



**HAL**  
open science

## Voice characteristics from isolated rapid eye movement sleep behavior disorder to early Parkinson's disease

Laetitia Jeancolas, Graziella Mangone, Dijana Petrovska-Delacrétaz, Habib Benali, Badr-Eddine Benkelfat, Isabelle Arnulf, Jean-Christophe Corvol, Marie Vidailhet, Stéphane Lehericy

### ► To cite this version:

Laetitia Jeancolas, Graziella Mangone, Dijana Petrovska-Delacrétaz, Habib Benali, Badr-Eddine Benkelfat, et al.. Voice characteristics from isolated rapid eye movement sleep behavior disorder to early Parkinson's disease. *Parkinsonism & Related Disorders*, 2022, 95, pp.86-91. 10.1016/j.parkreldis.2022.01.003 . hal-03630971

**HAL Id: hal-03630971**

**<https://hal.science/hal-03630971>**

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

## Voice characteristics from isolated rapid eye movement sleep behavior disorder to early Parkinson's disease

Laetitia Jeancolas, PhD <sup>1,2\*</sup>, Graziella Mangone, MD, PhD <sup>3,4</sup>, Dijana Petrovska-Delacrétaz, PhD <sup>2</sup>, Habib Benali, PhD <sup>5</sup>, Badr-Eddine Benkelfat PhD <sup>2</sup>, Isabelle Arnulf, MD, PhD <sup>3,6</sup>, Jean-Christophe Corvol, MD, PhD <sup>3,4</sup>, Marie Vidailhet, MD <sup>#3,4</sup>, Stéphane Lehericy, MD, PhD <sup>#1,3,7</sup>

<sup>1</sup> Paris Brain Institute - ICM, Centre de NeuroImagerie de Recherche – CENIR, Paris, France

<sup>2</sup> Laboratoire SAMOVAR, Télécom SudParis, Institut Polytechnique de Paris, France

<sup>3</sup> Sorbonne University, Inserm, CNRS, Paris Brain Institute - ICM, Paris, France

<sup>4</sup> Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Department of Neurology, Clinical Investigation Center for Neurosciences, Paris, France

<sup>5</sup> PERFORM Centre, Electrical & Computer Engineering Department, Concordia University, Montreal, Canada

<sup>6</sup> Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Sleep disorders unit, Paris, France

<sup>7</sup> Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Department of Neuroradiology, Paris, France

# These two authors contributed equally to the work

### (\* Corresponding Author Contact Details:

Paris Brain Institute - ICM  
Hôpital Pitié-Salpêtrière,  
47 Boulevard de l'Hôpital, 75013 PARIS, France  
Phone number: +33 6 75 53 18 00  
Email: [laetitia.jeancolas@icm-institute.org](mailto:laetitia.jeancolas@icm-institute.org)

**Submission Type:** Full-length Article

Word count: Abstract: 245; Text: 3099

Number of Tables: 3; Number of Figures: 1

Number of References: 30

**Keywords:** Parkinson's disease; REM sleep behavior disorder; Speech disorders; Acoustic analysis; Supervised classification

## Abstract

**Background:** Speech disorders are amongst the first symptoms to appear in Parkinson's disease (PD).

**Objectives:** We aimed to characterize PD voice signature from the prodromal stage (isolated rapid eye movement sleep behavior disorder, iRBD) to early PD using an automated acoustic analysis and compare male and female patients. We carried out supervised learning classifications to automatically detect patients using voice only.

**Methods:** Speech samples were acquired in 256 French speakers (117 participants with early PD, 41 with iRBD, and 98 healthy controls), with a professional quality microphone, a computer microphone and their own telephone. High-level features related to prosody, phonation, speech fluency and rhythm abilities were extracted. Group analyses were performed to determine the most discriminant features, as well as the impact of sex, vocal tasks, and microphone type. These speech features were used as inputs of a support vector machine and were combined with classifiers using low-level features.

**Results:** PD related impairments were found in prosody, pause durations and rhythmic abilities, from the prodromal stage. These alterations were more pronounced in men than in women. Early PD detection was achieved with a balanced accuracy of 89% in males and 70% in females. Participants with iRBD were detected with a balanced accuracy of 63% (reaching 70% in the subgroup with mild motor symptoms).

**Conclusions:** This study provides new insight in the characterization of sex-dependent early PD speech impairments, and demonstrates the valuable benefit of including automated voice analysis in future diagnostic procedures of prodromal PD.

## **INTRODUCTION**

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects 1% of people over 60 years and 4% over 80.[1] The standard diagnosis is based upon the presence of motor symptoms (mainly bradykinesia, rigidity and rest tremor), which develop when 60% of the dopaminergic neurons in the substantia nigra are already irrecoverably lost. For this reason, PD detection at an earlier stage is an important challenge.

Voice impairments, commonly described under the name of hypokinetic dysarthria,[2] are among the first symptoms in PD,[3] and are already present in isolated rapid eye movement sleep behavior disorder (iRBD, a prodromal stage of PD).[4] They include disruptions in articulation, prosody, phonation, and speech fluency. Although speech impairments in later stages have been well characterized and automatically quantified,[5–9] they are few studies focusing on the objective identification of vocal disorders patterns in the early and prodromal course of PD neurodegeneration.[10–12] Furthermore, they were usually performed on small databases, with the exception of a recent large multicenter study that investigated speech impairments in early PD and iRBD subjects across 7 centers and 5 languages.[13] Moreover, most studies on early PD speech impairments did not analyze men and women separately, although in PD there are sex differences in the phenotypic expression[14,15], brain structure[16] and dopaminergic changes.[17]

Here, we aimed to characterize speech impairments in a large database of French patients with early PD and iRBD, focusing on the effect of sex. We also analyzed the impact of the types of microphone on speech analyses. In addition to phonation, prosody, speech fluency and articulation, we investigated the rhythmic abilities, which had not been explored in iRBD before.

