Acoustic analysis of voice in Parkinson's disease: a systematic review of voice disability and meta-analysis of studies

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Aim. To systematically review all the literature, focusing on instrumental quantitative assessment of voice in patients with Parkinson's disease (PD). Furthermore, a meta-analysis was performed to identify the main characteristics of voice disturbances in PD.

Patients and methods. Literature searches with the keywords 'Parkinson' and 'voice' were conducted in PubMed, EMBASE, Cochrane Library and Web of Science. Main inclusion criteria were: clinically confirmed PD and instrumented measurement of voice parameters with acoustic analysis of voice.

Results. Fourteen publications met the inclusion criteria and were included in the meta-analysis. The data within the meta-analysis revealed that several voice parameters including jitter, shimmer and fundamental frequency variation presented significant variations between patients with EP and healthy controls. Significant variations of fundamental frequency, maximum phonation time, harmonic to noise ratio, standard deviation of fundamental frequency were observed, but with a high heterogeneity between the studies. On the other hand, significant variations of noise to harmonic ratio, s/z ratio, variation of amplitude were not observed.

Conclusion. Acoustic analysis of voice, using an electronic system, allows the identification of changes in voice parameters for predicting the worsening of disease and for targeting specific intervention. Among the voice parameters, jitter and shimmer significantly increased in patients with PD.

Key words. Disability. Meta-analysis. Parkinson's disease. Speech pathology. Systematic review. Voice.

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Introduction

Parkinson's disease and oral communication disorders

Oral communication disorders as voice, speech and articulation disorders are clinically present in 40-80% of patients with PD [1,2]. These impairments are due to the lack of coordination of muscles responsible for speech, causing vocal and articulation disorders and swallowing difficulties [3,4]. The degree of speech intelligibility must not be underestimated because it reduces the quality of life and the ability to communicate with social isolation [3]. Instrumented voice analysis allows an early identification in order to design supportive interventions. For this reason, voice analysis is a useful tool to obtain more specific and subclinical information about the progression of voice disorders in PD.

Diagnosis of voice disorders in Parkinson's disease

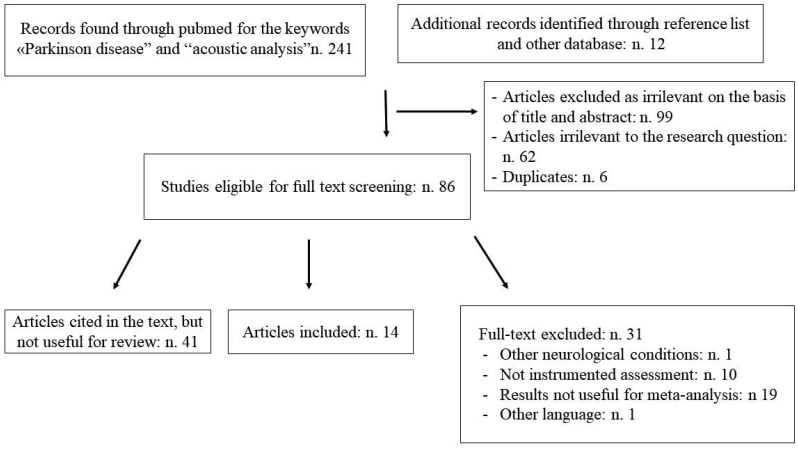
Phonatory symptoms are often the first signs of many neurological disorders, as PD, cerebellar disease, Amyotrophic lateral sclerosis, traumatic brain injury, unilateral hemispheric stroke and essential tremor [5]. Thus, the acoustic analysis is helpful to have a non-invasive and easy tool to make the diagnosis and follow the evolution of the disease and choose the better speech therapy.

The voice disability in PD is generally well known, but very often underestimated. Changes are observed in all speech subsystems, both the phonatory and articulatory subsystems, but voice analysis yields quantitative measures with more accuracy and repeatability than a clinical articulatory analysis. Acoustic analysis of voice could be a mean for more objective description of voice disorders in patients with PD and could allow a more precise estimation of PD-related changes in vocal performance. Voice is affected earlier in patients with PD, followed by articulation and fluency disorders [6]. For these reasons, focusing on voice decline is a way to track and follow up PD.

Voice, articulation and fluency disorders in Parkinson's disease

Vocal disorders in PD commonly affect the com-

Figure. Flowchart of the process of initial literature search and extraction of studies meeting the inclusion criteria.



munication, making the diagnosis important for treatment and health promotion in patients with PD. The identification of objective changes in voice parameters is relevant for targeting specific interventions and for following the rehabilitation of the patients.

Voice, articulation and fluency disorders can be present in the early phases of PD [6-8], even if voice disorders occur more frequently than articulation ones [6] and are affected earlier in patients with PD followed by articulation and fluency abnormalities [6].

Table I shows the features of hypokinetic dysarthria, diagnosed by an accurate neurological and ENT (ear, nose and throat) examination of patients with PD.

Acoustic analysis of voice is a mean for more objective description of voice disturbance in patients with PD and allows a more precise estimation of PD-related changes in vocal performance.

Purpose

The aim of this study was to perform a meta-analysis to better clarify the effects of PD on voice, as revealed by acoustic analysis of voice. We assessed the subjective and objective changes in voice quality in patients with PD. We analyzed which acoustic parameters of voice characterize the patients with PD and which differences in the objective and subjective voice parameters are present between patients with PD and healthy subjects.

