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ORIGINAL COMMUNICATION

Distinctive speech signature in cerebellar and parkinsonian subtypes of multiple system atrophy

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Abstract

Although motor speech disorders represent an early and prominent clinical feature of multiple system atrophy (MSA), the potential usefulness of speech assessment as a diagnostic tool has not yet been explored. This cross-sectional study aimed to provide a comprehensive, objective description of motor speech function in the parkinsonian (MSA-P) and cerebellar (MSA-C) variants of MSA. Speech samples were acquired from 80 participants including 18 MSA-P, 22 MSA-C, 20 Parkinson's disease (PD), and 20 healthy controls. The accurate differential diagnosis of dysarthria subtypes was based on quantitative acoustic analysis of 14 speech dimensions. A mixed type of dysarthria involving hypokinetic, ataxic and spastic components was found in the majority of MSA patients independent of phenotype. MSA-P showed significantly greater speech impairment than PD, and predominantly exhibited harsh voice, imprecise consonants, articulatory decay, monopitch, excess pitch fluctuation and pitch breaks. MSA-C was dominated by prolonged phonemes, audible inspirations and voice stoppages. Inappropriate silences, irregular motion rates and overall slowness of speech were present in both MSA phenotypes. Speech features allowed discrimination between MSA-P and PD as well as between both MSA phenotypes with an area under curve up to 0.86. Hypokinetic, ataxic and spastic dysarthria components in MSA were correlated to the clinical evaluation of rigidity, cerebellar and bulbar/pseudobulbar manifestations, respectively. Distinctive speech alterations reflect underlying pathophysiology in MSA. Objective speech assessment may provide an inexpensive and widely applicable screening instrument for differentiation of MSA and PD from controls and among subtypes of MSA.

Keywords Multiple system atrophy · Parkinson's disease · Atypical parkinsonism · Dysarthria · Speech disorder · Acoustic analyses

Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset, fatal neurodegenerative disease characterized by progressive autonomic failure, parkinsonian features, and any combination of cerebellar and pyramidal features [1]. Patients with MSA are clinically classified as parkinsonian variant (MSA-P) if parkinsonism is the predominant feature and as cerebellar variant (MSA-C) if cerebellar features predominate [2]. Due to variable clinical manifestations, MSA presents a major diagnostic challenge as it may masquerade as Parkinson's disease (PD) or idiopathic late-onset cerebellar ataxia until advanced stages of the disease. Therefore, reliable screening instruments are pivotal as an accurate diagnosis of MSA has important prognostic and therapeutic implications.

As the most complex human motor skill, speech is a sensitive marker of damage to neural structures engaged in motor system control [3]. Speech abnormalities develop in the majority of patients with parkinsonism [4, 5], and represent one of the first prodromal markers of motor dysfunction [6, 7]. MSA patients typically develop mixed dysarthria with various combinations of hypokinetic, spastic and ataxic components [5]. Unfortunately, complex investigation of speech disorder in MSA has rarely been performed and

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limited to perceptual assessment [5, 8]. Only a few studies have provided objective descriptions of specific dysarthria manifestations in MSA [9–14]. Dysarthria in MSA has been reported to be more pronounced than in PD and characterized by excess pitch fluctuations, excess loudness variations, increased voice pitch, slow rate, imprecise consonant articulation, prolonged phonemes, vocal tremor, and strained-strangled voice [9–14]. Nothing, however, is known so far about the prevalence and patterns of abnormal speech features in the different phenotypes of MSA and their relation to clinical features. Moreover, speech-based differentiation between MSA phenotypes may be challenging as a substantial overlap of speech abnormalities across different dysarthria subtypes can be expected [5, 15, 16].

Therefore, we quantitatively assessed 14 speech dimensions by objective acoustic analyses to determine specific dysarthric patterns and estimate their reliability in differentiating among PD and both subtypes of MSA. We hypothesized that quantitative acoustic measures would be affected differently between PD, MSA-P, and MSA-C. An additional aim was to explore the relationship between speech and clinical motor manifestations to provide more insights into the pathophysiology of dysarthria in MSA. We hypothesized that the extent of bradykinesia and rigidity would be related to the severity of hypokinetic dysarthria elements, cerebellar clinical manifestations to ataxic dysarthria components, and bulbar/pseudobulbar clinical signs to spastic dysarthria dimensions.

Methods

Participants

From 2015 to 2018, 40 consecutive patients with a clinical diagnosis of probable MSA were recruited for the current study. In this cohort, 22 patients (12 men) were diagnosed with MSA-C and 18 (9 men) with MSA-P. In addition, 20 patients with idiopathic PD (11 men) were recruited to match the MSA groups according to disease duration, age, gender, and cognitive status. A healthy control (HC) group consisting of 20 participants comparable for gender distribution (11 men) and age (mean 62.3, standard deviation 6.7, range 47–73 years) with no history of neurological or communication disorders was also included. All participants were native Italian speakers.