## **MATERIALS AND METHODS**

### **Participants**

A total of 256 French speakers were included in this study (Table 1), comprising 117 participants with PD (75 males, 42 females), 41 with iRBD (males only) and 98 controls (54 males, 44 females). All PD and iRBD participants and 50 controls were recruited within the framework of the ICEBERG cohort (clinicaltrials.gov, NCT02305147), a longitudinal observational study conducted at the Clinical Investigation Center for Neurosciences at the Paris Brain Institute (ICM). An additional 48 controls were recruited to balance the number of patients and controls for voice analyses. Inclusion criteria were as follows: (1) clinical diagnosis of idiopathic PD according to United Kingdom Parkinson's Disease Society Brain Bank criteria PD with less than 4 years of disease duration; or (2) clinical diagnosis of RBD according to International Classification of Sleep Disorders (third edition) and absence of parkinsonism or dementia; and (3) absence of neurological disorders for controls.

All participants signed an informed consent prior to any investigation. The study was sponsored by Inserm and received approval from the ethical committee (IRBParis VI, RCB: 2014-A00725-42) according to local regulations.

## Audio recordings

Participants were recorded via three microphone types to assess the effect of microphone, recording environment and transmission channel on the analyses. They were recorded during a single session with a professional quality head mounted microphone, at the same time with the internal microphone of a laptop computer and finally once a month with their own telephone at home (5 sessions per person on average). The speech tasks were composed of sustained vowels, free speech, fast syllable repetitions, slow syllable repetitions following a given pace, short sentences repetition, and text, dialog and short sentences readings. Details about audio acquisition and speech tasks contents are provided in Supplementary Material.

## High-level feature extraction

Different quantitative acoustic features have been automatically extracted from the speech recordings, using PRAAT[18] and Matlab (*MathWorks Inc, Natick, MA*) software. These high-level features (calculated at the speech task level) were related to several vocal systems such as: prosody, pause durations, ability to follow a given rhythm and phonation. For telephonic recordings, voice features were calculated in each recording session then averaged over all the sessions. Prosodic impairments were analyzed using pitch (melody) and intensity variations (stresses on words or syllables). Pitch variations were assessed by the standard deviation of the fundamental frequency (*SD log F0*), computed using the reading, sentence repetition and free speech tasks. Intensity fluctuations were assessed by the standard deviation of the sound intensity level (*SD Int*) during the dialog reading. Verbal fluency disruptions were analyzed using the number of pauses and their duration, during the free speech and the text and dialog reading tasks. Rhythmic abilities were studied by asking the participants to repeat some syllables during 30 s, at a slow and steady pace (1 syllable per second) given beforehand in a 5 s example. The ability to maintain a steady rhythm was quantified by the relative standard deviation (RSD) of pace, and the ability to globally follow an imposed pace was characterized by the average pace and by the absolute difference with the given pace (Absolute rhythm feature). Phonatory impairments were analyzed using three types of voice measures extracted from the sustained vowel tasks: jitter, shimmer and Noise-to-Harmonics Ratio (NHR). These features characterize pitch instability, intensity instability and voice harmony, respectively. More details about speech feature extraction are provided in Supplementary material.

## Statistical analyses

The first statistical analysis, using the professional microphone recordings, consisted in a multivariate two-way analysis of covariance (MANCOVA), in order to examine main effects due to PD, due to sex, the interaction effect between both, and a potential effect of the age covariate of no interest, on the whole set of voice features. Then we performed a univariate two-way ANOVA for each voice feature, in order to assess which were the ones with significant PD effect. P-values were adjusted with false discovery rate (FDR) to compensate for the multiple comparisons.

For each significant feature, we went further into the analysis to assess the impact of the different vocal tasks and sex on PD effect. We performed Welch's t-tests between PD and control groups and computed Cohen's *d* effect sizes, for each task and sex. To evaluate the impact of the microphone type on PD voice analyses, we conducted the same group analyses, this time using the computer

microphone and telephone recordings. We ended with iRBD vs. control and iRBD vs. PD group analyses to characterize iRBD speech impairments. More details are provided in Supplementary material.

## **Classification**

First, we performed classifications from a subset of the high-level speech features, using support vector machines (SVM). Then we merged the SVM classifier (detailed in Supplementary material) with two classifiers,[19,20] based on short-term features, which characterize the spectral envelope and capture the articulatory disruptions. The fusion consisted on a majority vote of the three classes predictions, using the classifiers equal error rate thresholds as decision threshold.

## **RESULTS**

### **Clinical characteristics**

Participants with PD were treated, and their voices were recorded during ON-state. The participants' demographic, and clinical characteristics are shown in Table 1.

