Spoken Language Alterations can Predict Phenoconversion in Isolated Rapid Eye Movement Sleep Behavior Disorder: A Multicenter Study

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Objective: This study assessed the relationship between speech and language impairment and outcome in a multicenter cohort of isolated/idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD).
Methods: Patients with iRBD from 7 centers speaking Czech, English, German, French, and Italian languages underwent a detailed speech assessment at baseline. Story-tale narratives were transcribed and linguistically annotated using fully automated methods based on automatic speech recognition and natural language processing algorithms, leading to the 3 distinctive linguistic and 2 acoustic patterns of language deterioration and associated composite indexes of their overall severity. Patients were then prospectively followed and received assessments for parkinsonism or dementia during follow-up. The Cox proportional hazard was performed to evaluate the predictive value of language patterns for phenoconversion over a follow-up period of 5 years.

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Results: Of 180 patients free of parkinsonism or dementia, 156 provided follow-up information. After a mean follow-up of 2.7 years, 42 (26.9%) patients developed neurodegenerative disease. Patients with higher severity of linguistic abnormalities (hazard ratio [HR = 2.35]) and acoustic abnormalities (HR = 1.92) were more likely to develop a defined neurodegenerative disease, with converters having lower content richness (HR = 1.74), slower articulation rate (HR = 1.58), and prolonged pauses (HR = 1.46). Dementia-first (n = 16) and parkinsonism-first with mild cognitive impairment (n = 9) converters had higher severity of linguistic abnormalities than parkinsonism-first with normal cognition converters (n = 17).

Interpretation: Automated language analysis might provide a predictor of phenoconversion from iRBD into synucleinopathy subtypes with cognitive impairment, and thus can be used to stratify patients for neuroprotective trials.

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Isolated/idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is a parasomnia characterized by loss of muscle atonia during REM sleep and dream-enactment behaviors.[1] Multiple studies have found a strong association between iRBD and the development of neurodegenerative synucleinopathies, particularly Parkinson's disease (PD) and dementia with Lewy bodies (DLB).[2–4] The iRBD is now considered an important prodromal stage of synucleinopathies, with patients developing into overt neurodegenerative disease after a decade or more. Such a long prodromal window provides a unique opportunity to offer potential neuroprotective therapy early,[5] possibly halting or slowing the development of parkinsonism and dementia.

Reliable biomarkers are essential in identifying patients with iRBD who are most likely to phenoconvert within several years and monitoring the neurodegenerative process and treatment outcomes. Although several quantitative biomarkers have already been determined to predict the conversion from iRBD to neurodegenerative synucleinopathies,[6] those allowing the prediction of synucleinopathy subtypes are scarce.[7,8] The largest multicenter trial in 1,280 patients with iRBD showed that the only clear differentiating variables between dementia and parkinsonism were based on cognitive impairment and abnormal color vision testing.[9]

Alternatively, language impairment represents a core feature of a cognitive domain, which can be a strong predictor of cognitive impairment in the early stages of various neurodegenerative diseases.[10] In Lewy body spectrum disorder, various linguistic changes have been reported, including alterations in lexical-semantic comprehension, syntactic complexity, frequency, and type of words/pauses, speech rate, and others.[11] In prodromal synucleinopathies, a single study has reported that patients with iRBD manifest a reduction of content words and modifiers, less occurrence of unique words, and poorer lexical richness.[12] Whether altered language function could predict the development of manifest synucleinopathy, and which subtypes, in patients with iRBD has never been investigated.

Language biomarkers can be derived from natural, spontaneous speech, which can be acquired even outside the laboratory environment and processed automatically via a combination of automatic speech recognition (ASR) and natural language processing (NLP) techniques.[13] ASR applies statistical models and digital signal processing algorithms to transcribe audio speech recordings into written text; NLP uses advanced statistical methods to analyze the structure of sentences, words, and phrases to gain an understanding of the context and meaning behind them. However, different languages with various extents of morphological complexity[14] impose considerable practical challenges for developing a unified language assessment framework.

This article reports the results of a multicenter, multilanguage observational study aimed at advancing the understanding of possible linguistic alterations in patients with prodromal synucleinopathy. We implemented a protocol specifically tailored to simulate a clinical trial, including aspects like rapid data acquisition, rigorous quality assurance and quality control, and blinded (fully automated) and centralized language analysis. From our cohort's initial baseline assessment, patients have been continuously and prospectively monitored at each center. We aimed to assess (1) whether language impairment may quantify the risk of phenoconversion to neurodegeneration and (2) whether language deficits differ in primary parkinsonism with and without mild cognitive impairment (MCI) and primary dementia.

Methods

Study Design and Participants

The study obtained approval from the local responsible ethical committees on human experimentation and was conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki. It was registered under reference number NCT03133611 on April 28, 2017, at https://clinicaltrials.gov/. All participants provided written, informed consent.

In the recruitment period from 2017 to 2018, we conducted baseline examination on participants from 7 different centers (Medical University of Innsbruck, Innsbruck,

Austria; University of Marburg, Marburg, Germany; San Raffaele Hospital, Milano, Italy; Gui-de-Chauliac Hospital, Montpellier, France; the Research Institute of the McGill University and the CIUSSS-NÎM Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada; Charles University and General University Hospital, Prague, Czech Republic; and the Mayo Clinic, Rochester, Minnesota, USA). We investigated 5 languages that belong to 3 different Indo-European language families, namely Slavic (Czech), Germanic (English and German), and romance (French and Italian). All participants were fluent speakers of one of the languages. The target for baseline recruitment was to enroll 30 individuals with iRBD and 30 age- and sex-matched healthy controls for each language group.

Patients diagnosed with iRBD were assessed following the diagnostic criteria outlined in the third edition of the International Classification of Sleep Disorders, which included video-polysomnography.[15] Inclusion criteria for iRBD encompassed (1) the onset of RBD occurring after the age of 50 years, (2) the absence of any communication disorders, such as difficulties in speech comprehension or expression, that would significantly interfere with the recording protocol or present other significant neurological disorders, and (3) no medical history of therapy involving antiparkinsonian medication. The exclusion criteria comprised (1) the onset of RBD within 12 months of commencing antidepressant treatment and (2) a diagnosis of dementia or parkinsonism. The duration of RBD symptoms was documented through self-reported information provided by the patients. Controls were included based on the criterion that they had no history of neurological or communication disorders and no record of parasomnias or other sleep disorders.

