Neuroscience and Biobehavioral Reviews 167 (2024) 105922

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

From prodromal stages to clinical trials: The promise of digital speech biomarkers in Parkinson's disease

Jan Rusz [a,*], Paul Krack [b], Elina Tripoliti [c]

[a] Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic
[b] Movement Disorders Center, Department of Neurology, University Hospital of Bern, Bern, Switzerland
[c] UCL, Institute of Neurology, Department of Clinical and Movement Neurosciences, and National Hospital for Neurology and Neurosurgery, UCLH NHS Trust, London, UK

ARTICLE INFO

Keywords:
Parkinson's disease
Speech
Voice
Dysarthria
Acoustic
Machine learning
Neurological diseases

ABSTRACT

Speech impairment is a common and disabling symptom in Parkinson's disease (PD), affecting communication and quality of life. Advances in digital speech processing and artificial intelligence have revolutionized objective speech analysis. Given the complex nature of speech impairment, acoustic speech analysis offers unique biomarkers for neuroprotective treatments from the prodromal stages of PD. Digital speech biomarkers can monitor levodopa-induced motor complications, detect the effects of deep brain stimulation, and provide feedback for behavioral speech therapy. This review updates the mechanisms underlying speech impairment, the impact of speech phenotypes, and the effects of interventions on speech. We evaluate the strengths, potential weaknesses, and suitability of promising digital speech biomarkers in PD for capturing disease progression and treatment efficacy. Additionally, we explore the translational potential of PD speech biomarkers to other neuropsychiatric diseases, offering insights into motion, cognition, and emotion. Finally, we highlight knowledge gaps and suggest directions for future research to enhance the use of quantitative speech measures in disease-modifying clinical trials. The findings demonstrate that one year is sufficient to detect disease progression in early PD through speech biomarkers. Voice quality, pitch, loudness, and articulation measures appear to capture the efficacy of treatment interventions most effectively. Certain speech features, such as loudness and articulation rate, behave oppositely in different neurological diseases, offering valuable insights for differential diagnosis. In conclusion, this review highlights speech as a biomarker in tracking disease progression, especially in the prodromal stages of PD, and calls for further longitudinal studies to establish its efficacy across diverse populations.

1. Introduction

Speech represents the most complex quantitative marker of motor function highly susceptible to neurodegeneration, providing a window into brain health. Speech in Parkinson's disease (PD) is affected by common pathological manifestations such as akinesia, bradykinesia, and hypokinesia, leading to the reduced amplitude and automaticity of speech movements (Ho et al., 1999; Duffy, 2019; Bloem et al., 2021). The distinctive alteration of speech, characterized as hypokinetic dysarthria (Ho et al., 1999), represents early and frequent sign of disease with an estimated area under the curve of up to 0.93 between de-novo PD and healthy controls (Rusz et al., 2022a). Since speech problems worsen as the disease progresses (Skodda et al., 2013), dysarthria is gradually becoming one of the most disabling symptoms affecting social interaction and the quality of patients' life (Finnimore et al., 2022). Although dopaminergic medications might ameliorate some aspects of dysarthria mainly in the early stages (Rusz et al., 2021a), pharmacological and neurosurgical treatments of PD can further impair speech, including the development of dyskinetic speech fluctuations, stuttering-like behaviour, or stimulation-induced dysarthria (Tripoliti et al., 2014). Therefore, optimal evaluation and treatment of speech alterations in patients with PD demand an understanding of the multiple mechanisms and factors contributing to these problems.

Given the increasingly well-recognized link between speech deterioration and neurodegeneration, speech assessment is becoming a focus of interest in PD and related progressive neurological disorders. Vocal assessment offers intriguing potential advances because it is inexpensive and noninvasive, and recordings can be made remotely using commonly

* Correspondence to: Department of Circuit Theory, Czech Technical University in Prague, Technická 2, Prague 160 00, Czech Republic.
E-mail address: rusz.mz@gmail.com (J. Rusz).

https://doi.org/10.1016/j.neubiorev.2024.105922
Received 26 July 2024; Received in revised form 19 September 2024; Accepted 13 October 2024
Available online 18 October 2024

Table 1
Definition of basic terms relevant to speech disorders in PD.

Term	Definition	Pathophysiological interpretation
Dysprosody		
Monoloudness	Speech lacks normal variations in loudness. In Parkinsonian hypophonia, a key feature is decreasing volume during speech (similar to micrographia, a decreasing amplitude of writing), which is yet another complex, learned motor program requiring automatic execution disturbed in basal ganglia disorder.	Decreased amplitude of respiratory and thyroarytenoid muscles.
Monopitch	Pitch corresponds to the physiological parameter of the fundamental frequency of vibration of the vocal folds. Parkinsonian voice is characterized by monopitch or monotone. It lacks normal pitch variation.	Reduced amplitude of vocal cord movements, glottal incompetence.
Imprecise articulation		
Imprecise vowels	Vowels are distorted in their phonetic accuracy due to reduced range of articulatory movements of tongue, lips, and jaw.	Decreased range of movements of tongue and lips.
Articulatory decay	Articulation sounds less distinct due to reduced dynamical ability (akinesia/bradykinesia) of tongue and lip and jaw motion.	Reduced dynamical ability of tongue and lip motion.
Imprecise consonants	Consonants lack articulatory precision and show distortions and inadequate sharpness.	Inappropriate timing control of lip and tongue movements.
Dysphonia		
Harsh/breathy voice	Voice is perceived harsh, breathy, rough, and raspy.	Deteriorated control of vocal folds and laryngeal muscles, slow opening and inadequate closing of the vocal folds.
Pitch breaks	Subharmonic vibrations of the vocal folds representing a specific oscillatory pattern due to period and/or amplitude alternation of the glottal cycle, typically with half integer fraction of fundamental frequency. Pitch breaks can be perceived either as strained-strangled voice or voice sounding one octave lower. The pathophysiological mechanisms of pitch breaks are not well known, but can be related to two distinct vibrations with a frequency ratio of 3:2 or left-right asymmetry of vocal folds.	Asymmetry of vocal fold cycles.
Abnormal speech timing		
Abnormal rate	Rate of speech is abnormally low or rapid.	Impaired control of orofacial muscles.
Prolonged pauses	Prolongation of interword and intersyllable intervals.	Difficult initiation of speech, hesitations.
General terms associated with speech impairment and fluency severity		
Dysarthria	A collective name for a group of speech disorders resulting from disturbances in muscular control over the speech mechanism due to damage of the central or peripheral nervous system.	Problems in oral communication due to paralysis, weakness, or incoordination of the speech musculature.
Intelligibility	Measure of how comprehensible speech is, or the degree to which speech can be understood.	Problems in oral communication due to paralysis, weakness, or incoordination of the speech musculature.
Stuttering-like behaviour	This phemomena is characterized broadly as a group of variable speech dysfluencies that cover a heterogeneity of manifestations such as syllables/words repetitions, superfluous verbal behaviour, oral festination, palilalia and freezing of speech.	Impaired control of cortico-striato-cortical loop.
Festination of speech	Festination corresponds to a tendency to speed up and lose normal amplitude during quick, repetitive movements, such as speech.	Impaired control of motor preparation and execution processes
Freezing of speech	Freezing of speech definition can be adopted using freezing of gait definition. It can be defined as a brief, episodic absence of the speech despite the intention to speak. It includes episodes in which the patient cannot initiate speech (start hesitation) and arrests in forward progression during speech. It can become notable not only during fixed posture without audible airflow (e.g., "I… [no sound/pause] went…") but also fixed posture with audible airflow (e.g., "mmmmmy first ffffish") as in stuttering.	Impaired control of cortico-striato-cortical loop.
Palilalia	Involuntary repetition of syllables, words, and phrases. In PD, palilalia is mostly limited to repetition of syllables or words, not full sentences (at the difference to tic disorders), more similar to developmental stuttering. It usually appears along with an accelerating rate (or festination) and decreasing loudness (hypophonia).	Impaired control of cortico-striato-cortical loop.

available smartphone microphones, allowing clinicians to assess speech routinely at the clinic or during patients' daily life in home and community settings (Arora et al., 2018; Zhan et al., 2018; Omberg et al., 2022). In addition, the complex and early progressive nature of speech impairment captured and analysed digitally may provide unique access to a potential universal biomarker of diagnosis and progression of synucleinopathies for future neuroprotective trials (Rusz et al., 2021b). Digital speech biomarkers may also help in monitoring levodopa-induced motor complications (Omberg et al., 2022), detecting the footprint of deep brain stimulation side effects in speech related to current diffusion as opposed to specific beneficial effects of a given target and laying the foundation for closed loop treatments of dopaminergic treatments or postoperative deep brain stimulation management, (Little et al., 2016; Bouthour et al., 2019; Krack et al., 2019; Shah et al., 2023) as well as providing feedback for behavioural speech therapy efficacy (Tsanas et al., 2014). However, the current understanding of speech impairments is based mainly on cross-sectional studies that do not provide insight into the individual speech changes associated with disease progression (Moro-Velazquez et al., 2021; Ngo et al., 2022). The occasional use of quantitative speech assessment in routine clinical examination and poor understanding of the underlying mechanisms so far limit the use of speech measures as viable outcomes for both assessing disease progression and the effects of treatment (Pinto et al., 2004). Nonetheless, recent advances in digital speech biomarkers accompanied by clinical and imaging findings have generated knowledge relevant to the assessment, underlying mechanisms, and treatment of speech impairments in PD, resulting in the design of more effective clinical interventions (Narayana et al., 2022).

In this review, we first strive to assemble pieces of the puzzle regarding the mechanism underlying speech impairment, the impact of factors forming speech phenotypes, and the effect of interventions influencing speech. We then provide an overview of PD's most promising digital speech biomarkers and their reliability in capturing disease progression and treatment efficacy. We will also consider the translational potential of these digital speech biomarkers for other neurological diseases. Finally, we highlight knowledge gaps and provide insights that might lead to new discoveries and innovations to improve clinical decisions and treatments.

2. Mechanisms underlying speech disorder

2.1. Physiological basis of speech disorder

Speech is a complex task, and its intricate nature involves numerous anatomical structures and their coordinated interplay, encompassing both voluntary and reflex actions, modulated by cognition and emotion. Structures like the larynx, pharynx, tongue, oral cavity, and respiratory muscles, interconnected through a vast central network spanning cortical and subcortical regions (Ma et al., 2020). Beyond its role in motor function, the basal ganglia also project to limbic and associative territories (Castrioto et al., 2014), and their function can be extended to the automatic execution of learned behavioral plans. PD is also a neuropsychiatric disorder primarily affecting the basal ganglia, spreading to the neocortex at later stages (Weintraub et al., 2022). Given its complexity, speech is extremely sensitive to disturbances in the basal ganglia, resulting in a multidimensional impairment affecting mainly prosody, articulation, phonation, and speech timing (Table 1; see also Supplementary Material for associated references on individual speech symptoms) (Ho et al., 1999; Duffy, 2019).

The most typical clinical motor feature of dysarthria contributing particularly to *dysprosody* in PD is hypophonia, reflecting progressively decreasing loudness during speech or low variability of loudness (hereafter monoloudness) (Liotti et al., 2003). Loudness abnormalities can largely correspond to pure presynaptic nigrostriatal disorder and, similarly to bradykinesia in general, respond well to external stimuli. As the disease progresses, levodopa-induced dyskinesias develop in the majority of patients and might negatively impact speech by inducing fluctuations in loudness. In addition, the reduced amplitude of vocal cord movements leading to glottal incompetence is assumed to be responsible for monopitch, which is another core feature of dysprosody in PD (Bowen et al., 2013). Disturbance in motor planning also leads to poor coordination of the multiple muscles involved, including respiratory, laryngeal, pharyngeal, tongue, and lip movements, resulting in *imprecise articulation* and *dysphonia*. Articulatory abnormalities mainly reflect the decreased range and dynamical ability of movements of tongue and lips, leading to imprecise vowel articulation (Skrabal et al., 2022) and articulatory decay (Thies et al., 2023). Phonatory abnormalities result from irregular vocal fold vibrations leading to a harsh/-breathy voice (Blumin et al., 2004). As disease progresses, some patients may manifest asymmetry of vocal fold cycles, resulting in pitch breaks and perceptually rough voice (Hlavnicka et al., 2019). All these abnormalities represent spectral aspects of speech in principle.

Cognitive impairment of more advanced stage PD, also affecting cortical areas, is clinically characterized by dysexecutive syndrome, including problems in motor planning, slowness of thinking, or bradyphrenia. A*bnormal speech timing* is temporal speech deficit typically manifested by changes in the duration of basic physiological sources of speech, including voiced speech, unvoiced speech, pause, and respiration (Hlavnicka et al., 2017). The most typical features involve prolonged consonant duration associated with imprecise consonant articulation (Tykalova et al., 2017) and prolonged pauses disrupting the natural rhythm (Maffia et al., 2021). Also, abnormal speech rate in PD is typically associated with oral festinations and short “rushes” of speech (Skodda et al., 2011). All these aspects combined continuously contribute to reduced intelligibility (Chiu et al., 2020). The overall fluency of speech might also be compromised by stuttering-like behaviour, which might develop in some PD patients (Benke et al., 2000; Gooch et al., 2023). Clinically slowed cognitive processing speed results in bradyphrenia, further contributing to decreased fluency but also slow speech rate (Weintraub at al., 2022).

2.2. Speech and Braak staging system

The neuropathological mechanisms underlying speech disorders in PD are not well understood. Human vocalization engages many cortical and subcortical areas, including the midline structures of the brain (Kelm-Nelson et al., 2020). According to the Braak staging system of Parkinson’s disease (Braak et al., 2003), synucleinopathy starts in the lower brainstem, then spreads progressively to the midbrain dopaminergic neurons, is transported along the nigrostriatal and mesocorticolombic projections to the striatum and prefrontal cortex, and finally also by a transsynaptic cell to cell transmission from the striatum to larger cortical areas (Luk et al., 2012). This staging system allows for inferring the origin of speech dysfunction from different brain structures over the course of disease progression.