### **Speech features in participants with early PD vs. controls**

The two-way MANCOVA revealed significant main effects due to PD ( $P < 0.0001$ ) and sex ( $P < 0.0001$ ) and no significant disease\*sex interaction effect ( $P = 0.22$ ), nor significant effect of the age covariate ( $P=0.11$ ), on the overall exploratory feature set, extracted from the professional microphone recordings, using all the tasks. Means and standard deviations of the voice features are presented in Table 2, as well as the univariate ANOVAs main effects due to PD and sex for each feature. Significant PD main effect (after FDR correction) was found in features related to prosody, pauses and rhythm. PD participants showed lower pitch variations ( $SD \log F0$ ). There was no difference in the total pause number, but fewer short pauses and an increased median pause duration in PD participants compared to controls. Participants with PD also showed impairments in relative and absolute rhythm, with increased RSD and Absolute features. Overall, these results indicated a more monotonous voice in PD participants as well as a jerky speech and difficulties in keeping a steady and imposed pace. The sex effect was significant for  $SD \log F0$  (higher pitch variations in women), median of pause durations (shorter in women) and shimmer measure (less intensity instability in women).

### *Comparison of speech tasks and sex effect*

The results of the PD vs. control group differences are detailed for each task and for each sex, in Supplementary Table S3. PD group showed decreased  $SD \log F0$  for all speech tasks. The decrease was more pronounced for tasks with emotional content (dialog reading and sentence repetitions) than neutral content (text reading), and among men than women regardless of the speech task. PD men and women also spoke with fewer short pauses and longer median pause duration. Unlike short pauses, the lengthening of the median pause duration in PD did not have the same magnitude depending on the

task and the sex (more pronounced during free speech, and in men). PD subjects showed higher RSD and Absolute pace values in all rhythmic tasks in both sexes, with an amplified effect when the syllables were repeated alternately. In order to assess whether the PD effect sizes, calculated from the most suited tasks, differed significantly between men and women, we performed univariate two-way ANOVAs with interaction terms. The results, detailed in Supplementary Table S4, showed a significant interaction effect after FDR correction for *SD log F0* ( $P = 0.036$ ).

### *Comparison of microphone types*

The different group analyses showed that the computer microphone was globally as efficient as the professional microphone in discriminating PD from controls (Supplementary Table S5). Effect sizes were smaller for telephone recordings, apart from the prosodic feature *SD log F0* which was as discriminant with a personal telephone as with the professional microphone.

### **Speech features in iRBD participants**

Results of iRBD vs control, and iRBD vs PD group differences are presented in Table S3 and Figure 1. Participants with iRBD had *SD log F0*, number of short pauses and median pause duration values comprised between those of PD and control participants. The difference between iRBD and controls was significant for median pause duration ( $P = 0.032$ ). Measures of rhythmic characteristics in iRBD were similar to those of PD subjects for RSD (with a significant difference from controls,  $P = 0.008$ ), and were similar to those of controls for Absolute pace feature. These results suggest that the reduction of intonation (nevertheless non-significant), the jerky voice and the incapability to keep a steady pace are already present at the PD prodromal stage.

### **Classifications of patients vs controls**

The selected features and the SVM classification results, for the three types of microphone, are provided in Supplementary Table S6. The final classification performances, resulting from the fusion of the three classifiers, using the professional microphone recordings, are presented in Table 3. Balanced accuracies (BA) were 89% for the classification of PD vs. controls in men and 70% in women. The BA to distinguish iRBD men from control men was 63% and increased up to 70% when the analysis was restricted to the 22 iRBD participants with mild motor symptoms (MDS-UPDRS III higher than  $2*SD$  from the controls mean).

## **DISCUSSION**

In this study, we analyzed in an automated way the voice characteristics in participants with early PD and iRBD compared to healthy controls, using high-level features. We found disruptions in pause durations and rhythmic abilities and a trend to a reduced prosody right from PD prodromal stage. We also observed that these impairments were more pronounced in PD men than women. Using these speech features as inputs of an SVM, combined with two classifiers based on low-level features, we were able to discriminate early PD participants from controls with a BA of 89% in males and 70% in females. We also detected iRBD participants from controls with 63% accuracy, which increased to 70% in iRBD participants with mild motor symptoms.

## Voice characteristics in Parkinson's disease

Prosody was altered in PD patients with reduced  $SD \log F0$ , a measure that quantified the well-known voice monotony related to PD.[11,13] This lack of intonation would be a consequence of the decrease of laryngeal movements due to excessive rigidity.[21] We observed prosody reduction during the sentence repetitions, free speech, and reading tasks. The decrease was more pronounced during tasks with emotional content (tasks that naturally lead to more intonation) in agreement with previous results conducted among Czech speakers.[11]

We found fewer short pauses, and longer median pause duration in PD subjects, during both reading and free speech tasks, reflecting the impression of jerky speech or "short rushes of speech" which can be encountered in PD.[2] The reduced number of short pauses would be related to the impaired ability to stop voicing properly, which could be due to a weak vocal fold adduction caused by bradykinesia and rigidity of laryngeal muscles.[10] It may also be related to the spirantization of stop consonants that are pronounced as fricatives due to incomplete oral closure.[22] The lengthening of the median pause duration was due to fewer short pauses and more long pauses, suggesting a cognitive component (i.e. syntax for reading and, in addition, speech content planification, word choice, and memory for the free speech task) in addition to the motor component of the disorder. The discriminant power of median pause duration was more pronounced during free speech, possibly due to a stronger cognitive component in this task, which in accordance with a recent study on Spanish speakers.[23]

The relative rhythm variation (RSD) during the slow syllable repetitions and the absolute variation of the averaged pace compared to the imposed rhythm were increased in PD patients. This increase showed the difficulty PD subjects had in keeping a constant rhythm and following a prescribed pace. These rhythmic impairments may be related to the loss of motor automaticity commonly observed in PD patients.[24] The rhythmic deteriorations were increased during the alternate repetition of syllables /pa/ and /ku/, compared to non-alternate repetitions. This last result was in agreement with previous results obtained with manual measurements of /pa/ and /ti/ syllable intervals in German speakers with more advanced PD.[25]

Regarding the intensity fluctuations and the phonation, we found no significant differences between PD and controls, whereas these vocal systems are also known to be impaired in PD. An explanation could be that these alterations may develop later in the disease progression, or be alleviated by the dopaminergic treatment,[21] as all patients were recorded in ON-state.

