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Faculty of Electrical Engineering

Doctoral Thesis

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Doctoral Thesis:

Evaluation of motor speech disorders by acoustic analysis: differential diagnosis and monitoring of medical intervention

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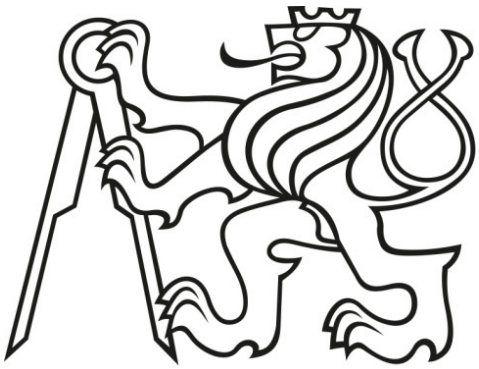

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Declaration

I declare that I accomplished the presented thesis independently and named all used sources of information in accordance with methodical instructions about ethical principles for writing academic thesis. Furthermore, I verify that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Date: …… Signature: ……

Abstract

Dysarthria is a motor speech disorder resulting from neurologic impairment affecting mainly the control and execution of movements related to speech production. Occurrence of dysarthria in adult age is commonly manifested as a consequence of degenerative disorder such as Parkinson's disease (PD), Huntington's disease (HD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cerebellar ataxia (CA). Interestingly, identification of specific deviant speech characteristics can provide important clues about the underlying pathophysiology and localization of neurological diseases. Speech may also serve as a valuable marker of disease onset or treatment efficacy. Therefore, the main aims of this doctoral thesis were (a) to design the feasible algorithms, methodologies or measurements that would be sensitive and accurate enough to capture pathological changes in speech, (b) to objectively quantify the effect of neurological disorder on speech production and (c) to relate the potentially observed speech changes to overall motor performance or medication doses in order to provide deeper insight into the pathophysiology of speech disturbances.

Several databases of PD, HD, MSA, PSP and CA patients as well as age-matched healthy controls were obtained. During recording, all participants were instructed to perform several speaking tasks such as sustained phonation, fast syllable repetition, reading passage or monologue. In addition, various clinical information about patient's motor skills, cognitive abilities or medication doses was available. The acoustic analyses were carried out to provide quantitative objective evaluation of speech performances. Statistical analyses were applied to search for possible group differences or correlations between speech and clinical metrics.

The results of this doctoral thesis are presented in the form of nine peer-reviewed journal papers. In summary, we managed to objectively quantify the effect of neurological disorder on speech production in PD, HD, MSA, PSP and CA patients. Furthermore, we proved that the separation of patients from healthy controls based solely on speech is possible. The differentiation among several types of parkinsonian disorders is also possible as we were able to discriminate between MSA/PSP and PD with 95 % accuracy and between PSP and MSA subjects with 75 % accuracy. In addition, a number of correlations were found between clinical and speech characteristics. Considering PD, an adverse effect of levodopa on speech fluency was found in PD patients after 3-6 years of taking medication. On the other hand, we found improved or maintained speech performances (related mainly to consonant and vowel articulation, pitch variability and number of pauses) in two-thirds of those PD patients whereas speech deteriorated only in one-third; indicating general positive effect of long-term dopaminergic therapy on dysarthria in early stages of PD. In conclusion, objective acoustic analysis of motor speech disorders can significantly contribute to early and correct diagnosis of the particular disorder and provide more insights into underlying pathophysiology of such diseases.

Keywords

Speech impairment; Dysarthria; Acoustic analysis; Parkinson's disease; Huntington's disease; Atypical parkinsonian syndromes; Levodopa; Contrastive stress; Dysfluency; Voice onset time; Vowel articulation.

Abstrakt

Dysartrie je porucha hlasu a řeči vznikající v důsledku poškození funkce části mozku, která je zodpovědná zejména za řízení a provádění pohybů souvisejících s tvorbou řeči. Dysartrie se v dospělosti běžně vyskytuje jako důsledek degenerativních onemocnění, mezi která patří i Parkinsonova nemoc (PN), Huntingtonova nemoc (HN), mnohočetná systémová atrofie (MSA), progresivní supranukleární obrna (PSO) nebo cerebelární ataxie (CA). Rozpoznání a klasifikace specifických řečových charakteristik souvisejících s dysartrií může poskytnout důležité informace o patofyziologii a lokalizaci neurologických onemocnění. Hodnocení míry poškození řeči pak může též sloužit jako cenný ukazatel pro stanovení doby nástupu nemoci či účinnosti léčby. Hlavní cíle této disertační práce jsou: (a) navrhnout vhodné algoritmy, metody a měření, které by byly dostatečně citlivé a přesné, aby zachytily patologické změny v řeči, (b) objektivně kvantifikovat vliv neurologických poruch na řečový projev a (c) hledat souvislosti mezi pozorovanými změnami v řeči a celkovým motorickým stavem pacienta či medikací, kterou užívá, za účelem hlubšího porozumění patofyziologii poruch řeči.

V rámci dizertace bylo pořízeno několik databází PN, HN, MSA, PSO a CA pacientů a zdravých kontrol odpovídajícího věku. V průběhu nahrávání byli všichni účastníci studie požádáni o provedení několika řečových úloh jako je prodloužená fonace, rychlé opakování slabik, přečtení úryvku textu nebo vyprávění krátkého monologu. Dále byly pořízeny záznamy s různými klinickými informacemi o stavu motorických či kognitivních schopností pacienta nebo dávkách užívaných léků. Objektivní kvantitativní hodnocení řeči bylo provedeno s pomocí akustických analýz. Statistické analýzy byly použity k hledání možných rozdílů mezi skupinami či korelací mezi řečovými a klinickými charakteristikami.

Výsledky této disertační práce jsou prezentovány v podobě devíti IF publikací. Vliv neurologické poruchy na produkci řeči se nám podařilo objektivně kvantifikovat u všech zkoumaných nemocí včetně PN, HN, MSA, PSO a CA. Dále se ukázalo, že oddělení pacientů od zdravých kontrol pouze na základě nahrávky řečového projevu je možné. Taktéž jsme prokázali, že i diferenciace mezi několika velmi podobnými nemocemi parkinsonského typu je možná. S použitím akustických analýz jsme byly schopni rozlišit mezi MSA/PSO a PN s přesností 95 % a mezi PSO a MSA s přesností 75 %. Dále jsme objevili řadu korelací mezi klinickými a řečovými charakteristikami. Nepříznivý účinek levodopy na plynulost řeči byl nalezen u pacientů s PN po 3-6 letech užívání tohoto léku. Na druhé straně jsme pozorovali zlepšení nebo alespoň zachování kvality řečového projevu (související zejména s přesností artikulace souhlásek a samohlásek, variabilitou výšky hlasu a počtem pauz) u 2/3 těchto PN pacientů, zatímco řeč se zhoršila pouze u 1/3. Tyto nálezy naznačující celkový pozitivní účinek dlouhodobého užívání levodopy na dysartrii v brzkých stádiích PN. Závěrem lze říci, že objektivní akustická analýza poruch řeči může významně přispět ke včasné a správné diagnóze dané nemoci a také přispět k hlubšímu porozumění patofyziologii těchto chorob.

