Voice Tremor in Parkinson's Disease: An Acoustic Study

***Patricia Gillivan-Murphy, †Nick Miller, and ‡Paul Carding,** **Dublin, Ireland, †Newcastle-Tyne, United Kingdom, and ‡Brisbane, Queensland, Australia*

Summary: Background: Voice tremor associated with Parkinson disease (PD) has not been characterized. Its relationship with voice disability and disease variables is unknown.
Objectives: This study aimed to evaluate voice tremor in people with PD (pwPD) and a matched control group using acoustic analysis, and to examine correlations with voice disability and disease variables.
Methods: Acoustic voice tremor analysis was completed on 30 pwPD and 28 age-gender matched controls. Voice disability (Voice Handicap Index), and disease variables of disease duration, Activities of Daily Living (Unified Parkinson's Disease Rating Scale [UPDRS II]), and motor symptoms related to PD (UPDRS III) were examined for relationship with voice tremor measures.
Results: Voice tremor was detected acoustically in pwPD and controls with similar frequency. PwPD had a statistically significantly higher rate of amplitude tremor (Hz) than controls ($P = 0.001$). Rate of amplitude tremor was negatively and significantly correlated with UPDRS III total score (rho −0.509). For pwPD, the magnitude and periodicity of acoustic tremor was higher than for controls without statistical significance. The magnitude of frequency tremor (Mftr%) was positively and significantly correlated with disease duration (rho 0.463). PwPD had higher Voice Handicap Index total, functional, emotional, and physical subscale scores than matched controls ($P < 0.001$). Voice disability did not correlate significantly with acoustic voice tremor measures.
Conclusion: Acoustic analysis enhances understanding of PD voice tremor characteristics, its pathophysiology, and its relationship with voice disability and disease symptomatology.
Key Words: Voice tremor−Parkinson disease−Acoustic analysis−Voice disability−Disease variables.

INTRODUCTION

Parkinson disease (PD) is strongly associated with phonatory dysfunction[1,2] and voice-related disability.[3−5] Tremor is one of the classic triad of motor symptoms in PD alongside rigidity and bradykinesia, and is a commonly described feature of voice quality in PD. Pathological voice tremor (ie, when associated with neurological disease) occurs when there is involuntary and rhythmical oscillatory movement in the vocal tract, which causes rhythmic fluctuations in the fundamental frequency and amplitude of the voice.[6,7] These fluctuations are perceived as rhythmic (quasi-rhythmic) fluctuations in pitch and loudness.

It is unclear how many people with PD have a clinically identified voice tremor. Auditory perceptual studies have reported a prevalence range of 13%−68%.[8,9] Visual (endoscopic) studies that identify tremor behavior have suggested a prevalence rate that varies from 14.6% to 55%.[10,11] One source of confusion is the varied terminology used in the literature: "tremorous voice"[12]; "tremulousness"[8]; "tremulous pitch (deficit in pitch steadiness)"[9]; "pitch unsteadiness"[13]; "perceptible vocal tremor"[12]; "flutter"[14]; "vertical laryngeal tremor"[11]; "laryngeal tremor"[15]; and "rhythmic amplitude tremor."[12] Further issues include the variance of the tasks used to elicit the tremor behavior and the lack of reported reliability of ratings.[5] Signal processing of the acoustic waveform may provide an accurate means of measuring voice tremor.

The acoustic waveform analysis has the potential to reflect the quasi-rhythmical movement of muscles in the vocal tract associated with voice tremor. The effect of oscillatory movement on the length of the vibratory cycle (frequency tremor) and/or the amplitude of the cycle (amplitude tremor)[16] can be measured in addition to the rate of the tremor (Hz).

Studies have used acoustic measurement to differentiate patients with neurological disease from healthy controls[16] and to differentiate between different neurological groups.[17]

Several previous studies have applied acoustic analysis to the study of voice tremor in people with PD (pwPD).[12,18−20] Two studies examined the presence of amplitude tremor[12,18] in pwPD. Ramig et al[12] described a "rhythmic amplitude tremor imposed upon cycle-to cycle deviancies," visually evident in the waveform of one of nine patients with PD, which differed from the waveform of the patients with myotonic dystrophy, and Huntington disease. Stewart et al,[18] using narrow band spectrographic analysis, visually identified fluctuations in both amplitude and frequency tremor aspects in 33% of a group of 12 patients with "early" PD. Zarzur et al[19] visually identified tremor in spectrogram tracings of VOXMETRIA and GRAM in 69.5% of a group of 26 pwPD. Across these studies, there was no quantification of the amplitude and/or frequency tremor, or comparisons with healthy controls.

