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'Voice quality severity and responsiveness to levodopa in Parkinson's disease

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ABSTRACT

The effect of levodopa on perceptual and acoustic measures of voice quality was examined in fifty-one individuals with Parkinson's disease (IWPD). IWPDs produced prolonged vowels while on and off levodopa. Acoustic measures included jitter, shimmer, harmonic-to-noise ratio, cepstral peak prominence and the Acoustic Voice Quality Index. A perceptual measure of overall voice quality was obtained from 3 listeners. When the IWPDs were examined as a group, no significant difference was found between on and off levodopa conditions. In contrast, when IWPDs were split into two groups based on voice quality severity, a significant group-by-medication state interaction emerged. In addition, there was a significant correlation (r = .55) between the magnitude of levodopa-related improvement in perceived voice quality and voice quality severity. In contrast, levodopa-related improvement in voice quality was not correlated with duration of disease or levodopa use. Results do not support the hypothesis of reduced levodopa-responsiveness to voice symptoms as disease duration increases. Instead, the results suggest that the magnitude of the levodopa response may increase with increasing severity of the voice quality symptoms. These results suggest that the severity of speech and voice symptoms needs to be given greater consideration in future studies of levodopa effectiveness in IWPDs.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a prevalence of about 160 per 100,000 in people over the age of 65 (Lill & Klein, 2017). Degeneration of dopaminergic neurons in PD leads to dopamine deficiency in the basal ganglia and related areas of the brain. Dopamine fine tunes neuronal excitability in the basal ganglia, and depletion results in physiologic imbalances which manifest as a variety of motor and non-motor symptoms (Obeso et al., 2010). Cardinal motor symptoms of PD include bradykinesia, rigidity of bodily movements, resting tremor, gait abnormalities and postural instability. Many additional symptoms have been found to be associated with PD, including dysphagia, anosmia, sleep disorders, cognitive abnormalities, depression, and a speech disorder known as hypokinetic dysarthria. Characteristics of hypokinetic dysarthria include hypophonia (low speech intensity), reduced stress and intonation patterns, abnormal voice quality, imprecise consonant articulation,

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abnormal speech rate and reduced pitch and loudness variation (Adams & Dykstra, 2008). Voice problems may be one of the most common and earliest speech symptoms, with as many as 89% of individuals with PD (IWPD) developing a voice problem over the course of the disease (Logemann, Fisher, Boshes, & Blonsky, 1978). Recent findings suggest that voice symptoms may be an identifiable feature of prodromal PD (Rusz et al., 2016).

Levodopa is widely considered to be the gold-standard for treatment of PD motor symptoms (Fahn & Poewe, 2015). Levodopa, a precursor to dopamine, is able to cross the blood-brain barrier and increases dopamine supply in the brain by facilitating dopamine synthesis. Early in the disease process, levodopa is highly effective at treating the cardinal PD symptoms, but its benefits have been reported to decline with disease progression (Obeso et al., 2010). While levodopa effectively treats many symptoms of PD, its effects on speech and voice are unclear (Spencer, Morgan, & Blond, 2009).

Previous studies of the effects of levodopa on speech and voice have typically involved a levodopa challenge, in which levodopa is withdrawn for at least 12 h. Testing is performed before and after administration of levodopa. Findings of these studies have varied, in part due to differences in study design. Studies varied in the number of participants, disease duration and severity of disease, as well as severity of voice symptoms in those who participated. Voice quality has been measured using diverse perceptual, acoustic and objective measures. Jiang, Lin, Wang, and Hanson (1999) investigated voice quality using electroglottography and acoustics, finding decreased laryngeal rigidity, shimmer and vocal tremor, indicating an improvement of voice quality on medication. Similarly, Sanabria et al. (2001) found decreased jitter, fundamental frequency and harmonic-to-noise, indicating improved voice quality with levodopa. However, they found no significant differences in shimmer. Goberman, Coelho, and Robb (2002) did not find significant group differences in fundamental frequency variability in prolonged vowels, though some individuals demonstrated improvement. Plowman-Prine et al. (2009) also did not find a significant medication effect on perceptual ratings of voice quality. A recent investigation by Fabbri et al. (2017) studied motor, speech and voice symptoms in individuals with late-stage PD. They did not find a significant effect of levodopa on speech or voice. Disease duration was correlated with pitch and rate, though these findings may be related to age, rather than disease duration.

