# Accurate telemonitoring of Parkinson's disease progression by non-invasive speech tests

**Authors:** Athanasios Tsanas[1,2], Max A. Little[1,2], Patrick E. McSharry[1,2], Lorraine Ramig[3,4]

**Affiliations:** [1]*Systems Analysis, Modelling and Prediction (SAMP), Mathematical Institute, University of Oxford, Oxford, UK*

[2]*Oxford Centre for Industrial and Applied Mathematics (OCIAM), University of Oxford, Oxford, UK*

[3]*Speech, Language, and Hearing Science, University of Colorado, Boulder, Colorado, USA*

[4]*National Center for Voice and Speech, Denver, Colorado, USA*

**Contact Information:**

Athanasios Tsanas

OCIAM

Mathematical Institute

24-29 St. Giles

Oxford, UK

OX 1 3LB

**Emails:** (A. Tsanas) athanasios.tsanas@stx.ox.ac.uk, tsanas@maths.ox.ac.uk

(M. Little) littlem@maths.ox.ac.uk

(P. McSharry) patrick@mcsharry.net

(L. Ramig) Lorraine.Ramig@colorado.edu

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**Tracking Parkinson's disease (PD) symptom progression often uses the Unified Parkinson’s Disease Rating Scale (UPDRS), which requires the patient's presence in clinic, and time-consuming physical examinations by trained medical staff. Thus, symptom monitoring is costly and logistically inconvenient for patient and clinical staff alike, also hindering recruitment for future large-scale clinical trials. Here, for the first time, we demonstrate rapid, remote replication of UPDRS assessment with clinically useful accuracy (5% prediction error), using only simple, self-administered, and non-invasive speech tests. We characterize speech with signal processing algorithms, and statistically map these algorithms to UPDRS. We verify our findings on the largest database of PD speech in existence (~6,000 recordings from 42 PD patients, recruited to a six-month, multi-centre trial). This supports the feasibility of frequent, remote and accurate UPDRS tracking. This technology could play a key part in telemonitoring frameworks that enable large-scale clinical trials into novel PD treatments.**

## Introduction

We are aware of neurological control through muscle movement and sensing so early in life that is easy to take it for granted. However, neurological disorders affect people profoundly and claim lives at an epidemic rate worldwide. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's[1], and it is estimated that more than one million people in North America alone are affected[2]. Rajput et al. report that incidence rates have been approximately constant for the last 55 years, with 20/100,000 new cases every year[3]. A further estimated 20% of *people with Parkinson's* (PWP) are never diagnosed[4]. Moreover, these statistics are expected to increase because worldwide the population is growing older[5]. In fact, all studies suggest age is the single most important risk factor for the onset of PD, which increases steeply after age 50[6]. Although medication and surgical intervention can hold back the progression of the disease and alleviate some of the symptoms, there is no available cure[7,8]. Thus, early diagnosis is critical in order to improve the patient's quality of life and prolong it[9].

The etiology of PD is largely unknown, but the symptoms result from substantial dopaminergic neuron reduction, leading to dysfunction of the basal ganglia circuitry mediating motor and some cognitive abilities[8]. *Parkinsonism* exhibits similar PD-like symptoms, but these are caused by drugs, exposure to neurotoxins etc. The main symptoms of PD are tremor, rigidity and other general movement disorders. Of particular importance to this study, vocal impairment is also common[10,11], with studies reporting 70-90% prevalence after the onset of the disease[11,12,13]. In addition, it may be one of the earliest indicators[14,15] of the disease and 29% of patients consider it one of their greatest hindrances[13]. There is supporting evidence of degrading performance in voice with PD progression[14,16,17], with *hypophonia* (reduced voice volume) and *dysphonia* (breathiness, hoarseness or creakiness in the voice) typically preceding more generalized speech disorders[11,12].

Management of PD typically involves the administration of physical examinations applying various empirical tests, including speech and voice tests, with a medical rater *subjectively* assessing the subject's ability to perform a range of tasks. However, the necessity for the development of reliable, *objective* tools for assessing PD is manifested in the fact that current diagnosis is poor[2] and autopsy studies are reportedly inaccurate[18,19].

Physical test observations are mapped to a metric specifically designed to follow disease progress, typically the Unified Parkinson's Disease Rating Scale (UPDRS), which reflects the presence and severity of symptoms (but does not measure their underlying causes). For untreated patients it spans across 0-176, with 0 representing healthy state and 176 total disability, and consists of three sections: (1) Mentation, Behavior and Mood; (2) Activities of daily living; (3) Motor. The *motor* UPDRS ranges from 0-108, with 0 denoting symptom free and 108 severe motor impairment, and encompasses tasks such as speech, facial expression, tremor and rigidity. Speech has two explicit headings, and ranges between 0-8 with 8 being unintelligible communication.

Noninvasive telemonitoring is an emerging option in general medical care, potentially affording reliable, cost-effective screening of PWP alleviating the burden of frequent and often inconvenient visits to the clinic. This also relieves national health systems from excessive additional workload, decreasing the cost and increasing the accuracy of clinical evaluation of the subject's condition.

The potential for telemonitoring of PD depends heavily on the design of simple tests that can be self-administered quickly and remotely. Since the recording of speech signals is noninvasive and can be readily integrated into telemedicine applications, such tests are good candidates in this regard. The use of *sustained vowel phonations* to assess the extent of vocal symptoms, where the patient is requested to hold the frequency of phonation steady for as long as possible, is common in general speech clinical practice[20] and in PD monitoring[21,22]. This circumvents some of the confounding articulatory effects and linguistic components of *running speech*, i.e. the recording of standard phrases read aloud by the subject. In order to objectively characterize dysphonic symptoms, the recorded voice signals are analyzed by speech processing algorithms[22,23].

Intel Corporation's *At-Home Testing Device* (AHTD) is a novel telemonitoring system facilitating remote, Internet-enabled measurement of a range of PD-related motor impairment symptoms, recently described in detail[24]. It records both manual dexterity and speech tests; in this study we concentrate only on sustained vowel phonations.

Previous studies have focused on separating PWP from healthy controls[14,22]; we extend this concept to map the severity of voice symptoms to UPDRS. We also wanted to determine the feasibility of remote PD clinical trials on large scale voice data recorded in typical home acoustic environments, where previous studies have been limited to controlled acoustic environments and small numbers of recordings[22].

Recent studies have raised the important topic of finding a statistical mapping between speech properties and UPDRS as an issue worthy of further investigation, but have not addressed it explicitly[17,24]. Here we present a method that first computes a range of classical and non-classical speech signal processing algorithms, which act as *features* for statistical regression techniques. These features establish a relationship between speech signal properties and UPDRS. We show that this method leads to clinically useful UPDRS estimation, and demonstrate remote PD monitoring on a weekly basis, tracking UPDRS fluctuations for a six-month period. This can be a useful guide for clinical staff, following the progression of clinical PD symptoms on a regular basis, tracking the UPDRS that would be obtained by a subjective clinical rater. We envisage this method finding applications in future clinical trials involving the study of large populations remote from the clinic.

# Results

## Overview and novel results of this study

**Fig. 1** concisely summarizes the study with the recording, transmission, analysis of the speech signals, and the UPDRS estimation/tracking accuracy. We demonstrate UPDRS tracking of a typical patient throughout the six-month trial for the best linear method, *iteratively re-weighted least squares* (IRLS), and for *classification and regression tree* (CART). CART achieves the smallest prediction error, and tracks the linearly interpolated UPDRS more accurately.

## Data exploration and correlation analysis

**Table 1** summarizes the dysphonia measures used in this study. All measures were significantly correlated ($p$<0.001) with linearly interpolated motor-UPDRS and total-UPDRS scores. Although statistically significant, none of the measures taken individually appears to have a large magnitude of correlation to either motor or total-UPDRS. Following normalization to the range 0 to 1, the probability densities of each dysphonia measure are shown in **Fig. 2a**. The jitter, shimmer and NHR measures are distributed close to zero, whereas HNR, RPDE, DFA and PPE are more evenly distributed. **Table 2** presents the Spearman rank-correlations between all the dysphonia measures. All measures were statistically significantly correlated ($p$<0.001). **Fig. 2 (b, c)** displays the normalized dysphonia measures against motor and total-UPDRS, providing an indication of their associated relationship to UPDRS.

## Regression analysis

**Table 3** presents the regression coefficient values for all dysphonia measures, for all three linear prediction methods. The obtained coefficients differed over cross-validation runs for all three linear models, as evidenced by the large standard deviation of some of the coefficients. However, the testing mean absolute error (MAE) and its standard deviation across the 1,000-run cross-validation was relatively low (**Supplementary Table 1**), suggesting that these indicative coefficients are sufficient for useful UPDRS prediction. The training MAE for the linearly interpolated motor-UPDRS was 6.7 for *least squares* (LS) and IRLS, and 6.8 for *least absolute shrinkage and selection operator* (Lasso). The testing MAE was 6.7 for LS and IRLS, and 6.8 for Lasso. The CART method outperforms the linear predictors with a training MAE of 4.5 and testing MAE of 5.8. The training error for the linearly interpolated total-UPDRS was 8.5 for LS, 8.4 for IRLS, and 8.5 for Lasso. The testing error was 8.5 for LS, 8.4 for IRLS, and 8.6 for Lasso. CART performs better again, producing a training MAE of 6.0 and testing MAE of 7.5. Given that the maximum value of motor-UPDRS is 108, the testing error is 6.2% for IRLS and 5.3% for CART. Similarly, the maximum value of total-UPDRS is 176, and the testing error is 4.8% for IRLS, and 4.2% for CART. IRLS is slightly superior compared to the linear predictors. However, CART outperforms it, displaying the smallest deviation from the interpolated score.

**Model selection and validation**

**Supplementary Table 1** summarizes the subset selection of dysphonia measures, which were dictated by sweeping the Lasso algorithm regularization parameter $\lambda$, along with the out-of-sample MAE results for IRLS and CART. The pruning level for CART was set to minimize the MAE, following manual spot-checks. We noted that a difference in value of up to 20 for the pruning level did not produce significantly different results, given that the number of splits of the data was in excess of 5,000. **Supplementary Fig. 2** displays the Bayesian Information Criterion (BIC) results aiming to determine the optimal subset which obtains the best trade-off between model complexity and prediction accuracy (similar results were obtained with the Akaike Information Criterion (AIC)). Both criteria agree on a subset containing six measures: MDVP: Jitter (Abs), MDVP: Shimmer, NHR, HNR, DFA, PPE for the CART method. This subset is used for the subsequent analysis.

