Committee on biomarkers in phoniatrics
Union of European phoniatricians

National Institute of Health -NIH 1998 – Biomarker: a characteristic that is **objectively measured and evaluated** as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions

Overview of Voice Parameters in Parkinson’s Disease eventually usable as biomarkers

6th of September 2023

Mette Pedersen MD Ph.D. the Medical Center Østergade 18 and Vitus Girelli Meiner IT-University, Copenhagen Denmark

Mieke Moerman suggestions for now:

- A validation,
- **and distraction of the most valuable voice parameters**
- **(NHR, FO, dB, voice-related questionnaires, MaximumPhonationTime**, etc.)
- and their respective value.

- The article about genetics is a very nice addition.

- Speech biomarkers (such as rhythm, tempo, linguistics, vocabulary etc.) are not to be focused upon now - cf Mieke Moerman

LITERATURE SEARCH I

“Vocal Biomarkers and Artificial Intelligence - all to 2023”

The Royal Society of Medicine Library for

Dr M Pedersen, 2 March 2023

332 papers here of 54 papers with included Parkinson’s disease

LITERATURE SEARCH II

”**Voice Parameters in Parkinson’s Disease from 2013 to 2023”**

The Royal Society of Medicine Library for

Dr M Pedersen 22 August 2023

98 papers

Mette Pedersen MD PhD and Vitus Girelli Meiner IT-University of Copenhagen

47 papers with Voice Parameters in Parkinson's Disease from 2013 to 2019, 3 including AI

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Author	Number	Year	Patient nu	prospective	Randomize	Case/Control	Retrospective	HNR	SNR	F0(st)	Intensity	MPT	JITTER APS/%	SHIMMER APS/%	Spekt LTAS	CEPSTRUM	VRP	Telephone	Praat	VHI	GRBAS	Deep Brain.s	AI	Deep Learning	laryngoscopic	Software	Others
Louis, E. et al	98	2013	85			100	1													1							
Bauer,V. et al	97	2013	22			plus cc														1							
Péron, J. et al	96	2013				plus cc					1											1					
Bang, Y. et al	95	2013	7			7		1		1	1		1	1	1				1								
Teixeira, E. et al	94	2013	60			48				1	1																
Silbergleit, AK. et al	93	2014	27			22				1			1	1			1										
Jafari, A. et al	92		25			10		1		1						1											1
Smith, L. et al	91	2014	28			10									1												
Yang, S. et al	90	2014																					1	Kernal/SVM			
Silbergleit, AK. et al	89	2015	26			22			1			1	1				1										Cspeech Waveform Analysis Pr
Soares, DP. et al	88	2015	22				1	1		1	1		1	1													
Spazzapan, EA. et al	87	2015	19	1				1		1	1		1						1				1	peak-to peak amp var			
Tanaka, Y. et al	86	2015	108																	1	1	1			1		68 dps/40 Med
Manor, Y. et al	85	2015	21	1		11				1	1	1	1	1					1								
Tsuboi, T. et al	84	2015	47																	1	1		1	1	1		22 dps/25 Med
Crino, C. et al	83	2016										1								1							Acoust analysis
Watts, C. et al	82	2016	78				1				1																
Postuma, R.B	81	2016																									Editorial
Gillivan-Murphy, P.	80	2016	30	1		28														1					1		
Abrahao, L.J. et al	79	2016	15	1		5				1									1								Pharynx Pressure
Cannito, M.P. et al	78	2016	16				1	1							1												H1, H2, F3
Vernier, L.S. et al	77	2016																									Reaview
Neves, MRL. et al	76	2016	46					1		1	1								1		1						
Novotný, M. et al	75	2016	37	1		37																					1/3-octave band
Majdinasab, F. et al	74	2016	27	1		21		1		1			1	1					1								
Roubeau, B. et al	73	2016																		1					1		Acoustanal
Sidits, D. et al	72	2017							1	1			1	1								1					
Wu, Y. et al	71	2017								1	1												1			SVM	
Stegenmöller, E.L. et al	70	2017																									Voicequl
Parveen, S. et al	69	2017																		1							
Butala, A. et al	68	2017	30		1	32		1			1		1	1													singing, crossovers
Da Silva, V.G. et al	67	2017	10	1				1		1	1		1	1													Tube Treatment
kacha, A. et al	66	2017	205			74		1					1														No statistical difference
Lechien, J.R. et al	65	2018	20	1		10		1				1	1							1							Early diagnosis
Abur, D. et al	64	2018	16			19				1																	JND paradim, feedback
Vieira, M. et al	63	2018	23	1		20				1																	Vawel lenghtining
Motto, S. et al	62	2018	15	1		15					1	1								1							MESGP,MPR
Lechien, J.R. et al	61	2018																							1		Review, 1980-2017
Abur, D. et al	60	2018	20	1		23			1																		loudness slopes
Ko ,E.j. et al	59	2018	30									1															plus swallowing
Han, E.y. et al	58	2018										1							1	1							Singing
Manor, Y. et al	57	2018	26	1		13														1	1						
Pinho, P. et al	56	2018								1	1																review 1960-2016, meta A
Gillivan-Murphy, P.	55	2019	38	1		28														1							
Shen, J. et al	54	2019	52	1		32		1		1			1	1	1					1							formant ratio
Saffarian, A. et al	53	2019	23	1	1															1							treatment
Romann, A.J. et al	52	2019	16							1												1					