Clinical Examination

The clinical assessment of each participant contained (1) an in-depth exploration of their personal and medical history, including a review of their drug and substance use history, as well as their current medication use, (2) the quantitative evaluation of both motor and non-motor symptoms related to PD, conducted using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, Parts II and III (MDS-UPDRS),[16] (3) an assessment of global cognitive function utilizing the Montreal Cognitive Assessment (MoCA),[17] and (4) an evaluation of autonomic functioning using the Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction scale (SCOPA-AUT).[18] All diagnoses and the administration of clinical rating scales were carried out by a neurologist with expertise in movement disorders. Moreover, the scales were applied with versions that had been validated across the examined languages.

Speech Examination

To ensure uniformity in the recording process for cross-site comparability, each center received standardized on-site speech assessment training delivered by a speech specialist (authors J.R., M.N., or T.T.). Speech recordings were conducted in a quiet environment with minimal background noise, utilizing a head-mounted condenser microphone (Shure Beta 53; Shure Inc., Niles, IL, USA) positioned approximately 5 cm from the subject's mouth. The speech signals were sampled at a rate of 48 kHz with 16-bit resolution. Each participant was recorded in a single session under the supervision of a trained specialist. All participants undertake a storytelling task, with an average duration of 111 s (standard deviation [SD] = 34) and an average word count of 234 (SD = 97), involving the narration of a self-selected story. The task's length was comparable to previous studies on linguistic biomarkers in dementia.[19] The content of narration was monitored and classified into 6 topics, including (1) Red Riding Hood (27.4%), (2) fictional story (24.0%), (3) Cinderella (7.9%), (4) Hansel and Gretel (5.2%), (5) the Three Little Pigs (4.6%), and (6) other (31.0%).

Speech Transcription and Annotation

The speech recordings underwent transcription using the Google Cloud Speech-to-Text API,[20] selected based on reported accuracy and documentation quality. The ASR generates a transcription into a TXT file, including punctuation. The pause intervals were determined from speech signal using an automatic segmentation tool for connected speech.[21] NLP techniques were utilized to conduct linguistic analysis on each word in the transcribed recordings and assign them their respective word types. To achieve this, spaCy[22] was used to analyze English, French, German, and Italian transcriptions, and MorphoDiTa[23] to analyze Czech transcriptions. Comprehensive details on speech transcription and annotation, including testing of algorithms' accuracy, have been published previously.[12]

Linguistic and Acoustic Feature Analysis

We selected 3 linguistic and 2 acoustic parameters that were previously associated with significant cognitive language decline in parkinsonism.[12,24–26] The feature selection considered 3 main criteria: (1) proved sensitivity to MCI, (2) covering complex aspects of language impairment (namely lexical domain, vocabulary, grammar, and syntax), which requires distinctive computational principle, and thus minimal correlation among the parameters could be anticipated, and (3) the potential for complete automation of the analysis process. By including a restricted set of features, we decrease the likelihood of encountering a type II error and mitigate the risk of

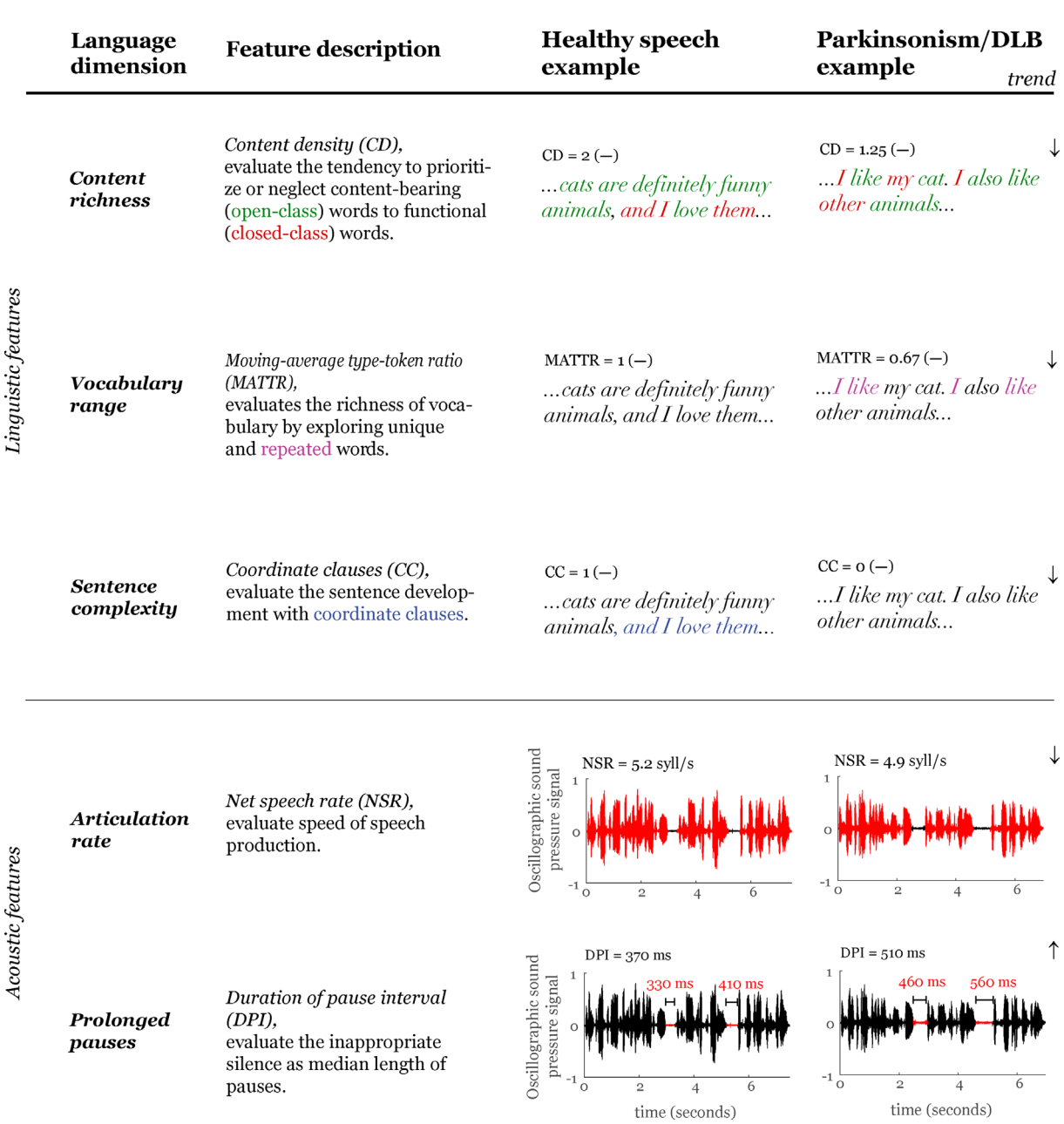

Figure 1: Overview of linguistic and acoustic features. DLB = dementia with Lewy bodies. [Color figure can be viewed at www.annalsofneurology.org]

excessive overfitting in the regression analysis. The demonstrations of these 5 parameters are summarized in Figure 1.