Involvement of dorsal motor nuclei in Braak stage 1 unlikely influences speech. However, as it is challenging to have speech recordings of the first Braak stage, some signs of PD in speech could still exist. Empirical evidence assumes very early subclinical speech involvement in PD in Braak stage 2. This evidence comes from recent studies on isolated rapid eye movement sleep behavior disorder (Rusz et al., 2022b, Skrabal et al., 2022), which is now considered a prodromal or premotor stage of synucleinopathies, as the majority of patients develop overt parkinsonism after a decade or more (Joza et al., 2023). Monopitch and imprecise vowel articulation have been shown to be already present in subjects with isolated rapid eye movement sleep behavior disorder and impaired olfaction despite a still largely functional nigrostriatal dopaminergic transmission according to clinical evaluation and imaging of the dopaminergic system (Fig. 1) (Rusz et al., 2022b, Skrabal et al., 2022).

Only in Braak stage 3, after approximately 80 % of the nigrostriatal dopaminergic neurons have degenerated and dopaminergic synapses are depleted by over 50 %, will patients and neurologists be able to detect the motor symptoms of PD. The degradation of nigral dopaminergic neurons by Lewy pathology in Braak stage 3 accounts for clinically detectable akinesia of speech musculature, leading to further worsening of dysprosody and imprecise articulation and aggravation of other voice dysfunction (Rusz et al., 2021a). These spectral speech features are typically responsive to levodopa therapy (Rusz et al., 2021a), supporting their connection with substantia nigra neuronal loss. Such assumption was further confirmed by the relationship between the extent of monopitch and nigro-putaminal dopaminergic deficits in de-novo PD (Rusz et al., 2022a).

Speech deficits involving the timing of speech subcomponents can be attributed to the degeneration of non-dopaminergic pathways affecting extranigral cortical and/or subcortical regions, i.e., Braak stage 4 and higher. A specific speech phenotype with predominant voice onset time dyscoordination has been revealed in de-novo PD patients with older age, greater severity of axial gait symptoms, and impaired cognitive performance (Rusz et al., 2021a). Further confirmation for non-dopaminergic pathways involved in PD dysarthria comes from the relationship between temporal speech and gait abnormalities typical for postural instability/gait disorder PD subtype (Rusz et al., 2023) that has been shown to be associated with diffuse regional grey matter atrophy (Boonstra et al., 2020). Furthermore, non-dopaminergic lesions account for the limited response of speech to pharmacological and neurosurgical interventions (Tripoliti et al., 2014). This evidence altogether supports a link between temporal speech abnormalities and cognitive deterioration, which correlates with the severity of PD and axial non-dopaminergic features.

In advanced Braak stages 5 and 6, the neocortex is finally affected, leading to more severe cognitive impairment (Braak et al., 2003), which further worsens temporal aspects of dysarthria in advanced PD and likely contributes to abnormal speech rate and stuttering-like behaviour (Tykalova et al., 2015). In this stage, not only dysarthria but also language and cognitive changes substantially affect communication in PD (Yorkston et al., 2017).

2.3. Neural correlates of speech

Precise vocal timing in humans requires accurate cortical control

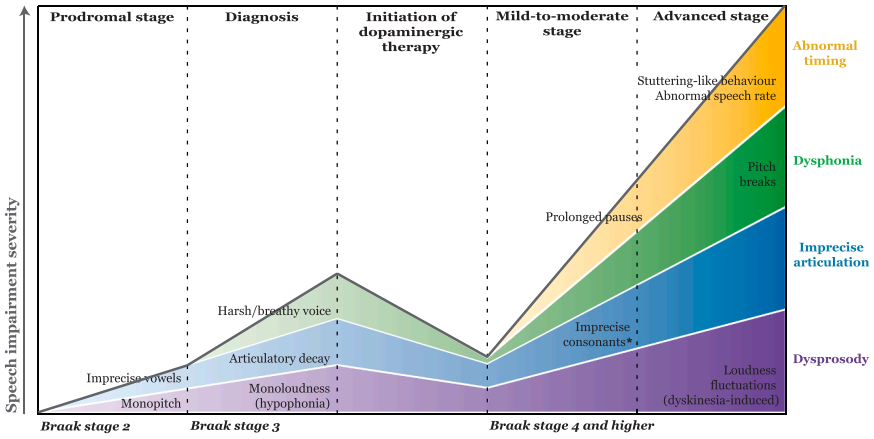


Fig. 1. Characteristic speech impairments in patients with PD as a function of disease stage. This hypothesized evolution of speech disorder in PD is based on expert opinion compiled from available empirical studies. *Articulatory-timing deficiency can already be a prominent sign at the time of diagnosis in patients with late PD onset.

(Fig. 2) (Sörös et al., 2006; Hage, 2020). The central executive of this network is in the ventrolateral prefrontal cortex (Simonyan et al., 2016). This is where the intricate coordination of breathing articulation and laryngeal control is enabled through the interaction with the subcortical vocal pattern-generating network, the periaqueductal grey. The precise input from the limbic system and the activity of the lower brainstem that controls vocal fold tension and respiration require further research.

While the perceptual and acoustic characteristics of speech in patients with PD have been extensively described (Ho et al., 1999; Duffy, 2019; Rusz et al., 2022a), few neuroimaging studies have investigated its neural underpinnings. Changes in cortical activation during phonation and reading have been reported using both positron emission tomography (Narayana et al., 2020) and functional magnetic resonance imaging (Narayana et al., 2022). These studies have shown both increases and decreases in activity of critical regions of the speech motor network, including primary orofacial sensorimotor cortices, the supplementary motor area, dorsal premotor cortex (including Broca's area), somatosensory and auditory cortices. The increased activity in these regions has been interpreted as a compensatory strategy (Rektorova et al., 2012), whereas the decreased activity is assigned to the reduced input to the cortex from the basal ganglia. Some discrepancies in the findings may also result from the variability of the patients' speech impairment, disease severity, methodological issues of speech imaging and limited sample size.

A recent study, in which the author studied the effects of intensive voice treatment compared to intensive articulation over 7 months, linked the effects of behavioural therapy to the activation of the auditory cortex (Narayana et al., 2022). The intensive voice treatment group showed increased activation of the right primary laryngeal/mouth motor cortex and left middle temporal gyrus, correlating with increased loudness. These changes were not observed in the intensive articulatory treatment. The latter group showed increased activation in the left posterior insula, an area involved in articulation and rate control (Ackermann and Riecker, 2010). Untreated controls showed a continued decrease in brain activity in motor, premotor, and auditory cortices, highlighting the need for early intervention.

The increased activation in the right posterior superior temporal gyrus in both groups post-treatment was interpreted as an intermediate phase in skill learning. This area has been associated with auditory feedback, as the link between the cortical control of vocalisation and articulation to the subcortical modulation of prosody in healthy controls, mammals and songbirds (Rektorova et al., 2012; New et al., 2015; Okobi et al., 2019; Moorman et al., 2021). Auditory feedback impairment is implicated in hypokinetic dysarthria and represents the main target of intensive voice therapy (Kiran and Larson, 2001; Stathopoulos et al., 2014; Mollaei et al., 2016).

3. Speech phenotypes

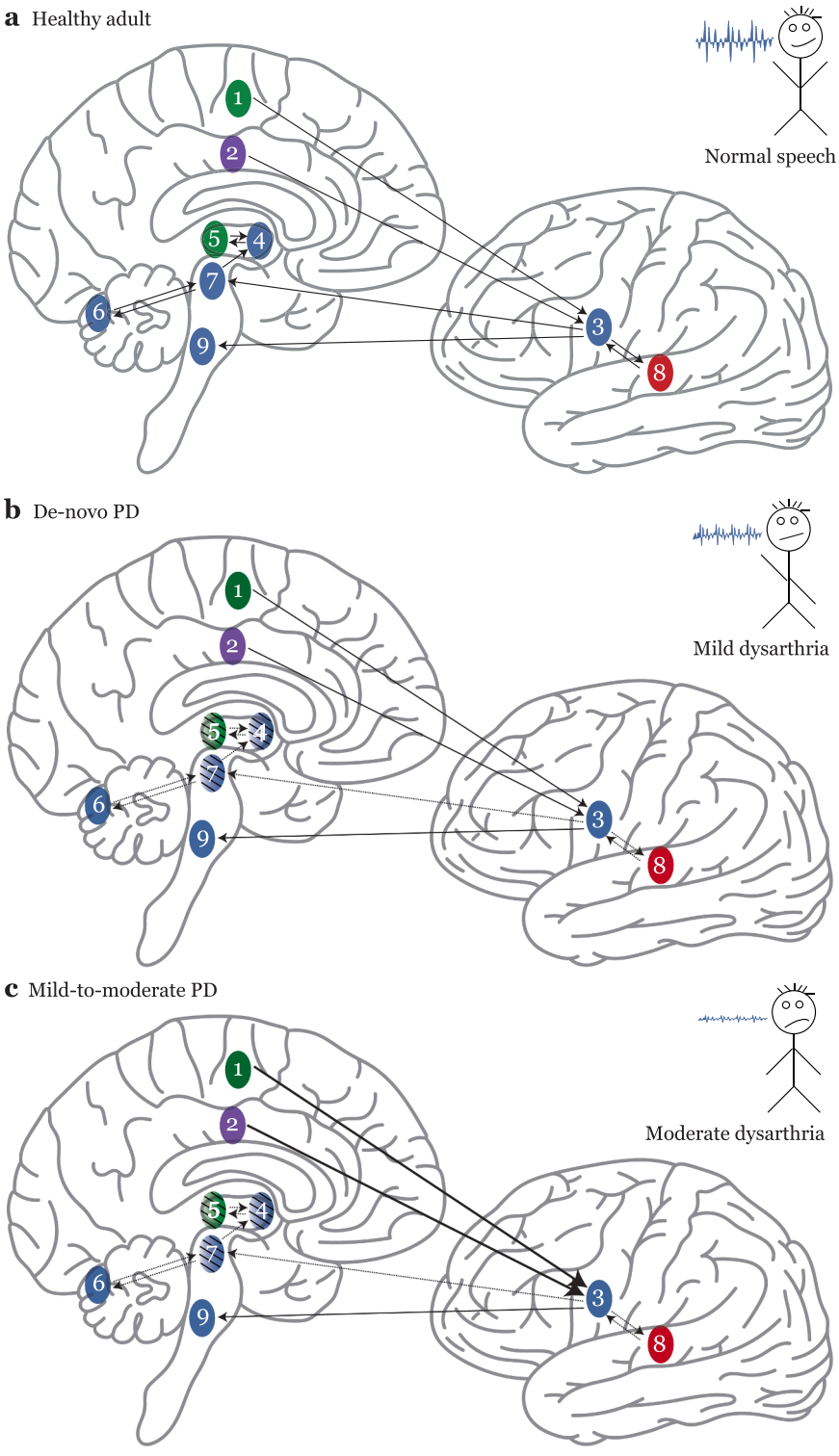
3.1. Factors influencing dysarthria in PD

Speech impairment in PD is a complex and variable phenomenon associated with multiple factors such as gender, age, and cognition, but also scaling and maintaining movement amplitude and effort, preprogramming and initiation of movements, internal cueing, sensory and temporal processing, automaticity, emotive vocalization, auditory feedback, and vocal vigilance (Pinto et al., 2004; Moreau and Pinto, 2019). Current evidence did not indicate that speech production is differentially affected by gender in PD (Rusz et al., 2022a, Houle et al., 2024). Considering age-specific voice changes, subjects with a late age at PD onset manifested decreased voice quality and more imprecise articulation compared to their younger counterparts (Rusz et al., 2021c). Cognitive impairment can also affect motor speech performance by impairing temporal coordination, including voicing leakage, prolonged pauses, and decreased rate, particularly during spontaneous speech (García et al., 2021; Rusz and Tykalova, 2021d). In general, compensatory adjustments to these factors and various non-motor factors (e.g., cognitive decline, depression, anxiety, and apathy) may complicate speech symptomatology.

3.2. Speech and clinical phenotypes of PD

Heterogeneous speech patterns and severity across individual patients also partially mimic clinical subtypes of PD. Specifically, PD patients with the non-tremor dominant subtype exhibit significantly lower voice quality and higher transglottal airflow than patients with the tremor-dominant phenotype (Burk et al., 2019). Similarly, speech impairment of PD patients with the postural instability/gait disorder subtype manifested more severe speech impairment, including pitch breaks, articulatory decay, decreased rate, and prolonged pauses, than those with the tremor-dominant subtype (Tykalova et al., 2020), likely reflecting faster disease progression, more severe akinesia, faster development of dyskinesia, non-motor symptoms, and cognitive impairment in this subtype (Aleksovski et al., 2018).