One of the main interests of this study was the analysis of sex effect on PD speech impairments and on classification performances. We observed alterations of intonation, pause durations and rhythm in male and female patients but to different degrees. Although there was no significant interaction effect between group and sex with the global set of exploratory features, when we fine-tuned the vocal tasks and the features, we observed a significant interaction effect on  $SD \log F0$ . The intonation was significantly more impaired by the disease in men than in women, and overall, speech impairments seemed to be more pronounced in men. Several explanations can be proposed. Women with PD have been reported to have a less pronounced brain atrophy than men[16] and less network disruptions in the first stages, with a 2-year delayed symptom onset.[15] This resulted in a lower MDS-UPDRS III



score for the PD women in our database compared to the age-matched men. In comparison, Ruzs et al.[26] did not observe any group\*sex interaction and Skodda et al. even found more prosody reduction in PD females. Nevertheless, in both studies, PD men and PD women had similar motor scores and in Skodda et al.[27] the database was composed of more advanced PD stages.

Another interest of this work was the assessment of the microphone impact on the discriminant power of the high-level features. Results obtained from computer microphone recordings were similar to professional microphone recordings, in line with a previous analysis that compared the same professional microphone with a smartphone (same recording quality as a computer microphone) in the assessment of voice impairments in early and prodromal PD.[28] Our features extracted from the telephone network recordings were, however, less discriminating, apart from the prosodic feature. This lower efficiency could be the consequence of a lower recording quality (due to the much lower sampling frequency and the narrower frequency bandwidth of the transmission channel) and of a poorer performance of the tasks carried out in total autonomy by the participants.

A limitation of this study is the fact that our groups were not totally age-matched. Although no global age effect was found on the speech features using MANCOVA, this does not guarantee a complete absence of age effect for each feature individually considered.

### **Voice characteristics in isolated REM sleep behavior disorder**

Interestingly, although most participants with iRBD had no perceptible speech impairment (as indicated by the MDS-UPDRS III speech item 1), we objectively captured abnormalities among the vocal features affected in the PD group. For example, *SD log F0* was reduced and the median pause duration was significantly lengthened, implying that prosody and pause durations would be altered during the prodromal stage of PD. For rhythmic features, only RSD was altered in iRBD subjects. This suggested that the ability to keep a constant rhythm and the ability to follow an imposed rhythm would involve different physiological processes. The former would be impaired during the prodromal stage of PD whereas the latter would be impaired later in PD. Results in iRBD were consistent with previous studies regarding prosodic alterations[13,28] and pause duration modifications.[10,28] To our knowledge, this work provides the first characterization of speech rhythm alteration in iRBD.

### **Classification**

Early PD patients were efficiently discriminated from controls with a BA of 89% in men and 70% in age-matched women. Recent studies using voice for early PD detection reported BA between 71% to 85%,[10,13,28,29] but classification performances are difficult to compare as they did not analyze men and women separately. Previously, one study in English speakers recorded via a smartphone, separated men and women for early PD detection.[30] The performances we obtained were more accurate for both sexes than the ones they reported (BA= 64% for males and 42.5% for females). Moreover, the use of the telephone network instead of a smartphone app has the advantage of being more easily applicable, because it does not require any specific telephone. Finally, participants with iRBD were distinguished from controls with an accuracy of 63%, increasing to 70% in iRBD subjects with mild motor symptoms. In comparison, two recent studies obtained balanced accuracies of

60%[13] and 65.15%[30] for iRBD vs control classification.

## **CONCLUSION**

Using automated speech analysis, our study precisely characterized PD related speech impairments from the prodromal stage to a couple of years after the diagnosis. This work showed sex-related patterns of speech impairments in early PD and demonstrates the valuable benefit of including sex-specific automated voice analysis for PD monitoring or for prodromal screening.

## **Acknowledgment**

The authors would like to thank Samovar laboratory, CIC Neurosciences, sleep disorders unit and CENIR teams. The authors are also grateful to Anna Skrzatek and Rahul Gaurav for the manuscript revision. Finally, the authors express their sincere appreciation to the subjects and their families for their participation in this research.

## **Contributors**

LJ: experimental design, data collection, data analysis and interpretation, and manuscript draft.

GM: participants' diagnosis, clinical scores, analysis interpretation and manuscript revision.

DP: experimental design, research project organization and manuscript revision.

HB: validation of statistical analysis, research project organization and manuscript revision.

BB: research project organization.

IA, JC, MV, SL: design and development of ICEBERG study, research project organization, diagnosis and recruitment of participants, analysis interpretation and manuscript revision.

## **Conflict of interest**

No relevant conflict of interest related to the present study.

## **Funding**

This work was supported by grants from Institut Mines-Télécom, Fondation Télécom and Institut Carnot Télécom & Société Numérique through "Futur & Ruptures" program; Agence Nationale de la Recherche through "Investissements d'avenir" program (ANR-10-IAIHU-06 and ANR-11-INBS-0006); Fondation EDF; Fondation Planiol; Société Française de Médecine Esthétique and Energipole.

