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Speech acoustic indices for differential diagnosis between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy

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ABSTRACT

While speech disorder represents an early and prominent clinical feature of atypical parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), little is known about the sensitivity of speech assessment as a potential diagnostic tool. Speech samples were acquired from 215 subjects, including 25 MSA, 20 PSP, 20 Parkinson's disease participants, and 150 healthy controls. The accurate differential diagnosis of dysarthria subtypes was based on the quantitative acoustic analysis of 26 speech dimensions related to phonation, articulation, prosody, and timing. A semi-supervised weighting-based approach was then applied to find the best feature combinations for separation between PSP and MSA. Dysarthria was perceptible in all PSP and MSA patients and consisted of a combination of hypokinetic, spastic, and ataxic components. Speech features related to respiratory dysfunction, imprecise consonants, monopitch, slow speaking rate, and subharmonics contributed to worse performance in PSP than MSA, whereas phonatory instability, timing abnormalities, and articulatory decay were more distinctive for MSA compared to PSP. The combination of distinct speech patterns via objective acoustic evaluation was able to discriminate between PSP and MSA with very high accuracy of up to 89% as well as between PSP/MSA and PD with up to 87%. Dysarthria severity in MSA/PSP was related to overall disease severity. Speech disorders reflect the differing underlying pathophysiology of tauopathy in PSP and α -synucleinopathy in MSA. Vocal assessment may provide a low-cost alternative screening method to existing subjective clinical assessment and imaging diagnostic approaches.

Introduction

Idiopathic Parkinson's disease (PD) is a common neurological disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, affecting 1.6% of persons over the age of 65 years¹. Dopamine concentrations have been shown to be significantly reduced before distinct motor deficits become apparent². The cardinal signs of PD, often referred to as parkinsonism, include resting tremor, bradykinesia, muscular rigidity and postural instability. Other neurodegenerative diseases that go beyond the signs and symptoms of parkinsonism are known as atypical parkinsonian syndromes (APS). Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are subgroups of APS, with an estimated prevalence of 30–40 per 100,000 among persons older than 65 years³. Characteristic clinical features of PSP include supranuclear gaze palsy, frequent falls, bradykinesia, axial rigidity, cognitive decline and communication disorders^{4,5}, reflecting widespread neurodegeneration involving the midbrain as well as the globus pallidus, striatum, hypothalamic nucleus, pons, superior cerebellar peduncle and cerebellar dentate nucleus⁴. Conversely, MSA manifests by various combinations of autonomic, cerebellar and parkinsonian features⁶, corresponding to degeneration of striatum, substantia nigra, cerebellum, middle cerebellar peduncle, inferior olivary nucleus and pons⁷. APS differ from PD by poor levodopa response and more rapid disease progression resulting in shorter life expectancy^{8,9}.

The majority of PD and APS patients manifest similar clinical features which might render very challenging a correct differential diagnosis¹⁰. There exists clinical criteria for the diagnosis of "probable" and "possible" MSA and PSP, based on clinical or/and imaging features, but the definite MSA and PSP diagnosis requires postmortem confirmation by a neuropathological examination⁷. Currently, a variety of imaging techniques such as magnetic resonance imaging, diffusion tensor

imaging, positron emission tomography, single-photon emission computed tomography and transcranial sonography may be used in the assessment of various parkinsonian syndromes¹¹. In particular, automatic image-based classification based on metabolic patterns is highly accurate in distinguishing between PD, PSP and MSA patients at early stages of the disease, with more than 84% sensitivity and 94% specificity¹². However, metabolic imaging is burdened by the invasive application of radiopharmaceuticals, whilst technical demands and financial costs may limit the application of other imaging methods.

It is now well established that dysarthria, a class of motor speech impairments resulting from neurological disorders, is an early clinical feature of PD and APS¹³. Due to dysfunction of the basal ganglia, the majority of PD patients manifest hypokinetic dysarthria characterized by monopitch, monoloudness, reduced stress, variable rate, imprecise articulation, harsh voice quality, speech dysfluencies and inappropriate silence^{14,15}. Conversely, PSP and MSA patients typically evolve mixed dysarthria with a combination of hypokinesia, ataxia and spasticity as a result of more widespread neuronal atrophy^{16–18}. Indeed, previous studies^{16,17} investigating 46 MSA and 44 PSP patients using oral motor and perceptual speech analysis have reported mixed dysarthria with combinations of all hypokinetic, spastic and ataxic components in two-thirds of APS patients. Hypokinetic components followed by ataxic components were predominant in MSA patients, while spastic components were mostly present in PSP patients^{16,17}. Dysarthria can manifest in all the levels of speech production¹⁹: respiration, articulation, phonation, timing and prosody (and nasality to a lower extent).

During the last decades, there has been an increasing interest in PD speech and voice analysis. The large majority of research have however focused on discriminating between PD and healthy controls with the motivation to use speech assessment as a supporting method for early PD diagnosis. While this can have an interest from a fundamental perspective and for monitoring purposes, it has actually a limited impact in clinical diagnosis. Indeed, early diagnosis of PD cannot be claimed (as often done) because APS dysarthria is not taken into account. Moreover, most of the time the clinical diagnosis even neglects the possibility of an APS. The resulting speech dataset can thus be noisy in the sense that patients considered as PD may actually be APS. Such studies may claim at best methods/features which correlate with a diagnosis of *parkinsonism* (which groups PD and APS), acknowledging that parkinsonism does not require speech analysis to be correctly diagnosed.

On the other hand, there exists only few studies on comparison/discrimination between PD and APS or between APS subgroups^{13,20–31}. In this work we focused on this challenging problem by using, first, an assessment of all basic subsystems of connected speech: timing, prosody, articulation, phonation and respiration. Then, based on the findings, we proposed an assessment based dysarthria subtypes: hypokinetic, ataxic and spastic.

Methods

Participants

From 2011 to 2018, we enrolled a total of 65 consecutive patients via a single center for the present study, including 20 with a medical diagnosis of probable PSP (13 men and 7 women), 25 with a medical diagnosis of probable MSA (15 men and 10 women) and 20 with a medical diagnosis of idiopathic PD (13 men and 7 women). A movement disorders specialist established the clinical diagnoses of all patients according to the Movement Disorder society diagnostic criteria for PSP³², the consensus diagnostic criteria for MSA⁷ and the Movement Disorder Society clinical diagnostic criteria for PD³³. The PSP group consisted of 17 subjects diagnosed with PSP-Richardson (PSP-R) syndrome, 2 with PSP-parkinsonism (PSP-P), and 1 with PSP-pure akinesia with gait freezing (PSP-PGF) while the MSA group was composed of 19 subjects diagnosed with MSA-parkinsonian (MSA-P) subtype and 6 patients with MSA-cerebellar (MSA-C) subtype. At the time of examination, each treated PSP or MSA patient was on stable medication for at least 4 weeks consisting of various doses of levodopa alone or combined with different dopamine agonists and/or amantadine. PD patients were investigated immediately after the diagnosis was established before the initiation of dopaminergic treatment. No PD subject manifested dyskinesias at the time of the examination. Disease duration was determined based on the self-reported occurrence of the first motor symptoms. Each PSP and MSA patient underwent neurological examination including scoring according to the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) scale³⁴, while PD patients were rated by the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscore. None of the patients reported a history of speech-language disorders unrelated to possible neurologic disease manifestations. No statistically significant differences were found between PSP and MSA groups for disease duration, medication doses, cognitive status, motor or speech severity (Mann-Whitney U test: $p=0.11–0.59$). The dysarthria presence, type, and severity estimates were evaluated based on the auditory-perceptual judgment of a speech-language specialist experienced in movement disorders using audio recordings of vowel phonation, /pa/-/ta/-/ka/ syllable repetition, and monologue following the perceptual criteria outlined by¹⁴. Patient clinical and demographic characteristics are summarised in Table 1. The control group consisted of 150 healthy subjects of comparable gender distribution (95 men and 55 women; 63% male gender) as well as age (mean age 65.5, SD 7.1, range 45–83 years, $p = 0.08$ between controls and PSP and MSA). No control subject reported a history of neurological disorders or other disorders that may affect speech, language or hearing. A significant difference in age distribution was detected among PSP, MSA, PD and controls (analysis of variance: $p=0.002$) mainly due to the slightly younger PD group compared to PSP ($p=0.01$) as well as MSA ($p=0.01$). All subjects were Czech native speakers,

and none manifested marked depressive or cognitive deficits that would interfere with the recording procedure. The study was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic (approval number 34/18 Grant AZV VES 2019 1.LF UK) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written, informed consent to the neurological examination and recording procedure.