Duration of levodopa use may play a role in the effects of medication on voice quality. Rusz et al. (2013) studied a group of de novo IWPDs, prior to onset of dopamine therapy and then after a month of stable medication use. They found significant improvements in voice quality in these new levodopa users. These de novo PD findings support the idea of voice symptoms having high early responsiveness to levodopa. In addition, it has been suggested that speech becomes less responsive to levodopa (levodopa resistance) as PD progresses, particularly after 10 years of levodopa use (Bonnet, Loria, Saint-Hilaire, Lhermitte, & Agid, 1987; Klawans, 1986). Unfortunately, this hypothesis of increased levodopa resistance with progression of PD has not been systematically examined in previous studies of speech and voice in PD.

Perceived voice quality can be described using a variety of dimensions such as breathy, harsh, hoarse, rough or strained, or can be rated based on the overall perceived quality. Research by Kreiman and Gerratt (2000) suggests that listeners do not reliably agree on the type or degree of particular voice quality dimensions that are present in a voice sample. Eadie and Doyle (2005) further discuss this issue, suggesting that overall voice quality or pleasantness measures are more appropriate. A global measure of voice quality may also facilitate examining potential associations between perceptual and acoustic measures of voice quality in PD because of variability across dimensions. When measuring perceived voice quality, several methods are available for listeners to provide ratings. These include equal-appearing interval scales (EAIS), direct magnitude estimation (DME), visual-analogue scales (VAS), or choosing one item from a matched pair. Research by Kreiman, Gerratt, Kempster, Erman, and Berke (1993) indicated that VAS offers better reliability than equal-appearing interval scales (EAIS). This was further supported by Karnell et al. (2007), who noted that while EAIS and VAS can both offer strong reliability, VAS offers greater resolution which may improve reliability.

Many acoustic measures of voice quality rely on quantifying the periodicity of a signal. Voice quality can be measured using jitter, shimmer and harmonic-to-noise ratio (HNR). Jitter and shimmer are perturbation measures, indexing the cycle-to-cycle variation in frequency and amplitude, respectively. A signal with higher jitter and shimmer is more variable and less periodic, representing poorer voice quality. Similarly, HNR indexes the relative amplitude of the signal and its harmonics over non-harmonic frequencies, with higher HNR representing a less noisy signal and thus better voice quality. While these measures are frequently reported in the literature, concern has been expressed regarding their relationship with perceived voice quality (Kreiman, Gerratt, & Gabelman, 2002; Martin, Fitch, & Wolfe, 1995). A meta-analysis by Maryn, Roy, De Bodt, Van Cauwenberge, and Corthals (2009) reported that for vowels, smoothed cepstral peak prominence (CPP) was more strongly correlated with perceived voice quality than jitter, shimmer and harmonic-to-noise across various populations. CPP measures periodicity in a cepstrum, rather than a spectrum. A cepstrum is the result of taking an inverse Fourier transform of the logarithm of a spectrum. Signals with prominent cepstral peaks have a well-defined harmonic structure, so a high CPP value means that the signal emerges well from the background noise (Hillenbrand, Cleveland, & Erickson, 1994). Further work by Maryn and colleagues included the creation and refinement of an algorithm called the acoustic voice quality index (AVQI), which combines several acoustic measures using relative weighting (Maryn & Weenink, 2015; Maryn, Corthals, Van Cauwenberge, Roy, & De Bodt, 2010). The AVQI includes HNR, CPP, absolute and percent shimmer, slope of the long-term average spectrum and tilt of the trendline through the long-term average spectrum. While jitter, shimmer and HNR have been used in previous PD studies that examined the effect of levodopa on voice quality, CPP and AVQI have not yet been examined.

As outlined above, previous studies of levodopa have shown inconsistent results. Some of the limitations of these studies include small sample sizes, restricted disease duration, limited range of disease severity or symptom severity, and differences in the voice quality measures selected for study. The purpose of this study was to examine the effect of levodopa on voice quality in a relatively large number of IWPDs who demonstrate a wide range of PD duration and symptom severity using both perceptual and acoustic measures of voice quality. An additional purpose of the study was to examine the hypotheses that voice symptoms show increasing levodopa resistance with progression of PD and with increasing duration of use of levodopa.

Table 1
Descriptive statistics of each voice quality group.