Klíčová slova

Poruchy hlasu a řeči; Dysartrie; Akustické analýzy; Parkinsonova choroba; Huntingtonova nemoc; Atypické parkinsonské syndromy; Levodopa; Kontrastivní větný důraz; Neplynulost řeči; Artikulace souhlásek; Artikulace samohlásek.

Abbreviations

AMR	alternating motion rate
APS	atypical parkinsonian syndromes
CA	cerebellar ataxia
DBS	deep brain stimulation
GPi	globus palllidus interna
HC	healthy control
HD	Huntington's disease
L-dopa	levodopa
LSVT	Lee Silverman Voice Treatment
MSA	multiple system atrophy
MSD	motor speech disorders
PD	Parkinson's disease
PSP	progressive supranuclear palsy
STN	subthalamic nucleus

CONTENTS

#

1. Introduction

Speech is a unique, complex, dynamic motor activity through which we express thoughts and emotions and respond to and control our environment (1). It is one of the most powerful tools possessed by the human species, and it contributes enormously to the character and quality of a person's life. In fact, communication is central to everything we do. It affects who we are, how we learn, how we interact with other people or how successful we are at work. Speech requires the integration of numerous activities including cognitive-linguistic processes, motor speech planning and programming, and neuromuscular execution (1). Thus, the large span of brain functions may be surveyed with analysis of speech functions, explaining why they have become extensively studied in both basic research as well as clinical practice.

1.1. Motivation

The elderly population is growing fast all over the world and, as a consequence, the number of elderly subjects with speech/language disorders has also increased rapidly (2). Occurrence of voice and speech disorders in adult age is commonly manifested as a consequence of degenerative, traumatic, vascular, infectious, demyelinating or other diseases. Among these, various neurological disorders such as Parkinson's disease (PD), Huntington's disease (HD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), cerebellar ataxia (CA), Lewy body dementia or amyotrophic lateral sclerosis are responsible for development of dysarthria in approximately 50 % of all etiologies (1).

Interestingly, it has been previously demonstrated that abnormalities of speech in some of these disorders may appear several years before the diagnosis is established (3, 4, E1) and can be even the earliest indicator of the disease (1, 5). In addition, identification of specific deviant speech characteristics can provide important clues about the underlying pathophysiology and localization of neurological diseases (1). Speech may also serve as a valuable marker of treatment efficacy (A1, A4), disease progression (6, 7) or disease severity (8).

Voice and speech disorders can be investigated by perceptual, acoustic, physiologic or visual imaging methods. Among these, perceptual methods are presumably the most commonly used being the gold standard for clinical differential diagnosis, judgements of severity, many decisions about management, and the assessment of meaningful temporal changes (1). However, at the same time, they are subjective in nature, difficult to quantify and may significantly differ when performed by two independent speech specialists. In addition, perceptual assessment can hardly be used to capture speech changes in early stages of disease (A8) where dysarthria is often non-perceptible or to capture slight alterations in speech due to various effects such as medical interventions (A4). See Figure 1 for an example of perceptible and non-perceptible alterations of speech that might be observed in phonation of patients with HD.

Contrary, acoustic methods can visually display and objectively quantify many temporal components of speech signals. To this extent, acoustic analysis of speech has

the unique potential to provide objective, sensitive, cheap and relatively easy to administer method to precisely assess the degree of speech impairment (9).

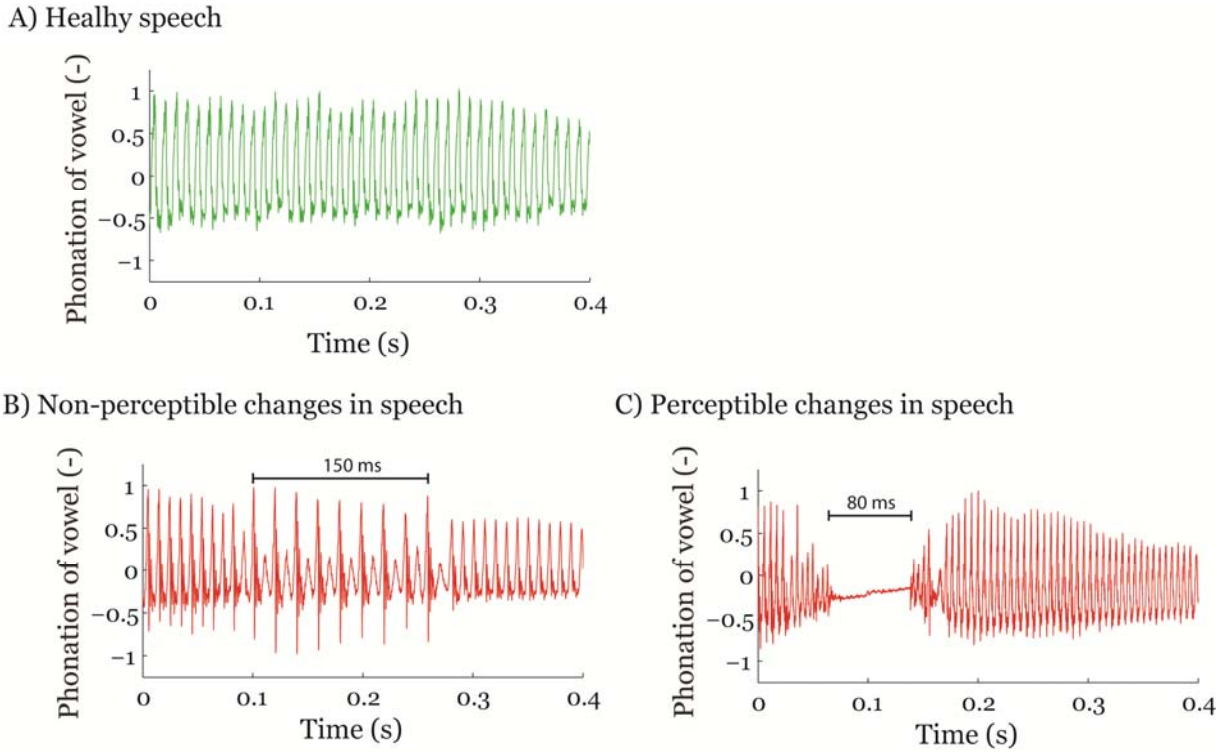

Figure 1: The example of perceptible and non-perceptible alterations in speech. A) Healthy phonation of vowel /a/. B) Non-perceptible changes in pathological phonation of vowel /a/; the frequency of vocal folds vibration drops to half of its original value for a short period of time. C) Perceptible changes in pathological phonation of vowel /a/; the vibration of vocal folds is vanished for a short period of time.

1.2. Organisation of the thesis

Presented doctoral thesis is submitted as a collection of nine author's main research papers (A1-A8, B1) related to the topic of the doctoral thesis accompanied by the integrating text[1].

