with a 40-mm optical lens to record high speed video and a steady xenon light was used for imaging (300 W KayPentax Model 7162B). A set sampling rate of 1 kHz was chosen as gross adductory gestures occur over a longer duration of 150 – 250 ms per gesture (Dailey et al., 2005; McKenna et al., 2016; Stepp et al., 2010) compared to typical vocal fold vibrations and imaging was captured by Photron Fastcam Viewer software (v. 3.6.6). Participants were also fitted with a Shure SM35 XLR, a directional headset microphone, 7 cm from the corner of the mouth and placed 45 degrees from the midline, as recommended by Patel et al. (2018). The microphone recorded the acoustic output of the utterances, pre-amplified via a Xenyx 802 preamplifier (Behringer, Willich,

Germany) and digitized the output at 30kHz via a National Instruments 6312 USB Data Acquisition device (NIDAQ; National Instruments, Austin, TX).

Data Collection

During the endoscopy, participants were recorded producing /ifi/ repetitions under each condition in the following order: slow rate, regular rate, fast rate, mild effort, moderate effort, and maximum effort, in a sound attenuated booth. Each recording was triggered by a custom MATLAB algorithm (version 9.3; The MathWorks, Natick, Massachusetts: The MathWorks Inc.) that aligned the microphone signal to the high-speed video (HSV) recording at the point of acquisition. For each condition, a minimum of two recordings were completed. Additional recordings were conducted in the event of unclear vocal fold movement as determined by the investigator conducting endoscopy, resulting in a minimum of 12 recordings for each participant. Due to the memory limitations of HSV imaging, the recordings were limited to a duration of 7.94 seconds when the adult endoscope was used, and a duration of 8.73 seconds when the smaller pediatric endoscope was used.

Data Analysis

Technician Training. Eleven technicians were trained to use a semi-automated algorithm to determine the change over the glottal angle waveform over time. The training was split into two portions – manual glottal angle tracking and the use of the semi-automated algorithm. The technicians were first trained on manual glottic angle determination. This training was performed on unobstructed, well-lit imaging collected via a flexible endoscope equipped with a halogen light source recording at a standard

sampling rate of 30 frames per second (fps). Technicians were required to attain a two-way mixed-effects intraclass correlation coefficients (ICC) of at least 0.8, when comparing their angles to a pre-determined gold standard before they were permitted to continue. Thereafter, the technicians were trained to utilize a semi-automated glottic angle tracking algorithm to estimate the change in glottic angles of video frames captured during an /ifi/ productions that were time aligned to the NIDAQ microphone signal (Diaz-Cadiz et al., 2019). To use the interactive algorithm, technicians were first required to demarcate the midline of the glottis from the anterior commissure to the bilateral vocal processes (Figure 1A), confirm the desired rotation (Figure 1B), and restrict the window of the position of the anterior commissure during the automated tracking (Figure 1C and 1D). Following this, they selected exemplary pixel shades from the glottis to differentiate the vocal fold edges from the glottis (Figure 1E). Using this information, a least square regression was used to determine the vocal fold edges (Figure 1F). The angle made from their intersection was then used to determine the corresponding glottic angle. Technicians were similarly required to attain a two-way mixed-effects ICC of at least 0.8 when comparing their angles to a pre-determined gold standard before they were deemed proficient in glottal angle tracking with the algorithm.

HSV Data Processing. The technicians first determined the usability of the recordings of the /ifi/ utterances via visual inspection. Utterances were excluded if they had insufficient image resolution, obstruction of the glottis, or incomplete capturing of an /ifi/ production due to the duration limitations during HSV recording. Of the remaining recordings, the technicians made use of the aforementioned semi-automatic angle tracking algorithm to

track the change of the glottic angles over time using a graphical user interface. The glottic angle profile was subsequently time-aligned with the microphone and accelerometer signals and the glottic angular velocity waveform of the relevant /ifi/ utterance (Figure 2). During tracking, cases with extraneous variables, such as image darkness and partial obstruction from supraglottic structures that resulted in an inappropriate determination of the glottic angles using the algorithm, were separated and technicians were given the option to manually mark the angles at a rate of 50fps. Thereafter, their markings were incorporated into the determination of the position of the