	PSP (n=20)	MSA (n=25)	PD (n=20)	p-value
General				
Male gender (%)	13 (65)	15 (60)	13 (65)	0.92
Age (years)	67.1 ± 6.2 (54-84)	62.5±6.7 (45-72)	59.1±13.6 (37-81)	0.07
Disease duration* (years)	4.0±1.5 (2-7)	3.9±1.6 (2-7.5)	3.0±1.7 (0.3-6.7)	0.07
Levodopa equivalent (mg/day)	545±501 (0-1500)	371±457 (0-1500)	0	< 0.001 [€]
Amantadine (mg/day)	155±167 (0-500)	82±120 (0-400)	0	< 0.001 [€]
NNIPPS total	69.7±25.4 (19-116)	79.0±23.5 (35-123)	-	0.29
NNIPPS mental function	8.4±4.6 (0-17)	6.8±3.9 (0-14)	-	0.35
MDS-UPDRS III total	-	-	30.3±11.0 (10-53)	-
MDS-UPDRS III speech item	2.0±0.7 (1-3)	1.8±0.6 (1-3)	0.6±0.5 (0-1)	< 0.001 [€]
Dysarthria severity[#]				
None (%)	0	0	2 (10)	0.10
Mild (%)	3 (15) PSP-R, 1 (5) PSP-P	5 (20) MSA-P, 1 (4) MSA-C	16 (80)	< 0.001 [€]
Moderate (%)	7 (35) PSP-R, 1 (5) PSP-PGF	7 (28) MSA-P, 4 (16) MSA-C	2 (10)	0.04 [€]
Severe (%)	7 (35) PSP-R, 1 (5) PSP-P	7 (28) MSA-P, 1 (4) MSA-C	0	0.007 [€]
Dysarthria type[#]				
Hypokinetic (%)	1 (5) PSP-R	4 (16) MSA-P	18 (100)	< 0.001 [€]
Hypokinetic - spastic (%)	7 (35) PSP-R, 1 (5) PSP-P, 1 (5) PSP-PGF	4 (16) MSA-P, 1 (4) MSA-C	0	0.002 [€]
Hypokinetic - ataxic (%)	2 (10) PSP-R	7 (28) MSA-P	0	0.02 [€]
Hypokinetic - spastic - ataxic (%)	6 (30) PSP-R	3 (12) MSA-P, 4 (16) MSA-C	0	0.03 [€]
Ataxic (%)	1 (5) PSP-P	1 (4) MSA-P, 1 (4) MSA-C	0	0.44
Ataxic - spastic (%)	1 (5) PSP-R	0	0	0.32

Data are mean±SD (range) or number (percent) including p-values between PSP, MSA and PD analyzed using Kruskal–Wallis test or number (%) analyzed using Chi-square test.

[€] No significant differences between PSP and MSA groups.

* Based on the self-reported occurrence of first motor symptoms.

[#] Based on perceptual criteria outlined by Darley et al. (1969)¹⁴.

PSP, progressive supranuclear palsy; MSA, multiple system atrophy; PD, Parkinson's disease; MSA-P, multiple system atrophy parkinsonian subtype, MSA-C, multiple system atrophy cerebellar subtype, PSP-R, progressive supranuclear palsy Richardson syndrome, PSP-P, progressive supranuclear palsy parkinsonism, PSP-PGF, progressive supranuclear palsy pure akinesia with gait freezing. NNIPPS, Natural History and Neuroprotection on Parkinson plus syndromes-Parkinson plus scale; MDS-UPDRS, Movement Disorder Society - Unified Parkinson's disease Scale.

Table 1. Patient clinical and demographic characteristics

Speech recording

Speech recordings were performed in a quiet room with a low ambient noise level using a head-mounted condenser microphone (Beyerdynamic Opus 55, Heilbronn, Germany) placed approximately 5 cm from the subject's mouth. Speech signals were sampled at 48 kHz with 16-bit resolution. Each subject was recorded during a single session with a speech specialist. All participants were instructed to perform four vocal tasks of (i) sustained phonation of the vowel /a/ per one breath for as long and steadily as possible, (ii) fast /pa/-/ta/-/ka/ syllable repetition at least seven times per one breath, and (iii) reading a short paragraph of standardized text composed of 80 words, and (iv) monologue on a self-chosen topic for approximately 90 seconds. These speaking tasks were chosen as they can provide comprehensive information necessary for the objective description and interpretation of motor speech disorders³⁵. Sustained phonation, fast syllable repetition and reading passage were performed two times per session for every subject.

Initial acoustic speech features

We performed a quantitative acoustic vocal assessment of 26 distinct speech dimensions related to hypokinetic (19), ataxic (4) and spastic (3) dysarthria with subsystems consisting of respiration (4), phonation (7), articulation (7), prosody and speech timing (8). Acoustic analysis was preferred because it provides objective, sensitive and quantifiable information for the precise assessment of speech performance from very early stages of PD³⁶. Considering hypokinetic dimensions and respiratory features, we obtained relative loudness respiration (RLR), rate of speech respiration (RSR) and pause intervals per

Deviant speech dimension (unit)	Vocal task	Subsystem	Definition	Description
Hypokinetic:				
RLR: Relative loudness of respiration (db)	Mlg	Respiration	Computed as difference between median loudness of respiration and median loudness of speech.	Decreased or increased inspiratory effort.
RSR: Rate of speech respiration (ms)	Mlg+Txt	Respiration	Estimated as median duration between respirations.	Increased rate of speech respiration. Inefficient respiration due to weakness of respiratory muscles or restricted range of movements.
PIR: pause intervals per respiration (respiration/mn)	Mlg+Txt	Respiration	Measured as mean number of pauses between respirations.	Decreased ability to control respiratory airflow.
Jitter (%)	Sustained phonation	Phonation	Short-time fundamental frequency perturbation	Harsh voice
GVI: Gaping in-between voiced intervals (pause/mn)	Mlg+Txt	Phonation	Clear pauses (i.e. pauses in-between voiced speech)	Decreased ability of vocal folds to stop voicing by adduction.
DUS: Duration of stop consonants (ms)	Mlg+Txt	Articulation	Articulatory aspects were quantified for unvoiced fricatives and stop consonants independently	The stability of supra-laryngeal movements and explosion about its preciseness
RFA: Resonance frequency attenuation (db)	Mlg+Txt	Articulation	RFA is measured as the difference between the second formant region and the minima of the local valley.	Acoustic resonances are less prominent due to articulatory imperfections such as mumbling.
EST: Entropy of speech timing (-)	Mlg+Txt	Timing	EST is defined as Shannon entropy applied on incidences of speech intervals.	Limited control and coordination of articulators yield ordered and predictable speech.
RST: Rate of speech timing (intervals/mn)	Mlg+Txt	Timing	RST is defined as the total number of voiced, unvoiced, and pause intervals was accumulated during the time course.	Reduced range of movement disturb the timing and coordination of speech subsystems.
AST: Acceleration of speech timing ($\%/m^2$)	Txt	Timing	Computed as the difference of RST between two overlapping halftimes divided by total time.	The tendency to accelerate speech rate.
stdF0: Standard deviation of fundamental frequency (semitone)	Mlg+Txt	Prosody	The stdF0 is computed as the standard deviation of detected modal F0 in semitones estimated via the median absolute deviation.	Monotone voice, lacking normal pitch and inflection changes
Ataxic:				
stdF0 _v : Pitch fluctuation (semitone)	Sustained phonation	Phonation	The stdF0 is estimated as the standard deviation of the F0.	Irregular or timing deficits of vocal folds vibration.
stdPSD: Standard deviation of the power spectral density (db)	Sustained phonation	Articulation	The stdPSD is calculated as the mean value of the standard deviations in band power	The severity of involuntary movements of articulators.
VD: Vowel duration (ms)	Syllable repetition	Timing	The VD is estimated as the mean duration of detected voiced intervals.	The slowness of repetitive movements with excessive vocal emphasis.
DDKI: Diadochokinetic instability (ms)	Syllable repetition	Timing	The DDKI is estimated as the standard deviation of the measured durations between consecutive voice onsets.	Irregular or timing deficits of repetitive movements.
Spastic:				
PSI: Proportion of sub-harmonic intervals (%)	Sustained phonation	Phonation	PSI is calculated as the ratio between the total duration of sub-harmonic intervals per total duration of voicing.	Changes in the mass or control of vocal folds.
DDKR: Diadochokinetic rate (syllables/s)	Syllable repetition	Articulation	The DDKR is estimated as the inversion of the median duration between consecutive voice onsets.	Abnormally slow motion rate of articulators
NSR: Net speech rate (syllables/s)	Txt	Timing	The total number of syllables was divided by the total duration of speech.	Slowness of individual movements of articulators.