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From the *Speech & Language Therapy Department, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland; †Newcastle University Institute for Ageing, Speech and Language Sciences, George VI Building, Newcastle University, Newcastle-Tyne NE1 7RU, United Kingdom; and the ‡National Course Coordinator in Speech Pathology, School of Allied and Public Health, Faculty of Health Sciences, Australian Catholic University, Brisbane Campus, Room 1 MCA Building, 1100 Nudgee Road, Banyo, Brisbane, Queensland 4014, Australia.
Address correspondence and reprint requests to Patricia Gillivan-Murphy, Speech & Language Therapy Department, Mater Misericordiae University Hospital, Eccles Street, Dublin 7, Ireland. E-mail: pgmurphy@mater.ie
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In contrast, Tanaka et al[20] compared male and female pwPD with age-matched healthy controls on a range of acoustic voice measures, including tremor parameters using the Multi-Dimensional Voice Program from the Computerized Speech Laboratory (CSL). They found that fundamental frequency tremor intensity index (%) and fundamental frequency tremor frequency (Hz) was significantly higher in male PD relative to controls, and that frequency tremor intensity index (%) only differentiated female PD from controls. It is not clear from the study if findings are based on one trial of a sustained /a/ vowel or on a number of trials.

Acoustic analysis of the waveform has significant potential value to enable an improved understanding of voice tremor in pwPD and help determine if there are differences between pwPD and neurologically healthy age-matched controls. The current literature is limited and has no clear conclusions regarding the characteristics of frequency and amplitude tremor in PD due to a combination of a small sample size; lack of a control group; a heterogenous grouping of patients; and the paucity of detailed information relating to the methods used. Therefore, the primary aim of the current study is to determine if acoustic voice tremor analysis differentiates pwPD from neurologically healthy controls, and to describe tremor characteristics in pwPD. A secondary aim is to place the acoustic voice tremor findings in the broader context of voice disability and disease variables.

METHODS

Participants

Ethical approval for the study was granted by the Ethics Committee of the Mater Misericordiae University Hospital. Two groups were recruited for the study: patients with idiopathic PD (PD group) and neurologically healthy controls (control group).

PD group

Consecutive patients attending a routine hospital movement disorders outpatient clinic with a diagnosis of PD[21] made by a consultant neurologist specialist in PD were screened for eligibility to take part. Presence of perceived voice tremor was not a requirement for entry inclusion. The following exclusion criteria were applied: a concomitant neurological disease; dementia [score $\leq$23 on the Mini-Mental State Examination][22]; a psychological/psychiatric disorder; taking tremor-inducing medication (lithium, anticonvulsant medication, immunosuppressants, bronchodilators); a current smoker or an ex-smoker for less than 5 years; a history of cancer of the head and neck region, speech or voice problems unrelated to and before the onset of PD; receiving speech/voice treatment or received Lee Silverman Voice Treatment in the previous 2 years; reported inadequate hearing (unable to hear conversational speech comfortably), and/or wearing hearing aids; unable to postpone dopaminergic medication for 12 hours in advance of study testing, and unable to fast for food and liquids (excepting water) on the morning that testing was carried out; non-native English speaker; and presence of dyskinesias severe enough to contraindicate vocal tract examinations (patients had a range of assessments carried out, including nasendoscopy for visual perceptual rating of tremor).

Control group

A healthy neurological age- and sex-matched group was recruited. The same inclusion and exclusion criteria applied as to the PD group. Controls were recruited by inviting family members of participants with PD, staff at the hospital, and parents of colleagues to get involved in the study.

General procedures

PwPD on a dopaminergic medication regime were tested in a practically defined "off" medication state, that is, after a 12-hour overnight withdrawal of anti-parkinsonian medication.[23] All PD and control participants were evaluated in the morning between 8:00 AM and 10.00 AM in a single visit to the hospital.

Disease duration was measured in years from the time of neurological diagnosis. PD overall severity was evaluated using the patient-derived questionnaire of Activities of Daily Living (part II) and the clinician-derived test of motor function (part III) from the Unified Parkinson's Disease Rating Scale (UPDRS).[21] Possible scores for UPDRS II range from 0 (unaffected) to 52 and 0 (unaffected) to 108 for UPDRS III.

A range of assessments were carried out as part of a larger study on voice tremor in PD. In addition to UPDRS testing, auditory perceptual speech and voice measures and nasendoscopy were carried out. Patients and controls completed the Voice Handicap Index (VHI) for patient self-rated voice disability.[24]

Voice recordings and data preparation

Voice recordings were carried out in a sound-treated room with ambient noise levels measured at 50 dB sound pressure level. An AKG-C420 head-mounted microphone connected to the CSL was placed on the participant's head and placed 10 cm from the angle of the mouth. A sustained /a/ vowel of 4.5-second duration was recorded directly onto the CSL, at a sampling rate of 50,000 Hz. Training trials were carried out before the test trials to ensure participants understood the task, and that any technical problems that might arise could be rectified in advance of the test trials. Participants were instructed to sustain the vowel /a/ at a comfortable pitch and loudness. The Voice & Tremor Protocol from CSL provides an example of a sustained /a/ vowel audio signal with additional visual wave form from a male voice (5-second duration). The participants were asked to listen to the registered voice from CSL, and then repeat the task. For the test trials, each participant sustained the vowel /a/ three

times and each recording was saved to the Kay data file for later analysis.