	Poor voice quality *(N = 26; 24 male, 2 female)*		Better voice quality *(N = 25; 15 male, 10 female)*	
	Mean(SD)	Range	Mean(SD)	Range
Age	67.39(7.78)	47–82	64.12(6.74)	53–77
Duration of diagnosis	9.39(4.40)	3–16	9.04(4.05)	2–16
Duration of levodopa use	7.50(4.15)	2–16	7.52(3.70)	2–15
UPDRS off-medication	32.12(7.32)	17–43	28.12(9.45)	14–51
UPDRS on-medication	18.92(7.42)	7–32	14.52(6.44)	3–26
LED	1068.9(402.51)	400-2081	992.64(505.36)	300–2200

2. Methods

2.1. Participants

Fifty-one individuals with idiopathic Parkinson's disease (IWPDs) participated in the study. This study was approved by the Human Research Ethics Board (REB #107253) of Western University. IWPDs were included based on the following criteria: 1) have been diagnosed with idiopathic PD for at least 2 or more years; 2) 45 to 85 years of age; 3) have been on stable doses of anti-Parkinson medication, including any levodopa preparation (stable doses indicate that no adjustments to medications have been made within the last 6 months); and 4) able to give informed, written consent. IWPDs were excluded on the following criteria: 1) history of any surgical intervention for treating PD (i.e. deep brain stimulation, Duodopa pump); 2) extreme physical disability that impairs mobility assessment; 3) history or current diagnosis of a psychiatric condition requiring hospitalization; and 4) pregnant, planning on becoming pregnant or breastfeeding; 5) deemed unable to understand or speak sufficient English; and 6) history of speech impairments aside from those related to PD. IWPDs were recruited from the Movement Disorders Centre, University Hospital, London, Ontario, Canada. Control participants for the study were spouses of PD participants.

IWPDs included 39 men and 12 women with a mean age of 65.78 years, standard deviation (SD) of 7.40, and a range of 47–82 years. Average duration of diagnosis was 9.22 years (SD 4.19), with a range of 2–16 years. Average duration of levodopa use was 7.51 years (SD 3.90), with a range of 2–16 years. Average levodopa equivalent dose (LED) was 1030.77 (SD 453.79), with a range of 300-2200. Average PD motor score off-medication, obtained on the Unified Parkinson Disease Rating Scale (UPDRS: Part III), was 30.16 (SD 8.59), with a range of 14–51 (total possible = 108). Average UPDRS score on-medication was 16.77 (SD 7.24), with a range of 3–32.

For part of this study, IWPDs were divided into two groups based on their perceived voice quality off-medication (scoring and grouping discussed below). Descriptive statistics on each group are presented in Table 1.

Eleven individuals without PD and of comparable age participated as controls in the study. These individuals were native speakers of English with no history of speech impairments. Three men and 8 women participated in the study; mean age was 62.09 years (SD 6.55), with a range of 52–75 years.

2.2. Procedure

IWPDs were evaluated off and on levodopa medication. For the off-state evaluation, the IWPDs arrived in the morning having been off medication overnight. Testing was scheduled at least 12 h after their last dose of levodopa to ensure an off-state. Participants were asked to produce a sustained 'ah' vowel and keep it as steady as possible. The sustained vowels were recorded using an M-Audio Microtrack-2 audio recorder (16bits; 44.1 kHz) and a DPA 4060 headset microphone placed 6 cm from the mouth and calibrated with a sound level meter positioned at 15 cm from the mouth (dBA SPL). An assessment of motor symptoms was conducted using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS). Following the completion of the off-state evaluation, the IWPDs took a controlled dose of 300 mg of levodopa that was provided in the form of 3 pills containing 100/25 of levodopa/carbidopa. Levodopa equivalent dose (LED) was calculated as per Tomlinson et al. (2010). One hour after taking the levodopa medication, the on-state evaluation was performed by having the IWPDs repeat the sustained vowel production and UPDRS motor symptom assessment. Controls produced a sustained vowel sample, collected in the same manner as those produced by IWPDs.

2.3. Acoustic analysis

Two second samples from the middle of each audio-recorded vowel were extracted for analysis. The mid-portion of the vowel was selected in order to obtain a fairly steady sample of voice and to avoid the acoustic variability that is frequently associated with the onset and offset of phonation. Acoustic analysis was applied to the 2-second vowel segments using Praat software (Boersma & Weenink, 2017). These measures included percent jitter, absolute shimmer, percent shimmer, harmonic-to-noise ratio, spectral slope, spectral trendline tilt, cepstral peak prominence and the Acoustic Voice Quality Index (AVQI). AVQI calculation was informed by the AVQI script published by Maryn and Weenink (2015).

2.4. Perceptual analysis

Perceptual judgments of the audio-recorded vowel segments were provided by 3 listeners using a visual-analogue scale (VAS) for each sample. Listeners were asked to rate the overall voice quality of each voice sample. The scale was 10 cm in length, and the endpoint descriptors were "poor voice quality" on the left and "better voice quality" on the right. VAS score was recorded as the distance from the left endpoint to the listeners' mark. Listeners were graduate students in speech-language pathology who had completed coursework and clinical placements in voice disorders. Voice samples were provided in a random order, with 20% of items randomly repeated to allow intra-rater reliability to be calculated.