Table 2. List of the initial acoustic features: Mlg = Monologue task. Txt = Reading passage task.

respiration (PIR) via reading passage/monologue. To assess hypokinetic dimensions and phonatory features, we calculated jitter, shimmer and harmonics-to-noise ratio (HNR) via sustained phonation and gaping in-between voiced intervals (GVI) via reading passage/monologue. To examine hypokinetic dimensions and articulatory features, we assessed duration of stop consonants (DUS), resonance frequency attenuation (RFA) via reading passage/monologue, as well as voice onset time (VOT) via syllable repetition. To explore hypokinetic dimensions and timing features, we calculated duration of pause intervals (DPI), entropy of speech timing (EST), rate of speech timing (RST) and acceleration of speech timing (AST) via reading passage/monologue. To investigate hypokinetic features and prosody, we assessed standard deviation of fundamental frequency (stdF0) via reading passage/monologue. Subsequently, ataxic features of pitch fluctuation (stdF0_v; phonation) and standard deviation of the power spectral density (stdPSD; articulation) were examined via sustained phonation which represent phonation and articulation deficits, respectively, while vowel duration (VD; timing) and diadochokinetic instability (DDKI; timing) were assessed via syllable repetition. Finally, three spastic features of proportion of sub-harmonic intervals (PSI; phonation), diadochokinetic rate (DDKR; articulation) and net speech rate (NSR; timing) were calculated via sustained phonation, syllable repetition and reading passage, respectively. The list of initial speech features we used is given in Table 2. Comprehensive algorithmic details on individual acoustics measures have been reported previously³⁷. Also, the accuracy of algorithms for the identification of glottal cycles, temporal intervals, and pitch sequence has been thoroughly tested in previous studies^{22,37,38}.

Design of acoustic indices by subsystem tasks

We first carried out a univariate statistical analysis of the features presented above. This analysis showed that individual features do not lead to an acceptable discrimination performance. We thus considered linear combination of different features as described in the following.

Individual features were first converted to the z-score using the HC mean and standard deviation. For acoustic features in which lower raw scores was associated with greater dysarthria, the z-score was reversed. Thus, higher z-scores were indicating more speech impairment. We then followed a semi-supervised approach to find feature combinations. As our ultimate goal was to design indices that would not be overfitted to our dataset and would allow easy reproducibility, we restricted feature combinations to averaging. Moreover, the designed features were chosen carefully to minimize the potential overlap between subsystem dysarthria in order to achieve a certain orthogonality between indices. For each subsystem task, to find the best

combination of measures for separation between groups (HC vs. MSA, HC vs. PSP and MSA vs. PSP), an exhaustive search over all averages over the acoustic features of that task was performed. The separation performance was measured in term of minimizing the p-value of difference between MSA and PSP groups (threshold of significance was set at $p < 0.05$). Using this search, a combination satisfying this criterion was found only in the articulation subsystem. We thus added an additional step for the other subsystems, we combined the two first averages which yielded the lowest p-value and by multiplying the lowest one by 2 in order to give it more weight as compared to the second lowest. If no statistical significance was achieved, such as in the prosodic and timing subsystems, then average giving the lowest p-value was kept as the feature assessing that subsystem. Different weighting factors were inspired by University of Michigan Classification of different dysarthria subtypes in APS¹⁷. We emphasize that we never used PD data in the design of the new features nor indices. PD data was used a posteriori as "controls" to potentially state the unreliability of a particular new feature or index.