51 papers with Voice Parameters in Parkinson's Disease from 2019 to 2023, 20 including AI

Mette Pedersen MD PhD
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Author	Number	Year	Patient nu	prospective	Randomize	Case/Control	Retrospective	HNR	SNR	F0(st)	Intensity	MPT	JITTER APS/%	SHIMMER APS/%	Spekt LTAS	CEPSTRUM	VRP	Telephone	Praat	VHI	GRBAS	Deep Brain.s	AI	Deep Learning	laryngoscopic	Software	Others
Arora, S. et al	51	2019	1483	1														1					1			Random forest	3+A51:AB10207 measures, crossover
Behroozmand, R. et al	50	2019	10		1					1			1									1					
Finger, M.E. et al	49	2019																		1							
Karlsson, F. et al	48	2019	22	1																							
Lechien, J.R. et alt	47	2019	20					1				1	1	1						1							Phonation quotient
manor, Y. et al	46	2019	104			82				1		1								1	1		1				
Sheiban, R. et al	45	2019								1													1			Class label prediction	Root Mean Score
Tamplin, J. et al	44	2020	75			44				1																	Singing, VQOL
Viswanathan, R. et al	43	2020	24			22			1	1													1			SVM	Glottal Closure qu
nakayama, K.	42	2020	24							1	1																Treatment
Ma, A. et al	41	2020	3032																								Review
Morello; A.N.D.C	40	2020																			1	1	1			acoustanal	acoustanal
Chiaramonte, R. et al	39	2020																									Review, 14 pub, meta
Viswanathan, R. et al	38	2020	26			22																	1			LASSO ranking	
Altay, E.V. et al	37	2020																					1			nicgar, Voice data	
Park, J.E. et al	36	2020	47												1								1				Comparred to 39 tremor
Sarac, E.T. et al	35	2020	12					1		1			1	1					1								
Reyes, A. et al	34	2020	31		1							1														peak subg press	Treatment
Lechien, J.R. et al	33	2020	32			20		1		1	1																
Gaballah, A. et al	32	2021	51			51		1								1										SVR/RPDE	
Lechien, J.R. et al	31	2021		1																							Acoust meassurements
Jain, A. et al	30	2021	14																				1	1		p-CRNN	Ative phon plus pros features
Gaballah, A. et al	29	2021	51						1						1	1										svr	VAT, RPDE
Rajasekar, S.S	28	2021	23							1	1		1	1									1				AdaBoost classifier
Da Silva,j.M.S. et al	27	2021	20			20				1	1			1													treatment
Searl, J. et al	26	2021	15																	1							Vocal Monitor
Koyuncu, H. et al	25	2021	74																	1						diet	
Yasar, O.C. et al	24	2022	20					1		1			1	1	1				1				1	1			
Rajasekar, S.S	23	2022					1	1					1										1	1		lstm cnn	accuracy 85%
Suppa, A. et al	22	2022	115			108														1			1			Sup vector machine classifier	Audio recorder, LR- value