The particular organisation of the thesis is as follows. The basic notions and facts regarding the topic of the thesis are described and the relevant literature is provided in Chapter 2. In Chapter 3 the goals of the thesis are clearly defined. Subsequently, the general approach considering methods used is explained in Chapter 4 and the results in the form of nine main author's articles (A1-A8, B1) are shortly introduced in Chapter 5. Furthermore, the summary of the achieved results and their contributions to the aims of the doctoral thesis are explicitly stated in Chapter 6. Finally, a conclusion is made in Chapter 7 and possible future directions suggested in Chapter 8.

[1] This format of the doctoral thesis is approved on the Faculty of Electrical Engineering, Czech Technical University in Prague by the Dean's directive from the 1st November 2014.

2. State of the art

This chapter presents an overview about the current stage of the problem and the literature connected with the topic of the doctoral thesis. In the first part, some basic information about motor speech disorders, methodology for categorizing of dysarthria subtypes and breakdown on selected degenerative diseases leading to development of dysarthria are provided. In the second part, the basic medical interventions related to treatment of PD, HD, PSP, MSA or CA are introduced including pharmacological and surgical interventions, physiotherapy and speech therapy.

2.1. Motor speech disorders

Motor speech disorders (MSD) can be defined as speech disorders resulting from neurologic impairments affecting the planning, programming, control or execution of speech (1). MSD include the dysarthria and apraxia of speech. While both dysarthria and apraxia of speech are neurologic in origin, resulting from damage to central nervous system, dysarthria is a disorder of movement control and execution whereas apraxia of speech impairs especially the processes of planning or programming of movements of essentially normal strength, speed, and coordination of the speech musculature (1, 10). Among acquired neurologic communication disorders, dysarthria accounts for about 53.0 % of the primary diagnoses and it is far more prevalent than any other category including aphasia (25.8 %), nonaphasic cognitive-communication disorders (16.8 %) or apraxia of speech (3.9 %) (1).

2.1.1. Dysarthria

Dysarthria is a speech disorder that reflects abnormalities in the strength, speed, range, steadiness, tone or accuracy of movements required for the breathing, phonatory, resonatory, articulatory, or prosodic aspects of speech production (1). Dysarthria is associated with one or more sensorimotor abnormalities including weakness, spasticity, slowness or incoordination of the musculature used to produce speech. Dysarthria occurs with considerable frequency in individuals with PD, multiple sclerosis, traumatic brain injury, small stroke, cerebellar diseases, amyotrophic lateral sclerosis or cerebral palsy (11-14). Voice and speech disorders have also been recognised to be one of the first manifestations in persons with HD, PD or amyotrophic lateral sclerosis (1, 5, 15, 16).

Generally, the dysarthrias have global, rather than focal, effect on the speech production affecting multiple dimensions of spoken language, i.e. phonation, respiration, articulation, prosody or resonance at the same time (10, 17, 18). While perceptual methods are still considered to be a gold standard for evaluation of dysarthria (1), significant progress has been made in description of various dysarthria subtypes using acoustic analyses (14, 19, 20) and physiological methods (21).

2.1.2. Categorizing of dysarthria subtypes

The modern classification of the dysarthrias rests largely on two articles published three decades ago (22, 23). In these studies (22, 23), Darley et al. investigated large sample of speakers with dysarthria resulting from different neurological conditions using auditory-perceptual based evaluation of voice and speech deficits. Darley et al. (22, 23) noted that constellation of specifically affected speech dimensions is related to localization in the nervous system and typically reflects the presumed underlying pathophysiology. Based on these findings, authors defined seven dysarthria subtypes including flaccid, spastic, ataxic, hypokinetic, hyperkinetic, unilateral upper motor neuron and mixed (1, 22, 23); see Table 1 for more details.

Table 1: Breakdown of dysarthria subtypes.

Dysarthria subtype	Localization	Pathophysiology
Flaccid	Lower motor neuron	Weakness
Spastic	Bilateral upper motor neuron	Spasticity
Ataxic	Cerebellum	Incoordination
Hypokinetic	Basal ganglia circuit (substantia nigra)	Rigidity, bradykinesia
Hyperkinetic	Basal ganglia circuit (putamen or caudate)	Involuntary movements
Unilateral upper motor neuron	Unilateral upper motor neuron	Upper motor neuron weakness, incoordination or spasticity
Mixed	More than one	More than one

For each dysarthria subtype the distinctive cluster of deviant speech dimensions was identified. It should be noted that the classification method itself covers approximately 50 different perceptually distinguishing speech dimensions. See Table 2 for example of deviant speech dimensions manifested in each of four fundamental dysarthria subtypes. Although there are currently several more elaborated perceptual scales (for example Dysarthria Profile or Frenchay Dysarthria Assessment) (14), the Darley's approach remains landmark achievement and it is still fundamental for clinical practice.

Table 2: Breakdown on clusters of deviant speech dimensions in individual dysarthria subtypes according to studies (1, 22, 23). The list includes only certain selected dimensions.

Deviant speech dimensions	Dysarthria subtype			
	Spastic	Ataxic	Hypokinetic	Hyperkinetic
Harshness	↑↑	–	–	↑
Slow rate	↑↑	↑	–	↑
Pitch breaks	↑↑	–	–	↑
Slow and regular AMRs	↑↑	–	↑	–
Excess and equal stress	↑	↑↑	–	–
Distorted vowels	–	↑↑	–	↑↑
Excess loudness variations	–	↑↑	–	↑↑
Prolonged phonemes	–	↑	–	↑
Reduced stress	–	–	↑↑	–
Monoloudness	↑	–	↑↑	–
Inappropriate silences	–	–	↑↑	↑
Increased overall rate	–	–	↑↑	–
Reduced loudness	–	–	↑↑	–
Voice tremor	–	–	–	↑↑
Prolonged intervals	–	–	–	↑↑
Intermittent hypernasality	–	–	–	↑↑
Echolalia	–	–	–	↑↑

Captions: *AMR* alternating motion rate; ↑ particular deviant speech dimension that may or may not be preserved but it is not distinguishing by itself; ↑↑ particular deviant speech dimension that is prominent or distinguishing.

2.1.3. Selected degenerative diseases leading to development of dysarthria

Parkinson's disease

PD is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in part of the brain called substantia nigra, affecting 1.6 % of persons over the age of 65 years (24). It commonly begins in middle to late decade of life and the life expectancy after diagnosis is about 15 years. Its occurrence is usually sporadic, but nearly one third of people with two or more affected first-degree relatives are likely to acquire the disease (1). The cardinal motor signs of PD are resting tremor, bradykinesia, rigidity and postural instability. In addition, many patients with PD develop other motor or non-motor deficits such as autonomic dysfunction, cognitive decline, depressions, sleep alterations or speech and swallowing impairment (12, 25, 26). Currently, there is no available causal cure, although medical interventions, including pharmacological and surgical ones, offer alleviation of some symptoms, especially in the early stages of the disease.

Up to 90 % of individuals with PD developed an alteration of speech termed as hypokinetic dysarthria (17, 27). Hypokinetic dysarthria might be one of the earliest

symptoms and exhibits even several years before the diagnosis is established (5, 28). Commonly reported speech deficits experienced by PD individuals include monoloudness, monopitch, reduced stress, imprecise articulation, variability of speech rate, a breathy, harsh voice, dysfluency, voice tremor, and other manifestations that lead to overall reduced speech intelligibility (1, 22). Although the PD patients ordinarily exhibit pure hypokinetic dysarthria, the emergence of various hyperkinetic features may appear in later stages as a consequence of ON-OFF fluctuations related to long-term usage of high dosage of dopaminergic medication (29).