Feature	HC	PD	PSP	MSA	HC vs PD	HC vs PSP	HC vs MSA	PSP vs MSA
	Mean/SD (Range)	Mean/SD (Range)	Mean/SD (Range)	Mean/SD (Range)	p-value	p-value	p-value	p-value
Hypokinetic:								
<i>RLR_m</i>	-24.66/3.80 (-33.09-14.77)	-25.47/3.46 (-30.63-16.72)	-28.35/5.11 (-37.89-18.49)	-27.21/3.47 (-36.25-22.10)	0.28	0.002	0.005	0.26
<i>RSR_m</i>	17.08/4.36 (8.02-33.13)	16.22/4.58 (9.35-26.99)	21.68/5.51 (9.18-34.54)	18.57/4.12 (9.82-24.74)	0.36	0.0004	0.06	0.06
<i>RSR_t</i>	17.03/4.00 (7.41-27.93)	18.11/4.10 (9.23-26.08)	21.48/6.17 (11.68-32.81)	18.63/5.26 (7.09-27.43)	0.38	0.004	0.12	0.18
<i>PIR_m</i>	5.13/1.76 (2.00-13.00)	5.47/2.11 (2.00-12.00)	2.76/1.52 (1.00-6.00)	3.18/1.47 (1.00-6.50)	0.53	0	0	0.26
<i>PIR_t</i>	6.43/1.78 (3.00-13.75)	6.44/1.52 (4.00-10.00)	4.24/2.58 (1.50-11.00)	4.55/1.85 (2.25-10.00)	0.78	0	0	0.33
<i>jitter_a</i>	0.48/0.24 (0.00-2.58)	0.47/0.23 (0.23-1.30)	0.65/0.35 (0.27-1.42)	0.71/0.37 (0.32-1.79)	0.34	0.2	0.0006	0.25
<i>GVI_m</i>	43.53/11.22 (11.45-72.14)	40.58/14.28 (15.32-66.33)	24.97/11.42 (8.66-44.47)	24.06/9.06 (7.94-40.72)	0.41	0	0	0.87
<i>GVI_t</i>	56.50/11.00 (24.90-78.96)	55.66/13.54 (25.91-74.56)	39.78/16.46 (13.84-65.76)	40.20/12.22 (18.64-66.77)	0.96	0	0	0.93
<i>DU_m</i>	25.24/9.89 (13.38-85.38)	29.91/16.60 (17.88-74.12)	48.78/17.40 (22.38-85.38)	39.20/13.61 (17.88-67.38)	0.46	0	0	0.06
<i>DU_t</i>	22.42/7.43 (11.12-66.25)	27.38/14.48 (15.62-73.00)	37.30/13.49 (20.12-62.88)	33.72/16.36 (15.62-92.12)	0.28	0	0.00001	0.23
<i>RFA_m</i>	9.42/1.40 (6.32-13.35)	8.22/1.37 (5.61-10.79)	9.95/1.63 (7.70-14.02)	8.64/1.26 (6.54-10.98)	0.001	0.25	0.013	0.013
<i>RFA_t</i>	10.68/1.54 (7.40-15.76)	9.61/1.22 (7.55-11.18)	11.24/1.78 (8.93-14.97)	10.19/1.25 (7.54-12.57)	0.007	0.25	0.18	0.06
<i>EST_m</i>	1.55/0.01 (1.50-1.58)	1.55/0.01 (1.53-1.56)	1.54/0.01 (1.51-1.56)	1.53/0.02 (1.47-1.56)	0.11	0.012	0.0003	0.62
<i>EST_t</i>	1.55/0.01 (1.50-1.57)	1.55/0.01 (1.53-1.57)	1.54/0.02 (1.49-1.57)	1.54/0.01 (1.52-1.56)	0.58	0.002	0.0007	0.45
<i>RST_m</i>	364.11/60.58 (170.97-511.27)	356.40/82.75 (198.44-524.13)	241.96/86.53 (128.34-410.73)	247.24/76.25 (127.60-411.75)	0.45	0.00001	0	0.73
<i>RST_t</i>	433.34/52.65 (270.35-595.46)	434.83/79.03 (304.48-653.87)	315.13/113.02 (148.11-498.11)	338.58/69.85 (206.45-474.38)	0.91	0.00001	0	0.51
<i>AST</i>	19.37/13.88 (-12.30-56.94)	21.49/14.26 (-8.74-47.81)	8.74/10.47 (-8.23-30.16)	7.15/15.05 (-15.46-40.13)	0.35	0.002	0.0001	0.49
<i>stdF0_m</i>	2.00/0.73 (0.84-6.26)	1.47/0.40 (0.81-2.29)	1.72/0.46 (1.09-2.64)	1.48/0.34 (0.88-2.35)	0.0002	0.1	0.00003	0.16
<i>stdF0_t</i>	2.51/0.75 (0.93-5.80)	1.72/0.60 (0.97-3.16)	1.28/0.27 (0.81-1.91)	1.38/0.51 (0.76-3.23)	0.000004	0	0	0.95
Ataxic:								
<i>stdF0_a</i>	0.35/0.24 (0.11-2.00)	0.36/0.28 (0.13-1.38)	0.50/0.30 (0.16-1.08)	0.69/0.25 (0.28-1.14)	0.85	0.02	0	0.01
<i>stdPSD_a</i>	2.22/0.39 (1.37-3.48)	2.12/0.37 (1.41-3.04)	2.22/0.34 (1.65-2.91)	2.56/0.42 (1.85-3.96)	0.36	0.97	0.0004	0.06
<i>VD_a</i>	49.63/9.82 (28.16-86.72)	50.38/9.45 (37.88-74.56)	95.08/52.53 (44.34-221.91)	73.96/21.67 (38.03-116.88)	0.89	0.000002	0.000001	0.4
<i>DDKI_a</i>	22.50/11.82 (8.37-86.02)	26.90/12.05 (10.02-47.57)	85.75/55.11 (11.04-215.26)	63.85/29.47 (22.85-119.87)	0.1	0	0	0.29
Spastic:								
<i>PSI_a</i>	4.96/10.06 (0.00-71.64)	6.24/9.35 (0.00-35.70)	11.51/15.06 (0.00-55.02)	10.69/13.02 (0.00-55.87)	0.4	0.2	0.003	0.55
<i>DKR_s</i>	6.45/0.72 (3.97-8.51)	6.61/0.78 (5.26-8.19)	4.93/1.44 (2.31-7.78)	5.35/0.94 (3.52-7.23)	0.35	0.000007	0.000001	0.18
<i>NSR_t</i>	2.41/0.27 (1.67-3.17)	2.43/0.28 (1.98-2.99)	2.04/0.60 (1.01-3.61)	2.14/0.39 (1.24-2.82)	0.94	0.0003	0.0009	0.4

Table 3. Statistical difference between groups. Bold numbers indicate significant differences ($p < 0.05$). Only features which yielded a significant difference between at least two groups are reported. Subscripts *a*, *s*, *m* and *t* indicate that the feature is computed using sustained /a/, syllable repetition, monologue and reading passage, respectively.

Using the scheme described above, for each subsystem task we ended up with the following features for each subsystem:

- **Respiration subsystem:**

$$F_{resp} = \frac{1}{2} \left(\frac{RLR_m + RLR_t + PIR_m + PIR_t}{4} + RSR_m + RSR_t \right)$$

Hence, more weight/importance is given to *RSR* than *RLR* and *PIR* in the design of F_{resp} , by a factor of 2.

- **Phonation subsystem:**

$$F_{phon} = \frac{1}{2} \left(\frac{Jitter + GVI_m + GVI_t}{3} + 2stdF0_a \right)$$

Hence, more weight/importance is given to $stdF0_a$ than *Jitter* and *GVI* in the design of F_{phon} , by a factor of 2.

- **Articulation subsystem:**

$$F_{art} = \frac{RFA_m + RFA_t + stdPSD}{3}$$

- **Prosodic subsystem:**

$$F_{pros} = \frac{stdF0_m + stdF0_t}{2}$$

- **Timing subsystem:**

$$F_{time} = \frac{EST_m + RST_m + AST_t}{3}$$

These new features showed interesting behaviour in term of statistical difference between groups, however they could not achieve a good classification accuracy, neither individually nor by a bivariate analysis where a classification was performed by considering a 2-dimensional input space with a feature in one dimension and another one in the second. We then grouped (and

combined) the features in term of the class of impairment predominance. That is, the features reflecting an impairment which is more predominant in PSP (resp. MSA) are linearly combined by giving more weight to the feature showing the most significant impairment in PSP (resp. MSA). This led us to define 2 new speech subsystem indices (SSI) as:

- SSI_1 as a combination of the 3 features F_{resp}, F_{pros}, DUS where we put more emphasize on the feature F_{resp} :

$$SSI_1 = F_{resp} + \frac{DUS_m}{2} + \frac{F_{pros}}{2},$$

- and SSI_2 as a combination of the 3 features $F_{art}, F_{phon}, F_{time}$ where we put more emphasize on the feature F_{art} :

$$SSI_2 = F_{art} + \frac{F_{phon}}{2} + \frac{F_{time}}{2}.$$

Note that while DUS_m and F_{art} both assess the articulation subsystem, they actually capture distinct articulation mechanisms. Finally, we defined the composite speech subsystem index (CSSI) as the vector:

$$CSSI = (SSI_1, SSI_2).$$

Design of acoustic indices by dysarthria type

After designing the 2 acoustic indices based on subsystem tasks, we used the findings to develop new indices which can be associated with subtypes of dysarthria. To do so, we first observed that SSI_1 can be seen as an hypokinetic feature, we rename it then $H1$:

$$H1 = SSI_1 = F_{resp} + \frac{DUS_m}{2} + \frac{F_{pros}}{2}$$

As for SSI_2 , it is a combination of an hypokinetic feature $H2$ and an ataxic one $A2$:

$$H2 = H_{art} + \frac{H_{phon}}{2} + \frac{H_{time}}{2},$$

where H_{art} , H_{phon} and H_{time} are hypokinetic articulation, phonation and timing features respectively: $H_{art} = \frac{RFA_m + RFA_t}{2}$, $H_{phon} = \frac{Jitter + GVI_m + GVI_t}{3}$, $H_{time} = \frac{EST_m + RST_m + AST_t}{3}$, and

$$A2 = \frac{stdF0_a + stdPSD}{2}.$$

We then looked whether we could design other distinctive features related to particular dysarthria types. To do so, first we observe that $A2$ is obtained from the sustained phonation task only. On the other hand, it is known that syllables repetition is a fertile task to detect ataxic impairments. Following the same methodology as in subsystem feature design, we ended up defining an ataxic feature $A1$ which reflects a higher impairment in PSP:

$$A1 = \frac{VD + DDKI}{2}.$$

Similarly, there is a relative consensus that PSP develop spastic dysarthria. We thus defined a spastic feature $S1$ as:

$$S1 = \frac{1}{2} \left(\frac{NSR + DDKR}{2} + PSI \right).$$

This led us to define 2 dysarthria type indices (DTI) as:

$$DTI_1 = H1 + \frac{A1 + S1}{2}$$

and

$$DTI_2 = H2 + A2.$$

Finally, we defined the composite dysarthria type index (CDTI) as the vector:

$$CDTI = (DTI_1, DTI_2).$$

Statistical analysis

All analyses were performed in Python. The final speech values from the first and second run of sustained phonation, syllable repetition and reading task were averaged to provide greater stability of speech assessment³⁵. The one-sample Kolmogorov–Smirnov test was used to evaluate the normality of distributions; the majority of acoustic features were found to be normally distributed. Group differences were calculated using analysis of variance for normally distributed data and the Kruskal–Wallis test for non-normally distributed data with the possible presence of outliers. A post hoc Tukey’s test was then applied to find differences between individual groups (HC vs. PD, HC vs. PSP, HC vs. MSA, PSP vs. MSA). Pearson and Spearman correlations were applied to test for significant relationships between normally and non-normally distributed data, respectively.