The diagnosis of MSA was established by the consensus diagnostic criteria for MSA [2], whereas the diagnosis of PD was based on the UK Parkinson's Disease Society Bank Criteria [17]. The diagnosis was confirmed by a neurologist with experience in movement disorders (M.T.P.). The presence of dysarthria was not considered as a part of the inclusion criteria as the acoustic analyses have the potential to reveal subperceptual speech deviations [16]. Disease duration was estimated based on the self-reported occurrence of first motor symptoms. MSA patients were rated by the Natural History of Neuroprotection in Parkinson plus syndromes-Parkinson plus scale (NNIPPS) [18], while PD patients were scored according to the motor subscore of Unified Parkinson's Disease Rating Scale (UPDRS III). The NNIPPS scale was chosen as it allows evaluating all clinical symptoms encountered in parkinsonism that may potentially influence speech production. Parkinsonian features in both MSA and PD patients were treated with levodopa alone or in combination with dopamine agonists and/or amantadine. All patients were investigated in the on-drug state. No participants received antipsychotic medication.

The dysarthria presence, type, and severity estimates were based on the auditory-perceptual judgment of a speech-language pathologist experienced in movement disorders. The judgment was based on offline audio recordings including vowel prolongation, sequential motion rates, and connected speech following the perceptual criteria outlined by Darley et al. [19, 20]. In addition, perceptual speech severity was estimated for all patients using speech item of the UPDRS III (item 18). Detailed patient characteristics are listed in Table 1.

Speech examination

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 participant's mouth. Speech signals were sampled at 48 kHz with 16-bit resolution. Each participant was recorded during a single session. All participants were instructed to perform three vocal tasks of (i) sustained phonation of the vowel /a/ per one breath for as long and steadily as possible, (ii) rapid /pa/-/ta/-/ka/ syllable repetition at least seven times per one breath (oral diadochokinesis), and (iii) monologue on a given topic for approximately 90 s. These three speaking tasks were chosen as they can provide most of the information necessary for the objective description and interpretation of motor speech disorders [15]. Sustained phonation and syllable repetition paradigms were repeated two times for every participant.

Speech analyses

The primary outcome represented the assessment of the hypokinetic dysarthria index, ataxic dysarthria index, spastic dysarthria index and overall dysarthria index. These dysarthria indexes were based upon the quantitative acoustic analysis, which provides objective, sensitive and quantifiable information for the precise assessment of speech performance. We selected 14 individual speech dimensions,

Table 1 Clinical characteristics of patients

	PD ($n=20$)	MSA-P ($n=18$)	MSA-C ($n=22$)	p value
General				
Mean age (years)	63.0 (SD 8.6, range 45–77)	63.6 (SD 7.9, range 45–75)	62.7 (SD 6.5, range 51–78)	0.75
Disease duration (years)	4.0 (SD 2.4, range 1–9)	4.0 (SD 1.7, range 1.5–8)	3.6 (SD 1.8, range 1–7)	0.67
MMSE	26.4 (SD 3.5, range 18–30)	24.7 (SD 3.2, range 18–29)	25.2 (SD 3.3, range 17–30)	0.27
L-dopa equivalent (mg/day)	317 (SD 156, range 0–520)	431 (SD 315, range 0–1200)	141 (SD 268, range 0–1000)	$<0.01^{b,c}$
UPDRS speech item 18	0.75 (SD 0.55, range 0–2)	1.78 (SD 0.88, range 1–3)	1.73 (SD 0.77, range 0–3)	$<0.001^{a,b}$
UPDRS III motor score	16.4 (SD 7.2, range 6–28)			
Male (%)	55 ($n=11$)	50 ($n=9$)	55 ($n=12$)	0.94
L-dopa therapy (%)	90 ($n=18$)	83 ($n=15$)	32 ($n=7$)	$<0.001^{b,c}$
Amantadine therapy (%)	0 ($n=0$)	6 ($n=1$)	9 ($n=2$)	0.40
Antidepressant therapy (%)	25 ($n=5$)	44 ($n=8$)	18 ($n=4$)	0.18
NNIPPS				
Overall score		100 (SD 40, range 35–167)	74 (SD 18, range 44–103)	0.05
Bradykinesia		26.9 (SD 13.9, range 4–47)	20.5 (SD 9.1, range 2–34)	0.15
Bulbar/pseudobulbar		9.2 (SD 4.1, range 2–16)	7.8 (SD 2.3, range 3–12)	0.28
Cerebellar		5.6 (SD 4.0, range 0–13)	5.9 (SD 3.1, range 1–12)	0.62
Pyramidal		1.4 (SD 0.8, range 0–3)	1.1 (SD 0.9, range 0–3)	0.23
Rigidity		7.7 (SD 3.5, range 1–14)	2.4 (SD 1.8, range 0–7)	$<0.001^{c}$
Tremor		5.2 (SD 4.0, range 0–13)	1.9 (SD 2.1, range 0–7)	$<0.01^{c}$
Dysarthria severity				
None (%)	15 ($n=3$)	0 ($n=0$)	0 ($n=0$)	0.05
Mild (%)	80 ($n=16$)	22 ($n=4$)	27 ($n=6$)	$<0.01^{a,b}$
Moderate (%)	5 ($n=1$)	50 ($n=9$)	68 ($n=15$)	$<0.05^{a,b}$
Severe (%)	0 ($n=0$)	28 ($n=5$)	5 ($n=1$)	$<0.05^{a,c}$
Dysarthria type				
Hypokinetic (%)	85 ($n=17$)	6 ($n=1$)	9 ($n=2$)	$<0.001^{a,b}$
Hypokinetic-ataxic (%)	0 ($n=0$)	6 ($n=1$)	9 ($n=2$)	$<0.001^{a,b}$
Hypokinetic-spastic (%)	0 ($n=0$)	50 ($n=9$)	23 ($n=5$)	$<0.001^{a}$
Ataxic-spastic (%)	0 ($n=0$)	0 ($n=0$)	23 ($n=5$)	$<0.05^{b,c}$
Hypokinetic-ataxic-spastic (%)	0 ($n=0$)	38 ($n=7$)	36 ($n=8$)	$<0.05^{a,b}$