## **Appendix**

- Supplementary information on audio acquisition
- Supplementary information on the speech feature extraction
- Supplementary information on the statistical analyses
- Supplementary information on the SVM classification

## References

- 1 De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *The Lancet Neurology* 2006;**5**:525–35.
- 2 Darley Frederic L., Aronson Arnold E., Brown Joe R. Differential Diagnostic Patterns of Dysarthria. *Journal of Speech and Hearing Research* 1969;**12**:246–69. doi:10.1044/jshr.1202.246
- 3 Brabenec L, Mekyska J, Galaz Z, *et al.* Speech disorders in Parkinson's disease: early diagnostics and effects of medication and brain stimulation. *Journal of Neural Transmission* 2017;**124**:303–34. doi:10.1007/s00702-017-1676-0
- 4 Postuma RB, Lang AE, Gagnon JF, *et al.* How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. *Brain* 2012;**135**:1860–70. doi:10.1093/brain/aws093
- 5 Arias-Vergara T, Vásquez-Correa JC, Orozco-Arroyave JR. Parkinson's Disease and Aging: Analysis of Their Effect in Phonation and Articulation of Speech. *Cognitive Computation* 2017;**9**:731–48. doi:10.1007/s12559-017-9497-x
- 6 Brückl M, Ghio A, Viallet F. Measurement of Tremor in the Voices of Speakers with Parkinson's Disease. *Procedia Computer Science* 2018;**128**:47–54. doi:10.1016/j.procs.2018.03.007
- 7 Gamboa J, Jiménez-Jiménez FJ, Nieto A, *et al.* Acoustic voice analysis in patients with Parkinson's disease treated with dopaminergic drugs. *Journal of Voice* 1997;**11**:314–20. doi:10.1016/S0892-1997(97)80010-0
- 8 Gómez-Vilda P, Mekyska J, Ferrández JM, *et al.* Parkinson Disease Detection from Speech Articulation Neuromechanics. *Front Neuroinform* 2017;**11**. doi:10.3389/fninf.2017.00056
- 9 Mucha J, Galaz Z, Mekyska J, *et al.* Identification of hypokinetic dysarthria using acoustic analysis of poem recitation. In: *2017 40th International Conference on Telecommunications and Signal Processing (TSP)*. Barcelona, Spain: 2017. 739–42. doi:10.1109/TSP.2017.8076086
- 10 Hlavnička J, Čmejla R, Tykalová T, *et al.* Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. *Scientific Reports* 2017;**7**. doi:10.1038/s41598-017-00047-5
- 11 Rusz J, Cmejla R, Ruzickova H, *et al.* Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated Parkinson's disease. *The Journal of the Acoustical Society of America* 2011;**129**:350. doi:10.1121/1.3514381
- 12 Rusz J, Hlavnička J, Tykalová T, *et al.* Quantitative assessment of motor speech abnormalities in idiopathic rapid eye movement sleep behaviour disorder. *Sleep Medicine* Published Online First: September 2015. doi:10.1016/j.sleep.2015.07.030
- 13 Rusz J, Hlavnička J, Novotný M, *et al.* Speech Biomarkers in Rapid Eye Movement Sleep Behavior Disorder and Parkinson Disease. *Annals of Neurology* 2021;**90**:62–75. doi:10.1002/ana.26085
- 14 Iwaki H, Blauwendraat C, Leonard HL, *et al.* Differences in the Presentation and Progression of Parkinson's Disease by Sex. *Mov Disord* 2021;**36**:106–17. doi:10.1002/mds.28312

- 15 Haaxma CA, Bloem BR, Borm GF, *et al.* Gender differences in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;**78**:819–24. doi:10.1136/jnnp.2006.103788
- 16 Tremblay C, Abbasi N, Zeighami Y, *et al.* Sex effects on brain structure in de novo Parkinson's disease: a multimodal neuroimaging study. *Brain : a journal of neurology* Published Online First: 27 September 2020. doi:10.1093/brain/awaa234
- 17 Kaasinen V, Joutsa J, Nojonen T, *et al.* Effects of aging and gender on striatal and extrastriatal [123I]FP-CIT binding in Parkinson's disease. *Neurobiol Aging* 2015;**36**:1757–63. doi:10.1016/j.neurobiolaging.2015.01.016
- 18 Boersma P. PRAAT, a system for doing phonetics by computer. *Glott international* 2001;**5**:341–5.
- 19 Jeancolas L, Mangone G, Corvol J-C, *et al.* Comparison of Telephone Recordings and Professional Microphone Recordings for Early Detection of Parkinson's Disease, Using Mel-Frequency Cepstral Coefficients with Gaussian Mixture Models. In: *Interspeech 2019*. Graz, Austria: : ISCA 2019. 3033–7. doi:10.21437/Interspeech.2019-2825
- 20 Jeancolas L, Petrovska-Delacrétaz D, Mangone G, *et al.* X-Vectors: New Quantitative Biomarkers for Early Parkinson's Disease Detection From Speech. *Front Neuroinform* 2021;**15**. doi:10.3389/fninf.2021.578369
- 21 Ruzs J, Čmejla R, Růžičková H, *et al.* Evaluation of speech impairment in early stages of Parkinson's disease: a prospective study with the role of pharmacotherapy. *Journal of Neural Transmission* 2013;**120**:319–29. doi:10.1007/s00702-012-0853-4
- 22 Kent RD, Rosenbek JC. Prosodic disturbance and neurologic lesion. *Brain and Language* 1982;**15**:259–91. doi:10.1016/0093-934X(82)90060-8
- 23 García AM, Arias-Vergara T, Vasquez-Correa J, *et al.* Cognitive Determinants of Dysarthria in Parkinson's Disease: An Automated Machine Learning Approach. *Mov Disord* 2021;;mds.28751. doi:10.1002/mds.28751
- 24 Wu T, Hallett M, Chan P. Motor automaticity in Parkinson's disease. *Neurobiology of Disease* 2015;**82**:226–34. doi:10.1016/j.nbd.2015.06.014
- 25 Skodda S, Lorenz J, Schlegel U. Instability of syllable repetition in Parkinson's disease—Impairment of automated speech performance? *Basal Ganglia* 2013;**3**:33–7. doi:10.1016/j.baga.2012.11.002
- 26 Ruzs J, Tykalová T, Novotný M, *et al.* Automated speech analysis in early untreated Parkinson's disease: relation to gender and dopaminergic transporter imaging. *European Journal of Neurology* 2021;**n/a**. doi:10.1111/ene.15099
- 27 Skodda S, Visser W, Schlegel U. Gender-Related Patterns of Dysprosody in Parkinson Disease and Correlation Between Speech Variables and Motor Symptoms. *Journal of Voice* 2011;**25**:76–82. doi:10.1016/j.jvoice.2009.07.005
- 28 Ruzs J, Hlavnička J, Tykalová T, *et al.* Smartphone Allows Capture of Speech Abnormalities Associated With High Risk of Developing Parkinson's Disease. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2018;**26**:1495–507. doi:10.1109/TNSRE.2018.2851787

