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MUDr. Dominik Škrabal

Speech disorders and analysis of their mechanisms in neurodegenerative diseases

Poruchy řeči a analýza jejich mechanismů u neurodegenerativních onemocněních

Dissertation Thesis

Supervisor: doc. Ing. Jan Rusz, Ph.D.

Advisor: Ing. Tereza Tykalová, Ph.D.

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Declaration

I declare that I have prepared the thesis independently and have duly cited all the sources and literature used. Simultaneously, I confirm that this work has not been utilized to obtain another university degree.

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In Prague, 5.12.2023

Dominik Škrabal

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Abstract

As the population is growing older, we face new challenges to cope with an increased number of people with neurodegenerative neurological diseases. Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by pathological deposits of α-synuclein that lead to the loss of dopaminergic neurons in the substantia nigra, which is the direct cause of principal motor manifestations, including bradykinesia, rigidity, and resting tremor. Unfortunately, no sufficiently accurate biomarkers are available to detect PD prodromally, differentiate it from other types of parkinsonism and measure its disease progression. As the most complex human motor skill involving numerous muscles, speech is a sensitive marker of damage to neural structures engaged in motor system control. This dissertation aims to explore the potential of objective acoustic evaluation of vowel articulation in comparison with other measures of speech dysfunction as a surrogate biomarker of α-synucleinopathies. To achieve this aim, we collected speech data from patients with isolated rapid eye movement sleep behavior disorder (iRBD), a special case of prodromal PD, de-novo PD, advanced PD, atypical parkinsonian syndromes, and other progressive neurodegenerative diseases, as well as healthy control speakers. We discovered that vowel articulation impairment was already affected in iRBD, especially in patients with hyposmia before nigrostriatal dopaminergic transmission was affected, suggesting that speech production is already slightly affected very early in the synucleinopathology process. We found distinct speech adaptation in atypical parkinsonian syndromes and other progressive neurodegenerative diseases compared to PD, reflecting sensitivity variations in vowel articulation in disease pathophysiology. Also, we showed that vowel articulation is age-independent. The findings of this thesis imply that vowel articulation may provide a robust digital speech biomarker for early presymptomatic diagnoses, differential diagnosis, and disease progression, bolstering its use in future clinical trials for developing neuroprotective therapies.

Keywords: Speech impairment; Dysarthria; Vowel articulation; Acoustic analysis; Automated Vowel Articulation Analysis; Parkinson's disease; Isolated REM sleep behaviour disorder; Atypical parkinsonian syndromes; Neurodegenerative disorders

Abstrakt

S narůstajícím věkem populace čelíme novým výzvám v souvislosti se zvyšujícím se počtem lidí trpících neurologickými chorobami. Parkinsonova nemoc (PN) je druhé nejčastější neurodegenerativní onemocnění, charakterizované patologickými depozity α-synukleinu.Ztráta dopaminergních neuronů v substantia nigraje přímou příčinou hlavních motorických projevů jako bradykineze, rigidity, porucha chůze a klidový třes. Bohužel nejsou k dispozici dostatečně přesné biomarkery, které by umožňovaly detekci prodromálního stadia PN, odlišení od jiných typů parkinsonských syndromů nebo sledování progrese onemocnění. Řeč, jako nejsložitější lidská motorická dovednost, je citlivým ukazatelem poškození nervových struktur zapojených do kontroly motorického systému. Tato disertační práce si klade za cíl zkoumat potenciál objektivní akustické analýzy artikulace samohlásek. Pro dosažení tohoto cíle jsme získaly řečová data od pacientů s izolovanou poruchou chování v REM spánku (iRBD) reprezentující prodromální stádium PN, nově diagnostikovanou PN před zahájením terapie, pokročilou PN, atypickými parkinsonovskými syndromy a jinými progresivními neurodegenerativními onemocněními. Byla zjištěna porucha artikulace samohlásek již u pacientů s iRBD, a to zejména u pacientů s iRBD a hyposmií před tím, než je ovlivněn nigrostriatální dopaminergní přenos. Toto zjištění naznačuje, že tvorba řeči je již velmi brzy ovlivněna procesem synukleinopatie. Zaznamenali jsme odlišnou modifikaci řeči u atypických parkinsonovských syndromů a jiných progresivních neurodegenerativních onemocnění ve srovnání s PN, což odráží citlivost poruch artikulace samohlásek na patofyziologii onemocnění. Také jsme prokázali, že artikulace samohlásek není významně ovlivněna věkem/stárnutím. Závěry této práce naznačují, že artikulace samohlásek může poskytnout robustní digitální řečový biomarker pro brzkou presymptomatickou diagnostiku, diferenciální diagnostiku a sledování progrese onemocnění, což umožňuje její využití v budoucích klinických studiích zaměřených na vývoj neuroprotektivních terapií.

Klíčová slova: Porucha řeči; Dysartrie; Artikulace samohlásek; Akustická analýza; Automatizovaná analýza artikulace samohlásek; Parkinsonova nemoc; Izolovaná porucha chování v REM spánku; Atypické parkinsonovské syndromy; Neurodegenerativní poruchy

List of abbreviations

ANOVA - Analysis of Variance

ALS - Amyotrophic Lateral Sclerosis

ALSFRS-R - ALS Functional Rating Scale-Revised

APS - Atypical Parkinsonian Syndromes

CA - Cerebellar Ataxia

DAT-SPECT - Dopamine Transporter Single-Photon Emission Computed Tomography

EDSS - Expanded Disability Status Scale

ET - Essential Tremor

f0 - Fundamental Frequency

F1 - First Formant Frequency

F2 - Second Formant Frequency

F3 - Third Formant Frequency

F4 - Fourth Formant Frequency

FRI - Formant Ratio Index

HC – Healthy Control

HD - Huntington's Disease

iRBD - Isolated Rapid Eye Movement Sleep Behavior Disorder

iRBD-POF - iRBD Group with Preserved Olfactory Function

iRBD-AOF - iRBD Group with Abnormal Olfactory Function

RM-ANOVA - Repeated Measures ANOVA

MDS-UPDRS - Movement Disorders Society-Unified Parkinson's Disease Rating Scale

MS - Multiple Sclerosis

MSA - Multiple System Atrophy

NINDS-PSP - Natural History and Neuroprotection in Parkinson Plus Syndromes–Parkinson Plus Scale

NRMSE - Normalized Root-Mean-Square Error

PD - Parkinson's Disease

de-novo PD - newly diagnosed patients with Parkinson's Disease

PSP - Progressive Supranuclear Palsy

REM - Rapid Eye Movement

SARA - Scale for the Assessment and Rating of Ataxia

SFRI - Second Formant Ratio Index

TETRAS - Tremor Research Group Essential Tremor Rating Assessment Scale

UHDRS - Unified Huntington's Disease Rating Scale

VAI - Vowel Articulation Index

VSA - Vowel Space Area

Contents

1. Introduction

Ever since the population is growing older implying socio-economical changes (He et al., 2015), science and medicine face the new challenge to cope with an increased number of people with neurodegenerative diseases. Speech, the most intricate human motor skill, results from the coordinated actions of approximately 100 muscles. Successful speech production relies on the integrity and seamless integration of various components, including speech planning and programming, cognitive-linguistic processes, and neuromuscular execution. Therefore, it's not surprising that the intricate nature of speech is highly sensitive to central nervous system diseases.

In some cases, speech alterations may be the only significant initial indication of a neurological disorder. In addition, the identification of distinctive irregularities in speech characteristics can offer valuable insights into the underlying pathophysiology of neurological diseases. Speech can also serve as a valuable marker for evaluating treatment effectiveness, tracking disease progression, and assessing disease severity. Acoustic analyses represent an innovative method for assessing speech disorders and offer a promising solution to address these challenges. This approach involves the use of digital signal processing to analyze acoustic speech signals recorded by microphones. Acoustic evaluation of speech has the potential to be a reliable, cost-effective, valid, and user-friendly biomarker for neurological diseases, facilitating precise and timely diagnosis and enhancing disease management.

1.1. Dysarthria

Dysarthria is a motor speech disorder resulting from abnormalities in various aspects of speech control, including accuracy, speed, range, strength, duration, or tone. It is characterized by a notable decrease in speech intelligibility while the content of spoken language remains intact, allowing the patient to write and comprehend both spoken and written language correctly.

Speech is a complex neuromuscular process that relies on the coordinated functioning of five subsystems: articulation, respiration, prosody, phonation, and resonance. Dysfunction in any of these subsystems can lead to difficulties in intelligibility, naturalness, audibility, and overall communication capability (Duffy, 2019). Dysarthria has a significant impact on both the patient and their families, as effective communication

plays a vital role in expressing one's personality and maintaining social relationships. Given the interconnected nature of muscle function, it's not uncommon for patients with dysarthria to experience challenges related to feeding and swallowing, which significantly affect physical health and quality of life (Miller et al., 2008, Sapir et al., 2008).

Dysarthria can be a result of various neurological disorders and may originate from various neuroanatomical structures. These include cranial nerve nuclei, peripheral nerves, cerebral cortex, cerebellum, and basal ganglia. In this context, dysarthria encompasses various etiologies, including vascular disorders, demyelinating conditions, trauma, toxic influences, infections, neoplasms, genetic factors, and notably, neurodegenerative diseases (Duffy, 2019). Based on their etiologies, progressive neurological diseases commonly lead to various subtypes of dysarthria (or its combination in some cases) classified based on their distinctive characteristics (Duffy, 2019):

Flaccid dysarthria: This type of dysarthria emerges due to damage to the lower motor neurons. Speech is characterized by hypernasality, breathiness, harsh vocal quality, and difficulty in pronouncing consonants often presented in amyotrophic lateral sclerosis.

Spastic dysarthria: This type of dysarthria emerges due to upper motor neuron damage. Speech is characterized by harsh or strained-strangled voice quality, low pitch, pitch breaks, and a slow speech rate. Patients may show signs of pseudobulbar palsy, including dysphagia, a hyperactive jaw jerk, and pseudobulbar affect. It is often presented in amyotrophic lateral sclerosis, multiple system atrophy, progressive supranuclear palsy, or multiple sclerosis.

Hypokinetic dysarthria: Individuals with this type of dysarthria typically display monopitch, monoloudness, and reduced vocal loudness. They exhibit decreased use of emotive pitch, linguistic, pragmatic, and loudness inflection leading to reduced stress. Additionally, they may have impaired pronunciation of consonants and vowels due to hypokinetic articulation, hesitations, brief bursts of speech, voice tremor, dysfluency, or a combination of these features. This type of dysarthria is typically associated with Parkinson's disease but can be also presented in multiple system atrophy or progressive supranuclear palsy (Duffy, 2019).

Hyperkinetic dysarthria: This type of dysarthria is associated with basal ganglia control circuit abnormalities, clinically leading to dyskinesias, chorea, tremor, or myoclonus. Speech is characterized by features like voice tremor, intermittent hypernasality, distorted vowels, harshness, and excessive variations in loudness. This type is dysarthria is typically associated with Huntington's disease but

can also be presented in severe stages of Parkinson's disease.

Ataxic dysarthria: This type of dysarthria is frequently observed in conditions affecting the cerebellum or its connections. Speech displays an irregular rhythm, excess and equal stress, distorted vowels, or excess loudness variations. This type is dysarthria is typically associated with cerebellar ataxia, multiple system atrophy, or multiple sclerosis.

Mixed dysarthria:

Mixed dysarthria is linked to damage in multiple neuroanatomical areas, leading to distinctive speech dysfunction associated with at least two predefined dysarthria groups. It is frequently observed in conditions such as multiple sclerosis and amyotrophic lateral sclerosis.

1.2. Vowel space area (VSA)

Several different acoustic features related to respiration, prosody, phonation, articulation, and resonance can be used to identify various speech abnormalities (Rusz et al., 2020). In this cumulative thesis, the central emphasis has been put on exploring vowel articulation abnormalities within the context of different dysarthria subtypes related to various neurodegenerative disorders. Indeed, numerous studies have reported the presence of abnormalities in vowel articulation in various progressive neurological diseases (Whitfield, 2019). The disruption of vowel articulation is particularly prevailing in Parkinson's disease (Lam & Tjaden, 2016; Skodda et al., 2011; Tjaden et al., 2013; Whitfield & Goberman, 2014; Whitfield & Mehta, 2019) but to a certain extend presented also in in multiple-system atrophy, progressive supranuclear palsy, essential tremor, cerebellar ataxia, amyotrophic lateral sclerosis, Huntington's disease and multiple sclerosis (Rusz et al., 2014, 2015; Tjaden et al., 2005; Tykalova et al., 2016; Yunusova et al., 2013).

Considering vowel disturbances, the understanding of the crucial role of the first (F1) and second (F2) formant frequencies is pivotal for recognizing the distinct phonemic attributes of different vowels (Kent & Vorperian, 2018). From a physiological perspective, it's important to highlight that F1 and F2 frequencies primarily convey information about tongue position and lip rounding (Kent et al., 1999), whereas F3 and F4 are primarily associated with lip spreading or protrusion (Waaramaa et al., 2006). The cardinal acoustic feature of vowel articulation represents VSA, which is a traditional and probably the most used articulatory-acoustic measure (Kent et al., 2018; Fant et al., 1973). It represents the acoustic space in which vowel sounds are produced by a speaker. In other words, it's the area within which the various vowel sounds can be located based on their specific values of the first and second formants. This concept is often used to quantify the precision and distinctiveness of particular vowels in speech analysis. A larger vowel space area indicates more distinct and precise vowel articulation, while a smaller space suggests less distinct or less precise vowel production. The calculation of VSA is straightforward using the formula below (Liu et al., 2005):

$$0.5 \times ([F2/u/ + F2/i/] \times [F1/u/ - F1/i/] - [F2/a/ + F2/u/] \times [F1/a/ - F1/u/] - [F2/a/ + F2/i/] \times [F1/a/ - F1/i/]).$$

In the study by Skrabal et al. (2022), an adaptation to VSA called the Vowel Articulation Index (VAI) was involved. The primary goal of VAI construction is to mitigate inter-speaker variability and enhance sensitivity to formant centralization. The calculation is as follows (Roy et al., 2009):

$$VAI = (F2/i/ + F1/a/)/(F1/i/ + F1/u/ + F2/u/ + F2/a/).$$

The assessment of the VSA/VAI has demonstrated its applicability in various domains. For instance, it can be employed to evaluate the impact of voice and speech therapy (Sapir et al., 2007; Takatsu et al., 2017) to serve as an early marker of Parkinson's disease (Rusz et al., 2013b) or other neurological conditions, (Rusz et al., 2016) or to monitor disease progression or the effect of antiparkinsonian drug introduction or deep brain stimulation surgery (Rusz et al., 2013a).

1.3. Neurodegenerative disorders and state-of-the-art

1.3.1. Parkinson's disease (PD)

PD is a progressive neurodegenerative condition characterized by the gradual deposition of α-synuclein aggregates across the peripheral and central nervous systems. According to Braak's hypothesis, these α-synuclein clusters trace predetermined pathways, originating in the olfactory bulb and gut nerve plexus, then advancing to the brainstem, and eventually infiltrating the cerebral cortex (Braak et al., 2004). The accumulation of α-synuclein aggregates is harmful to affected cells, ultimately resulting in the loss of specific neuronal populations, particularly dopaminergic neurons in the substantia nigra. This neuronal loss underlies the core motor symptoms of PD, which encompass bradykinesia, rigidity, and resting tremors (Poewe et al., 2017). PD affects a significant portion of the aging population, with an estimated incidence of 1.8% in individuals aged 65 and older (de Rijk et al., 2000).

Given the growing economic burden resulting from increased life expectancy, there is a critical need for neuroprotective treatments for neurodegenerative diseases like PD (Findley, 2007). However, there is currently no therapy capable of halting or slowing the progression of PD. The available pharmacotherapy and neurosurgical interventions can only provide symptomatic treatment. Furthermore, by the time PD is diagnosed, up to 50% of substantia nigra neurons may already be irreparably damaged, and as much as 80% of striatal dopamine may have been depleted (Rodriguez-Oroz et al., 2009). The challenge in developing disease-modifying therapies may lie in the fact that the disease progresses for many years before the emergence of its defining motor symptoms, making it challenging to intervene effectively. Therefore, early detection of PD in its prodromal stages becomes paramount for the development of neuroprotective treatments (Schenck et al., 2013; Postuma et al., 2015). Establishing a suitable biomarker would be a groundbreaking achievement, significantly impacting PD diagnosis and future treatment strategies.