The testing errors remain low and close to the training error, indicating that the model has achieved a reasonable estimate of the performance we might expect on novel data. The probability densities of the 1,000-runs 10-fold cross-validation out-of-sample differences between the predicted and the linearly interpolated UPDRS values for all methods are seen in **Supplementary Fig. 3**. The difference between predicted and linearly interpolated UPDRS values is typically low.

## Discussion

In this study, we have established a mapping between dysphonia measures and UPDRS. The association strength of these measures and (motor and total) UPDRS was explored, using three linear and one nonlinear regression methods. We have selected an optimally reduced subset of the measures producing a clinically useful model, where each measure in the subset extracts non-overlapping physiological characteristics of the speech signal. The comparatively small MAE is notable: the sustained vowel phonations convey sufficient information to predict UPDRS to clinically useful accuracy. It has been demonstrated that motor-UPDRS can be estimated within approximately 6 points (out of 108) and total-UPDRS within 7.5 points (out of 176), predictions which are within 5-6% of the clinician's observations. Furthermore, we showed the feasibility of tracking UPDRS changes in time (**Fig. 1**). Perhaps most importantly, the satisfactory reception of the patients themselves towards the AHTD and speech tests[24] makes this a promising field for further experimentation. The 42 PWP in the present study were diagnosed within the previous five years at trial onset and displayed moderate symptoms (max motor-UPDRS 41, max total-UPDRS 55), so it would be important to look at a more severely impaired group in the future. The satisfactory UPDRS estimation in moderate symptoms, which are difficult to detect, accentuates the potential of the dysphonia measures in PD assessment and supports the feasibility of successful UPDRS tracking in more severely affected patients.

*Speech* appears explicitly in two UPDRS categories (part II, activities of daily living section and part III, motor section). One could argue that speech is more strongly related to the motor section rather than daily living activities and mentation, behavior and mood (part I), because the underlying etiology of dysphonic sustained phonations may be physiologically attributed to flawed muscle control, most likely caused by dopaminergic neuron reduction. This would imply that *only* motor-UPDRS estimation would be tractable. However, the results of this study indicate that total-UPDRS estimation with clinically useful accuracy is plausible, suggesting that PD speech dysphonias could be at least partly related to mood as well. This makes it possible to suggest the generalization that the underlying causes of PD symptoms such as tremor and mood are manifested in impaired speech control. Stebbins et al.[25] have reported that motor-UPDRS can be explained by six distinct and clinically useful, underlying factors: speech, facial expression, balance and gait (factor I), rest tremor (factor II), rigidity (factor IV), right and left bradykinesia (factors III and V), and postural tremor (factor VI). They found relatively low correlations between the six factors, suggesting all contribute to accurate UPDRS estimation by capturing different aspects of PD symptoms. In terms of that study, we have used measures *within* factor I, extracting PD information properties only from speech. The implicit argument is that the dysphonia measures can adequately reveal PD symptom severity estimated by UPDRS, because they capture the effects of PD motor impairment manifested in speech production. We have demonstrated that predicting both motor and total-UPDRS scores to useful precision is possible, because the dysphonia measures aid in uncovering functional features of PD impairment.

Additionally, our findings support the argument that non-classical dysphonia measures convey important information for clinical speech signal processing. This is evidenced in the results of the Lasso algorithm, which selected non-standard dysphonia measures in all the performed tests (especially HNR, RPDE, DFA and PPE), and reflected in the optimal dysphonia measure subset selected by the BIC in

**Supplementary Table 1**. This suggests that these dysphonia measures contain significant information for tracking UPDRS. It also reinforces the conclusion reached in a previous study[22], where these non-standard measures outperformed their classical counterparts in separating PWP from healthy controls. Nevertheless, the classical measures convey useful information which may not be captured by the non-classical techniques: a parsimonious combination of classical and non-classical is optimal. That is, different dysphonia measures appear to characterize different aspects of the PD symptoms represented in the speech signal, so that their combination in a regression method captures properties useful for clinical purposes.

Interestingly, the linear predictors performed very well, with the IRLS always presenting slightly better prediction results than LS and Lasso. This indicates that the tails of the error distributions of UPDRS around the regression line may depart from Gaussianity and outliers need to be eliminated from the Gaussian prediction error supposed by classical least squares methods. Still, its performance is not usefully superior to the standard linear LS method. However, CART always provides approximately 1-2 UPDRS points' improvement in prediction performance over the linear methods.

Some of the dysphonia measures are highly correlated with each other (**Table 2**), which suggested the removal of those with insignificant contribution towards UPDRS estimation. This large correlation between measures manifests in the parameter values obtained through LS regression, where two highly correlated measures are allocated opposite signed, but similar magnitude, large value parameters. For example, the measures Shimmer APQ5 and MDVP: APQ have a correlation coefficient 0.96 and their parameters almost exactly cancel each other. To address this artifact, the Lasso algorithm offers a principled mathematical framework for reducing the number of relevant input variables. Furthermore, recent theoretical work has shown that, remarkably, where there is a subset of input measures that contribute no additional information over others in the set, this algorithm is essentially *equivalent to a brute force search* through all possible combinations of measures to find the smallest combination that produces the minimum prediction error[26].

The principle of parsimony suggests that given several different combinations of dysphonia measures that have equal prediction accuracy, preference should be given to the combination with the smallest number of measures. To account for estimation precision versus model complexity (number of dysphonia measures in the subset), we used the AIC and BIC values to determine the 'optimal' subset. The selected subset according to these criteria is given in bold in **Supplementary Table 1**. Both criteria suggest using the subset with the six measures: (MDVP: Jitter (Abs), MDVP: Shimmer, NHR, HNR, DFA, PPE) in combination with the CART method, which offers an attractive compromise between performance and complexity. That is, the selected dysphonia measures in this subset complement each other with minimal overlapping information, and at the same time capture practically the entire range of possible differentiating features of the speech signals useful in determining UPDRS values.

This selected subset and associated coefficients can be given a tentative physiological interpretation. Fundamental frequency variations (measured with absolute jitter) and variations in signal amplitude (shimmer), are well established methods, capturing symptoms manifested in vocal fold vibration and lung efficiency. NHR and HNR suggest that UPDRS is affected by increased noise, caused by turbulent airflow in the glottis, often resulting from incomplete closure of the vocal folds. This concept is further backed up by the inclusion of DFA. Finally PPE indicates impaired pitch control which could be interpreted as deteriorating muscle co-ordination. This is a sign of flawed neuron action potential averaging, suggesting the reduction of dopaminergic neurons devoted to speech control. The remaining dysphonia measures were shown to convey insignificant *additional* information to be included in the model.

We believe these exploratory results could be of value in clinical trials, presenting clinical staff with a useful guide to clinical rater tracking of PD symptoms by UPDRS remotely, and at weekly intervals. This could be particularly useful in those cases where the patients are reluctant or unable to make frequent physical visits to the clinic. This may also be invaluable for future clinical trials of novel treatments which will require high-frequency, remote, and very large study populations. We remark that it is highly likely that combining these results with other PD symptom measures such as those obtained using the AHTD dexterity tests may well help to reduce the UPDRS prediction error and enhance the clinical value of such multimodal testing in telemedicine applications.

We stress again the fact that UPDRS is *subjective*, and the clinicians' verdict on a patient's score could vary. In the end, often the most relevant aspect of disease progression (or PD treatment) is the patient's *perception* of symptoms, i.e. symptom self-rating. This study was confined to using dysphonia measures to predict the average clinical overview of the widely used PD metric, the UPDRS. Although the dysphonia measures have physiological interpretation, it is difficult to link self-perception and physiology. In ongoing research work we focus our attempts to establish a more physiologically-based model, which will explain the data-driven findings in this study in terms of the relevant physiological changes that occur in PD.

# Methods

## Subjects

This study makes use of the recordings described in Goetz et al.[24], where 52 subjects with idiopathic PD were recruited. The study was supervised by six US medical centers: Georgia Institute of Technology (7 subjects), National Institutes of Health (10 subjects), Oregon Health and Science University (14 subjects), Rush University Medical Center (11 subjects), Southern Illinois University (6 subjects) and University of California Los Angeles (4 subjects). All patients gave written informed consent. We disregarded data from 10 recruits – two that dropped out the study early, and a further eight due to insufficient performed tests. The selected subjects had at least 20 valid study sessions during the trial period. We used data from the 42 PWP (28 males) with diagnosis within the previous five years at trial onset (mean 72 ± 69, min. 1, max. 260, median 48 weeks since diagnosis), with an age range 64.4 ± 9.24, min. 36, max. 85, median 65 years. All subjects remained un-medicated for the six-month duration of the study. UPDRS was assessed at baseline (onset of trial), and after three and six months, the scores were 20.84 ± 8.82, min. 5, max. 41, median 19.5 points for motor UPDRS, and 28.44 ± 11.52, min. 7, max. 55, median 26.5 points for total UPDRS.

**Data acquisition**

**Fig. 1a** displays graphically the data acquisition and UPDRS estimation procedure. The data is collected at the patient's home, transmitted over the internet, and processed appropriately in the clinic to predict the UPDRS score. The data was collected using the Intel At-Home Testing Device (AHTD), which is a *telemonitoring* system designed to facilitate remote, Internet-enabled measurement of a variety of PD-related motor impairment symptoms. It contains a docking station for measuring tremor, paddles and pegboards for assessing upper body dexterity, a high-quality microphone headset for recording patient voice signals and a USB data stick to store test data. A LCD displays instructions for taking the tests. Typical audible prompts instruct the patient to undertake tasks to measure tremor, bradykinesia (slow movement), complex co-ordinated motor function, speech and voice. As part of a trial to test the effectiveness of the AHTD system in practice, PWP were recruited and trained to use the device. Subsequently, an AHTD was installed in their home and they performed tests on a weekly basis. Each patient specified a day and time of the week during which they had to complete the protocol, prompted with an automatic alarm reminder on the device. The collected data was encrypted and transmitted to a dedicated server automatically when the USB stick was inserted in a computer with internet connection. Further details of the AHTD apparatus and trial protocol can be found in the work of Goetz et al[24].

The audio recordings are of two types: sustained phonations, and running speech tests in which the subject is instructed to describe static photographs displayed on the AHTD's screen. They were recorded using a head-mounted microphone placed 5 cm from the patient's lips. The AHTD software was devised such that an initial audible, spoken instruction followed by a “beep” prompted the subject to begin phonation: an audio amplitude threshold detector triggered the capture of audio, and subsequently the capture was stopped one second after the detected signal amplitude dropped below that threshold, or 30 seconds of audio had been captured (whichever occurred sooner). The voice signals were recorded directly to the AHTD USB stick sampled at 24 KHz with 16 bit resolution.