PD Parkinson's disease, *MSA-P* parkinsonian variant of multiple system atrophy, *MSA-C* cerebellar variant of multiple system atrophy, *NNIPPS* natural history and neuroprotection on Parkinson plus syndromes-Parkinson plus scale, *UPDRS* unified Parkinson disease rating scale, *MMSE* Mini-Mental State Examination

[a]Significant difference between PD and MSA-P

[b]Significant difference between PD and MSA-C

[c]Significant difference between MSA-P and MSA-C

which correspond to the previous description of speech and neuropathological findings in patients with MSA [1, 2, 5, 13]. The selection of the deviant speech dimensions was particularly inspired by the Mayo System [15]. However, only those speech dimensions that can be objectively assessed via acoustic analyses were preferred. Last but not least, the acoustic measures were chosen carefully to minimize the potential overlap between hypokinetic, ataxic and spastic dysarthria elements. To this extent, we also utilized previous experience with acoustic analysis of individual speech components in untreated PD (for selection of suitable hypokinetic components) [21] and atypical parkinsonism (for selection of suitable ataxic and spastic components) [13, 22]. Computationally, each measurement was converted to the z-score using its HC mean and standard deviation. For those measures in which lower raw scores were associated with greater dysarthria, the z-scores were reversed, allowing all results to be interpreted as higher z-scores indicating more speech impairment. Each dysarthria index was then estimated as the mean value from the calculated z-scores of the listed acoustic characteristics for each dysarthria subtype.

We evaluated five dimensions widely observed in hypokinetic dysarthria of PD, including harsh voice (harmonics-to-noise ratio), imprecise consonants (voice onset time),

articulatory decay (resonant frequency attenuation), inappropriate silences (duration of pause intervals), and monopitch (standard deviation of pitch contour). Considering elements of ataxic dysarthria, we assessed excess pitch fluctuations (standard deviation of pitch contour), irregular motion rates (diadochokinetic irregularity), prolonged phonemes (vowel duration), excess loudness variations (standard deviation of speech intensity contour) and audible inspirations (relative loudness of respiration). To capture components related to spastic dysarthria, we examined pitch breaks (proportion of subharmonic intervals), voice stoppages (degree of voice stoppages), slow motion rates (diadochokinetic rate) and slow rate (net speech rate). The definition of all acoustic parameters is summarized in Table 2. Comprehensive details on individual acoustics measures have been reported previously [23]. In addition, the accuracy of algorithms for the identification of temporal intervals and pitch sequences has been thoroughly tested in previous studies [7, 23].

Statistical analyses

All analyses were performed in Matlab (MathWorks, Natick, MA, USA). As the test–retest reliability between repetition of the first and second run of sustained phonation and syllable repetition showed moderate (VOT, F0 SD, PSI, DVS: $r = 0.53$–0.68, $p < 0.001$) to strong correlations (HNR, DDKI, VD, DDKR: $r = 0.73$–0.88, $p < 0.001$), the final speech values used for statistical analyses were averaged across two repetitions to provide greater stability of speech assessment [24]. An ad-hoc power analysis based on analysis of variance with one covariate (group) indicated a recommended minimum overall sample size of 76 for 4 groups, given a large effect size (Cohen's f of 0.4) with the error probability α set at 0.05 and a false negative rate β set at 0.2 (i.e., power of 0.8) [25]. 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 vs. MSA-P vs. MSA-C). Pearson and Spearman correlations were applied to test for significant relationships between normally and non-normally distributed data, respectively. To find the best combination of measures for separation between groups (PD vs. MSA-P, PD vs. MSA-C and MSA-P vs. MSA-C), an exhaustive search for all combinations across 14 acoustic features through classification experiment was performed. The classification performance (sensitivity/specificity) of the acoustic speech features in differentiating between groups was calculated using binary logistic regression with leave-one-out cross-validation. An overall indication of diagnostic accuracy was reported as area under the curve (AUC) obtained from the operating characteristic curve. Bonferroni's adjustment for multiple comparisons was applied for primary outcomes (dysarthria indexes) according to the four tests performed, i.e., a threshold of significance was set at $p < 0.0125$. Considering the explorative nature of secondary outcomes (quantitative analysis of 14 unique speech aspects and search for the most prominent relationships between dysarthria indexes and clinical data), adjustment for multiple comparisons was not performed, i.e., a threshold of significance was set at $p < 0.05$.

Results

According to the clinical perceptual evaluation (Table 1), all 40 MSA patients (100%) and 17 PD patients (85%) manifested dysarthria. Most of the MSA patients including 9 MSA-P (50%) and 15 MSA-C (68%) showed moderate dysarthria. Severe dysarthria was most frequent in MSA-P with five patients (28%) affected. In PD, mild dysarthria was found in 16 patients (80%) while moderate dysarthria was present only in 1 patient (5%). PD patients manifested pure hypokinetic dysarthria whereas MSA patients had dysarthria with different combinations of hypokinesia, ataxia, or spasticity. Hypokinetic components of dysarthria were found in the majority of MSA patients. Only five MSA-C patients (23%) had ataxic-spastic dysarthria without the occurrence of hypokinetic components. Hypokinetic-spastic dysarthria predominated in MSA-P with nine patients (50%) compared to five MSA-C patients (23%) affected. Seven MSA-P (38%) and eight MSA-C (36%) patients had all three components of dysarthria affected. Pure hypokinetic or hypokinetic-ataxic dysarthrias were less common and observed in two MSA-P (12%) and four MSA-C (18%) patients. No MSA patient manifested pure ataxic or spastic dysarthria.