Multiple system atrophy

Degenerative diseases that include but go beyond the manifestations of parkinsonism are known as atypical parkinsonian syndromes (APS). However, in contrast to PD, APS respond poorly to levodopa (L-dopa) treatment and exhibit more rapid disease progression (30, 31). In particular, APS cover MSA, PSP, Lewy body dementia and corticobasal degeneration (30). An estimated prevalence of MSA is about 30 persons per 100,000 among people older than 65 years (32). MSA is manifested by various combination of autonomic, cerebellar, parkinsonian and pyramidal features (33).

MSA patients typically develop mixed dysarthria with combination of hypokinetic, ataxic and spastic components as a result of more widespread neural atrophy including damage in the basal ganglia circuit and cerebellum (34). Indeed, the previous study (34) investigating 46 MSA patients by perceptual speech analysis reported presence of mixed dysarthria in two-thirds of subjects. Specifically, hypokinetic components were found to be predominated in 48 % of patients, whereas ataxic components predominated in 35 % and spastic in 11 % (34). With respect to particular speech dimensions voice perturbations, slow and variable alternating motion rates, imprecise consonant articulation and increased loudness were documented to be most affected (35, 36).

Progressive supranuclear palsy

PSP is a neurodegenerative disorder of unknown origin with disease onset in middle to late age that belongs among APS. The incidence of disease is estimated as 40 persons per 100,000 in population over the age of 65 years, and the average life expectancy is about 5.3 years after disease onset (32, 37). Characteristic clinical features of PSP are supranuclear gaze palsy, frequent falls, bradykinesia, axial rigidity, cognitive decline and communication disorders (38, 39).

In accordance with MSA, PSP patients also commonly evolve mixed dysarthria with combination of all hypokinetic, ataxic and spastic components mainly due to damage in the basal ganglia circuit and corticobulbar pathways (40). In compliance with MSA (34), the research focused on examination of 44 PSP patients using oral motor assessment and perceptual speech analysis revealed mixed dysarthria in two-thirds of PSP subjects. Nevertheless, the dysarthria in PSP patients, contrary to MSA, was characterized by predominated spastic components in 50 % of patients, while hypokinetic components were most severely affected in 34 % of subjects and ataxic in 14 % of subjects (40). Interestingly, dysarthria in PSP was also characterized by stuttering-like behaviour in 31 % of individuals

(40). As stuttering-like behaviour was not observed in MSA, it seems to be specific only for PSP (34, 40).

Huntington's disease

HD is an autosomal-dominant inherited neurodegenerative disorder caused by an expansion in the number of CAG repeats on the short arm of chromosome 4p16.3 in the Huntington gene (41), which is characterized by uncoordinated body movements, psychological dysfunction and a reduction in cognitive decline resulting in dementia. The prevalence of HD is estimated to be about 4-8 subjects for 100,000 people (42, 43). From a clinical perspective, HD is primarily manifested by involuntary movements termed as chorea, which may be accompanied by bradykinesia, motor impersistence, and deficits in movement planning, aiming, tracing and termination (44).

Voice and speech disorders, known as hyperkinetic dysarthria, are a common sign of HD, developing in more than 90 % of HD patients in the course of the disease. Based upon 30 speakers with various underlying choreatic movement disorders, Darley et al. (22,23) perceptually defined the characteristic patterns of hyperkinetic dysarthria mainly by the presence of imprecise consonants, prolonged intervals, variable rate, monopitch, harsh voice, inappropriate silence, distorted vowels, and excess loudness variations. Subsequently, only a few studies have provided more accurate description of hyperkinetic dysarthria in patients with genetically confirmed HD documenting mainly the abnormalities in voice function (45) and speech timing (16, 46, 47).

Cerebellar ataxia

Sporadic and hereditary CAs are associated with progressive degeneration of the cerebellum and its afferent and efferent pathways. Spinocerebellar ataxia is a rare, autosomal-dominant neurological disorder with an estimated prevalence of approximately 3-4 cases per 100,000 individuals (48). On the contrary, idiopathic late-onset cerebellar ataxia refers to a group of sporadically occurring degenerative diseases of the cerebellum and the brainstem of unknown etiology (49). Despite differing pathogenesis, pathologic changes in these disorders are very similar with consistent involvement of the cerebellum, which is essential for posture and fine motor control. From a clinical perspective, CA is dominated by progressive gait ataxia characterized by staggering gait, increased step width, incorrect foot placement, increased variability in stride length and poor inter-limb coordination resulting in loss of balance and a high risk of falling (50).

Speech impairment associated with CA is assumed to be dominated by ataxic dysarthria, but because multiple portions of the motor system can be involved, combination with other dysarthria subtypes is possible (1). The first complex description of ataxic dysarthria was based on of speech samples elicited from 30 patients with etiologically different cerebellar disorders (22). Prosodic modulations such as excess and equal stress and excess loudness variations as well as articulatory features including irregular breakdowns, distorted vowels, prolonged phonemes and slow and irregular alternating motion rates were perceptually identified to be distinctive for ataxic dysarthria (22). Especially, rhythmical irregularities during fast repetitive productions of multiple syllables have been assumed

to be a specific oral motor feature of ataxic impairment (1, 51). Later descriptions of ataxic dysarthria based primarily on objective kinematic and acoustic methods in spinocerebellar ataxia patients confirmed previous findings and emphasized the role of imprecise consonant and vowel articulation (52-54).

2.2. Effect of medical interventions on dysarthria

A number of approaches may be used to manage dysarthria. These treatment methods include mainly various forms of speech therapy, however, positive effect might also be induced by some of the pharmacological or surgical interventions commonly used for treatment of neurodegenerative diseases; either intended or as a side-effect. The influence of other interventions such as physiotherapy remains generally unknown.

In the following section, especially treatment approaches related to management of hypokinetic dysarthria of PD are reviewed as PSP, MSA and HD patients are not principal targets with respect to speech therapy due to rapid disease progression of these diseases. Some comments are also noted with respect to CA patients manifesting ataxic dysarthria.

2.2.1. Speech therapy

The speech therapy approaches for treatment of hypokinetic dysarthria are based either on behavioural treatment (conscious training to strengthen muscles involved with coordination of respiration, phonation and articulation) or on the use of devices and biofeedback (55). In addition, a novel approaches requiring motor learning and increased sensory awareness such as Lee Silverman Voice Treatment (LSVT) have been introduced. The commonly used devices include voice amplifier, delayed auditory feedback, a wearable intensity biofeedback or masking noise device. The main goal of these devices is to improve patient's intelligibility through increment in vocal loudness, therefore their positive effect is usually directly limited to their usage and diminished when not worn (56, 57).