Statistical analysis was conducted using SPSS (IBM Corp, 2016). Differences between IWPDs and controls were examined for each dependent measure using the independent *t*-test. Differences between ON and OFF levodopa medication were examined for each dependent measure using the matched-pair *t*-test. After the initial group analysis, it was observed that many of the IWPDs had voice quality ratings that appeared to be within the range found for the controls. In order to examine the effect of medication on IWPDs who were demonstrating abnormal voice quality, the IWPDs were then split into groups for further analysis. IWPDs were split into two groups based on their perceived voice quality off-medication. IWPDs whose perceived voice quality off-medication fell at or below the 95% CI for controls were placed in a poor voice quality group. IWPDs whose perceived voice quality off-medication fell within the 95% CI for controls were placed in the better voice quality group.

A series of independent samples *t*-tests were used to compare IWPDs with poor voice quality off-medication, IWPDs with better voice quality off-medication and controls on each of the dependent measures of voice quality. Levene's test was used to assess homogeneity of variance for each comparison, and when significant, a Welch *t*-test was used instead of the Student *t*-test. A two-way mixed ANOVA examined the two IWPD groups with poor and better voice quality (between-subjects) during the ON and OFF medication conditions (within-subjects, repeated measures) for each of the dependent measures. Bivariate correlations investigated the associations between the dependent measures and the medication-related changes in the dependent measures. Pearson's correlations were computed to investigate relationships between patient characteristics and voice quality, and between voice quality measures in different medication conditions. A Bonferroni correction for multiple measures was not used, because such a low *p*-value would be associated with a high risk of Type II errors (Nakagawa, 2004). Instead, Bonferroni corrections were applied for each group comparison as a more liberal correction. For the 2 comparisons involving the IWPDs off-medication vs. IWPDs on-medication, and the IWPDs off-medication vs. controls, a critical *p*-value of $p = .025$ was used (.05/2 = .025). For the 3 comparisons involving IWPDs with poor voice quality vs. controls, IWPDs with better voice quality vs. controls and IWPDs with poor voice quality vs. IWPDs with better voice quality, a critical *p*-value of .016 was used (.05/3 = .016). A correction was not applied to correlation analyses in the absence of group comparisons.

3. Results

3.1. Inter-rater and intra-rater reliability

Reliability of the perceptual judgments of voice quality was examined using the intraclass correlation coefficient (ICC), guided by Koo and Li's (2016) review of the application of ICC models. Inter-rater reliability across the 3 raters was examined using average consistency in a two-way random model (ICC 2, k): average ICC = .826 (95% CI: .770–.870). This can be interpreted as good inter-rater reliability (Koo & Li, 2016). Intra-rater reliability for each rater was examined using average agreement in a two-way mixed model (ICC 3, k): average ICC across all raters = .754 (95% CI: .378–.903). This can be interpreted as moderate intra-rater reliability (Koo & Li, 2016).

Table 2
Average values for perceptual and acoustic measures of voice quality obtained from individuals with Parkinson's disease (n = 51) in the on and off levodopa medication states and controls (SD in parentheses).

	IWPD Off	IWPD On	*Off-On p-value*	Controls	*Off-C p-value*
Perceived voice quality	44.34(18.5)	47.1(17.8)	.300	55.6(14.4)	.062
Harmonic-to-noise ratio	19.6(4.1)	20.3(5.6)	.285	21.9(3.5)	.093
Percent shimmer	5.10(3.3)	4.99(3.5)	.847	3.52(1.38)	.014$^{+,*}$
Absolute shimmer	0.45(0.29)	0.44(0.30)	.717	0.31(0.12)	.011$^{+,*}$
Percent jitter	0.59(0.38)	0.59(0.62)	.943	0.38(0.14)	.003$^{+,*}$
CPP	15.4(2.77)	15.6(3.2)	.583	14.4(2.4)	.272
AVQI	2.26(1.53)	2.03(1.90)	.330	1.90(0.83)	.449

The p-values obtained for the IWPD on versus off medication paired t-tests and the p-values for the IWPD off medication versus controls t-tests are also presented.

* Significant at $p < .025$.

$^{+}$ Welch test.

Table 3
Average values for perceptual and acoustic measures of voice quality obtained from the individuals with Parkinson's disease (IWPD) with poor voice quality (VQ) (n = 26), IWPD with better voice quality (n = 25), and controls (SD in parentheses).