1.3.2. Isolated rapid eye movement sleep behaviour disorder (iRBD)

The iRBD is a parasomnia characterized by dream-enactment behavior and a loss of muscle atonia during the rapid eye movement (REM) sleep phase. iRBD is considered a prodromal stage of neurodegeneration since up to 80% of diagnosed patients go on to develop alpha-synuclein-aggregation disorders such as PD, Lewy body dementia, or multiple system atrophy (Boeve et al., 2013; Miglis et al., 2021). In the context of

developing Parkinson's disease-modifying treatments (Dawson & Dawson, 2019) a multicenter study involving 1,280 iRBD patients identified quantitative fine motor skill testing as the strongest predictor for conversion to these disorders (Postuma et al., 2019). Another study by Postuma et al. (2012) revealed that voice and face akinesia represent the earliest prodromal motor manifestations in iRBD subjects, often preceding the onset of parkinsonism by an average of 9.8 years.

Hypokinetic dysarthria is present in more than 90% of PD patients over the course of the disease (Ho et al., 1999; Duffy, 2019). Furthermore, speech impairment has been observed in the majority of newly diagnosed PD patients (Rusz et al., 2021, 2022a). Given that patients with iRBD are at a high risk of developing PD, the assessment of speech behavior in iRBD is under thorough investigation.

1.3.3. Atypical parkinsonian syndromes (APS)

APS is a group of related disorders characterized by parkinsonism alongside a range of overlapping symptoms. Differing from PD, APS show limited response to levodopa treatment and have a more rapid disease progression (Wenning et. al., 2011; O'Sullivan et. al., 2008). APS encompasses conditions like multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia, and corticobasal degeneration (Wenning et al., 2011).

MSA is estimated to affect 30 individuals per 100,000 among those over 65 years (Schrag et al., 1999) and is characterized by various combinations of autonomic, cerebellar, parkinsonian, and pyramidal features (Wenning et al., 2004). Notably, patients with MSA commonly present mixed dysarthria involving hypokinetic, ataxic, and spastic components due to widespread neural atrophy, affecting the basal ganglia circuit and cerebellum (Kluin et al., 1996).

PSP is a neurodegenerative disorder characterized by the accumulation of abnormal tau protein in specific brain regions, leading to cell damage and loss. It typically occurs in middle to late age. The estimated incidence is approximately 40 cases per 100,000 individuals over 65 years old, with an average life expectancy of around 5.3 years after disease onset (Schrag et al., 1999). PSP is marked by clinical features such as supranuclear gaze palsy, frequent falls, bradykinesia, axial rigidity, cognitive decline, and communication disorders (Nath et al., 2003). Like MSA, PSP patients often develop

mixed dysarthria involving hypokinetic, ataxic, and spastic components, primarily due to damage in the basal ganglia circuit and corticobulbar pathways (Kluin et al., 1993).

1.3.4. Huntington's disease (HD)

HD is an autosomal-dominant inherited neurodegenerative disorder. It is caused by an expansion in the number of CAG repeats on the short arm of chromosome 4p16.3 within the Huntington gene (Gusella et al., 1983). HD is characterized by uncoordinated body movements, psychological dysfunction, and a progressive decline in cognitive function, ultimately leading to dementia. The occurrence of Huntington's disease varies among populations, affecting approximately 2-7 individuals per 100,000 people (Pringsheim et al., 2012).

Clinically, HD is primarily characterized by involuntary movements known as chorea. These movements may be accompanied by symptoms such as bradykinesia, motor impersistence, and deficits in movement planning, aiming, tracing, and termination (Paulsen, 2011). In addition, the speech impairment called hyperkinetic dysarthria develop more than 90% of HD patients during the course of the disease (Darley et al., 1969a; Darley et al., 1969b; Skodda et al., 2014).

1.3.5. Cerebellar ataxia (CA)

Cerebellar ataxias (CAs), whether sporadic or hereditary, are linked to the gradual deterioration of the cerebellum and its associated neural pathways. Spinocerebellar ataxia is a rare autosomal-dominant neurological disorder, with an estimated prevalence of approximately 3-4 cases per 100,000 individuals (Craig et al., 2004). In contrast, idiopathic late-onset cerebellar ataxia refers to a group of sporadic degenerative diseases affecting the cerebellum and brainstem, with unknown causes. Despite variations in their origins, these conditions share similar pathological changes, notably cerebellar involvement, crucial for posture and fine motor control. Clinically, cerebellar ataxia is characterized by progressive gait abnormalities, including an unsteady gait, widened step, misplacement of the feet, stride length variability, and poor inter-limb coordination, leading to balance loss and an elevated risk of falling.

Speech difficulties related to cerebellar ataxia are often attributed to ataxic dysarthria but given the potential involvement of various parts of the motor system, a combination with other dysarthria subtypes is possible (Skodda et al., 2013; Schalling & Hartelius, 2013).

1.3.6. Amyotrophic lateral sclerosis (ALS)

ALS is a motor neuron disease characterized by progressive degeneration of nerve cells in the spinal cord and brain. The incidence of ALS is approximately 1-2 cases per 100,000 persons per year (Talbot et al., 2016). As the disease progresses, the muscles responsible for speech become weaker and less coordinated, resulting in slurred speech, reduced voice clarity, and difficulties with articulation. Different types of dysarthria can manifest in ALS, including spastic, flaccid, and mixed types (Tomik et al., 2010). Speech therapy and assistive communication devices are often used to help individuals with ALS maintain effective communication as the disease advances.

1.3.7. Multiple sclerosis (MS)

MS is a chronic autoimmune disease that affects the central nervous system. The global estimated prevalence of MS is 35.9 per 100,000 population, with an increase observed in all world regions since 2013, totaling approximately 2.8 million individuals affected (Walton et al., 2020). One of the common symptoms associated with MS is dysarthria, characterized by a combination of spastic and ataxic components, reflecting pyramidal-cerebellar pathophysiology (Rusz et al., 2018). This condition affects up to 50 % of MS patients (Rusz et al., 2018).

1.3.8. Essential tremor (ET)

ET is a neurological disorder characterized by rhythmic, involuntary shaking, often affecting the hands and arms. Its pathophysiology is understood to be linked to the cerebellum (Benito-León et al., 2016). Generally, ET is considered to be one of the most common movement disorders. The prevalence of ET in the global population is 0.9% and markedly increase with age (Louis & Ferreira, 2010). ET is commonly associated with hyperkinetic dysarthria, a speech disorder associated with the underlying hyperkinesia-related pathophysiology.

1.4. Speech therapy

Speech therapy plays a crucial role in helping individuals with speech disorders regain and enhance their communication abilities. Two well-known speech therapy programs, “Lee Silverman Voice Treatment” (LSVT) and “SpeakOUT”, have shown significant benefits for patients with PD (Sapir et al., 2007; Behrman et al., 2020). However, effectiveness of another novel behavioural speech therapy such as “Clear Speech” is investigated for different neurological conditions. Clear speech is a speaking style in

which speakers deliberately alter their everyday speech to optimize intelligibility. This is typically achieved through exaggerated articulation, a slower speaking pace, and increased vocal volume. Acoustic analyses of clear speech production have shown that individuals with PD can utilize similar strategies as those without speech impairments (Goberman & Elmer, 2005; Kearney et al., 2017). Additionally, consistent use of clear speech techniques has been recommended as an effective behavioral therapy for individuals with dysarthria resulting from various neurological conditions, including PD (Beukelman et al., 2002; Duffy, 2019). Although only a few studies have explored the application of speech therapy to APS, they have indicated a potential positive impact (Sale et al., 2015; Park et al., 2016).

2. Goals, state-of-the-art, and hypothesis

This cumulative dissertation consists of four published peer-reviewed journal papers (Skrabal et al., 2020, Skrabal et al., 2022; Tykalova et al., 2021; Illner et al., 2023). These papers present a range of different interrelated research goals that track the progress of research related to the analysis of vowel articulation impairment. The specific goal, state-of-the-art, and hypothesis for each manuscript are presented below.

2.1. Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease

State-of-the-art

To date, the only reported acoustic measure that separate iRBD patients and controls was the monopitch (Rusz et al., 2021). Notably, monopitch was identified in iRBD subjects with impaired olfactory function before the nigrostriatal dopaminergic transmission was affected (Rusz et al., 2022b), corresponding to Braak stage 2, preceding synucleinopathy's impact on the substantia nigra (Braak et al., 2003). Among all speech characteristics, vowel articulation impairment stands out as a core deficit contributing to hypokinetic dysarthria of PD. It reflects the range of articulatory movements and strongly correlates with overall intelligibility (Lee & Hustad, 2013; Carl & Icht, 2021). The potential of imprecise vowel articulation to serve as an early biomarker is also supported by a previous pilot study where deficits in vowel articulation were detected in a small sample of 20 patients with de-novo PD (Rusz et al., 2013b). However, investigations into potential changes in vowel articulation in iRBD have not been previously conducted. Additionally, no prior research has independently linked articulation impairment to other crucial prodromal features of synucleinopathy, such as olfactory dysfunction.

Goals

To assess vowel articulation in individuals with iRBD and early-stage PD in comparison to healthy control (a) to determine if vowel articulation measurements can serve as a biomarker for early detection of prodromal PD and (b) to investigate the links between articulation measures and the degree of motor and olfactory dysfunction.

Hypothesis

a) Vowel articulation will be more significantly affected in de-novo PD compared to iRBD and HC.
b) Vowel articulation measures will be sensitive enough to detect the deterioration in vowel articulation in iRBD patients.
c) The degree of vowel articulatory undershoot in iRBD will correlate with the presence of olfactory impairment.
d) The degree of vowel articulatory undershoot in PD will correlate with certain motor impairment features.

2.2. Dysarthria enhancement mechanism under external clear speech instruction in Parkinson's disease, progressive supranuclear palsy, and multiple system atrophy

State-of-the-art

Speech and voice impairment are fundamental clinical features that manifest in 90-100% of patients with PD, PSP, and MSA as the diseases progress (Ho et al., 1998; Kluin et al. 1993, 1996; Rusz et al., 2015). Dysarthria tends to be more severe in PSP and MSA compared to PD (Rusz et al., 2015; Tykalova et al. 2017). In the case of PD, the majority of patients typically present with pure hypokinetic dysarthria (Darley et al., 1969a, 1969b; Ho et al., 1998). Conversely, PSP and MSA patients often develop mixed dysarthria, characterized by a combination of hypokinetic, ataxic, and spastic components, due to more extensive neurodegeneration (Kluin et al., 1993, 1996; Rusz et al., 2015). MSA patients frequently exhibit prominent ataxic patterns of dysarthria linked to cerebellar dysfunction, while in PSP, spastic elements predominate due to damage to the corticobulbar pathways. These distinct dysarthria patterns, associated with different underlying pathophysiological mechanisms involving α-synucleinopathy in MSA and tauopathy in PSP, may hold significant implications for prognosis and treatment, especially in the context of speech rehabilitation management.

Goals

To examine speech patterns in patients with PSP and MSA in comparison to individuals with PD and healthy controls. This investigation encompassed both conversational and clear speech conditions, intending to enhance our understanding of speech alterations.

Ultimately, the study aimed to contribute to the improvement of speech therapy management and support more effective differential diagnosis.

Hypothesis

a) Speech performance of PD patients will be significantly enhanced under clear speech instruction.
b) Speech performance of APS patients will be significantly enhanced under clear speech instructions.
c) We anticipate distinct approaches to speech adaptation in MSA and PSP under clear speech conditions, reflecting variations in disease pathophysiology.

2.3. Automated vowel articulation analysis in connected speech among progressive neurological diseases, dysarthria types and dysarthria severities

State-of-the-art

Distinct progressive neurological diseases typically manifest in various dysarthria subtypes, including hypokinetic, hyperkinetic, spastic, ataxic, or flaccid variants (Duffy, 2019). These subtypes reflect the underlying pathophysiology and offer insights for differential diagnosis (Duffy, 2019). Additionally, extensive research has consistently identified vowel articulation abnormalities in various progressive neurological diseases (Tjaden et al., 2005, 2013; Whitfield, 2019; Lam & Tjaden, 2016; Rusz et al., 2014, 2015; Tykalova et al., 2016). Given the established connections between vowel articulation impairment severity and perceptual impressions of unintelligibility in dysarthric speakers (Kim et al., 2011; Liu et al., 2005; Weismer et al., 2001), vowel articulation analysis holds the potential to serve as a measure of speech severity in dysarthria. Nevertheless, prevailing approaches to assess vowel articulation in dysarthrias using formants often involve accurate and time-consuming hand-labeling of predefined speech utterances (Shimon et al., 2010; Skodda et al., 2011).

There is a need for a dependable and automated approach that can be applied to natural, spontaneous speech without imposing any financial cost or administrative burden on either the patient or the investigator. This is essential to promote the utilization of vowel articulation assessment in routine clinical practice.

Goals

To develop an entirely automated method for analyzing vowel articulation impairment caused by dysarthria applicable to a substantial sample of patients affected by diverse progressive neurological conditions that would enable quantitatively evaluate the sensitivity of inaccurate vowel articulation concerning (a) various types of neurological diseases, (b) different types of dysarthria, and (c) the severity of dysarthria.

Hypothesis

a) A fully automated vowel articulation assessment would discover significant vowel impairment across various neurological disorders and different types of dysarthria.
b) A fully automated vowel articulation assessment would identify specific features of vowel articulation impairment in individual neurological disorders.
c) VSA would be a suitable marker for dysarthria severity.

2.4. Effect of ageing on acoustic characteristics of voice pitch and formants in Czech vowels

State-of-the-art

The aging population is surging worldwide, leading to a rapid rise in speech and language disorders among the elderly.

As people age, they generally exhibit slower speaking and reading rates, along with longer vowel segments (Harnsberger et al., 2008). In older female subjects, f0 was reported to consistently decreased (Torre & Barlow, 2009; Eichhorn et al., 2018), but findings for men vary, with f0 decreased (Cox & Selent, 2015), remained unchanged (Eichhorn et al., 2018), or even increase with age (Harnsberger et al., 2008, Torre & Barlow, 2009).

Age-related changes in F1 and F2 formants have been observed, with some studies suggesting vowel centralization due to neuromuscular changes or vocal tract lengthening (Rastatter & Jacques, 1990). However, more recent research doesn't confirm these assumptions, as it shows no significant changes in F1 and F2 for both men and women over the age of 60, nor a trend towards VSA reduction (Fletcher et al., 2015; Eichhorn et al., 2018). Hence, further investigation regarding how aging affects vowel articulation is relevant, given the inconsistent findings in previous research.

Goals

To analyze the acoustic features of vowels in a wide range of Czech healthy native speakers ranging in age from 20 to 90 years (a) to assess how the process of aging impacts vowel articulation and additionally, (b) to offer normative data for Czech vowels.

Hypothesis

a) Fundamental frequency would be sex-dependent
b) VSA would be age- and sex-independent

3. Methods

Although the specific methods employed for speech evaluation depend on the goals of each study, the general approach can be outlined in four steps: (1) selecting an appropriate population sample and establishing inclusion/exclusion criteria; (2) recording a comprehensive speech protocol, including connected speech; (3) assessing vowel articulation and other relevant speech patterns in accordance with the study's design; (4) developing a suitable statistical approach to meet the intended objectives.