The recordings for each participant were trimmed to 3 seconds (the initial 1-second and final 0.5-second segment of the signal was removed) and re-digitized. Consistent with other studies, the value of 3 seconds was chosen because it was considered to be sufficiently long to afford reliable analysis.[25,26] The trimmed voice signals for the PD and control groups were used for acoustic analyses.

Acoustic analyses

The Voice and Tremor Protocol (VTP) from the Motor Speech Profile (MSP) (Advanced), a module of the CSL, Model 5141 from Kay Pentax (Lincoln Park, NJ), was used for the analysis.[27] The VTP yields a range of 9−13 voice- and tremor-related parameters, based on a sustained /a/ vowel task. An important aspect of measuring and classifying tremor is identifying the rate measured in cycles per second (Hz), the regularity or periodicity, and the extent or magnitude. Involuntary movement (nonperiodic) may be present in the vocal tract and is distinct from tremor. It is important to capture this phenomenon also with long-term measures of instability, which are sensitive to the detection of nonperiodic tremor.

For this study, the rate, periodicity, and magnitude of frequency and amplitude tremor were selected from the VTP as the key tremor measures for further analyses. The rate of tremor refers to the rate of modulation of fundamental frequency and/or amplitude in the voice signal, measured in cycles per second (Hz). In order for the rate of tremor to be determined, the voice tremor has to have a certain level of regularity. Periodicity (%) is a measure of the regularity of the tremor. The higher the periodicity, the more regular is the tremor. The magnitude (%) of tremor (frequency and amplitude) is a measure of the extent of variation in frequency and/or amplitude secondary to the effect of involuntary movement in the muscles of the vocal tract. Adjunctive measures of unsteadiness were also included. The selected VTP measures for the study are outlined below and for the purpose of completeness, descriptions of all the measures[27] generated from the VTP are outlined in the Appendix.

Key tremor measures

- Rate of frequency tremor [Rftr (Hz)]
- Rate of amplitude tremor [Ratr (Hz)]
- Periodicity of frequency tremor [Pftr (%)]
- Periodicity of amplitude tremor [Patr (%)]
- Magnitude of frequency tremor [Mftr (%)]
- Magnitude of amplitude tremor [Matr (%)]

Adjunctive measures of unsteadiness

- Coefficient of variations in fundamental frequency [(vFo) (%)]
- Coefficient of variations in amplitude [(vAm) (%)]

Data preparation

The mean value across the three /a/ trials was calculated for each acoustic measure.

Total scores for UPDRS II and III were recorded separately. For the VHI, a summed total score was obtained. Additionally, the scores from the physical, emotional, and functional items of the VHI were also summed, yielding three different subscale scores.

Data analysis

Statistical analysis was conducted in *SPSS* program version 17.0 (SPSS Inc. for Windows, Chicago, IL). Differences were considered significant at alpha level <0.05. Normality of distribution was determined for ordinal (UPDRS II and III, VHI) and for continuous data (acoustic measures) using the Kolmogoov-Smirnov test. To determine whether statistically significant differences existed between median sores of pwPD and control groups, a Mann-Whitney *U* test was applied to the acoustic measures and VHI scores. Spearman rho was calculated to examine the relationship between acoustic voice tremor measures and disease duration, UPDRS II Activities of Daily Living, UPDRS III motor symptoms, and the VHI. When the acoustic tremor measures were plotted against disease duration, PD 5 emerged as an outlier. A review of the raw acoustic data showed wide variability of values across the three /a/ trials for Mftr, Matr, vFo, and vAm; thus, PD 5 was removed from the data pool for the correlational analysis. In the absence of previous studies that could provide reliable estimates of anticipated effect sizes for the chosen variables between people with and without PD, a *post hoc* power analysis of the acoustic tremor measures obtained for this study was carried out. The effect sizes established for this study formed the basis of estimates of the power of the current study to detect differences, given the sample sizes used.

Reliability

Twelve (20%) acoustic signal wave forms were independently re-digitized by a second researcher. For consistency's sake the first trial of each participant was chosen. Following re-digitization, a comparison was made by the independent researcher with the values from the original acoustic signal to determine (1) if both researchers were consistent in the way they trimmed the data for analysis; (2) if the values from the analysis had been correctly read off from the print out of the automatic analysis. Identical values were found for repeated analyses of the same segments; therefore, no further measures of agreement were calculated.

RESULTS

Table 1 shows the descriptive statistics for gender, age, age at diagnosis, disease duration, UPDRS II, and UPDRS III scores. There were no significant differences between PD and control groups by age or gender proportions, or between gender groups according to age.