The comparison between groups across dysarthria indexes is provided in Fig. 1. Compared to HC, the hypokinetic dysarthria index was increased in PD ($p < 0.001$), MSA-P ($p < 0.001$) as well as MSA-C ($p < 0.001$), whereas ataxic and spastic dysarthria indexes were greater only for the MSA-P ($p < 0.001$) and MSA-C groups ($p < 0.001$). MSA-P showed greater speech severity than PD in the hypokinetic dysarthria index ($p = 0.008$), ataxic dysarthria index ($p = 0.007$), spastic dysarthria index ($p = 0.004$), as well as in overall dysarthria index ($p < 0.001$). The overall dysarthria index was significantly increased in PD ($p = 0.002$), MSA-P ($p < 0.001$), and MSA-C ($p < 0.001$) in comparison to HC. On an individual level, prominent dysarthria (based on comparison of speech severity to HC 95% confidence interval) was acoustically found in 83% of MSA-P, 100% of MSA-C, and 55% of PD patients. The overall dysarthria severity by

Table 2 Overview of applied acoustic measures

Deviant speech dimension (derived from vocal task)	Acoustic feature (unit)	Definition	Description
Hypokinetic			
Harsh voice (sustained phonation)	HNR (dB)	Harmonics-to-noise ratio, defined as the amount of noise in the speech signal	Reduced rate of airflow and improper control of vocal folds causes increased turbulent noise
Imprecise consonants (syllable repetition)	VOT (ms)	Voice onset time, defined as the length of the entire consonant from initial burst to vowel onset	Slowing of lip and tongue movements, leading to impaired pronunciation of individual consonants
Articulatory decay (monologue)	RFA (dB)	Resonant frequency attenuation, defined as the differences between the maxima of the second formant region and minima of local valley region called antiformant	Decrease of spectral energy as a result of decayed articulatory movements
Inappropriate silences (monologue)	DPI (ms)	Duration of pause intervals, defined as the median length of pause intervals	Difficult initiation of speech leading to prolonged pause intervals
Monopitch (monologue)	F0 SD (st)	Standard deviation of fundamental frequency contour converted to semitone scale	Reduced amplitude of vocal cord movements, leading to glottal incompetence
Ataxic			
Excess pitch fluctuations (sustained phonation)	F0 SD (st)	Standard deviation of fundamental frequency contour converted to semitone scale	Uncontrolled alterations in voice pitch
Irregular motion rates (syllable repetition)	DDKI (ms)	Diadochokinetic irregularity, defined as the standard deviation of distances between following syllable nuclei	Inappropriate timing of speech movements
Prolonged phonemes (syllable repetition)	VD (%)	Vowel duration, defined as the ratio of vowel duration compared to duration of entire syllable (including consonant) expressed in the percentage	Reduced ability to program movement sequences in advance of movement onset
Excess loudness variations (monologue)	Int SD (dB)	Standard deviation of speech intensity contour extracted from voiced segments	Inappropriate regulation of loudness
Audible inspirations (monologue)	RLR (dB)	Relative loudness or respiration, defined as the difference between the median loudness of inspirations and median loudness of speech	Reduced respiratory support for speech and sudden forced inspiratory sighs
Spastic			
Pitch breaks (sustained phonation)	PSI (%)	Proportion of subharmonic intervals, defined as the ratio of total duration of subharmonic intervals per total duration of all voiced segments	Changes in mass or control of vocal folds leading to abrupt drop of fundamental frequency
Voice stoppages (sustained phonation)	DVS (%)	Degree of voice stoppages (vocal arrests) defined as the proportion of silent intervals to the total time of phonation	Abnormal contraction of laryngeal muscles causes intermittent voice stoppage, as if airflow has been impeded
Slow motion rates (syllable repetition)	DDKR (syll/s)	Diadochokinetic rate, defined as the number of syllable vocalizations per second	Reduced motor ability of speech apparatus makes the movements of articulators slower
Slow rate (monologue)	NSR (words/s)	Net speech rate, defined as the total number of words divided by the total duration of speech including only voiced and unvoiced intervals. All pauses were removed prior to the analysis	Impaired control of orofacial muscles leading to decrease of speech rate