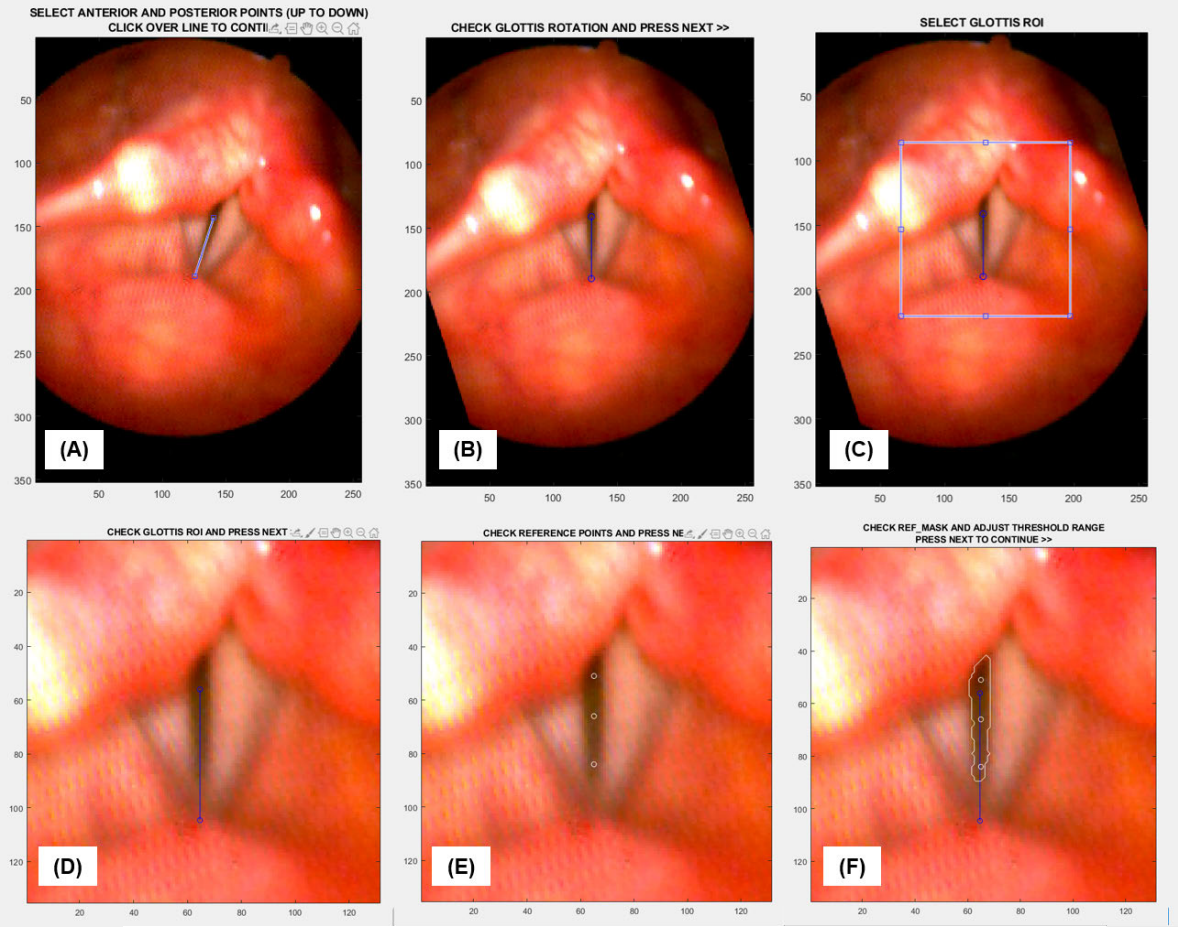

Figure 1. ***Semi-automated glottic angle tracking algorithm***

anterior commissure. In cases where errors occurred, the HSV recordings were ultimately recorded as unusable.