In total, after initial screening, 5,923 sustained phonations of the vowel “ahhh…” were digitally processed using algorithms implemented in the Matlab software package. The patients were required to keep their frequency of phonation as steady as possible, for as long as possible. Six phonations were recorded each day on which the test was performed: four at comfortable pitch and loudness and two at twice the initial loudness (but without shouting). A typical sustained phonation speech signal appears in **Supplementary Fig. 1**, with **Supplementary Fig. 1a** exhibiting it from a macroscopic view over the duration of phonation, and **Supplementary Fig. 1b** exhibiting a zoomed in view.

**Feature extraction and statistical regression techniques**

The aim of this study is to analyze the signal, extract *features* representing its characteristics, and map these features to UPDRS using regression methods. Ultimately, we want to mimic the UPDRS to useful precision with clinical importance from the speech signal.

*Feature extraction*

Algorithms aiming to characterize clinically relevant properties from speech signals can be broadly categorized into classical *linear* and non-classical, *nonlinear* methods, see[22,27,28,29]) and the references therein for a detailed overview. With the term *linear* we refer to a method where the output is proportional to a linear combination of the inputs; conversely, *nonlinear* methods have more general relationships between the inputs and the output. Here, we applied a range of classical, and more recently proposed, speech signal processing techniques (henceforth we will collectively refer to these as '*dysphonia measures*') to all the 5,923 signals. Each of the dysphonia measures is aimed at extracting distinct characteristics of the speech signal, and produces a single number. Inevitably, some of them are highly correlated, a concept we discuss elsewhere in this paper.

The classical methods are largely based on linear signal processing techniques such as short-time autocorrelation, followed by 'peak picking' to estimate the *fundamental frequency F0*, which corresponds to the vibration frequency of the vocal folds (on average 120 Hz for men and 200 Hz for women). The *pitch period* (or simply pitch), is the reciprocal of F0. The voice amplitude also has clinical value and is determined as the difference between maximum and minimum values within a pitch period. Successive cycles are not exactly alike (see also **Supplementary Fig. 1b**); the terms *jitter* and *shimmer* are regularly used to describe the cycle to cycle variability in F0 and amplitude, respectively. Similarly, the harmonics to noise ratio (HNR) and noise to harmonics ratio (NHR) denote the signal-to-noise estimates. Please refer to[27, 30] for a more detailed description of these classical speech processing techniques. The software package Praat[27] was used to calculate the classical algorithms: for comparison, the corresponding algorithms in the well-used Kay Pentax Multi-Dimensional Voice Program (MDVP)[30] are prefixed by 'MDVP' in Table 1.

The recently proposed speech signal processing methods are Recurrence Period Density Entropy (RPDE), Detrended Fluctuation Analysis (DFA) and Pitch Period Entropy (PPE)[22,29]. The RPDE addresses the ability of the vocal folds to sustain simple vibration, quantifying the deviations from exact periodicity. It is determined from the entropy of the distribution of the signal recurrence periods, representing the uncertainty in the measurement of the exact period in the signal. Dysphonias such as hoarseness or creaky voice typically cause an increase in RPDE. DFA characterizes the extent of turbulent noise in the speech signal, quantifying the stochastic self-similarity of the noise caused by turbulent air-flow in the vocal tract. Breathiness or other similar dysphonias caused by, e.g. incomplete vocal fold closure can increase the DFA value. Both methods have been shown to contain clinically valuable information regarding general voice disorders[29], and PD-dysphonia in particular[22]. PPE measures the impaired control of stable pitch during sustained phonation[22], a symptom common to PWP[31]. The novelty of this measure is that it uses a logarithmic pitch scale and is robust to confounding factors such as smooth vibrato which is present in healthy voices as well as dysphonic voices. It has been shown that this measure contributes significant information in separating healthy controls and PWP[22].

*Data exploration and correlation analysis*

In the AHTD trial, UPDRS values were obtained at baseline, three-month and six-month trial periods, but the voice recordings were obtained at weekly intervals. Therefore, a straightforward piecewise linear interpolation was used to obtain weekly

UPDRS values to associate with each phonation. We interpolated both motor UPDRS and total UPDRS to assess the efficacy of the dysphonia measures for predicting both scores. The tacit assumption is that symptom severity did not fluctuate wildly within the three-month intervals over which the UPDRS were obtained.

Initially, we performed correlation analysis to identify the strength of association of dysphonia measures with the linearly interpolated UPDRS values. The data was non-normal, so we used non-parametric statistical tests. We computed $p$-values (at the 95% level) of the null hypothesis having no linear correlation $\rho$, between each measure and UPDRS. Similarly, we calculated correlation coefficients between the dysphonia measures. We used the Spearman correlation coefficient to assess the strength of association between each measure and UPDRS, and between measures. The probability densities were computed with kernel density estimation with Gaussian kernels.

*Regression mapping of dysphonia measures to UPDRS*

This preliminary correlation analysis suggests that, taken individually, the dysphonia measures are weakly correlated to UPDRS. However, individual correlations alone do not reveal the (potentially nonlinear) functional relationship between these measures combined together and the associated UPDRS. To find this relationship, statistical regression techniques have been proposed, the simplest of which is classical *least-squares regression*[32]. Our aim is to maximally exploit the information contained in the combined dysphonia measures to produce a predictor that maximizes the accuracy of UPDRS prediction. We used three linear and one nonlinear regression method to map the dysphonia measures to interpolated UPDRS values, and compared their predictive performance[32]. *Linear regression* methods assume that the regression function $f(\mathbf{x})=y$, which maps the dysphonia measures $\boldsymbol{x}=(x_1,\ldots,x_M)$ ($M$ is the number of inputs) to the UPDRS output $y$, is linear in the inputs. It can be expressed as $f(\boldsymbol{x}) = b_0 + \sum_{j=1}^{M} x_j b_j$, with the use of the bias term $b_0$ being optional, i.e. $b_0 = 0$ is quite common (this study does not use a bias term). The aim is to determine the coefficients (or parameters) $\boldsymbol{b}$, given a large number of input values $\boldsymbol{x}$ and output values $f(\mathbf{x})=y$, that minimizes the error in the predictions of UPDRS over the whole data set. The linear techniques used were classical *least squares* (LS), *iteratively re-weighted least squares* (IRLS), and *least absolute shrinkage and selection operator* (Lasso). We describe these techniques next.

LS determines the coefficients $\boldsymbol{b}$ that minimize the residual sum of squares between the actual (measured) UPDRS and the predicted UPDRS:

$$\hat{\boldsymbol{b}} = \underset{\boldsymbol{b}}{\arg\min} \sum_{i=1}^{N} \left( y_i - f(\boldsymbol{x}_i) \right)^2 = \underset{b}{\arg\min} \sum_{i=1}^{N} \left( y_i - \sum_{j=1}^{M} x_{ij} b_j \right)^2 ,$$

where $\boldsymbol{x}_i = (x_{i1},\ldots,x_{ij})$ is a vector of input measurements giving rise to the measured quantity $y_i$, for each $i$th case and $N$ is the number of observations. The statistical assumption underlying LS is that the *residuals* (the difference between the actual and predicted UPDRS) are independent and identically distributed Gaussian random variables, which may not always be a valid assertion, and this can lead to poor estimates of the parameters. Thus, to mitigate any large deviations from Gaussianity, our proposed IRLS method effectively reduces the influence of values distant from the main bulk of the data (*outliers*) by making iterative LS predictions that reweight outliers at each step. This robust estimator is computed using the following algorithm:

1) Determine the residuals: $\boldsymbol{r} = \sum_{i=1}^{N} \left| y_i - \sum_{j=1}^{M} x_{ij} b_j \right|$

2) Determine the weights $\boldsymbol{w}$ using $\boldsymbol{r}$: $\boldsymbol{w} = \left(\exp\left(-2 \cdot \boldsymbol{r} / \max(\boldsymbol{r})\right)\right)^T$

3) Solve the least squares problem using $\boldsymbol{w}$: $\hat{\boldsymbol{b}} = \arg\min_{\boldsymbol{b}} \sum_{i=1}^{N} w_i \left( y_i - \sum_{j=1}^{M} x_{ij} b_j \right)^2$

4) Repeat from the 1st step, for a pre-specified number of iterations (we used 100).

In the first iteration, the coefficients $\boldsymbol{b}$ are determined using the LS method.

A problem often encountered in such regression methods when using a large number of input variables (16 in this case) is the *curse of dimensionality*: fewer input variables could potentially lead to a simpler model with more accurate prediction. Research has shown that many of the dysphonia measures are highly correlated[22] and this finding is confirmed in this study (see Table 2), so we can assume that taken together, highly correlated measures contribute little additional information for UPDRS prediction. Following the general principle of *parsimony*, we would like to reduce the number of measures in the analysis and still obtain accurate UPDRS prediction.

Little et al. used *pre-filtering* to reduce the number of dysphonia measures[22]: this method combines pairs of measures and computes correlation coefficients; when the correlation is above a pre-defined high threshold, one of the pair of measures is removed. The process continues until no more coefficients can be eliminated. Although viable, it is less principled than *shrinkage methods* such as the Lasso, which also offers a mathematical framework enhancing the physiological interpretability of the resulting regression coefficients[33]. The Lasso has the desirable characteristic of simultaneously minimizing the prediction error whilst producing some coefficients that are effectively zero (reducing the number of relevant input variables) by adjusting a *shrinkage parameter*. The algorithm selects the best, smallest subset of variables for the given shrinkage parameter. Decreasing this parameter value causes additional coefficients to shrink towards zero, further reducing the number of relevant input variables. Then it becomes a matter of experimentation to find the optimal compromise between reducing the number of relevant input measures and minimizing the error in the UPDRS prediction. Specifically, the Lasso induces the *sum of absolute values penalty*:

$$\hat{\boldsymbol{b}}_{Lasso} = \arg\min_{\boldsymbol{b}} \sum_{i=1}^{N} \left( y_i - \sum_{j=1}^{M} x_{ij} b_j \right)^2 \text{ subject to } \sum_{j=1}^{M} \left| b_j \right| \leq t$$

where $t$ is the shrinkage parameter, and the constraint $\sum_{j=1}^{M} \left| b_j \right| \leq t$ can be seen as imposing the penalty $\lambda \sum_{j=1}^{M} \left| b_j \right|$ to the residual sum of squares, which yields:

$$\hat{\boldsymbol{b}}_{Lasso} = \arg\min_{b} \sum_{i=1}^{N} \left( y_i - \sum_{j=1}^{M} x_{ij} b_j \right)^2 + \lambda \sum_{j=1}^{M} \left| b_j \right|$$

Other penalties are possible, including the sum of squares of coefficients ***b*** (*ridge regression*), but it can be shown that the sum of absolute values penalty leads to many coefficients which are almost exactly zero, when the problem is underdetermined due to highly redundant inputs, as in this case[26]. In practical terms, this also enhances the *interpretability* of the model.