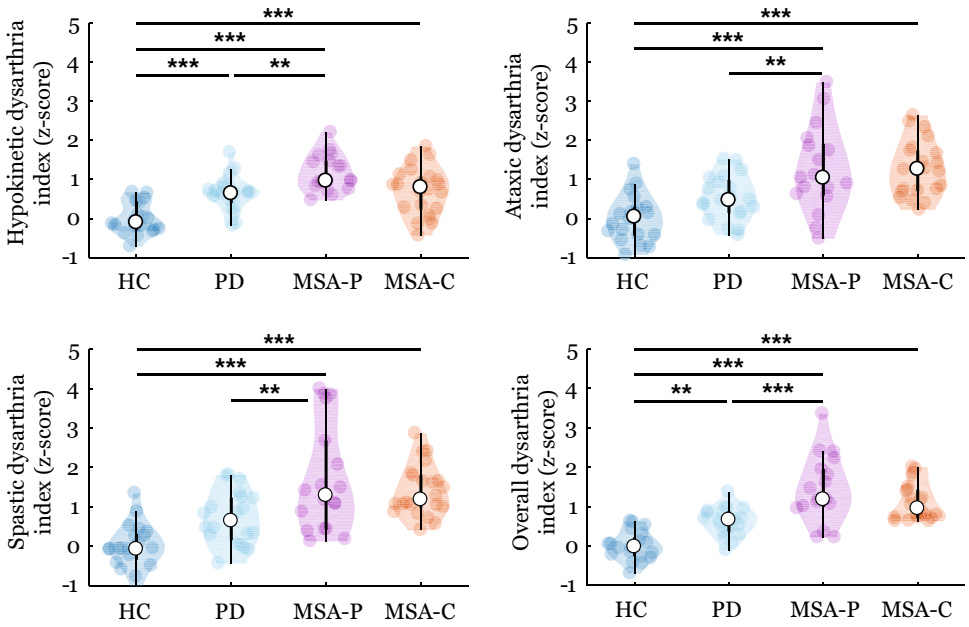


Fig. 1 Violin plots of dysarthria characteristics. The plot shows the median (indicated by the black open circle), the first through the third interquartile range (the thick, solid vertical band), estimator of the density (colour vertical curves) of the individual scores in each group (comparable to a box plot, except that the distribution of the variable is illustrated as density curves), and individual scores (colour-filled circles). Statistically significant differences between groups (uncorrected): $^{**}p<0.01$, $^{***}p<0.001$. *HC* healthy controls, *PD* Parkinson's disease, *MSA-P* parkinsonian variant of multiple system atrophy, *MSA-C* cerebellar variant of multiple system atrophy

acoustic evaluation was strongly correlated with the clinical perceptual dysarthria severity ($r=0.79$, $p<0.001$) as well as perceptual speech severity by UPDRS speech item ($r=0.72$, $p<0.001$).

Group differences across individual speech dimensions are shown in Fig. 2. In PD, two hypokinetic elements of articulatory decay ($p=0.007$) and monopitch ($p=0.001$) were significantly altered compared to HC. In MSA-P, all five hypokinetic dimensions including harsh voice ($p=0.01$), imprecise consonants ($p<0.001$), articulatory decay ($p=0.008$), inappropriate silences ($p=0.02$) and monopitch ($p=0.002$), two ataxic dimensions including excess pitch fluctuation ($p=0.004$) and irregular motion rates ($p<0.001$), and three spastic dimensions including pitch breaks ($p=0.004$), slow motion rates ($p<0.001$) and slow rate ($p<0.001$) were affected compared to HC. In MSA-C, one hypokinetic component including inappropriate silences ($p=0.02$), three ataxic components including irregular motion rates ($p<0.001$), prolonged phonemes ($p=0.004$) and audible inspirations ($p=0.04$), and three spastic components including voice stoppages ($p=0.02$), slow motion rates ($p<0.001$) and slow rates ($p<0.001$) were impaired compared to HC. Notably, only one dimension of audible inspirations was able to significantly separate the MSA-P and MSA-C groups ($p=0.002$).

The combination of acoustic features including imprecise consonants (AUC = 0.79), slow motion rates (AUC = 0.74), and voice stoppages (AUC = 0.56) allowed the best differentiation between PD and MSA-P with an overall AUC of 0.86 (accuracy 73.7%, sensitivity 75.0%, and specificity 72.2%). The combination of acoustic features representing slow motion rates (AUC = 0.83), prolonged phonemes (AUC = 0.73), and audible inspirations (AUC = 0.60) distinguished most accurately between PD and MSA-C with an AUC of 0.85 (accuracy 81.0%, sensitivity 80.0%, and specificity 81.8%). Finally, the combination of acoustic features related to audible inspirations (AUC = 0.81) and imprecise consonants (AUC = 0.73) was able to best separate MSA-P from MSA-C with an AUC of 0.84 (accuracy 82.5%, sensitivity 82.4%, and specificity 82.6%).

The cross-correlations between the dysarthria indices and bradykinesia, rigidity, cerebellar, bulbar/pseudobulbar, and overall NNIPPS (sub)scores in MSA are demonstrated in Table 3. The most prominent relationships between the dysarthria indexes and NNIPPS subscales are then highlighted in Fig. 3. The overall NNIPPS score was related to all speech indices but mainly to the overall dysarthria index ($r=0.66$, $p<0.001$). The hypokinetic dysarthria index showed strongest correlation with the rigidity NNIPPS subscore ($r=0.57$, $p<0.001$). Except to the relationship to overall NNIPPS score, the ataxic dysarthria index showed particular correlation to the cerebellar NNIPPS subscore ($r=0.36$, $p=0.02$) and the spastic dysarthria index to the bulbar/pseudobulbar NNIPPS subscore ($r=0.48$, $p=0.002$). No correlations were detected between dysarthria indexes and pyramidal or tremor NNIPPS subscores. In addition, there was no relationship between dysarthria indexes and disease duration.