Patients and methods

Information sources and database search

This meta-analysis is consistent with the PRISMA statement [9] and the MOOSE checklist [10]. Searches were conducted between January and May 2019 in the following databases: PubMed, Wiley Online Library Cochrane Library, EMBASE. The reference lists of related articles were also searched for eligible papers. The review was conducted from 10 March 2019 till 10 September 2019.

Study selection

We searched PubMed for the following terms and keywords: 'Parkinson's disease' and 'acoustic analysis'. The database searches yielded 241 references from 1972 to 2019, with an additional 11 papers found from reference lists and the other databases. Then, 252 titles and abstracts were screened and then 87 papers remained for full text screening, of these 14 met the inclusion criteria (Figure).

We included original articles, patients with confirmed diagnosis of PD, having undergone to acoustic analysis of voice obtained by instrumental analysis. We excluded animal studies, participants with other neurological diseases and comorbid larynx disorders (e.g. vocal cord lesions). Other exclusion criteria were: the use of qualitative results and arbitrary units, the use of statistical values without the mean values of each parameter, that is we excluded articles that did not provide data useful for meta-analysis (i.e. mean and standard deviation). This meta-analysis focused on voice parameters that were reported in more than one article.

In our meta-analysis we considered the studies in which the Authors compared voice parameters between patients with PD and healthy controls. Holmes et al [11] compared the voice parameters of healthy controls both to those of patients at an early stage of PD and at a later stage of PD. We analyzed both samples separately and assessed them twice in the meta-analysis. Lee et al [12] compared voice parameters of healthy controls to those of a group of patients with PD who received deep brain stimulation. In the same paper, the authors [12] also compared a group of non-surgical patients with PD to healthy controls. Both samples were analyzed separately and assessed twice in the meta-analysis.

Two reviewers independently screened the titles and abstracts from the initial search to identify relevant records and to identify eligible studies based

Table I. Clinical aspects of hypokinetic dysarthria and typical features of voice disorders in Parkinson's disease.

Voice and speech parameters	Alteration of voice and speech in PD	Explication	Clinical implication	References of current literature	Note
Lung function	Rigidity of the muscles involved in respiration	Poor coordination in inspiration and expiration	Weakened inspiration due to the weak inspiratory musculature, with small inspiratory volume	[49,50]	
Voice quality	Rough voice	Involuntarily raspy voice sound	Patient's compensation mechanism facing the frame stiffness	[4,6,11,16,20,30]	
	Hoarseness	Involuntarily scratchy voice	Rigidity of the cricothyroid muscle	[6,31]	
	Asthenic voice	Involuntarily weak voice sound	Associated with an inadequate respiratory support and with a limitation of adduction of the vocal folds	[16,26]	
	Breathiness	Involuntarily whisper voice sound	Air escape during voice production	[6,20,31,32]	No breathiness in PD [4]
Prosody	Lower loudness level	Low volume of voice: hypophony	Increased rigidity of the laryngeal and respiratory muscles	[7,11,16,18,26]	
	Decrease phonation range	Decrease range of frequencies	Laryngopharyngeal tract hypomobility	[4,11,12,16,24,26,29]	
	Monopitch, monoloudness	Prosodic insufficiency	Rigidity of the cricothyroid muscle	[4,7,11,12,22-24,31,33,51]	
Acoustic parameters	High value of F0	Altered periodicity of vocal fold vibration and difficulty to achieve a steady-state phonation	Reduced function of crico-thyroid and crico-arythenoid muscle and high degree of spasticity or flaccidity of laryngeal muscles Increased rigidity of the laryngeal and respiratory muscles, besides the laryngopharyngeal tract hypomobility	[4,10,14,17,21,23,24, 32-35,37]	
	High value of vF0	Altered periodicity of vocal fold vibration and difficulty to achieve a steady-state phonation	Impaired ability to keep the laryngeal muscles in a fixed position for vowel prolongation Increased rigidity of the laryngeal and respiratory muscles, besides the laryngopharyngeal tract hypomobility	[12,16,23,26,27,33]	
	High value of jitter	Measure of short-term frequency instability and of involuntary changes in frequency	Irregular contraction of laryngeal muscles during sound production, loss of motor control of the vocal folds, aperiodicity in the acoustic signal	[7,11,20,24,35,36,52,53]	No significant difference in jitter between PD and healthy controls [3,11,16,34]
	High value of shimmer	Measure of short-term intensity instability	Reduced laryngeal control and degenerative changes in laryngeal tissue Breathiness is related to shimmer, less periodic voice and is roughness or hoarseness	[12,19,21,23,34,35,52,53]	No significant difference in shimmer between PD and healthy controls [3,4, 11,16,18,20,24,34,36,37]
	Low NHR	Perturbation and irregularity in noise/harmonic ratio	Dysphonia with increased phonatory instability Turbulent noise due to incomplete glottal closure during sound production	[4,5,7,20,37]	According to Vizza et al [21] NHR is higher for PD compared to healthy controls According to Holmes et al [11], NHR value is non-significant between patients with PD and healthy controls
	Low HNR	Perturbation and irregularity in harmonic/noise ratio	Evaluates the degree of hoarseness	[4,18,23]	

Table I. Clinical aspects of hypokinetic dysarthria and typical features of voice disorders in Parkinson's disease *(cont.)*.