	IWPD Poor VQ OFF *(N = 26)*	IWPD Poor VQ ON *(N = 26)*	IWPD Better VQ OFF *(N = 25)*	IWPD Better VQ ON *(N = 25)*
Perceived voice quality	29.40(10.76)	43.17(17.48)	59.92(9.75)	51.26(17.57)
Harmonic-to-noise ratio	18.17(4.53)	19.00(6.16)	21.17(3.02)	21.75(4.60)
Percent shimmer	6.32(3.81)	5.37(3.69)	3.83(1.61)	4.60(3.26)
Absolute shimmer	0.56(0.35)	0.47(0.32)	0.34(0.15)	0.40(0.28)
Percent jitter	0.71(0.41)	0.72(0.75)	0.47(0.30)	0.44(0.41)
Cepstral peak prominence	14.72(3.24)	14.87(3.20)	16.15(1.67)	16.46(3.12)
AVQI	2.79(1.99)	2.44(1.80)	1.70(0.92)	1.60(0.92)

3.2. Effects of levodopa and PD on voice quality

The descriptive statistics and results of the on-off medication paired t-tests for the complete group of IWPD (n = 51) are summarized in Table 2. For the perceptual and acoustic measures of voice quality, none of the on versus off-medication paired t-tests were significant. The descriptive statistics and results for the independent t-tests involving the IWPDs off-medication versus the controls are provided in Table 2. Percent shimmer ($t(51) = 2.59$, $p = .014$, $d = .552$), absolute shimmer ($t(51) = 2.67$, $p = .011$, $d = .520$) and percent jitter ($t(51) = 3.13$, $p = .003$, $d = .597$) were significant in the comparison of IWPDs off-medication versus controls.

3.3. Severity of perceived voice quality and effects of levodopa medication

The descriptive statistics for the IWPD with poor voice quality, the IWPD with better voice quality, and the controls are presented in Table 3. The results of the two-way mixed ANOVA involving the medication conditions (on and off) and the IWPD groups (poor and better voice quality) found a statistically significant interaction between medication conditions and the groups on perceived voice quality, $F(1, 51) = 27.31$, $p < .001$, $\eta^2 = .358$.

The results of the related post-hoc comparisons found that the IWPDs with poor voice quality had significantly improved perceived voice quality on medication ($p < .001$, $d = .734$), while IWPDs with better voice quality had significantly poorer voice quality on medication ($p = .007$, $d = .609$). A plot of this interaction is shown in Fig. 1.

With regard to the acoustic measures, the results of the two-way mixed ANOVAs found no significant interactions between the medication conditions (on and off) and the groups (better and worse voice quality) for any of the acoustic measures of voice quality.

To further examine the medication-related changes in perceived voice quality, an on-off voice quality difference score was obtained for each IWPD (perceived voice quality on-medication minus perceived voice quality off-medication) and examined in relation to the off-medication voice quality scores. A plot of the voice quality difference scores versus the off-medication voice quality scores is shown in Fig. 2.

A significant negative correlation was found between perceived voice quality off-medication and medication-related change in perceived voice quality, $r(51) = -.55$, $p < .001$. Correlations were computed between acoustic voice quality measures off-medication and medication-related change in acoustic measures and presented in Table 4. Significant results were found for correlations

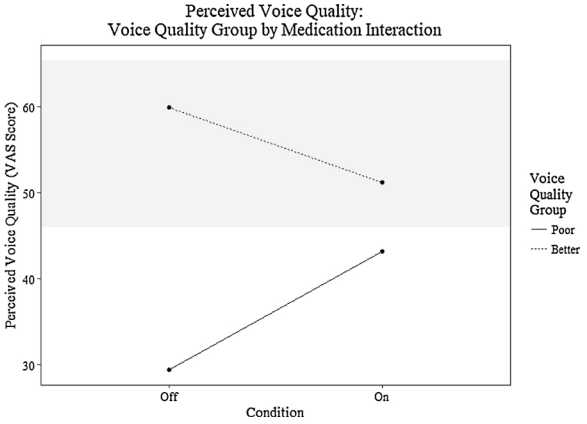

Fig. 1. Average perceived voice quality ratings (visual analogue scale) for the groups of individuals with Parkinson's disease (IWPD) with poor voice quality and the IWPD with better voice quality obtained for the on and off medication conditions. The significant interaction is reflected by the different effects of medication conditions in the two IWPD groups. Shaded area represents the 95% confidence interval for controls.