An overall indication of diagnostic accuracy was reported as the area under the curve (AUC), which we obtained from the receiver operating characteristic curve. The classification performance (sensitivity/specificity) of differentiating between groups was calculated using binary logistic regression with leave-one-speaker-out (LOSO) cross-validation. In PSP vs. MSA classification, the PSP group is considered as the positive label. In PD vs PSP/MSA classification, the PSP/MSA group is considered as the positive label.

Results

Univariate statistical analysis

The overview of methodology and major findings can be seen in Figure 1 (Supplementary Audio S1-S4). Univariate statistical analysis of the initial acoustic features is shown in Table 3. Only 2 features yielded individually a significant group difference between PSP and MSA, $stdF0_a$ and RFA_m ($p \sim 0.01$). DUS_m , $stdPSD$ and RFA_t approached significant group difference with $p \sim 0.06$. However, classification accuracy was poor using these features individually.

The result of the statistical analysis of the designed subsystem features is illustrated in Figure 2. The comparison between groups using F_{resp} is shown in Figure 2(a). Using this feature, a respiration deficit is reflected in both MSA and PSP, the latter showed however a greater severity compared to MSA ($p < 0.05$). As shown in Figure 2(b), we found that both MSA and PSP develop a significant phonation impairment as measured by F_{phon} ($p < 0.00001$ when compared to HC). However, this impairment was more pronounced for MSA ($p = 0.08$ for MSA vs. PSP). Using the articulation feature F_{art} , we did not find a statistical significance between PSP and HC as shown in Figure 2(c), suggesting that F_{art} does not capture a particular articulation impairment in PSP (this does not mean that PSP do not develop articulation impairment in general). On the other hand, we found that it reflects a significant articulation impairment in MSA ($p < 0.0001$ compared to both PSP and HC). We did not find group difference between PSP and MSA using F_{pros} , as illustrated in 2(d). However, as could be expected, we found that monopitch (measured by F_{pros}) was prominent not only for PSP and MSA but also for PD, ($p < 0.00001$ compared to HC). We did not find group difference between PSP and MSA using F_{time} , as illustrated in 2(e). However, timing deficit (measured by F_{time}) showed a severe impairment for PSP and MSA, as compared to HC ($p < 0.00001$) and PD ($p < 0.0001$).

The result of the statistical analysis of the designed indices is illustrated in Figure 3. Using the index SSI_1 , the impairment is more predominant in PSP as shown in Figure 3(a). Moreover, the SSI_1 yields a mutual statistically significant difference between all pairs of groups. We recall here that we did not use neither PD nor HC data in the design process. This indicates that SSI_1 has a strong potential in the discrimination between all groups. Using the index SSI_2 , the impairment is more predominant in MSA as shown in Figure 3(b). However, it does not select a particular impairment of PD. Using the index DTI_1 , the impairment is more predominant in PSP as shown in Figure 3(c). Moreover, as SSI_1 , DTI_1 yields a mutual statistically significant difference between all pairs of groups. This indicates that DTI_1 has also a strong potential in the discrimination between all groups. Using the index DTI_2 , the impairment is more predominant in MSA as shown in Figure 3(d). Moreover, DTI_2 yields a mutual statistically significant difference between all pairs of groups, except between PD and PSP.

Bivariate classification analysis

Figure 4(a) (resp. (b)) displays the 2-dimensional distribution of the subsystem indices SSI_1 and SSI_2 (resp. DTI_1 and DTI_2). One can visually observe that both representations achieved a good mutual separation between PD, MSA and PSP groups. Table 4 shows the scores of classification between PSP and MSA using all indices. Individual indices did not give a good classification performance. However, the composite indices, $CSSI$ and $CDTI$, yielded a high classification performance, thanks to the orthogonality incorporated in their design. $CSSI$ gave very good classification scores (84%) which is already significantly higher than accuracies reported in the literature. $CDTI$ yielded an even higher performance ($> 88\%$) showing that including prior knowledge on predominant dysarthria types in PSP and MSA does indeed improve the discriminative power.

Table 5 shows the scores of classification between PD and MSA. Individual indices yielded a relatively low specificity, except DTI_2 . However, the composite indices, $CSSI$ and $CDTI$, yielded a high classification performance. Table 6 shows the scores of classification between PD and PSP. Here, DTI_1 alone yield a high classification performance. We recall that PD data

was not used in the design of the features and indices. These results can be thus seen as an additional posterior validation of the pertinence of our approach.

Feature	AUC	Accuracy (%)	Specificity (%)	Sensitivity (%)
<i>SSI</i> ₁	0.68	72.7	80.0	63.1
<i>SSI</i> ₂	0.72	70.4	92.0	42.1
CSSI	0.82	84.0	84.0	84.2
<i>DTI</i> ₁	0.65	75.0	96.0	47.3
<i>DTI</i> ₂	0.74	70.4	92.0	42.1
CDTI	0.89	88.6	88.0	89.4

Table 4. Classification accuracy between PSP and MSA

Feature	AUC	Accuracy (%)	Specificity (%)	Sensitivity (%)
<i>SSI</i> ₁	0.73	71.1	65.0	76.0
<i>SSI</i> ₂	0.88	84.4	75.0	92.0
CSSI	0.88	86.6	85.0	88.0
<i>DTI</i> ₁	0.88	84.4	75.0	92.0
<i>DTI</i> ₂	0.87	82.2	80.0	84.0
CDTI	0.91	86.6	85.0	88.0

Table 5. Classification accuracy between PD and MSA

Feature	AUC	Accuracy (%)	Specificity (%)	Sensitivity (%)
<i>SSI</i> ₁	0.85	79.5	80.0	78.9
<i>SSI</i> ₂	0.51	56.4	95.0	15.8
CSSI	0.85	82.0	75.0	89.4
DTI ₁	0.92	87.1	90.0	84.2
<i>DTI</i> ₂	0.46	51.2	100	5.2
<i>CDTI</i>	0.90	84.6	85.0	84.2

Table 6. Classification accuracy between PD and PSP

Relation between speech and motor manifestations

The correlations between the speech indices and bradykinesia/rigidity, bulbar, cerebellar and overall NNIPPS scores in the APS (PSP+MSA) group are shown in Table 7. The overall NNIPPS score was related to the indices *SSI*₂ and *DTI*₂ ($r = 0.5, p < 0.01$). These two indices also showed strong correlation with the bradykinesia/rigidity and cerebellar NNIPPS subscores ($r \sim 0.5, p < 0.01$). They were not however correlated to the bulbar subscore. No correlation were detected between the NNIPPS (sub)scores and the indices *SSI*₁ and *DTI*₁.