3.1. Research participants

Across the four individual journal papers composing this cumulative thesis, patients with iRBD, PD, MSA, PSP, CA, HD, MS, ALS, and ET, as well as healthy control participants were recruited and examined from 2011 to 2021. Diagnoses were established as follows: iRBD subjects met the diagnostic criteria based on the International Classification of Sleep Disorders, third edition, with confirmation through polysomnography to detect REM sleep without atonia (Mansukhani et al., 2014). De-novo PD patients were diagnosed based on the Parkinson's Disease Society Brain Bank Criteria (Postuma et al., 2015). The diagnosis of probable MSA followed the consensus diagnostic criteria for MSA (Gilman et al., 2008), and for probable PSP, the NINDS-PSP clinical diagnosis criteria were applied (Höglinger et al., 2017). The diagnosis of CA was made through genetic testing or the results of neurological, neuropsychological, and magnetic resonance imaging testing. HD diagnosis was confirmed by genetic testing and the onset of disease relied on the motor score of the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996). MS diagnosis adhered to the revised McDonald Criteria (Thompson et al., 2018). ALS diagnosis followed the El Escorial Criteria from the World Federation of Neurology (Brooks et al., 2000), and ET diagnosis was based on published clinical research criteria (Louis et al., 2007). All diagnoses were conducted by neurologists experienced in movement disorders.

The basic inclusion criteria for healthy control participants were no history of neurological or communication disorders. Ethics approval for each project was obtained from the Ethics Committee of the General University Hospital, Prague, Czech Republic, and all participants provided written, informed consent.

The disease severity of iRBD and PD was assessed using the motor score of the Movement Disorders Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (Goetz et al., 2008). MSA and PSP severity was measured by The Natural History and Neuroprotection in Parkinson Plus Syndromes–Parkinson Plus Scale (NNIPPS-PPS; Payan et al., 2011), CA was assessed using the Scale for the Assessment and Rating of Ataxia (SARA; Schmitz-Hübsch et al., 2006), and HD was determined by the motor score of the UHDRS (Huntington Study Group, 1996). MS disease severity was measured using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), and ALS by the ALS Functional Rating Scale–Revised (ALSFRS-R; Cedarbaum et al., 1999). Finally, ET disease severity was assessed using the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS; Elble et al., 2012).

3.2. Speech recording

Speech recordings were conducted in a quiet environment with minimal background noise, using a professional head-mounted condenser microphone. The audio signals were sampled at a rate of 48 kHz with a 16-bit resolution. The recordings were done in a single session, guided by a speech specialist who provided instructions to the participants. There were no strict time limits during the recording, and participants were encouraged to redo their speech performance if they or the examiner were not entirely satisfied with the initial attempt.

Each participant underwent a comprehensive speech examination as a part of a longer protocol, typically lasting 20 minutes. The examination included various speech tasks including "connected speech" where participants read a standardized passage containing 80 words (Figure 1) and a 2-minute monologue on topics related to family, work, childhood, or interests. To evaluate clear speech, participants also read a specific passage under both clear speech and conversational instructions (Figure 2).

Figure 1: The reading passage with labeled corner vowels /a/, /i/, and /u/ utilized in the acoustic analysis. The figure is adopted from the study published by Skrabal et al. (2021).

Když člověk poprvé vsadí do země sazeničku, chodí se na ni dívat třikrát denně: tak co, povyrostla už nebo ne? I tají dech, naklání se nad ní, přitlačí trochu půdu u jejích kořínků, načechrává jí lístky a vůbec ji obtěžuje různým konáním, které považuje za užitečnou péči. A když se sazenička přesto ujme a roste jako z vody, tu člověk žasne nad tímto divem přírody, má pocit čehosi jako zázraku *a* považuje to za jeden ze svých největších osobních úspěchů.

Figure 2: The reading passage with labeled corner vowels /a/, /i/, and /u/ employed in the acoustic analysis of clear vs. conversational speech. The figure is adopted from the study published by Skrabal et al. (2020).

I na tom, že člověk si opatří psa, aby nebyl sám, je mnoho pravdy. Pes opravdu nechce být sám. Jen jednou jsem nechal Mindu o samotě v předsíni; na znamení protestu sežrala všechno, co našla, a bylo jí pak poněkud nedobře. Po druhé jsem ji zavřel do sklepa s tím výsledkem, že rozkousala dveře. Od té doby nezůstala sama ani po jedinou minutu. Když píši, chce, abych si s ní hrál. Když si lehnu, považuje to za znamení, že si mně smí lehnout na prsa a kousat mě do nosu. Přesně o půlnoci s ní musím provádět Velkou Hru, při níž se s velikým hlukem honíme, koušeme a kutálíme po zemi. Když se uříti, jde si lehnout; pak si smím lehnout i já, ovšem s tou podmínkou, že nechám dveře do ložnice otevřené, aby se Mindě nestýskalo.

3.3. Acoustic analysis

For all studies (Skrabal et al., 2020, Skrabal et al., 2022; Tykalova et al., 2021, Illner et al., 2023) analyses were conducted using Praat software (Boersma, 2014) that involved both the combined wideband spectrographic display and power spectral density. A customary approach validated across various languages was employed (Roy et al., 2009; Rusz et al., 2013a; Skodda et al., 2011). The first and second formant frequencies were measured in Hertz (Hz). Additionally, in a study by Tykalova et al. (2021) frequencies F3, and F4 were obtained. A total of 10 instances per passage for each vowel of interest were extracted (see Fig. 1 and 2 for example). The F1, F2, F3, and F4 frequencies were averaged separately for each participant's individual vowel. We utilized VSA, a traditional and widely-used articulatory-acoustic measure (Kent et al., 2018; Fant et al. 1973), as previously outlined and in details described in the introduction. Furthermore, in

study published by Tykalova et al. (2021), vowel duration was calculated as the time between the vowel onset and offset.

In addition, in study published by Illner et al. (2023), the formants values were extracted based on two approaches Praat and newly designed automatic algorithm for vowel articulation features. This algorithm applies a formant tracker in conjunction with a phoneme recognizer and subsequent signal processing analysis, as illustrated in Figure 3. For a detailed description see Illner et al. (2023).

For overview of all acoustic features included within the thesis see Table 1.

Figure 3. Illustrative schema of the automated method for formants estimation. The figure is adapted from the study published by Illner et al. (2023). F1 = first formant frequency; F2 = second formant frequency; VSA = vowel space area; FRI = formant ratio index; SFRI = second formant ratio index.

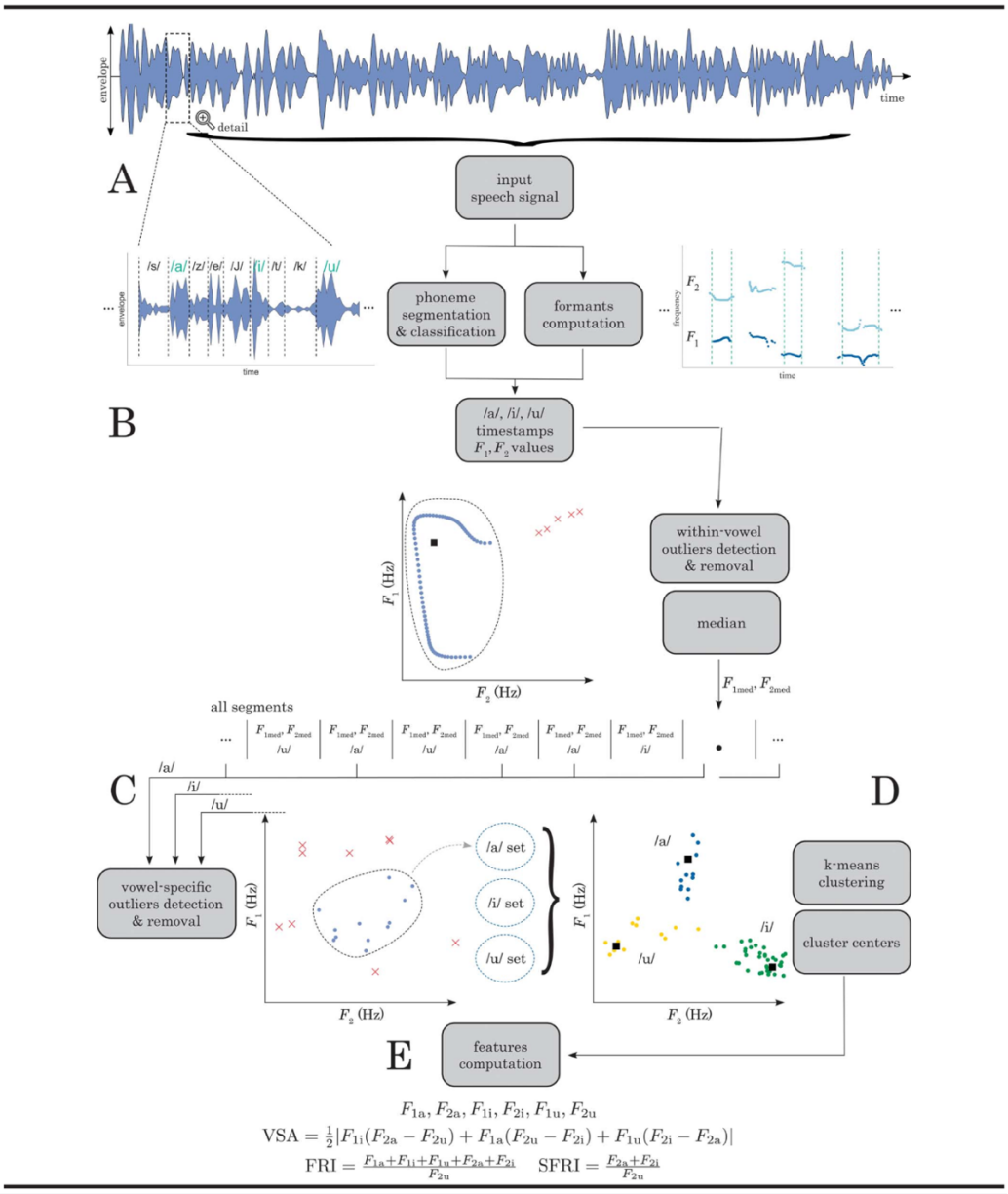


Table 1: Recap of commonly used acoustic features included within the thesis.

Feature name	Abbrevations	Definition	Reference
Vowel articulation features			
1st, 2nd, 3rd, 4th formant	F1, F2, F3, F4 (Hz)	Formants are frequency peaks in the spectrum which have a high degree of energy. Formants result from an acoustic resonance of the human vocal tract and are therefore connected with specific frequency for particular vowel.	Zwirner & Barnes, 1992
Vowel duration	VD (ms)	Vowel duration is measured as the difference between the onset and offset of each vowel.	Tykalová et al., 2021
Vowel space area	VSA (kHz2)	Defined as the Euclidean distances between the first (F1) and second (F2) formant coordinates of the corner vowels in the F1–F2 vowel space.	Liu et al., 2005
Vowel articulation index	VAI (-)	VAI enhance sensitivity to formant centralization and is calculated according to following formula VAI = (F2/i/ + F1/a/)/(F1/i/ + F1/u/ + F2/u/ + F2/a/).	Roy et al., 2009
Other speech features			
F0 variability	f0 SD (semitones)	Standard deviation of fundamental frequency (f0) contour.	Zwirner & Barnes, 1992
Articulation rate	NSR (syll/s)	Net speech rate, defined as the total number of syllables divided by the total duration of speech after removal of pauses.	Zwirner & Barnes, 1992
Mean intensity	Intensity (dB)	Average squared amplitude within a predefined time-energy segment.	Rusz & Cmejla, 2008
Intensity variability	Intensity SD (dB)	Standard deviation of intensity contour.	Rusz & Cmejla, 2008

3.4. Auditory–perceptual assessment of dysarthria

In study published by Illner et al. (2023), the presence, type, and severity of dysarthria was evaluated by experienced speech-language pathologists, who were aware of each patient's medical diagnosis and conducted a consensus auditory–perceptual assessment. This evaluation was based on offline audio recordings and followed the perceptual criteria established by Darley et al. in 1969b. The dysarthria types identified across the eight neurological conditions included hypokinetic, hyperkinetic, ataxic, spastic, flaccid–spastic, spastic–ataxic, hypokinetic–spastic, hypokinetic–ataxic, and hypokinetic–spastic–ataxic. Additionally, the severity of dysarthria was rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Individuals with speech issues unrelated to

their diagnosed neurological disorder were excluded from this study. See Table 2 for details.

Table 2. Clinical features of the cohort of subjects under investigation. The table is adopted from the study published by Illner et al. (2023).

Disease	Sex	Motor score (disease severity) *M/SD* (range)	Age (years) *M/SD* (range)	Symptom duration (years) *M/SD* (range)	Dysarthria type (auditory–perceptual)	Dysarthria severity (auditory–perceptual)
PD	F = 10	38.7/14.7[a]	63.5/8.9	1.6/1.3	Hypokinetic (*n* = 20)	Mild (*n* = 13)
	M = 10	(18–70)	(42–79)	(0.3–5.9)		Moderate (*n* = 7) Severe (*n* = 0) Mean severity: 1.35[h]
PSP	F = 5	65.7/28.9[b]	66.0/5.1	4.7/2.7	Hypokinetic (*n* = 3)	Mild (*n* = 3)
	M = 10	(19–132)	(54–71)	(2.0–11.0)	Hypokinetic–spastic (*n* = 4)	Moderate (*n* = 5)
					Hypokinetic–ataxic (*n* = 3)	Severe (*n* = 7) Mean severity: 2.27
					Hypokinetic–spastic–ataxic (*n* = 5)	
MSA	F = 12	79.1/21.1[b]	62.0/7.0	4.4/1.8	Hypokinetic (*n* = 3)	Mild (*n* = 1)
	M = 8	(35–115)	(45–73)	(2.0–7.5)	Spastic–ataxic (*n* = 1)	Moderate (*n* = 12)
					Hypokinetic–spastic (*n* = 8)	Severe (*n* = 7)
					Hypokinetic–ataxic (*n* = 3)	Mean severity: 2.30
					Hypokinetic–spastic–ataxic (*n* = 5)	
HD	F = 10	24.8/9.9[c]	53.1/11.0	5.2/3.6	Hyperkinetic (*n* = 20)	Mild (*n* = 1)
	M = 10	(8–42)	(34–69)	(1.0–16.0)		Moderate (*n* = 13)
						Severe (*n* = 6) Mean severity: 2.25
ET	F = 10	17.5/7.6[d]	64.3/11.1	28.9/17.5	Hyperkinetic (*n* = 18)	Mild (*n* = 5)
	M = 10	(6–35)	(40–82)	(3.0–60.0)	Hypokinetic (*n* = 1)	Moderate (*n* = 9)
					Spastic (*n* = 1)	Severe (*n* = 6) Mean severity: 2.05
CA	F = 8	13.9/4.8[e]	54.7/12.6	11.0/8.5	Ataxic (*n* = 5)	Mild (*n* = 5)
	M = 10	(4–24)	(34–72)	(0.5–28.0)	Spastic (*n* = 1)	Moderate (*n* = 7)
					Spastic–ataxic (*n* = 11)	Severe (*n* = 6) Mean severity: 2.06
					Hypokinetic–ataxic (*n* = 1)	
MS	F = 11	4.6/0.8[f]	52.2/10.1	17.8/8.6	Ataxic (*n* = 7)	Mild (*n* = 16)
	M = 9	(4–7)	(33–74)	(6.0–32.0)	Spastic (*n* = 3)	Moderate (*n* = 3)
					Spastic–ataxic (*n* = 10)	Severe (*n* = 1) Mean severity: 1.25[h]
ALS	F = 14	35.6/6.5[g]	62.1/11.1	1.9/1.2	Spastic (*n* = 4)	Mild (*n* = 5)
	M = 6	(22–45)	(37–85)	(0.5–5.0)	Flaccid–spastic (*n* = 16)	Moderate (*n* = 6)
						Severe (*n* = 9) Mean severity: 2.20
Total	F = 80		59.7/9.6	9.4/5.7	Hypokinetic (*n* = 27)	Mild (*n* = 49)
	M = 73		(33–85)	(0.3–60.0)	Hyperkinetic (*n* = 38)	Moderate (*n* = 62)
					Ataxic (*n* = 12)	Severe (*n* = 42)
					Spastic (*n* = 9)	Mean severity: 2.09
					Flaccid–spastic (*n* = 16)	
					Spastic–ataxic (*n* = 22)	
					Hypokinetic–spastic (*n* = 12)	
					Hypokinetic–ataxic (*n* = 7)	
					Hypokinetic–spastic–ataxic (*n* = 10)	

Note. PD = Parkinson's disease; F = female; M = male; PSP = progressive supranuclear palsy; MSA = multiple system atrophy; HD = Huntington's disease; ET = essential tremor; CA = cerebellar ataxia; MS = multiple sclerosis; ALS = amyotrophic lateral sclerosis; MDS-UPDRS = Movement Disorders Society–Unified Parkinson's Disease Rating Scale; NNIPPS-PPS = Natural History and Neuroprotection in Parkinson Plus Syndromes–Parkinson Plus Scale; UHDRS = Unified Huntington's Disease Rating Scale; TETRAS = Tremor Research Group Essential Tremor Rating Assessment Scale; SARA = Scale for the Assessment and Rating of Ataxia; EDSS = Expanded Disability Status Scale; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised.