Yu, Q. et al	21	2022	80			40		1		1		1	1						1				1	1		SVM, accuracy 73%	27 voice features
Paulino, C.E.B. et al	20	2022	20			20									1	1											
Kopf, L.M. et al	19	2022	24																	1		1					Compares 12 STN/12 GPI
Vojtech, J.M. et al	18	2022	20			20																			1	utterance /ifi/	
Dos Santos, A.P. et al	17	2022	14	1	1	1				1	1					1										Voiss/V-RQOL	
Pah, N.D. et al	16	2022	50			50					1							1								SVM	Acuraccy 84%
Bao, G. et al	15	2022						1					1	1									1			PCA	SSCL, acuraccy 83%
Marchese, M.R. et al	14	2022	15							1	1	1					1			1	1						
Dao, S.V et al	13	2022																					1			GWO/LGBM	
Sapmaz, A.M. et al	12	2022	43			43		1		1		1	1	1					1	1			1			Audacity	WAS
Butala, A. et al	11	2022	26					1		1	1		1	1													singing
Lim, W.S. et al	10	2022	371															1					1			auroc	
Good, A. et al	9	2023	22							1	1		1	1					1								
Cabestany, J. et al	8	2023																									Editorial
Constantini, G. et al	7	2023	124	1		266		1	1	1	1		1	1	1				1				1	1		SVM/CFS	453 vocal features
Qiang, L. et al	6	2023	55	1		55															1						Not described accoustics
Olivares, A. et al	5	2023	20	1						1													1	1			
Silva, J. M. S. et al	4	2023	20	1		20			1	1	1		1	1													
Abraham, E. A. et al	3	2023	12	1		12				1			1	1							1						11 accoustic parameters MDVP
Lima, H. V. S. L. et al	2	2023	30			30	1		1				1	1			1										
Romero Arias, T. et al	1	2023	20	1						1		1	1	1						1	1						the Online Lab App tool?
Total			7561(23 without patienter)	25	5	1513	6	23	8	40	24	14	29	23	9	5	4	3	13	25	10	7	24	7	6	0	1

This validation is based on 7561 patients (23 papers without numbers) and 1513 controls (58 without numbers) in 98 papers from 2013 to 2023 (minus 5 reviews)

Most studies are on early and moderate cases of Parkinson's' disease. 7 papers present results of deep brain treatment

Mostly, validations in non-AI papers are:
HNR F0 intensity Jitter Shimmer and VHI
Also, in non-AI papers are:
SNR MPT Spectrography Cepstrum analysis
VRP GRBAS

Praat is used in both non-AI and some AI cases. AI is used for validation in 24 papers and is often based on many more parameters

Parameters	Total
No Patient (cases)	7561 (23 without no.)
Prospective	25
Randomized	5
(Case) Controls	1513 (58 without no.)
Retrospective	6
HNR	**23**
SNR	8
F0 (+stnd. dv.)	**40**
Intensity	**24**
MPT	14
JITTER APS/%	**29**
SHIMMER APS/%	**23**
Spekt LTAS	9
CEPSTRUM	5
VRP	4
Telephone	3
Praat	13
VHI	**25**
GRBAS	10
Deep Brain.s	7
AI	**24**
Deep Learning	9
Laryngoscopy	6

