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Summary of Dissertation Thesis

Speech disorders and analysis of their mechanisms in neurodegenerative diseases

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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

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. Consequently, it's not surprising that the intricate nature of speech renders it highly sensitive to central nervous system diseases.

In some cases, speech alterations may be the sole initial indication of a neurological disorder, occasionally standing as the only significant neurological impairment. Consequently, the identification of distinctive irregularities in speech characteristics can offer valuable insights into the underlying pathophysiology of neurological diseases.

Furthermore, speech can also serve as a valuable marker for evaluating treatment effectiveness, tracking disease progression, and assessing disease severity.

Acoustic analyses 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, representing an innovative method for assessing speech disorders. It has the potential to establish a reliable, cost-effective, valid, and user-friendly biomarker for neurological diseases, facilitating precise and timely diagnosis and enhancing disease management.

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., 2022), 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. 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, and atypical parkinsonian syndromes (APS); a group of related disorders characterized by parkinsonism alongside a range of overlapping symptoms and more rapid progression represented with conditions like multiple system atrophy (MSA), progressive supranuclear palsy (PSP) (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., 1969). 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. Given the established connections between vowel articulation impairment severity and perceptual impressions of unintelligibility in dysarthric speakers (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 (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 decrease (Torre & Barlow, 2009; Eichhorn et al., 2018), but findings for men vary, with f0 decreased, 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 (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 idiopathic iRBD, PD, probable MSA probable PSP, cerebellar ataxia (CA), Huntington's disease (HD), Multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and essential

tremor (ET), as well as healthy control participants were recruited and examined from 2011 to 2021.

Diagnoses and disease severity were determined according to globally recognized criteria, and all assessments were conducted by neurologists experienced in movement disorders. Healthy control participants had no history of neurological or communication disorders.

3.2. Speech recording

Each participant underwent a comprehensive speech examination, which was part of a larger protocol and typically lasted no more than 20 minutes. This examination included various speech tasks, such as "connected speech," where participants read a standardized passage containing 80 words or 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.

3.3. Acoustic analysis

All analyses were conducted using Praat software (Boersma, 2014) and 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., 2013b; Skodda et al., 2011); The first (F1) and second (F2) formant frequencies were measured in Hertz (Hz). Additionally in study by Tykalova et al. (2021) frequencies F3, and F4 were obtained. A total of 30 vowels per passage were examined, consisting of 10 instances of /a/, 10 instances of /i/, and 10 instances of /u/. The F1 and F2 frequencies were averaged separately for each participant's individual corner vowel. We utilized Vowel space area (VSA), a traditional and widely-used articulatory-acoustic measure (Kent et al., 2018; Fant et al. 1973) and the Vowel Articulation Index (VAI) constructed to enhance sensitivity to formant centralization.

Furthermore, vowel duration was calculated as the time between the vowel onset and offset, following established procedures (Tykalova et al., 2021). Automatic Algorithm for Vowel Articulation Features apply a formant tracker in conjunction with a phoneme recognizer and subsequent signal processing analysis. For a detailed description see Illner et al. (2023).

3.4. Auditory–perceptual assessment of dysarthria

To evaluate the presence, type, and severity of dysarthria, experienced speech-language, who were aware of each patient's medical diagnosis, conducted a consensus auditory–perceptual assessment.

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) in a slightly condensed fashion, as outlined below. 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 [$F(2,177) = 7.4$, $p = 0.001$, $\eta 2 = 0.08$]. Post hoc comparisons revealed significantly smaller VSA in both iRBD ($p = 0.01$) and PD ($p = 0.001$). 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) [$F(1,54) = 5.4$, $p = 0.024$, $\eta 2 = 0.094$]. 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 [$F(1,31) = 4.2$, $p = 0.049$, $\eta 2 = 0.140$].

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 ($r = -0.29$, $p = 0.03$). In addition, bradykinesia and rigidity subscore in PD patients showed negative correlation with VSA ($r=-0.33$, $p=0.01$) while neither correlation between postural instability and gait difficulty (PIGD) subscore and VSA ($r = -0.04$, $p = 0.75$) nor between tremor subscore and VSA ($r = 0.01$, $p = 0.96$).

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.

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

Acoustic analyses encompassed assessments of mean loudness, loudness variability, pitch variability, vowel articulation, articulation rate, and speech severity. Notably, during clear speech production, individuals with PD demonstrated significant improvements in loudness ($p < 0.05$) and pitch variability ($p < 0.001$), resulting in a notable reduction in overall speech severity ($p < 0.001$). In contrast, individuals with progressive supranuclear palsy PSP and MSA exhibited the capacity to modulate only their articulation rate ($p < 0.05$). Furthermore, in contrast to healthy controls (HC) and the PD group, which either slowed or maintained their articulation rate, the PSP and MSA groups noticeably increased their articulation rate during clear speech. This indicates a distinct approach to speech adaptation among patients with atypical Parkinsonism, as they responded differently to a simple request for clearer speech production compared to individuals with PD.