Currently, probably the most widely used speech therapy for PD is LSVT, which was developed by Ramig et al. (58). The LSVT focuses on increasing of both respiratory effort and vocal fold adduction during therapy lasting 16 sessions per one month with the emphasis on recalibration of speech effort so that speakers appreciate the level of effort needed to speak (59). Positive outcomes have been documented at the level of speech intelligibility, pitch range, articulation rate, facial expression and swallowing (60, 61). Furthermore, unlike other respiratory-based speech therapy LSVT is supported by evidence of maintained enhancements following 24 months after the end of therapy (62). In particular, higher level of loudness and pitch variability was observed immediately as well as 24 months after therapy in speaking tasks of sustained phonation, reading passage and monologue (62).

2.2.2. Pharmacological interventions

Many different drugs have been developed to treat PD including L-dopa and dopamine agonists. These drugs replace and enhance the level of dopamine in the brain of persons with PD. Parkinsonian patients have usually a favourable response to dopaminergic therapy

at the start of the treatment leading to temporarily diminishing of most cardinal motor symptoms. However, the motor ON-OFF fluctuations may occur after several years of dopaminergic replacement therapy, i.e. motor improvements in the ON periods begin to wane and become shorter in duration while the person with PD experience severe disability due to prolonged reappearance of PD symptoms during OFF periods (63). These fluctuations lead to necessity to increase L-dopa dosages.

While the beneficial effect of dopaminergic therapy on the principal motor manifestations of PD has been clearly documented, its effect on overall speech performance remains inconclusive with mixed and contradictory results (55, 64). These ambiguous findings have been reported considering both long-turn as well as short-term (comparison ON versus OFF condition) effect of dopaminergic therapy. In general, a number of former reports based on perceptual analyses have reported an improvement of speech performance under dopaminergic therapy, while most of the recent studies found no significant treatment effects (55, 64). Such discrepancies across previous studies may be attributable to participant related differences (size of the database, dosage of medication, speech severity, disease severity and motor phenotype) or various methodological settings (64). In fact, most of the studies have focused on only particular aspects of speech and have not tried to assess complex speech behaviour, whereas parkinsonian patients may manifest varied deficits across individual measures and characteristics (17, 65).

2.2.3. Surgical interventions

Deep brain stimulation (DBS) is currently the most commonly used surgical procedure for treatment of movement and affective disorders. During surgery implantation of a medical device called a neurostimulator, which sends electrical impulses through implanted electrodes to specific parts of the brain, is performed. Stimulators are most frequently implanted in subthalamic nucleus (STN), but also other targets such as globus palllidus interna (GPi), caudal zona incerta or ventralis intermediate nucleus can be utilized. DBS in select brain regions provides therapeutic benefits for patients with otherwise pharmacologic treatment-resistant movement disorders such as PD, HD, dystonia, essential tremor or Tourette syndrome. DBS has not been developed specifically to improve speech, although improvements have been occasionally noted; for review see (66).

A vast body of evidence have proven the positive effect of STN-DBS on cardinal motor symptoms in PD. However, the effect of STN-DBS on voice and speech has been reported to be variable or even adverse (55, 66). According to simple clinical perceptual evaluation, a meta-analysis of 37 cohorts comprised of 921 patients reported an incidence of dysarthria after STN-DBS in 9.3 % of cases (67). On the other hand, beneficial effect of STN-DBS on dysarthria have been documented at least in individual patients, although the improvements were much less pronounced than that on limb movements and tend to decrease in the long term (66). It has been also suggested that STN-DBS has a differential impact on different speech subsystems with the potential to ameliorate phonation, however, at the cost of a deterioration of articulatory capacities leading to a reduction of overall speech intelligibility (66).

The effect of other DBS potential targets on parkinsonian speech has only scarcely been investigated so far. However, based on previous results that compared the effect of GPi-DBS and STN-DBS using identical methodology, the negative effect on speech production appears to occur less frequently under GPi-DBS than under STN-DBS (68).

2.2.4. Physiotherapy

Considering ataxic dysarthria, efforts to increase physiologic support by increasing muscle strength are generally unnecessary for ataxic speakers, and there is no compelling evidence to support their effectiveness to the disorder (1). Similarly, surgical or pharmacologic interventions do not provide any relieve of dysarthria. Therefore, the treatment approaches for ataxic dysarthria are usually focused on improving or compensating for problems related to motor control and coordination (1). Particularly, the training of coordination of oral movements may be effective (69). On the other hand, one might expect that patients could also benefit from physiotherapy focused on enhancement of body balance and trunk stability due to several reasons. Firstly, it has been documented that good postural alignment is an important element for the optimization of vocal function (70). Another mechanism may be connected to increased proprioceptive awareness, especially related to better perception of articulatory position and muscle strength. Finally, the principle of transference in neural plasticity states that plasticity following training in one function may enhance related behaviours (71). Nevertheless, the effect of physiotherapy targeted on improvement of body stability on speech has not been investigated so far.

3. Goals of the thesis

The presented cumulative dissertation comprises nine peer-reviewed journal papers (A1-A8, B1) and several other publications (C1, D1-D10). As a result, there might be a number of various aims stated, some of which are mentioned below. In general, the aims are of two-types: (a) overlapping, interrelated aims belong to several papers, and (b) specific, particular aims strongly related to the topic of the presented article. The goals of the doctoral thesis have been defined as follows:

General goals (aim 1-4)

1) To objectively quantify the effect of neurological disorder on speech production.

2) To design the feasible algorithms, methodologies or measurements that would be sensitive and sufficiently accurate to capture pathological changes presented in particular speech dimensions.

3) To relate the potentially observed speech changes to overall motor performance or medication doses in order to provide deeper insight into the pathophysiology of speech disturbances.

4) To critically discuss the revealed findings in the context of wide state-of-the-art.

Specific goals (aim 5-10)

5) To determine specific dysarthric patterns and estimate their reliability in differentiating between PD, PSP and MSA patients.

6) To search for possible early markers of PD that would separate healthy control (HC) speakers from de-novo PD patients.

7) To design innovative measurement that would reflect the effect of all main acoustic cues exploited during stress production.

8) To design methodology for evaluation of imprecise vowel articulation based on spontaneous speech such as monologue.

9) To investigate the effect of different speaking tasks on assessment of vowel articulation.

10) To examine the effectiveness of a 2-week intensive coordinative motor training on speech production in CA patients.

4. Methods

Although the particular methods used for speech evaluation are strongly dependent on the aim of each study, the general approach might be described in the following four steps: (1) selection of available population sample for given aim and defining the inclusion/exclusion criteria, (2) recording of the participants and speaking tasks, (3) selection or development of suitable acoustic features for evaluation of voice and speech performances, (4) statistical analysis. See Figure 2 for schematic overview of methods applied to evaluate MSD.