Discussion

Our findings indicate that speech disorders reflect the differing underlying pathophysiology of tauopathy in PSP and α -synucleinopathy in MSA. The combination of distinct speech patterns via objective acoustic evaluation was able to discriminate between PSP and MSA with a very high accuracy of up to 88.6%, though the difference was not perceptually identifiable using the UPDRS III speech item. This is in accordance with systematic perceptual assessment, which was not able to distinguish between the speech of PSP and MSA³⁹. To the best of our knowledge, this is the best accuracy reported in the literature concerning speech-based discrimination between two APS with diverging pathophysiology. Although PD data was not used in training, our approach also separated both PSP and MSA from PD with an accuracy of up to 87%, reflecting the fact that dysarthria severity was considerably higher in APS than PD. This finding is consistent with previous studies showing that, at mid/late stages, APS can be distinguished from PD by speech deterioration severity using both perceptual and acoustic analysis^{13,39}. The greater severity of dysarthria in APS was reflected likely because early-stage PD patients manifest

Speech index / NNIPPS score and subscores	Bradykinesia/Rigidity	Bulbar	Cerebellar	NNIPPS score
<i>SSI</i> ₁	-0.05	0.18	-0.2	-0.06
<i>SSI</i> ₂	0.52**	0.18	0.48**	0.5**
<i>DTI</i> ₁	0.02	0.25	-0.16	0.15
<i>DTI</i> ₂	0.53**	0.16	0.49**	0.51**

Table 7. Correlations between speech and clinical motor indices. Statistically significant differences between groups: * $p < 0.05$, ** $p < 0.01$.

pure hypokinetic dysarthria⁴⁰, whereas APS patients had dysarthria with different combinations of hypokinesia, ataxia, or spasticity^{16,17}.

Speech features related to respiratory dysfunction, imprecise consonants, and monopitch, assessed via the *SSI*₁ dimension, contributed to worse performance in PSP than MSA. The influence of respiratory dysfunction on speech was not yet systematically studied. However, it is well known that patients with PSP have profound impairment of voluntary respiratory control⁴¹. In addition, PSP patients had significantly more frequent respiratory infections and respiratory-related deaths when compared to PD patients⁴². Voiceless consonant abnormalities in PSP have also been reported and associated with perceptual severity of dysarthria²⁹. Although a similar extent of monotone speech was found in both PSP and MSA, the distinguishing accuracy of pitch variability might be attributed to wider performance variability in MSA due to more frequent ataxic components causing excessive pitch fluctuations^{17,18}, as compared to the typical occurrence of hypokinetic and spastic elements of dysarthria in PSP^{16,43}. The relevance of spastic speech components in PSP was further underlined by findings of slow speaking rate and subharmonics that contributed to discrimination accuracy between PSP and MSA via the *DTI*₁ dimension. Both slow speaking rate and subharmonics are considered to be the core features encountered in spastic dysarthria as a result of more widespread neuronal atrophy^{44,45}. In particular, the relation between slow articulation rate and bilateral white and grey matter volume loss was observed in patients with progressive spastic dysarthria⁴⁶ and patients with multiple sclerosis with predominant spastic-ataxic dysarthria⁴⁷. Surprisingly, ataxic features reflecting higher diadochokinetic irregularity and prolonged phonemes were affected on average more in PSP than MSA. While the longer phonemes may reflect a slower diadochokinetic rate, the slightly higher diadochokinetic irregularity in PSP might be simply caused by a higher number of patients with severe dysarthria (40% in PSP vs. 32% in MSA), which appear to be the main significant factor influencing oral diadochokinetic performance^{48,49}. Another possible explanation is that cerebellar characteristics in PSP may be related to the high concentration of tau-protein deposits in the brainstem where the cerebello-thalamo-cortical and cortico-ponto-cerebellar pathways pass⁵⁰.

The phonation and timing abnormalities and articulatory decay generally contributed to worse performance in MSA compared to PSP via both *SSI*₂ and *DTI*₂ indices. Our findings demonstrate overall poorer voice control in MSA, typically manifested as the strained-strangled voice that may give the perceptual impression of quivery-croaky strained speech with increased pitch¹⁸. This observation is generally in agreement with a recent study showing that 93% of patients with MSA manifested laryngeal dysfunction during an endoscopic task, in contrast with only 1.8% of patients with PD⁵¹. The slightly worse performance in articulatory decay in MSA than PSP might be attributed to more distorted vowels that are more common in ataxic dysarthria^{45,52}. Timing abnormalities were relatively non-specific and affected to a similar extent in both PSP and MSA; however, some timing abnormalities in individual MSA patients might still contribute to discrimination accuracy together with phonatory and articulatory dysfunction.

In patients with APS, an overlap of individual speech features among dysarthria subtypes can be expected⁴⁵, which makes the correct recognition of a specific dysarthria subtype challenging. Although we strived to separate hypokinetic, ataxic and spastic components of dysarthria as much as possible to eliminate most of this overlap, some dysarthric manifestations may still originate from different neuronal dysfunctions and more than anticipated. For instance, subharmonics may arise due to the involvement of the corticobulbar pathways but also cerebellum and basal ganglia. In particular, variation in speech severity within a dysarthria subtype may explain as much variance in acoustic or perceptual data as variation across dysarthria type⁵³. This assumption was further confirmed by the relationships revealed only between *SSI*₂ and *DTI*₂ dysarthria indexes and overall disease severity by NNIPPS, with no specific correlations observed between hypokinetic, ataxic and spastic speech dimensions and bradykinesia/rigidity, ataxia, and bulbar motor manifestations, respectively.

Our findings are based on sophisticated acoustic analyses, which might limit their application to movement disorders specialists or general neurologists. On the other hand, the majority of applied acoustic features correspond to the main perceptual dimensions encountered in dysarthria of parkinsonism (Figure 1)^{16,17}, and therefore we believe experience clinicians can still profit from the knowledge of distinctive speech characteristics revealed in the present study. In addition, the fully-automated Dysarthria Analyzer used in this study remains under development, but the free beta version is already available⁵⁴. The most of investigated speech features can also be analyzed using widely-used, freely-available Praat software, although hand-labelling or

additional user control of the analysis is required for some features. Last but not least, the detailed protocol on speech tasks and speech metrics used in this study has already been published within a recent guideline for speech recording and acoustic analyses in dysarthrias of movement disorders³⁵.

One potential limitation of the present study is that we did not differentiate between speech in the various subtypes of PSP and MSA due to the limited opportunity to recruit a larger number of participants via a single center. According to the previous research, it appears that different subtypes of disease have no substantial effect on individual acoustic features²¹, although more perceptual ataxic abnormalities can be observed in MSA cerebellar subtype compared to parkinsonian subtype³¹. In our study, patients with MSA cerebellar subtype had mostly all components of dysarthria affected and thus did not principally differ from type of dysarthria observed in MSA parkinsonian subtype. Another limitation is that we did not perform additional testing including cerebrospinal fluid biomarkers and radionuclide scanning to improve the accuracy of clinical diagnosis. Also, our results are based on participants recruited from a single centre and thus might not be universal among races. Future research is warranted to confirm and extend our findings via international collaborative effort leading to involvement of different languages and various racial groups. Finally, we did not investigate loudness of speech, which is an important distinguishing feature of hypokinetic dysarthria, because of the need for precise microphone calibration to obtain reliable estimates via acoustic analysis.

In conclusion, our findings highlight that detailed speech analysis can be used as a potential diagnostic screening tool to distinguish between PSP, MSA, and PD. Therefore, this study can become the basis for future multicenter studies in parkinsonism with speech testing. Future studies based on the earlier stages of the disease and potentially accompanied by longitudinal assessment should further elaborate and extend our findings and show the sensitivity of speech investigation in the differentiation between APS. Since the speech impairment in PD appears to be a progressive biomarker that reflects dopaminergic treatment response⁴⁰ and progression in APS is more rapid and less responsive to L-dopa therapy³, longitudinal in-home assessment over a short period could substantially improve our reported sensitivity of speech-based evaluation. As a result, a vocal assessment may provide a no-cost alternative screening method to existing clinical and imaging diagnostic approaches.

Competing interests

The Authors declare no Competing Financial or Non-Financial interests.

Data availability

Individual participant data that underlie the findings of this study are available upon reasonable request from the corresponding author. The speech data are not publicly available due to their contain of information that could compromise the privacy of study participants.

Code availability

The analyses were performed using a publicly available Dysarthria Analyzer (Czech Technical University in Prague, available at <http://dysan.cz/>).