[a]MDS-UPDRS Part III total scale. [b]NNIPPS-PPS total scale. [c]UHDRS total scale. [d]TETRAS score scale. [e]SARA total scale. [f]EDSS total scale. [g]ALSFRS-R total scale. [h]This group was found to have significantly lower disease severity compared to PSP, MSA, HD, ET, CA, and ALS groups with $p < .01$.

3.5. Statistics

Each parameter was assessed for normality using the Kolmogorov-Smirnov test (Skrabal et al., 2020, Skrabal et al., 2022; Tykalova et al., 2021). In one case (Illner et al., 2023),

normality was confirmed through the Shapiro–Wilcoxon and Bartlett tests for data distribution. For normally distributed data, t-tests, analysis of variance, or Fisher's Least Significant Difference for group difference assessments was used. Additionally, Pearson analysis was employed to explore correlations between variables. The significance threshold was consistently set at $p < 0.05$ and adjusted for multiple comparisons using the Bonferroni method.

3.6. Dopamine transporter imaging

In a study conducted by Skrabal et al. (2022), both PD and iRBD patients underwent a Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SCAN) assessment, following the procedure guidelines of the European Association of Nuclear Medicine (Dacourt et al., 2010). It is a diagnostic imaging technique used to assess dopamine levels and transporters in the brain. In the context of PD, DAT-SCAN plays a crucial role in confirming the diagnosis. PD is characterized by a progressive loss of dopamine-producing neurons in the brain, which significantly impacts motor function. DAT-SCAN provides visual evidence of dopamine transporter function and helps differentiate PD from other movement disorders with similar symptoms.

In individuals with iRBD, DAT-SCANs are employed to assess their risk of developing PD or other synucleinopathies. iRBD is often considered a prodromal stage of PD, and DAT-SCANs can reveal changes in dopamine transporter function in these individuals. Identifying such changes in iRBD patients can provide valuable insights into their risk of developing more advanced neurodegenerative conditions, allowing for early intervention and monitoring.

4. Results

Results of the cumulative dissertation present the outcomes of four individual journal papers (Skrabal et al., 2020, 2022; Tykalova et al., 2021; Illner et al., 2023). Only the main results are presented within this thesis. For more detailed information, please refer to each specific paper.

4.1. Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease

Group differences

VSA was found to be the best parameter for differentiating between groups [$F(2,177) = 7.4$, $p = 0.001$, $\eta 2 = 0.08$] (Figure 4). Post hoc comparisons revealed significantly smaller VSA in both iRBD ($p = 0.01$) and PD ($p = 0.001$) compared to HC individuals. In addition, group differences were also detected for Vowel Articulation Index (VAI) [$F(2,177) = 6.3$, $p = 0.002$, $\eta 2 = 0.07$], as the PD group manifested significantly smaller VAI ($p=0.002$) compared to HC group. Slight vowel duration differentiation was also observed across groups [$F(2,177) = 3.2$, $p = 0.04$, $\eta 2 = 0.04$), associated with differences between PD and iRBD groups ($p = 0.04$). The subexperiment concerning olfactory function in iRBD showed that iRBD group with preserved olfactory function (iRBD-POF) had greater VSA than iRBD group with abnormal olfactory function (iRBD-AOF) [$F(1,54) = 5.4$, $p = 0.024$, $\eta 2 = 0.094$] (Figure 5a). In addition, iRBD-AOF with normal dopamine transporter single-photon emission computed tomography (DAT-SPECT) showed greater VSA than iRBD-AOF with abnormal DAT-SPECT [$F(1,31) = 4.2$, $p = 0.049$, $\eta 2 = 0.140$] (Figure 5b). No significant differences for VAI and vowel duration were found.

Correlations between speech and motor variables

Movement Disorder Society Unified Parkinson's Disease Rating Scale motor part (MDS-UPDRS III) total in PD patients showed negative correlation with VSA ($r = -0.29$, $p = 0.03$) and VAI ($r=-0.29$, $p=0.03$). In addition, bradykinesia and rigidity subscore in PD patients showed negative correlation with VSA ($r=-0.33$, $p=0.01$) and VAI ($r=-0.34$, $p<0.01$) while neither correlation between postural instability and gait difficulty (PIGD) subscore and VSA ($r = -0.04$, $p = 0.75$) or VAI ($r = -0.12$, $p = 0.75$) nor between tremor subscore and VSA ($r = 0.01$, $p = 0.96$) or VAI ($r = 0.06$, $p = 0.64$) was detected.

Regarding brain imaging, the putamen binding ratio in iRBD showed positive correlation with VSA (r = 0.35, p = 0.01). No other significant correlations were found between vowel articulation parameters and clinical scales in PD or iRBD.

Figure 4. Comparison of vowel measurements including VSA, VAI, and vowel duration between HC, iRBD, and PD using boxplots. The figure is adopted from the study published by Skrabal et al. (2022). The center line indicates the median and the bounds of the box indicate the 25th and 75th percentiles. The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the 'x' symbol. VSA, vowel space area, VAI vowel articulation index, and "Asterisks" indicate significant differences after Bonferroni correction: *p < 0.05; **p < 0.01.

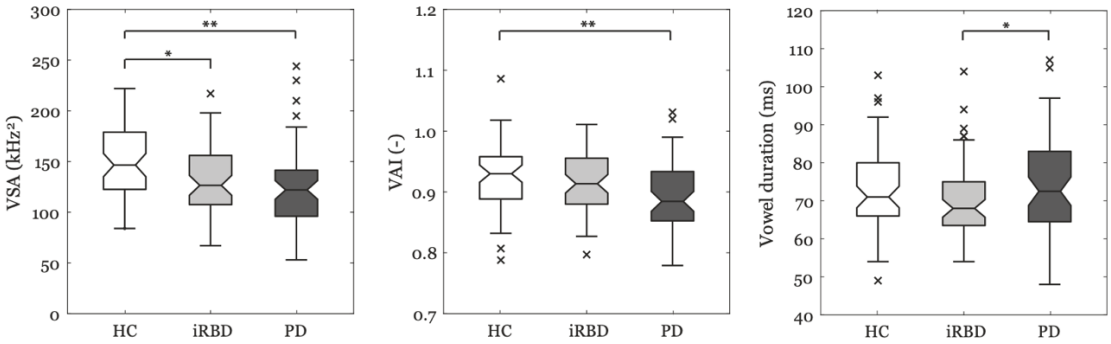
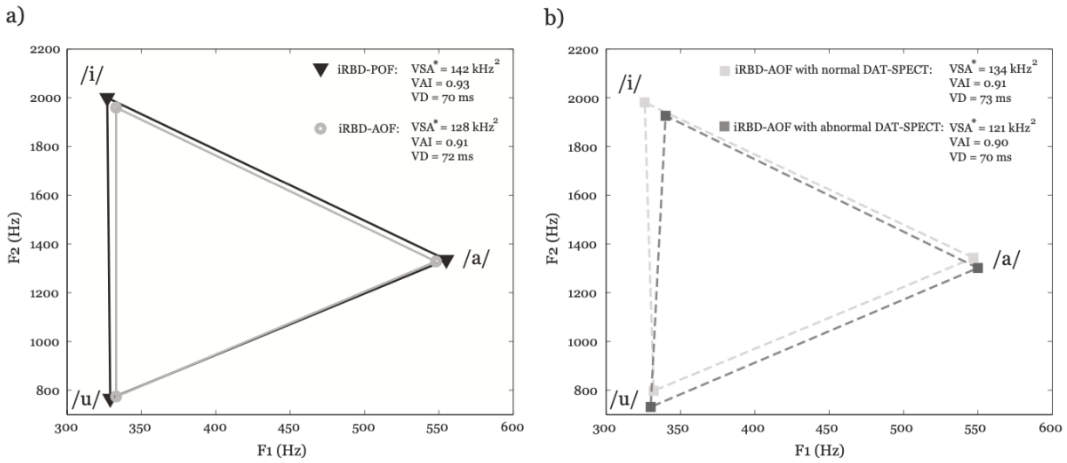


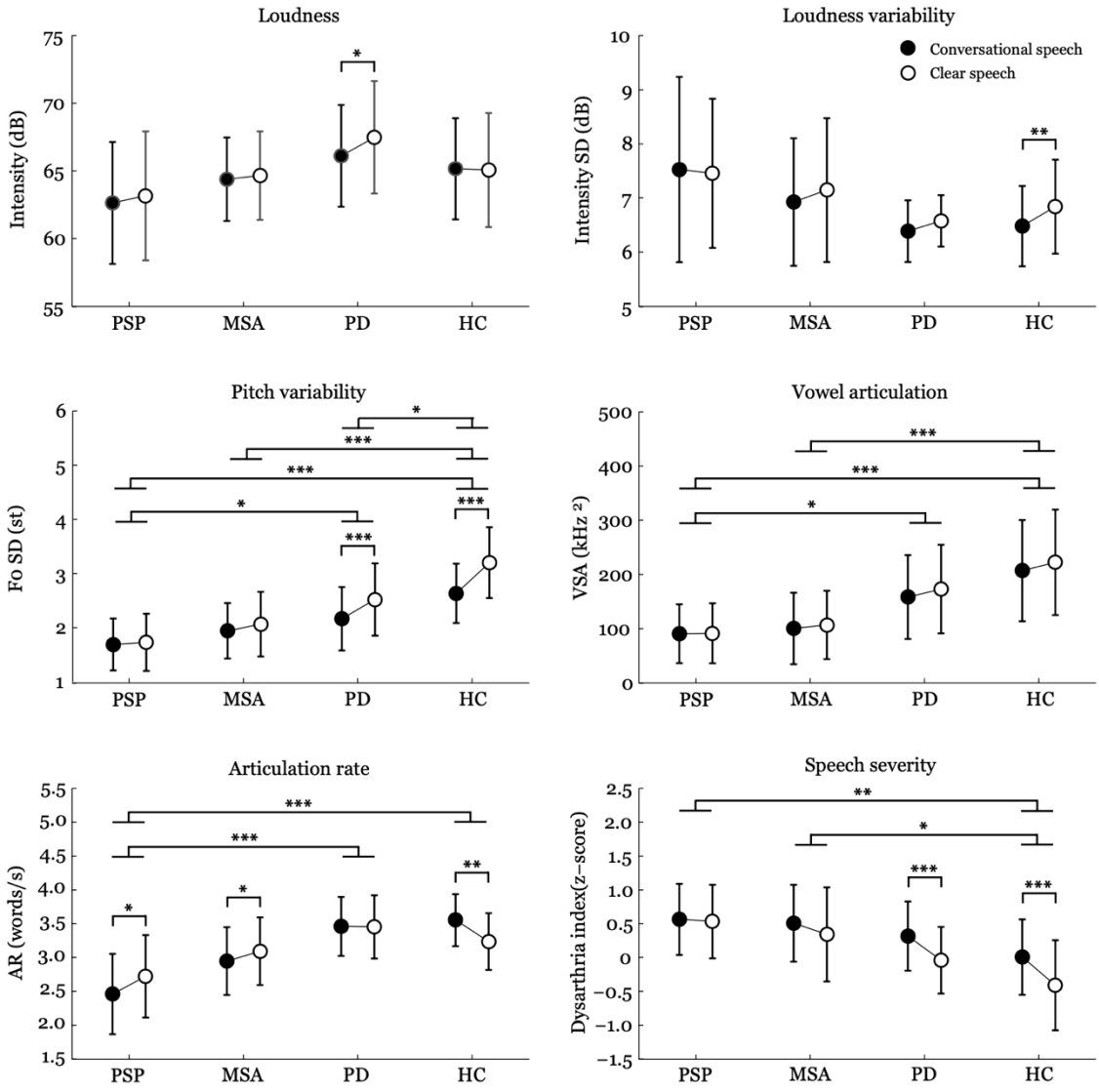
Figure 5 a/b. Mean F1 and F2 values and vowel space area for a) iRBD-POF compared iRBD-AOF subgroups and b) iRBD-AOF with normal DAT- SPECT compared to iRBD-AOF with abnormal DAT-SPECT. VSA vowel space area, VAI vowel articulation index, VD vowel duration, iRBD-POF isolated rapid eye movement sleep behaviour disorder patients with preserved olfactory function, iRBD-AOF isolated rapid eye movement sleep behaviour disorder patients with abnormal olfactory function, DAT-SPECT dopamine transporter single-photon emission computed tomography; "Asterisks" indicate significant differences: *p < 0.05.



4.2. Dysarthria enhancement mechanism under external clear speech instruction in Parkinson's disease, progressive supranuclear palsy, and multiple system atrophy

Figure 6 depicts the results of acoustic analyses for clear vs. conversational speech among PSP, MSA, PD, and HC subjects.

Figure 6. Comparison of results of acoustic analyses among PSP, MSA, PD, and HC groups under conversational and clear speech conditions. The figure is adopted from the study published by Skrabal et al. (2020). *Intensity SD* intensity variability; *F0 SD* fundamental frequency variability, *VSA* vowel space area, *AR* articulation rate, *PSP* progressive supranuclear palsy, *MSA* multiple system atrophy, *PD* Parkinson's disease, *HC* healthy controls. "Asterisks" indicate significant differences after Bonferroni correction: *p<0.01; **p<0.001; *** p < 0.0001.



For loudness, RM-ANOVA showed a significant effect for TASK [F(1,64) = 8.5, p = 0.03, η2 = 0.12], particularly as the PD group increased loudness (average change from conversational to clear speech 1.36 dB, p = 0.03). No signifi- cant effect was found for GROUP [F(3,64) = 2.9, p = 0.25, η2 = 0.12] or GROUP × TASK [F(3,64) = 3.0, p = 0.21, η2 = 0.13].

For loudness variability, we detected a significant effect for TASK [F(1,64) = 7.6, p = 0.046, η2 = 0.11], particularly as the HC group increased loudness variability (average change from conversational to clear speech 0.36 dB, p = 0.002). No significant effect was

found for GROUP [$F(3,64) = 2.9$, $p = 0.24$, $\eta 2 = 0.12$] or GROUP × TASK [$F(3,64) = 2.0$, $p = 0.75$, $\eta 2 = 0.09$].

For pitch variability, a significant effect was found for TASK [$F(1,64) = 85.6$, $p < 0.001$, $\eta 2 = 0.57$], mainly as the PD group increased pitch variability (average change from conversational to clear speech 0.36 st, $p < 0.001$) as well as HC group increased pitch variability (average change from conversational to clear speech 0.57 st, $p < 0.001$). In addition, a significant effect was found for GROUP [$F(3,64) = 14.4$, $p < 0.001$, $\eta 2 = 0.40$], mainly due to differences between PSP and HC ($p < 0.001$), MSA and HC ($p < 0.001$), PD and HC ($p = 0.02$), and PSP and PD ($p = 0.01$) groups. Finally, a significant interaction was revealed for GROUP × TASK [$F(3,64) = 16.3$, $p < 0.001$, $\eta 2 = 0.43$] as both PD and HC groups ($p < 0.001$) were able to increase pitch variability in the clear condition while PSP ($p = 1$) and MSA ($p = 0.23$) groups were not.

For vowel articulation, we revealed a significant effect for TASK [$F(1,64) = 7.9$, $p = 0.04$, $\eta 2 = 0.11$] as well as GROUP [$F(3,64) = 10.3$, $p < 0.001$, $\eta 2 = 0.33$]. Post-hoc tests showed significant differences between HC and both APS groups ($p < 0.001$) as well as PSP and PD groups ($p = 0.03$). No significant effect was found for GROUP × TASK [$F(3,64) = 1.1$, $p = 1.0$, $\eta 2 = 0.05$].