It may well be the case that the dysphonia measures do not combine linearly to predict the UPDRS. Thus, *nonlinear regression* may be required, where the prediction function *f(**x**)* is a nonlinear combination of the inputs ***x***. To test this idea, we used the *classification and regression tree* (CART) method, which is a conceptually simple nonlinear method that often provides excellent regression results[32]. The key idea behind CART is in finding the best split of the input variables, and partitioning the ranges of these variables into two sub-regions. This partitioning process is repeated on each of the resulting sub-regions, recursively partitioning the input variables into smaller and smaller sub-regions. This recursive procedure can be represented graphically as a tree that splits into successively smaller branches, each branch representing a sub-region of input variable ranges. This tree is "grown" up to $T_0$ splits, learning a successively detailed mapping between all the available data and the UPDRS. Although this process is in principle very flexible and hence able to reproduce highly convoluted mappings, it can easily *overfit* the data: that is, become highly sensitive to noisy fluctuations in the input data. To address this danger some splits are collapsed (a process known as *pruning*) and the amount of split reduction is determined by the *pruning level*.

Here we employed the following strategy: we have experimented with the Lasso method by adjusting the constant parameter $\lambda$, and then observed the surviving and shrinking coefficients associated with each dysphonia measure. Subsequently, various reduced sets of dysphonia measures have been tested with all the regression methods (LS, IRLS and CART).

*Model selection – Bayesian Information Criterion and Akaike Information Criterion*

The Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) offer a framework of comparing fits of models with a different number of parameters[32], and have often been used in the context of medical applications[34]. These criteria induce a penalty on the number of measures in the selected subset, offering a compromise between in-sample error and model complexity. The 'optimal' subset of dysphonia measures is the model with the lower BIC and AIC values. These two criteria are defined as[32]:

$$\mathrm{BIC} = \frac{\sum_{i}^{N}\left(U_i - \hat{U}_i\right)^2}{\sigma_\varepsilon^2} + \log(N)D$$

$$\mathrm{AIC} = \frac{\sum_{i}^{N}\left(U_i - \hat{U}_i\right)^2}{\sigma_\varepsilon^2} + 2D/N$$

where $N$ is the number of data samples, $D$ is the number of measures, $U_i$ is the true UPDRS value as provided by the dataset, $\hat{U}_i$ the predicted estimate and $\sigma_\varepsilon^2$ is the mean squared error (MSE) variance, where the MSE is defined as $MSE = \frac{1}{N}\sum_{i=1}^{N}\left(U_i - \hat{U}_i\right)^2$.

**Cross-validation and model generalization**

To objectively test the generalization performance of the proposed regression methods in predicting UPDRS (that is, the ability of the models to perform well on data not used in estimating the model parameters), we used cross validation, a well-known statistical re-sampling technique[35]. Specifically, the data set of 5,923 phonations was split into a *training* subset (5,331 phonations) and a *testing* subset (592 phonations), which was used to assess generalization performance. The model parameters were derived using the *training* subset, and errors were computed using the *testing* subset (out-of-sample error or testing error). The process was repeated a total of 1,000 times, with the data set randomly permuted in each run prior to splitting in training and testing subsets, in order to obtain confidence in this assessment. On each test repetition, we recorded the *mean absolute error* (MAE) for both training and testing subsets:

$$MAE = \frac{1}{N}\sum_{i \in Q}\left|U_i - \hat{U}_i\right|$$

where $U_i$ is the true UPDRS value as provided by the dataset, $\hat{U}_i$ the predicted estimate and $N$ is the number of phonations in the training or testing dataset, denoted by $Q$, containing the indices of that set. Testing errors from all 1,000 repetitions were averaged. In all cases, the prediction performance results were determined following cross-validation.

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**Conflict of interest:** We have no conflict of interest.

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## Figure Legends

Fig. 1a Schematic diagram depicting the Parkinson’s disease patients’ speech signal recorded on the telemonitoring At-Home-Testing-Device (AHTD) in the patient’s home, transmitted to a dedicated server at the clinic through the internet, and calculation of the speech signal processing (dysphonia) measures, which are then input to a regression method that predicts the symptom score on the Unified Parkinson's Disease Rating Scale (UPDRS). (b) Motor Unified Parkinson's Disease Rating Scale (UPDRS) and (c) total-UPDRS tracking over the 6-month trial period for one of the patients. The dots denote the piecewise linearly interpolated UPDRS value and the circles, predicted UPDRS. The light gray bands are the 5-95 percentile confidence interval of the UPDRS prediction, and the dark gray bands are the 25-75 percentile confidence intervals. Confidence intervals are estimated using 1,000-runs of 10-fold cross-validated out-of-sample UPDRS prediction. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. The Classification And Regression Tree (CART) method tracks Parkinson's disease symptom progression more accurately than Iteratively Reweighted Least Squares (IRLS). The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset (n = 592 phonations).

Fig. 2 (a) Probability densities of the dysphonia measures applied to the 5,923 sustained phonations. The vertical axes are the probability densities of the normalized measures, estimated using kernel density estimation with Gaussian kernels. (b) Dysphonia measures against motor Unified Parkinson's Disease Rating Scale (UPDRS). The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to motor UPDRS. The grey lines are the best linear fit obtained using Iteratively Reweighted Least Squares (IRLS - see methods section for description of the algorithm). The R-values denote the Spearman correlation coefficient of each measure with motor UPDRS. See also Table 2 for the correlation coefficients between the measures. (c). Dysphonia measures against total Unified Parkinson's Disease Rating Scale (UPDRS). The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to total UPDRS. The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to total UPDRS. The grey lines are the best linear fit obtained using Iteratively Reweighted Least Squares (IRLS - see methods section for description of the algorithm). The R-values denote the Spearman correlation coefficient of each measure with total UPDRS. See also Table 2 for the correlation coefficients between the measures. All phonations were used to generate these results ($n$=5,923).

Supplementary Fig. 1 (a) Typical sustained vowel phonation signal over the duration of phonation. The horizontal axis is time in seconds and the vertical axis is amplitude (no units). (b) The same signal zoomed in. The horizontal axis is time in seconds and the vertical axis is amplitude (no units).

Supplementary Fig. 2 Selection of the optimal subset of all voice dysphonia measures (see Table 1) used as predictors, for Unified Parkinson's Disease Rating Scale (UPDRS) prediction, using the in-sample Bayesian Information Criterion (BIC), for Iteratively Reweighted Least Squares (IRLS) and Classification And Regression Tree (CART) models. The vertical axes are the BIC, and the horizontal axes are the subsets (see supplementary Table 1) found by sweeping through values of the Lasso predictor regularization parameter $\lambda$. Numbers in parenthesis are the number of measures in the subset. The label '+Jit' refers to a subset including the jitter measure, to distinguish subsets with the same number of measures. BIC selects the same subsets for the CART method for both motor UPDRS and total UPDRS, here the selected subset is labeled by the arrow. Although not shown here, the Akaike Information Criterion (AIC) selected exactly the same optimal subset of measures. The BIC for the smallest subset of size four, for the CART method, is off the scale and omitted for clarity. The in-sample error was computed by taking the average error of the 1,000 runs of the cross-validation of each training subset ($n$ = 5,331 phonations).

Supplementary Fig. 3 (a, b) Probability density of the 1,000-runs 10-fold cross-validation out-of-sample differences between model predicted ($\hat{\boldsymbol{U}}$) and piecewise linearly interpolated ($U$) Unified Parkinson's Disease Rating Scale (UPDRS) values, using Least Squares (LS), Iteratively Reweighted Least Squares (IRLS) and Classification And Regression Tree (CART) models to predict (a) motor-UPDRS and (b) total-UPDRS. The vertical axes are the probability densities of the regression methods, estimated using kernel density estimation with Gaussian kernels. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. IRLS outperforms the other linear regression methods, in terms of smallest MAE. The distribution of prediction errors for the CART method has the smallest spread and is also the most unimodal. The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset (n = 592 phonations).

**Fig. 1a**

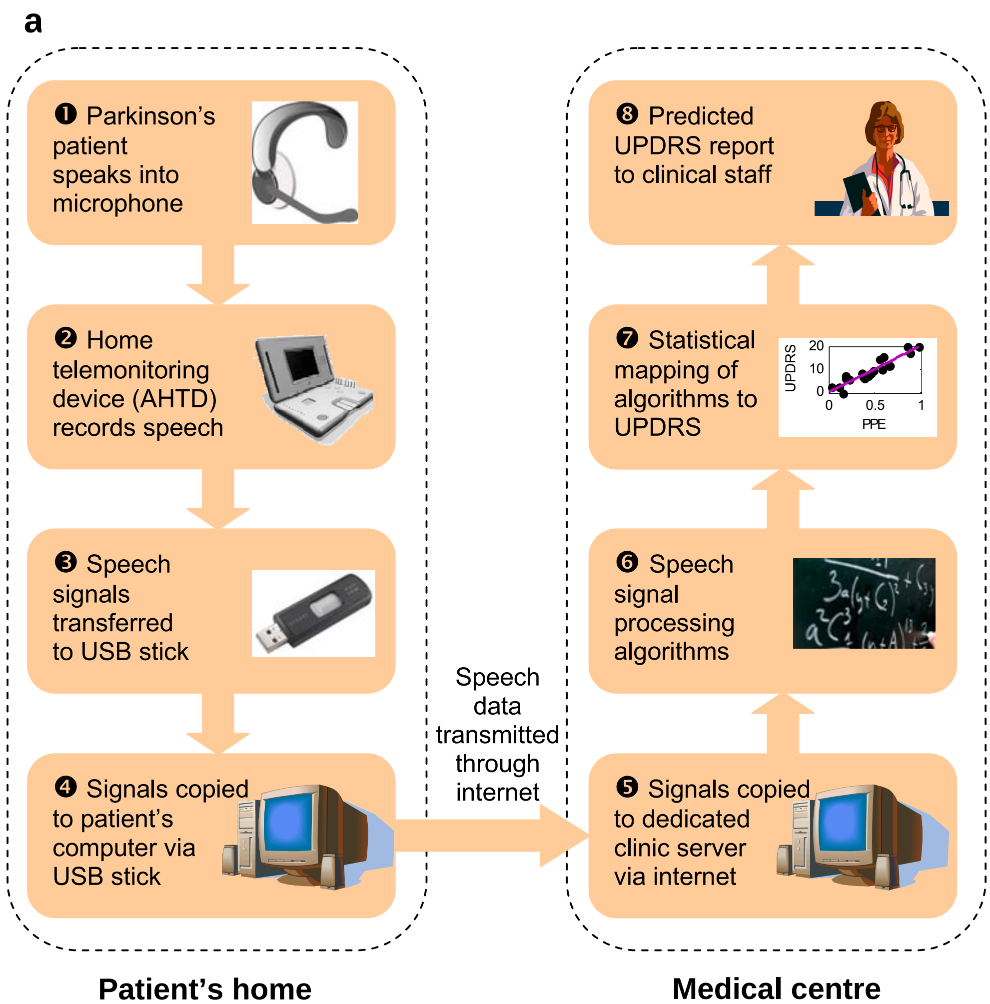



Fig. 1a Schematic diagram depicting the Parkinson's disease patients' speech signal recorded on the telemonitoring At-Home-Testing-Device (AHTD) in the patient's home, transmitted to a dedicated server at the clinic through the internet, and calculation of the speech signal processing (dysphonia) measures, which are then input to a regression method that predicts the symptom score on the Unified Parkinson's Disease Rating Scale (UPDRS).