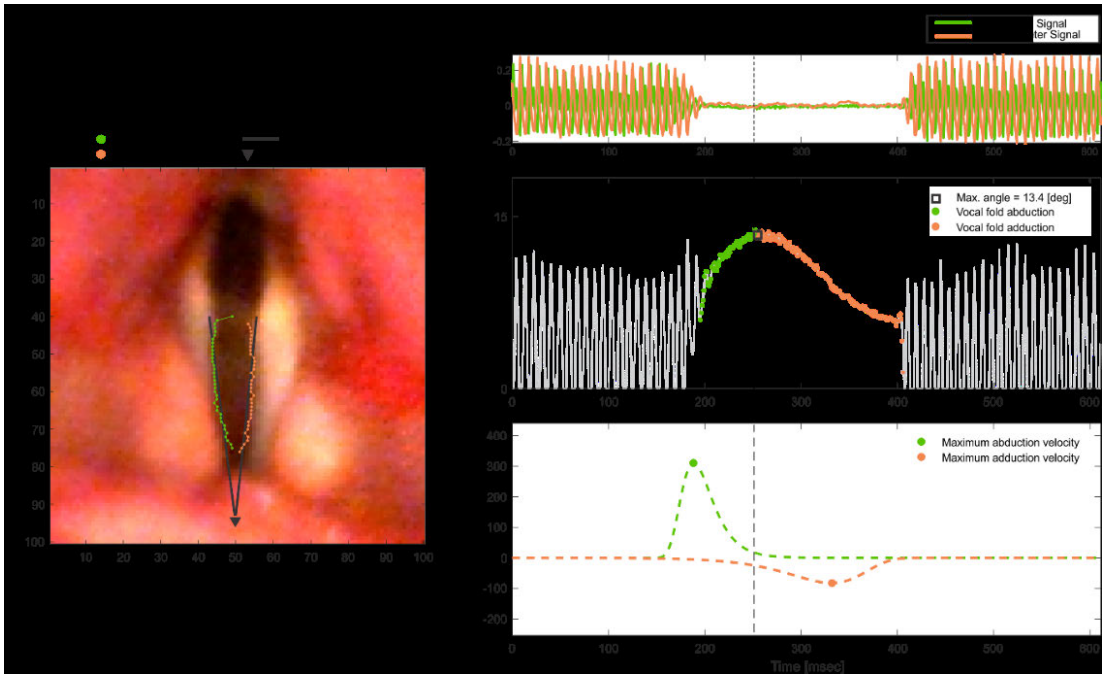

Figure 2. ***Glottic Angle Extraction from a Participant without PD***

Of the usable HSV recordings, glottic angle profiles were extracted. Smoothing of the raw profiles was given precedence over the use of a sigmoidal function fit due to the comparable frame rates that HSV provides in the characterization of vocal fold movement (Diaz-Cadiz et al., 2019). The data were smoothed with a 15th order, zero-phase, low-pass, Hamming-window-based FIR filter with a cut off at 25 Hz (Diaz-Cadiz et al., 2019).

Subsequently, three technicians made use of the combination of a quick vibratory profile (QVP), the time-aligned microphone signal, and the changes in the glottic angle waveform to determine the points of maximum abductory (t_{max}) and the offset (t_{off}) and

onset (t_{on}) times with a custom MATLAB graphic user interface (Diaz-Cadiz et al., 2019). The QVP is a one-dimensional waveform characterizing vocal fold vibration during phonation while considering other non-glottic movements, such as camera and epiglottic movement (Ikuma et al., 2013). The QVP was implemented to supplement the glottal area waveform as it provides a clearer representation of the harmonic structure, is highly sensitive to HSV, and its implementation of 3D glottal area segmentation effectively depicts phonation. The QVP was determined with the following measures: (i) The HSV frames were centred on the glottis using the semi-automatic glottic angle extraction, (ii) horizontal and vertical profiles of the HSV frames were calculated as described in Ikuma et al. (2013), (iii) The resultant QVP was filtered to attenuate low frequency energy below 50 Hz using a 7th order Butterworth filter. Of the three time points collected, t_{max} corresponds to the point in the recording at which the maximum abductory glottal angle during the production of /f/ is observed, whereas t_{off} corresponds to the discontinuation of vocal fold vibration before /f/. t_{on} corresponds to the commencement of vocal fold vibration during the onset of /i/ given there was no abrupt closing of the vocal folds before vibration commenced. In cases with an abrupt closing, t_{on} corresponded to the timing right before the abrupt closure. The time points determined via the glottal waveform and the microphone signal were then verified by inspection of the respective HSV images. This ensured that errors such as changes in lighting and small glottal gaps did not affect the determination of the selected timings. The time-aligned microphone signal was an additional fall-back measure to orient the technicians if either of the initial measures were compromised. However, use of the microphone signal

warranted flagging for reprocessing or rejection of the /ifi/ utterance. For detailed methodology employed, refer to McKenna et al. (2016), McKenna et al. (2019), Vojtech et al. (2021), Groll et al. (2020), and Park et al. (2021).

Secondary Tracking. Previous studies employing the semi-automated glottic angle tracking algorithm and manual angle tracking were focused on single-point data measures, including maximum angles and time points. However, the present study was additionally concerned with the accuracy of the glottic angle waveform, since the kinematic measure of STI is concerned with variations from a predetermined movement template. Therefore, two trained technicians determined the usability of the remaining extracted glottic angle profiles. The technicians considered additional factors including the degree of movement of the anterior commissure, inaccurate demarcation of analysis window, and early termination of the adductory phase of vocal fold vibration.

Kinematic Analyses

Spatiotemporal Index (STI). One speculation is that, similar to articulatory movement in PwPD, vocal fold movement will also be more variable compared to controls. To determine the extent of the variability, an STI will be calculated. Initially employed to measure spatial and temporal variability in articulatory movement in speech, the STI is the sum of standard deviations from the average pattern of movement of the articulator by time- and amplitude- normalizing each production (Smith et al., 1995; Wohlert & Smith, 1998). In this study, the data parsing began at t_{max} and concluded at $t_{on,}$ to reflect the period of adduction for each /ifi/ utterance. Data was subsequently filtered via a low-pass filter, as described earlier, in both the forward and backward directions,

before the displacement signal is interpolated in the time and amplitude domains with a cubic spine procedure, as described by previous studies employing STI as a measure of variability in movement (Anderson et al., 2008; Chu et al., 2020; Kleinow et al., 2001; Lucero, 2005).

Asymmetry Index (AI). As mentioned in Adams et al. (1993), according to past research, velocity profiles of both laryngeal movements (Munhall et al., 1985) and articulatory movements (Ostry et al., 1987) have been observed to approximate a symmetric bell-like shape. The regularity in the shape of velocity profiles suggests an underlying optimization mechanism that results in the most efficient motor plan to achieve the speech movements necessary for each rate and effort condition. This is likely a reflection of well-defined feedforward motor plans that are habitually adopted by the laryngeal and articulatory subsystems to maximize the efficacy of speech movements. However, PwPD, as previously mentioned, have weak motor control in their feedforward systems, resulting in hyperactivity in auditory feedback and atypical sensorimotor integration. This may be reflected on the velocity profile in the form of multiple subpeaks, a skew in the peak timing of velocity, or increased acceleration and deceleration (the steepness of the resultant profile). Therefore, we determined the asymmetry of the velocity of the movement of the vocal folds by finding the ratio between $t_{max} - t_{on}$ and $t_{off} - t_{max}$ durations. Thereafter, the specific characteristics of each skew better allowed us to determine the contributions of the feedforward and feedback systems for each rate and effort condition within the performance of each participant.