For articulation rate, a significant effect was detected for GROUP [$F(3,64) = 12.3$, $p < 0.001$, $\eta 2 = 0.37$], reflecting differences between PSP and both PD and HC groups ($p < 0.001$). Importantly, a significant effect was revealed for GROUP × TASK [$F(3,64) = 11.0$, $p < 0.001$, $\eta 2 = 0.34$], as the PSP group increased articulation rate (average change from conversational to clear speech 0.26 words/s, $p = 0.01$) as well as MSA group increased articulation rate (average change from conversational to clear speech 0.15 words/s, $p = 0.04$), whereas the HC group decreased articulation rate (average change from conversational to clear speech − 0.32 words/s, $p = 0.004$). No significant effect was detected for TASK [$F(1,64) = 0.3$, $p = 1$, $\eta 2 = 0.01$].

For dysarthria index, we revealed a significant effect for TASK [$F(1,64) = 72.8$, $p < 0.001$, $\eta 2 = 0.53$], reflecting increased speech performance (average change from conversational to clear speech) in PD (z-score change of − 0.36, $p < 0.001$), HC (z-score change of − 0.42, $p < 0.001$), and partially MSA (z-score change of − 0.17, uncorrected $p = 0.03$) groups. In addition, a significant effect was found for GROUP [$F(3,64) = 5.9$, $p = 0.007$, $\eta 2 = 0.22$], mainly attributed to differences between PSP and HC ($p = 0.001$), and MSA and HC ($p = 0.01$) groups. Finally, a significant interaction was revealed for

GROUP × TASK [$F(3,64) = 9.7$, $p < 0.001$, $\eta 2 = 0.31$] as both PD and HC ($p < 0.001$) groups were able to improve speech performance while PSP ($p = 1$) and MSA ($p = 0.18$) groups were not.

For the assessment of the first vs. second reading, no significant effect was observed for TASK or a GROUP × TASK in all examined acoustic features.

4.3. Automated vowel articulation analysis in connected speech among progressive neurological diseases, dysarthria types, and dysarthria severities

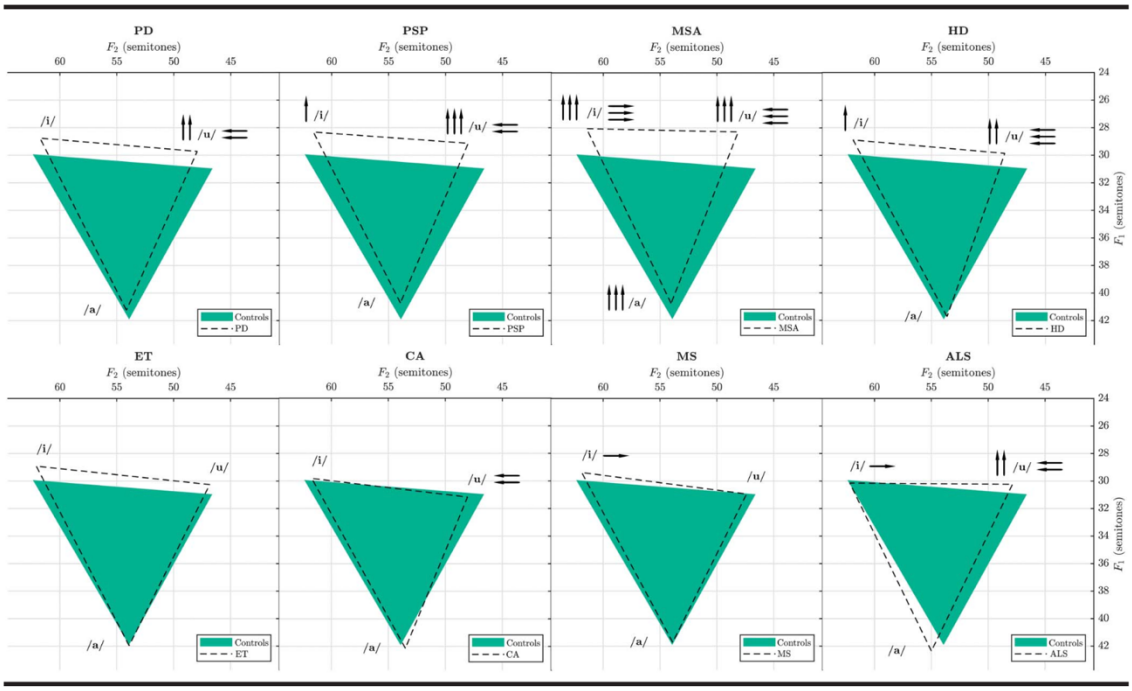
4.3.1. Algorithm performance

Compared to manual hand labels (based on 1,760 vowels), the phoneme recognizer attained an F-score of 0.84, whereas the formant tracker achieved 1-NRMSE of 0.93 for F1 and 0.84 for F2 across all vowels. After combining the error rate of the phoneme recognizer and formant tracker (based on 1,760 vowels), the F-score for all vowels was 0.77. Concerning the final averaged vowel articulation features (based on 20 utterances), the estimation of individual formants achieved 1-NRMSE of 0.88 for F1a, 0.85 for F2a, 0.73 for F1i, 0.89 for F2i, 0.72 for F1u, and 0.67 for F2u, leading to the 1-NRMSE of 0.84 for VSA, 0.71 for FRI, and 0.71 for SFRI. In summary, considering the final shape of vowel areas, the most notable difference between automated and manual labels is due to lower estimates of F1 frequencies of vowel /i/ and /u/ and F2 of /u/ by the automated approach.

4.3.2. Neurological disease type

Compared to controls, the change in vowel articulation due to neurodegeneration in monologues was primarily demonstrated by trends toward the shift of formants across vowels /i/ and /u/, including an increase in F2u and decrease in F1i, F1u, and F2i frequencies across PD, PSP, MSA, HD, and ALS (Figure 7). Among diseases, MSA tended to decrease F1 and CA tended to increase F1 compared to other neurological diseases, leading to a significantly lower F1 for MSA than CA across all corner vowels (Figure 8). Considering complex formant measures, compared to controls, VSA was significantly decreased for MSA, whereas FRI and SFRI were decreased for all neurological diseases except ET and MS (Figure 9).

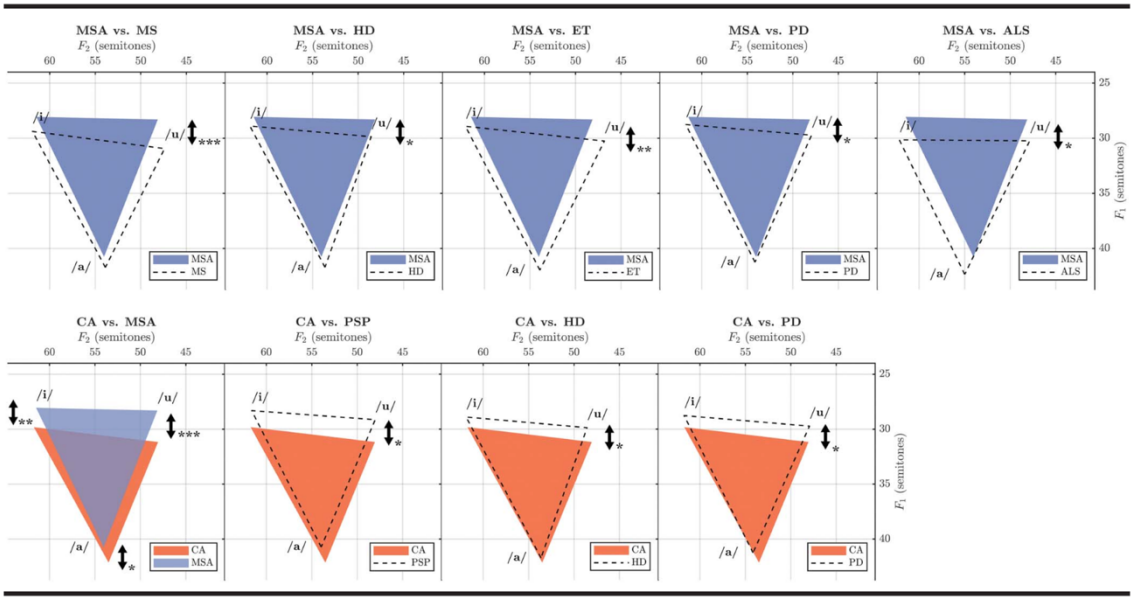
Figure 7. Corner vowel production triangles estimated from monologues for individual neurological disease types compared to healthy controls. The figure is adopted from the study published by Skrabal et al. (2022). The arrows indicate significant differences in the values to healthy controls adjusted by age and sex, with three, two, and one arrows referring to $p < .001$, $p < .01$, and $p < .05$, respectively. To minimize the effects of sex between individual speakers, the estimated formant frequencies were converted into a logarithmic tonal scale (semitones). F_1 = first formant frequency; F_2 = second formant frequency; PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA = multiple system atrophy; HD = Huntington's disease; ET = essential tremor; CA = cerebellar ataxia; MS = multiple sclerosis; ALS = amyotrophic lateral sclerosis.



4.3.3. Effect of dysarthria type

Compared to controls, the trends toward the shift of formants across vowels /i/ and /u/ including increase in F2u and a decrease in F1i, F1u, and F2i frequencies in monologues were demonstrated mainly for hypokinetic and hyperkinetic dysarthria, mixed dysarthrias involving hypokinetic components, and flaccid–spastic subtype. Among dysarthrias, there was a particular difference between ataxic dysarthria manifested by the decrease of F1a, F2a, and F2i compared to spastic dysarthria (and its mixed variants with ataxic and flaccid elements) and in addition by a trend toward increase of F1u to hypokinetic dysarthria. Additionally, spastic–ataxic dysarthria showed a trend toward an increase of F1a, F1i, and F1u compared to hypokinetic dysarthria (and its mixed variants with spastic elements).

Figure 8. Corner vowel production triangles estimated from monologues across two pairs of neurological disease types. The figure is adopted from the study published by Illner et al. (2023). The double-headed arrows indicate significant differences across diseases adjusted by age, sex, and dysarthria severity with ***, **, * referring to $p < .001$, $p < .01$, and $p < .05$. To minimize the effects of sex between individual speakers, the estimated formant frequencies were converted into a logarithmic tonal scale (semitones). F_1 = first formant frequency; F_2 = second formant frequency; MSA = multiple system atrophy; MS = multiple sclerosis; HD = Huntington's disease; ET = essential tremor; PD = Parkinson's disease; ALS = amyotrophic lateral sclerosis; CA = cerebellar ataxia; PSP = progressive supranuclear palsy.



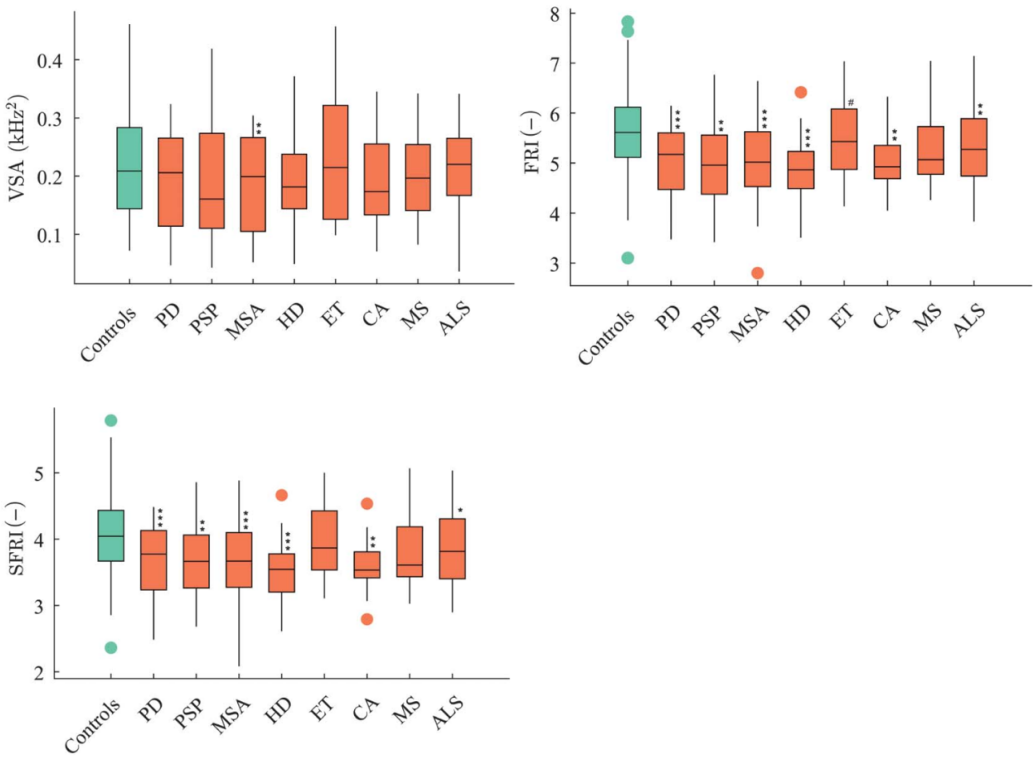
4.3.4. Dysarthria severity

Compared to controls, the shift of formants across vowels /i/ and /u/ in dependence on auditory–perceptual dysarthria severity in monologues was observed, including an increase in F2u and a decrease in F1i, F1u, and F2i frequencies. Considering complex formant measures, both measures of FRI and SFRI were reduced across all dysarthria severities.

4.3.5. Classification analysis

The classification analysis among vowel articulation features in monologues manifested accuracy of up to 39.7% for disease type, 37.3% for dysarthria type, and 49.2% for dysarthria severity; the probability of correct factor identification by chance using a random vector showed 5.3% accuracy for disease type, 4.2% for dysarthria type, and 19.8% for dysarthria severity. Acoustic metrics reflecting the shift in formant frequencies of FRI and SFRI were more sensitive to capturing the change of vowel articulation than VSA.

Figure 9. Figure Statistically significant group differences for estimated articulation features in monologues among the different types of neurological disease types compared to healthy controls adjusted by age and sex with ***,** ,* referring top <.001, p<.01, and< .05, respectively. # indicates significant differences to MSA (p < .05) after adjusting for age, sex, and dysarthria severity. The figure is adopted from the study published by Illner et al. (2023). Middle bars represent median, and rectangles represent the interquartile range. Maximum and minimum values are by error bars. Outliers are marked as dots. VSA = vowel space area; PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA = multiple system atrophy; HD = Huntington's disease; ET = essential tremor; CA = cerebellar ataxia; MS = multiple sclerosis; ALS = amyotrophic lateral sclerosis; FRI = formant ratio index; SFRI = second for- mant ratio index.



4.4. Effect of ageing on acoustic characteristics of voice pitch and formants in Czech vowels

The results of the acoustic analysis of the corner vowels /a/, /i/, and /u/ for the male and female populations are presented in Tables 3. and 4.

For the vowel /a/, the RM-ANOVA showed a significant effect for AGE in F2 [F(5,88) = 5.1, P = 0.002, h2 = 0.23] and in vowel duration [F(5,88) = 9.7, P < 0.001, h2 = 0.36]. Post hoc comparisons revealed significantly higher F2 in 20 −29 age group compared to 40−49 (P = 0.03), 50−59 (P < 0.001), 60−69 (P = 0.004) and 70−89 (P < 0.001) age groups as well as significantly increased vowel duration in 70−89 age group compared to 20−29 (P < 0.001), 30−39 (P < 0.001), 40−49 (P < 0.001), 50−59 (P = 0.007), and 60−69 (P < 0.001) age groups. The significant main effect for SEX was detected in f0, F1, F2, F3, and F4 [F(1,88) = 90397, p < 0.001, h2 = 0.510.82], as well as for VOWEL in f0, F1, F2,

F3, and for vowel duration [F(1,88) = 38−2396, P < 0.001, h2 = 0.310.97]. Importantly, significant interaction was revealed for AGE x SEX in f0 [F(5,88) = 3.5, P = 0.04, h2 = 0.17]. In addition, we observed a significant interaction for VOWEL x SEX in F1 [F(1,88)=8.3,P=0.03,h2= 0.09] and for vowel duration [F(1,88) = 10.3, P = 0.01, h2 = 0.11].