TABLE 1.
Mean (SD), Range Values for Gender, Age, Age at Diagnosis, Disease Duration, UPDRS II, UPDRS III, and *P* Values for PD and Control Group

	PD Group (n = 30)	Control Group (n = 28)
Gender		
Males	22 (73%)	20 (71%)
Females	8 (27%)	8 (29%)
Age (y)		
Mean (SD)	61.40 (10.31)	60.11 (9.54)
Range	(34–76)	(36–74)
Males	60.95 (10.82)	59.55 (10.24)
Females	62.63 (9.29)	61.50 (7.96)
Age at diagnosis	56.17 (9.56)	
Range	32–70	
Disease duration (y)	5.23 (3.17)	
Range	(1–12)	
UPDRS II	10.20 (3.85)	
Range	(4–19)	
UPDRS III	25.00 (9.23)	
Range	(8–41)	

Acoustic tremor measures

Because of technical difficulties with the re-digitization, seven of the pwPD group had data on two instead of three trials. For controls, three participants had data on two trials and one participant had data on one trial. For pwPD and control participants with two trials, the mean value of the two trials was calculated.

The detection rate for frequency and amplitude tremor together with tremor rate, periodicity, and magnitude, effect sizes, and *P* values for pwPD and control groups is shown in Table 2. The MSP gives values for tremor rate and periodicity only for those speakers where it detects periodic perturbation. Therefore, data are based on the number in each group and condition where tremor was detected by MSP. Tremor was detected in pwPD and controls with similar frequency. For frequency tremor, pwPD had a higher rate, greater periodicity, and greater magnitude of tremor than controls. However, the difference was not statistically significant. For amplitude tremor, pwPD had a statistically significantly ($P = 0.001$) higher rate of amplitude tremor than controls. Periodicity of amplitude tremor was higher in pwPD than in controls, and approached significance. Magnitude of tremor was higher in pwPD than in controls without statistical significance. For coefficient of variation in fundamental frequency, pwPD had a higher percentage than controls without statistical significance. For coefficient of variation in amplitude, pwPD had a lower percentage than controls, although not statistically significant. Effect sizes (Cohen *d*) for rate, periodicity, and magnitude of frequency and amplitude tremor ranged from medium to large,

TABLE 2.
Tremor Detection Rate [n (%)], and Mean (SD), Range, Median, and IQR Values for Tremor Rate, Periodicity, Magnitude of Tremor (Frequency and Amplitude), and Coefficient of Variation (Fundamental Frequency, Amplitude) for pwPD and Control Groups

	Frequency Tremor			Amplitude Tremor		
Tremor Detected by MSP	PD	Control	Effect Size	PD	Control	Effect size
n (%)	13 (43.3)	10 (35.7)		16 (53.3)	17 (60.7)	
Tremor rate (Hz)						
Mean (SD)	4.39 (2.59)	3.03 (1.33)	0.661	4.94 (2.25)	2.85 (0.72)	1.251
Median	3.25	2.66		4.44	2.66	
IQR	2.43–6.54	2.29–3.03		3.40–5.69	2.30–3.35	
	$P = 0.19$			**$P = 0.001$**		
Periodicity %						
Mean (SD)	30.22 (16.50)	24.09 (8.11)	0.472	45.07 (10.64)	37.12 (12.35)	0.690
Median	25.14	22.61		43.40	38.84	
IQR	19.67–39.52	18.44–27.53		34.21–55.39	31.33–44.37	
	$P = 0.38$			$P = 0.057$		
Magnitude %						
Mean (SD)	0.91 (0.73)	0.71 (0.12)	0.382	3.23 (2.08)	2.27 (0.91)	0.598
Median	0.69	0.68		2.50	2.10	
IQR	0.40–0.69	0.37–0.63		1.49–3.11	1.59–2.22	
	$P = 0.71$			$P = 0.16$		
Variation of fundamental frequency (vFo%)				**Variation of amplitude (vAm %)**		
Mean (SD)	1.58 (2.5)	1.06 (0.5)	0.288	7.86 (3.43)	8.26 (3.03)	0.124
Median	1.06	0.93		6.85	7.93	
IQR	0.86–1.36	0.71–1.22		5.98–8.49	6.12–9.27	
	$P = 0.164$			$P = 0.335$		

Abbreviation: IQR, interquartile range.

TABLE 3.
Mean (SD), Range, Median, (IQR), and *P* Values for Total and Subscale VHI Scores for PD and Control Group

	PD (n = 30) M22, F8	Control (n = 27) M19, F8	*U*	*Z*	*P* Value
Total VHI					
Mean (SD)	19.50 (15.11)	4.00 (6.02)	156.000	−4.012	**<0.001**
Range	(0–49)	(0–24)			
Median (IQR)	19.00 (5.75–33.25)	1.00 (0.00–6.00)			
Subtests					
Functional					
Mean (SD)	6.53 (4.92)	2.00 (2.51)	185.500	−3.558	**<0.001**
Range	(0–16)	(0–9)			
Median (IQR)	6.50 (1.00–11.00)	1 (0.00–4.00)			
Emotional					
Mean (SD)	4.97 (5.16)	0.67 (2.13)	179.000	−4.025	**<0.001**
Range	(0–17)	(0–10)			
Median (IQR)	3.50 (0.00–9.00)	0.00 (0.00–0.00)			
Physical					
Mean (SD)	8.00 (6.16)	1.33 (2.34)	164.500	−3.964	**<0.001**
Range	(0–18)	(0–10)			
Median IQR	9.50 (0.75–13.00)	0.00 (0.00–2.00)			