Kinematic Stiffness Ratio (KS). PwPD have increased baseline laryngeal tension due to hyperactivation of intrinsic laryngeal musculature at rest (Zarzur et al., 2014; Zarzur et al., 2007). This may affect their ability to vary laryngeal tension across different rate and effort conditions. Therefore, we used KS as a potential correlate of laryngeal tension, calculating it via the equation below:

$$Kinematic\ Stiffness\ Ratio\ = \frac{Maximum\ Adduction\ Velocity}{Maximum\ Glottic\ Angle}$$

Statistical Analysis

Each participant had at least one sample deemed usable in each rate and effort condition, as determined by the technicians. Thereafter, any rate or effort condition with less than seven samples was discarded for that participant. For the STI measure in particular, values were only used if 7 tokens were available in the rate or effort condition to be calculated, as using fewer tokens deflates corresponding STI measures (Wisler et al., 2022). Statistical analyses were conducted with *Minitab* statistical software (Version 17; Minitab Inc., State College, PA). Three repeated-measures analysis of variances (ANOVAs) were carried out to determine the impact of group (PwPD and age- and sex-matched controls) and rate (slow rate, regular rate, fast rate) on the three respective kinematic measures (STI, AI, and KS). Three separate repeated-measures analysis of variances (ANOVAs) were carried out to determine the impact of group (PwPD and age- and sex-matched controls) and speaker-modulated effort (regular effort, mild effort, moderate effort, maximum effort) on the three respective kinematic measures (STI, AI, and KS). The ANOVAs were used to examine the presence of significant interactions

between group and rate or group and effort for the kinematic outcome measures of STI, AI, and KS, thus addressing hypotheses 1a, 2a, and 3a respectively. An alpha value of < 0.05 was used for significance testing. Partial eta-squared (η_p^2) was used to determine the effect sizes of significant main effects.

Results

The 48 participants (24 PwPD, 24 age- and sex-matched controls) produced /ifi/ utterances across six conditions, generating data for STI, AI, and KS. Of the possible 864 data points (48 participants × 6 conditions × 3 variables), 776 were analyzed. The first 69 missing data points were discarded when participants had fewer than 7 usable /ifi/ utterances, corresponding to 40% of the data expected. For STI in particular, we wanted a minimum threshold of 7 utterances as reducing the number of utterances contributes to the deflation of STI values (Wisler et al., 2022). Thereafter, the remaining 19 data points discarded were extreme outliers (x), where x < Q1 - 3 * IQR or x > Q3 + 3 * IQR, where Q1 was the first quartile value, Q3 was the third quartile value, and IQR was the interquartile range. The missing data points did not appear to influence the distribution of the data set as they were spread across participants. All data met the assumptions of the selected statistical model.

Across all voice tasks, PwPD exhibited higher STI values at each condition. AI values were higher for PwPD for all conditions except the mild effort condition. KS values were higher for PwPD in all conditions except the regular effort condition. Figure 3 shows the changes in kinematic measures for each group at each rate and effort

condition. Table 2 reflects the significance of the repeated measures ANOVAs for the main effects of group and condition, and the interaction effects between group × condition. Figure 4 shows the overall differences in kinematic measures between groups for rate and effort conditions respectively.