Linguistic Features. Content richness was assessed using content density (CD), which reflects a potential tendency to prioritize or neglect content-bearing words over functional words that serve grammatic or syntactic roles, thereby altering the distribution of meaningful content and linguistic function. It is computed as the ratio of open-class words to closed-class words.[12] Vocabulary range was assessed with moving-average type–token ratio (MATTR), which quantifies lexical diversity. MATTR is computed with function F looping with selected window size through the text with step size 1 and counts the number of unique words in the current window, divided by the total number of words in the window. The resulting values are averaged to obtain the final score. For our study, the window size was set to 58 words in accordance with our available sample length and previous recommendations for determining the subject's vocabulary.[27] Sentence complexity was assessed using coordinate clauses (CCs). It evaluates sentence development based on the number of CCs, which are predominant clauses used in spontaneous speech.[28] CC is defined as the number of CCs normalized to the total number of clauses.[29] The

linguistic features were found only weakly correlated (Pearson: $|r| < 0.31$).

Acoustic Features. The articulation rate was assessed using net speech rate (NSR), which evaluates the speed of speech production. NSR is defined as the number of syllables extracted using hyphenation techniques divided by the length of speech after removing all pauses longer than 30 ms.[24] Prolonged pauses were assessed using duration of pause interval (DPI), which assesses the inappropriate silence and is defined as the median length of pause intervals equal to or longer than 250 ms.[21] The threshold of 200 to 250 ms has been widely adopted in the literature to determine pauses associated with cognitive decline.[30] No correlation was found between the acoustic features (Pearson: $r = -0.09$).

Primary End Points. Based on general least-squares linear models, the effect of the language across controls was found for all 3 linguistic ($p < 0.001$) and 2 acoustic

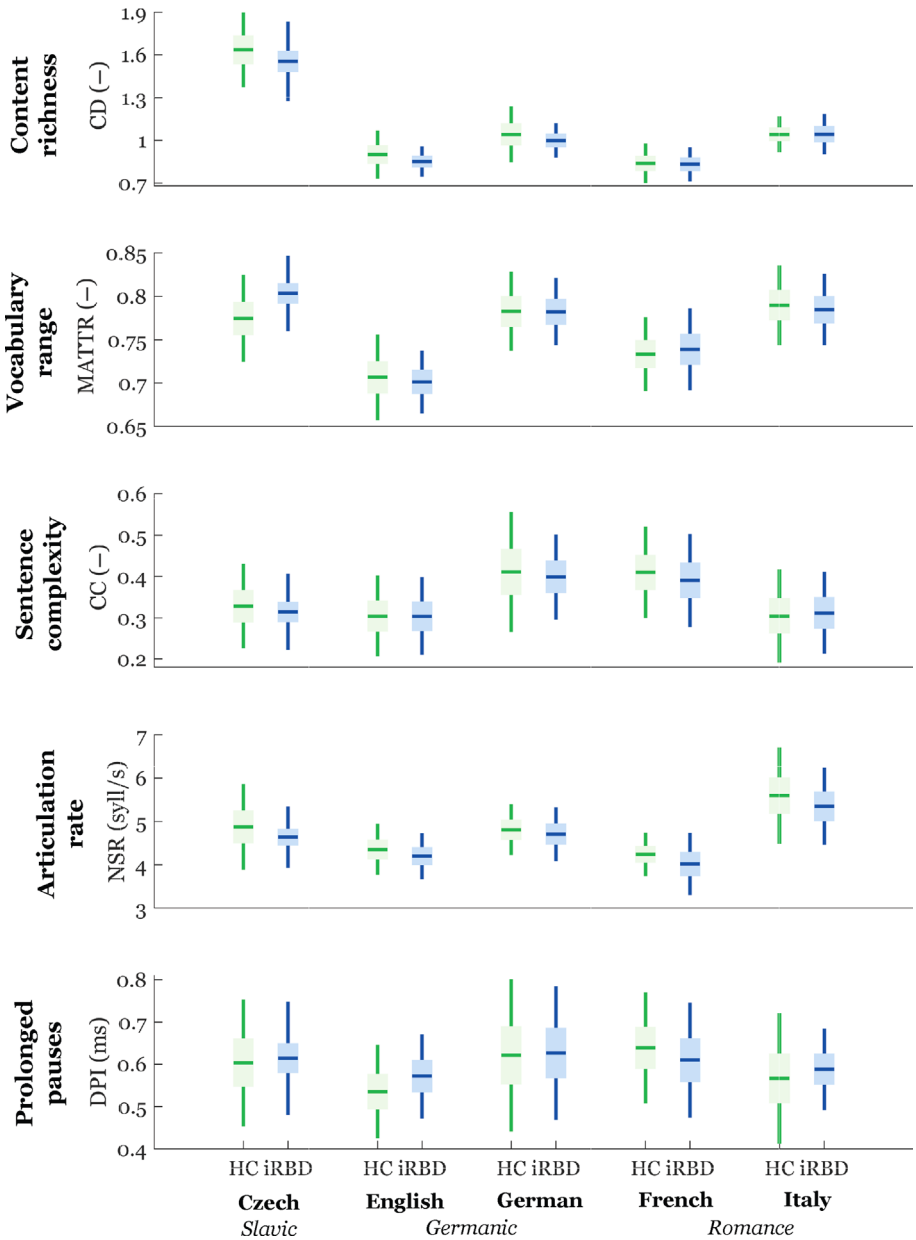

Figure 2: Normative data of linguistic and acoustic measures across 5 languages. Boxplots of individual linguistic and acoustic features across five languages. Horizontal lines represent the means, boxes represent 95% confidence interval, and whiskers represent standard deviation. CC = coordinate clauses; CD = content density; DPI = duration of pause intervals; HC = healthy controls; iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; MATTR = moving-average type-to-token ratio; NSR = net speech rate. [Color figure can be viewed at www.annalsofneurology.org]