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5 reviews

- Lechien JR, Blecic S, Huet K, Delvaux V, Piccaluga M, Roland V, Harmegnies B, Saussez S. Voice quality outcomes of idiopathic Parkinson's disease medical treatment: A systematic review. Clin Otolaryngol. 2018 Jun;43(3):882-903. doi: 10.1111/coa.13082. Epub **2018** Mar 12. PMID: 29443454.
  From 1980 - 106 studies, hereof acoustic testing in 27. The methods varied substantially.
- Pinho P, Monteiro L, Soares MFP, Tourinho L, Melo A, Nóbrega AC. Impact of levodopa treatment in the voice pattern of Parkinson's disease patients: a systematic review and meta-analysis. Codas. **2018** Oct 4;30(5):e20170200. doi: 10.1590/2317-1782/20182017200. PMID: 30304100.
  From 1960 - modifications in F0 and jitter were found, but not in intensity.
- Ma A, Lau KK, Thyagarajan D. Voice changes in Parkinson's disease: What are they telling us? J Clin Neurosci. **2020** Feb;72:1-7. doi: 10.1016/j.jocn.2019.12.029. Epub 2020 Jan 14. PMID: 31952969. -
  Acoustical and perceptual analysis and laryngoscopy–computed tomography and others are described as valid for early diagnosis.
- Chiaramonte R, Bonfiglio M. Acoustic analysis of voice in Parkinson's disease: a systematic review of voice disability and meta-analysis of studies. Rev Neurol. **2020** Jun 1;70(11):393-405. Spanish, English. doi: 10.33588/rn.7011.2019414. PMID: 32436206. The **Meta-analysis revealed that several voice parameters including jitter, shimmer, and fundamental frequency variation presented significant deviation from healthy controls. Significant variations of F0, MPT, HNR, were observed but with high heterogeneity between the studies.**
- Pu T, Huang M, Kong X, Wang M, Chen X, Feng X, Wei C, Weng X, Xu F. Lee Silverman Voice Treatment to Improve Speech in Parkinson's Disease: A Systemic Review and Meta-Analysis. Parkinson's Dis. **2021** Dec 27;2021:3366870. doi: 10.1155/2021/3366870. PMID: 35070257; PMCID: PMC8782619. -
  An increase in semitone standard deviation was found.

Machine Learning Studies

no in libary	No of patients/controls	features	ML	Support vector machines	Others	Telephone	Praat	Acuracy	sensitivity	specifity	comments
90		4		1	map classifier			91.8%			
85	31						1				
72		22	1	1					0,85%		
51	2759	307	1		Random forest				64,90%	67,90%	
46	104		>5	1	classifier						
43	24	4	1	1				>80%			
40	19	2									
38	26 patients/22 controls	6	1		AdaBoost recreation learner classifier						
37			1		Nicgar						
36	86	1	1					68%			
35	12	4					1				
32	51		1	1	vat						
30	14		1		p/CRN PAC	1		73,00%	0,69%	0,77%	
28	23	>5	1		AdaBoost recreation learner classifier						
24	20						1				
23		>4	1		CNN/LSTM			85%			
22	115		1	1	LR score value						
21	40 patients/40 controls	27		1				73,50%	71,40%	75,70%	
20	20 patients/20 controls	>4					1				
16	72 patients/ 72 controls	>4	1	1				84,30%			Two different test
15		8	1		SSCL algorithm			0,83%		0,85%	
13			1		LGBM						GWO feature selecion
11	16	>5					1				Version 5.4.01
10	112 patients/111 controls		1		9 ML classifiers AUROC	1		0,85%			
7	124 patients/266 controls	453	1	1	CNN KNN/CFS	1	1				CFS feature selector
Sum	3.488 patients	>860	16	9	14	3	6				
	531 controls										

*To be accounted for faults in references.