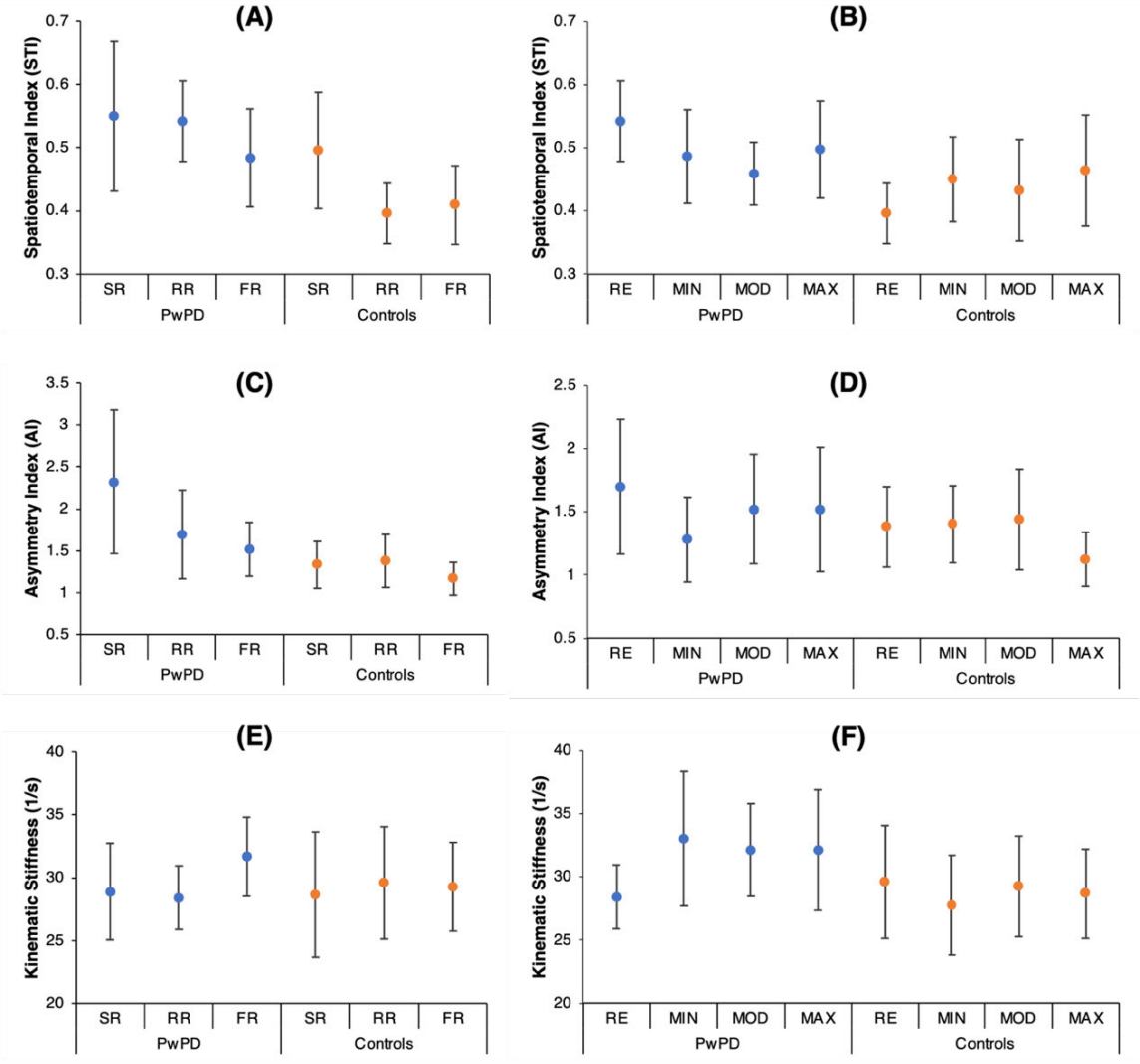

Figure 3. ***Interval Plots for Kinematic Measures – 95% Confidence Interval***

Table 2.

Results of Repeated Measures Analyses of Variance for Kinematic Measures.

Measure	Rate/ Effort	Effect	*df*	*F*	*p*	η_p^2	Effect size
Spatiotemporal Index (STI)	Rate	Group	1	8.27	0.005**	0.065	Medium
		Condition	2	1.87	0.159	–	–
		Group x Condition	2	0.76	0.469	–	–
	Effort	Group	1	5.64	0.019*	0.032	Small
		Condition	3	1.24	0.810	–	–
		Group x Condition	3	0.32	0.299	–	–
Asymmetry Index (AI)	Rate	Group	1	9.42	0.003**	0.072	Medium
		Condition	2	2.38	0.097	–	–
		Group x Condition	2	1.38	0.256	–	–
	Effort	Group	1	0.56	0.248	–	–
		Condition	3	0.68	0.656	–	–
		Group x Condition	3	0.03	0.590	–	–
Kinematic Stiffness Ratio (KS)	Rate	Group	1	0.09	0.762	–	–
		Condition	2	0.45	0.640	–	–
		Group x Condition	2	0.45	0.640	–	–
	Effort	Group	1	3.08	0.081	–	–
		Condition	3	0.26	0.852	–	–
		Group x Condition	3	0.83	0.481	–	–

Note. *Significant at $p < .05$. **Significant at $p < .01$.