Table 3. Normative values of Czech vowels analyzed for female population. The table is adopted from the study published by Tykalova et al. (2021).

The Acoustic Characteristics of Czech Vowels for the Adult Female Population

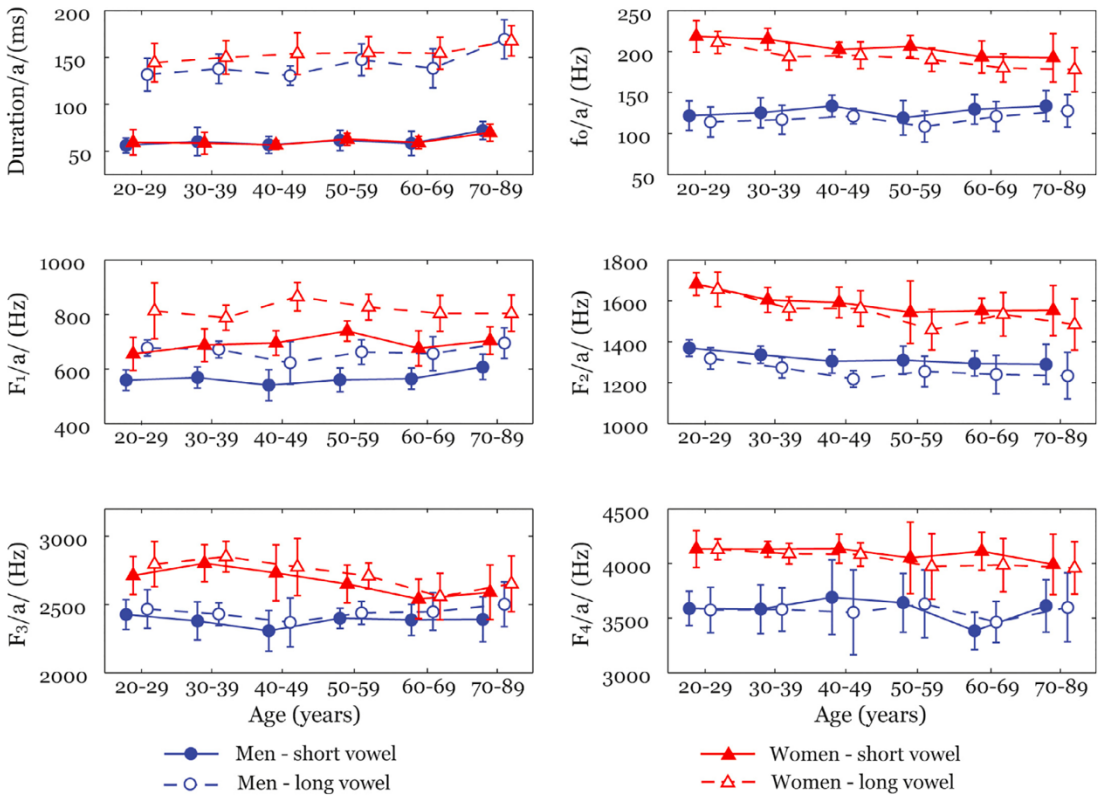
	Duration (ms) Mean/SD (range)	f_o (Hz) Mean/SD (range)	F_1 (Hz) Mean/SD (range)	F_2 (Hz) Mean/SD (range)	F_3 (Hz) Mean/SD (range)	F_4 (Hz) Mean/SD (range)
Short						
/a/	62/10 (43–86)	203/22 (127–246)	692/57 (543–780)	1584/104 (1336–1841)	2659/181 (2218–2985)	4084/213 (3476–4671)
/ɛ/	66/10 (48–100)	196/25 (121–247)	551/39 (464–625)	1935/105 (1626–2137)	2787/149 (2375–3057)	4103/186 (3656–4440)
/ɪ/	62/11 (45–87)	206/25 (122–256)	432/28 (384–485)	2279/155 (1885–2648)	2988/152 (2554–3287)	4209/193 (3770–4632)
/o/	66/12 (40–98)	202/25 (119–254)	526/36 (447–621)	1206/91 (1022–1429)	2701/185 (2179–3037)	3890/183 (3534–4435)
/u/	68/15 (47–129)	189/24 (110–238)	423/22 (374–476)	990/90 (814–1189)	2745/163 (2344–3074)	3925/183 (3492–4342)
Long						
/aː/	155/19 (110–203)	190/21 (117–233)	815/68 (631–925)	1539/114 (1308–1805)	2711/189 (2264–3092)	4029/205 (3404–4369)
/ɛː/	137/17 (106–179)	194/24 (116–250)	651/57 (531–772)	1952/113 (1727–2210)	2820/147 (2437–3113)	4171/179 (3719–4532)
/iː/	108/18 (61–151)	199/24 (116–243)	376/34 (306–457)	2633/180 (2186–2991)	3302/187 (2902–3713)	4216/191 (3715–4607)
/oː/	145/21 (106–191)	194/22 (115–240)	537/33 (457–608)	1073/92 (914–1295)	2738/204 (2193–3070)	3833/209 (3334–4427)
/uː/	115/23 (79–169)	189/23 (117–240)	394/26 (311–476)	930/89 (758–1163)	2767/179 (2370–3172)	3935/210 (3496–4338)

Table 4. Normative values of Czech vowels analysed for male population. The table is adopted from the study published by Tykalova et al. (2021).

The Acoustic Characteristics of Czech Vowels for the Adult Male Population

	Duration (ms) Mean/SD (range)	f_o (Hz) Mean/SD (range)	F_1 (Hz) Mean/SD (range)	F_2 (Hz) Mean/SD (range)	F_3 (Hz) Mean/SD (range)	F_4 (Hz) Mean/SD (range)
Short						
/a/	62/12 (39–84)	128/18 (89–173)	572/47 (458–674)	1316/72 (1139–1425)	2387/129 (2101–2700)	3586/241 (3116–4191)
/ɛ/	63/12 (42–97)	123/19 (81–169)	469/32 (371–538)	1658/74 (1514–1842)	2469/123 (2254–2835)	3609/218 (3211–4351)
/ɪ/	64/12 (40–106)	127/19 (88–173)	359/23 (304–410)	1962/112 (1659–2191)	2632/143 (2383–3207)	3685/223 (3268–4348)
/o/	63/12 (35–93)	126/20 (85–174)	460/32 (389–556)	1052/80 (894–1263)	2391/162 (2009–2735)	3424/217 (3079–4247)
/u/	72/19 (38–124)	120/19 (78–164)	369/24 (329–452)	910/81 (755–1085)	2418/158 (2128–2779)	3437/215 (2876–4088)
Long						
/aː/	146/23 (96–208)	119/18 (82–158)	669/54 (524–768)	1257/84 (1086–1442)	2452/138 (2146–2769)	3573/269 (3112–4235)
/ɛː/	127/18 (80–165)	122/18 (85–158)	525/42 (402–610)	1659/77 (1531–1835)	2495/117 (2306–2949)	3648/246 (3185–4327)
/iː/	107/19 (66–155)	124/19 (83–165)	310/18 (278–366)	2206/115 (1871–2402)	2945/193 (2526–3562)	3717/255 (3316–4532)
/oː/	133/23 (94–194)	121/20 (77–172)	465/35 (353–585)	930/78 (787–1177)	2432/164 (2062–2793)	3369/231 (3020–4314)
/uː/	109/21 (65–173)	119/18 (79–161)	347/22 (320–422)	887/94 (667–1096)	2446/154 (2144–2858)	3476/250 (2870–4259)

Figure 10. The comparison of speech measurements of the vowel /a/. The figure is adopted from the study published by Tykalova et al. (2021). Mean values and standard deviations (error bars) are depicted for both sexes (men, women), and vowel quantities (short, long), presented as a function of age.

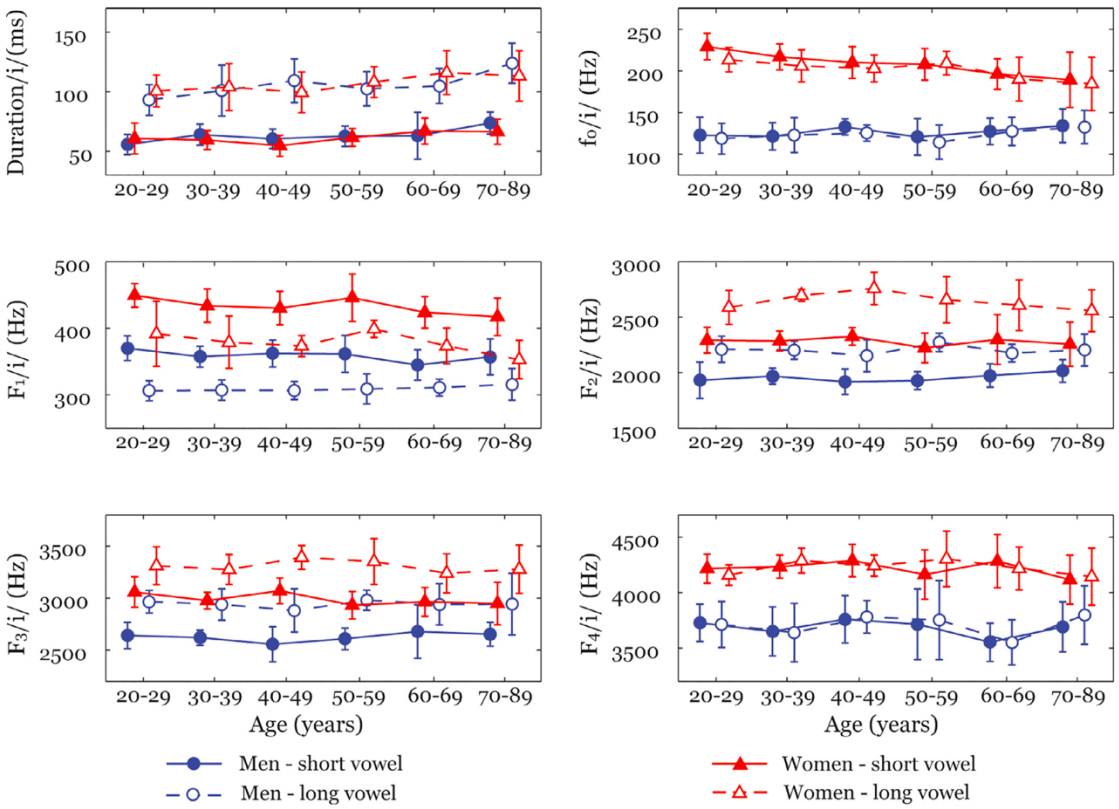


For the vowel /i/, a significant effect for AGE was found in the vowel duration [F(5,88) = 5.0, P = 0.003, h2 = 0.22]. Post hoc comparisons revealed significantly increased vowel duration in 70−89 age group compared to 20−29 (P < 0.001), 30−39 (P = 0.02), 40−49 (P = 0.009), and 50−59 (P = 0.05) age groups. In addition, a significant main effect was revealed for SEX in f0, F1, F2, F3, and F4 [F(1,88) = 141365, P < 0.001, h2 = 0.620.81], as well as for VOWEL in f0, F1, F2, F3, and vowel duration [F(1,88) = 27829, P < 0.001, h2 = 0.230.90]. Importantly, we observed a significant interaction of AGE x SEX in f0 [F(5,88) = 3.6, P = 0.03, h2 = 0.17]. We also found a significant interaction of AGE x VOWEL in F2 [F (5,88) = 4.6, P = 0.006, h2 = 0.21] associated with increase of F2 in long vowels in 50−59 male age group and of VOWEL x SEX in F2 [F(1,88) = 30, P < 0.001, h2 = 0.26].

For the vowel /u/, the RM-ANOVA showed a significant effect for AGE in F2 [F(5,88) = 4.3, P = 0.009, h2 = 0.20] and for vowel duration [F(5,88) = 5.1, P = 0.002, h2 = 0.23]. Post hoc comparisons revealed significantly higher F2 in 20 −29 age group compared to

50−59 (P = 0.05), 60−69 (P = 0.006), and 70−89 (P < 0.001) age groups as well as significantly increased vowel duration in 70−89 age group compared to 20−29 (P < 0.001), 30−39 (P = 0.01), 40−49 (P < 0.001), and 50−59 (P = 0.02) age groups. A significant main effect was revealed for SEX in f0, F1, F3, F4 [F(1,88) = 106348, P < 0.001, h2 = 0.550.80] and F2 [F(1,88) = 15.1, P = 0.001, h2 = 0.15], as well as for VOWEL in F1, F2, and for vowel duration [F (1,88) = 34489, P < 0.001, h2 = 0.280.85]. Interestingly, a significant interaction was observed for AGE x SEX in f0 [F(5,88) = 4.2, P = 0.01, h2 = 0.19]. Finally, we also found a significant interaction of VOWEL x SEX in F2 [F (1,88) = 8.5, P = 0.03, h2 = 0.09] and in vowel duration [F (1,88) = 7.8, P = 0.04, h2 = 0.08].

Figure 11. The comparison of speech measurements of the vowel /i/. The figure is adopted from the study published by Tykalova et al. (2021). Mean values and standard deviations (error bars) are depicted for both sexes (men, women), and vowel quantities (short, long), presented as a function of age.



The results of the statistical analysis for the articulation rate and VSA are presented in Figure 13. For the articulation rate, the ANOVA showed a significant effect of AGE [F(5,88) = 7.5, P < 0.001]. Post hoc comparisons revealed a significantly slower articulation rate in 70−89 age group compared to 20−29 (P < 0.001), 30−39 (P < 0.001),

40−49 (P < 0.001), 50−59 (P < 0.001), and 60−69 (P = 0.004). With regard to the VSA, there was a significant effect of AGE [F(5,88) = 2.8, P = 0.02] and SEX [F(1,88) = 53, P < 0.001]. Post hoc comparisons revealed significantly greater VSA in 70−89 age group compared to 20−29 (P < 0.001) and 40−49 (P = 0.04) age groups. In addition, we found statistically significant correlations between the articulation rate and the average vowel duration (r = 0.83, P < 0.001) calculated across all monophthongs, as well as between the VSA and the average vowel duration (r = 0.40, P < 0.001).

Figure 12. The comparison of speech measurements of the vowel /u/. The figure is adopted from the study published by Tykalova et al. (2021). Mean values and standard deviations (error bars) are depicted for both sexes (men, women), and vowel quantities (short, long), presented as a function of age.