($p < 0.05$) measures (Fig 2). Therefore, for analysis using the entire dataset consisting of all 5 languages, each of the 3 linguistic and 2 acoustic parameters was transformed into z-score using the mean and standard deviation of the control group separately for each language; this approach has been shown to be effective in a previous multilanguage study on speech impairment in iRBD and PD.[25] The one-sample Kolmogorov–Smirnov test did not indicate non-normally distributed features, which allows the proper application of z-score transformation. The primary end points were represented by the linguistic composite index (LCI) and acoustic composite index (ACI), estimated as the mean z-score value of 3 linguistic features and the mean z-score value of 2 acoustic features, respectively. The language parameters, where lower raw scores indicate higher language impairments (ie, CD, MATTR, CC, and NSR), were reversed in z-score transformation. As a result, a higher score of linguistic or acoustic variables indicates greater abnormalities.

Follow-Up Study and Disease Conversion

All centers prospectively followed patients with iRBD for 60 months; phenoconversion was noted upon the occurrence of parkinsonism or dementia. Parkinsonism was

Table 1. Demographics and clinical data of participants at baseline

Baseline	Group	Male	Age (yr)	Disease duration (yr)	Education (yr)	MDS-UPDRS II	MDS-UPDRS III	MoCA	SCOPA-AUT	Anti-depressant therapy	Benzo-diazepine therapy
Czech (n = 90)	Controls (n = 30)	27 (90%)	66.1/7.3 (52–81)	-	15.1/3.3 (8–21)	1.1/1.4 (0–5)	2.7/2.8 (0–13)	25.7/2.0 (19–29)	6.7/4.1 (1–21)	1 (3%)	0 (0%)
	iRBD (n = 60)	52 (87%)	68.4/6.1 (54–80)	0.4/0.9 (0–5)	14.6/3.2 (9–24)	2.2/2.9 (0–17)	7.0/6.5 (0–24)	23.7/3.6 (14–29)	11.5/7.7 (2–35)	14 (23%)	10 (17%)
English (n = 60)	Controls (n = 30)	18 (60%)	67.8/8.1 (52–81)	-	16.1/3.9 (10–25)	0.6/1.4 (0–7)	0.7/1.1 (0–4)	26.5/3.1 (18–30)	6.9/5.3 (0–22)	2 (7%)	0 (0%)
	iRBD (n = 30)	21 (70%)	68.3/6.5 (56–81)	2.4/2.5 (0–9)	16.0/2.3 (11–20)	1.6/3.3 (0–18)	3.1/3.8 (0–15)	26.5/2.9 (14–30)	11.1/5.7 (1–25)	2 (7%)	3 (10%)
French (n = 60)	Controls (n = 30)	24 (80%)	69.0/6.6 (53–80)	-	14.2/3.1 (7–20)	0.7/1.2 (0–5)	2.2/2.6 (0–10)	27.7/1.7 (23–30)	10.3/8.7 (1–35)	3 (10%)	2 (7%)
	iRBD (n = 30)	25 (83%)	68.6/7.1 (53–85)	3.5/3.2 (0–13)	14.6/3.9 (5–25)	1.8/2.2 (0–8)	4.6/3.5 (0–11)	26.2/2.4 (19–30)	11.4/6.2 (3–30)	6 (20%)	13 (43%)
German (n = 59)	Controls (n = 29)	21 (72%)	69.7/8.3 (50–82)	-	13.7/4.0 (8–20)	0.6/1.1 (0–5)	1.0/2.1 (0–10)	27.0/2.4 (22–30)	7.2/5.5 (0–24)	3 (10%)	0 (0%)
	iRBD (n = 30)	25 (83%)	69.7/7.0 (58–85)	3.2/3.6 (0–12)	12.9/3.9 (8–23)	2.0/2.8 (0–13)	3.6/3.2 (0–11)	26.4/3.6 (15–30)	12.5/8.0 (0–33)	8 (27%)	4 (13%)
Italian (n = 60)	Controls (n = 30)	20 (67%)	70.7/9.7 (50–94)	-	13.7/4.4 (5–19)	0.2/0.5 (0–2)	0.3/0.5 (0–4)	24.4/2.4 (21–30)	2.9/4.8 (0–18)	0 (0%)	2 (7%)
	iRBD (n = 30)	23 (77%)	70.9/6.0 (54–79)	2.1/3.7 (0–13)	11.3/4.6 (3–17)	0.4/1.3 (0–6)	1.9/3.3 (0–13)	22.0/6.8 (12–30)	7.9/6.8 (0–25)	6 (20%)	14 (47%)
All languages (n = 329)	Controls (n = 149)	110 (74%)	69.7/8.1 (50–94)	-	14.6/3.8 (5–25)	0.6/1.2 (0–7)	1.4/2.2 (0–13)	26.3/2.6 (18–30)	6.8/6.3 (0–35)	9 (6%)	4 (3%)
	iRBD (n = 180)	123 (68%)	69.1/6.5 (53–85)	2.0/3.0 (0–13)	13.9/3.8 (3–25)	1.7/2.7 (0–18)	4.5/5.1 (0–24)	24.8/3.8 (12–30)	11.0/7.1 (0–35)	36 (20%)	44 (24%)

Note: Data are mean/SD (range) or number (%).

Abbreviations: iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction Scale.

defined as the presence of bradykinesia plus either rigidity or rest tremor.[31] For dementia conversions, all patients had polysomnographic-diagnosed RBD and thus met the 2017 criteria for probable DLB with a clinical core symptom plus biomarker loss of REM sleep atonia.[32] For patients with parkinsonism-first manifestations, clinical diagnosis of PD and multiple system atrophy (MSA) were made according to the best clinical impression, supplemented by diagnostic criteria described by the MDS/UK brain bank and Gilman et al.[31,33] If both parkinsonism and dementia were diagnosed at the same visit, the patient was classified as a dementia-first converter. Parkinsonism-first patients were also stratified according to the presence of MCI based on the MDS level I criteria (ie, MoCA and regional cutoffs)[34] to parkinsonism-first alone and parkinsonism-first and MCI groups; the subjective cognitive complaint was not considered. All follow-up information was used to make the differential diagnosis as accurate as possible (diagnosis was reclassified if necessary, concerning updated information about disease status).