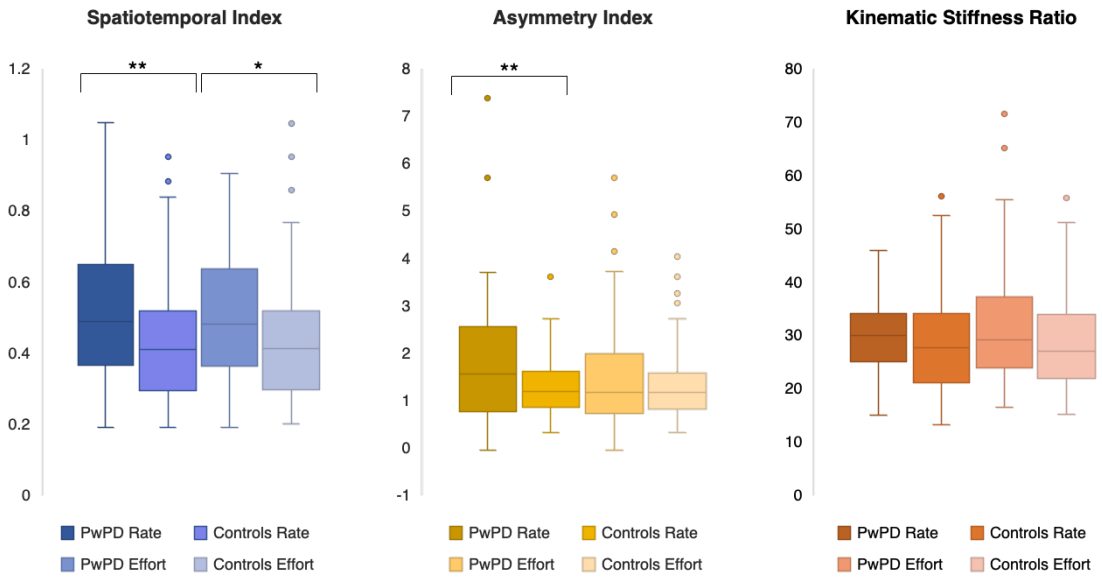

Figure 4. ***Box and Whisker Plots Depicting Overall Differences Between Groups. Asterisks are placed for significant (*p < .05, ** p < .01) differences.***

Spatiotemporal Index (STI)

PwPD exhibited higher STI overall for both the rate (*M* = 0.52*, SD* = 0.19, Range: 0.19 – 1.05) and speaker-modulated vocal effort (*M* = 0.50*, SD* = 0.16, Range: 0.19 – 0.91) conditions compared to controls, with lower STI for rate (*M* = 0.43*, SD* = 0.17, Range: 0.19 – 0.95) and effort (*M* = 0.44*, SD* = 0.18, Range: 0.20 – 1.05) respectively (Figure 3). For the rate conditions, there was a statistically significant main effect of group on STI derived from vocal fold movement, F (1, 24) = 8.27, $p < .05$, with a medium effect size of $\eta_p^2 = .065$. However, there was no statistically significant main effect of rate on STI. There was additionally no statistically significant interaction effect of group × rate. For the effort conditions, there was a statistically significant main effect of group on STI, F (1,24) = 5.64, $p < .05$, with a small effect size of $\eta_p^2 = .032$. However, there was no statistically significant main effect of effort, or interaction effects of group × effort.

Asymmetry Index (AI)

PwPD exhibited higher AI overall for both the rate (*M* = 1.79, *SD* = 1.30, Range: -0.06 – 7.39) and speaker-modulated effort (*M* = 1.51, *SD* = 1.09, Range: -0.05 – 5.70) conditions compared to controls, with lower AI for rate (*M* = 1.29, *SD* = 0.63, Range: 0.32 – 3.61) and effort (*M* = 1.34, *SD* = 0.76, Range: 0.31 – 4.03) respectively. Across rate conditions, there was a statistically significant main effect of group on AI observed, F (1, 24) = 9.42, $p < .05$, with a medium effect size of $\eta_p^2 = .072$. There was no statistically significant main effect of rate or interaction effect of group x rate. For effort conditions, there were no statistically significant main effects of group or effort, or

interaction effects of group × effort**.**

Kinematic Stiffness Ratio (KS)

Overall, PwPD exhibited higher KS overall for both the rate (*M* = 29.74, *SD* = 7.17, Range: 14.99 – 45.92) and speaker-modulated effort (*M* = 31.42, *SD* = 10.05, Range: 16.46 – 71.49) conditions compared to controls, with lower KS values for rate (*M* = 29.18, *SD* = 10.20, Range: 13.23 – 56.04) and effort (*M* = 28.84, *SD* = 9.47, Range: 15.09 – 56.21) respectively. However, across both the rate and effort conditions, there was no statistically significant difference of both the main effects of group and rate or group and effort, as well as no statistically significant interaction effect of group × rate or group × effort**.**

Effect Sizes

Partial eta squared (η_p^2) was used to determine the effect size of significant main effects. STI was statistically significantly higher in PwPD compared to controls across rate conditions, with a medium effect size, η_p^2 = .065, and across effort conditions, with a small effect size, η_p^2 = .032. AI was statistically significantly higher in PwPD compared to controls across rate conditions, with a medium effect size, η_p^2 = .072.

Discussion

The present clinical diagnosis of PD involves observation of emerging cardinal motor features, including rest tremor, rigidity, bradykinesia, and postural instability (Duffy, 2019). However, these motor symptoms become readily apparent later in the disease process, when 60–80% of striatal dopamine has been lost (Bernheimer et al.,

1973). Considering the prevalence of communication issues in PwPD, it is pivotal to consider symptoms that manifest earlier in the disease course of PD to encourage early intervention, minimizing the negative impact impaired communication has on interpersonal relationships (Miller et al., 2006). The purpose of this study was to determine if speech rate and speaker-modulated vocal effort affect kinematic measures of vocal fold movements observed using HSV in PwPD differently than age- and sex-matched controls, as a means of providing more information regarding laryngeal involvement in the pathophysiological profile of PwPD.

Notably, for both AI and KS measures, there were no statistically significant differences between groups across speaker-modulated effort conditions, and no significant interactions between groups and speaker-modulated effort conditions. This could be attributed to the effect of conscious phonatory effort on voice outcomes in PwPD (Ramig et al., 2001).