**Fig. 1b**

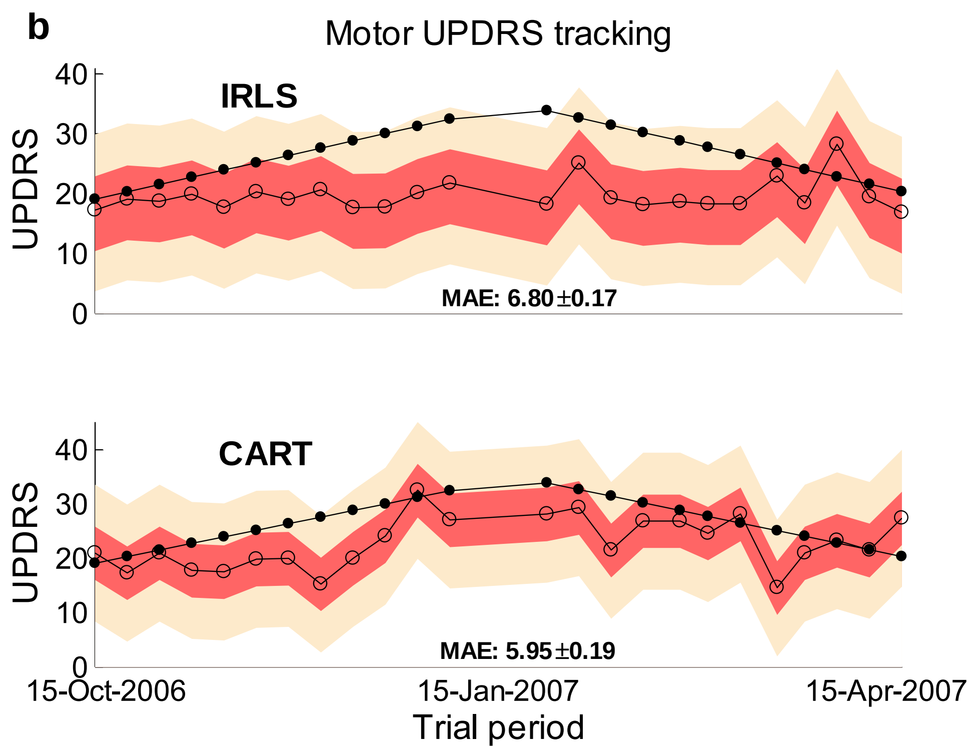



Fig. 1b Motor Unified Parkinson's Disease Rating Scale (UPDRS) tracking over the 6-month trial period for one of the patients. The dots denote the piecewise linearly interpolated UPDRS value and the circles, predicted UPDRS. The light gray bands are the 5-95 percentile confidence interval of the UPDRS prediction, and the dark gray bands are the 25-75 percentile confidence intervals. Confidence intervals are estimated using 1,000-runs of 10-fold cross-validated out-of-sample UPDRS prediction. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. The Classification And Regression Tree (CART) method tracks Parkinson's disease symptom progression more accurately than Iteratively Reweighted Least Squares (IRLS). The out-of-sample MAE was computed by

taking the average MAE of the 1,000 runs of the cross-validation of each testing subset ($n$ = 592 phonations).

**Fig. 1c**

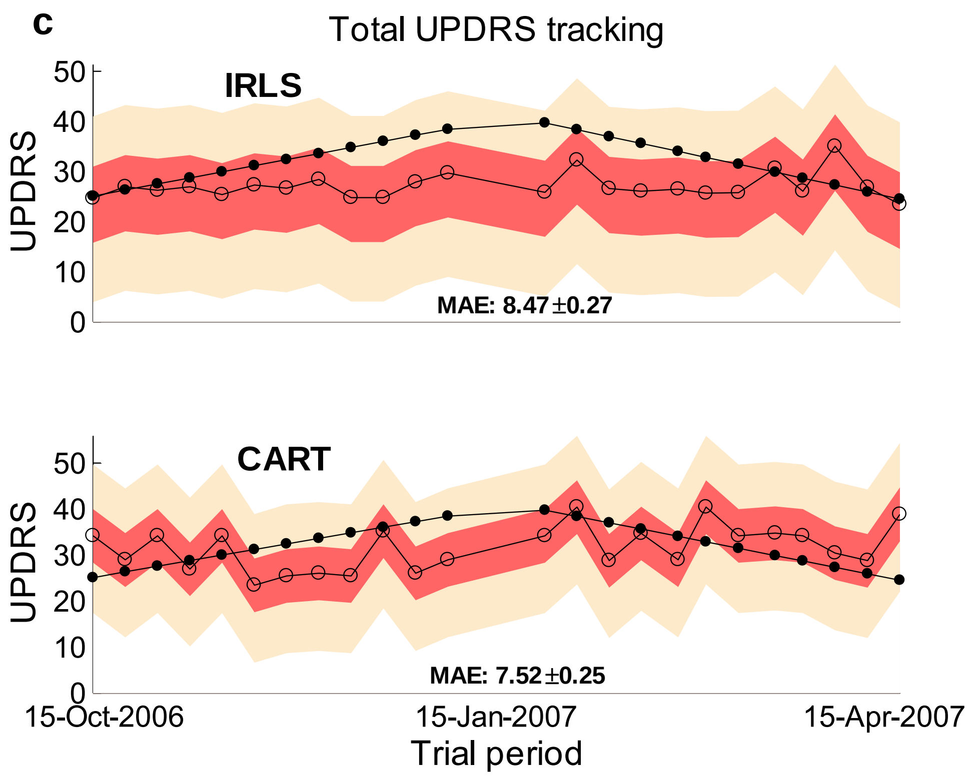



Fig. 1c Total Unified Parkinson's Disease Rating Scale (UPDRS) tracking over the 6-month trial period for one of the patients. The dots denote the piecewise linearly interpolated UPDRS value and the circles, predicted UPDRS. The light gray bands are the 5-95 percentile confidence interval of the UPDRS prediction, and the dark gray bands are the 25-75 percentile confidence intervals. Confidence intervals are estimated using 1,000-runs of 10-fold cross-validated out-of-sample UPDRS prediction. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. The Classification And Regression Tree (CART) method tracks Parkinson's disease symptom progression more accurately than Iteratively Reweighted Least Squares (IRLS). The out-of-sample MAE was computed by

taking the average MAE of the 1,000 runs of the cross-validation of each testing subset (*n* = 592 phonations).

**Fig. 2 (a)**

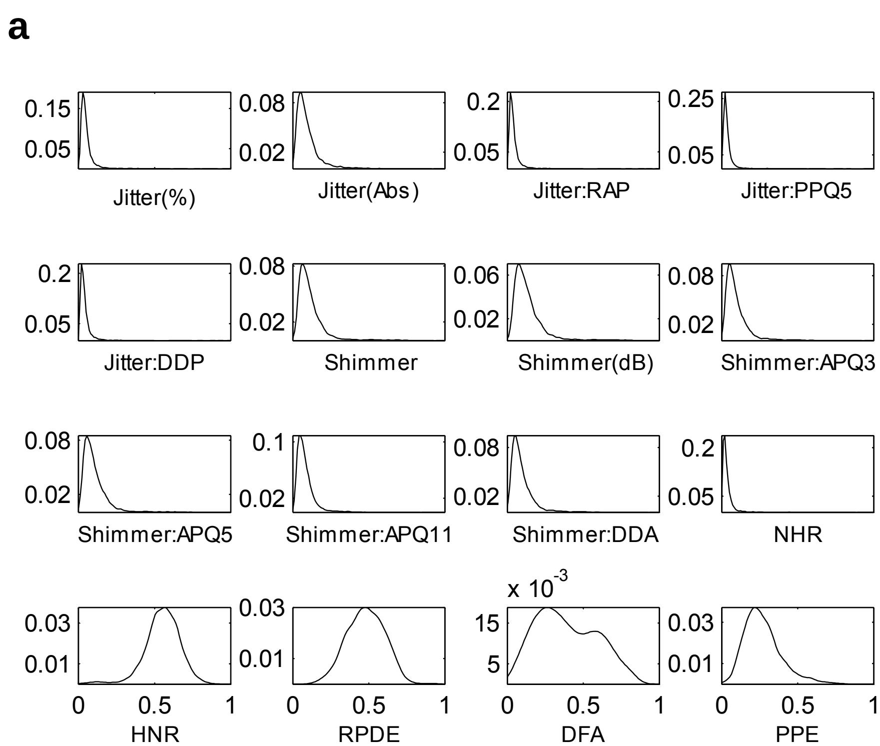



Fig. 2a Probability densities of the dysphonia measures applied to the 5,923 sustained phonations. The vertical axes are the probability densities of the normalized measures, estimated using kernel density estimation with Gaussian kernels.