Statistical Analysis

To analyze disease risk, the time variable was set as months from baseline assessment to the censoring date (60 months) for non-converters, or the date of first diagnosis of parkinsonism or dementia onset for converters. The Cox proportional hazard analysis was performed to evaluate the predictive value of risk factors for disease

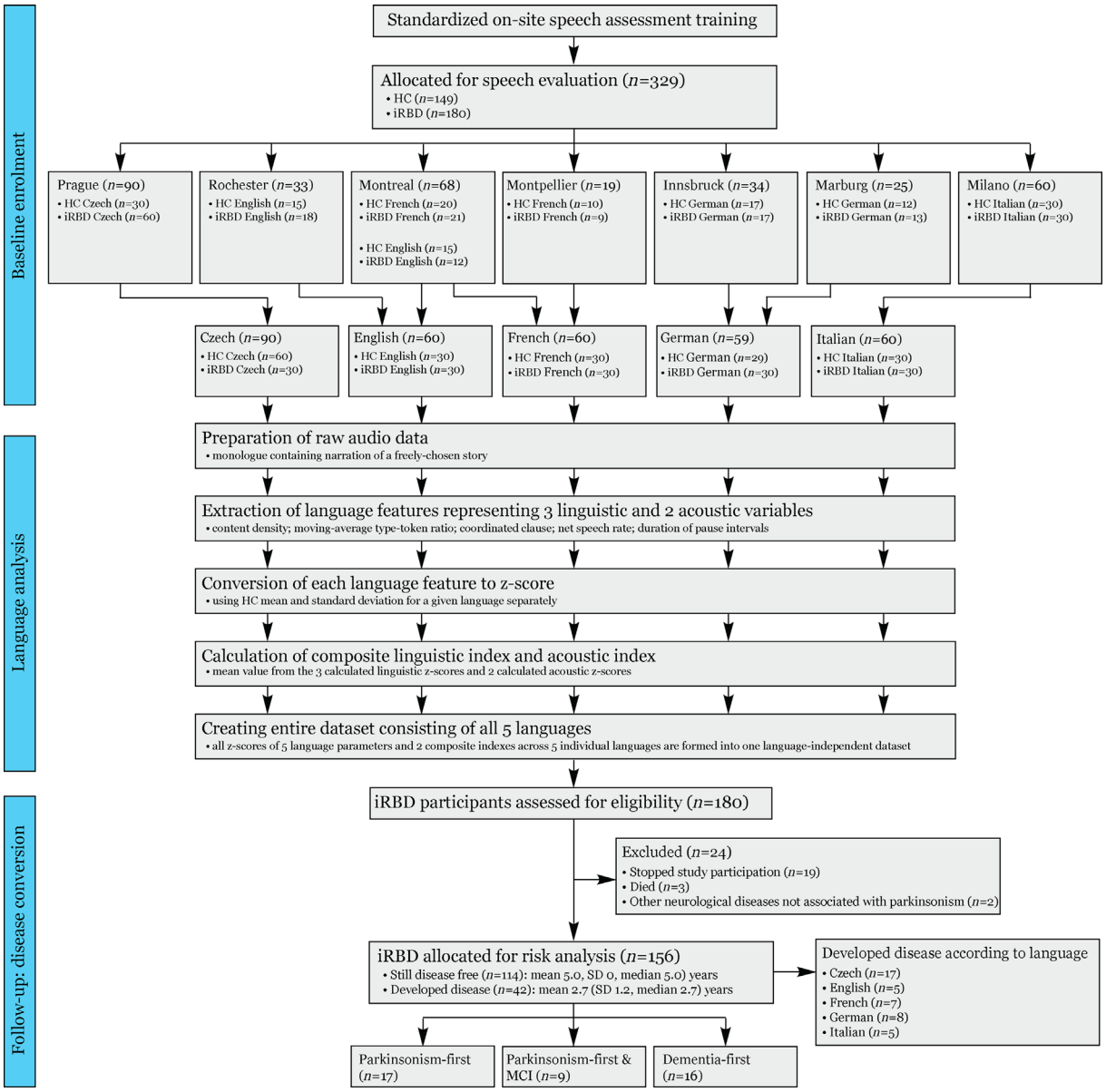

Figure 3: Scheme depicting enrollment of research subjects and process of language and statistical analysis of speech data. HC = healthy controls; iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; MCI = mild cognitive impairment. [Color figure can be viewed at www.annalsofneurology.org]

conversion. Each clinical, linguistic, and acoustic variable was analyzed using Cox regression with hazard ratios (HRs). Subsequently, we performed logistic regression analyses to compare variables between dementia-first, parkinsonism-first and MCI, and parkinsonism-first converters with odds ratios (ORs). Both HRs and ORs were adjusted for baseline age, sex, study site, years of education, and narrative topic. The effectiveness of disease classification was estimated with positive (LR+) and negative (LR−) likelihood ratios. The analyses were conducted in MATLAB (MathWorks, Natick, MA).

Results

Participants: Baseline

The baseline sample comprised 329 participants, including 149 controls and 180 patients with iRBD (Table 1). Speech data were similarly distributed among English, French, German, and Italian languages, including data from 6 centers; the only exception was the Czech language, where 60 individuals with iRBD were possible to assess due to long-term involvement of Czech site in speech-related research.

Participants: Follow-Up

A total of 156 patients (86.7%) participated in the follow-up study on risk predictors (Figure 3), and 24 were excluded: 19 stopped study participation, 3 died, and 2 were diagnosed with other neurological diseases not associated with parkinsonism. During follow-up, 114 patients (73.1%) did not convert, whereas 42 (26.9%) developed overt neurodegenerative synucleinopathy. The fixed follow-up was 5 years. The mean interval between baseline speech assessment and disease phenoconversion was 2.7 (SD = 1.2, median = 2.7) years. According to the Kaplan–Meier analysis of disease-free survival, the risk of developing a neurodegenerative disease from the baseline was 9.0% after 2 years, 17.3% after 3 years, 22.4% after 4 years, and 26.9% after 5 years (Figure 4). The diagnosis was PD in 25 patients (59.5%), DLB in 16 patients (38.1%), and MSA in 1 patient (2.4%). Among participants with parkinsonism-first manifestation, 17 patients (65.4%) were without MCI (parkinsonism-first), and 9 patients (34.6%) were with MCI (parkinsonism-first and MCI); the patient with MSA was with MCI.