Voice and speech parameters	Alteration of voice and speech in PD	Explication	Clinical implication	References of current literature	Note
Acoustic parameters *(cont.)*	High FTRI and fftr	Alteration of low-frequency modulating component and long-term tremor frequency modulating component	Trembling voice	[19]	
	ATRI and Fatr	No alteration of low-amplitude-modulating component and long-term tremor amplitude modulation	No difference with healthy control	[19]	
	DVB	Difficulty to maintain phonation for some time without intervals	Voice arrests	[4]	
	VTI	Index of breathiness	High-frequency noise in voice. It is related to turbulence caused by abnormal closure of vocal folds	[52]	No statistically significant differences of VTI in patients with PD compared to healthy controls [34]
	s/z ratio	Ratio of length of time a person can sustain the sound 's' divided the length of time a person can sustain the sound 'z'	Correlation with dysphonia	[4,23]	According to Bauer et al [3], no significant differences were found for s/z ratio in patients with PD
	Decrease MPT	Reduce period during which a patient can sustain phonation of a vowel sound (< 10 s)	Respiratory decline, difficulty in glottal closure during speech production, increase muscular tension	[3,16,29]	Gamboa et al [4] and Ramig et al [7] fail to detect any statistical difference between patients with PD and healthy controls

ATRI: amplitude tremor intensity index; DVB: degree of voice break; FO: fundamental frequency; Fatr: amplitude tremor frequency; Fftr: fundamental frequency tremor frequency; FTRI: frequency tremor intensity index; jitter: frequency perturbation; MPT: maximum phonation time; NHR: noise to harmonic ratio; PD: individuals with Parkinson's disease; shimmer: amplitude perturbation; vFO: fundamental frequency variation; VTI: voice turbulence index.

on title and abstract. Selected full texts were then reviewed and included in the meta-analysis.

Meta-analysis calculations

The SPSS v. 18.0 software was used for data analysis. Inconsistency test (I^2) verified the impact of study heterogeneity on the results of the meta-analysis. An I^2 value < 25% was indicative of low risk of heterogeneity, a value between 25% and 50% of a moderate level of heterogeneity and > 50% was considered statistically significant between included studies [13]. We used a random-effect model to estimate the combined effect sizes [14]. The quality of identified studies followed the methods of the Cochrane Collaboration [15]. The publication bias was examined using funnel plots.

Results

The number of studies yielded at each stage of the search is displayed in figure. A total of 14 studies were included in this meta-analysis with the sample characteristics and details of the design of each included study displayed in figure.

Experimental conditions across studies

All study groups were homogeneous for relevant general clinical features as clinical presentation, electronic device used to obtain acoustic parameters, kinds of voice parameters (Table II).

A large variation existed in other features, such as the number of samples, mean age which ranged from 59.41 to 69.8 years old, the duration of the dis-

ease and of the treatment with Levodopa and the values of parameters of voice, even when the same electronic instrument was used for the evaluation.

Comparing studies

The studies focused on the relationship between PD and analysis of voice.

The most studied parameters of acoustic analysis in the current literature are shimmer in percentage [11,12,16-22], shimmer in decibel (dB) [4,23-25], HNR [4,12,17,18,22,23,25], vF0 [12,16], F0 [4,11,12, 16-18,20-23,25,26], SD F0 [11,17,22,26], NHR (n = 4) [11,16,20,21], and jitter in percentage [4,11,12,16-25]. Other searches considered also MPT [4,16,23] and s/z ratio (n = 2) [4,23].

Other interesting parameters, as vAm, ATRI, FTRI, Fatr, Fftr and diadochokinetic rate (DDK) were investigated only by a few studies: vAm by Lee et al [12], ATRI, FTRI, Fatr, Fftr by Shao et al [19], DDK by Midi et al [16]. We couldn't include them in the meta-analysis, but we hope this review could be an incentive to other similar researches.

Meta-analysis of voice parameters

Pooling of data within the meta-analysis revealed that several voice parameters including jitter (in percentage) (Table III) and shimmer (in percentage) (Table IV) presented significant variations between PD and healthy controls ($p < 0.001$), with statically significant difference (odds ratio < 1). Shimmer (dB) (Table IV) and vF0 (Table IV) presented significant variations between PD and healthy controls ($p < 0.005$) too, with statically significant difference (odds ratio < 1).

On the contrary, we did not observe significant variations of F0, HNR, SD F0, NHR and s/z ratio in people with PD compared to healthy controls.

MPT presented significant variations between PD and healthy controls ($p < 0.005$), but using a fixed-effect model, with an I^2 of 57.55%.

Heterogeneity and publication bias

The heterogeneity between studies was low for jitter %, shimmer dB and vF0 (I^2 = 0.00), for shimmer % (I^2 = 38.68%), for s/z ratio (I^2 = 21.17%). The heterogeneity was moderate-high (I^2 between 57.55 and 98.00%) for F0, HNR, SD F0, NHR, MPT. The funnel plot (Tables III and IV) showed that there was symmetry between the studies and no significant publication bias was seen, or small study effect was insignificant. The sensitivity analysis also showed the absence of an excessive influence of individual studies.