**Fig. 2b**

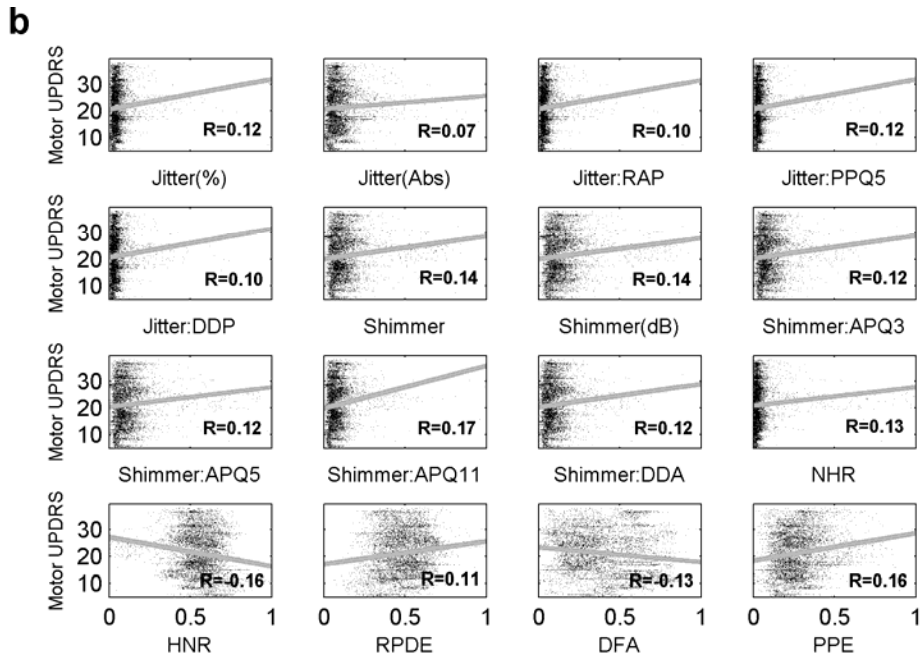



Fig. 2b Dysphonia measures against motor Unified Parkinson's Disease Rating Scale (UPDRS). The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to motor UPDRS. The grey lines are the best linear fit obtained using Iteratively Reweighted Least Squares (IRLS - see methods section for description of the algorithm). The R-values denote the Spearman correlation coefficient of each measure with motor UPDRS. See also Table 2 for the correlation coefficients between the measures. All phonations were used to generate these results (*n*=5,923).

**Fig 2c**

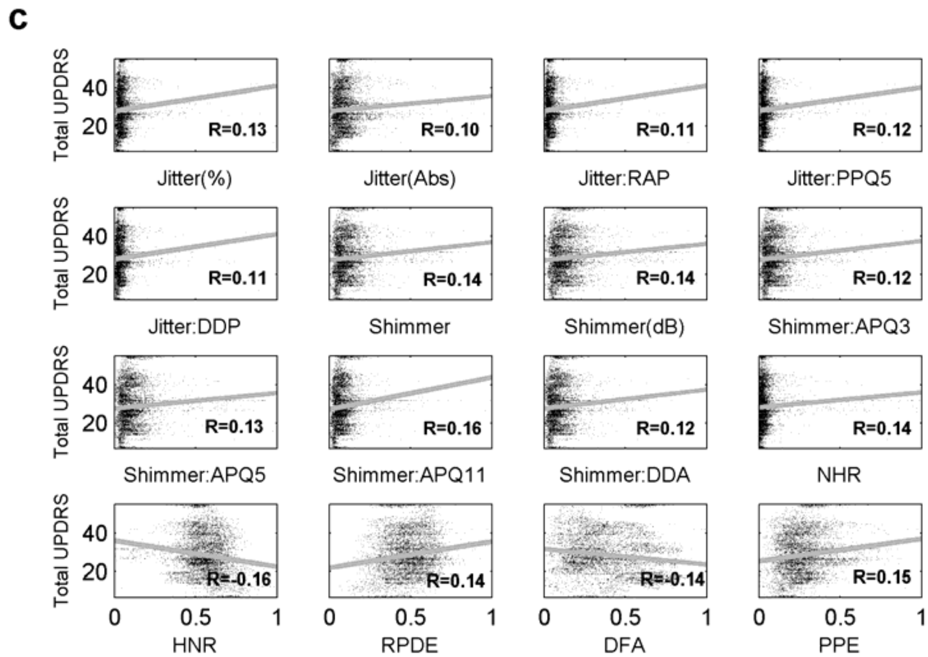
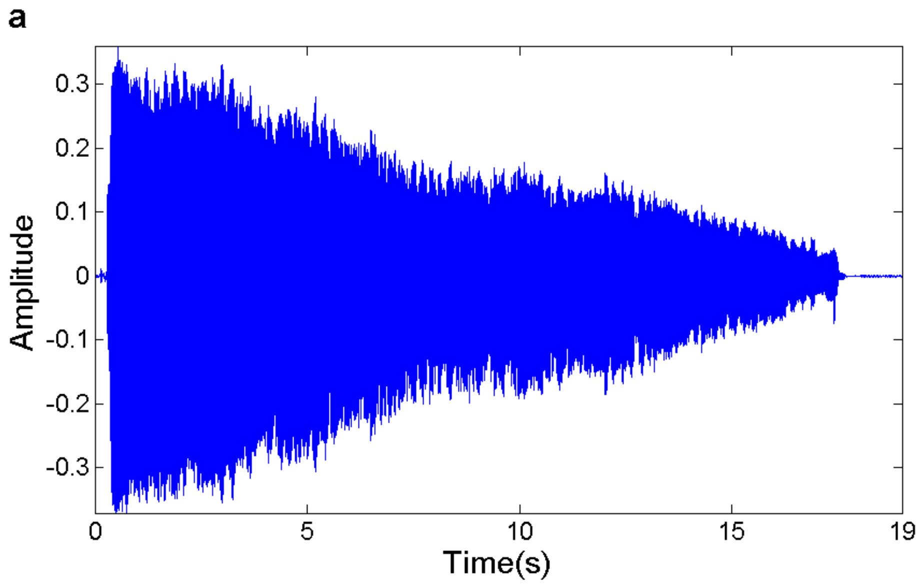


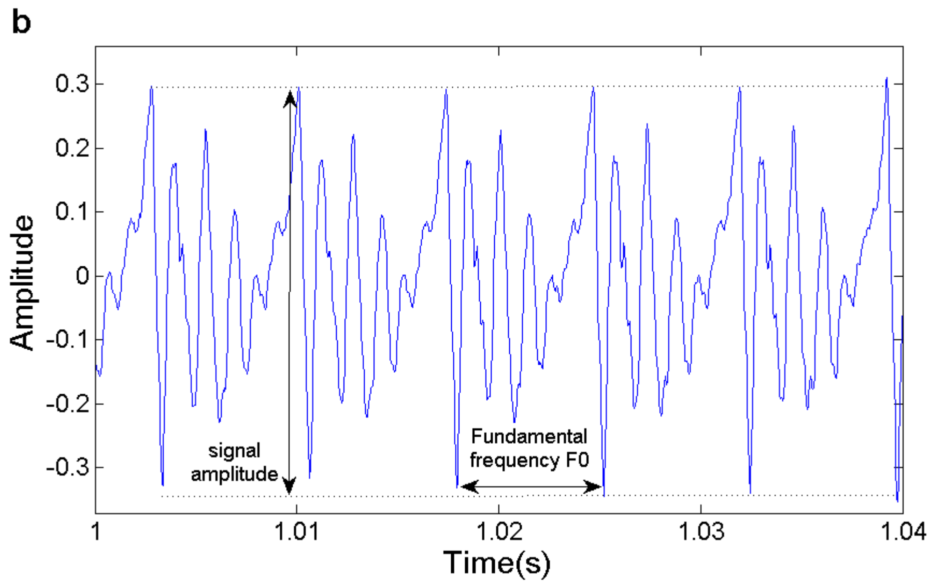

Fig. 2c Dysphonia measures against total Unified Parkinson's Disease Rating Scale (UPDRS). The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to total UPDRS. The horizontal axes are the normalized dysphonia measures and the vertical axes correspond to total UPDRS. The grey lines are the best linear fit obtained using Iteratively Reweighted Least Squares (IRLS - see methods section for description of the algorithm). The R-values denote the Spearman correlation coefficient of each measure with total UPDRS. See also Table 2 for the correlation coefficients between the measures. All phonations were used to generate these results ($n$=5,923).

**Supplementary Fig. 1a**



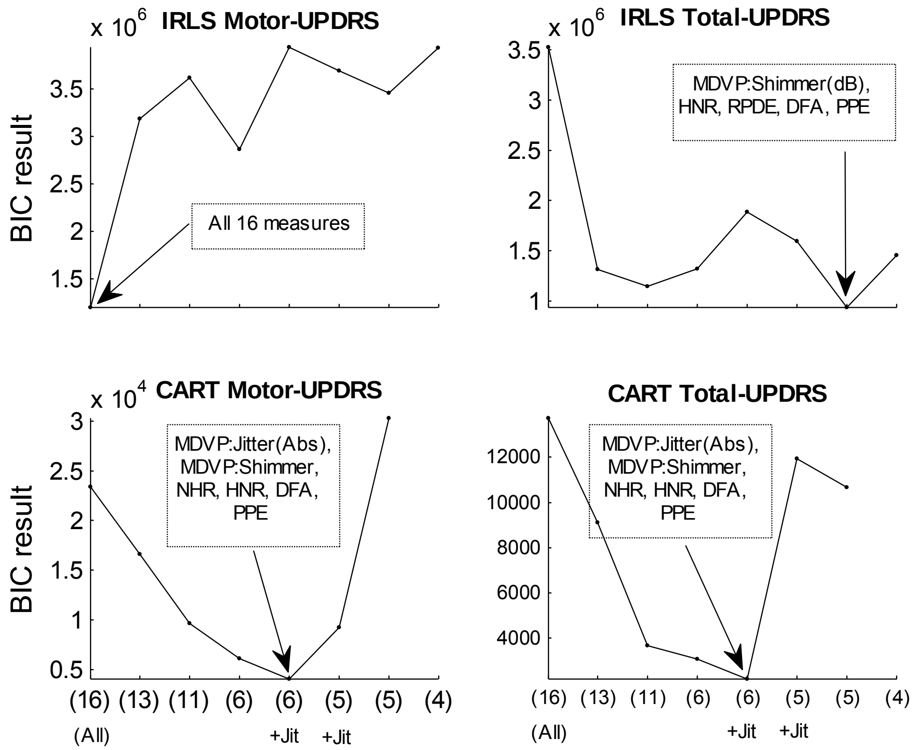

Supplementary Fig. 1 (a) Typical sustained vowel phonation signal over the duration of phonation. The horizontal axis is time in seconds and the vertical axis is amplitude (no units).