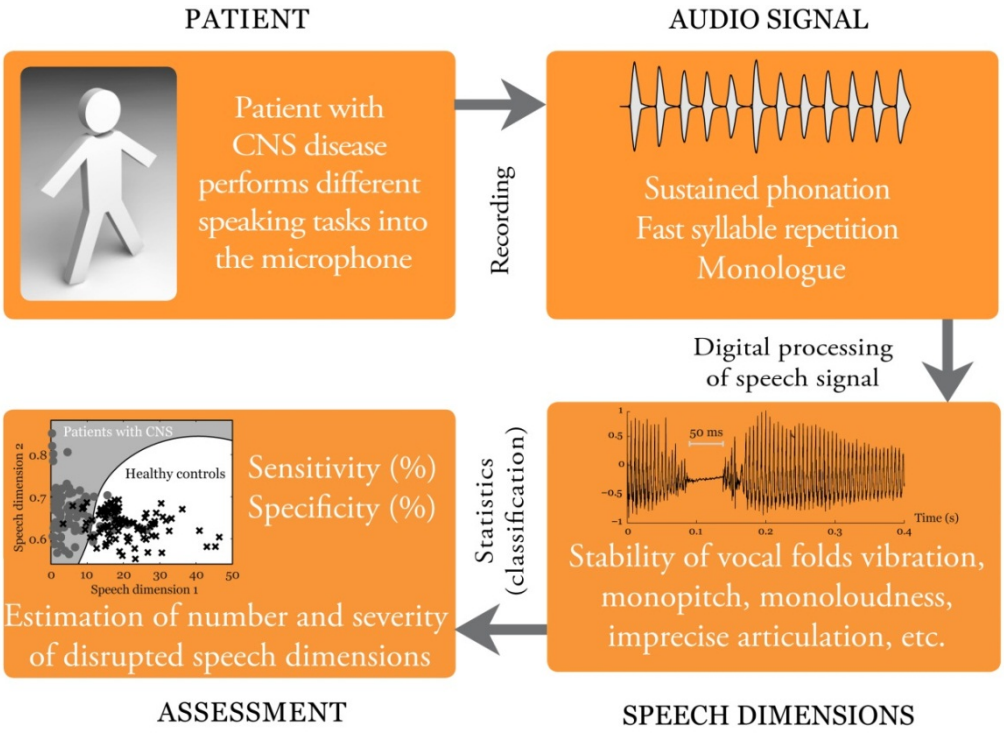

Figure 2: Schematic overview of methods applied to evaluate MSD including recording of participant, digital processing of speech signal and statistical assessment/classification experiment.

4.1. Recording of the participants and speaking tasks

Speech samples were recorded in a quiet room with a low level of ambient noise using recorder and an external condenser microphone. The signals were sampled at 48 kHz with 16-bit resolution. Recordings were obtained during one session with a speech specialist who conveyed instructions to the subjects. There were no time limits during the recordings. All participants were asked to repeat their performance at any time if they or the examiner were not fully satisfied with their initial attempt.

Investigation protocol consisted from various kind of speaking tasks such as: (a) sustained phonation of the vowel /a/ as long and stable as possible repeated two times, (b) fast repetition of syllables /pa/-/ta/-/ka/ at least 10 times per one breath repeated two times, (c) reading of the Czech phrase “Kolik mate ted u sebe asi penez.”(How much money do you have in your wallet?) per one breath repeated five times, (d) reading of standardized passage composed of 80 words, (e) reading of a short block of text with denoted words were unnatural

emphasize should be placed, (f) reading of cards with 18 different words composed to assess consonant articulation repeated two times or (g) a monologue lasting at least 2 minutes on given topics including family, work, childhood or interests.

The exclusion criteria for HC participants were the history of neurological or communication disorders, the serious problems with respiration or hearing or the suspicion of memory deficits. The inclusion and exclusion criteria for patients were different reflecting the specific aims of particular studies (A1-A8, B1).

4.2. Acoustic evaluation of voice and speech performances

The speech characteristics were examined using commercial program environments, namely Praat and Multi-Dimensional Voice Program, or original algorithms developed in Matlab as a part of our previous (17, 72) or currently presented studies (A3, A5, A7, B1). Several acoustic measurements were applied to investigate alterations in various speech dimensions. Both standard as well as innovative measurements were used. Some of them are mentioned in the following paragraph.

To assess ***voice quality***, we investigated jitter, shimmer, harmonic-to-noise ratio, degree of pitch breaks, or pitch variability extracted from sustained phonation. With respect to ***vowel articulation***, vowel space area, formant centralization ratio or vowel articulation index were computed based on analyses of the first and second formant frequencies using monologue and reading passage. The ***consonant articulation*** was assessed by measuring voice onset time, diadochokinetic regularity or diadochokinetic rate using fast repetition of /pa/-/ta/-/ka/ syllables. To evaluate ***aerodynamic efficiency***, maximum phonation time of sustained phonation was measured. To capture problems with prosody, the ***ability to modulate pitch and loudness*** was surveyed computing variability of fundamental frequency and intensity using reading text and monologue. Considering ***timing problems***, number of pauses lasting more than 60 ms, pause time percentage relative to total speech time or articulation rate was measured. To determine reduced ***ability to express word stress***, average value of pitch and intensity contour, duration of word or stress pattern index were elicited. With respect to ***dysfluency***, the percentage of within- and between-word dysfluencies was determined based on reading text and monologue using the Lidcombe Behavioral Data Language of stuttering taxonomy (73).

4.3. Statistical analysis

Individual parameters were firstly assessed using Kolmogorov-Smirnov test for testing of normality of data distribution. On the basis of these tests, the alternative parametric or non-parametric tests were chosen. For normally distributed data, we used the t-test or analysis of variance to assess group differences and Pearson analysis to evaluate correlations between speech and other clinical data. In case of other distributions, the nonparametric Wilcoxon test was used to determine group differences and Spearman correlation to search for relationships between speech and other clinical metrics. Moreover, we applied where appropriate modern methods of statistical decision tools (e.g., support vector machine, minimax task) or regression analysis.

5. Results and Papers

This chapter covers the main results of the author's research related to the topic of the presented thesis in the form of eight articles (A1-A8) published or accepted for publication in peer-reviewed journals and one additional manuscript (B1) submitted for review process; author of this dissertation is the first author of four papers (A1-A3, B1). For each article a short summary is inserted including information about authors and their affiliations, journal, year of publication, journal statistics and abstract.

5.1. Speech changes after coordinative training in patients with cerebellar ataxia: a pilot study (A1)

Authors and affiliations:

Tereza Tykalová[1], Mariana Pospíšilová[2], Roman Čmejla[1], Jaroslav Jeřábek[3], Pavel Mareš[4], Jan Rusz[1]

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[3]*Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital*
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Journal, year of publication: Neurological Sciences, 2016

Journal statistics according to the Journal Citation Report® (2015):

Impact factor: 1.783
5-year impact factor: 1.494
Category: Clinical neurology / Neurosciences
Quartile in category: Q3 / Q3

Abstract:

Although rehabilitative training is a necessary adjunct in the management of gait ataxia, it remains unknown whether the possible beneficial effect of intensive coordinative training may translate to activities of daily living, which are closely connected with postural alignment. The aim of the present study was to examine the effectiveness of a 2-week intensive coordinative motor training on speech production. Speech and motor performances in a cohort of ten individuals with cerebellar degeneration were examined three times; before the introduction of training, directly and 4 weeks after the last training session. Each patient was instructed to perform a speaking task of fast syllable repetition and monologue. Objective acoustic analyses were used to investigate six key aspects of speech production disturbed in ataxic dysarthria including accuracy of consonant articulation, accuracy of vowel articulation, irregular alternating motion rates, prolonged phonemes, slow alternating motion rates and inappropriate segmentation. We found that coordinative training had a mild beneficial effect on speech in cerebellar patients. Immediately after the last training session, slight speech improvements were evident in all ten patients. Furthermore, follow-up assessment performed 4 weeks later revealed that 90 % of the patients showed better speech performance than before initiation of the therapy. The present study supports evidence that the intensive rehabilitative training may positively affect finemotor movements such as speech in patients with cerebellar ataxia.