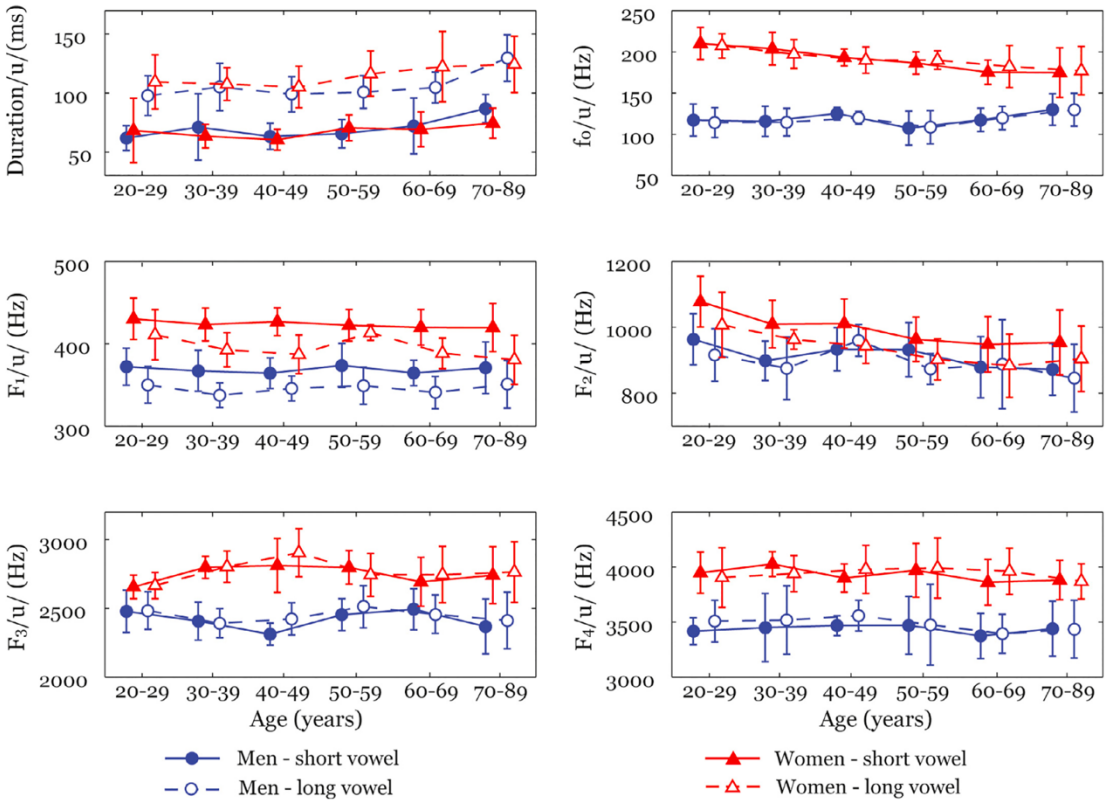
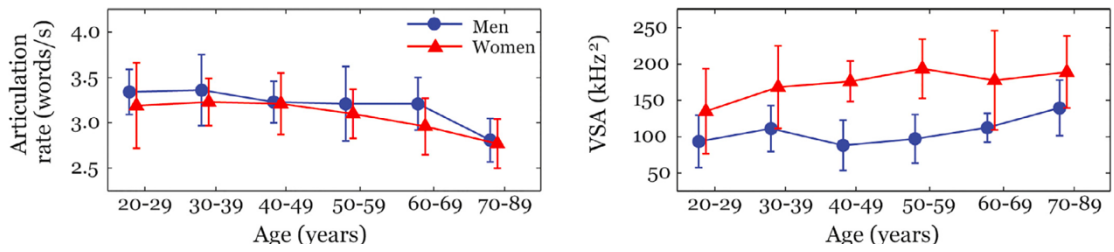


Figure 13. The results of the articulation rate and VSA. The figure is adopted from the study published by Tykalova et al. (2021). Mean values and standard deviations (error bars) are shown for both sexes (men, women), presented as a function of age.



5. Discussion

Discussion of the cumulative dissertation presents the outcomes of four individual journal papers (Skrabal et al., 2020, 2022; Tykalova et al., 2021; Illner et al., 2023). Only the main results are presented within this thesis. For more detailed information, please refer to each specific paper.

5.1. Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease

Our study found early vowel articulation issues in prodromal synucleinopathy. These issues were detectable in iRBD through objective acoustic analysis, despite minimal perceptual dysarthria noted during clinical examination. In our PD group, articulatory undershoot related to bradykinesia and rigidity, suggesting a link to nigrostriatal degeneration. We assessed a large sample of iRBD and de-novo PD patients, highlighting the importance of studying drug-naïve patients, as dopaminergic treatment can impact speech disorders (Rusz et al., 2013a). Vowel articulation performance in iRBD suggests a potential diagnostic and prognostic biomarker in α-synuclein-aggregation disorder.

Our results show that vowel articulation is affected in the early stages of synucleinopathy, especially in iRBD patients with severe hyposmia. This condition is closely related to brainstem nuclei (Braak et al., 2003), which play a vital role in controlling vocal fold tension. (Zhang et al., 1995).

According to our findings, especially within the iRBD subgroup with impaired olfactory function, suggest that articulatory undershoot is a consequence of nigrostriatal neurodegeneration. This suggestion is strongly supported by the significant differences in vowel deficits observed in patients with abnormal DAT-SPECT scans compared to those with normal scans. This inference is further bolstered by the observed link between vowel deficits and bradykinesia and rigidity, as well as the correlation between improvements in vowel articulation and the effects of dopaminergic treatment (Rusz et al., 2013a). However, as PD progresses, it is likely that non-dopaminergic brain regions also play a role in the deterioration of vowel articulation.

In line with these findings, it is essential to consider that vowel articulation deficits are not solely a result of dopaminergic involvement in the early stages of PD. Instead, they represent a complex interplay between dopaminergic and non-dopaminergic lesions as

the disease advances. This is consistent with previous longitudinal studies, which have reported a progressive decline in vowel articulation in PD patients over time (Skodda et al., 2012). As the disease advances, the severity of cerebral non-dopaminergic lesions becomes a more significant factor in worsening dysarthria.

Furthermore, the correlation between vowel articulation impairments and overall intelligibility (Lee & Hustad, 2013; Carl & Icht, 2021) highlights the clinical relevance of tracking these deficits. In the later stages of PD, when multiple brain regions are affected, the impact on speech becomes more pronounced.

Considering this evidence, we may hypothesize that vowel articulation assessments can serve as surrogate markers of neurodegeneration, providing valuable insights into disease progression from the prodromal stages to more advanced synucleinopathy. This approach can be particularly beneficial when a robust feature for monitoring dysarthria progression is needed throughout the disease.

In our investigation, VSA demonstrated speech impairment in drug-naive PD patients, aligning with findings from a previous pilot (Rusz et al., 2013b). Notably, the individual vowel /u/, characterized by its high and backward tongue positioning (Hasegawa-Johnson et al., 2003), appears to be the most prominently affected vowel in the early stages of PD (Rusz et al., 2013b). This observation leads us to hypothesize that PD-related vowel articulatory impairment primarily involves the tongue and initially manifests in the posterior regions of the articulatory system. (Mefferd et al., 2019; Thies et al., 2020). Consequently, it's crucial that VSA construction take into account the significant shifts in single-vowel frequencies to effectively capture these early changes.

While previous research suggested that speaking rate could impact vowel articulation in dysarthrias (Tjaden et al., 2005), we observed no significant differences in vowel duration at the group level between healthy controls and both patient cohorts. This lack of distinction may be due to the very early stages of synucleinopathy we investigated. Our findings are consistent with a recent study that reported no speech rate changes in de-novo PD and only a potential trend toward slower speech rate in iRBD (Illner et al., 2022). The faster speech rate observed in advanced PD might result from a tendency to accelerate speech due to impaired motor planning (oral festination) (Delval et al., 2016), while the inclination toward a slower speech rate may be linked to the degeneration of non-dopaminergic pathways (Rusz et al., 2021).

5.2. Dysarthria enhancement mechanism under external clear speech instruction in Parkinson's disease, progressive supranuclear palsy, and multiple system atrophy

This study explores differences in clear speech strategies among APS and PD. While prior research has examined clear speech in PD (Goberman & Elmer, 2005; Kearney et al., 2017; Lam & Tjaden, 2016; Tjaden et al., 2013, 2014; Whitfield & Goberman, 2014).

During clear speech, PD patients improve loudness and pitch variability, enhancing overall performance. In contrast, PSP and MSA patients mainly adjust articulation rate. One explanation is that PD patients respond well to external cues (Sapir, 2014) which can enhance performance in tasks like handwriting and gait (Ford et al., 2010; Oliveira et al., 1997). External cueing involves the cerebellum (Brown and Marsden, 1998), which may be affected in PSP and MSA. Additionally, some speech dimensions in PD, such as pitch and loudness, respond to dopaminergic therapy (Rusz et al., 2013a) potentially resulting in better speech compared to APS. Notably, postsynaptic receptors in the striatum are preserved in PD, whereas APS is associated with reduced binding due to dopaminergic degeneration, leading to various adaptive changes.

In contrast to the HC and PD groups with stable articulation rates, the PSP and MSA groups showed significantly faster articulation rates during clear speech. While this change didn't significantly reduce speech severity, it wasn't merely a result of repeated reading, as no significant increase in articulation rate was observed in APS during habitual text reading. Notably, there was no statistically significant difference in speech severity between APS groups, although there was a trend toward improved speech in MSA ($p = 0.03$, uncorrected).

At the task level, our findings show that participants enhanced their speech by simply being asked to speak clearly, making intentional adjustments in loudness, loudness variability, pitch, vowel formants, and articulation rate. Importantly, no distinctions were observed between two repeated readings, affirming the immediate impact of clear speech instructions.

Interestingly. In contrast to prior studies (Tjaden et al., 2013, 2014), we did not find slower articulation rates in the clear speech of PD subjects. This variation could be attributed to differences in the PD cohorts. The studies by Tjaden et al. (2013, 2014) focused on PD patients with longer post-diagnosis disease duration and consequently

faster habitual articulation rates compared to controls. In our case, we included patients in earlier disease stages with articulation rates similar to controls. As a result, it's possible that our PD patients did not require as much compensation for faster articulation rates.

Clear speech has traditionally been associated with rate reduction, allowing for better vocal tract organization and more precise articulation (Yorkston et al., 2010). This concept applies to various neurological conditions, including PD, multiple sclerosis, and traumatic brain injury (Beukelman et al., 2002; Goberman and Elmer 2005; Tjaden et al., 2013, 2014). Surprisingly, during clear speech, our MSA and PSP groups exhibited a faster articulation rate, suggesting an opposing approach to speech adaptation in APS. It's worth noting that, on a group level, PSP and MSA patients generally exhibited slower articulation rates compared to healthy controls and PD subjects. This slow rate was particularly pronounced in PSP patients. This suggests that the very slow articulation rate in APS might not yield better speech performance, and accelerating articulation rate could be advantageous. Research by Tjaden et al. (2013, 2014) supports this, revealing that artificially decreased articulation rate doesn't necessarily improve speech performance. Instead, clear speech enhances vowel space areas (Tjaden et al., 2013) and overall perceived intelligibility (Tjaden et al., 2014) in patients with PD and multiple sclerosis, despite a significant reduction in rate during slow speech.

At the group level, pitch variability emerges as the most prominent distinguishing factor HC from the PSP, MSA, and PD groups, as well as PD from the PSP group. Darley et al. (1969b) identified monopitch as the dominant characteristic of hypokinetic dysarthria in PD.

Collectively, these results suggest the possibility of a positive impact from speech therapy, not only for PD but also for APS. Long-term speech therapy, such as SPEAK OUT or LSVT, has shown significant effects in both MSA and PSP groups (Park, 2016; Sale et al., 2015).

5.3. Automated vowel articulation analysis in connected speech among progressive neurological diseases, dysarthria types, and dysarthria severities

This is the first study to showcase a fully automated method for objectively evaluating vowel articulation quality in a sizable group of 459 speakers, encompassing both healthy

individuals and patients with diverse neurological conditions, featuring various dysarthria types and severity levels. This approach utilizes natural, unscripted speech recordings.

Neurological disease type

Our findings confirm vowel articulation impairment in various neurological diseases, consistent with the common characteristic of dysarthrias (Darley et al., 1969b). Notably, specific patterns of imprecise vowel articulation were observed in this study. We could presume that the more pronounced vowel articulation deficits, characterized by reduced F2i and increased F2u, are linked to bradykinesia. This motor sign is commonly observed not only in parkinsonism but also in HD (Reilmann, 2019). Notably, the concurrent reduction in F1 across all corner vowels proved effective in statistically distinguishing MSA from CA, even after accounting for dysarthria severity. This suggests that it may be linked to damage in basal ganglia structures and concomitant cerebellar dysfunction, which are characteristic features of both diseases. This discovery could hold significant clinical relevance, particularly in addressing the challenge of early differentiation between the cerebellar variant of MSA and idiopathic late-onset CA, a complex diagnostic task (Lin et al., 2016).

Dysarthria type

Consistent with observations in various neurological conditions, vowel articulation deficits were present in different dysarthria subtypes. This outcome is expected, given the strong association between dysarthria type and underlying disease, and the presence of vowel articulation impairment across all studied causes. The formant shifts observed for vowels /i/ and /u/ exhibited common characteristics across all dysarthria types. This aligns with prior research indicating that complex formant-based measures are not effective in distinguishing dysarthria subtypes (Lansford & Liss, 2014). However, one potentially valuable phenomenon for dysarthria differentiation involves shifts in vowel frequencies, particularly in vowel /a/. While both formants of vowel /a/ remained relatively stable in individuals with hypokinetic or hyperkinetic dysarthria, they tended to decrease in ataxic dysarthria and increase in spastic dysarthria, as well as in mixed dysarthrias featuring spastic elements. Additionally, a previous study reported a decrease in F2 for vowel /a/ in patients with spinocerebellar ataxia (Skodda et al., 2014), which might be linked to inconsistent tongue movement range (Saigusa et al., 2006).

Dysarthria severity

This result aligns with previous findings, highlighting a robust link between vowel formant measures and the perceptual assessment of dysarthria severity (Fletcher et al., 2017). Recent research indicating a progressive pattern of vowel articulation impairment from the early stages of parkinsonism lends further support (Skrabal et al., 2022). In comparison to VSA, formant indexes proved more effective in capturing dysarthria severity, in line with a prior study demonstrating the greater stability and reliability of a vowel articulation index based on changes in individual formants over repeated assessments (Caverlé & Vogel, 2020). The effectiveness of formant indexes, in contrast to the limited sensitivity of VSA, suggests that articulatory deficits primarily stem from alterations in the vowel /u/, followed by the vowel /i/, while the vowel /a/ remains the least affected by dysarthria. This may be attributed to differing tongue positions and lip postures during the production of individual corner vowels. For instance, the tongue is held low for the vowel /a/, high and forward for the vowel /i/, and high and backward for the vowel /u/, with lip posture being spread for both /a/ and /i/ and rounded for /u/ (Hasegawa-Johnson et al., 2003). Therefore, it's reasonable to assume that producing the vowel /a/ is less demanding than producing /i/ and /u/. Additionally, articulating the vowel /u/ requires more intricate engagement of orofacial muscles to maintain a tightly rounded lip posture, and its limitations may be related to swallowing difficulties in dysarthria (Sapir et al., 2008; Tjaden, 2008).

Type of speaking task

The findings suggest that both monologue and reading speech are effective for evaluating articulation deficits in neurological diseases. However, a notable difference is that significant differences in dysarthria severities were only observed in reading passages, while the classification accuracy for dysarthria severity across both tasks remained consistent. Indeed, within this study, PD was the sole group that exhibited significantly better vowel articulation during reading compared to monologues. This implies that reading passages may be more suitable for tracking speech changes related to vowel articulation, particularly in PD patients. Therefore, when conducting clinical trials with a focus on vowel articulation as an outcome measure, assessing PD participants through spontaneous speech may be more relevant.

The factors that contribute to vowel articulation impairment

One of the study's aims was to determine whether vowel articulation impairment is primarily influenced by disease type, dysarthria type, or dysarthria severity. The discriminant analysis results indicated scores of up to 41.0% for neurological disease type, 39.3% for dysarthria type, and 49.2% for dysarthria severity.

Vowel impairment appears to be more indicative of dysarthria severity than a specific disease or dysarthria subtype. However, it's essential to consider the probability of chance factor identification, which resulted in 5.3% accuracy for disease type, 4.2% for dysarthria type, and 19.8% for dysarthria severity, roughly corresponding to the number of groups examined for each factor. The best ratio between accurate classification and chance identification seems to be for dysarthria type, although none of the factors showed superior classification performance. Despite some observed differences, imprecise vowels seem to be a universal sign of articulatory disorder with severity-related variations across various dysarthria types and disease etiologies (Weismer, 2006). This aligns with previous findings that suggest neuropathologies can lead to similar acoustic manifestations in speech (Kim et al., 2011). On the other hand, combining vowel articulation characteristics with distinct cues specific to certain dysarthria types may significantly improve classification accuracy for dysarthria type or disease etiology.