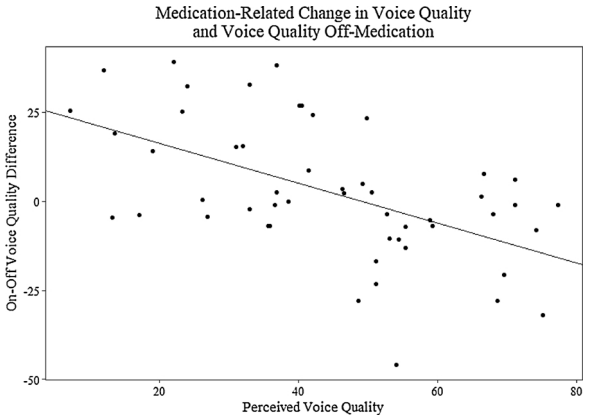

Fig. 2. Relationship between perceived voice quality off-medication and medication-related change in perceived voice quality. Voice quality scores are based on visual analogue ratings with higher scores perceived as better voice quality.

Table 4
Correlations obtained for voice quality off-medication versus medication-related change in voice quality for each of the acoustic measures of voice quality (* = significant at p < .05; n = 51).

	Pearson's *r*	*p*
Harmonic-to-noise ratio	0.20	.158
Percent shimmer	0.51	< .001*
Absolute shimmer	0.55	< .001*
Percent jitter	0.34	.016*
CPP	0.34	.016*
AVQI	−0.29	.036*

related to five of the six acoustic measures. However, it should be noted that while significant, most of these effects are small. Percent and absolute shimmer were found to have moderate effect sizes, and harmonic-to-noise ratio's nonsignificant effect was negligible.

The series of independent-samples *t*-tests indicated that IWPDs with poor voice quality (off medication) were significantly different from controls on several acoustic measures: percent shimmer ($t(37) = -3.27$, $p = .002$, $d = .848$), absolute shimmer ($t(37) = -3.32$, $p = .002$, $d = .845$), and percent jitter ($t(37) = -2.58$, $p = .001$, $d = .923$). IWPDs with better voice quality (off medication) were not significantly different from controls on any of the 6 acoustic measures. IWPDs with better voice quality were found to be significantly different from IWPDs with poor voice quality on harmonic-to-nose ratio ($t(51) = 3.02$, $p = .004$, $d = .776$), percent shimmer ($t(51) = 3.06$, $p = .004$, $d = .845$), absolute shimmer ($t(51) = 3.06$, $p = .004$, $d = .823$), and AVQI ($t(51) = 2.74$, $p = .009$, $d = .759$). Results of these *t*-tests are presented in Table 5.

3.4. Associations between perceptual and acoustic measures of voice quality

Pearson's product-moment correlations were used to examine the association between the acoustic measures of voice quality and the perceived voice quality. Results of these correlations can be found in Table 6.

Table 5
p-values for the independent-samples t-tests comparing IWPDs with poor voice quality (off-medication), IWPDs with better voice quality (off-medication) and controls on acoustic voice quality measures.

	Poor VQ (N = 26)	Better VQ (N = 25)	Controls (N = 11)	*Poor VQ-C p-value*	*Better VQ-C p-value*	*Better VQ-Poor VQ p-value*
HNR	18.2(4.5)	21.2(3.0)	21.9(3.5)	.020	.52	.004*
Percent shimmer	6.3(3.8)	3.8(1.6)	3.52(1.38)	.002+*	.59	.004+,*
Absolute shimmer	.56(.35)	.34(.15)	0.31(0.12)	.002+*	.55	.004+,*
Percent jitter	.71(.41)	.47(.30)	0.38(0.14)	.001+*	.34	.023+
CPP	14.7(3.2)	16.2(1.7)	14.5(2.4)	.809	.02	.054+
AVQI	2.8(1.8)	1.7(.92)	1.90(0.83)	.124	.56	.009+,*

* significant at $p < .016$.
\+ Welch test.

Table 6
Correlations between acoustic and perceptual measures of voice quality (* $p < .05$).

	Pearson's *r*	*p*
Harmonic-to-noise ratio	0.69	< .001*
Percent shimmer	−0.64	< .001*
Absolute shimmer	−0.40	< .001*
Percent jitter	−0.48	< .001*
Cepstral peak prominence	0.54	< .001*
AVQI	−0.65	< .001*

3.5. Associations between voice quality and selected characteristics of the IWPDs

A significant correlation was found between perceived voice quality and severity of motor symptoms $r(51) = -.38$, $p = .007$. However, medication-related changes in motor symptoms (on-off UPDRS difference scores) were not significantly correlated with medication-related changes in perceived voice quality (on-off voice quality difference scores), $r(51) = .11$, $p = .464$. A significant correlation was found between age and perceived voice quality, $r(51) = -.31$, $p = .029$. No significant correlations were found between voice quality and dosage, disease duration, or duration of levodopa use. These results are presented in Table 7.