Rather than discrete subtypes, new arguments support data-driven subtyping covering a multidimensional continuum that accounts for



(caption on next page)

Fig. 2. Simplified theoretical model of speech production in healthy persons and in PD patients. Speech in PD is impaired by akinesia/bradykinesia related to the well-known dysfunction of cortico-basal ganglia-thalamocortical loops under dopaminergic control, impacting the automatic execution of learned motor programs (Pinto et al., 2004). Based on the theoretical model of speech production adapted from (Sörös et al., 2006), this figure highlights what is already known about mechanisms involved in healthy speech production and extends the hypothesized mechanism beyond for different disease stages of PD; the advanced stage of PD is not covered due to lack of evidence. Areas activated during speaking are shown for initiation (green), execution (blue), limbic integration (purple), and sensory-motor (auditory) integration (red) across brain centers including supplementary motor area (1), cingulate motor area (2), primary motor cortex (3), thalamus (4), putamen (5), vermal and paravermal cerebellum (6), red nucleus (7), bilateral posterior superior temporal gyrus (8), and nuclei innervating articulatory organs (9). Schematic fibre tracts connecting those areas are shown in black arrows. **a,** Speech in healthy subject is achieved via processing across the supplementary motor area (1) and the cingulate motor cortex (2) which are connected with the primary motor cortex (3). Automaticity of speech requires several connections between the cortical and subcortical motor and limbic systems. Subcortical activation is found in the thalamus (4), putamen (5) and the red nucleus (7). The vermal and paravermal cerebellum (6) is activated with longer utterances and has been found to control a fast speech rate. In addition, the bilateral posterior superior temporal gyrus (8) is activated. The brain stem nuclei (9) innervate the articulatory organs. **b,** Speech in de-novo PD patients is affected by substantial degeneration of nigral-striatal dopaminergic neurons (shown by stripy area). There is reduced left thalamus /putamen connectivity (dashed arrows) to the superior temporal gyrus, only partially normalised by levodopa. There is also increased activation in the primary motor cortex (3) possibly as a compensatory strategy for the impaired recruitment of subcortical structures. **c,** Speech in patients with mild-to-moderate stages of PD and longer disease duration is related to increased connectivity between the supplementary motor area (1), cingulate motor area (2), and the primary motor cortex (3) (bold arrows). An unanticipated increased connectivity between the right primary motor cortex (3) and the right putamen (5) may be due to dopaminergic medication, speech therapy, or other compensatory strategy. Despite the intact cortical connectivity, there is decreased connectivity between the right superior temporal gyrus/the right primary motor cortex (3) and the right putamen/left thalamus (cortical-subcortical connectivity), which can account for the monotonicity-low volume and the difficulties initiating speech.

various modifiers, including non-motor symptoms (Berg et al., 2021). In this regard, a recent study revealed three distinct motor speech subtypes among de-novo PD with similar prevalence, symptom duration and motor severity (Rusz et al., 2021a). Beside monopitch and monoloudness that were common in each subtype, speech impairment was more severe in the phonatory-prosodic subtype with predominant dysphonia and the articulatory-prosodic subtype with predominant imprecise consonant articulation than in the prosodic subtype (Rusz et al., 2021a). Most importantly, the phonatory-prosodic subtype was associated with preserved cognitive performance and good response to levodopa therapy, while the articulatory-prosodic subtype with older age, greater severity of axial gait symptoms, and poorer cognitive performance (Rusz et al., 2021a).

3.3. Stuttering-like behaviour

Acquired neurogenic stuttering is characterized broadly as a group of variable speech dysfluencies covering a heterogeneity of manifestations such as syllables/word repetitions, superfluous verbal behaviour, oral festination, palilalia, and speech freezing. This behaviour is one of the most debilitating and challenging to assess with no available therapies, contributing to limited intelligibility and social isolation, and degradation of interpersonal interactions of patients with PD. Different theories have been proposed to explain the underlying mechanisms, including advanced disease stage, severity of motor impairment and cognitive decline, presence of dyskinesias, or even re-emergence of childhood stuttering (Gooch et al., 2023; Im et al., 2018). One possible theory behind the stuttering-like behaviour is the excess dopamine theory of stuttering (Wu et al., 1997). The cortico-basal ganglia-cortical network was implicated as a neural substrate of acquired neurogenic stuttering (Max et al., 2019). A recent study investigating stroke-induced stuttering revealed a common network centred around the left putamen, including the claustrum, and amygdalostriatal transition area (Theys et al., 2024), that might also explain acquired neurogenic stuttering in PD. In addition, a faster speaking rate (i.e., a possible precursor of oral festination) was observed mainly in the postural instability/gait disorder subtype of PD (Rusz et al., 2023), characterized by more severe alterations of cortico–basal pathways (Boonstra et al., 2020). A faster speaking rate is also a well-known aspect of hypomania or mania, which can occur as a side effect of dopaminergic treatment (Weintraub et al., 2022). Clinical observations of speech festination in PD could be explained by two separate networks responsible for speech motor preparation and execution processes, including the medial and dorsolateral premotor cortex, anterior insula, and superior cerebellum versus sensorimotor cortex, basal ganglia, and inferior cerebellum (Riecker et al., 2005).

4. Interventions influencing speech

4.1. Pharmacological interventions

As the vast majority of patients are treated by dopaminergic medication, pharmacological interventions represent the most common factor influencing speech disorders in PD. The effect of dopaminergic medication for motor speech control in PD is not as effective as for gross motor manifestations, including rigidity, bradykinesia, and resting tremor. Inconclusive findings across the literature even led to a common belief that speech disorder is a "levodopa-resistant" axial motor symptom of PD. Such inconsistency might be caused by mixing results obtained via both short-term (i.e., levodopa challenge) and long-term design. A poor short-term effect of dopaminergic therapy on speech in early PD is possibly masked by the long-duration response of dopaminergic treatment (Tykalova et al., 2022). It has been suggested that a prolonged washout of 15 days from chronically administered levodopa would be needed for evaluation of actual short-term response on speech (Sciacca et al., 2023). In clinical practice, this is not feasible as it would put patients at risk for worsening motor symptoms or even developing an akinetic crisis.

However, in de-novo PD patients, speech impairment has a favourable response to long-term dopaminergic therapy after treatment starts (Rusz et al., 2021a). The beneficial effect of levodopa was particularly notable for dysphonia (Rusz et al., 2021a), although some improvements in all spectral aspects of speech, such as intonation, loudness, and vowel articulation, might also be expected (Fig. 1). Further supporting this, a meta-analysis concluded that levodopa therapy in PD mainly improves voice quality associated with akinetic-rigid syndrome (Lechien et al., 2018). Although effective, the severity of speech impairment in these very early stages is mild on average and thus typically results in only slight perceptual improvement. In general, dopaminergic therapy appears to stabilize spectral aspects of speech, while little improvements can be expected for temporal deficits arising in more advanced stages of PD due to ensuing cognitive deterioration (García et al., 2021; Rusz and Tykalova, 2021d). Indeed, as PD progresses, the beneficial levodopa response decreases, possibly due to non-dopaminergic lesions involved in speech production (Bonnet et al., 1987). In the long term, some speech deterioration can also be related to levodopa-induced dyskinesia in advanced PD (Cavallieri et al., 2021). Additionally, chronic use of levodopa might contribute to developing stuttering-like behaviour and freezing of speech (Tykalova et al., 2015).

4.2. Surgical interventions

The role of deep brain stimulation in both beneficial and adverse

speech responses following stereotactic neurosurgery is still debated due to the variability and high occurrence of speech deficits (Pinto et al., 2023). Although some studies examined the effects of the thalamic ventral intermediate nucleus and the globus pallidus pars interna deep brain stimulation on speech, most of the available evidence refers to subthalamic nucleus stimulation (Lachenmayer et al., 2021).

Short-term improvement in non-speech oral movements is possible with subthalamic nucleus stimulation (Krack et al., 2003; Pinto et al., 2005; Bobin et al., 2024), however overall speech intelligibility is the only function not improved following 5 years of subthalamic nucleus stimulation (Hariz et al., 2022), with some patients reporting unequivocal worsening of speech over time, not modifiable with adjustment of stimulation and medication (Rodriguez-Oroz et al., 2012; Deuschl et al., 2013). There is a discrepancy between improvement in simple oromotor tasks and the deterioration in connected speech (Tripoliti et al., 2014). This discrepancy has been attributed to surgical parameters such as electrode positioning and the spread of electrical current outside of the subthalamic nucleus to surrounding fibre tracts, including pyramidal, cerebellothalamic, and pallidothalamic tracts (Lange et al., 2023). Higher electrical parameters have been implicated in speech deterioration (Krack et al., 2002; Pinto et al., 2005). However, a decrease in pulse width (Petry-Schmelzer er al, 2022), frequency (Nirosen et al., 2021), or amplitude (Tripoliti et al., 2008) of stimulation often cannot be sustained in the long term due to deterioration of motor symptoms (Fabbri et al., 2019). Longer disease duration was linked to worse speech outcome (Tripoliti et al., 2014), a finding reflecting the complexity of speech neural control. The relative late onset of speech problems- in some patients more than one year after surgery- and the perceptually distinct non-parkinsonian speech quality renders any pre-operative factors harder to investigate (Tsuboi et al., 2017). New means for reprogramming stimulation parameters are emerging based on use of focal bipolar stimulation, current steering away from incriminated fibre systems, imaging-based modelling of the shape of the volume of tissue activated and its distance to fibre tracts (Krack et al., 2002; Jorge et al., 2020; Wardell et al., 2022; Debove et al., 2023; Schulder et al., 2023).

Also, focused ultrasound technology offers a promising alternative for patients with PD, particularly those who are not ideal candidates for deep brain stimulation or other more invasive procedures (Martínez-Fernández et al., 2023). However, no study has yet performed detailed analysis on potential adverse effects of such therapy in speech.

4.3. Behavioural interventions

The most effective treatment for dysarthria in patients with PD is behavioral speech therapy, focusing on one or a combination of different aspects of speech production via exercises (Muñoz-Vigueras et al., 2021; Perry et al., 2024). In the last two decades, intensive voice therapy, particularly the Lee Silverman Voice Treatment (LSVT LOUD) (Ramig et al., 2018), has been most commonly applied in clinical practice. LSVT LOUD aims to increase good-quality vocal loudness through high-effort, intensive treatment over four weeks. Recent randomized controlled trials found that LSVT LOUD significantly improved intelligibility, loudness level and functional communication with therapy gains lasting from seven months post-treatment to two years (Ramig et al., 2018; Levy et al., 2020). The effectiveness of the LSVT LOUD relies on salience (treatment individually tailored to patient interests and voice) and calibration through retraining of auditory-sensory feedback and internal cueing (Narayana et al., 2022).

Challenges related to the maintenance of gains motivated further development of group treatments (Behrman et al., 2020; Schalling et al., 2021). Among them, group singing is a promising medium to address both speech and neuropsychiatric symptoms in PD, as it may improve mood and motivation. It requires respiratory support and higher vocal effort and can provide rhythmic cues to regulate tempo and stress through stimulation and organization of motor output. Twelve months of participation in a PD-specific therapeutic singing program had positive and sustained effects on vocal loudness and voice-related quality of life (Tamplin et al., 2020).

5. Digital speech biomarkers

5.1. Acoustic measures in PD

Technological advances have produced relatively low-cost microphones that can convert the patients' sound pressure signal into an electric signal. Acoustic analysis of these digitalized speech signals revolutionised objective assessment, allowing the quantitative and more granular evaluation of individual dysarthria components, including the detection of subtle, subliminal deviations in speech and their changes over time (Rusz et al., 2021a). Recording of three simple types of vocal tasks, including connected speech (e.g., reading, monologue, retelling), sustained vowel, and fast syllable repetition, can give us representative speech material to obtain a complete profile of motor speech disorder in patients with PD (Duffy, 2019; Rusz et al., 2021).

In current clinical practice, the Mayo Clinic dysarthria rating scale is most commonly used to perceptually rank different aspects of motor speech disorder (e.g., harsh/breathy voice, imprecise vowels, monopitch, monoloudness, prolonged pauses) (Duffy, 2019). In the same principle, acoustic analyses can provide objective markers on different components of speech impairment corresponding with these landmark perceptual characteristics (Duffy, 2019). There is no consensus about the ideal acoustic outcome measures used for the evaluation of speech disorders. Amongst numerous existing outcome measures (Moro-Velazquez et al., 2021; Ngo et al., 2022), recent guidelines on speech recording and acoustic analysis in dysarthria recommended several representative aspects to quantify motor speech profile objectively (Rusz et al., 2021). This review lists 9 main acoustic digital speech biomarkers that form a representative spectrum of fundamental acoustic speech changes due to Parkinsonian dysarthria (Fig. 3). These were chosen according to the following criteria: (i) the high level of diagnostic validation for dysarthria in PD confirmed at least by three high-quality studies, (ii) validation in two or more independent languages, (iii) availability of pathophysiological and perceptual interpretation, (iv) each measure represents unique aspect of speech (i.e., these measures are generally uncorrelated one to each other), (v) possibility of fully-automated analysis for clinical trials.

Considering dysprosody, changes in natural loudness of speech can be analyzed using an acoustic measure of intensity variability (Rusz et al., 2011), which reflects the auditory perception of *monoloudness*. Natural changes in intonation can be assessed using the acoustic prosodic measure of fundamental frequency variability (Rusz et al., 2011), with auditory-perceptual correlate of *monopitch*. In the articulation domain, a shift in the first two formant frequencies reflecting mainly tongue and lips movement reduces the vowel space area or leads to a vowel centralization (Illner et al., 2023a). These correlate with the auditory perception of *imprecise vowels*. The overall dynamic movement ability of individual vocal tract elements can be captured by mel-frequency cepstral coefficients or specifically by the distance between the second formant and antiformant (Illner et al., 2023b), which can perceptually mirror *articulatory decay*. Coordination of speech articulation and voicing is measured by voice onset time, reflecting *imprecise consonants* (Novotny et al., 2014). Most typically used phonatory measures involve perturbation measures (jitter, shimmer, and its variants), noise measures (harmonics-to-noise ratio or noise-to-harmonics ratio), and cepstral peak prominence (Šimek and Rusz, 2021); these correlate with the auditory perception of decreased voice quality leading to *harsh/breathy voice*. In addition, subharmonic vibrations of the vocal folds, typically at half fundamental frequency are called *pitch breaks* (Hlavnicka et al., 2019), which perceptually resemble a rough voice or a voice sounding one octave lower. Speech timing abnormalities can be reflected by *abnormal rate,* which is commonly measured by net speech rate as the number of syllables per second after