Abbreviation: IQR, interquartile range.

with rate of amplitude tremor showing the largest effect size of 1.2. In contrast, effect sizes were smaller for long-term measures of frequency (vFo%) and amplitude (vAm%) variation (Table 2). Power analysis yielded values of 0.79 (Rftr Hz), 0.58 (Pftr%), 0.40 (Mftr%), and 0.29 (vF0%) for frequency tremor differences between pwPD and controls. For amplitude tremor differences, values of 0.999 (Ratr Hz), 0.86 (Patr%), 0.71 (Matr %), and 0.12 (vAm%) were found.

Relationship between tremor measures and VHI

Table 3 displays summary statistics for the VHI total and subscore results.

Correlational analysis of tremor measures and VHI total and subscale scores showed no significant correlations, positive or negative, for pwPD or controls (Table 4).

Relationship between tremor measures, and disease variables, and age

Table 5 shows that the magnitude of frequency tremor was positively and significantly correlated with disease duration. To ensure that increasing age was not a contributory factor to results, further analysis was carried out to explore the relationship between voice tremor measures and age for pwPD and controls. The findings show that there was no relationship between acoustic measures and age for pwPD. There were positive, significant relationships between acoustic measures and age for controls (Table 6).

Table 7 displays the correlational findings for acoustic measures and total score for UPDRS II and III. Rate of amplitude tremor was negatively and significantly correlated with UPDRS III total score.

TABLE 4.
Spearman (Rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and VHI Total and Subscale Scores, for PD and Control Group

	VHI Total and Subscale Scores							
	PD Group (n = 30)				Control Group (n = 27)			
Acoustic Measures	Total	Functional	Physical	Emotional	Total	Functional	Physical	Emotional
Rftr (Hz)	0.280	0.265	0.188	0.170	−0.351	−0.436	−0.149	−0.114
Ratr† (Hz)	−0.096	0.034	−0.044	−0.299	−0.219	−0.173	−0.173	−0.364
Mftr (%)	0.007	−0.049	0.047	−0.061	0.333	0.312	0.269	0.107
Matr (%)	−0.107	−0.150	−0.011	−0.123	0.213	0.186	0.185	0.049
vF0 (%)	0.052	0.085	0.028	0.026	0.145	0.161	0.078	0.112
vAm (%)	−0.155	−0.212	−0.126	−0.129	0.264	0.354	−0.042	0.251

TABLE 5.
Spearman Correlation Coefficient (Rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and Disease Duration With Outlier (PD5) Removed From the Analysis

Acoustic Measures	Disease Duration
Rate frequency tremor Rftr (Hz)	−0.147 (n = 12)
Rate amplitude tremor Ratr (Hz)	0.192 (n = 15)
Magnitude frequency tremor Mftr (%)	0.463*
Magnitude amplitude tremor Matr (%)	0.355
Variation in frequency vFo (%)	0.344
Variation in amplitude vAm (%)	0.202

* <0.05.

DISCUSSION

This is the first prospective study and the largest data set to report on acoustic voice tremor measures in pwPD and neurologically healthy controls. A primary aim of this study was to determine if there are differences between pwPD and neurologically healthy controls in relation to acoustic voice tremor measures. A secondary aim was to place the acoustic voice tremor findings in the broader context of voice disability and disease variables.

There were more males than females recruited into this study of 30 pwPD, with a male-to-female ratio of 2.75:1. In comparison with other studies, the ratio of males to females in this study is both higher than the 1.5 male-to-female ratio reported by Midi et al,[5] and lower than the 3.4 and 3.1 reported by Perez et al[11] and Goberman,[28] respectively. The age profile [(mean 61 (standard deviation (SD) 10), range 34 −76 years)] of the pwPD in this study was very similar to D'Alatri et al[29] (mean 60 years), Stewart et al[18] (mean 59 years), and Perez et al's[11] study (mean 65 years). The PD group represented the milder end of the disease spectrum in relation to disability. Disease duration was relatively short with almost 40% receiving their PD diagnosis within the previous 3 years.

TABLE 6.
Spearman Correlation Coefficient (Rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and Age (Years) for PD and Control Group, With PD 5 Excluded

	Age	
	PD Group (n = 29)	Control Group (n = 28)
Acoustic Measures	Rho	Rho
Rate of frequency tremor Rftr (Hz)	0.014 (n = 12)	−0.401 (n = 10)
Rate of amplitude tremor Ratr (Hz)	−0.284 (n = 15)	0.193 (n = 17)
Magnitude of frequency tremor Mftr (%)	0.1533	0.509†
Magnitude of amplitude tremor Matr (%)	−0.094	0.407*
Variation in fundamental frequency vFo (%)	0.103	0.528†
Variation in amplitude vAm (%)	0.160	0.340

* <0.05.
† <0.01.