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Author contributions

Research project: (A) Conception: K.D. and J.R. (B) Organization: K.D. and J.R. (C) Execution: K.D., B.D., J.K., T.T., and J.R. Statistical analysis: (A) Design: K.D. (B) Execution: K.D. and B.D. (C) Review and critique: B.D., J.K., T.T., and J.R. Manuscript preparation: (A) Writing of the first draft: K.D. and J.R. (B) Review and critique: B.D., J.K., and T.T.

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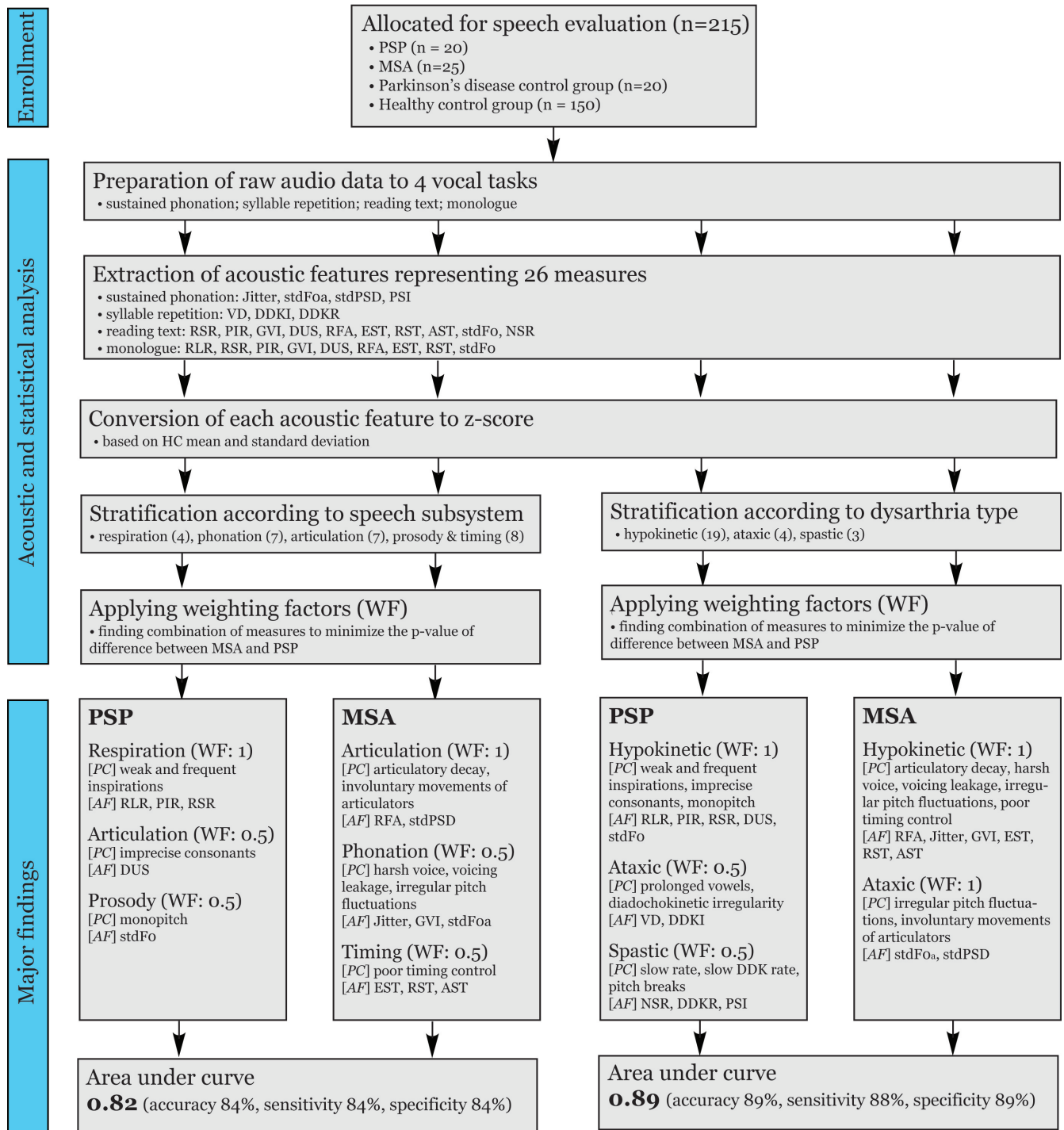


Figure 1. Scheme chart depicting the methodology and major findings.

[PC] hypothesized perceptual correlates.

[AF] acoustic features.

WF = weighting factor, RLR = relative loudness of respiration, PIR = pause intervals per respiration, RSR = rate of speech respiration, DUS = duration of stop consonants, stdFo = standard deviation of fundamental frequency, RFA = resonant frequency attenuation, stdPSD = standard deviation of the power spectral density, GVI = gapping in-between voiced intervals, stdFoa = pitch fluctuations, EST = entropy of speech timing, RST = rate of speech timing, AST = acceleration of speech timing, VD = vowel duration, DDKI = diadochokinetic instability, NSR = net speech rate, DDKR = diadochokinetic rate, PSI = proportion of sub-harmonic intervals, PSP = progressive supranuclear palsy, MSA = multiple system atrophy.