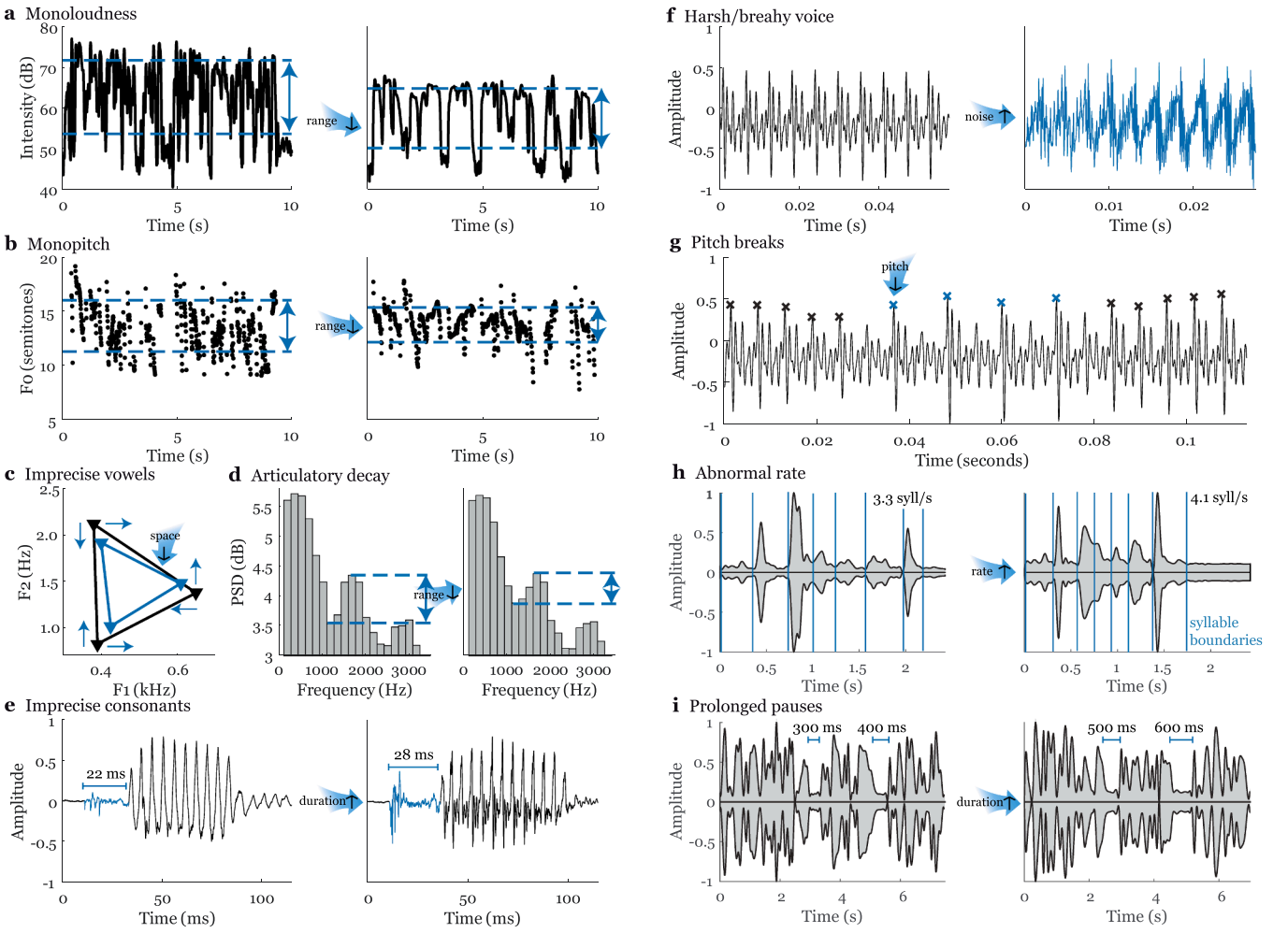


Fig. 3. Demonstration of change in digital speech biomarkers due to dysarthria. Measures capturing the representative spectrum of fundamental acoustic speech changes due to Parkinsonian dysarthria: **a,** *Intensity variability*, defined as the standard deviation of intensity contour. **b,** *Pitch variability* is defined as the standard deviation of fundamental frequency (F0) contour. **c,** *Vowel space area* is calculated as the area of a triangular or quadrilateral polygon formed by the corner vowels. The triangular vowel space area is constructed using the Euclidean distances between the first (F1) and second (F2) formant coordinates of the corner vowels /a/, /i/, and /u/ in the triangular F1–F2 vowel space. Alternatively, vowel centralization measures are defined as the ratio of the sum of individual formant frequencies of corner vowels. **d,** *Resonant frequency attenuation* is defined as the differences between the maxima of the F2 region and the minima of the local valley region called antiformant. The same principle can be applied using mel-frequency cepstral coefficients, where the selection of coefficients determines the frequency bandwidth of interest. **e,** *Voice onset time* is defined as the length of the consonant from initial burst to vowel onset. **f,** Measures of microperturbations and noise. *Jitter* is designed to assess the frequency of microinstability in vocal fold vibrations and measures the variability of fundamental frequency from one cycle to the next. *Shimmer,* is designed to assess the amplitude of microinstability in vocal fold vibrations and measures the variability of the maximum extent of the amplitude of each vocal fold vibration from one cycle to the next. *Harmonics-to-noise ratio,* which represents the amount of noise in voice signals, is derived from the signal-to-noise estimates in the autocorrelation of each cycle. Alternatively, *cepstral peak prominence* is defined as the measure of cepstral peak amplitude normalized for overall amplitude. **g,** *Degree of unvoiced segments* or *proportion of subharmonic intervals* is defined as the ratio of the total duration of subharmonic intervals per total duration of all voiced intervals. **h,** *Net speech rate* is defined as the total number of syllables divided by the total duration of speech after the removal of pauses. g, *Duration of pauses intervals* is defined as the median length of pause intervals.

the removal of pauses (Illner et al., 2022). *Prolonged pauses* are then typically measured as a median duration of pauses (Hlavnicka et al., 2017).

5.2. Defining dysarthria severity outcomes

The percentage of intelligible words is currently the standard objective marker to estimate speech impairment severity. It is easy to interpret and can be evaluated both perceptually by listeners transcribing what they understood (Chiu et al., 2020), or algorithmically by comparing the accuracy of automatic speech-to-text conversion to the original text (Dimauro et al., 2017). Still, reduced intelligibility is not PD-specific, does not inform about underlying mechanisms, and may be unsuitable for characterizing and monitoring subtle speech changes.

Another approach is to group key acoustic measures of hypokinetic dysarthria into a composite speech index (Rusz et al., 2021a), which can potentially improve the sensitivity and clinical interpretation as the basis of individualized therapeutic interventions. Also, machine learning and deep neural networks have been extensively adopted to provide speech outcomes based on combined features for PD detection over the last few years (Moro-Velazquez et al., 2021; Ngo et al., 2022). Recently, embeddings extracted using pre-trained deep neural networks outperformed traditional clinically interpretable features in detecting PD speech disorder (Favaro et al., 2023). However, the disadvantage is the limited clinical interpretability of such an approach (Ge et al., 2023).

The estimation of stuttering-like behaviour as a proxy of fluency is currently based on the auditory-perceptual calculation of the percentage of disfluent events that can be separated into different categories (Gooch

et al., 2023). There is an absence of automated measures to measure speech fluency in patients with neurological diseases, as stuttering in parallel with dysarthria makes developing robust technology difficult. Also, the protocols used to assess speech fluency are typically based on short speech material that is unrepresentative of everyday situations and thus might not be sufficient to produce the number of stuttering episodes needed for advanced analyses.

5.3. Sensitivity for clinical trials

The most plausible application of digital speech biomarkers is for detecting disease progression and treatment efficacy. Available prospective observational speech studies reported one year as a sufficiently long interval to detect natural disease progression already in prodromal stages of PD, suggesting digital speech assessment as one of the most sensitive progressive markers available (Miglis et al., 2021). Composite speech impairment score combining relevant aspects of dysarthria was the most sensitive to disease progression, although a speech deterioration was detectable across the majority of individual speech measures (Table 2, Fig. 4; see also Supplementary Material for associated references). However, there is still a deficient number of longitudinal studies researching speech progression over durations relevant to clinical trial timelines. Although a vast number of cross-sectional studies report a very high accuracy of speech biomarkers in differentiation between PD and healthy speakers (Moro-Velazquez et al., 2021; Ngo et al., 2022), these accuracies have to be interpreted with caution as measures successful in cross-sectional comparisons do not need to predict longitudinal behaviour (Stegmann et al., 2020). This is because algorithm performance might be more vulnerable to dysarthria, thus contributing to better separation accuracy between healthy and dysarthric speech than is reality.

Considering treatment efficacy, the effect of dopaminergic therapy can be captured via spectral aspects of speech associated with harsh/breathy voice quality, monopitch, monoloudness, and vowel

Table 2
Sensitivity of speech biomarkers in PD for clinical trials.

Speech dimensions affected in PD		Sensitivity to			
[measurement(s)]		Natural disease progression	Pharmacological interventions	Surgical interventions	Behavioural interventions
Dysprosody					
Monoloudness #	Time interval	No change 1 yr	1.4 yr, Two conditions	1 yr, Two conditions	Two conditions
[intensity variability,	Stage of PD	Prodromal, Early	Early, Late	Late	Late
sound pressure level]	Level of evidence	Moderate	Moderate	High	High
Monopitch	Time interval	2 yrs	1.4 yr, Two conditions	1 yr, Two conditions	Two conditions
[fundamental frequency	Stage of PD	Prodromal, Late	Early	Late	Late
variability]	Level of evidence	Moderate	High	High	High
Imprecise articulation					
Imprecise vowels	Time interval	2.8 yrs	1.4 yr, Two conditions	Two conditions	Two conditions
[vowel space area,	Stage of PD	Late	Early	Late	Late
formant indexes]	Level of evidence	Low	Moderate	High	Low
Articulatory decay	Time interval		Two conditions	Two conditions	Two conditions
[F2 to antiformant distance,	Stage of PD		Late	Late	Late
MFCCs variability]	Level of evidence		Low	Low	Low
Imprecise consonants	Time interval	1 yr	No change 1 yr	No change	
[voice onset time]	Stage of PD	Early	Early	Late	
	Level of evidence	Low	Moderate	Low	
Dysphonia					
Harsh/breathy voice	Time interval	1 yr, 2.7 yrs	1 yr	Two conditions	Two conditions
[Jitter, Shimmer,	Stage of PD	Prodromal, Late	Early, Late	Late	Late
HNR, CPP]	Level of evidence	Moderate	High	High	High
Pitch breaks	Time interval		No change	Two conditions	
[degree of unvoiced segments,	Stage of PD		Late	Late	
subharmonics]	Level of evidence		Low	Low	
Abnormal speech timing					
Abnormal rate	Time interval	2.7 yrs	No change	1 yr, Two conditions	Two conditions
[net speech rate]	Stage of PD	Late	Early, Late	Late	Late
	Level of evidence	Low	High	High	Low
Prolonged pauses	Time interval	2.7 yrs	No change	Two conditions	
[duration of pauses]	Stage of PD	Late	Early, Late	Late	
	Level of evidence	Low	High	Low	
Speech impairment and fluency severity					
Dysarthria severity	Time interval	1 yr	1 yr		Two conditions
[composite score,	Stage of PD	Prodromal, Early	Early		Late
machine learning endpoint]	Level of evidence	Moderate	Moderate		Low
Intelligibility	Time interval	No change 1 yr	Two conditions	1 yr	Two conditions
[percentage intelligible	Stage of PD	Late	Late	Late	Late
words]	Level of evidence	High	Low	High	High
Stuttering-like behaviour	Time interval	4.5 yrs	No change	No change	
[percentage disfluent	Stage of PD	Early	Late	Late	
words]	Level of evidence	Low	Low	Low	

Time interval refers to average time necessary to capture disease progression/treatment efficacy on a group level in years. "Two conditions" refers to investigation between 2 follow-up conditions performed in a relatively short time, for instance in ON and OFF medication state, ON and OFF stimulation state and/or before and immediately after stopping therapy (Pre vs Post). tage of PD refers to three stages considered including prodromal (before diagnosis and dopaminergic therapy initiation), early (disease duration < 5 years since diagnosis), and late (not fulfilling prodromal/early stage). For level of evidence, an entry of 'low' implies a single high-quality study, 'moderate' implies at least one high-sample (n>100) or two high-quality studies, and 'high' implies at least three high-quality studies. If there was probability that same cohort of patients was used for two studies, only one study was considered.
The same measurement is also effective to capture excessive loudness fluctuations due to dyskinesia (i.e., values will be above the normal speech).
Absolute intensity level reflecting hypophonia is hard to capture by acoustic analysis because the need for precise microphone calibration to obtain reliable estimates.
F2 = second formant, MFCC = mel-frequency cepstral coefficients, HNR = harmonics-to-noise ratio, CPP = cepstral peak prominence.

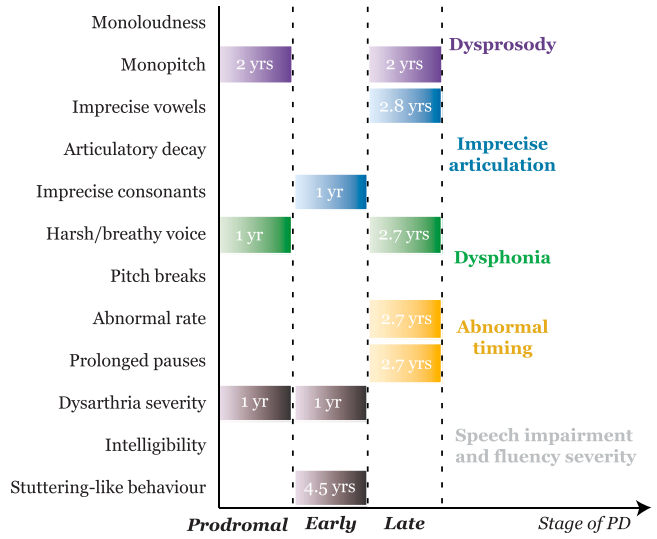


Fig. 4. Sensitivity of speech biomarkers in PD to natural disease progression. While the progression of many speech aspects will likely be confirmed, the figure lists only those already supported by current literature findings. Time interval refers to the average time necessary to capture disease progression on a group level in years. Stage of PD refers to three stages considered, including prodromal (before diagnosis and dopaminergic therapy initiation), early (disease duration < 5 years since diagnosis), and late (not fulfilling prodromal/early stage).

articulation (Table 2; see also Supplementary Material for associated references). Intelligibility and monoloudness appear to be the most validated measures to detect the effect of surgical intervention. Nevertheless, deep brain stimulation might influence most available speech features in PD, with the highest level of evidence for monopitch, imprecise vowels, harsh/breathy voice, and abnormal rate (Table 2; see also Supplementary Material for associated references). Similarly, the most reliable measures to detect the beneficial effect of behavioural speech therapy are intelligibility and monoloudness. While monopitch and harsh/breathy voice appear also to be improved by behavioural speech therapy, more evidence is needed regarding problems with articulation and speech timing (Table 2; see also Supplementary Material for associated references). The challenge in selecting suitable speech biomarkers to detect treatment efficacy arises from limited evidence due to the small sample sizes available, heterogeneity of the studied population, and lack of standardized examination protocol and acoustic methodology. Also, the effect of therapy might differ significantly in various PD populations. Therefore, it is important to report speech problems in PD in conjunction with exhaustive information on the stage of the disease, preferably accompanied by disease phenotype and a detailed evaluation of motor and non-motor symptoms. Another common issue limiting the estimation of sensitivity of therapy outcomes is the missing control group, which should be ideally composed of non-treated patients of similar disease duration (Hariz and Blomstedt, 2022). Because of the lack of a control group, it cannot be excluded that the reported effect of treatment is related to simple speech variability (typically around 10 % in mildly impaired speech) (Kothare et al., 2022; Stipancic et al., 2022) or learning effect (particularly in shorter speaking tasks such as sustained vowel or syllable repetition) (Feng et al., 2024). This issue is mainly relevant for studies seeking machine learning outcomes using many clinically non-interpretable features applied to relatively small sample size cohorts (i.e., the number of features tends to exceed the number of samples) (Ge et al., 2023).