TABLE 7.
Spearman Correlation Coefficient (Rho) for Rftr, Ratr, Mftr, Matr, vFo, Vam, and UPDRS II, UPDRS III, and UPDRS III Tremor Score

	UPDRS II Total Score	UPDRS III Total Score
Acoustic Measure	Rho	Rho
Rate frequency tremor (Hz)	0.283 (n = 13)	0.168 (n = 13)
Rate amplitude tremor (Hz)	−0.425 (n = 16)	−0.509* (n = 16)
Magnitude frequency tremor (%)	−0.009	0.099
Magnitude amplitude tremor (%)	−0.018	0.299
Variation in frequency (%)	−0.149	0.110
Variation in amplitude (%)	−0.126	0.111

* <0.05.

In the current study, frequency and amplitude tremor was detected by MSP in approximately 50% of pwPD. Amplitude tremor was detected in a slightly higher number of pwPD than frequency tremor. Other studies have reported the presence of frequency and amplitude tremor in a small sample of pwPD[12,18] on the basis of visual perception of tremor in a waveform. However, this study goes further with a larger sample size and quantification of the acoustic tremor measures.

An important finding is that frequency and amplitude tremor was also detected in controls, and that amplitude tremor was detected in a similar number of pwPD and controls. The study findings therefore indicate that frequency and amplitude tremor is a feature of this group of pwPD, and of neurologically healthy controls. Boutsen et al,[30] in a study of patients with ataxic dysarthria, also reported detection of frequency and amplitude tremor in a comparison group of 19 controls, using the same tremor protocol from MSP. However, they reported lower rates of detection than the current study, and this is likely to be explained by the fact that control participants in the current study were older than those in Boutsen et al's,[30] study.

The rate of tremor is one of the parameters used in the classification of tremors with a 4−6 Hz tremor rate

associated with rest tremor in PD.[31] In this study, the rate of frequency tremor did not differentiate pwPD from controls. However, the rate of amplitude tremor differentiated the groups. It appears, therefore, that the rate of amplitude tremor may be one useful diagnostic indicator in relation to PD voice symptomatology.[30]

The measure of periodicity relates to the regularity of the detected tremor. The detected frequency and amplitude tremor was more periodic (closer to 100%) in pwPD than in controls. Periodicity of frequency tremor varied much more in pwPD than in controls. This variability, coupled with the small sample size, may have resulted in the lack of statistical significance between the groups. The difference between the groups for periodicity of amplitude tremor approached significance.

The magnitude of frequency and amplitude tremor was greater in pwPD than in controls. However, it did not differentiate the groups. In relation to findings for pwPD, there were important similarities and differences between the present study findings and other studies. The magnitude of frequency tremor (median 0.69%) for pwPD in the current study was very similar to D'Alatri et al's[29] reported value (0.63%) in their study of 12 pwPD. In contrast, the magnitude of amplitude tremor (median 2.50%) was lower in the present study than the value of 4.72% reported by D'Alatri et al.[29] Both studies were similar with respect to acoustic analysis software, mean age of participants, and data collection in an off-medication state. However, there were also important differences between the studies, which may explain the difference in findings. Firstly, D'Alatri et al's study[29] reported median values were based on a single sustained /a/ trial, whereas the current study was based on the mean of three trials for each participant. Secondly, the pwPD group had deep brain stimulation carried out 2−5 years before the study evaluation was carried out. Finally, the participants in D'Alatri et al's study[29] had greater disease severity [higher scores on the UPDRS motor scale]. Deep brain stimulation is generally carried out on patients at the severe end of the disease spectrum, who are no longer benefiting from dopaminergic medication, and have significant tremor and/or dyskinesias. The mean disease duration for the present study was much lower at 5.23 years (range 1−12) versus 12.50 years (range 7−28) in D'Alatri et al's study.

In contrast to the present study findings, Jiang et al[17] reported that the "magnitude of amplitude modulation" differentiated their "pathological" tremor group (n = 10) from the normal control group. However, caution is required regarding interpretation of their findings in the context of the current study for two reasons. Firstly, they had a heterogeneous study group; seven had PD and one had "idiopathic tremor" (understood by this study's main author to be an "essential tremor"). Diagnostic information was not provided on the remaining two participants. Secondly, their method of quantifying the magnitude of amplitude tremor was different from the current study and from D'Alatri et al's[29] study. Jiang et al[17] applied Fast Fourier transform to generate power spectra from a 2-second simultaneously recorded acoustic and airflow signal. They developed a peak detecting algorithm to identify spectral peaks below 30 Hz and then calculated the peak prominence ratio for each spectral peak using a formula.