**Supplementary Fig. 1b**




Supplementary Fig. 1 (b) The same signal zoomed in. The horizontal axis is time in seconds and the vertical axis is amplitude (no units).

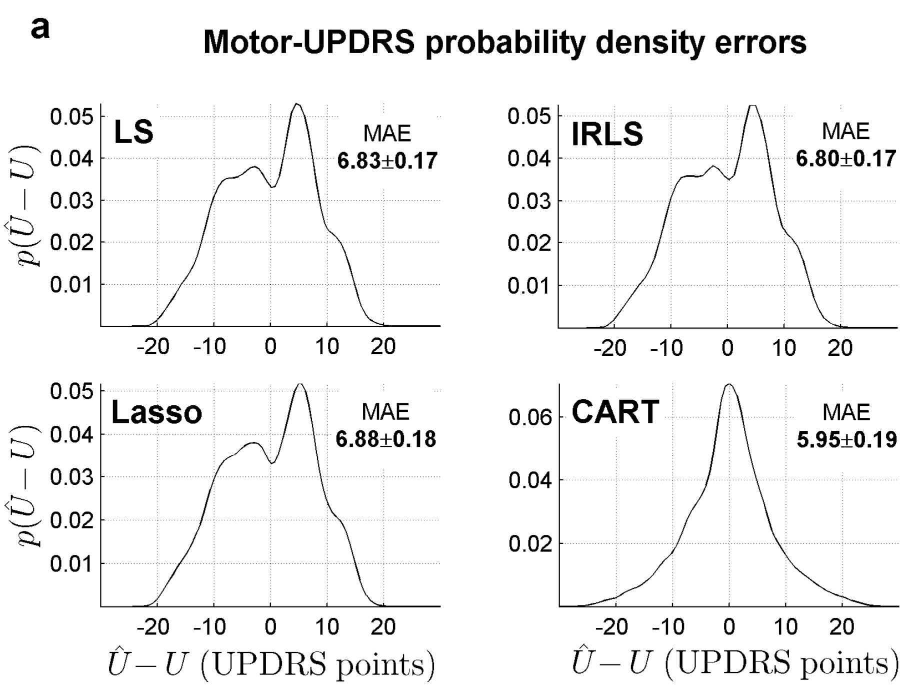
**Supplementary Fig. 2**




Supplementary Fig. 2 Selection of the optimal subset of all voice dysphonia measures (see Table 1) used as predictors, for Unified Parkinson's Disease Rating Scale (UPDRS) prediction, using the in-sample Bayesian Information Criterion (BIC), for Iteratively Reweighted Least Squares (IRLS) and Classification And Regression Tree (CART) models. The vertical axes are the BIC, and the horizontal axes are the subsets (see supplementary Table 1) found by sweeping through values of the Lasso predictor regularization parameter λ. Numbers in parenthesis are the number of measures in the subset. The label '+Jit' refers to a subset including the jitter measure, to distinguish subsets with the same number of measures. BIC selects the same subsets for the CART method for both motor UPDRS and total UPDRS, here the selected subset is labeled by the arrow. Although not shown here, the

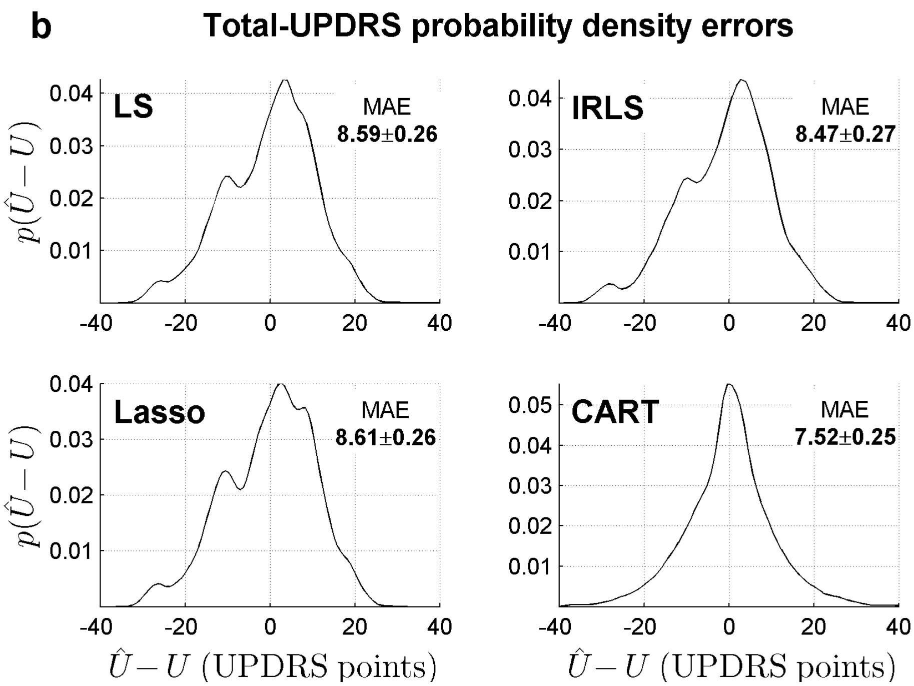
Akaike Information Criterion (AIC) selected exactly the same optimal subset of measures. The BIC for the smallest subset of size four, for the CART method, is off the scale and omitted for clarity. The in-sample error was computed by taking the average error of the 1,000 runs of the cross-validation of each training subset (*n* = 5,331 phonations).

**Supplementary Fig. 3a**




Supplementary Fig. 3a Probability density of the 1,000-runs 10-fold cross-validation out-of-sample differences between model predicted ($\hat{U}$) and piecewise linearly interpolated ($U$) Unified Parkinson's Disease Rating Scale (UPDRS) values, using Least Squares (LS), Iteratively Reweighted Least Squares (IRLS) and Classification And Regression Tree (CART) models to predict motor-UPDRS. The vertical axes are the probability densities of the regression methods, estimated using kernel density estimation with Gaussian kernels. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. IRLS outperforms the other linear regression methods, in terms of smallest MAE. The distribution of prediction errors for the CART method has the smallest spread and is also the most unimodal. The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset (*n* = 592 phonations).

**Supplementary Fig. 3b**




Supplementary Fig. 3b Probability density of the 1,000-runs 10-fold cross-validation out-of-sample differences between model predicted ($\hat{U}$) and piecewise linearly interpolated ($U$) Unified Parkinson's Disease Rating Scale (UPDRS) values, using Least Squares (LS), Iteratively Reweighted Least Squares (IRLS) and Classification And Regression Tree (CART) models to predict total-UPDRS. The vertical axes are the probability densities of the regression methods, estimated using kernel density estimation with Gaussian kernels. The mean absolute prediction error (MAE) of each model is also quoted, along with the standard deviation. IRLS outperforms the other linear regression methods, in terms of smallest MAE. The distribution of prediction errors for the CART method has the smallest spread and is also the most unimodal. The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset ($n$ = 592 phonations).

# Table Legends

## Table 1: Classical and non-classical dysphonia measures applied to sustained vowel phonations, and their Unified Parkinson's Disease Rating Scale (UPDRS) correlations.

KP-MDVP stands for Kay Pentax Multidimensional Voice Program. Classical measures were obtained using the Praat software package. The Unified Parkinson's Disease Rating Scale (UPDRS) correlation columns are the Spearman non-parametric correlation coefficient between each measure and piecewise linearly interpolated motor and total UPDRS. All measures were statistically significantly correlated ($p < 0.0001$) with UPDRS. All speech signals were used to generate these results ($n = 5{,}923$ phonations).

## Table 2: Correlation coefficients between dysphonia measures.

The correlation columns are the Spearman non-parametric correlation coefficients $\rho$ between two measures. All measures were statistically significantly correlated ($p < 0.0001$). Bold italic entries indicate high correlation between measures (*Spearman* $\rho \geq 0.95$). All speech signals were used to generate these results ($n = 5{,}923$ phonations).

## Table 3: Regression coefficients of the three linear methods (LS, IRLS, Lasso, see text) for all dysphonia measures and piecewise linearly interpolated motor and total Unified Parkinson's Disease Rating Scale (UPDRS).

The coefficients in this table are indicative (derived over one run of cross-validation with the training subset, $n = 5{,}331$). We have noticed considerably different values in the 1,000 runs of 10-fold cross validation. However, the fact that the cross-validated test error and test error standard deviation remained small, suggests that confidence can be assumed for the above coefficient values.

**Supplementary Table 1: Subsets of dysphonia measures and out-of-sample MAE for the Iteratively Reweighted Least Squares (IRLS) and the Classification And Regression Tree (CART) method.**

The particular subsets above were dictated by sweeping the regularization parameter λ in the Least Absolute Shrinkage and Selection Operator (Lasso) prediction model. The numbers in parenthesis denote the chosen pruning level of the CART method that minimizes the MAE, and ± denotes one standard deviation around the quoted MAE. The bold subset is the optimal subset, minimizing the Bayesian Information Criterion. The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset (*n* = 592 phonations).

TABLE 1

**Table 1: Classical and non-classical dysphonia measures applied to sustained vowel phonations, and their Unified Parkinson's Disease Rating Scale (UPDRS) correlations.**

| Measure | Description | Motor UPDRS correlation | Total UPDRS correlation |
|---|---|---|---|
| MDVP: Jitter(%) | KP-MDVP jitter as a percentage | 0.124 | 0.125 |
| MDVP: Jitter(Abs) | KP-MDVP absolute jitter in microseconds | 0.072 | 0.103 |
| MDVP:RAP | KP-MDVP Relative Amplitude Perturbation | 0.105 | 0.107 |
| MDVP:PPQ | KP-MDVP five-point Period Perturbation Quotient | 0.120 | 0.117 |
| Jitter:DDP | Average absolute difference of differences between cycles, divided by the average period | 0.105 | 0.107 |
| MDVP: Shimmer | KP-MDVP local shimmer | 0.138 | 0.139 |
| MDVP: Shimmer(dB) | KP-MDVP local shimmer in decibels | 0.139 | 0.139 |
| Shimmer: APQ3 | Three point Amplitude Perturbation Quotient | 0.116 | 0.122 |
| Shimmer: APQ5 | Five point Amplitude Perturbation Quotient | 0.123 | 0.127 |
| MDVP:APQ | KP-MDVP 11-point Amplitude Perturbation Quotient | 0.166 | 0.163 |
| Shimmer: DDA | Average absolute difference between consecutive differences between the amplitudes of consecutive periods | 0.116 | 0.122 |
| NHR | Noise-to-Harmonics Ratio | 0.131 | 0.139 |
| HNR | Harmonics-to-Noise Ratio | -0.159 | -0.163 |
| RPDE | Recurrence Period Density Entropy | 0.112 | 0.143 |
| DFA | Detrended Fluctuation Analysis | -0.131 | -0.141 |
| PPE | Pitch Period Entropy | 0.160 | 0.152 |

KP-MDVP stands for Kay Pentax Multidimensional Voice Program. Classical measures were obtained using the Praat software package. The Unified Parkinson's Disease Rating Scale (UPDRS) correlation columns are the Spearman non-parametric correlation coefficient between each measure and piecewise linearly interpolated motor and total UPDRS. All measures were statistically significantly correlated ($p < 0.0001$) with motor-UPDRS and total-UPDRS. All speech signals were used to generate these results ($n = 5{,}923$ phonations).