Algorithm performance

While articulatory deficits are a central feature of most dysarthrias, automated methods for assessing these deficits in connected speech are limited. Our study introduces a fully automated approach to evaluating "undershoot of vowels" across various neurological diseases, dysarthria types, and a wide range of severities. This approach addresses two main error sources: incorrect phoneme recognition (16% error based on 1-F score) and inaccurate formant tracking (7% error for F1 and 16% error for F2 based on NRMSE). By implementing multiple error correction levels, including outlier exclusion and vowel identification correction through clustering, we achieved an overall accuracy of 77%. This accuracy is promising given the diversity of etiologies and dysarthria severities involved. It's important to note that current technologies for phoneme recognition and formant tracking, even for healthy speech, have limitations. For example, the automated method captured lower F1 values for vowels /i/ and /u/ with increasing dysarthria severity, while manual labeling did not detect such changes. (Roy et al., 2009; Rusz et al., 2013b). This inconsistency may result from formant tracker confusion related to the fundamental

frequency and harmonics close to F1 of vowels /i/ and /u/. We introduced an alternative FRI that reflects the dysarthria-related lowering of F1 in these vowels as captured by the automated method. The SFRI, based on F2 values, showed similar classification accuracy for detecting neurological disease type or dysarthria type. However, automated tracking exhibited an inaccuracy in estimating F2 values for vowel /u/, capturing lower values than hand-labeling. These discrepancies may partially result from inaccuracies in formant tracking rather than actual disease effects. Nevertheless, we believe the automated method's error bias is consistent across different conditions and does not significantly affect group differences.

5.4. Effect of ageing on acoustic characteristics of voice pitch and formants in Czech vowels

This study investigated age-related acoustic changes in vowels from a group of 100 healthy Czech speakers aged 20 to 90. The primary goal was to assess the impact of aging on vowel articulation, addressing gaps in previous research. Understanding typical age-related voice and speech parameter changes is important for distinguishing normal from pathological speech. Additionally, as Czech is an underdocumented language, we aimed to establish normative data for the fundamental frequencies and formant frequencies of all Czech monophthongs.

Consistent with previous research (Torre & Barlow, 2009; Eichhorn et al., 2018), we found a notable age-related decline in f0 in women. However, no significant f0 changes were observed in men, aligning with the study by Eichhorn et al. (2018) but differing from other studies. The f0 alterations in women may be attributed to various age-related physiological factors, including hormonal shifts post-menopause, laryngeal muscle size reduction, laryngeal cartilage hardening or ossification, reduced glandular function, and vocal fold thickening. In this study, only women displayed a significant age effect, suggesting that the f0 decrease in women could be linked to increased vocal fold mass resulting from menopausal hormonal changes (Abitbol et al., 1999). Additionally, we found a significant increase in vowel duration with age, consistent with previous research showing longer vowel duration in older individuals, both in men and women (Albuquerque et al., 2014; Fletcher et al., 2015). This lengthening effect was most pronounced in the oldest age group (70-89). Furthermore, a strong negative correlation

between articulation rate and average vowel duration was observed, suggesting that longer vowel duration is linked to a slower overall speech tempo.

In contrast to previous studies showing age-related and sex-specific changes in F1 and F2 frequencies (Xue & Hao, 2003; Torre & Barlow, 2009; Rastatter & Jacques, 1990) our results indicated that F1 frequency remained consistent across age and sex for all investigated vowels. F2 frequencies for /a/ and /u/ decreased in both men and women, while F2 for /i/ remained unchanged. These findings align with recent research on native English speakers (Eichhorn et al., 2018), which also observed limited alterations in F1 and F2 frequencies. While the alterations in F1 and F2 within our study were minimal, they played a role in the increased VSA, which can be attributed, in part, to the extended vowel duration, aligning with previous observations (Fletcher et al., 2015; Rastatter & Jacques, 1990). We substantiated this hypothesis by establishing a positive correlation between VSA size and the average vowel duration. Notably, no significant changes in F3 or F4 frequencies were observed in our study in agreement with previous research (Xue & Hao, 2003; Torre & Barlow, 2009; Eichhorn et al., 2018), negating the hypothesis of age-related vocal tract lengthening that should affect all formant frequencies.

6. Conclusions and evaluation of the goals and hypotheses

6.1. Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease

Hypothesis

a) Vowel articulation will be more significantly affected in de-novo PD compared to iRBD and HC - **Confirmed**
b) Vowel articulation measures will be sensitive enough to detect the deterioration in vowel articulation in iRBD patients - **Confirmed**
c) The degree of vowel articulatory undershoot in iRBD will correlate with the presence of olfactory impairment - **Confirmed**
d) The degree of vowel articulatory undershoot in PD will correlate with certain motor impairment features - **Confirmed**

Conclusion

Compared to healthy controls VSA was found to be smaller in both iRBD ($p = 0.01$) and PD ($p = 0.001$). Within the iRBD group, those with abnormal olfactory function exhibited smaller VSA compared to those with preserved olfactory function ($p = 0.02$). Our findings, especially in iRBD with impaired olfactory function, suggest that articulatory undershoot is related to nigrostriatal neurodegeneration. This is supported by differences in vowel deficits between abnormal and normal DAT-SPECT scans, along with correlations between vowel deficits, bradykinesia, rigidity, and dopaminergic treatment effects. The impairment in vowel articulation serves as an early prodromal symptom in the synucleinopathy disease process. Utilizing acoustic assessment of vowel articulation may offer a surrogate marker for synucleinopathy, particularly in situations requiring a single robust feature to monitor dysarthria progression.

6.2. Dysarthria enhancement mechanism under external clear speech instruction in Parkinson's disease, progressive supranuclear palsy, and multiple system atrophy

Hypothesis

a) Speech performance of PD patients will be significantly enhanced under clear speech instruction - **Confirmed**
b) Speech performance of APS patients will be significantly enhanced under clear speech instructions - **Declined**
c) We anticipate distinct approaches to speech adaptation in MSA and PSP under clear speech conditions, reflecting variations in disease pathophysiology – **Declined**

Conclusion

During clear speech production, PD patients demonstrated notable improvements, particularly in loudness and pitch variability resulting in a significant reduction in overall speech severity. In contrast, PSP and MSA patients exhibited changes mainly in articulation rate. Unlike the HC and PD groups, which either slowed down or maintained their articulation rate, the PSP and MSA groups notably increased their articulation rate when prompted to speak more clearly. This indicates a differing approach to speech adaptation in patients with atypical Parkinsonism compared to PD. These findings have important implications for speech rehabilitation management.

6.3. Automated vowel articulation analysis in connected speech among progressive neurological diseases, dysarthria types, and dysarthria severities

Hypothesis

a) Fully automated vowel articulation assessment would discover significant vowel impairment across various neurological disorders and different types of dysarthria - **Confirmed**
b) Fully automated vowel articulation assessment would identify specific features of vowel articulation impairment in individual neurological disorders - **Confirmed**
c) VSA would be a suitable marker for dysarthria severity - **Confirmed**

Conclusion

Articulatory vowel undershoot was observed in a wide range of progressive neurodegenerative diseases and extended to related dysarthria subtypes. Formant ratios exhibited greater sensitivity to vowel deficits than vowel space area. Notably, the first

formants of corner vowels (i.e. /a/, /i/, and /u/) were notably lower in multiple-system atrophy compared to cerebellar ataxia, and the second formants of vowels /a/ and /i/ showed lower values in ataxic compared to spastic dysarthria. A discriminant analysis demonstrated promising classification scores, with up to 41.0% accuracy for disease type, 39.3% for dysarthria type, and 49.2% for dysarthria severity. The algorithm achieved an F-score of 0.77. In conclusion, distinctive alterations in vowel articulation serve as markers reflecting the underlying pathophysiology of various neurological diseases. Objective acoustic analysis of vowel articulation holds the potential to offer a universal method for screening motor speech disorders.

6.4. Effect of ageing on acoustic characteristics of voice pitch and formants in Czech vowels

Hypothesis

a) Fundamental frequency would be sex-dependent - **Confirmed**
b) VSA would be sex- and age-independent - **Confirmed**

Conclusion

Age-related variations in pitch were influenced by sex, whereas age-related changes in F2/a/, F2/u/, VSA, and vowel duration appeared to be unrelated to sex. In terms of formants, we observed a decrease in F2/a/ and F2/u/ as age increased, but no statistically significant changes in F1, F3, or F4 frequencies with advancing age. Although the alterations in F1 and F2 frequencies were relatively minor, they suggested a trend away from vowel centralization, resulting in a notably larger VSA in the older population. The increase in VSA was partially associated with extended vowel duration. In summary, changes in vowel formant frequencies across several decades of adult life appear to be modest and suggest a tendency away from vowel centralization, indicating the preservation of articulatory precision in older individuals.

7. Summary

The cumulative dissertation consists of four journal papers that collectively address various aspects of imprecise vowel articulation in different neurological conditions as well as in wide range of healthy speakers.

In particular, study by Tykalova et al., (2021), which examines age-related changes in vowel articulation of healthy speakers, did not observe any age-related trends toward the reduction or centralization of the VSA in older speakers. Conversely, findings from Skrabal et al. (2022) revealed that individuals with de-novo Parkinson's disease (PD) and those at a high risk of developing parkinsonism (i.e. patients with iRBD) exhibited a reduction in vowel space area and centralization of formants. These findings together support the suitability and sensitivity of vowel articulation measurements for the early detection of neurodegeneration.

Furthermore, iRBD patients exhibiting olfactory dysfunction demonstrated more pronounced vowel impairment supporting Braak's theory of α-synuclein-induced neurodegeneration spreading through the brain. iRBD represent Braak stage 2, occurring before clinical manifestation of PD when the substantia nigra is affected; a critical stage to consider for future neuroprotective trials. To ease this goal as a part of the study by Illner et al. (2023) we introduce a fully automated method for analyzing dysarthria-related vowel articulation impairment and test its feasibility across different neurological diseases, offering a universal approach for screening motor speech disorders. Finally, within study by Skrabal et al. (2020), we compared speech behavior in patients with PD, PSP, and MSA under clear speech conditions, highlighting differing strategies for speech adaptation and investigating the potential of vowel articulation measures to serve as a feedback during different behavioural speech therapies.

Together, these studies contribute to our understanding of speech changes especially vowel articulation in neurological conditions, and offer potential diagnostic,

pathophysiologic, and therapeutic insights. It holds the promise of establishing a reliable, cost-effective, valid, and user-friendly biomarker for neurological diseases, streamlining accurate and timely diagnosis while enhancing disease management.

8. Souhrn

Disertační práce je tvořena souborem čtyř vědeckých článků publikovaných v odborných impaktovaných časopisech, které kolektivně zkoumají různé aspekty poruchy artikulace samohlásek u různých neurologických onemocněních, stejně jako u zdravých kontrolních subjektů.

Studie Tykalova et al. (2021) se věnovala věkově vázaným změnám v artikulaci samohlásek u zdravé populace a nezaznamenala žádné věkově podmíněné trendy směrem k redukci nebo centralizaci vokální oblasti (Vowel Space Area, VSA) u subjektů vyššího věku. Naopak zjištění dle Skrabal et al. (2022) prokázalo, že jedinci s de-novo Parkinsonovou nemocí (PN) a zejména pak jedinci s vysokým rizikem rozvoje parkinsonismu (t.j., pacienti s izolovanou poruchou chování v REM spánku, iRBD) vykazovali redukci VSA a centralizaci formantů. Tyto závěry společně podporují vhodnost a citlivost měření artikulace samohlásek pro brzkou detekci neurodegenerace. Dále pacienti s iRBD, kteří vykazovali hyposmii, projevovali výraznější poruchy artikulace samohlásek, což podporuje Braakovu teorii o šíření neurodegenerace způsobené α-synukleinem v mozku. Pacienti s iRBD představují Braakovu fázi 2, která se objevuje před klinickým projevem PN, kdy je postižena substantia nigra; jedná se o klíčové stadium onemocnění z pohledu výzkumu neuroprotektivní léčby v klinických studiích. S cílem usnadnit tento cíl, v rámci studie Illner et al. (2023) byla představena plně automatizovaná metoda pro analýzu poruchy artikulace samohlásek, která byla úspěšně otestována napříč velkým spektrem neurodegenerativních chorob nabízející univerzální přístup pro plošný screening motorických poruch řeči v širší populaci. Na závěr, v rámci studie Skrabal et al. (2020) jsme porovnávali změny v tvorbě řeči u pacientů s PD, supranukleární paralýzou a multisystémovou atrofii za podmínek „clear speech“ a odhalili odlišné strategie při adaptaci řeči. Měření artikulace samohlásek se nabízí jako nástroj sledování efektu různých behaviorálních terapií řeči.

Tyto studie kolektivně přispívají k našemu porozumění chování řeči a to zejména artikulaci samohlásek napříč neurologickými choroby a nabízejí potenciální diagnostické, patofyziologické a terapeutické poznatky.

Akustická analýza artikulace samohlásek představuje spolehlivý, cenově efektivní, a uživatelsky přívětivý biomarker pro neurologická onemocnění, usnadňující přesnou a včasnou diagnostiku.

9. Future work

Several future topics related to dissertation thesis should be elaborated:

a) In our thesis, we identified vowel impairment in the preclinical stages of PD in "at high risk" patients with iRBD. A longitudinal study, ideally with a fixed one-year follow-up is essential to track the evolution of vowel articulation deficits in PD from prodromal through early, moderate, and severe stages. This setup would help estimate the sensitivity of vowel articulatory features and enhance predictions of phenoconversion from iRBD to established parkinsonism. Additionally, due to the physiological male predominance of iRBD, we encompassed solely male subjects with iRBD; future studies should elaborate on findings in the female population.

b) Within the thesis, we included a large number of iRBD and PD subjects. Nevertheless, it is relevant to expand our groups encompassing ALS, ET, HD, MS, MSA, and PSP subjects to affirm the reliability of algorithms and acoustic analysis methodologies on a larger sample.

c) In the context of the relevant effect of clear speech strategies enhancing speech performance in PD and APS, future studies should evaluate the impact of long-term intensive clear speech therapy in parkinsonian patients to ascertain whether clear speech techniques enhance speech performance solely within a single session or have carryover effects to real-life communication contexts.

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11. Publication record

a) List of the four peer-reviewed journal papers comprising the cumulative dissertation:

1) **Skrabal, D.**, Rusz, J., Novotny, M., Sonka, K., Ruzicka, E., Dusek, P., & Tykalova, T. (2022). Articulatory undershoot of vowels in isolated REM sleep behavior disorder and early Parkinson's disease. NPJ Parkinson's disease, 8(1), 137. https://doi.org/10.1038/s41531-022-00407-7
5-year IF = 9.1 (2022)

2) **Skrabal, D**., Tykalova, T., Klempir, J., Ruzicka, E., & Rusz, J. (2020). Dysarthria enhancement mechanism under external clear speech instruction in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Journal of Neural Transmission, 127, 905-914 https://doi.org/10.1007/s00702-020-02171-5
IF = 3.85 (2023)

3) Illner, V., Tykalova, T., **Skrabal, D.**, Klempir, J., & Rusz, J. (2023). Automated Vowel Articulation Analysis in Connected Speech Among Progressive Neurological Diseases, Dysarthria Types, and Dysarthria Severities. Journal of Speech, Language, and Hearing Research, 66(8), 2600-2621. https://doi.org/10.1044/2023_JSLHR-22-00526
IF = 2.674 (2023)

4) Tykalova, T., **Skrabal, D**., Boril, T., Cmejla, R., Volin, J., & Rusz, J. (2021). Effect of ageing on acoustic characteristics of voice pitch and formants in Czech vowels. Journal of Voice, 35(6), 931-e21. https://doi.org/10.1016/j.jvoice.2020.02.022
IF = 2.3 (2023)

b) Record of the peer-reviewed journal paper unrelated to the cumulative dissertation:

5) Manusript “in press” in Annals of Neurology medical journal

Subert, M., Novotny, M., Tykalova, T., Hlavnicka, J., Dusek, P., Ruzicka, E., **Skrabal, D.**, Pelletier, A., Postuma, RB., Montplaisir, JY., Gagnon, JF., Galbiati, A., Ferini-Strambi, L., Marelli, S., St. Louis, E., Timm, P., Teigen, L., Janzen, A., Oertel, W., Heim, B., Holzknecht, E., Stefani, A., Högl, B., Dauvilliers, Y., Evangelista, E., Sonka, K., & Rusz, J. (expected 2024). Spoken language alterations predict phenoconversion in isolated REM sleep behavior disorder: a multicentric study.

IF = 11.274 (2023)