Ancillary tremor measures of overall variation in frequency (vFo%) and amplitude (vAm%) were included in this study to broaden the scope of the analysis and increase understanding of tremor measures. The findings show that pwPD had a greater amount of overall frequency variation (vFo) than controls, although the difference was not significant. An unexpected finding was the greater amount of variations in amplitude (vAm%) in the control than in the PD group, albeit again the difference was not significant. vAm % is a measure of the long-term variation in amplitude from any variations in the amplitude of the voice (periodic modulations, nonperiodic modulation, rising or falling amplitude).[27] The study findings indicate, therefore, that vFo and vAm do not differentiate pwPD from their matched controls, and suggest that pwPD and controls have similar levels of overall unsteadiness in the voice, using acoustic measurement.

An important additional finding in this study which has implications for clinicians and researchers using MSP is that the control group values for Mftr%, Matr%, vFo%, and vAm% were higher than the CSL-published norms.[27] These differences may be explained by a number of factors. Firstly, the participants were older in the current study than they were in the CSL sample. The mean (SD) age of the male and female combined group in this study was 60.11 (9.54); the mean (SD) age of the combined group published in the CSL manual was 37.9 (11.3) years. Age positively influences measures of frequency and amplitude modulation and overall variation. Secondly, CSL norms are based on speakers from the USA and it is unclear if these are representative of other cultures and nationalities. Thirdly, there were methodological differences, which may explain the different findings for controls. In the current study, the mean value of three trials was used in the analysis and the middle 3 seconds was selected for analysis. For CSL norms, two trials were obtained, but it is not reported if the mean value of the trials was used and/or if the middle 3 seconds was included.[27] Therefore, caution should be exercised when interpreting results generated from the MSP voice and tremor protocol for older patients.

Given the variability of populations examined, parameters measured, algorithms used, and methods for calculation of variables used in previous studies, it was not possible to arrive at a reliable *a priori* estimation of effect sizes that might exist between people with and without PD. To aid the interpretation of our findings and provide guidelines for future studies we conducted *post hoc* power analyses based on effect sizes found. In the context of some of the differences found between groups being small and statistically nonsignificant, coupled with large degrees of variability within groups, it was unsurprising that some of the resultant power estimations were small and indicated the need for much

larger group sizes if statistically significant differences were to be sought. This was true in particular for Mftr%, vF0%, and vAm%. However, for other measures, this study was sufficiently powered, adding to the conclusion that the differences observed were valid and reliable differences. This was true in particular for Rftr Hz, Ratr Hz, and Patr%. Matr % still attained a power of approximately 0.70, whereas Pftr% was somewhat lower (approaching 0.6). Although power analyses are necessary to rule out or minimize type 1 and II errors, it is also useful to view outcomes in the context of clinical utility.

Based on these findings one can infer that Rftr Hz, Ratr Hz, and Patr% represent good candidate variables for the differentiation of normal age-related tremor from pathological tremor, with Matr % and Pftr% not to be ignored. They should, therefore, form the core of future investigations into the topic. By contrast, the remaining variables appear not to be reliable differentiators. Even if a study were to have sufficient participants to be adequately powered to detect a difference in the variables that showed small effect sizes, the clinical utility of those differences would be arguably low.

The results show that the selected acoustic tremor measures were not predictive of the total VHI, or the VHI subscale scores, for pwPD. The finding that there was no relationship identified between acoustic tremor measures and voice disability is not surprising. It is difficult to relate objective acoustic measures to the self-perceived impact of a voice disorder which varies for each patient depending on their personality, social networks, family relationships, and occupation.[32] Although a number of studies have used acoustic and self-report measures[4,5,32,33] in voice evaluation of pwPD, no previous study has explored the relationship between acoustic voice tremor and self-reported voice disability. The current findings highlight the nonlinear relationship that exists between impairment and disability.[34] Acoustic tremor measures and self-report voice disability measures are not interchangeable, therefore, based on the current results.

An important finding is that this group of pwPD was found to have a significantly greater voice disability than an age- and sex-matched control group. Self-perceived voice problems in pwPD have been reported in other studies, some of which have also used the VHI.[4,5,33] The total VHI score for pwPD in the current study indicated a mild disability and was similar to the values reported by Frost et al.[4] Conversely, in their study, Carmichael et al[33] reported higher mean VHI scores [(mean 39.99 (SD) 22.35)] than those in the current study, which may be explained by the fact that their group had a greater disease severity profile than pwPD in the current study. There was a wide range of total VHI scores in the PD group (0–49), with some participants showing little or no voice-related disability. This is plausible because participants were not selected for the study based on auditory perceived speech or voice difficulties.

This preliminary work exploring voice tremor in the context of PD disease duration raises some interesting findings and questions. Results show that there was a significantly positive correlation between magnitude of frequency tremor Mftr% and disease duration in the current cohort. Therefore, as the length of time from diagnosis increased, there was a corresponding increase in the magnitude of tremor. This may be revealing of the pathophysiology of PD voice tremor. For example, the fact that Mftr% showed a stronger correlation with disease duration relative to Matr% may reflect that changes in the physiology of tremor over time impact more on the length of the vibratory cycle than on the amplitude. This is a preliminary supposition based on findings from a small sample of pwPD with relatively short disease duration.