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

Vowel articulation undershoot was evident across a wide range of progressive neurodegenerative diseases, including Parkinson's disease, progressive supranuclear palsy, multiple-system atrophy, Huntington's disease, essential tremor, cerebellar ataxia, multiple sclerosis, and amyotrophic lateral sclerosis, as well as various related dysarthria subtypes encompassing hypokinetic, hyperkinetic, ataxic, spastic, flaccid, and mixed variants. Formant ratios exhibited a heightened sensitivity to vowel deficits compared to vowel space area. Among the corner vowels, the first formants were notably lower in individuals with multiple-system atrophy than those with cerebellar ataxia. Additionally, the second formants of the vowels /a/ and /i/ were lower in individuals with ataxic dysarthria compared to those with spastic dysarthria. The application of discriminant analysis yielded classification scores of up to 41.0% for disease type, 39.3% for dysarthria type, and 49.2% for dysarthria severity, while the algorithm's accuracy achieved an F-score of 0.77.

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

Age-related changes in pitch were influenced by the individual's sex, whereas age-related alterations in F2/a/, F2/u/, VSA, and vowel duration appeared to be sex-independent. Specifically, we observed a noticeable decrease in fundamental frequency (fo) with age among

women, but no significant change among men. In terms of formants, we observed a decrease in F2/a/ and F2/u/ frequencies with advancing age, while there were no statistically significant changes in F1, F3, or F4 frequencies as individuals grew older. Although the modifications in F1 and F2 frequencies were relatively small, they seemed to counteract vowel centralization tendencies, resulting in a considerably larger VSA in the older population. The increased VSA was partly associated with longer vowel duration.

5. Evaluation of Hypothesis & Discussion

5.1. 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**

Discussion

Our study found that individuals with de-novo PD and those at high risk (i.e.,patients with iRBD) showed a reduction in vowel space area and centralization of formants. This acoustic analysis highlights early vowel articulation impairment in the initial stages of alpha-synuclein-induced neurodegeneration, serving as sensitive markers for early detection, especially at Braak stage 2 before the clinical onset of PD (Braak et al., 2003).

This hypothesis was futher strongly supported by the significant differences in vowel deficits observed in patients with abnormal DAT-SPECT scans compared to those with normal scans. Additionally in previous studies we observed the 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).

It is essential to consider that vowel articulation deficit is not solely a result of dopaminergic involvement in the early stages of PD but involve a complex interplay with non-dopaminergic

lesions as the disease advances. Longitudinal studies show a progressive decline in vowel articulation over time (Skodda et al., 2012). As PD advances, the severity of non-dopaminergic lesions becomes a significant factor in worsening dysarthria. The correlation between vowel articulation impairments and overall intelligibility underscores the clinical importance of monitoring these deficits (Carl & Icht, 2021), especially in later PD stages when multiple brain regions are affected, leading to a more pronounced impact on speech.

5.2. 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**

Discussion

This study explores differences in clear speech strategies among APS and PD, while prior research has examined clear speech only in PD (Goberman & Elmer, 2005**;** Tjaden et al., 2013, 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). External cueing involves the cerebellum (Brown and Marsden, 1998), which may be affected in PSP and MSA.

Clear speech has traditionally been associated with rate reduction, allowing for better vocal tract organization and more precise articulation. 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, HC and PD groups performed stable articulation rates during clear speech, while our MSA and PSP groups exhibited a faster articulation rate, suggesting an opposing approach to speech adaptation in APS. 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.

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. 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). Importantly, no distinctions were observed between two repeated readings, affirming the immediate impact of clear speech instructions.

Collectively, these results suggest the possibility of a positive impact from speech therapy, not only for PD but also for APS.

5.3. 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**

Discussion

This is the first study to showcase a fully automated method for objectively evaluation of 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. Utilizing natural, unscripted speech recordings, the study confirms vowel articulation impairment across different neurological diseases (Darley et al., 1969). Imprecise vowel articulation is observed in various dysarthria subtypes.

The effectiveness of formant indexes 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/.

Further, the concurrent reduction in F1 across all corner vowels proved effective in statistically distinguishing MSA from CA, even after accounting for dysarthria severity. 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).

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).

Additionally, findings suggest that both monologue and reading speech are effective for evaluating articulation deficits, with reading passages being more suitable for tracking speech changes related to vowel articulation, especially in Parkinson's disease (PD) patients. Vowel impairment is found to be more indicative of dysarthria severity than a specific disease or dysarthria subtype. The study introduces an automated approach addressing phoneme recognition and formant tracking errors, achieving an overall accuracy of 77%. Despite limitations in current technologies, the method shows promise in assessing articulatory deficits in connected speech across diverse conditions and severities.

5.4. 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**

Discussion

This study investigated age-related acoustic changes in vowels from a group of 100 healthy Czech speakers aged 20 to 90.

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 (Torre & Barlow, 2009) 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). 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 (Torre & Barlow, 2009; Eichhorn et al., 2018), negating the hypothesis of age-related vocal tract lengthening that should affect all formant frequencies.

6. 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.

7. 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.

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9. 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)

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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)