Spatiotemporal Index (STI)

The basal ganglia-supplementary motor area (SMA) circuit is one of the areas that is pivotal in feedforward control (Cunnington et al., 1996; Nixon & Passingham, 1998). However, previous literature has revealed breakdowns in the basal ganglia-SMA circuit in PwPD (Haslinger et al., 2001), which might lead to feedforward control dysfunction (Alm, 2004). Thereafter, PwPD exhibit hyperactive feedback systems as a compensatory mechanism to account for the decreased involvement in the feedforward control system (Yu et al., 2007). Increased incorporation of feedback into speech motor control increases the variability of movement. Considering similar increases in variability noted for

articulatory movement (Kleinow et al., 2001) and acoustic signals (Anderson et al., 2008) in PwPD, we anticipated increased variability would likewise be observed with vocal motor control, as reflected in an increased STI. Therefore, we hypothesized that PwPD would exhibit greater STI in their vocal fold movements than their control counterparts at each condition. Our results were consistent with what we expected, with STI of PwPD being higher for all rate and speaker-modulated vocal effort conditions compared to controls. When comparing PwPD to controls, PwPD had statistically significantly higher STI values across both rate and effort conditions.

When evaluating across the various rate conditions, it is important to consider the time needed to incorporate feedback into the /ifi/ productions and how it would impact the variability in vocal motor control within PwPD. PwPD demonstrate relatively intact auditory vocal motor control (Abur et al., 2021). However, increases in speaking rate limit the incorporation of feedback motor control mechanisms in real-time productions. Since vocal fold adduction has an average duration of 104 – 227 ms (Dailey et al., 2005) and correction following auditory feedback takes between 100 – 120 ms (Burnett et al., 1998), we theorized that the slow rate would allow for more incorporation for auditory feedback. Considering the hyperactivity of the feedback system in PwPD, we hypothesized that this would account for greater changes in STI across rate conditions, and PwPD would demonstrate greater decreases in STI as rate increases. However, the results of this study revealed greater differences in STI between the fast and slow rates in the controls compared to PwPD, though the differences between rates and group × rate interactions were not statistically significant. These findings suggest that greater baseline

hyperactivity of feedback in PwPD does not result in larger increases in variability given sufficient time for incorporation of auditory feedback. One possible explanation for this observation is that PwPD have a higher baseline level of STI due to high production variability in repeated productions compared to controls. Thus, even with additional auditory feedback, there might exist a ceiling effect that minimizes the change in variability in PwPD.

Finally, we hypothesized smaller decreases in STI as effort increases in PwPD compared to controls. As effort increases, the degrees of freedom for movement, and subsequently the range of motion, decrease. However, since PwPD present with a higher baseline level of tension, there is a smaller increase from the baseline regular effort condition to the maximum effort condition. This results in less contributions in effort in minimizing the variability of VF movement in PwPD, and results in smaller decreases in STI as effort increases. However, our findings did not confer with our hypothesis, as STI decreased more in PwPD as speaker-modulated vocal effort increased in PwPD compared to controls. Notably, the STI in controls increased as the speaker-modulated effort level increased. This is not consistent with anticipated reductions in degrees of freedom as effort increases, which would result in decreases in STI rather than an increase. One possible explanation for this phenomenon might be that the control group has robust feedforward systems. As such, at a regular rate and effort, the glottic waveform is optimized. As effort increases, there is increased variability as controls must adjust for unprecedented exertion of effort during the utterance.

Asymmetry Index (AI)

Similar to STI, the AI is impacted by the contributions of the feedforward and feedback systems into the final motor target. Feedforward driven movement patterns were anticipated to be symmetric, as they have been continually fine-tuned to optimize efficiency of reaching the desired movement. However, due to impaired feedforward control in PwPD, we anticipated less symmetrical movement, and higher AI values across all rate and effort conditions. Our observations largely aligned with out hypothesis, as PwPD demonstrated higher AI values across all conditions compared to controls, except the mild effort condition. Overall, PwPD demonstrated statistically significantly higher AI values across rate conditions.

When accounting for differences across rate conditions, we hypothesized that there would be larger differences in AI between slow and fast rates for PwPD compared to age- and sex-matched controls. Slow rates of speech provide the speaker with more time for auditory feedback, which might further destabilize the movement of the vocal folds. For PwPD with atypical sensorimotor integration, this may manifest as subpeaks in the velocity profile due to multiple movement start points as a result of delayed feedback incorporation. Since we calculated the AI as the ratio of the deceleration duration to the acceleration duration, incorporation of auditory feedback from slower rates might increase the amount of time in deceleration, as there is no longer one smooth, symmetrical velocity profile. Our findings were congruent with our hypothesis, as there was a statistically significant interaction effect of group and rate condition on asymmetry, with the AI of the slow rate in PwPD being significantly higher than that of controls.

Finally, we hypothesized that PwPD would exhibit smaller differences in AI between mild, moderate, and maximum effort conditions compared to controls. Baseline levels of tension in PwPD reduce the degrees of freedom in movement, even for milder effort conditions. Therefore, the maximum effort condition in PwPD would have smaller absolute changes in effort, which may result in smaller differences in AI values across effort conditions. Our findings were not fully congruent with our hypothesis. Although PwPD demonstrated smaller difference across effort conditions compared to controls, there was no significant interaction effect of group × effort to differentiate PwPD from controls across effort conditions.