5.2. Effect of dopaminergic medication on speech dysfluency in Parkinson's disease: a longitudinal study (A2)

Authors and affiliations:

Tereza Tykalová[1], Jan Rusz[1,2], Roman Čmejla[1], Jiří Klempíř[2], Hana Růžičková[2], Jan Roth[2], Evžen Růžička[2]

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Journal, year of publication: Journal of Neural Transmission, 2015

Journal statistics according to the Journal Citation Report® (2014):

Impact factor: 2.402
5-year impact factor: 2.732
Category: Clinical neurology / Neurosciences
Quartile in category: Q2 / Q3

Abstract:

Although speech dysfluencies have been hypothesized to be associated with abnormal function of dopaminergic system, the effects of dopaminergic medication on speech fluency in Parkinson's disease (PD) have not been systematically studied. The aim of the present study was, therefore, to investigate the long-term effect of dopaminergic medication on speech fluency in PD. Fourteen de novo PD patients with no history of developmental stuttering and 14 age- and sex-matched healthy controls (HC) were recruited. PD subjects were examined three times; before the initiation of dopaminergic treatment and twice in following 6 years. The percentage of dysfluent words was calculated from reading passage and monolog. The amount of medication was expressed by cumulative doses of L-dopa equivalent. After 3-6 years of dopaminergic therapy, PD patients exhibited significantly more dysfluent events compared to healthy subjects as well as to their own speech performance before the introduction of dopaminergic therapy ($p < 0.05$). In addition, we found a strong positive correlation between the increased occurrence of dysfluent words and the total cumulative dose of L-dopa equivalent ($r = 0.75$, $p = 0.002$). Our findings indicate an adverse effect of prolonged dopaminergic therapy contributing to the development of stuttering-like dysfluencies in PD. These findings may have important implication in clinical practice, where speech fluency should be taken into account to optimize dopaminergic therapy.

5.3. Acoustic Investigation of Stress Patterns in Parkinson's Disease (A3)

Authors and affiliations:

Tereza Tykalová[1], Jan Rusz[1,2], Roman Čmejla[1], Hana Růžičková[2], Evžen Růžička[2]

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Journal, year of publication: Journal of Voice, 2014

Journal statistics according to the Journal Citation Report® (2013):

Impact factor: 0.944
5-year impact factor: 1.208
Category: Otorhinolaryngology
Quartile in category: Q3

Abstract:

Although reduced stress is thought to be one of the most deviant speech dimensions in hypokinetic dysarthria associated with Parkinson's disease (PD), the mechanisms of stress production in PD have not been thoroughly explored by objective methods. The aim of the present study was to quantify the effect of PD on prosodic characteristics and to describe contrastive stress patterns in parkinsonian speech. The ability of 20 male speakers with early PD and 16 age- and gender matched healthy controls (HC) to signal contrastive stress was investigated. Each participant was instructed to unnaturally emphasize five key words while reading a short block of text. Acoustic analyses were based on the measurement of pitch, intensity, and duration. In addition, an innovative measurement termed the stress pattern index (SPI) was designed to mirror the effect of all distinct acoustic cues exploited during stress production. Although PD patients demonstrated a reduced ability to convey contrastive stress, they could still notably increase pitch, intensity, and duration to emphasize a word within a sentence. No differences were revealed between PD and HC stress productions using the measurements of pitch, intensity, duration, and intensity range. However, restricted SPI and pitch range were evident in the PD group. A reduced ability to express stress seems to be the distinctive pattern of hypokinetic dysarthria, even in the early stages of PD. Because PD patients were able to consciously improve their speech performance using multiple acoustic cues, the introduction of speech therapy may be rewarding.

5.4. Effects of dopaminergic replacement therapy on motor speech disorders in Parkinson's disease: a longitudinal follow-up study on previously untreated patients (A4)

Authors and affiliations:

Jan Rusz[1,2], Tereza Tykalová[1], Roman Čmejla[1], Jiří Klempíř[2], Evžen Růžička[2]

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[2]*Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague*
[3]*Institute of Anatomy, 1st Faculty of Medicine, Charles University in Prague*

Journal, year of publication: Journal of Neural Transmission, 2016

Journal statistics according to the Journal Citation Report® (2015):

Impact factor: 2.587
5-year impact factor: 2.662
Category: Clinical neurology / Neurosciences
Quartile in category: Q2 / Q3

Abstract:

Although speech disorders represent an early and common manifestation of Parkinson's disease (PD), little is known about their progression and relationship to dopaminergic replacement therapy. The aim of the current study was to examine longitudinal motor speech changes after the initiation of pharmacotherapy in PD. Fifteen newly-diagnosed, untreated PD patients and ten healthy controls of comparable age were investigated. PD patients were tested before the introduction of antiparkinsonian therapy and then twice within the following 6 years. Quantitative acoustic analyses of seven key speech dimensions of hypokinetic dysarthria were performed. At baseline, PD patients showed significantly altered speech including imprecise consonants, monopitch, inappropriate silences, decreased quality of voice, slow alternating motion rates, imprecise vowels and monoloudness. At follow-up assessment, preservation or slight improvement of speech performance was objectively observed in two thirds of PD patients within the first 3-6 years of dopaminergic treatment, primarily associated with the improvement of stop consonant articulation. The extent of speech improvement correlated with L-dopa equivalent dose (r = 0.66, p = 0.008) as well as with reduction in principal motor manifestations based on the Unified Parkinson's Disease Rating Scale (r = -0.61, p = 0.02), particularly reflecting treatment-related changes in bradykinesia but not in rigidity, tremor, or axial motor manifestations. While speech disorders are frequently present in drug-naive PD patients, they tend to improve or remain relatively stable after the initiation of dopaminergic treatment.