**Table 2: Correlation coefficients between dysphonia measures.**

| | MDVP Jitter (%) | MDVP Jitter (Abs) | MDVP RAP | MDVP: PPQ | Jitter: DDP | MDVP: Shimmer | MDVP: Shimmer (dB) | Shimmer APQ3 | Shimmer APQ5 | MDVP: APQ | Shimmer DDA | NHR | HNR | RPDE | DFA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MDVP: Jitter (Abs) | 0.90 | | | | | | | | | | | | | | |
| MDVP:RAP | ***0.96*** | 0.82 | | | | | | | | | | | | | |
| MDVP: PPQ | ***0.96*** | 0.89 | ***0.95*** | | | | | | | | | | | | |
| Jitter: DDP | ***0.96*** | 0.82 | ***1*** | ***0.95*** | | | | | | | | | | | |
| MDVP: Shimmer | 0.65 | 0.63 | 0.65 | 0.69 | 0.65 | | | | | | | | | | |
| MDVP: Shimmer (dB) | 0.68 | 0.64 | 0.66 | 0.70 | 0.66 | ***0.99*** | | | | | | | | | |
| Shimmer APQ3 | 0.62 | 0.58 | 0.63 | 0.66 | 0.63 | ***0.98*** | ***0.96*** | | | | | | | | |
| Shimmer APQ5 | 0.62 | 0.61 | 0.62 | 0.67 | 0.62 | ***0.99*** | ***0.97*** | ***0.98*** | | | | | | | |
| MDVP:APQ | 0.63 | 0.64 | 0.60 | 0.67 | 0.60 | ***0.96*** | ***0.95*** | 0.91 | ***0.96*** | | | | | | |
| Shimmer DDA | 0.62 | 0.58 | 0.63 | 0.66 | 0.63 | ***0.98*** | ***0.96*** | ***1*** | ***0.98*** | 0.91 | | | | | |
| NHR | 0.80 | 0.75 | 0.75 | 0.75 | 0.75 | 0.65 | 0.69 | 0.62 | 0.62 | 0.62 | 0.62 | | | | |
| HNR | -0.76 | -0.76 | -0.73 | -0.79 | -0.73 | -0.80 | -0.78 | -0.78 | -0.79 | -0.79 | -0.78 | -0.76 | | | |
| RPDE | 0.53 | 0.64 | 0.45 | 0.51 | 0.45 | 0.48 | 0.47 | 0.43 | 0.46 | 0.50 | 0.43 | 0.61 | -0.65 | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DFA | 0.44 | 0.50 | 0.43 | 0.48 | 0.43 | 0.29 | 0.27 | 0.26 | 0.29 | 0.31 | 0.26 | 0.15 | -0.36 | 0.19 | |
| PPE | 0.85 | 0.81 | 0.77 | 0.84 | 0.77 | 0.64 | 0.66 | 0.59 | 0.62 | 0.66 | 0.59 | 0.73 | -0.75 | 0.55 | 0.42 |

The correlation columns are the Spearman non-parametric correlation coefficients $\rho$ between two measures. All measures were statistically significantly correlated ($p < 0.0001$). Bold italic entries indicate high correlation between measures (Spearman $\rho \geq 0.95$). All speech signals were used to generate these results ($n$ = 5,923 phonations).

TABLE 3

**Table 3: Regression coefficients of the three linear methods (LS, IRLS, Lasso, see text) for all dysphonia measures and piecewise linearly interpolated motor and total Unified Parkinson's Disease Rating Scale (UPDRS).**

| Measure | Motor UPDRS Least squares coefficients | Motor UPDRS Iteratively re-weighted least squares coefficients | Motor UPDRS Lasso coefficients (λ=1) | Total UPDRS Least squares coefficients | Total UPDRS Iteratively re-weighted least squares coefficients | Total UPDRS Lasso coefficients (λ=1) |
|---|---|---|---|---|---|---|
| MDVP: Jitter (%) | -87.63 | -183.28 | -214.45 | -768.96 | -649.19 | -537.90 |
| MDVP: Jitter (Abs) | $-6.87 \cdot 10^4$ | $-7.64 \cdot 10^4$ | 0 | $-7.04 \cdot 10^4$ | $-8.49 \cdot 10^4$ | 0 |
| MDVP: RAP | $-6.02 \cdot 10^4$ | $-6.29 \cdot 10^4$ | 0 | $-2.91 \cdot 10^4$ | $-3.36 \cdot 10^4$ | 0 |
| MDVP: PPQ | -238.07 | -62.70 | 0 | 209.26 | 40.02 | 50.62 |
| Jitter: DDP | $2.02 \cdot 10^4$ | $2.12 \cdot 10^4$ | 75.59 | $1.02 \cdot 10^4$ | $1.17 \cdot 10^4$ | 241.81 |
| MDVP: Shimmer | 77.78 | 100.56 | 23.81 | 28.62 | 114.26 | 9.58 |
| MDVP: Shimmer (dB) | 0.31 | -2.49 | 4.37 | -0.38 | -4.74 | 1.67 |
| Shimmer: APQ3 | $-1.85 \cdot 10^4$ | $-2.43 \cdot 10^4$ | 0 | $-8.19 \cdot 10^4$ | $-7.24 \cdot 10^4$ | 0 |
| Shimmer: APQ5 | -108.01 | -126.06 | -66.68 | -93.05 | -138.32 | -2.75 |
| MDVP: APQ | 55.12 | 83.35 | 66.28 | 104.35 | 107.95 | 85.74 |
| Shimmer: DDA | $6.16 \cdot 10^3$ | $8.09 \cdot 10^3$ | -4.97 | $2.73 \cdot 10^4$ | $2.41 \cdot 10^4$ | 0 |
| NHR | 2.14 | -5.04 | -7.38 | -12.45 | -8.21 | -17.33 |
| HNR | 0.52 | 0.57 | 0.61 | 0.65 | 0.74 | 0.74 |
| RPDE | 16.62 | 20.24 | 15.25 | 26.21 | 30.77 | 23.81 |

| | | | | | | |
|---|---|---|---|---|---|---|
| DFA | -9.54 | -15.43 | -12.05 | -12.47 | -19.73 | -14.05 |
| PPE | 35.34 | 37.90 | 28.50 | 41.37 | 39.15 | 33.41 |

The coefficients in this table are indicative (derived over one run of cross-validation with the training subset, *n* = 5,331). We have noticed considerably different values in the 1,000 runs of 10-fold cross validation. However, the fact that the cross-validated test error and test error standard deviation remained small, suggests that confidence can be assumed for the above coefficient values.

**Supplementary Table 1: Subsets of dysphonia measures and out-of-sample Mean Absolute Error (MAE) for the Iteratively Reweighted Least Squares (IRLS) and the Classification And Regression Tree (CART) method.**

| Number of measures | Measures used | Testing MAE Motor UPDRS IRLS | Testing MAE Total UPDRS IRLS | Testing MAE Motor UPDRS CART | Testing MAE Total UPDRS CART |
|---|---|---|---|---|---|
| 16 | MDVP:Jitter (%), MDVP:Jitter(Abs), MDVP: RAP, MDVP:PPQ, Jitter:DDP MDVP:Shimmer, MDVP:Shimmer (dB), Shimmer:APQ3,Shimmer:APQ 5, MDVP:APQ, Shimmer:DDA, NHR, HNR RPDE, DFA, PPE | 6.71±0.18 | 8.46±0.27 | 5.77±0.20 (830) | 7.45±0.27 (850) |
| 13 | MDVP:Jitter (%), MDVP:PPQ, Jitter:DDP MDVP:Shimmer, MDVP:Shimmer (dB), Shimmer:APQ5, MDVP:APQ, Shimmer:DDA, NHR, HNR RPDE, DFA, PPE | 6.73±0.17 | 8.49±0.25 | 6.01±0.26 (800) | 7.64±0.29 (800) |
| 11 | MDVP:Jitter(%),MDVP:Shimmer, MDVP:Shimmer(dB), Shimmer:APQ5, MDVP:APQ, Shimmer:DDA, NHR, HNR RPDE, DFA, PPE | 6.74±0.16 | 8.83±0.26 | 6.06±0.25 (850) | 7.67±0.27 (800) |
| 6 | MDVP: Shimmer(dB), NHR, HNR, RPDE, DFA, PPE | 6.91±0.17 | 8.60±0.30 | 6.08±0.19 (780) | 7.75±0.26 (750) |
| **6** | **MDVP:Jitter(Abs), MDVP:Shimmer, NHR, HNR, DFA, PPE** | 6.80±0.17 | 8.47±0.27 | **5.95±0.19 (780)** | **7.52±0.25 (780)** |
| 5 | MDVP:Jitter(Abs), MDVP:Shimmer, HNR, DFA, PPE | 6.88±0.17 | 8.71±0.26 | 5.96±0.19 (750) | 7.59±0.25 (780) |
| 5 | MDVP:Shimmer(dB), HNR, RPDE, DFA, PPE | 6.79±0.17 | 8.49±0.26 | 6.14±0.19 (780) | 7.72±0.26 (780) |
| 4 | MDVP:Shimmer(dB), HNR, RPDE, PPE | 6.91±0.17 | 8.57±0.26 | 6.82±0.23 (700) | 8.43±0.28 (700) |

The particular subsets above were dictated by sweeping the regularization parameter $\lambda$ in the Least Absolute Shrinkage and Selection Operator (Lasso) prediction model. The numbers in parenthesis denote the chosen pruning level of the CART method that minimizes the MAE, and ± denotes one standard deviation around the quoted MAE. The bold subset is the optimal subset, minimizing the Bayesian Information Criterion. The out-of-sample MAE was computed by taking the average MAE of the 1,000 runs of the cross-validation of each testing subset ($n$ = 592 phonations).