Kinematic Stiffness Ratio (KS)

PwPD have increased levels of baseline laryngeal tension in intrinsic laryngeal musculature (Zarzur et al., 2014; Zarzur et al., 2007). As a result, we expect KS to have higher baseline values across all conditions in PwPD. However, there was no statistically significant difference between the KS of PwPD and controls in any condition.

For rate conditions, we hypothesized smaller differences in KS between the slow and fast production rates for PwPD compared to controls, consistent with other populations, such as individuals with hyperfunctional voice disorders, who have increased baseline levels of tension (Stepp et al., 2010). However, our results were not in agreement with our hypothesis. KS was not statistically significantly different across group and rate, as well as across interactions of group × rate. This difference might be explained by the low sampling rate (30 fps) adopted in the aforementioned study, which could be a source of estimation error. Vocal fold assessment via HSV, particularly

determination of mucosal wave magnitude and extent, are sensitive to frame rate (Popolo, 2018). The raw adductory vocal fold trajectories based on HSV data can be sufficiently accurately fitted by sigmoidal curves generated with at least 120 frames per second (Diaz-Cadiz et al., 2019). In addition, adductory trajectories for the vowel consonant vowel (VCV) utterance /ifi/ occur over 150 ms (McKenna et al., 2016). Taken together, this postulates that a minimum frame rate of 1000 fps can sufficiently characterize the vocal fold trajectory of adduction during an /ifi/ utterance. Therefore, the low sampling rate of 30 fps in previous research might have resulted in estimation errors that led to overall differences in the KS results observed in prior studies compared to the current study.

For effort conditions, previous research has attributed greater contributions to changes in vocal effort to be made by extrinsic laryngeal musculature relative to intrinsic laryngeal musculature. (McKenna et al., 2019). Therefore, we anticipated that there would be negligible differences in KS between effort conditions when comparing controls and PwPD. The findings were consistent with our hypothesis, as there was no statistically significant effect of group, effort, or the interaction between group and effort on KS.

Limitations and Future Work

One of the primary limitations of the study is that all rate and effort conditions were initiated with auditory cues. In fact, the rate conditions included the use of metronomes for rate regulation. Gait studies have previously shown that auditory cues are effective in treating gait disorders (Spaulding et al., 2013). Therefore, use of auditory

cueing could have had a priming effect on the participants with PD in the study. This priming effect has likewise been observed in speech movements, as external auditory cues facilitate auditory-motor integration in PwPD (Huang et al., 2016; Weir-Mayta et al., 2017). As a result, the use of external cuing may have obfuscated any differences that would have otherwise been noted between the two groups. The interpretation of results from the effort conditions is further limited by the ambiguity of the multidimensional concept of "vocal effort". Although Hunter et al. (2020) have attempted to formulate a consensus description of vocal effort among practicing clinicians, vocal effort is speaker modulated exertion associated with voicing. It cannot be fully encompassed by tangible physical changes. Therefore, the participants' interpretation of instructions to increase their effort in the mild, moderate, and maximum effort conditions were likely individualized and subjective, and the minimal significance of the interaction effects between groups and effort conditions could reflect minimal physical variability when cued to increase vocal effort instead.

In addition to cuing, the decontextualized nature of the experimental stimuli limited the generalizability of conclusions within the context of functional communication. The /ifi/ utterances used are dissimilar to conversational speech. Additionally, repeated utterances of /ifi/ over the course of the study might have automatized its production as the nasoendoscopy proceeded. As a result, the findings should not be generalized to typical speech. Future studies should consider the use of spontaneous speech samples to simulate naturalistic conversation.

Finally, the AI values in PwPD during the slow condition should be interpreted with caution. Excessive incorporation of auditory feedback in PwPD for the slow condition might result in multiple peaks and movement commands, rather than one smooth movement. Since the asymmetry index in this study was calculated finding the ratio between t_{max} to t_{on} (deceleration) and t_{off} to t_{max} (acceleration), additional peaks might modify the t_{max} value, and thus, the AI values for PwPD.

Conclusion

The present study found that STI and AI were statistically significantly higher in PwPD compared to controls across rate conditions, and STI was statistically significantly higher in PwPD compared to controls across effort conditions. Additionally, no statistically significant differences were observed across speaker-modulated effort conditions in AI and KS between PwPD and controls in this study, suggesting a net positive effect of increasing speaker-modulated vocal effort on normalizing laryngeal movements within PwPD. These results endorse continued use of programs encouraging increases in phonatory effort, including the Lee Silverman Voice Therapy, as increasing speaker-modulated vocal effort minimized statistically significant differences in measures of variability of vocal fold movement. These findings suggest that laryngeal kinematics in PwPD might be different from that of age- and sex-matched controls, and further investigation is required and warranted to quantify consistently measurable differences between the two populations to bolster our current understanding and diagnoses in the early stages of PD.

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