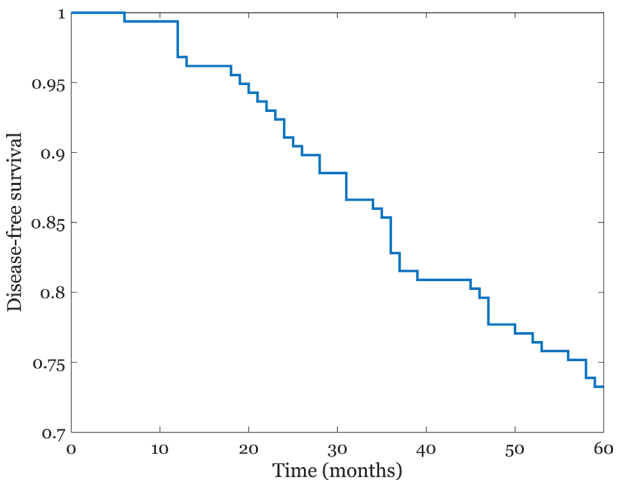

Figure 4: Kaplan–Meier analysis of disease-free survival in patients with iRBD (ie, free of parkinsonism-first, parkinsonism-first with MCI, or dementia-first). HC = healthy controls; iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; MCI = mild cognitive impairment. [Color figure can be viewed at www.annalsofneurology.org]

Phenoconversion to Neurodegenerative Synucleinopathy

Patients with higher severity of linguistic abnormalities (HR = 2.35, 95% confidence interval [CI] = 1.14–4.82) and acoustic abnormalities (HR = 1.92, 95% CI = 1.34–2.75) were more likely to develop a defined neurodegenerative disease (Table 2, Table S1). When evaluating individual variables, patients with lower content richness (HR = 1.74, 95% CI = 1.19–2.54), slower articulation rate (HR = 1.58, 95% CI = 1.19–2.10), and prolonged pauses (HR = 1.46, 95% CI = 1.09–1.96) were associated with a higher risk of disease conversion, whereas reduced vocabulary range or sentence complexity demonstrated no association with phenoconversion.

Converted patients were 2.1 years older on average than non-converters. Sex and education did not exhibit a significant predictive effect on the conversion. When assessing clinical measures, higher UPDRS III (HR = 1.10, 95% CI = 1.04–1.16) and lower MoCA score (HR = 0.91, 95% CI = 0.84–0.98) were associated with an increased risk of phenoconversion.

Phenoconversion to Synucleinopathy Subtypes

Patients with higher severity of linguistic abnormalities showed a significantly increased risk of converting into parkinsonism-first and MCI (OR = 109.18, 95% CI = 2.08–5742.14) as well as dementia-first (OR = 21.17, 95% CI = 1.49–300.34) in comparison to those converting into parkinsonism-first alone (Table 3, Table S1). Lower content richness was associated with the conversion into parkinsonism-first and MCI as compared to parkinsonism-first only (OR = 7.46, 95% CI = 1.14–49.03), whereas lower vocabulary range (OR = 4.08, 95% CI = 1.19–14.92) suggested an increased risk of converting into dementia-first compared to parkinsonism-first alone. We did not find any significant predictors that could differentiate between patients converting into parkinsonism-first and MCI versus dementia-first. No significant association was observed between acoustic variables and an increased risk of

Table 2. Baseline predictors of neurodegenerative phenoconversion in iRBD

	Developed disease within 5 yr (n = 42)	Still disease-free in 5 yr (n = 114)	HR (95% CI)
Demographics			
Age (yr)	70.3 (6.5)	68.2 (6.3)	1.05 (0.99–1.10)
Male sex	37 (88%)	94 (82%)	0.63 (0.25–1.61)
Disease duration	2.5 (3.8)	1.7 (2.4)	1.07 (0.97–1.18)
Education (yr)	14.4 (3.5)	14.3 (3.4)	1.00 (0.91–1.09)
MDS-UPDRS II	1.8 (2.1)	1.8 (2.9)	1.00 (0.89–1.11)
MDS-UPDRS III	6.8 (6.4)	4.1 (4.5)	**1.10 (1.04–1.16)**
MoCA	24.0 (4.2)	25.4 (3.3)	**0.91 (0.84–0.98)**
SCOPA-AUT	12.4 (8.6)	10.7 (6.3)	1.03 (0.99–1.07)
Antidepressant therapy	6 (14%)	23 (20%)	0.79 (0.33–1.90)
Benzodiazepine therapy	9 (21%)	27 (24%)	0.95 (0.45–2.01)
Language analysis			
Content richness (CD)	0.48 (0.85)	0.09 (0.92)	**1.74 (1.19–2.54)**
Vocabulary range (MATTR)	−0.26 (1.00)	−0.09 (0.99)	0.85 (0.62–1.16)
Sentence complexity (CC)	0.29 (0.79)	−0.03 (0.93)	1.37 (0.99–1.89)
Linguistic abnormalities (LCI)	0.17 (0.42)	−0.01 (0.47)	**2.35 (1.14–4.82)**
Articulation rate (NSR)	0.70 (1.02)	0.14 (0.90)	**1.58 (1.19–2.10)**
Prolonged pauses (DPI)	0.36 (1.08)	−0.06 (0.79)	**1.46 (1.09–1.96)**
Acoustic abnormalities (ACI)	0.53 (0.74)	0.04 (0.68)	**1.92 (1.34–2.75)**

Note: Data are presented as mean (SD) or number (%). Language features are z-scored across 5 languages. HRs for demographics were adjusted for age, sex, and study site. HRs for language features were adjusted for baseline age, sex, study site, years of education, and narrative topic. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: ACI = acoustic composite index; CC = coordinate clauses; CD = content density; CI = confidence interval; DPI = duration of pause intervals; HR = hazard ratio; iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; LCI = linguistic composite index; MATTR = moving-average type-to-token ratio; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NSR = net speech rate; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction Scale.

conversion into a specific diagnostic category. Similarly, we did not find any clinical measure as a risk predictor of conversion into a specific diagnostic category.