UPDRS II is used widely clinically to document the impact of the disease on the person's activities of daily living. Speech and voice studies do not generally report data on UPDRS II; therefore, the findings here are novel and exploratory. Acoustic voice tremor was found not to relate positively or negatively to activities of daily living measured with UPDRS part II. Possible reasons for the lack of a relationship between the two measures are firstly, the level of disability as measured with UPDRS II may have been too low (mild) for any meaningful relationships to emerge. Secondly, computerized acoustic voice analysis was carried out at a discrete point in time, whereas global disability related to PD was measured on the basis of the pwPD self-perception of specific symptoms and activities (tremor, speech, handwriting, etc) over the preceding 2-week period. Item 5, which is the speech item in UPDRS II, relates to pwPD self-perception of speech intelligibility only and not to voice tremor or other speech/voice variables specifically. Finally, UPDRS II is a composite measure of pwPD self-reporting on different aspects of PD (walking, falling, tremor, handwriting, etc) and may not relate in any way to voice tremor.

The relationship between acoustic voice tremor and motor symptom severity (UPDRS III) showed mixed findings. As PD motor symptoms become more pronounced, there is a lowering of the rate of amplitude tremor (Ratr Hz). Neither the magnitude of tremor (frequency, amplitude) nor the overall variation of frequency or amplitude related in any way to UPDRS III scores. The findings suggest that as the disease process develops (increase in motor symptoms), the rate of tremor (amplitude) becomes slower. The rate of amplitude tremor differentiated pwPD from controls, which strengthens the finding that Ratr and UPDRS are related at least in this group of pwPD. Pathological tremor is associated with a lower rate of tremor than normal "physiological tremor." One could speculate, therefore, that the pathophysiology of voice tremor changes over the course of the disease, leading to a lowering of the rate which translates into it being more noticeable clinically in more advanced stages of the disease.

CONCLUSION

The findings show that there are similarities and differences between pwPD and healthy controls when voice

tremor is measured acoustically. Voice tremor is a feature of pwPD and controls, and, thus, it is imperative to have an age-matched control group when studying voice tremor in PD. To differentiate pwPD from neurologically healthy controls, the rate of tremor (Hz) (amplitude and frequency) and the periodicity (%) of amplitude tremor appear to be the most useful acoustic measures. Voice tremor increases in magnitude as the length of time from PD diagnosis increases. Although pwPD had significantly greater voice-related disability than controls, acoustic voice tremor was not a contributory factor. As PD motor symptoms increase, the rate of amplitude tremor lowers. Oscillatory movement in the vocal tract in pwPD appears to impact more on the amplitude of the cycle than it does on the length of the cycle in this group of pwPD. Voice tremor analysis in PD contributes to increased understanding of phonatory dysfunction and its relationship with disease symptomatology. Acoustic analysis of PD voice tremor as conducted in this study enhances our understanding of the characteristics of voice tremor in pwPD in terms of rate, periodicity, and magnitude of frequency and amplitude components. Further studies are required using additional measurement tools to determine the source of voice tremor, that is, which structure/s in the vocal tract are oscillating involuntarily during phonation and resulting in auditory perceived tremor. Additional studies could evaluate voice tremor in people with late-stage PD and/or follow up individuals longitudinally to determine the natural history of voice tremor in PD.

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APPENDIX

Tremor-related measures from the Voice and Tremor Protocol from Motor Speech Profile (MSP) Model 5141 of the Computerized Speech Laboratory (CSL)

1. Rate of frequency tremor (Rftr) measured in Hz
   The frequency of the most intensive low-frequency Fo-modulating component in the specified Fo-tremor analysis range
2. Rate of amplitude tremor (Ratr) measured in Hz
   The frequency of the most intensive low-frequency amplitude-modulating component, in the specified amplitude-tremor analysis range
3. Periodicity of the frequency tremor [Pftr (%)]
   The periodicity of the frequency tremor. If the rate of tremor is very consistent, then it is a periodic tremor.
4. Periodicity of the amplitude tremor [Patr (%)]
   The periodicity of the amplitude tremor. If the rate of tremor is very consistent, then it is a periodic tremor.
5. Magnitude of frequency tremor (Mftr), measured in %
   The magnitude or the extent of frequency tremor which can be from periodic or nonperiodic modulations
6. Magnitude of amplitude tremor (Matr), measured in %
   The magnitude or the extent of amplitude tremor which can be from periodic or from nonperiodic modulations
7. Coefficient of variations in the fundamental frequency (vFo), measured in %
   vFo is the long-term variation in fundamental frequency (Fo) from any variations in the Fo of the voice. Fo variations include periodic modulations, nonperiodic modulations, and rising or falling Fo across the recorded segment.
8. Coefficient of variations in the amplitude (vAm) measured in %
   vAm is the long-term variation in amplitude from any variations in the amplitudes of the voice. Amplitude variations include periodic modulations, nonperiodic modulations, and rising or falling amplitude.

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