4. Discussion

The absence of a consistent effect of medication on voice quality across all IWPDs studied is not surprising, considering similar reports in the literature (Fabbri et al., 2017; Goberman et al., 2002; Plowman-Prine et al., 2009). However, other reports found voice quality improved on-medication (Jiang et al., 1999; Rusz et al., 2013; Sanabria et al., 2001). When voice severity was factored into the analysis, a novel finding was observed. IWPDs with poor voice quality off-medication showed improvements in voice quality on-medication, and those with better voice quality off-medication showed worsened voice quality on-medication. Based on these novel observations, we propose a new "speech severity responsiveness hypothesis" as a potential explanation for previously unexplained variations and inconsistencies within and across previous studies of the effects of levodopa on speech and voice symptoms in PD. The results of the present study suggest that differences in voice symptom severity may be responsible for a substantial amount of the variation in levodopa responsiveness. In contrast to the present study, most previous studies used smaller sample sizes and/or a more restricted range of symptom severity, which may have obscured the proposed relationship between symptom severity and response to levodopa. Unless symptom severity is controlled for, the high degree of individual variation between IWPDs may continue to obscure trends related to speech symptom responsiveness to levodopa.

IWPDs varied significantly from controls on percent and absolute shimmer. These findings may suggest that shimmer is a sensitive measure for separating IWPDs from controls. However, these results must be interpreted with caution, as previous findings have indicated that jitter and shimmer may not be strong indices of voice quality (Maryn et al., 2010; Parsa & Jamieson, 2001). Within this study, on the other hand, jitter and shimmer both demonstrated moderate correlations with perceived voice quality and showed sensitivity to group and medication differences on voice quality within sustained vowels. Jitter and shimmer have been used in automatic detection of Parkinson's disease from speech samples (Orozco-Arroyave et al., 2016, 2017) with high classification accuracy. Further investigation may seek to clarify the use of shimmer in assessment of voice quality in Parkinson's disease.

Findings of this study do not support the longstanding "levodopa resistance hypothesis" for speech and voice symptoms. This hypothesis proposes that speech and voice symptoms become increasingly less responsive to levodopa and that after 10 years of levodopa use speech symptoms demonstrate levodopa resistance (Klawans, 1986; Bonnet et al., 1987). In the present study, neither disease duration nor duration of levodopa use were found to be associated with severity of abnormal voice quality or with medication-related change in voice quality. In addition, it appears that there was some dissociation between the effects of levodopa on motor symptoms and its effects on voice symptoms. Fabbri et al. (2017) found a similar gap between motor symptom responsiveness and speech symptom responsiveness to levodopa. This gap suggests that there is a difference in the way speech and voice symptoms react to levodopa compared to general motor symptoms. One explanation for these differences in limb and speech responsiveness may be the presence of a unique combination of dopaminergic and nondopaminergic mechanisms in speech production (as discussed by Kompoliti, Wang, Goetz, Leurgans, & Raman, 2000; Skodda, Grönheit, Mancinelli, & Schlegel, 2013).

A complicating factor in interpreting the effects of dopaminergic medication on speech production in IWPDs is a lack of

Table 7
Pearson's correlations between perceived voice quality and selected characteristics of the IWPDs (* p < .05).

	Pearson's *r*	*p*
LED	0.03	.812
Disease duration	0.05	.705
Duration of levodopa use	0.16	.266
Age	−0.31	.029*

understanding of the role of dopamine in normal speech production. Simonyan, Herscovitch, and Horwitz (2013) discuss gaps in the literature in this area: while DOPA has been shown to affect cognition and language functions in normal subjects, effects on speech motor control are less clear, with most of the evidence related to dopamine's role in speech motor control coming from clinical populations. In this study, Simonyan et al. (2013) found support for left lateralization of dopamine during speech production. Higher left striatal dopaminergic transmission findings align with left-hemispheric lateralization of brain activation during speech production, which the authors suggest may indicate adaptation of striatal networks to support speech function. A limitation of the present study is that participants' handedness was not controlled, and there is evidence that handedness affects left lateralization of dopaminergic transmission (de la Fuente-Fernández, Kishore, Calne, Ruth, & Stoessl, 2000). It is not yet understood how these differences could interact with the effects of dopaminergic medication.

In addition to lateralization of dopaminergic transmission, it is not well understood how basal ganglia structures connect to other areas of the brain during speech production. An improved understanding of this connectivity may inform explanations of speech production deficits in individuals with basal ganglia pathology, such as IWPDs. Meta-analytic findings from Manes et al. (2014) suggest functional connections during speech production emerge from shared cortico-basal ganglia pathways. The premotor cortex was found to be more likely to coactivate with the GPi (more related to speech motor control) and the supplementary motor area and insula were found to be more likely to coactivate with the STN (cognitive-linguistic processing relevant to speech).