Discussion

Acoustic analysis of voice, using an electronic system, allows the identification of changes in voice parameters for predicting the worsening of disease and for targeting specific intervention. We systematically review all the literature, focusing on instrumental quantitative assessment of voice in patients with PD. Furthermore, we performed a meta-analysis to identify the main characteristics of voice disturbances in PD. The data within the meta-analysis revealed that several voice parameters including jitter (%), shimmer (% and dB) and vF0 presented significant variations between PD and healthy controls. Significant variations of F0, MPT, HNR, SD F0 were observed, but with a high heterogeneity between the studies. On the other hand, significant variations of NHR, s/z ratio, variations of amplitude were not observed.

Relationship between voice and motor disabilities in Parkinson's disease

A limited relationship was observed between voice and motor disabilities [16,27]. It may suggest that the motor speech control system is basically different from peripheral motor control mechanisms [16,27]. The neurological assessment and treatment outcomes did not always correspond with the voice problems [3,4,16].

According to several searches, the clinical profile, severity, duration and time of evolution of PD influenced neither acoustic measurements of voice nor laryngeal examination, with no significant correlation between motor disorders and voice disorders in PD [3,4,16,22,28]. Several voice features did not appear to deteriorate with disease progression (i.e. harshness, high modal pitch and F0 in males patients with PD, vF0 in females patients with PD, low intensity and jitter) [11].

According to other searches, several voice features had a significant correlation with the duration of the disease as F0 and vF0 [17], jitter and shimmer [16], voice arrests [4,11], breathiness, monopitch and monoloudness, low loudness and reduced maximum phonational frequency range [11] that were all worse in the later stages of PD. According to Holmes et al [11] a higher F0 was associated with advanced disease only in males, with no differences found for females with PD compared to healthy con-

Table II. Demographic and morphological characteristics of patients with Parkinson's disease

	Study design	Sample	Mean age ± SD (years)	Duration of disease (years)	Instruments	Voice parameters
Gamboa (1997)	Case-control study	41 PD (24 m, 17 f) 28 HC (16 m, 12 f)	69.8 ± 6.8 PD 67.0 ± 6.8 HC	4.8 ± 3.5	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, jitter, shimmer, HNR, MPT, s/z ratio
Hertrich (1995)	Case-control study	24 PD (9 f, 15 m) 25 HC (13 f, 12 m)	64,5 PD 54.5 HC	ns	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, jitter, shimmer, HNR
Holmes (2000)	Case-control study	30 early PD (15 f, 15 m) 30 later PD (15 f, 15 m) 30 HC (15 f, 15 m)	68.4 PD	2.4	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, SD FO, jitter, shimmer, NHR
Jiménez-Jiménez (1997)	Case-control study	22 PD (12 m, 10 f) 28 HC (16 m, 12 f)	65.3 ± 12.5 PD 65.8 ± 6.8 HC	2.5 ± 2.3	Computerized Speech Lab (CLS) Kay Elemetrics	FO, jitter, shimmer, HNR, MPT, s/z ratio
Lee (2008)	Case-control study	19 surgical PD (11 m, 8 f) 10 non-surgical PD (4 m, 6 f) 11 HC (6 f, 5 m)	63.84 PD 65.36 HC	ns	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, vF_0, jitter, shimmer, NHR, vAm
Majdinasab (2016)	Cross-sectional study	27 PD (15 m, 12 f) 21 HC (10 m, 11 f)	61.6 ± 8.9 PD ns HC	8.6 ± 4.5	Software program Praat	F_0, SD F_0, shimmer, jitter, HNR
Midi (2008)	Case-control study	20 PD 12 m, 8 f) 20 HC (10 m,10 f)	61.5 PD 59.4 HC	4,7 ± 3.0	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, vF_0, jitter, shimmer, NHR, MPT
Oguz (2006)	Prospective study	14 PD (14 f) 22 HC (22 f)	65.7 ± 10.6 PD 59.4 ± 10.0 HC	ns	Software program Praat	Jitter, shimmer, HNR
Rahn (2007)	Case-control study	41 PD (20 f, 21 m) 40 HC (22 f, 18 m)	58 ± 9.7 PD 46.5 ± 9.1 HC	ns	National Instruments AT-MIO-16	Jitter, shimmer
Shao (2010)	Case-control study	15 PD (ns) 24 HC (13 f, 11 m)	65.7 ± 10.6 PD 59.4 ± 10.0 HC	ns	Computerized Speech Lab (CLS) Kay Elemetrics	Jitter, shimmer, ATRI, FTRI, Fatr, Fftr
Silva (2012)	Cross-sectional study	27 PD (27 m) 27 HC (27 m)	59.9 PD 59.4 HC	ns	Computerized Speech Lab (CLS) Kay Elemetrics	F_0, jitter, shimmer, NHR
Skodda (2011)	Case-control study	169 PD (97 m, 72 f) 64 HC (31 m, 33 f)	67.1 PD 65.05 HC	ns	Software program Praat	F_0, SD F_0
Vizza (2018)	Case-control study	60 PD (35 m, 25 f) 39 HC (20 m, 19 f)	67 PD 46 HC	ns	Software program Praat	F_0, jitter %, shimmer, NHR
Zwirner (1991)	Case-control study	18 PD (12 m, 6 f) 12 HC (10 m, 2 f)	68 PD 58 HC	ns	Software program C-speech v. 2.1	F_0, SD F_0, jitter, shimmer, NHR

f: females; F_0: fundamental frequency; Fatr: amplitude tremor frequency; Fftr: fundamental frequency tremor frequency; HC: healthy controls; jitter: frequency perturbation; m: males; MPT: maximum phonation time; NHR: noise to harmonic ratio; ns: no specified; PD: Parkinson's disease patients; shimmer: amplitude perturbation; s/z ratio: s/z consonants ratio; vFO: fundamental frequency variation.

trols. A relationship was observed between body tremor and voice [17]. It indicated that tremor was an important main feature of PD that affected significantly phonation characteristics of the patients [4,11,17].