Discussion

In this large multicentric study, we have shown that language features estimated from natural, spontaneous speech predict conversion from iRBD into a defined neurodegenerative disease. Higher severity of linguistic abnormalities was a particularly strong risk factor in those patients converting to dementia or parkinsonism with MCI, suggesting that language assessment might provide a novel biomarker for the stratification of those developing cognitive impairment. Our approach demonstrated its effectiveness across various languages, significantly impacting its future application in multicenter clinical trials. The assessment of language shows promising potential, given its cost-effectiveness, noninvasive nature, and the ability to remotely record data via smartphones, making it conducive to scaling up for a broader population in the future. Consequently, our results underscore the possibility of developing an entirely automated, objective natural language processing approach for

Table 3. Baseline predictors of parkinsonism-first, parkinsonism-first and MCI, and dementia-first conversion in iRBD

	Parkinsonism-first within 5 yr (n = 17)	Parkinsonism-first and MCI within 5 yr (n = 9)	Dementia-first within 5 yr (n = 16)	Parkinsonism-first in 5 yr vs parkinsonism-first and MCI within 5 yr, OR (95% CI)	Parkinsonism-first within 5 yr vs dementia-first within 5 yr, OR (95% CI)	Parkinsonism-first and MCI within 5 yr vs dementia-first within 5 yr, OR (95% CI)
Demographics						
Age (yr)	70.0 (7.12)	69.2 (7.1)	71.1 (5.7)	0.98 (0.87–1.11)	1.03 (0.92–1.16)	1.04 (0.91–1.20)
Male sex	15 (88%)	8 (89%)	14 (88%)	1.02 (0.08–13.42)	1.02 (0.13–8.36)	1.23 (0.10–15.87)
Disease duration	2.6 (3.4)	2.1 (3.8)	2.6 (4.5)	0.90 (0.67–1.22)	0.98 (0.80–1.19)	1.05 (0.83–1.33)
Education (yr)	14.8 (2.7)	12.8 (2.9)	14.7 (3.8)	0.70 (0.46–1.08)	0.93 (0.76–1.14)	1.14 (0.88–1.48)
MDS-UPDRS II	2.2 (2.6)	2.3 (2.1)	1.0 (1.4)	1.06 (0.73–1.52)	0.66 (0.41–1.07)	0.60 (0.33–1.10)
MDS-UPDRS III	6.8 (6.4)	5.6 (3.4)	7.4 (7.8)	0.97 (0.81–1.17)	1.02 (0.90–1.15)	1.06 (0.91–1.25)
MoCA[a]	26.6 (1.7)	20.4 (2.9)	23.2 (5.0)	-	0.71 (0.51–1.00)	1.15 (0.94–1.41)
SCOPA-AUT	14.0 (9.5)	12.7 (11.5)	10.6 (5.5)	0.99 (0.91–1.07)	0.93 (0.84–1.04)	0.96 (0.86–1.07)
Antidepressant therapy	1 (6%)	3 (33%)	2 (13%)	7.80 (0.63–96.49)	1.99 (0.14–28.62)	0.33 (0.04–2.74)
Benzodiazepine therapy	2 (12%)	3 (33%)	4 (25%)	2.83 (0.31–25.64)	2.28 (0.32–16.09)	1.08 (0.13–8.76)
Language analysis						
Content richness (CD)	0.30 (0.62)	0.95 (1.03)	0.42 (0.90)	**7.46 (1.14–49.03)**	1.38 (0.49–3.93)	0.35 (0.11–1.16)
Vocabulary range (MATTR)	−0.60 (1.02)	−0.16 (0.56)	0.04 (1.11)	2.56 (0.59–11.19)	**4.08 (1.19–14.92)**	3.04 (0.53–17.53)
Sentence complexity (CC)	0.13 (0.62)	0.51 (0.42)	0.43 (1.06)	9.04 (0.80–102.34)	1.54 (0.55–4.32)	0.79 (0.26–2.41)
Linguistic abnormalities (LCI)	−0.06 (0.35)	0.43 (0.43)	0.27 (0.38)	**109.18 (2.08–5742.14)**	**21.17 (1.49–300.34)**	0.33 (0.03–3.30)
Articulation rate (NSR)	0.64 (1.00)	1.13 (0.90)	0.53 (1.11)	3.79 (0.78–18.25)	0.84 (0.39–1.83)	0.49 (0.19–1.26)
Prolonged pauses (DPI)	0.49 (1.12)	−0.05 (1.02)	0.46 (1.10)	0.37 (0.09–1.47)	0.87 (0.40–1.90)	2.51 (0.79–8.02)
Acoustic abnormalities (ACI)	0.56 (0.70)	0.54 (0.65)	0.49 (0.85)	1.01 (0.24–4.22)	0.78 (0.29–2.09)	0.93 (0.22–4.01)

Note: Data are presented as mean (SD) or number (%). Language features are z-scored across 5 languages. ORs for demographics were adjusted for age, sex, and study site. ORs for language features were adjusted for baseline age, sex, study site, years of education, and narrative topic. [a] The odds ratio for parkinsonism with and without MCI was not evaluated using MoCA because these two groups were determined based on their MoCA scores. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: ACI = acoustic composite index; CC = coordinate clauses; CD = content density; CI = confidence interval; DPI = duration of pause intervals; iRBD = isolated/idiopathic rapid eye movement sleep behavior disorder; LCI = linguistic composite index; MATTR = moving-average type-to-token ratio; MCI = mild cognitive impairment; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NSR = net speech rate; OR = odds ratio; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction scale.

the early detection and prediction of neurodegenerative synucleinopathies.

Predictive Language Markers of Phenoconversion

Grouping key linguistic and acoustic measures into composite indexes provided risk factors for conversion to synucleinopathy 2.7 years on average after baseline speech examination. This is intriguing given that language assessment was based on a simple story tale narrative task with an average number of 234 words that required approximately 2 minutes to administer. In the future, the sensitivity of this approach could likely be significantly enhanced by mass screening via smartphones outside a laboratory environment, enabling easy collection of considerably longer audio recordings.