One additional general challenge is a potential lingual-specific sensitivity of speech assessment. Although pilot cross-sectional findings revealed a broadly similar nature of speech impairment in PD across multiple languages (Rusz et al., 2021a; Kothare et al., 2024; Kovac et al., 2024), further research is required to validate the language-specific sensitivity of speech assessment to both disease progression and treatment efficacy. Future studies should also investigate changes in speech parameters in intervention studies to identify therapy endpoints and better estimate the duration and number of patients required for clinical trials.

5.4. Remote smartphone-based speech assessment

The smartphone-based approach can offer frequent, objective, real-world assessments with enormous amounts of data in a short time frame, leading to better sensitivity and stability of speech assessment compared to a single, time-limited laboratory evaluation. Thus, monitoring via smartphone could be extremely valuable in assessing treatment and disease-modifying effects in clinical trials (Lipsmeier et al., 2018). Indeed, pilot cross-sectional studies showed that smartphone-based voice assessment in combination with machine learning techniques might facilitate screening for prodromal neurodegeneration, monitoring daily fluctuations of response to medication, and quantifying disease severity (Arora et al., 2018; Zhan et al., 2018; Kothare et al., 2022b; Omberg et al., 2022). Monitoring patients with daily phone calls may capture how patients speak outside of the artificial laboratory setting, where other factors such as environmental noise, dual-tasking, social interactions, or emotional influence have important roles and thus provide a natural biomarker of PD progression (Illner et al., 2024). Furthermore, a range of mobile phone applications have been developed for managing PD on platforms like Google Play and the App store (Linares-Del Rey et al., 2019). In particular, many of these are useful for assistance in oral communication such as text to speech conversion and for providing speech rehabilitation guidance such as delayed auditory feedback to improve speech and reduce stuttering and voice volume training (Linares-Del Rey et al., 2019).

However, while many smartphone-based applications show potential, the scientific evidence of their efficacy is often limited (Linares-Del Rey et al., 2019), and there are many challenges in the validation of real-world data. These are obtained without an investigator guiding a recording protocol or labelling specific speech paradigms (van der Walt et al., 2022). The quality of the smartphone microphone is typically much lower than that of a professional condenser microphone used in research practice and differs from device to device (Rusz et al., 2018). Furthermore, the unstable direction and distance of the microphone from the lips due to holding the phone differently and background noise make speech assessment in everyday environments challenging (Rusz et al., 2018). Many clinical voice parameters listed in the present study are vulnerable to noise or channel variability (Schaeffler et al., 2019), and might only be robust using controlled environments and equipment; this requires further testing. From a legislative point of view, it is critical to ensure legal and ethical frameworks and social implications for ensuring passive monitoring can be conducted at scale while protecting privacy and security (Martinez-Martin et al., 2018).

6. Translational potential

6.1. Speech biomarkers in PD as a model

Although motor speech disorders are common in a number (if not all) neurological conditions, including impairment of pyramidal, extrapyramidal, and cerebellar pathways, cranial nerves, muscular apparatus, and neuromuscular plaque (Duffy, 2019), the most convincing data on automated speech analysis in neurological diseases currently comes from PD. In the last 10 years, there has been a nonlinear increase in published articles devoted to PD speech. PD is the second-most common neurodegenerative disease after Alzheimer's disease and the most common movement disorder. The pathophysiology of PD is well known, and there is a good Braak staging model for spreading the disease, which is relatively consistent across patient populations (Braak et al., 2003).

Although PD is still considered a movement disorder and is diagnosed by the presence of cardinal motor features, the high prevalence of cognitive impairment and numerous psychiatric complications suggests that it represents a good model for the neurocognitive-psychiatric component (Agid et al., 2003; Weintraub et al., 2022). There are powerful treatments, such as L-dopa and subthalamic deep brain stimulation, which can provide models to test therapy-related sensitivity of various speech biomarkers. Last but not least, there is rapid progress in neuroprotective treatments that might slow down neurodegeneration and delay worsening of clinical symptoms in the future. Today, we know much about the development of PD manifestations in the prodromal phase (Miglis et al., 2021). Speech could help identify the degenerative process early and speed up neuroprotective treatment development. If neuroprotective treatments are well tolerated, speech assessment is easily scalable to larger populations, allowing the possibility of high-throughput screening, followed by more detailed analysis if the screen is abnormal (Illner et al., 2024).

6.2. Speech biomarkers in motor neurological diseases

Neurodegenerative motor diseases manifest by different dysarthria subtypes (most common including hypokinetic, hyperkinetic, ataxic, spastic, bulbar, and their mixed variants) that reflect their underlying brain pathophysiology. Therefore, speech assessment may provide clues for differential diagnosis among neurological diseases with differing pathophysiology but similar clinical manifestations. Based on cross-sectional design, the digital speech biomarkers were researched mainly in Huntington's disease, multiple sclerosis, cerebellar ataxia, amyotrophic lateral sclerosis, multiple system atrophy, and progressive supranuclear palsy (Neumann et al., 2024; Noffs, 2020; Simmatis, 2023; Stegmann, 2024; Stegmann et al., 2020) (Table 3; see also Supplementary Material for associated references). Interestingly, in Huntington's disease and cerebellar ataxia, subliminal speech impairment has been detected in prodromal periods (Vogel et al., 2020, 2022; Kouba et al., 2023).

Some speech features affected in PD can be counteractive in other neurological diseases due to different neuronal dysfunctions. This antagonistic behaviour can be demonstrated by monoloudness and increased speech rate associated with hypokinetic dysarthria in PD, contrary to excessive loudness variations and slowed speech rate due to hyperkinetic dysarthria in Huntington's disease (Rusz et al., 2021). Subsequently, some aspects of speech, such as imprecise consonants and pitch breaks, might reflect disease severity and, therefore, could be more pronounced in diseases with faster disease progression. Indeed, differences in these measures have been proven to be useful for differential diagnosis between PD and multiple system atrophy or progressive supranuclear palsy (Tykalova et al., 2017; Hlavnicka et al., 2019; Daoudi et al., 2022). There is also a common overlap of speech features among different neurological diseases, making their application universal. In particular, articulation deficits across various neurological diseases are unsurprising because articulatory impairments represent all dysarthrias' most common and distinct characteristics (Duffy, 2019). Also, decreased voice quality is non-specific and typically encountered in most neurological diseases. Longer pauses have been reported in a majority of neurodegenerative diseases, including also mild cognitive impairment and Alzheimer's disease (Qiao et al., 2020), and therefore, might serve as a proxy for cognitive dysfunction. Finally, some features such as increased amplitude variability and prolonged vowels during syllable pronunciation, which is typical for ataxia (Ikui et al., 2012), rarely occur in early PD and might represent a red flag for other diagnoses (Daoudi et al., 2022).

6.3. From motion to cognition and emotions

Most of the evidence regarding digital speech biomarkers has focused on the motor aspects of Parkinsonian dysarthria. Still, emotional speech and cognitive language content (König et al., 2022; Šubert et al., 2022) are also essential for effective communication and social

Table 3
Applicability of speech biomarkers across neurological diseases.

Speech dimension	Proven to be sensitive in particular disease compared to healthy control group							Proven potential for differential diagnosis
	Parkinson's disease [PD]	Huntington's disease [HD]	Multiple sclerosis [MS]	Cerebellar ataxia [CA]	Amyotrophic lateral sclerosis [ALS]	Multiple system atrophy [MSA]	Progressive supranuclear palsy [PSP]	
Dysprosody								
Loudness variability	↓	↑	–			↑	–	HD>PD, MSA>PD
Pitch variability	↓	↓	↓		↓	↓	↓	
Imprecise articulation								
Vowel space area	↓	↓	↓	↓	↓	↓	↓	MSA>CA
Articulatory dynamics	↓		↓			↓	–	PSP>MSA
Consonant duration	↑	↑		↑	↑	↑	↑	MSA>PSP, MSA>PD
Dysphonia								
Voice quality	↓	↓	↓	↓	↓	↓	↓	PSP>PD
Pitch breaks	↑	↑				↑	↑	HD>PD, MSA>PD
Abnormal speech timing								
Speech rate	↑	↓	↓	↓	↓	↓	↓	HD>PD, PSP>PD
Pause duration	↑	↑	↑	↑	↑	↑	↑	PSP>PD, MSA>PD
Speech impairment and fluency severity								
Dysarthria severity	↑	↑	↑	↑	↑	↑	↑	CA>PD
Intelligibility	↓	↓	↓	↓	↓		↓	
Stuttering-like behaviour	↑					–	↑	PSP>MSA, PSP>PD

The symbols demonstrate trends toward increased (), decreased (↓) or unchanged (-) dysarthria characteristic compared to healthy speech.
Reference to support trend is selected based on the most up-to-date high-quality study.

functioning. In addition to akinesia, a de novo PD patient may also suffer from apathy, anxiety, and depression. Then, under dopaminergic treatment, these so-called hypodopaminergic features may disappear and be replaced by an overall hyperdopaminergic behaviour. During the honeymoon period, the patient may experience euphoria and reengage in previous hobbies and an active social life. With time, opposite mood and behavioural states with hypomania and impulse control disorder may appear, often evolving alongside neuropsychiatric fluctuations in parallel to the motor complications of levodopa treatment (Ardouin et al., 2009; Martínez-Fernández et al., 2016; Magalhães et al., 2024). With further progression to the advanced stage of the disease, cognitive deterioration up to PD with dementia will eventually occur. Memory and attentional problems typically translate into a state in which one cannot quite recall a given word or name, which has been described as a "tip of the tongue phenomenon" or "word production anomia" (Matison et al., 1982). Cognitive strategies circumventing this by using words of similar meaning will lead to cognitive double-tasking, contributing to interruption in the train of thought, translating linguistically into poverty of expression. Patients who are aware of these difficulties are stressed and frustrated, and that anticipatory anxiety can in turn lead to the mind going blank with an additional disastrous impact on communication and social isolation relating to shame and self-stigmatisation (Yorkston et al., 2017; Angulo et al., 2019). Thus, speech analysis in PD that addresses different features is expected to be quite variable throughout the disease and respond partly to treatment and/or drug intake. Future speech studies in PD will have to investigate whether specific biomarkers for the different domains will help dissect symptoms related to the individual patient's movement, cognition, and emotion and their changes over time so as to aid in closed-loop treatments (Bouthour et al., 2019; Krack et al., 2019).

Capitalizing on current knowledge from other spectra of neuropsychiatric diseases, most of what is known about cognitive speech biomarkers comes from Alzheimer's disease, the most frequent neurodegenerative disorder. While basic acoustic variables are not significantly altered and correlations between prosodic features and neuropsychological scores only show moderately significant power (Kato et al., 2013), temporal aspects of speech play a vital role in the differentiation of Alzheimer's disease from other neurodegenerative disorders and can even aid in the detection of early-stage Alzheimer's disease (Qi et al., 2023; Ivanova et al., 2024). Diagnostic accuracy of automatic speech analysis is close to 90 % for Alzheimer's disease and 80 % for mild cognitive impairment (Martínez-Nicolás et al., 2021; Popp et al., 2024; Roesler et al., 2024). Another disease influencing speech is depression, which affects 20 % of the population during their lives. However, it lacks a reliable biomarker for diagnosis and early detection. Several anomalies, such as lower speech rate, less pitch variability, and more self-referential speech, characterize depressive speech. With current computational modeling techniques, such features can be used to detect depression with an accuracy of up to 91 % (Koops et al., 2023). As with PD, depression is a fluctuating disease, with remission and recurrence or even opposite mood states with manic episodes in bipolar disorder, calling for easy-to-access biomarkers that can be continuously monitored over extended periods in everyday situations (Insel, 2018). Digital phenotyping promises that this objective measure can happen in the context of a patient's own lived experience, reflecting how they function in their world, and not in the artificial situation of the clinic (Insel, 2018). In schizophrenia-spectrum disorders, descriptions of speech are used to assess the severity of psychotic symptoms. Automatically extracted speech parameters using a machine learning speech-based classifier attained an accuracy of 86.2 % in classifying between patients with a schizophrenia-spectrum disorder and healthy controls on speech parameters alone. Patients with predominantly positive or negative symptoms could be classified with 74.2 % accuracy (de Boer et al., 2023). This distinction is crucial, as patients may fluctuate between psychotic episodes with positive symptoms, which respond well to pharmacological treatment, and longer periods dominated by negative symptoms, which significantly impact long-term quality of life. Notably, previous research mainly represents control-case studies in which no other groups or diseases are considered. At the same time, some of the digital speech biomarkers are not disease-specific; for instance, those associated with Alzheimer's disease can have similar expression in PD patients.