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It was noted there was a great variability of features.

Another comment is that Praat has two systems, one with and one without machine learning. We considered 6 papers as being machine learning related.

Parameters	**Total**
No Patient (cases)	6488
(Case) Controls	531 (6 well-defined)
Features	2-453 (6-453 well defined)
Vector Machines	9
Praat	6
Telephones	3
Accuracy	68-91%

2-3 reviews on artificial intelligence analysis

- ALPER IDRISOGLU *et al.* Applied Machine Learning Techniques to Diagnose Voice-Affecting Conditions and Disorders: Systematic Literature Review. Journal of Medical Internet Research, *[s. l.]*, v. 25, p. e46105, **2023**. DOI 10.2196/46105. Disponível em: https://research.ebsco.com/linkprocessor/plink?id=26168a01-16f6-3dbf-b8b5-0428c44a088d. Acesso em: 4 set. 2023.
- **review of voice as a biomarker analyzed from 2012-2022. 145 studies were included, where support vector machines were used in 35%. The most studied disease was Parkinson's Disease with 60%. Nearly 50% used ten distinct data sets. The problem is limited and unbalanced data set usage in many studies**.

- NGO, Q. C. *et al.* Computerized analysis of speech and voice for Parkinson's disease: A systematic review. Computer Methods and Programs in Biomedicine, *[s. l.]*, v. 226, 2022. DOI 10.1016/j.cmpb.**2022**.107133. Disponível em: https://research.ebsco.com/linkprocessor/plink?id=665a5d6f-4429-3d02-a7a7-6f5719ce1ee9. Acesso em: 4 set. 2023.
- **review from 2012-2021 of analysis methods and signal features (data sets, recording protocols, signal analysis). Values of features that separate Parkinson patients from healthy controls were focused upon, large differences were found between data sets.**

- WORASAWATE, D. *et al.* Classification of Parkinson's disease from smartphone recording data using time-frequency analysis and convolutional neural network. Technology and health care : Official journal of the European Society for Engineering and Medicine, *[s. l.]*, v. 31, n. 2, p. 705–718, **2023**. DOI 10.3233/THC-220386. Disponível em: https://research.ebsco.com/linkprocessor/plink?id=86521ee9-2f90-3cd0-8ca3-b8b8abecd0b0. Acesso em: 4 set. 2023.
- **4051 patients from the largest mobile Parkinson Disease studies, mPower study was used. A data set comprising 385,143 short one-second audio samples of/aa/is presented. The samples were converted to spectrograms. CNN models were applied to classify.**

Conclusion of our search of voice parameters in Parkinsons' Disease (to be discussed)

- Non-AI shows effective, clear differences in the measured parameters compared to healthy controls but mostly the studies are not comparable. The results were not compared with other disorders.
- **Quantitative validation of the single parameters can be done by comparing early, moderate, and heavy Parkinson's Disease to healthy controls at best, also to other disorders.**
- **---**
- The Artificial Intelligence studies had large variety. A third of Machine Learning papers use Support Vector Machine learning
- **Well-defined features and data sets are essential in the future to measure quantitative deviations of voice in Parkinson's Disease** (is Praat a possibility**)**

Praat /A Washington Post journalist asked me to validate:

Gisladottir, R. S., Helgason, A., Halldorsson, B. V., Helgason, H., Borsky, M., Chien, Y. R., Gudnason, J., Gudjonsson, S. A., Moisik, S., Dediu, D., Thorleifsson, G., Tragante, V., Bustamante, M., Jonsdottir, G. A., Stefansdottir, L., Rutsdottir, G., Magnusson, S. H., Hardarson, M., Ferkingstad, E., Halldorsson, G. H., … Stefansson, K. (2023). **Sequence variants affecting voice pitch in humans. *Science advances*, *9*(23)**

Voice pitch

Fundamental frequency (fo) was estimated using Praat's autocorrelation method, with a sex-specific setting (60 to 220 Hz for males, 100 to 300 Hz for females) (87). Over the duration of the whole vowel segment, an f_o contour was estimated from a sliding window analysis (with 60/40-ms-long windows for males/females and a 10-ms overlap). The resulting contour is further refined as the missing values are linearly interpolated and smoothed using median filtering over five neighboring values, and finally outlier values are automatically removed using the median absolute deviation (MAD) method. The reported values (median fo, SD fo, skew fo) are then estimated for each recording in Octave.