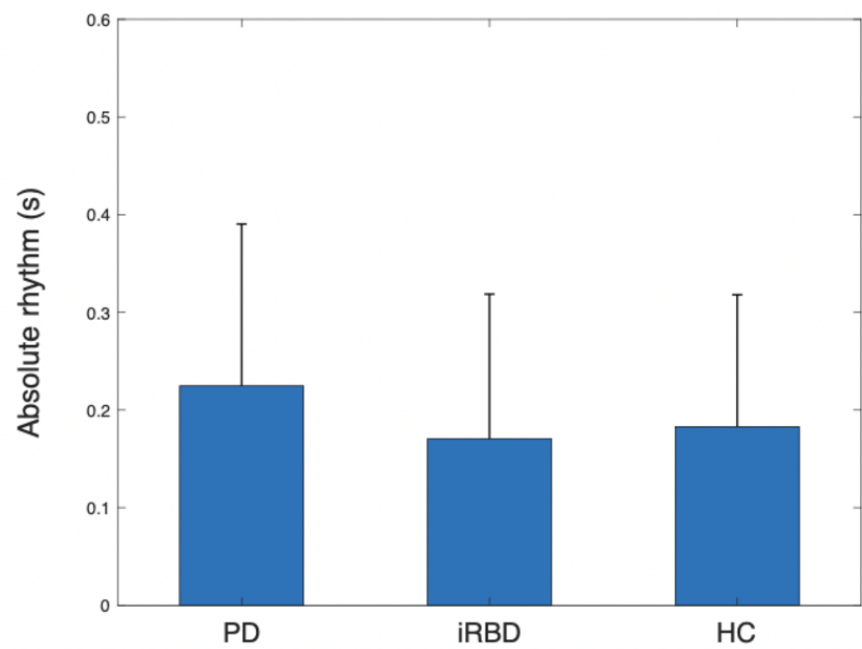
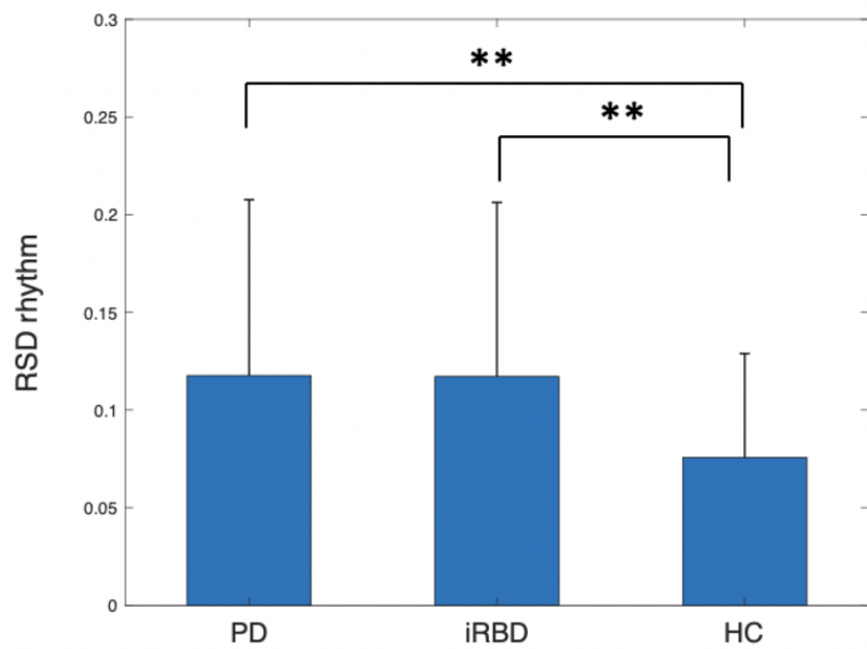
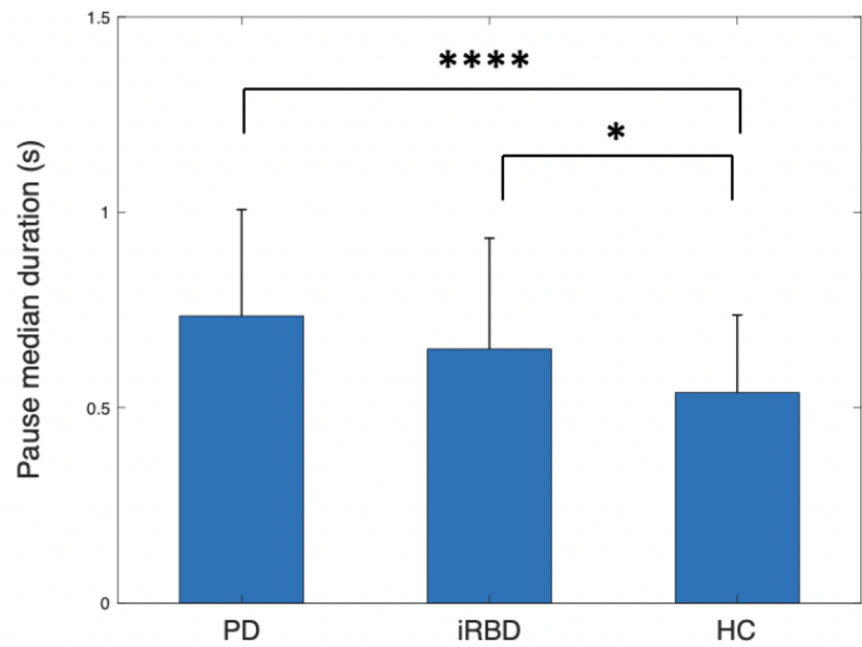
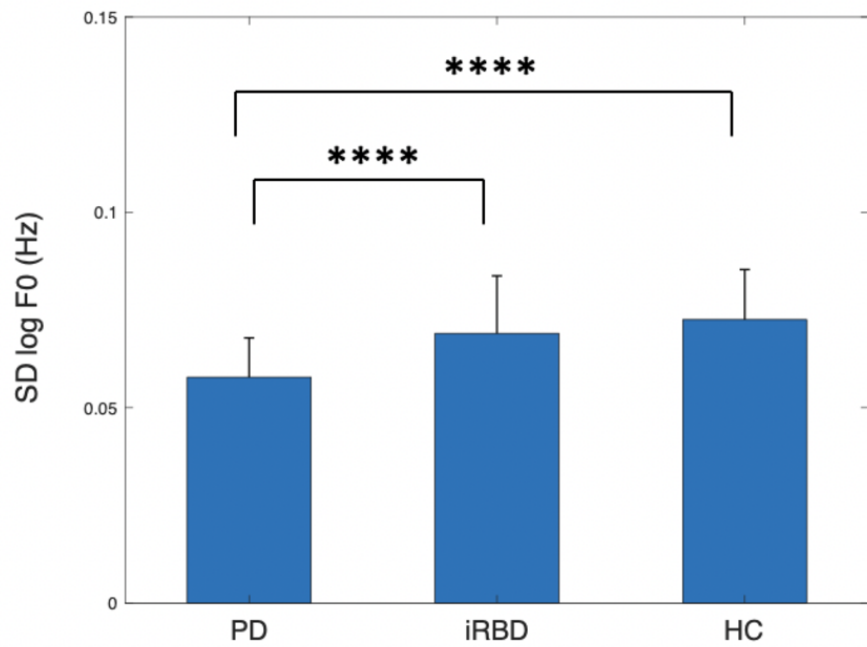
- 29 Benba A, Jilbab A, Sandabad S, *et al.* Voice signal processing for detecting possible early signs of Parkinson's disease in patients with rapid eye movement sleep behavior disorder. *Int J Speech Technol* 2019;**22**:121–9. doi:10.1007/s10772-018-09588-0
- 30 Arora S, Lo C, Hu M, *et al.* Smartphone Speech Testing for Symptom Assessment in Rapid Eye Movement Sleep Behavior Disorder and Parkinson's Disease. *IEEE Access* 2021;**PP**:1–1. doi:10.1109/ACCESS.2021.3057715