Altogether, speech biomarkers looking at acoustic and linguistic features will open a window into movement, cognition, and emotion. Recent advances in artificial intelligence and deep learning potentially allow for the screening and monitoring of not only PD and related neurodegenerative motor diseases but also dementia, depression, and schizophrenia (Robin et al., 2023). Indeed, digital phenotyping using broadly available smartphone technology, including screening for speech changes, has been suggested as a "game changer" in psychiatry (Insel, 2018).

7. Conclusions and future directions

Speech is essential to life. We have highlighted recent advances in digital speech biomarkers of PD to enhance clinical care and provide a roadmap for future research. More and more studies suggest that multiple aspects of speech disorder could improve the accuracy of diagnosis and allow for better tracking of disease progression in patients with PD (Skodda et al., 2013; Skrabal et al., 2022; Rusz et al., 2022b). The presence of distinct speech clusters in PD highlights dysarthria, a complex system forming its own phenotypes. It supports quantitative speech analysis as a potential instrument for understanding the mechanisms contributing to the variance of symptomatology across the phenotypes. Easy-to-perform and quick speech assessment at diagnosis may provide insights into the risk of developing more disabling cognitive or motor impairment (Polychronis et al., 2019), and therefore allow for improved prognosis prediction and personalized management promotion. Furthermore, cognitive impairment and various neuropsychiatric symptoms resulting from either excess dopaminergic treatment or from more widespread synucleinopathy may play a prominent role in speech impairments in PD (Riecker et al., 2005; Moreau et al., 2019; Weintraub et al., 2022; Rusz et al., 2023). So far, the impact of neuropsychiatric symptoms on speech has hardly been studied in PD, but studies focusing on speech biomarkers of other psychiatric diseases, such as depression, have been published recently (de Boer et al., 2021; Koops et al., 2023). Interdisciplinary collaborative efforts of movement disorder neurologists, speech-language pathologists, and data analysis specialists show great promise in improving our knowledge about speech impairment in PD, leading to better speech management, therapeutic outcomes, and patients' quality of life.

Despite the advances in quantitative speech assessment, several knowledge gaps remain (Table 4). The low number of available prospective, observational studies limits our understanding of how different measures of speech evolve with disease progression, change across phenotypes, and interact with other symptoms and treatments (Behrman et al., 2020; Levy et al., 2020; Rusz et al., 2021a, 2022a; Narayana et al., 2022; Pinto et al., 2023). Most of the research performed cross-sectional comparisons of patients with different subtypes and symptoms (Moro-Velazquez et al., 2021; Ngo et al., 2022), leading to the description of speech impairment without knowledge about the development, progression, or timing of impairments. In particular, prospective imaging and electrophysiological studies have a unique chance to enhance the understanding of underlying mechanisms and identify new targets for treatment and care. Real-world monitoring of speech through smartphones is a promising research area (Illner et al., 2024), but more work is needed to understand better the quality of the data collected by these devices. Speech contains information on motor, cognitive, and behavioral loops. Objective motor, cognitive, and emotional biomarkers that could easily be recorded in the natural environment of the patient would allow personalized adaptive pharmacological (e.g., adapting dosage of a pump) or deep brain stimulation

Table 4
Gaps in knowledge and possible future directions for research on speech impairments in PD.

Knowledge gap	Potential solution and future directions
Mechanisms underlying speech impairment	
The impact of cognitive and emotional aspects on motor aspects of speech disorder needs to be determined.	Studies considering multi-layered interactions of all three main aspects of motor, cognitive and emotional processing to enhance potential clinical applicability of assessing speech.
The traits of speech evolution remain unknown.	Longitudinal studies investigating speech change in prodromal and manifest stages of disease on yearly basis over several years of disease progression.
Neural correlates of dysarthria are still poorly understood. There is low evidence of longitudinal changes in speech and brain structure.	Incorporating neuroimaging technology with speech assessment to enhance the understanding of the mechanisms of speech impairment in patients with PD, potentially leading to new targets for therapy.
Speech phenotypes	
The impact of behavioural and physiological factors on speech parameters is poorly understood. It is currently unclear how all these factors interact, how they are etiologically related, or what weight each element has in the formation of complex speech impairment in PD.	Studies designed to better understand how non-motor factors such as scaling and maintaining movement amplitude and effort, pre-programming and initiation of movements, internal cueing, sensory and temporal processing, automaticity, auditory feedback, and vocal vigilance influence speech.
Speech phenotypes of PD including their stability and progression are not well established.	Studies designed to investigate data-driven phenotypic speech subtypes, their relation to other clinical and neuroimaging markers, their response to therapy and disease progression, and ability to predict disease disability.
Methods for predicting and preventing stuttering-like behaviour are insufficient. In the absence of objective measures and a good understanding of the problem, therapy and prevention will be suboptimal. No common definition of freezing of speech events exists. There is an absence of clear understanding linking specific freezing of speech, freezing of gait and freezing of finger movements.	Studies to (i) identify objective predictors of stuttering-like behaviour development in PD, (ii) define the duration of interruption in speech and a systematic cut-off for durations representing freezing of speech intervals, and (iii) explore the underlying mechanism of different effectors responsible for freezing phenomena, preferably with imaging data.
Interventions influencing speech	
Evidence on the effects of other non-dopaminergic pharmacological interventions on speech is scarce and mainly limited to single studies that have never been replicated.	Studies exploring the effects of medications commonly used for non-motor symptoms, such as anti-depressive, anti-anxiety, antipsychotic, or sedative drugs.
Deep brain stimulation can worsen speech gradually, mainly 6 months to 1 year after initiation of treatment, sometimes erroneously attributed to the progression of the disease. There is a lack of consecutive, longitudinal studies measuring the acoustic variables that could be predictive of deterioration.	Studies designing acoustic biomarkers specific for deep brain stimulation side-effects would help postoperative patient management allowing for early detection of deep brain stimulation-induced dysarthria and dissociating deep brain stimulation-induced dysarthria from progression of the disease.
Maintaining employment and social/family roles is the primary aim of therapy; there is a lack of studies focusing on the right time of the disease to provide therapy in order to support employment and other social family roles. There is an absence of studies to determine speech therapy's substantial effects on patients with different PD phenotypes.	Longitudinal studies on the provision of speech therapy as early in the disease process as possible. Studies investigating underlying motor learning mechanisms and enhancing the role of auditory feedback in maintaining the progress made in speech therapy. Studies investigating effect of behavioral therapy to different speech phenotypes will lead to greater precision in tailoring therapy and improve outcomes. Integrating concomitant motor and emotional aspects of the symptomatology into speech therapy would advance our knowledge for "difficult-to-treat" speech problems such as stuttering-like behaviour.
Overreaching issues	
Potential multimodal interventions on speech have rarely been investigated.	Multimodal interventions targeting more than one type (i.e., motor, cognitive and neuropsychological) might be able to maximise the outcome. Interventions such as repetitive transcranial magnetic stimulation in combination to behavioural therapies might provide long-term speech benefits.
Patient management including quantification of changes in speech in response to treatment needs to consider the different pathophysiological aspects typical for disease stages, as well as the treatment effects of dopaminergic and deep brain stimulation.	The field needs to move from the one-size-fits-all approach to the assessment and treatment of speech impairments toward more tailored interventions matching underlying aetiology and phenotypic speech impairments.

(adapting current intensity) treatments taking into account fluctuations in movement, in mood, and in emotion in everyday living. In addition, pilot studies suggest potential beneficial effects of repetitive transcranial magnetic stimulation on articulation in PD (Brabenec et al., 2021, 2023). If verified, this technique combined with behavioral therapies has a unique chance to provide a more sustainable beneficial effect on speech in PD (Li et al., 2023). Last but not least, additional research is needed to verify the utility of speech assessment as a susceptibility/risk biomarker across neurological diseases with similar clinical manifestations. For instance, a recent study showed that analysis of cognitive speech and language impairment has the potential to identify the risk of conversion into parkinsonism or dementia 2.7 years on average before diagnosis (Šubert et al., 2023). Thus, speech assessment has an enormous potential as a valuable addition to current biomarker batteries used in clinical trials, improving the accuracy and efficiency of diagnosis.

Technology-assisted speech evaluation can likely be introduced into routine practice if many of these gaps can be addressed. This may lead to better monitoring of therapeutic benefits and to detect side effects such as worsening of speech induced by deep brain stimulation, thus contributing to better management and outcomes (An et al., 2023). Quantifying key objective dimensions of dysarthria should be included in the patient's medical record as a part of a clinical assessment that may inform about symptom changes over time. Developing links between speech impairments, their underlying mechanisms, and interventions is integral to providing a personalized treatment approach.

Search strategy and selection criteria

References for this Review paper were identified by searches of PubMed between Jan 1, 1969 and April 30, 2024. References from relevant articles published over the past 5 years from 2019 were prioritized. The search terms "speech" (OR "voice" OR "dysarthria" OR "communication disorder") and "Parkinson's disease" (OR "parkinsonism" OR "Huntington" OR "multiple sclerosis" OR "cerebellar" OR "amyotrophic lateral sclerosis" OR "Alzheimer" OR "depression" OR "schizophrenia") were used. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Ethic approval and Informed consent

Not applicable.

Authors contributions

All authors developed the concept for this Review, wrote and critically revised the manuscript, and approved the final version.

Funding

This study was supported by the Czech Ministry of Health (grant no. NW24–04–00211). Czech Science Foundation (grant no. 21–14216L), Swiss National Science Foundation (grant no. SNF 32003BL_197709), and National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107 - Funded by the European Union – Next Generation EUs. The funder has no role in the design and writing of the manuscript.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105922.

Data Availability

All data used to write this review are derived from scientific publications that are listed in the References.