Summary of findings

Determining the voice features in PD has clinical implications in identifying sensitive markers for detecting and monitoring PD voice disorders.

Our systematic review collects data related to voice involvement in patients with PD and quantifies their importance in our meta-analysis. Our results show that PD has an important impact on specific voice parameters; the acoustic voice parameters correlate to voice disorders and disability in PD are jitter %, shimmer % and shimmer dB and vF0.

Table III. Forest plot illustrating the effect of bulbar Parkinson's disease on jitter (in percentage) when compared to cognitively healthy controls.

		Number of healthy controls	Number of PD patients	Mean healthy controls	Mean PD patients	Standard mean differences	Standard error	95% CI		Weight (%)	
								Lower limit	Upper limit	Fixed	Random
Gamboa (1997)		28	41	0.62 ± 0.12	0.98 ± 0.62	0.73	0.25	0.234	1.233	9.31	9.31
Hertrich (1995)		25	24	0.79 ± 0.76	1.44 ± 1.03	0.70	0.29	0.126	1.293	6.93	6.93
Holmes (2000)	Early PD	30	30	1.06 ± 0.89	1.21 ± 9.81	0.02	0.25	−0.488	0.532	8.98	8.98
	Later PD	30	30	1.06 ± 0.89	2.16 ± 2.83	0.51	0.25	0.00007	1.038	8.68	8.68
Jiménez-Jiménez (1997)		28	22	0.65 ± 0.15	1.16 ± 0.81	0.91	0.29	0.324	1.510	6.70	6.70
Lee (2008)	Non-surgical PD	5	4	0.32 ± 0.11	0.42 ± 0.24	0.50	0.60	−0.934	1.939	1.58	1.58
	Surgical PD	5	11	0.32 ± 0.11	0.60 ± 0.41	0.76	0.52	−0.369	1.894	2.10	2.10
Rahn (2007)		40	41	0.24 ± 0.27	0.67 ± 1.07	0.54	0.22	0.0965	0.989	11.6	11.6
Majdinasab (2016)		21	27	0.18 ± 0.10	0.36 ± 0.53	0.42	0.28	−0.157	1.008	6.96	6.96
Midi (2007)		20	20	0.65 ± 0.29	1.70 ± 1.61	0.89	0.32	0.231	1.549	5.51	5.51
Oguz (2006)		22	14	0.29 ± 0.14	0.50 ± 0.31	0.90	0.35	0.196	1.622	4.73	4.73
Shao (2010)		24	15	0.48 ± 0.20	0.80 ± 0.59	0.78	0.33	0.104	1.459	5.22	5.22
Silva (2012)		27	27	1.54 ± 2.83	2.32 ± 2.42	0.29	0.27	−0.249	0.833	8.02	8.02
Vizza (2018)		39	60	0.29 ± 0.16	0.97 ± 1.92	0.45	0.20	0.0396	0.860	13.67	13.67
Total random effects		344	366	*t* 7.334	$p < 0.001$	0.56	0.076	0.41	0.71	100	100
Odds ratio						0.49					

95% CI: 95% confidential interval; PD: Parkinson's disease.

To our knowledge, this is the only systematic review that provides a comprehensive overview and meta-analysis of studies using objective and electronic instrumental assessment of voice in PD.

The speech system is very often involved in PD, this is an important topic for the impact of the disease on speech function and for the need of more objective voice measurement in PD. Dysphonia is not the only contributor to the speech impairments associated with PD, also dysarthria could be present, but articulatory problems are more difficult to objectively quantify compared to phonatory problems [26].

Voice parameters

The alteration of voice and speech parameters in Parkinson affects the prosody (Table I). Phonation range is decreased in patients with PD, but it usually improves with voice therapy [4,29]. The abnormal voice quality is characterized by hypophonic and rough voice [4,6,11,16,30], hoarseness [6,31] and asthenic voice quality [16]. The asthenic voice, observed in PD, is associated with an inadequate respiratory support and with a limitation of adduction of the vocal folds [26]. It could be the result of a patient's compensation mechanism facing the frame stiffness, present in PD [20]. Some authors [6,20,31,32] report also breathiness, but this voice feature is not perceived in the study of Gamboa et al [4].

The high values of F0 and vF0 in patients with PD are usually attributed to the increased rigidity of the laryngeal and respiratory muscles, besides the laryngopharyngeal tract hypomobility [16,26]. Furthermore, the impaired ability to keep the laryngeal muscles in a fixed position for vowel pro-

Table IV. Forest plot illustrating the effect of Parkinson's disease on shimmer (in percentage and dB) and vF0 when compared to cognitively healthy controls.