Discussion

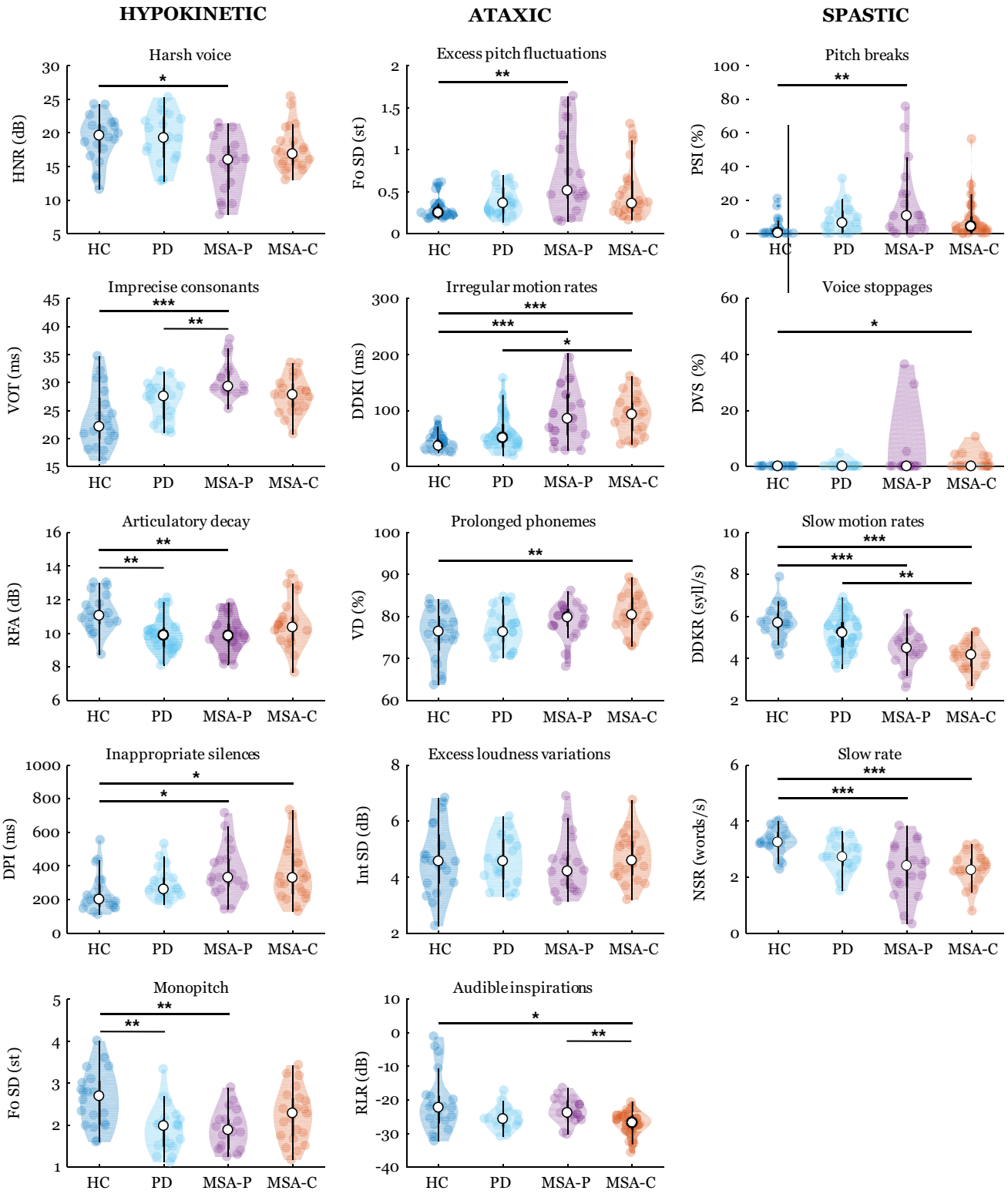
Our findings indicate that speech disorders reflect the underlying pathophysiology of MSA and that detailed speech analysis can be used as a potential diagnostic screening tool.

In agreement with previous studies [5, 8, 26], dysarthria was a prominent clinical feature found in all our MSA patients. The predominant type of dysarthria seems to correspond well to the variant of MSA. Hypokinetic-spastic dysarthria predominated in MSA-P while ataxic-spastic dysarthria without the occurrence of hypokinetic dimensions was found only in several MSA-C patients. The observed mixed type of dysarthria involving a various combination of hypokinetic, ataxic and spastic components conforms to known neuropathological changes, which include degeneration of the cerebellum, middle cerebellar peduncle, striatum, substantia nigra, inferior olivary nucleus and pons [2]. As the PD patients manifested a clear form of hypokinetic dysarthria, acoustic speech analyses were able to discriminate PD from MSA-P with a very promising AUC of 0.86. Indeed, the dysarthria profile in MSA-P can be distinguished from that of PD by its greater severity and the presence of spastic and ataxic components. Interestingly, more profound speech abnormalities in MSA-P compared to PD have been noted even in the very early stages of the disease [12]. We may also hypothesize that the presence of hypokinetic components could help us differentiate MSA-C from idiopathic late-onset cerebellar ataxia, where dysarthria is mainly ataxic [27].