From individual linguistic features, the most significant predictor of phenoconversion was content density, also reported as the only one to discriminate patients with iRBD without MCI from healthy controls in a previous single-center study.[12] Regarding acoustic features, patients with developed synucleinopathy exhibited a slower articulation rate, which is typically observed in patients with MCI[35] and DLB.[36] Because PD speakers commonly manifest normal or even increased articulation rate,[37] the slower articulation rate in our cohort likely reflected cognitive impairment. Indeed, PD with RBD represents a specific subtype of the disease, with more akinetic–rigid disease, gait dysfunction, autonomic dysfunction, and cognitive impairment,[38–40] and thus the decrease in articulation rate could also be expected. Finally, the production of longer pauses also indicated a higher risk of phenoconversion. Although we considered only pauses longer than 250 ms, which should be attributed to cognitive-linguistic processing, the contribution of speech-motor execution cannot be excluded. Indeed, longer pauses have been reported in all spectrums of neurodegenerative diseases, including PD,[25] MCI,[41] and Alzheimer's disease.[30]

Predictive Language Markers of Synucleinopathy Subtypes

Previous studies have indicated that cognitive performance is crucial in distinguishing between patients who developed dementia-first versus parkinsonism-first.[8,9] In the present study, linguistic analysis alone strongly predicted those developing dementia or parkinsonism with MCI. Indeed, language production is highly dependent on cognitive processes, from determining the utterance message, retrieving words from memory, creating grammatical sentences, and structuring coherent narratives.[42] In accordance with our results, a previous study has demonstrated that the presence of MCI in patients with PD is associated with higher language abnormalities,[12] likely due to the decline in cognitive abilities, such as memory, attention, and executive functions. Our findings clearly support that language analysis could provide a novel tool allowing differential diagnosis in the prodromal phase, particularly important considering the paucity of noninvasive and simple-to-administer techniques for discriminating dementia in synucleinopathy.

Patients with parkinsonism-first with MCI exhibited alterations primarily in content density and coordinate clauses, indicating lower use of content-bearing words and modifiers and difficulty constructing complex sentences. Patients with dementia-first showed poorer scores in MATTR, suggesting a deficiency in lexical richness and restriction in vocabulary. Although the rate of cognitive decline in the language domain is assumed to be more rapid for patients with DLB,[43] our patients with dementia-first and patients with parkinsonism-first with MCI exhibited largely overlapping patterns of language impairment. This would be in agreement with previous studies reporting similar language abnormalities in both patients with PD with dementia and patients with DLB.[11,36] On the other hand, it is important to note that our patients with parkinsonism and MCI already had a poor cognitive performance at baseline, which was retained until definitive conversion to synucleinopathy, and thus might contribute to the similar extent of linguistic abnormalities observed among both parkinsonism with MCI and dementia groups. In addition, it remains unknown whether the conversion to dementia versus parkinsonism first is related to a different top-down synuclein spread reaching the cortex before the substantia nigra or to the effects of co-morbid pathology.[44,45] For instance, Alzheimer's disease co-pathology and mutations in the glucocerebrosidase gene are more common in DLB,[46] which might influence resulting linguistic abnormalities.[47]

Automatic Language Analysis Approach

The use of ASR and NLP techniques for analyzing speech and language impairments in neurodegenerative diseases has the potential to revolutionize prediction and diagnosis. The accessibility and ease of use of these tools are significant advantages, as they are available in multiple languages, open-source, and free to use. The fully implemented and ready-to-use ASR and NLP tools secure a highly convenient approach for end-users without requiring additional extensive training datasets or higher coding skills. The objective analysis ensures consistent results, free from human observers' potential biases and subjectivity. Further advantages should also be noted, including noninvasiveness and low time consumption. Language analysis would not need specialized medical equipment because these tools can be

readily integrated into standard technology devices, such as smartphones or computers, making them highly accessible for use in clinical and research settings.

The advantage of the current approach is that we used only a limited set of non-overlapping language parameters with well-defined pathophysiology, making such analysis robust for potential overtraining. However, potential limitations of the speech and language analysis could be the ASR system's accuracy. Various elements can impact audio recordings, such as intricate accents, noisy environments, or speech impairments in the case of neurodegenerative diseases. Nevertheless, ongoing research in adapting the ASR system to impaired speech is already advancing and suggests greater improvements.[48] Although the word error rate of the ASR system used in this study has been reported to be up to 19% on similar data from patients with iRBD for the Czech language, the automated linguistic analysis provided highly comparable results to the one conducted manually by a human.[12] In addition, the Czech language poses a more challenging and complex task for ASR compared to more common Indo-European languages,[49] suggesting that we might already expect sufficient accuracy of language biomarkers that could be potentially added to the batteries used in clinical trials.

Limitations and Strengths

The strength of spoken language assessment is that it could be easily adopted at an individual patient predictive level. The presence of a slower articulation rate and an increased proportion of inappropriately placed pauses in subjects with iRBD has the highest chance of positively predicting phenoconversion. However, normal speech rate and pauses in subjects with iRBD do not imply a higher chance of a disease-free course. In addition, the presence of language abnormalities appears to be a strong marker for positively predicting the future development of dementia or parkinsonism with MCI, whereas normal language function is indicative of parkinsonism without cognitive impairment.

However, RBD in PD represents a so-called diffuse-malignant disease subtype with greater severity and faster progression.[50] Therefore, our predictor's value cannot be fully generalized to patients with PD/DLB without iRBD. Although this is the largest speech-based study performed including 180 patients with iRBD at baseline, only 42 patients developed neurodegenerative disease over a follow-up period of 5 years, which led to a relatively small sample size for the converter subtypes. In addition, it is not clear if results apply to the minority of iRBD developing MSA, as only one of the included subjects phenoconverted to MSA over the follow-up time. The phenoconversion of 26.9% of our patients with iRBD into overt synucleinopathy after 5-year follow-up is consistent with previous findings with an overall phenoconversion rate of 6.25% per year.[9] We can expect that the proportion of convertors will continue to increase with further follow-up. Indeed, the longest-term studies have found near inevitability of parkinsonism or dementia, with 73.5% of patients with iRBD converting after 12-year follow-up.[9] Therefore, we cannot determine whether disease risk estimated via language assessment changes over long disease durations. The designation of MCI was based on MDS level I criteria (ie, MoCA), which provides less diagnostic certainty than the MDS level II criteria (ie, neuropsychological battery).[34]

Conclusions

This study demonstrated that language analysis could predict phenoconversion from iRBD into defined synucleinopathy. Importantly, our findings highlight the potential of language impairments in identifying the risk of conversion into dementia-first or parkinsonism-first with MCI compared to parkinsonism-first alone. We analyzed our primary end points utilizing fully automated speech analysis of data from 7 clinical sites across 5 different languages, demonstrating the robustness of our approach. This noninvasive language assessment could offer a valuable addition to current biomarker batteries used in clinical trials, improving the accuracy and efficiency of synucleinopathy diagnosis.

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Author Contributions

M.Š. and J.R. contributed to the conception and design of the study, drafting the text and preparing the figure. All authors contributed to the acquisition and analysis of the data.

Potential Conflicts of Interest

Nothing to report.

Data availability

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

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