			Number of healthy controls	Number of PD patients	Mean healthy controls	Mean PD patients	Standard mean differences	Standard error	95% CI		Weight (%)	
									Lower limit	Upper limit	Fixed	Random
Shimmer (%)	Holmes (2000)	Early PD	30	30	6.98 ± 4.17	9.31 ± 6.75	0.41	0.25	−0.105	0.926	12.63	11.76
		Later PD	30	30	6.98 ± 4.17	8.74 ± 5.97	0.33	0.25	−0.177	0.850	12.72	11.81
	Lee (2008)	Non-surgical PD	5	4	2.43 ± 1.72	7.00 ± 3.40	1.57	0.70	−0.085	3.233	1.70	2.69
		Surgical PD	5	11	2.43 ± 1.72	6.61 ± 2.84	1.53	0.57	0.298	2.776	2.51	3.77
	Majdinasab (2016)		21	27	2.38 ± 1.60	2.85 ± 1.94	0.25	0.28	−0.322	0.835	10.15	10.42
	Midi (2007)		20	20	1.89 ± 0.95	3.13 ± 1.90	0.80	0.32	0.155	1.463	8.04	9.05
	Oguz (2006)		22	14	4.58 ± 2.45	5.46 ± 1.90	0.38	0.33	−0.304	1.067	7.37	8.55
	Shao (2010)		24	15	1.04 ± 0.84	1.90 ± 1.18	0.85	0.33	0.173	1.537	7.39	8.57
	Silva (2012)		27	27	7.87 ± 5.55	6.43 ± 5.60	−0.25	0.26	−0.795	0.286	11.55	11.21
	Vizza (2018)		39	60	3.74 ± 3.14	6.04 ± 6.28	0.43	0.20	0.022	0.842	19.67	14.49
	Zwirner (1991)		12	18	4.10 ± 0.02	6.00 ± 6.60	0.35	0.36	−0.389	1.108	6.27	7.67
	Total random effects		235	256	*t* 3.741	$p < 0.01$	0.45	0.20	0.216	0.695	100	100
	Odds ratio						0.81					
Shimmer (dB)	Gamboa (1997)		28	41	0.41 ± 0.17	0.50 ± 0.30	0.34	0.24	−0.139	0.835	27.33	27.33
	Hertrich (1995)		25	24	0.30 ± 0.27	0.52 ± 0.53	0.51	0.28	−0.064	1.086	19.94	19.94
	Jiménez-Jiménez (1997)		28	22	0.23 ± 0.17	0.40 ± 0.26	0.78	0.29	0.196	1.367	19.23	19.23
	Rahn (2007)		40	41	0.81 ± 0.48	0.95 ± 0.98	0.17	0.22	−0.260	0.618	33.50	33.50
	Total random effects		121	128	*t* 3.19	$p = 0.02$	0.40	0.12	0.156	0.659	100	100
	Odds ratio						0.72					
vF0	Lee (2008)	Non-surgical PD	6	6	1.35 ± 0.43	6.70 ± 8.32	0.83	0.56	−0.408	2.085	19.42	19.42
		Surgical PD	6	8	1.35 ± 0.43	1.81 ± 1.19	0.45	0.51	−0.666	1.568	23.14	23.14
	Midi (2007)		20	20	0.99 ± 0.24	2.58 ± 2.48	0.88	0.32	0.226	1.543	57.44	57.44
	Total random effects		32	34	*t* 3.144	$p = 0.003$	0.77	0.24	0.283	1.268	100	100
	Odds ratio						0.95					

95% CI: 95% confidential interval; PD: Parkinson's disease; vF_0: variation of fundamental frequency.

longation may be the cause of the increased vF0 in PD [27,33]. The study of Gamboa et al [4] shows a higher F0 in patients with PD compared to healthy controls, it is in line with the results reported by other studies [11,12,16-23,25,26]. Two other studies show a higher vF0 in patients with PD compared to healthy controls [12,16]. According to Midi et al [16] and Jiménez-Jiménez et al [23], mean F0 value is higher in patients with PD compared to healthy controls for both male and female subjects, howev-

er, the difference is statistically significant only for females. On the other hand, mean vF0 value is significantly higher in male patients with PD compared to gender-matched healthy controls [16] and it is significantly reduced in females with PD [11]. According to other searches, vF0 is reduced in male and female patients with PD [26], whereas mean F0 is elevated only in male patients with PD [11,26]. Oguz et al [18] show no differences in mean F0 between PD and healthy controls.

Gamboa et al [4] show a significantly higher jitter compared to healthy controls with consequently roughness, it is in line with the results reported by our study and other searches [4,11,12,16-25]. Holmes et al [11] suggest that this parameter is more altered in the later stage of PD. Other authors don't find any significant difference in jitter value between patients with PD and healthy controls [3, 11,16,34].

Our study shows a significantly higher shimmer compared to healthy controls, it is in line with the results reported by other searches [12,19,21,23,34,35]. According to other searches, shimmer values were not different between patients with PD and healthy controls [3,4,11,16,18,20,24,34,36,37].

NHR is significant higher in the healthy controls compared to patients with PD [4,20,37]. According to Vizza et al [21] NHR is higher for PD compared to healthy controls. According to Holmes et al [11], NHR value is non-significant between patients with PD and healthy controls.

HNR evaluates the degree of hoarseness. The value is significantly lower in PD compared to healthy controls [4,18]. According to Jiménez-Jiménez et al [23], when compared to controls, PD patients showed a lower HNR, especially in female patients.