In our study, a number of quantitative acoustic measures were affected differently between MSA-P and MSA-C. While MSA-P predominantly exhibited deviant speech dimensions of harsh voice, imprecise consonants, articulatory decay, monopitch, excess pitch fluctuation and pitch breaks, MSA-C was dominated by prolonged phonemes, audible inspirations and voice stoppages. Inappropriate silences, irregular motion rates and overall slowness of speech were present in both MSA phenotypes. Therefore, speech features prominent in our MSA-P cohort more closely resembled parkinsonian speech with poor articulation (imprecise consonants and articulatory decay), hypokinesia (reduced intonation) and harshness (increased noise and pitch breaks in speech). Indeed, in agreement with our findings, prominent perceptual features including harsh voice, imprecise consonants and reduced stress in MSA have been reported previously, where the majority of patients manifested the parkinsonian variant [8]. In contrast, our MSA-C group showed prominent ataxic features such as prolonged phonemes, which may contribute to the perceptual impression of scanning dysarthria. Overall, these phenotypic speech differences allowed us to distinguish between parkinsonian and cerebellar variants with a high AUC of 0.84, and may have important implications for speech rehabilitation management, especially considering individual speech dimensions affected in each MSA phenotype. As an example, the loudness should be targeted for therapy if the impaired loudness is the primary source of communication impairment, whereas increased articulatory precision should be targeted if imprecise articulation is the contributing feature. During treatment, automated acoustic analyses may assist in quantification of perceptual judgments made by the well-trained and experienced clinicians.

Interestingly, the greater extent of audible inspirations observed in MSA-C was the only individual speech pattern that permitted the separation of parkinsonian and cerebellar variants, although there is a strong overlap between both MSA groups. While audible inspirations are more typical for flaccid than ataxic dysarthria [15], they have been perceptually noted previously in olivopontocerebellar ataxia [28]. Indeed, respiratory dysfunction presenting with inspiratory stridor or deep involuntary sighs has been reported to be frequent in both MSA subtypes and represents one of the main warning signs for diagnosis [29]. We may assume that sudden forced audible inspirations share the same underlying pathophysiology with diurnal inspiratory stridor [15], which is a serious manifestation that requires immediate medical evaluation [30]. Therefore, audible inspirations may not reflect ataxia but rather a posterior cricoarytenoid muscle weakness or dystonia. However, the objective acoustic quantification of the extent of respiratory deficits such as audible inspiration or stridor in MSA has received little systematic attention [31], without considering potential differences concerning the disease phenotype. Our findings thus highlight the phenotypic differences in respiratory control and suggest the acoustic quantification of audible inspirations through spontaneous speech as a potential way to measure the extent of respiratory dysfunction in MSA.

In general, the types of dysarthria in MSA were similar to the motor disorders detected by clinical neurologic investigation. The results of the present study support the role of the cerebellum in the development of ataxic dysarthria in MSA, as we observed a relationship between the severity of ataxic speech components and cerebellar signs on clinical examination. Accordingly, a previous neuropathological study identified a relationship between the local cerebellar metabolic rates for glucose and the severity of speech ataxia in 30 patients with olivopontocerebellar atrophy [28]. Subsequently, we found a relationship between the severity of hypokinetic speech components and rigidity, which is at least partly in agreement with the assumption that hypokinetic speech problems are caused by increased rigidity and hypokinesia of the speech apparatus [32]. In agreement with this observation, individual hypokinetic speech dimensions, as well as rigidity manifestations, were more severe in MSA-P compared to MSA-C patients, while difference in bradykinesia severity was not significant. In agreement with a previous study on speech disorders in atypical parkinsonian syndromes [13], we observed a relationship between the severity of spastic elements and bulbar/pseudobulbar manifestations, supporting the role of the corticobulbar pathways in the development of mixed dysarthria in MSA. However, the extent of bradykinesia, rigidity, cerebellar,



bulbar/pseudobulbar, as well as overall motor manifestations was related to the overall severity of dysarthria, assuming that speech impairment in MSA partially parallels increasing overall limb motor disability due to the underlying neurodegenerative process. In addition, considerable overlap between these individual motor indices was present, supporting the mixed cases of dysarthria found in our MSA cohort.

Admittedly, there is even a common overlap of individual speech features among dysarthria subtypes [15], making the correct recognition of a specific dysarthria subtype

◂**Fig. 2** Violin plots of individual speech dimensions. The plot shows the median (indicated by the black open circle), the first through the third interquartile range (the thick, solid vertical band), estimator of the density (colour vertical curves) of the individual scores in each group (comparable to a box plot, except that the distribution of the variable is illustrated as density curves), and individual scores (colour-filled circles). Statistically significant differences between groups: $*p<0.05$, $**p<0.01$, $***p<0.001$. *HNR* harmonics-to-noise ratio, *VOT* voice onset time, *RFA* resonant frequency attenuation, *DPI* duration of pause intervals, *F0 SD* variability of fundamental frequency, *DDKI* diadochokinetic irregularity, *VD* vowel duration, *Int SD* variability of speech intensity, *RLR* relative loudness of respiration, *PSI* proportion of subharmonic intervals, *DVS* degree of voice stoppages, *DDKR* diadochokinetic rate, *NSR* net speech rate, *HC* healthy controls, *PD* Parkinson's disease, *MSA-P* parkinsonian variant of multiple system atrophy, *MSA-C* cerebellar variant of multiple system atrophy

challenging, especially in patients with widespread brain atrophy [28, 33]. Indeed, the previous study based on systematic perceptual evaluation blind to disease diagnosis showed that perceptual speech and voice ratings were unable to differentiate between mixed dysarthrias occurring in atypical parkinsonian syndromes [34]. Although we aimed to separate hypokinetic, ataxic and spastic dysarthria as clearly as possible to eliminate most of the overlap, certain speech manifestations may still originate from different neuronal dysfunctions than was anticipated (for example, monopitch may arise due to involvement of the basal ganglia as well as corticobulbar pathways). It is also noteworthy to point out that the MSA-P group showed greater variance, mainly considering ataxic and spastic dysarthria indexes. This is likely caused by a higher occurrence of severe dysarthria in our MSA-P compared to MSA-C cohort. In particular, variation in speech severity within a dysarthria type may explain as much variance in acoustic or perceptual data as variation across dysarthria type [33].