## Figures

### **Figure 1: Results across discriminant speech features: comparison of iRBD subjects with PD participants and controls.**

The speech features were computed from professional microphone recordings of iRBD, PD and HC male participants, using the most suited vocal tasks (i.e. average over reading, sentence repetition and free speech for SD log F0, free speech for pause median duration, and both /pa ku/ syllable repetition tasks for RSD rhythm and Absolute rhythm). Bars represent mean values and error bars represent standard deviation values. Group analyses (Welch's t-test) were performed, with uncorrected P-values (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ ).

Abbreviations: F0: fundamental frequency; HC: healthy control; iRBD: isolated rapid eye movement sleep behavior disorder; PD: Parkinson's disease; RSD: relative standard deviation; SD: standard deviation.





**Table 1:** Demographic, clinical and treatment characteristics of participants

	PD			iRBD	HC			Group effect P-value
	Male	Female	P-value		Male	Female	P-value	
No. of subjects	75	42		41	54	44		
Age (years)	63.8 ± 9.3	63.7 ± 9.3	0.96 <sup>A</sup>	68.2 ± 6.3	60.0 ± 10.6	59.3 ± 9.1	0.75 <sup>A</sup>	<0.001 <sup>C</sup>
Disease duration (years)	2.5 ± 1.4	2.7 ± 1.5	0.53 <sup>A</sup>	-	-	-		
Hoehn & Yahr	2.0 ± 0.1	2.0 ± 0.0	0.47 <sup>B</sup>	-	-	-		
MDS-UPDRS III total	34.2 ± 7.1	29.5 ± 5.8	< 0.001 <sup>A</sup>	13.5 ± 8.3	4.6 ± 3.4	4.9 ± 3.4	0.75 <sup>A</sup>	<0.0001 <sup>C</sup>
MDS-UPDRS III speech item	0.97 ± 0.59	0.69 ± 0.60	0.02 <sup>B</sup>	0.17 ± 0.44	0.04 ± 0.19	0.00 ± 0.00	0.39 <sup>B</sup>	<0.0001 <sup>D</sup>
MoCA	26.9 ± 2.2	27.5 ± 2.5	0.05 <sup>B</sup>	27.8 ± 1.9	28.0 ± 1.7	28.2 ± 2.0	0.32 <sup>B</sup>	0.02 <sup>D</sup>
LEDD (mg)	412 ± 297	351 ± 189	0.17 <sup>A</sup>	-	-	-		

Data are represented as means ± standard deviations.

A: Welch's *t*-test; B: Mann-Whitney *U*-test; C: One-Way ANOVA in men; D: Kruskal-Wallis test in men

Abbreviations: HC: healthy control; iRBD: isolated rapid eye movement sleep behavior disorder; LEDD: Levodopa Equivalent Daily Dose; MDS-UPDRS: Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease.

**Table 2:** Results of acoustic speech analysis and group differences.

Features	Male		Female		P-value	
	PD	HC	PD	HC	PD vs. HC	Male vs. Female
<b><i>Prosody</i></b>						
SD log F0 (10 <sup>-3</sup> Hz)	58 ± 10	73 ± 13	71 ± 14	76 ± 12	< <b>0.0001</b>	< <b>0.0001</b>
SD Int (dB)	5.4 ± 0.5	5.5 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	0.56	0.21
<b><i>Pauses</i></b>						
No. pauses (pauses/s)	0.63 ± 0.25	0.65 ± 0.20	0.54 ± 0.19	0.65 ± 0.35	0.17	0.33
No. short pauses (pauses/s)	0.24 ± 0.15	0.30 ± 0.14	0.26 ± 0.13	0.34 ± 0.15	<b>0.001</b>	0.33
Median duration (s)	0.68 ± 0.18	0.56 ± 0.12	0.56 ± 0.13	0.49 ± 0.09	< <b>0.0001</b>	< <b>0.0001</b>
<b><i>Rhythm</i></b>						
RSD	0.10 ± 0.07	0.07 ± 0.04	0.11 ± 0.09	0.09 ± 0.05	<b>0.003</b>	0.24
Absolute (s)	0.18 ± 0.12	0.14 ± 0.09	0.20 ± 0.11	0.15 ± 0.09	<b>0.017</b>	0.66
Pace (syll/s)	1.02 ± 0.21	0.98 ± 0.18	1.03 ± 0.16	0.96 ± 0.12	0.08	0.97
<b><i>Phonation</i></b>						
NHR (%)	4.5 ± 6.9	3.4 ± 3.5	4.0 ± 8.1	3.5 ± 7.8	0.44	0.90
Jitter (%)	1.0 ± 1.2	0.8 ± 0.5	0.9 ± 1.2	0.8 ± 1.0	0.44	0.90
Shimmer (%)	5.5 ± 3.0	5.4 ± 2.1	4.0 ± 2.7	3.6 ± 2.2	0.44	< <b>0.0001</b>

*Means and standard deviations of vocal features related to Prosody, Pauses, Rhythm and Phonation were computed using all the tasks performed by PD and HC participants, recorded with the professional microphone. Statistical differences were performed using two-way analyses of variance with disease status and sex as factors. P-values were adjusted according to false discovery rate correction.*

*Abbreviations: F0: fundamental frequency; HC: healthy control; Int: Intensity; NHR: noise-to-harmonics ratio; PD: Parkinson's disease; RSD: relative standard deviation; SD: standard deviation.*

**Table 3:** Final classification results.

	<b>Classification</b>	<b>BA (%)</b>	<b>Se (%)</b>	<b>Sp (%)</b>
<b>Males</b>	PD vs. HC	89 ± 4	86 ± 4	92 ± 4
	iRBD vs. HC	63 ± 8	59 ± 8	67 ± 7
	iRBD <sup>+</sup> vs. HC	70 ± 9	73 ± 9	67 ± 7
<b>Females</b>	PD vs. HC	70 ± 7	70 ± 7	70 ± 7

*Classification results (in %) were obtained from the fusion of three classifiers (two based on short-term features and the SVM using long-term features), using the professional microphone recordings. For the short-term classifications of males, we used the MFCC-GMM method (on the reading, the sentence repetitions and the fast syllable repetitions tasks) and the x-vectors technique (on the reading and the sentence repetitions tasks), described in a previous study.[19] For females, as we already proved that MFCC-GMM method was inappropriate, due to too much MFCC variability, we chose an additional x-vectors classifier instead, using the free speech task. For both sexes, the long-term classifier was the SVM, using the reading, the sentence repetitions, the free speech and the slow syllable repetitions (Supplementary Table S6).*

*Abbreviations: BA: balanced accuracy; GMM: Gaussian mixture model; HC: healthy control; iRBD: isolated rapid eye movement sleep behavior disorder; iRBD<sup>+</sup>: iRBD with motor symptoms; MFCC: Mel-frequency cepstral coefficients; PD: Parkinson's disease; Se: sensitivity; Sp: specificity; SVM: support vector machine.*