Interesting parameters, as amplitude tremor intensity index (ATRI), fundamental frequency tremor intensity index (FTRI), degree of voice break (DVB), soft phonation index (SPI), voice turbulence index (VTI), variation of amplitude (vAm), amplitude tremor frequency (Fatr) and fundamental frequency tremor frequency (Fftr) were less studied.

Patients with PD are previously found to be different from the control group mainly in F0 and frequency perturbation parameters (jitter), rather than in tremor parameters (ATRI and FTRI, Fftr and Fatr) [5], even if these values could be very interesting to follow the progression of the disease. Shao et al [19] find significantly higher FTRI and Fftr and no significant difference for ATRI and Fatr between PD and healthy controls.

Gamboa et al [4] find voice arrests and consequently altered DVB in 39.0 % of patients with PD.

There are no statistically significant differences of VTI in patients with PD compared to healthy controls [34].

Patients with PD have a reduced ability to sustain prolonged phonation following a deep inspiration, with a significant shorter MPT in patients with PD compared to healthy controls [3,16,29]. However, Gamboa et al [4] and Ramig et al [7] fail to detect any statistical difference between patients with PD and healthy controls in terms of MPT values. According to Midi et al [16] the average of MPT is shorter in PD group compared to healthy controls for both male and female subjects, but the value between groups is not statistically significant. Midi et al [16] do not find any correlation between rigidity and MPT.

According to Bauer et al [3], no significant differences were found for s/z ratio in patients with PD, unlike other searches [4,23].

The GRBAS (*Dysphonia Grade, Roughness, Breathiness, Asthenia and Strain*) scale was proposed by the Japanese Society of Logopedics and Phoniatrics [38]. It measures voice properties, such as the degree of dysphonia, roughness, breathiness, asthenia, strain and instability. According to Bauer et al [3], the voice of people with PD is coarser in texture, has more breathiness, is more phonastenic and strained than healthy controls. According to Santos et al [34], patients with PD present asthenia and instability parameters both during treatment with levodopa and during drug suspension [34]. Thus, medical therapy with levodopa does not interfere significantly in the vocal patterns of patients with PD [34]. Weak voice is the most frequent complaint, which justifies the asthenic voice [39].

A few studies examine the relation between voice parameters and Unified Parkinson's Disease Rating Scale (UPDRS) [40]. The UPDRS investigates the relationship between motor severity and the patients' voice characteristics in PD. Some studies report a strong relationship between motor UPDRS components and acoustic voice parameters in PD [16,27], as between facial expression and SD F0 and shimmer [17]. There is also a positive correlation between F0 and kinetic tremor of the hands evaluated with the UPDRS [17]. The presence of tremor on laryngeal examination is significantly more frequent in PD patients with higher score in the UPDRS [4]. Mean jitter % and shimmer % values increase with decreasing of postural stability evaluated with UPDRS [16]. The duration of PD shows a positive correlation with F0 and vF0, but no correlation with the disease severity evaluated with the UPDRS [17].

There is no correlation between the perceptual assessment of voice quality evaluated with the GRBAS and the total UPDRS motor scores in patients with PD [16].

Articulatory changes are measured by oral DDK rate and syllabic rate [34]. Rigidity and bradykinesia might affect the muscles and the movements of the lips and tongue leading to a lower DDK rate [16]. There is a significant negative correlation between DDK and rigidity, indicating a shorter speech DDK rate with increasing severity of rigidity. This may be related to the rigidity of jaw muscle, joint and rigidity and bradykinesia of the tongue. Impaired mouth opening may affect the speech repetition rate [16]. In the study of Midi et al [16], DDK rate is significantly lower in male patients than that of healthy controls, the difference does not reach statistical significance in female patients. Three authors, Midi et al [16], Goberman et al [27] and Gurd et al [41], find no association between movement DDK (finger taps, hand movement, rapid alternating movements and tap heel on ground) and rapid syllable repetitions in patients with PD [16,27,41]. This finding shows that neurological control of articulation is different from that of finger movements [16,27,41]. According to Skodda et al [26], there is no significant difference in the articulatory rate between patients with PD and healthy controls, but patients, especially the female, show a reduction of percentage pause time in polysyllabic words. Ackermann et al [42] and Harel et al [2] note that patients with PD are able to compensate for abnormally slow movement (bradykinesia) by reducing the amplitude of movement early in the course of the disease.

ENT examination also includes laryngostroboscopy, it often reveals an irregular mucosal wave [3] and laryngeal tremor [3,16,20,32,43]. Laryngeal tremor has been reported as 14.6% [4], 25% [16], 28.5% [3], 31.8% [23], 34.1% [4], 55% [44]. Although the patients with PD report a high occurrence of voice tremor, the tremor of the vocal folds is not confirmed in many cases with laryngeal examination [4]. Another feature of laryngoscopy is the degree of glottal closure, often incomplete [3,16,30,45], it may be a result of laryngeal and/or respiratory muscle rigidity [16]. The frequency of incomplete glottic closure is found in 60% of patients with PD [16]. The incomplete glottal closure prevents the increase of subglottic pressure and justifies the perception of a breathy voice or hoarse-harsh-breathy voice in patients with PD [34]. According to two searches, the degree of glottal closure is complete in patients with PD [4,23].