One potential limitation is that we did not acoustically investigate loudness of speech. Although it is an important distinguishing feature of hypokinetic dysarthria, we did not use the absolute value of intensity level in our cross-sectional acoustic analysis because the need for precise microphone calibration to obtain reliable estimates.

In conclusion, the present study demonstrates potential intriguing advances in speech analysis and provides new insights into the pathophysiology of motor speech disorders in MSA. As dysarthria is a frequent manifestation, objective identification of deviant speech dimensions may contribute to the differential diagnosis in potential MSA patients. Moreover, the observed relationship between speech and clinical motor features indicates that speech assessment may provide a sensitive measure of disease progression. Vocal assessment is rapid, easy to administer, and can be fully automated and performed remotely, possibly even by smartphone at home [35]. Since the progression of speech impairment in MSA is rapid, we may assume that regular longitudinal in-home assessment over a short period could substantially improve the reported sensitivity of speech-based evaluation and provide a no-cost alternative screening method to existing clinical and imaging diagnostic approaches [2, 36]. Future, studies based on the longitudinal assessment should further elaborate and extend our findings and show the sensitivity of speech investigation in the differentiation between MSA and PD or idiopathic late-onset cerebellar ataxia in the very early stage of disease manifestation.

Table 3 The cross-correlations between dysarthric and clinical motor indices

NNIPPS score/subscores	Bradykinesia	Rigidity	Cerebellar	Bulbar/pseudobulbar	Overall
Speech					
Hypokinetic dysarthria index	0.26	0.57***	0.14	0.17	0.47**
Ataxic dysarthria index	0.49**	0.42**	0.36*	0.47**	0.54**
Spastic dysarthria index	0.48**	0.29	0.27	0.48**	0.49**
Overall dysarthria index	0.58***	0.52***	0.46**	0.59***	0.66***
Motor					
Bradykinesia NNIPPS subscore		0.57***	0.47**	0.63***	0.88***
Rigidity NNIPPS subscore	0.57***		0.28	0.56***	0.76***
Cerebellar NNIPPS subscore	0.47**	0.28		0.44**	0.56***
Bulbar/pseudobulbar NNIPPS subscore	0.63***	0.56***	0.44**		0.74***
Overall NNIPPS score	0.88***	0.76***	0.56***	0.74***	

NNIPPS natural history and neuroprotection on Parkinson plus syndromes-Parkinson plus scale

Statistically significant differences between groups: $*p<0.05$, $**p<0.01$, $***p<0.001$

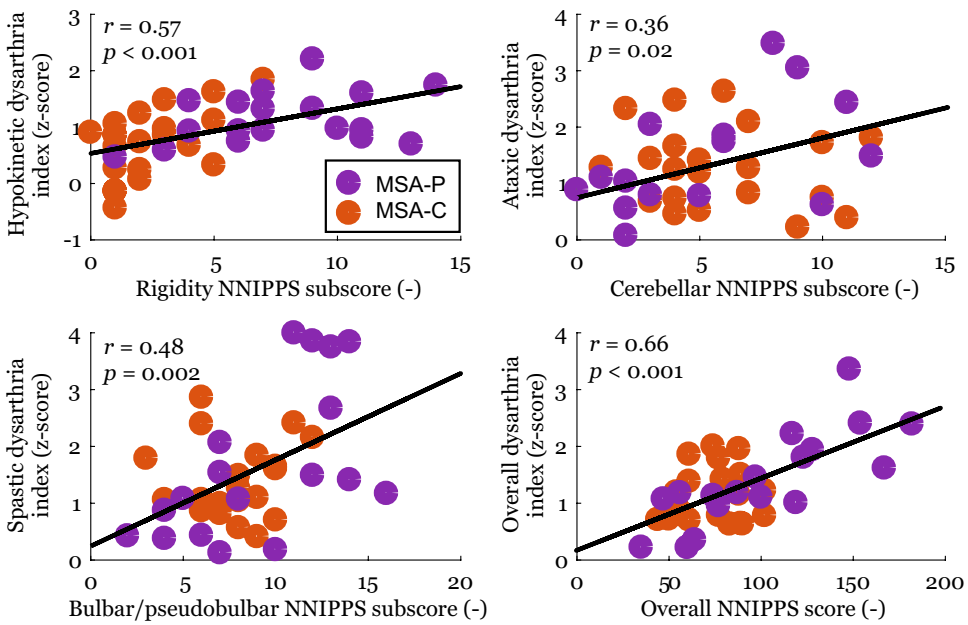


Fig. 3 Prominent correlations between dysarthria indexes and NNIPPS score/subscores. *NNIPPS* natural history of neuroprotection in Parkinson plus syndromes-Parkinson plus scale, *MSA-P* parkinsonian variant of multiple system atrophy, *MSA-C* cerebellar variant of multiple system atrophy

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Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest.

Ethical standards Each participant provided written, informed consent. The study received approval from an ethical standards committee on human experimentation, and has, therefore, been performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

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