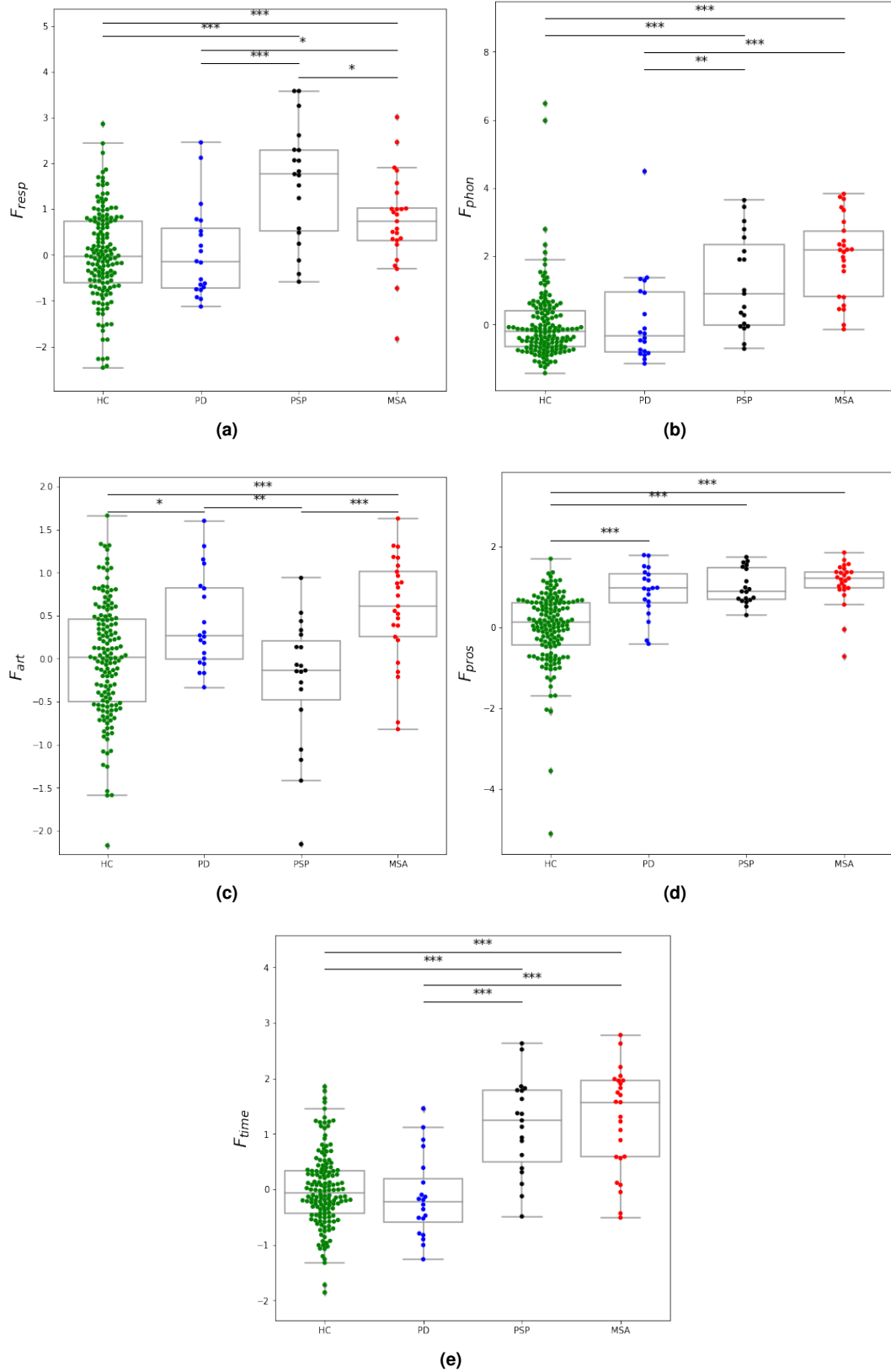


Figure 2. Boxplots of the distribution across groups of subsystem features: (a) F_{resp} = respiration feature; (b) F_{phon} = phonation feature; (c) F_{art} = articulation feature; (d) F_{pros} = prosodic feature; (e) F_{time} = timing feature. HC = healthy controls, PD = Parkinson's disease, MSA = multiple system atrophy, PSP = progressive supranuclear palsy. Statistically significant differences between groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

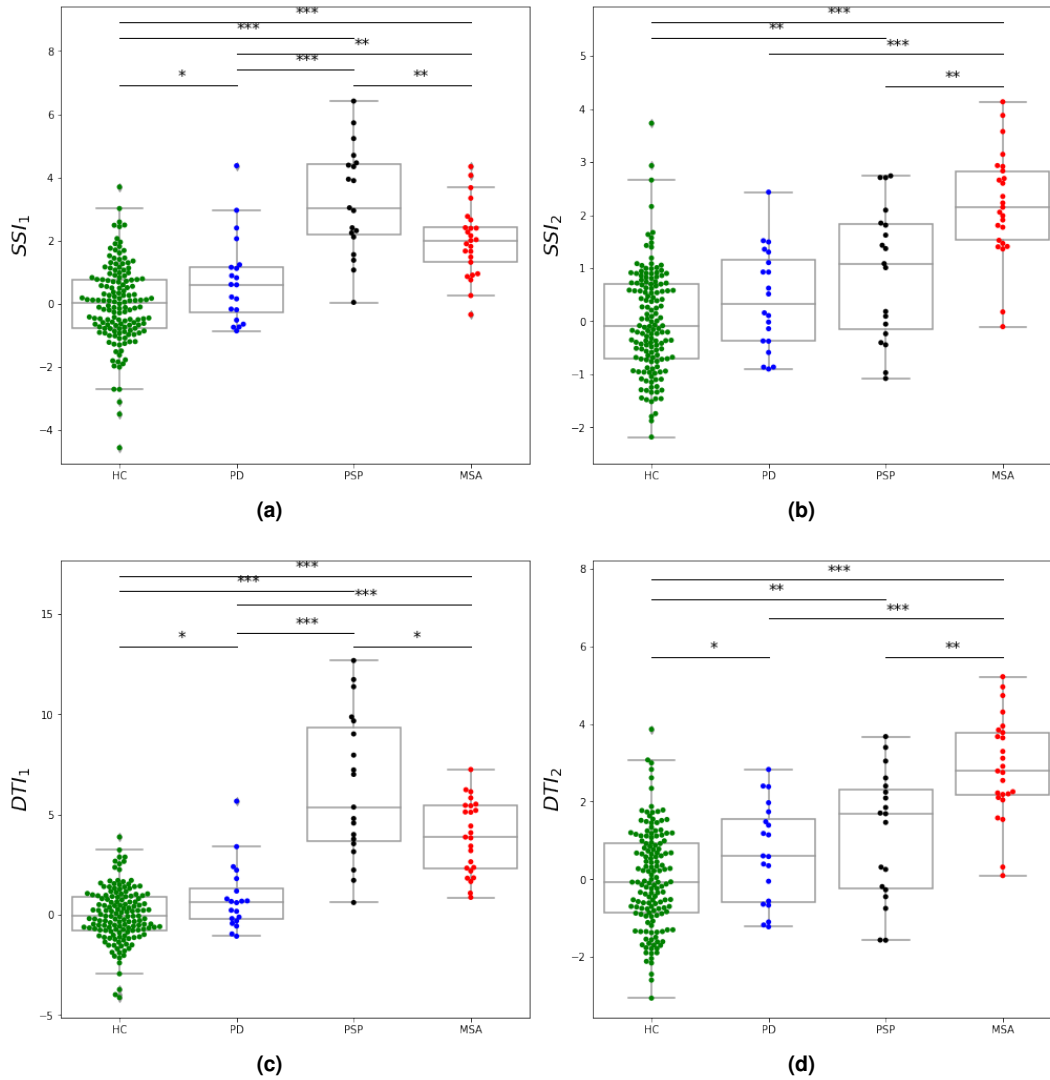


Figure 3. Boxplots of the distribution across groups of subsystem and dysarthria type indices. (a) SSI_1 = first subsystem index; (b) SSI_2 = second subsystem index; (c) DTI_1 = first dysarthria type index; (d) DTI_2 = second dysarthria type index. HC = healthy controls, PD = Parkinson's disease, MSA = multiple system atrophy, PSP = progressive supranuclear palsy. Statistically significant differences between groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

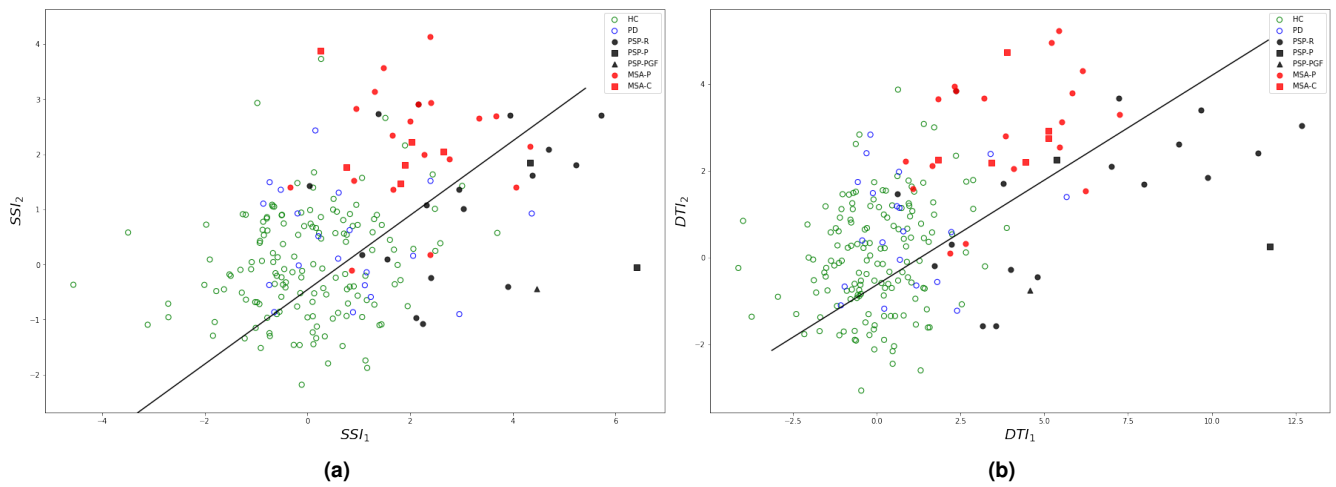


Figure 4. Two-dimensional projection of all subjects over the indices: (a) using the subsystem indices SSI_1 and SSI_2 , (b) using the dysarthria type indices DTI_1 and DTI_2 . The black line is the logistic regression boundary for the classification between PSP and MSA using all data.