The influence of treatment in voice parameters

Only few studies compare voice disorders in patients with PD before the treatment with levodopa and after influence of the drug, these searches demonstrate a partial response of speech and voice to levodopa therapy [27,34,39,46]. For this partial result, a study suggests that speech may be related to a non-dopaminergic mechanism [27]. De Letter et al [39] finds no statistically significant differences in vocal quality of individuals with neurological disease under dopaminergic medication.

According to other searches, when the patients are under the influence of the levodopa, the symptoms and the voice disorders disappear or reduce noticeably, and they reappear after ceasing the action of the drug [4,27,47,48]. Levodopa promotes articulation, sound, rhythm, vocal amplitude and speech intelligibility of speech in PD patients [48]. In the study of Gamboa et al [4], the patients with PD under drug treatment show increased measures of F0 and jitter and reduced measures of vocal intensity, of HNR values and of the variability of frequency and intensity compared to healthy controls [4]. Another study links the increase of F0 to an increase in tension of vocal cords caused by the use of the antiparkinsonian drug [27]. During treatment with levodopa, patients with PD present a significant increase of F0 and a significant reduction of jitter, HNR and VTI values [47], unlike the results from the study of Santos et al [34], whose F0 value, despite the treatment, is not significantly higher and jitter, HNR and VTI values are not significantly reduced in the treatment group, possibly the difference in the results is due to the significantly smaller sample in this study, besides the methodological differences of the type of extraction of acoustic parameters [34]. Another study [46] evaluates the voice and speech of patients with PD before and after pallidotomy during treatment with levodopa and after its suspension. The pallidotomy does not interfere significantly in the acoustic measurements. Only F0 increases with drug intake. There is no statistically significant difference in the values of jitter, shimmer and NHR, pre- and post-pallidotomy, both during drug assumption and during suspension [46].

Limitations

A lack of uniformity among the papers (measured parameters, electronic instrument, methodological differences in the laryngeal examination) may affect statistical analysis validity. The studies assess different parameters, so for parameters which are more

frequently reported, the results of meta-analysis are more accurate. The absence of information about some clinical characteristics, that could influence vocal parameters, represents another limitation, such as comorbidities affecting voice (vocal cord lesions, laryngeal surgery), the use of drugs. Furthermore, in some articles the sample is too small. Several studies do not assess what stages of the disease lead to specific speech profiles, they do not describe the duration and the severity of the disease. All these characteristics can be confounding factors and can influence results. Most of the studies do not assess separately men from women, but given that vocal parameters vary according to sex, a few studies do not identify properly voice modification related mainly to disease modification. In most of the studies how many times patients are tested, are not specified, during acoustic analysis, but weakness of respiratory support in voice production could influence the results.

Conclusions

Speech impairments are more prevalent in people with PD than healthy people. Acoustic analysis of voice could have potential clinical implications, could permit to identify sensitive markers of early deterioration of voice before the human ear distinguishes dysphonia, both in the early stages of diagnosis and as the disease progresses. This meta-analysis identifies pattern of voice disorders and the most sensitive parameters related PD voice disability, using acoustic analysis of voice, furthermore it identifies changes in voice parameters as predictors of functional dependence on communication and poor quality of life.

According to our meta-analysis, the acoustic voice parameters correlated to the voice disorders in PD are jitter (in percentage), shimmer (in two different units of measure: dB and percentage) and vF0.

Acoustic analysis of speech performance in PD could improve future researches to formulate hypotheses regarding different speech and respiratory pathophysiology as well as to investigate compensatory strategies for patients.

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Análisis acústico de la voz en la enfermedad de Parkinson: revisión sistemática de la discapacidad vocal y metaanálisis de estudios

Objetivo. Revisar de manera exhaustiva la bibliografía referente a la evaluación instrumental cuantitativa de la voz en pacientes con enfermedad de Parkinson (EP) y realizar un metaanálisis para definir las principales características de los trastornos de la voz en la EP.

Pacientes y métodos. Búsquedas bibliográficas con las palabras clave '*Parkinson*' y '*voice*' en PubMed, EMBASE, Cochrane Library y Web of Science. Los principales criterios de aceptación fueron: EP con confirmación clínica y medición instrumentada de los parámetros de la voz mediante análisis acústico.

Resultados. Catorce publicaciones cumplieron los criterios de aceptación y se incluyeron en el metaanálisis. De los datos incorporados al metaanálisis, se dedujo que varios parámetros vocales, como el *jitter,* el *shimmer* y la variación de la frecuencia fundamental, presentan variaciones significativas en los pacientes con EP frente a los controles sanos. Se hallaron variaciones significativas de la frecuencia fundamental y de su desviación estándar, del tiempo máximo de fonación y de la razón armónicos-ruido, si bien con una alta heterogeneidad entre los estudios. En cambio, no se observaron variaciones sustanciales de la razón ruido-armónicos, en el índice s/z ni en la variación de la amplitud.

Conclusión. El análisis acústico de la voz por medio de un sistema electrónico permite detectar los cambios de los parámetros vocales de cara a predecir el empeoramiento de la enfermedad y elegir una intervención específica. Entre dichos parámetros, el *jitter* y el *shimmer* aumentaron significativamente en los pacientes con EP.

Palabras clave. Discapacidad. Enfermedad de Parkinson. Metaanálisis. Patología del habla. Revisión sistemática. Voz.