Further understanding of both the role of DOPA in cortical-BG networks and the components of these networks in normal speech production may help to clarify the effects of dopaminergic medication on speech production in individuals with dopaminergic deficits.

Another possible explanation of the dissociation found between limb and speech responsiveness to dopaminergic medication may relate to the notion that each major symptom in PD has a unique levodopa dose-response curve (Nonnekes et al., 2016). Thus, some symptoms such as bradykinesia (i.e. finger tapping) may have a much more responsive and steeper dose-function curve than symptoms such as tremor, freezing, and dysphonia. This explanation would suggest that symptoms with flatter dose-functions may be undertreated or underdosed. It is possible that speech and voice symptoms may require higher doses of levodopa to treat, rather than that they are resistant to levodopa. To further explore this hypothesis, it is suggested that systematic dose escalation studies of speech and other symptoms should be conducted. These studies could provide symptom-specific dose-function curves and generally lead to a better understanding of levodopa responsiveness in PD.

Cepstral peak prominence (CPP) and the acoustic voice quality index (AVQI) had not previously been examined in a study of the effects of levodopa on voice quality. Results of this study indicate that for sustained vowels, CPP and AVQI offer similar associations with perceived voice quality as jitter, shimmer and harmonic-to-noise ratio (HNR). One potential advantage of the CPP and AVQI measures is their potential application to samples of connected speech whereas the measure of jitter and shimmer are typically restricted to use with prolonged vowels. Because one of the aims of the present study was to compare these acoustic measures of voice quality we limited our analysis to prolonged vowels. It is suggested that future studies continue to examine the sensitivity of the CPP and AVQI to levodopa effects in the connected speech samples obtained from IWPDs.

A limitation of the present study is that participants were given a standard dose of levodopa (300 mg), rather than their usual dose. While this standard dose provided increased inter-subject consistency in dosage, it introduced some new variability in terms of under- versus over-treatment of the voice symptoms. In general, a concern was that the patient's usual dose, while appropriate for the limb motor symptoms, may have be associated with undertreating the voice symptoms. It is also possible that the overnight washout period may have added an additional risk that the standard morning dose would undertreat the voice symptoms. As previously discussed, it is recommended that future studies examine speech symptom responsiveness across a range of levodopa dose levels. Another related limitation may be that the order of the medication states was not counterbalanced – the off-state always occurred first. While this is common for levodopa challenge studies (Fabbri et al., 2017; Goberman et al., 2002; Plowman-Prine et al., 2009; Sanabria et al., 2001; Skodda, Visser, & Schlegel, 2010; Spencer et al., 2009) counterbalanced medication states in their investigation of levodopa's effects on speech. Counterbalanced conditions would have improved the strength of the medication-related findings of the present study, and future studies should consider random assignment of the order of medication states. Additionally, regardless of the order of medication withdrawal, it is possible that the off-state is associated with factors that alter performance on speech and voice testing in ways other than a genuine effect of the dopaminergic medication. It is possible that worsened PD symptoms in the off-state could lead to physical discomfort and mood changes that could affect IWPD's speech and voice.

The present study includes a larger number of IWPDs than most levodopa challenge studies investigating speech. However, the sample size is still a limitation of this study, as the analysis was restricted to a single sustained vowel segment from each participant in each state. Future investigations should endeavour to include a greater number of speech samples per participant. These samples should also include a wider range of speech tasks, including connected speech. The findings of the present study indicate that CPP and AVQI demonstrate appropriate correlation with perceived voice quality. Both of these measures can be applied to connected speech, and future studies of levodopa's effects on speech and voice should consider their inclusion. The small number of listeners in the present study is also a potential limitation. However, ICC analysis indicates good inter-rater reliability between the 3 listeners providing perceptual judgments of voice quality.

5. Conclusion

The results of the present study do not support the hypothesis of reduced levodopa-responsiveness to voice symptoms as disease duration increases. Instead, the results suggest that the magnitude of the levodopa response may increase with increasing severity of the voice quality symptoms. These results suggest that the severity of speech and voice symptoms needs to be given greater

consideration in future studies of levodopa effectiveness in IWPDs.

Declarations of interest

We have no relevant interests to declare.

Author statement

Daryn Cushnie-Sparrow: Writing – Original Draft, Formal Analysis, Software, Data Visualization, Data Curation. **Scott Adams:** Conceptualization, Methodology, Supervision, Writing – Reviewing & Editing, Resources. **Anita Abeyesekera:** Methodology, Investigation, Data Curation. **Marcus Pieterman:** Conceptualization, Methodology, Investigation. **Greydon Gilmore:** Investigation. **Mandar Jog:** Resources, Supervision.

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