References

Ackermann, H., Riecker, A., 2010. The contributions of the insula to speech production: a review of the clinical and functional imaging literature. Brain Struct. Funct. 214, 419–433.
Agid, Y., et al., 2003. Parkinson's disease is a neuropsychiatric disorder. Adv. Neurol. 91, 365–370.
Aleksovski, D., Miljkovic, D., Bravi, D., Antonini, A., 2018. Disease progression in Parkinson subtypes: the PPMI dataset. Neurol. Sci. 39, 1971–1976.
An, Q., et al., 2023. Adaptive deep brain stimulation for Parkinson's disease: looking back at the past decade on motor outcomes. J. Neurol. 270, 1371–1387.
Angulo, J., Fleury, V., Péron, J.A., Penzenstadler, L., Zullino, D., Krack, P., 2019. Shame in Parkinson'S disease: a review. J. Park. Dis. 9 (3), 489–499.
Ardouin, C., et al., 2009. Evaluation des troubles comportementaux hyper- et hypodopaminergiques dans la maladie de Parkinson. Rev. Neurol. 165 (11), 845–856.
Arora, S., et al., 2018. Smartphone motor testing to distinguish idiopathic REM sleep behavior disorder, controls, and PD. Neurology 91, e1528–e1538.
Behrman, A., Cody, J., Elandary, S., Flom, P., Chitnis, S., 2020. The effect of SPEAK OUT! and the LOUD crowd on dysarthria due to Parkinson's disease. *Am J. Speech Lang. Pathol.* 29, 1448–1465.
Benke, T., Hohenstein, C., Poewe, W., Butterworth, B., 2000. Repetitive speech phenomena in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 69 (3), 319–324.
Berg, D., et al., 2021. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat. Rev. Neurol. 17, 349–361.
Bloem, B.R., Okun, M.S., Klein, C., 2021. Parkinson's disease. Lancet 397, 2284–2303.
Blumin, J.H., Pcolinsky, D., Atkins, J.P., 2004. Laryngeal findings in advanced Parkinson's disease. Ann. Otol. Rhinol. Laryngol. 113, 253–258.
Bobin, M., et al., 2024. Direct subthalamic nucleus stimulation influences speech and voice quality in Parkinson's disease patients. Brain Stimul. 17 (1), 112–124.
de Boer, J.N., et al., 2023. Acoustic speech markers for schizophrenia-spectrum disorders: a diagnostic and symptom-recognition tool. Psychol. Med 53 (4), 1302–1312.
Bonnet, A.M., Loria, Y., Saint-Hilaire, M.H., Lhermitte, F., Agid, Y., 1987. Does long-term aggravation of Parkinson's disease result from non-dopaminergic lesions? Neurology 37, 1539–1542.
Boonstra, J.T., Michielse, S., Temel, Y., Hoogland, G., Jahanshahi, A., 2020. Neuroimaging detectable differences between Parkinson's disease motor subtypes: a systematic review. Mov. Disord. Clin. Pr. 8, 175–192.
Bouthour, W., Mégevand, P., Donoghue, J., Lüscher, C., Birbaumer, N., Krack, P., 2019. Biomarkers for closed-loop deep brain stimulation in Parkinson disease and beyond. Nat. Rev. Neurol. 15 (6), 343–352.
Bowen, L.K., Hands, G.L., Pradhan, S., Stepp, C.E., 2013. Effects of Parkinson's disease on fundamental frequency variability in running speech. J. Med Speech Lang. Pathol. 21 (3), 235–244.
Braak, H., Tredici, Del, Rüb, K., de Vos, U., Jansen Steur, R.A., Braak, E.N., 2003. E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.
Brabenec, L., Klobusiakova, P., Simko, P., Kostalova, M., Mekyska, J., Rektorova, I., 2021. Non-invasive brain stimulation for speech in Parkinson's disease: a randomized controlled trial. Brain Stimul. 14, 571–578.
Brabenec, L., Simko, P., Sejnoha Minsterova, A., Kostalova, M., Rektorova, I., 2023. Repetitive transcranial magnetic stimulation for hypokinetic dysarthria in Parkinson's disease enhances white matter integrity of the auditory-motor loop. Eur. J. Neurol. 30, 881–886.
Burk, B.R., Watts, C.R., 2019. The effect of Parkinson disease tremor phenotype on cepstral peak prominence and transglottal airflow in vowels and speech, 580.e11-580.e19 J. Voice 33, 580.e11-580.e19.
Castrioto, A., Lhommée, E., Moro, E., Krack, P., 2014. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol. 13, 287–305.
Cavallieri, F., et al., 2021. Antonelli F. dopaminergic treatment effects on dysarthric speech: acoustic analysis in a cohort of patients with advanced Parkinson's disease. Front Neurol. 11, 616062.
Chiu, Y.F., Neel, A., 2020. Predicting intelligibility deficits in Parkinson's disease with perceptual speech ratings. **26** J. Speech Lang. Hear Res 63 (2), 433–443.
Daoudi, K., Biswajit, D., Tykalova, T., Klempir, J., Rusz, J., 2022. Speech acoustic indices for differential diagnosis between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. NPJ Park. Dis. 8, 142.
Debove, I., et al., 2023. Deep brain stimulation: when to test directional? Mov. Disord. Clin. Pr. 10 (3), 434–439.
van der Walt, A., et al., 2022. A prospective study of the feasibility of smartphone-based self-monitoring to characterise cognitive and neurological impairment in people with multiple sclerosis: floodlight MS MoreActive. Mult. Scler. 28 (3 Supplement).
Deuschl, G., Agid, Y., 2013. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. Lancet Neurol. 12 (10), 1025–1034.
Dimauro, G., Di Nicola, V., Bevilacqua, V., Caivano, D., Girardi, F., 2017. Assessment of speech intelligibility in Parkinson's disease using a speech-to-Text system. IEEE Access 5, 22199–22208.
Duffy J.R. Motor Speech Disorders: Substrates, Differential Diagnosis and Management, 4th ed., Mosby, St. Louis (2019).
Fabbri, M., et al., 2019. Is lowering stimulation frequency a feasible option for subthalamic deep brain stimulation in Parkinson's disease patients with dysarthria. Park. Relat. Disord. 64, 242–248.
Favaro, A., Tsai, Y.T., Butala, A., Thebaud, T., Villalba, J., Dehak, N., Moro-Velázquez, L., 2023. Interpretable speech features vs. DNN embeddings: What to use in the automatic assessment of Parkinson's disease in multi-lingual scenarios. Comput. Biol. Med 166, 107559.
Feng, F., et al., 2024. Test-retest reliability of acoustic and linguistic measures of speech tasks. Comp. Speech Lang., 101547
Finnimore, A., Theodoros, D., Rumbach, A., 2022. The impact of PD check-In, a model for supported self-managed maintenance of speech on the quality of life of people with parkinson's disease: a phase 1 study. Brain Sci. 12, 433.
García, A.M., et al., 2021. Cognitive determinants of dysarthria in Parkinson's disease: an automated machine learning approach. Mov. Disord. 36, 2862–2873.
Ge, W., Lueck, C., Suominen, H., Apthorp, D., 2023. Has machine learning over-promised in healthcare?: A critical analysis and a proposal for improved evaluation, with evidence from Parkinson's disease. Artif. Intell. Med 139, 102524.
Gooch, E.A., et al., 2023. Acquired stuttering following Parkinson's disease. Mov. Disord. Clin. Pr. 10, 956–966.
Hage, S.R., 2020. The role of auditory feedback on vocal pattern generation in marmoset monkeys. Curr. Opin. Neurobiol. 60, 92–98.
Hariz, M.I., Blomstedt, P., 2022. Deep brain stimulation for Parkinson's disease. J. Intern Med 292, 764–778.
Hlavnicka, J., Cmejla, R., Tykalova, T., Sonka, K., Ruzicka, E., Rusz, J., 2017. Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. Sci. Rep. 7, 12.
Hlavnicka, J., Cmejla, R., Klempir, J., Ruzicka, E., Rusz, J., 2019. Acoustic tracking of pitch, modal and subharmonic vibrations of vocal folds in Parkinson's disease and Parkinsonism. IEEE Access 7, 150339–150354.
Ho, A.K., Iansek, R., Marigliani, C., Bradshaw, J.L., Gates, S., 1999. Speech impairment in a large sample of patients with Parkinson's disease. Behav. Neurol. 11, 131–137.
Houle, N., Feaster, T., Mira, A., Meeks, K., Stepp, C.E., 2024. Sex differences in the speech of persons with and without Parkinson's disease. Am. J. Speech Lang. Pathol. 33 (1), 96–116.
Ikui, Y., Tsukuda, M., Kuroiwa, Y., Koyano, S., Hirose, H., Taguchi, T., 2012. Acoustic characteristics of ataxic speech in Japanese patients with spinocerebellar degeneration (SCD). Int J. Lang. Commun. Disord. 47 (1), 84–94.
Illner V., et al. Which aspects of motor speech disorder are captured by Mel Frequency Cepstral Coefficients? Evidence from the change in STN-DBS conditions in Parkinson's disease. *In: Proceedings of the Annual Conference of the International Speech Communication Association, Interspeech 2023*. Dublin, 5027-5031 (2023b).
Illner, V., Tykalova, T., Novotny, M., Klempir, J., Dusek, P., Rusz, J., 2022. Towards automated articulation rate analysis via connected speech in dysarthrias. J. Speech Lang. Hear Res 65, 1386–1401.
Illner, V., Tykalova, T., Skrabal, D., Klempir, J., Rusz, J., 2023a. Automated vowel articulation analysis in connected speech among progressive neurological diseases, dysarthria types, and dysarthria severities. J. Speech Lang. Hear Res 66, 2600–2621.
Illner V., Novotný M., Kouba T., Tykalová T., Šimek M., Sovka P., Švihlík J., Růžička E., Šonka K., Dušek P., Rusz J.,. Smartphone voice calls provide early biomarkers of parkinsonism in REM sleep behaviour disorder. *Mov Disord* in press (2024).
Im, H., Adams, S., Abeyesekera, A., Pieterman, M., Gilmore, G., Jog, M., 2018. Effect of levodopa on speech dysfluency in Parkinson's disease. Mov. Disord. Clin. Pr. 6, 150–154.
Insel, T.R., 2018. Digital phenotyping: a global tool for psychiatry. World Psychiatry 17 (3), 276–277.
Ivanova, O., Martínez-Nicolás, I., Meilán, J.J.G., 2024. Speech changes in old age: Methodological considerations for speech-based discrimination of healthy ageing and Alzheimer's disease. Int J. Lang. Commun. Disord. 59 (1), 13–37.

Jorge, A., et al., 2020. Anterior sensorimotor subthalamic nucleus stimulation is associated with improved voice function. Neurosurgery 87, 788–795.
Joza, S., Hu, M.T., Jung, K.Y., et al., 2023. Progression of clinical markers in prodromal Parkinson's disease and dementia with Lewy bodies: a multicentre study. Brain 146 (8), 3258–3272.
Kato, S., Endo, H., Homma, A., Sakuma, T., Watanabe, K., 2013. Early detection of cognitive impairment in the elderly based on Bayesian mining using speech prosody and cerebral blood flow activation. Annu Int Conf. IEEE Eng. Med Biol. Soc. 2013, 5813–5816.
Kelm-Nelson, C.A., Gammie, S., 2020. Gene expression within the periaqueductal gray is linked to vocal behavior and early-onset parkinsonism in Pink1 knockout rats. BMC *Genom.* 21, 625.
Kiran, S., Larson, C.R., 2001. Effect of duration of pitch-shifted feedback on vocal responses in patients with Parkinson's disease. J. Speech Lang. Hear Res 44 (5), 975–987.
König, A., et al., 2022. Detecting subtle signs of depression with automated speech analysis in a non-clinical sample. **27** BMC Psychiatry 22 (1), 830.
Koops, S., Brederoo, S.G., de Boer, J.N., Nadema, F.G., Voppel, A.E., Sommer, I.E., 2023. Speech as a Biomarker for Depression. CNS Neurol. Disord. Drug Targets 22 (2), 152–160.
Kothare, H., et al., 2022a. Statistical and clinical utility of multimodal dialogue-based speech and facial metrics for Parkinson's disease assessment. In *Proceedings of Interspeech*. Incheon, Korea 3658–3662.
Kothare, H., et al., 2024. HOw Consistent Are Speech-based Biomarkers In Remote Tracking of ALS Disease Progression Across Languages? A case study of english and Dutch. *Proc. Inter.*, Koss, Greece 2005–2009.
Kothare, H., Roesler, O., Burke, W., Neumann, M., Liscombe, J., Exner, A., Snyder, S., Cornish, A., Habberstad, D., Pautler, D., Suendermann-Oeft, D., Huber, J., Ramanarayanan, V., 2022b. Speech, facial and fine motor features for conversation-based remote assessment and monitoring of Parkinson's disease. Annu Int Conf. IEEE Eng. Med Biol. Soc. 2022, 3464–3467.
Kouba, T., et al., 2023. Speech biomarkers in Huntington disease: a cross-sectional study in pre-symptomatic, prodromal and early manifest stages. Eur. J. Neurol. 30, 1262–1271.
Kovac, D., et al., 2024. Exploring digital speech biomarkers of hypokinetic dysarthria in a multilingual cohort. Biomed. Signal Proces. Control 88, 105667.
Krack, P., et al., 2003. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N. Engl. J. Med 349, 1925–1934.
Krack, P., Fraix, V., Mendes, A., Benabid, A.L., Pollak, P., 2002. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Mov. Disord. 17 (Suppl 3), S188–S197.
Krack, P., Volkmann, J., Tinkhauser, G., Deuschl, G., 2019. Deep brain stimulation in movement disorders: from experimental surgery to evidence-based therapy. Mov. Disord. 34 (12), 1795–1810.
Lachenmayer, M.L., et al., 2021. Subthalamic and pallidal deep brain stimulation for Parkinson's disease-meta-analysis of outcomes. NPJ Park. Dis. 7, 77.
Lange, F., et al., 2023. Distinct phenotypes of stimulation-induced dysarthria represent different cortical networks in STN-DBS. Park. Relat. Disord. 109.
Lechien, J.R., et al., 2018. Voice quality outcomes of idiopathic Parkinson's disease medical treatment: a systematic review. Clin. Otolaryngol. 43, 882–903.
Levy, E.S., et al., 2020. The effects of intensive speech treatment on intelligibility in Parkinson's disease: a randomised controlled trial. EClinicalMedicine 24, 100429.
Li, Q., Millard, K., Tetnowski, J., Narayana, S., Cannito, M., 2023. Acoustic analysis of intonation in persons with Parkinson's disease receiving transcranial magnetic stimulation and intensive voice treatment. J. Voice 37, 203–214.
Linares-Del Rey, M., Vela-Desojo, L., Cano-de la Cuerda, R., 2019. Mobile phone applications in Parkinson's disease: a systematic review. Neurologia 34 (1), 38–54.
Liotti, M., et al., 2003. Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. **11** Neurology 60 (3), 432–440.
Lipsmeier, F., et al., 2018. Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov. Disord. 33, 1287–1297.
Little, S., et al., 2016. Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. J. Neurol. Neurosurg. Psychiatry 87, 1388–1389.
Luk, K.C., et al., 2012. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338 (6109), 949–953.
Ma, A., Lau, K.K., Thyagarajan, D., 2020. Voice changes in Parkinson's disease: what are they telling us? J. Clin. Neurosci. 72, 1–7.
Maffia, M., De Micco, R., Pettorino, M., Siciliano, M., Tessitore, A., De Meo, A., 2021. Speech rhythm variation in early-stage Parkinson's disease: a study on different speaking tasks. Front Psychol. 12, 668291.
Magalhães, A.D., et al., 2024. Subthalamic stimulation has acute psychotropic effects and improves neuropsychiatric fluctuations in Parkinson's disease. BMJ Neurol. Open 6 (1), e000524.
Martínez-Fernández, R., et al., 2023. Prospective long-term follow-up of focused ultrasound unilateral subthalamotomy for Parkinson disease. Neurology 100, e1395–e1405.
Martínez-Fernández, R., Schmitt, E., Martinez-Martin, P., Krack, P., 2016. The hidden sister of motor fluctuations in Parkinson's disease: A review on nonmotor fluctuations. Mov. Disord. 31 (8), 1080–1094.
Martinez-Martin, N., Insel, T.R., Dagum, P., Greely, H.T., Cho, M.K., 2018. Data mining for health: staking out the ethical territory of digital phenotyping. NPJ Digit Med 1, 68.
Martínez-Nicolás, I., Llorente, T.E., Martínez-Sánchez, F., Meilán, J.J.G., 2021. Ten years of research on automatic voice and speech analysis of people With Alzheimer's disease and mild cognitive impairment: a systematic review article. Front Psychol. 12, 620251.
Matison, R., Mayeux, R., Rosen, J., Fahn, S., 1982. "Tip-of-the-tongue" phenomenon in Parkinson disease. Neurology 32 (5), 567–570.
Max, L., Kadri, M., Mitsuya, T., Balasubramanian, V., 2019. Similar within-utterance loci of dysfluency in acquired neurogenic and persistent developmental stuttering. Brain Lang. 189, 1–9.
Miglis, M.G., et al., 2021. Biomarkers of conversion to α-synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder. Lancet Neurol. 20 (8), 671–684.
Mollaei, F., Shiller, D.M., Baum, S.R., Gracco, V.L., 2016. Sensorimotor control of vocal pitch and formant frequencies in Parkinson's disease. **1** Brain Res 1646, 269–277.
Moorman, S., Ahn, J.P., Kao, M.H., 2021. Plasticity of stereotyped birdsong driven by chronic manipulation of cortical-basal ganglia activity. Curr. Biol. 31, 1–14.
Moreau, C., Pinto, S., 2019. Misconceptions about speech impairment in Parkinson's disease. Mov. Disord. 34, 1471–1475.
Moro-Velazquez, L., Gomez-Garcia, J.A., Arias-Londoño, J.D., Dehak, N., Godino-Llorente, J.I., 2021. Advances in Parkinson's Disease detection and assessment using voice and speech: a review of the articulatory and phonatory aspects. Biomed. Signal Proces. Control 66, 102418.
Muñoz-Vigueras, N., et al., 2021. Speech and language therapy treatment on hypokinetic dysarthria in Parkinson disease: systematic review and meta-analysis. Clin. Rehabil. 35, 639–655.
Narayana, S., et al., 2020. Mapping typical and hypokinetic dysarthric speech production network using a connected speech paradigm in functional MRI. Neuroimage Clin. 27, 102285.
Narayana, S., et al., 2022. Immediate and long-term effects of speech treatment targets and intensive dosage on Parkinson's disease dysphonia and the speech motor network: Randomized controlled trial. Hum. Brain Mapp. 43, 2328–2347.
Neumann, M., Kothare, H., Ramanarayanan, V., 2024. Multimodal speech biomarkers for remote monitoring of ALS disease progression. Comput. Biol. Med 180, 108949.
New, A.B., et al., 2015. The intrinsic resting state voice network in Parkinson's disease. Hum. Brain Mapp. 36, 1951–1962.
Ngo, Q.C., Motin, M.A., Pah, N.D., Drotár, P., Kempster, P., Kumar, D., 2022. Computerized analysis of speech and voice for Parkinson's disease: A systematic review. Comput. Methods Prog. Biomed. 226, 107133.
Nirosen, V., et al., 2021. Long-Term success of low-frequency subthalamic nucleus deep brain stimulation for PD depends on tremor severity and symptom duration. Brain Commun. 3.
Noffs, G., et al., 2020. Acoustic speech analytics are predictive of cerebellar dysfunction in multiple sclerosis. Cerebellum 19 (5), 691–700.
Novotny, M., Rusz, J., Cmejla, R., Ruzicka, E., 2014. Automatic evaluation of articulatory disorders in Parkinson's disease. IEEE/ACM T Audio Speech Lang. Process 22, 1366–1378.
Okobi, D.E., Benerjee, A., Matheson, A., Phelps, S., Long, M.A., 2019. Motor Cortical control of vocal interaction in neotropical singing mice. Science 363, 983–988.
Omberg, L., et al., 2022. Remote smartphone monitoring of Parkinson's disease and individual response to therapy. Nat. Biotechnol. 40, 480–487.
Perry, S.E., et al., 2024. Behavioral management of respiratory/phonatory dysfunction for dysarthria associated with neurodegenerative disease: a systematic review. Am. J. Speech Lang. Pathol. 1–29.
Petry-Schmelzer, J.N., et al., 2022. A randomized, double-blinded crossover trial of short versus conventional pulse width subthalamic deep brain stimulation in Parkinson's disease. J. Park. Dis. 12, 1497–1505.
Pinto, S., et al., 2005. Changes induced by levodopa and subthalamic nucleus stimulation on parkinsonian speech. Mov. Disord. 20 (11), 1507–1515.
Pinto, S., et al., 2023. Results of a randomized clinical trial of speech after early neurostimulation in Parkinson's disease. Mov. Disord. 38, 212–222.
Pinto, S., Ozsancak, C., Tripoliti, E., Thobois, S., Limousin-Dowsey, P., Auzou, P., 2004. Treatments for dysarthria in Parkinson's disease. Lancet Neurol. 3, 547–556.
Polychronis, S., Niccolini, F., Pagano, G., Yousaf, T., Politis, M., 2019. Speech difficulties in early de novo patients with Parkinson's disease. Park. Relat. Disord. 64, 256–261.
Popp, Z., et al., 2024. Shifting from active to passive monitoring of alzheimer disease: the state of the research. J. Am. Heart Assoc. 13 (2), e031247.
Qi, X., Zhou, Q., Dong, J., Bao, W., 2023. Noninvasive automatic detection of Alzheimer's disease from spontaneous speech: a review. Front Aging Neurosci. 15, 1224723.
Qiao, Y., et al., 2020. Computer-assisted speech analysis in mild cognitive impairment and Alzheimer's disease: a pilot study from Shanghai, China. J. Alzheimers Dis. 75, 211–221.
Ramig, L., Halpern, A., Spielman, J., Fox, C., Freeman, K., 2018. Speech treatment in Parkinson's disease: randomized controlled trial (RCT). Mov. Disord. 33, 1777–1791.
Rektorova, I., Mikl, M., Barrett, J., Marecek, R., Rektor, I., Paus, T., 2012. Functional neuroanatomy of vocalization in patients with Parkinson's disease. J. Neurol. Sci. 313, 7–12.
Riecker, A., et al., 2005. fMRI reveals two distinct cerebral networks subserving speech motor control. Neurology 64, 700–706.
Robin, J., et al., 2023. Development of a speech-based composite score for remotely quantifying language changes in frontotemporal dementia. Cogn. Behav. Neurol. 36 (4), 237–248.
Rodriguez-Oroz, M.C., Moro, E., Krack, P., 2012. Long-term outcomes of surgical therapies for Parkinson's disease. Mov *Disord.* 27 (14), 1718–1728.
Roesler, O., et al., 2024. Towards scalable remote assessment of mild cognitive impairment via multimodal dialog. *Proc. Inter.*, Koss, Greece 1985–1989.