Vowel measures

Formant frequencies F1, F2, F3, and F4 were estimated from each short vowel recording with Praat's "To Formant (burg)" formant frequency estimator. Here, the estimator was configured to extract a fifth formant frequency in addition to the four, with a sex-specific setting of the maximum formant frequency parameter (5000 Hz for male speakers, 5500 Hz for female speakers). Other common parameter settings used for this estimation include a time step of 0.01 s, a window length of 0.025 s, and a pre-emphasis applied in Praat using the default setting of 50 Hz. From the results generated by Praat, formant frequencies were extracted only at the time positions where the signal intensity was higher than 0.5 times the maximum intensity of the utterance, i.e., time positions with a relatively high voice intensity. The median and SD were calculated (median F1, median F2, median F3, median F4, SD F1, SD F2, SD F3, SD F4).

Aggregated vowel measures

Two measures were used to describe the vowel space spanned by formant frequencies of the vowels in the vowel task. The quadrilateral vowel space area (34) was calculated on the basis of F1 and F2 of the corner vowels [i, a, ɔ, u], with a polygonal area calculated from the four two-dimensional formant frequency vectors. Another vowel space measure is formant centralization ratio (35), which is defined by a formula that depends on F1 and F2 of the vowels [i, a, u]. Last, we estimated apparent VTL in centimeters using the VTL(deltaF) formula based on formant spacing (24, 36), averaged for all short vowels ([i, ɛ, a, ɔ, u]), with estimations of formants F1, F2, F3, and F4 and c = 353 m/s for speed of sound.

Please consider the following information with a degree of skepticism. We have tried to dig down into the alleged biomarker used in this paper. The first problem met is that they used too few voice features. The second is that the ones they used have no clinical trial reference. The third is that there is no common agreement on which biomarker to be used in a new area like genetics.
The considerations show how important our group of biomarkers is to establish a fundamental reference frame.

- The methods used in the Praat program - with 72 voice parameters are presented. The reason why this is interesting is that this method of calculating could be clinically tested.
- ***Voice pitch***
- Fundamental frequency was estimated using Praat's autocorrelation method, with a sex-specific setting (60 to 220 Hz for males, 100 to 300 Hz for females). F0 autocorrelation of the F0 contour and Median Absolute Deviation (MAD) were made.
- (calculation of F0, standard deviation of F0, skew F0, and others)
- ***Vowel measures***
- Formant frequencies F1, F2, F3, and F4 were estimated from each short vowel recording with Praat's formant frequency estimator, [i, a, ɔ, u], F1, F2, F3. F4 (F5) (max 5500 Hz), time steps were 0,01s and window lengths 0,025s. Formant frequencies were extracted when frequency intensity was >0,5 times the maximum intensity of the utterance.
- (calculations of median, F1, F2, F3, F4, standard deviation (ST) F1, F2, F3, F4)
- ***Aggregated vowel measures***
- Two measures were used to describe the vowel space spanned by formant frequencies F1 and F2 of the vowels in the vowel task, the quadrilateral vowel space area and formant centralization ratio were calculated, etc.
- (calculation of Vocal Tract Lengths (VTL) in centimeters)

72 Praat parameters against the Genotype dataset:
39.2 million high-quality sequence variants, were detected through whole-genome sequencing of 63,460 Icelanders.
Variants in ABCC9 associated with Voice Pitch.

- Thank you for listening