Rusz, J., et al., 2018. Smartphone allows capture of speech abnormalities associated with high risk of developing Parkinson's disease. IEEE Trans. Neural Syst. Rehabil. Eng. 26, 1495–1507.
Rusz, J., et al., 2021a. Defining speech subtypes in de novo Parkinson's disease: response to long-term levodopa therapy. Neurology 97, e2124–e2135.
Rusz, J., et al., 2021b. Speech biomarkers in rapid eye movement sleep behaviour disorder and Parkinson's disease. Ann. Neurol. 90, 62–75.
Rusz, J., et al., 2022b. Dysprosody in Isolated REM Sleep Behavior Disorder with Impaired Olfaction but Intact Nigrostriatal Pathway. Mov. Disord. 37, 619–623.
Rusz, J., et al., 2023. Speech and gait abnormalities in motor subtypes of de-novo Parkinson's disease. CNS Neurosci. Rehab. 29 (8), 2101–2110.
Rusz, J., Tykalova, T., 2021d. Does Cognitive Impairment Influence Motor Speech Performance in De Novo Parkinson's Disease? Mov. Disord. 36, 2980–2982.
Rusz, J., Cmejla, R., Ruzickova, H., Ruzicka, E., 2011. Quantitative acoustic measurements for characterization of speech and voice disorders in early untreated Parkinson's disease. J. Acoust. Soc. Am. 129, 350–367.
Rusz, J., Tykalova, T., Ramig, L.O., Tripoliti, E., 2021. Guidelines for speech recording and acoustic analyses in dysarthrias of movement disorders. Mov. Disord. 36, 803–814.
Rusz, J., Tykalova, T., Novotny, M., Ruzicka, E., Dusek, P., 2021c. Distinct patterns of speech disorder in early-onset and late-onset de-novo Parkinson's disease. NPJ Park. Dis. 7, 98.
Rusz, J., Tykalova, T., Novotny, M., Zogala, D., Ruzicka, E., Dusek, P., 2022a. Automated speech analysis in early untreated Parkinson's disease: relation to gender and dopaminergic transporter imaging. Eur. J. Neurol. 29, 81–90.
Schaeffler F., Jannetts S., Beck J.M. Reliability of clinical voice parameters captured with smartphones–measurements of added noise and spectral tilt. In Proceedings of the 20th Annual Conference of the International Speech Communication Association INTERSPEECH, Graz, Austria, 15-19 September 2019. ISCA, 2019.
Schalling, E., Winkler, H., Franzén, E., 2021. HiCommunication as a novel speech and communication treatment for Parkinson's disease: a feasibility study. Brain Behav. 11, e02150.
Schulder, M., et al., 2023. Advances in technical aspects of deep brain stimulation surgery. Stereo Funct. Neurosurg. 101, 112–134.
Sciacca, G., Mostile, G., Disilvestro, I., Donzuso, G., Nicoletti, A., Zappia, M., 2023. Long-duration response to levodopa, motor learning, and neuroplasticity in early Parkinson's disease. Mov. Disord. 38, 626–635.
Shah, A., et al., 2023. Combining multimodal biomarkers to guide deep brain stimulation programming in Parkinson disease. Neuromodulation 26 (2), 320–332.
Šimek, M., Rusz, J., 2021. Validation of cepstral peak prominence in assessing early voice changes of Parkinson's disease: effect of speaking task and ambient noise. J. Acoust. Soc. Am. 150, 4522–4533.
Simmatis, L.E., et al., 2023. Validation of automated pipeline for the assessment of a motor speech disorder in amyotrophic lateral sclerosis (ALS), 20552076231219102 Digit Health 9, 20552076231219102.
Simonyan, K., Ackermann, H., Chang, E.F., Greenlee, J.D., 2016. New developments in Understanding the complexity of human speech production. J. Neurosci. 36, 11440–11448.
Skodda, S., 2011. Aspects of speech rate and regularity in Parkinson's disease. **15** J. Neurol. Sci. 310 (1-2), 231–236.
Skodda, S., Gronheit, W., Mancinelli, N., Schlegel, U., 2013. Progression of voice and speech impairment in the course of Parkinson's disease: a longitudinal study. Park. Dis., 389195
Skrabal, D., Rusz, J., Novotny, M., Ruzicka, E., Dusek, P., Tykalova, T., 2022. Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease. NPJ Park. Dis. 8, 137.
Sörös, P., Sokoloff, L.G., Bose, A., McIntosh, A.R., Graham, S.J., Stuss, D.T., 2006. Clustered functional MRI of overt speech production. Neuroimage 32, 376–387.
Stathopoulos, E.T., Huber, J.E., Richardson, K., et al., 2014. Increased vocal intensity due to the Lombard effect in speakers with Parkinson's disease: simultaneous laryngeal and respiratory strategies. J. Commun. Disord. 48, 1–17.
Stegmann, G., et al., 2024. Automated speech analytics in ALS: higher sensitivity of digital articulatory precision over the ALSFRS-R. *Amyotroph. Lateral Scler. Front. Degener.* 26 1–9.
Stegmann, G.M., et al., 2020. Early detection and tracking of bulbar changes in ALS via frequent and remote speech analysis. NPJ Digit Med 3, 132.
Stegmann, G.M., Hahn, S., Liss, J., et al., 2020. Repeatability of commonly used speech and language features for clinical applications. Digit Biomark. 4, 109–122.
Stipancic, K.L., Tjaden, K., 2022. Minimally detectable change of speech intelligibility in speakers with multiple sclerosis and Parkinson's disease. J. Speech Lang. Hear Res 65 (5), 1858–1866.
Šubert, M., et al., 2022. Linguistic abnormalities in isolated rapid eye movement sleep behavior disorder. Mov. Disord. 37 (9), 1872–1882.
Šubert, M., et al., 2023. Spoken language alterations can predict phenoconversion in isolated rapid eye movement sleep behavior disorder: a multicentric study. Ann. Neurol. 95, 530–543.
Tamplin, J., Morris, M.E., Marigliani, C., Baker, F.A., Noffs, G., Vogel, A.P., 2020. ParkinSong: outcomes of a 12-month controlled trial of therapeutic singing groups in Parkinson's disease. J. Park. Dis. 10, 1217–1230.
Theys, C., et al., 2024. Localization of stuttering based on causal brain lesions. Brain 147 (6), 2203–2213.
Thies, T., et al., 2023. Compensatory articulatory mechanisms preserve intelligibility in prodromal Parkinson's disease. Park. Relat. Disord. 112, 105487.
Tripoliti, E., et al., 2008. Effects of contact location and voltage amplitude on speech and movement in bilateral subthalamic nucleus deep brain stimulation. Mov. Disord. (16), 2377–2383.
Tripoliti, E., et al., 2014. Predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. Mov. Disord. 29, 532–553.
Tsanas, A., Little, M.A., Fox, C., Ramig, L.O., 2014. objective automatic assessment of rehabilitative speech treatment in Parkinson's disease. IEEE Trans. Neural Syst. Rehabil. Eng. 22 (1), 181–190.
Tsuboi, T., et al., 2017. Early detection of speech and voice disorders in Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation: a 1-year follow-up study. J. Neural Transm. 124, 1547–1556.
Tykalova, T., et al., 2015. Effect of dopaminergic medication on speech dysfluency in Parkinson's disease: a longitudinal study. J. Neural Transm. 122, 1135–1142.
Tykalova, T., Rusz, J., Klempir, J., Cmejla, R., Ruzicka, E., 2017. Distinct patterns of imprecise consonant articulation among Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Brain Lang. 165, 1–9.
Tykalova, T., Rusz, J., Švihlík, J., Bancone, S., Spezia, A., Pellecchia, M.T., 2020. Speech disorder and vocal tremor in postural instability/gait difficulty and tremor dominant subtypes of Parkinson's disease. J. Neural Transm. 127, 1295–1304.
Tykalova, T., Novotny, M., Ruzicka, E., Dusek, P., Rusz, J., 2022. Short-term effect of dopaminergic medication on speech in early-stage Parkinson's disease. NPJ Park. Dis. 8, 22.
Vogel, A.P., et al., 2020. Features of speech and swallowing dysfunction in pre-ataxic spinocerebellar ataxia type 2. Neurology 95 (2), e194–e205.
Vogel A.P., Chan C.S., Stuart G.W., Maruff P., Lie Y., Stout J.C. Automated and objective analysis of speech in premanifest and early-stage Huntington's disease. medRxiv, 2022-10 (2022).
Wardell, K., et al., 2022. Deep brain stimulation: emerging tools for stimulation, data analysis and visualisation. Front Neurosci. 16, 834026.
Weintraub, D., et al., 2022. The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol. 21, 89–102.
Wu, J.C., et al., 1997. Increased dopamine activity associated with stuttering. NeuroReport 8, 767–770.
Yorkston, K., Baylor, C., Britton, D., 2017. Speech Versus Speaking: The Experiences of People With Parkinson's Disease and Implications for Intervention. Am. J. Speech Lang. Pathol. 26 (2S), 561–568.
Zhan, A., et al., 2018. Using smartphones and machine learning to quantify Parkinson disease severity: the mobile parkinson disease score. JAMA Neurol. 75, 876–880.