5.5. Speech disorders reflect differing pathophysiology in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy (A5)

Authors and affiliations:

Jan Rusz[1,2], Cecilia Bonnet[2,3], Jiří Klempíř[2,4], Tereza Tykalová[1], Eva Baborová[2], Michal Novotný[1], Aaron Rulseh[5,6], Evžen Růžička[2]

[1]Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague;[2]Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague; [3]AP HP, Neurology Department, Pitie Salpetriere Hospital, Paris; [4]Institute of Anatomy, 1st Faculty of Medicine, Charles University in Prague; [5]Department of Radiology, Na Homolce Hospital, Prague; [6]Department of Radiology, 1st Faculty of Medicine and General University Hospital, Charles University in Prague

Journal, year of publication: Journal of Neurology, 2015

Journal statistics according to the Journal Citation Report® (2014):

Impact factor: 3.377
5-year impact factor: 3.495
Category: Clinical neurology
Quartile in category: Q2

Abstract: Although speech disorder is frequently an early and prominent clinical feature of Parkinson's disease (PD) as well as atypical parkinsonian syndromes (APS) such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA), there is a lack of objective and quantitative evidence to verify whether any specific speech characteristics allow differentiation between PD, PSP and MSA. Speech samples were acquired from 77 subjects including 15 PD, 12 PSP, 13 MSA and 37 healthy controls. The accurate differential diagnosis of dysarthria subtypes was based on the quantitative acoustic analysis of 16 speech dimensions. Dysarthria was uniformly present in all parkinsonian patients but was more severe in PSP and MSA than in PD. Whilst PD speakers manifested pure hypokinetic dysarthria, ataxic components were more affected in MSA whilst PSP subjects demonstrated severe deficits in hypokinetic and spastic elements of dysarthria. Dysarthria in PSP was dominated by increased dysfluency, decreased slow rate, inappropriate silences, deficits in vowel articulation and harsh voice quality whereas MSA by pitch fluctuations, excess intensity variations, prolonged phonemes, vocal tremor and strained-strangled voice quality. Objective speech measurements were able to discriminate between APS and PD with 95 % accuracy and between PSP and MSA with 75 % accuracy. Dysarthria severity in APS was related to overall disease severity (r = 0.54, p = 0.006). Dysarthria with various combinations of hypokinetic, spastic and ataxic components reflects differing pathophysiology in PD, PSP and MSA. Thus, motor speech examination may provide useful information in the evaluation of these diseases with similar manifestations.

5.6. Characteristics and occurrence of speech impairment in Huntington's disease: possible influence of antipsychotic medication. Journal of Neural Transmission (A6)

Authors and affiliations:

Jan Rusz[1,2], Jiří Klempíř[2], Tereza Tykalová[1], Eva Baborová[2], Roman Čmejla[1], Evžen Růžička[2], Jan Roth[2]

[1]*Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague*
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Journal, year of publication: Journal of Neural Transmission, 2014

Journal statistics according to the Journal Citation Report® (2013):

Impact factor: 2.871
5-year impact factor: 2.862
Category: Clinical neurology / Neurosciences
Quartile in category: Q2 / Q3

Abstract:

Although motor speech impairment is a common manifestation of Huntington's disease (HD), its description remains limited. The aim of the current study was therefore to estimate the occurrence and characteristics of speech disorder in HD and to explore the influence of antipsychotic medication on speech performance. Speech samples, including reading passage and monologue, were acquired from 40 individuals diagnosed with HD and 40 age- and sex-matched healthy controls. Objective acoustic analyses were used to evaluate key aspects of speech including vowel articulation, intensity, pitch and timing. A predictive model was constructed to detect the occurrence and most prominent patterns of speech dysfunction in HD. We revealed that 93 % of HD patients manifest some degree of speech impairment. Decreased number of pauses, slower articulation rate, imprecise vowel articulation and excess intensity variations were found to be the most salient patterns of speech dysfunction in HD. We further demonstrated that antipsychotic medication may induce excessive loudness and pitch variations perceptually resembling excess patterns of word stress, and may also accentuate general problems with speech timing. Additionally, antipsychotics induced a slight improvement of vowel articulation. Specific speech alterations observed in HD patients indicate that speech production may reflect the pathophysiology of the disease as well as treatment effects, and may therefore be considered a valuable marker of functional disability in HD.

5.7. Objective Acoustic Quantification of Phonatory Dysfunction in Huntington's Disease (A7)

Authors and affiliations:

Jan Rusz[1,2], Jiří Klempíř[2], Eva Baborová[2], Tereza Tykalová[1], Veronika Majerová[2,] Roman Čmejla[1], Evžen Růžička[2], Jan Roth[2]

[1]*Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague*
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Journal, year of publication: PLoS One, 2013

Journal statistics according to the Journal Citation Report® (2012):

Impact factor: 3.730
5-year impact factor: 4.244
Category: Multidisciplinary sciences
Quartile in category: Q1

Abstract:

Although speech motor changes are reported as a common sign of Huntington's disease (HD), the most prominent signs of voice dysfunction remain unknown. The aim of the current study was to explore specific changes in phonatory function in subjects with HD. 34 subjects with HD and 34 age- and sex-matched healthy controls were examined. Participants performed sustained vowel phonation for subsequent analyses of airflow insufficiency, aperiodicity, irregular vibrations of vocal folds, signal perturbations, increased noise, and articulation deficiency. In total, 272 phonations were collected and 12 voice parameters were extracted. Subsequently, a predictive model was built to find the most salient patterns of voice disorders in HD. The results were also correlated with disease severity according to the Unified HD Rating Scale (UHDRS) motor score. Subjects with HD showed deterioration in all investigated phonatory functions. Irregular pitch fluctuations, sudden phonation interruption, increased noise, and misplacement of articulators were found to be most significant patterns of phonatory dysfunction in HD ($p < 0.001$). The combination of these four dysphonia aspects contributed to the best classification performance of 94.1 % in the separation of HD patients from healthy participants. Our results further indicated stronger associations between sudden phonation interruption and voluntary components of the UHDRS ($r = 20.48$, $p < 0.01$) and between misplacement of articulators and involuntary components of the UHDRS ($r = 0.52$, $p < 0.01$). Our configuration of phonatory features can detect subtle voice abnormalities in subjects with HD. As impairment of phonatory function in HD was found to parallel increasing motor involvement, a qualitative description of voice dysfunction may be helpful to gain better insight into pathophysiology of the vocal tract.

5.8. Imprecise vowel articulation as a potential early marker of Parkinson's disease: Effect of speaking task (A8)

Authors and affiliations:

Jan Rusz[1], Roman Čmejla[1], Tereza Tykalová[1], Hana Růžičková[2], Jiří Klempíř[2], Veronika Majerová[2],Jana Picmausová[2], Jan Roth[2], Evžen Růžička[2]

[1]*Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague*
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Journal, year of publication: Journal of the Acoustical Society of America, 2013

Journal statistics according to the Journal Citation Report® (2012):

Impact factor: 1.646
5-year impact factor: 1.915
Category: Acoustics / Audiology & speech-language pathology
Quartile in category: Q2 / Q2

Abstract:

The purpose of this study was to analyze vowel articulation across various speaking tasks in a group of 20 early Parkinson's disease (PD) individuals prior to pharmacotherapy. Vowels were extracted from sustained phonation, sentence repetition, reading passage, and monologue. Acoustic analysis was based upon measures of the first (F1) and second (F2) formant of the vowels /a/, /i/, and /u/, vowel space area (VSA), F2i/F2u and vowel articulation index (VAI). Parkinsonian speakers manifested abnormalities in vowel articulation across F2u, VSA, F2i/F2u, and VAI in all speaking tasks except sustained phonation, compared to 15 age-matched healthy control participants. Findings suggest that sustained phonation is an inappropriate task to investigate vowel articulation in early PD. In contrast, monologue was the most sensitive in differentiating between controls and PD patients, with classification accuracy up to 80 %. Measurements of vowel articulation were able to capture even minor abnormalities in speech of PD patients with no perceptible dysarthria. In conclusion, impaired vowel articulation may be considered as a possible early marker of PD. A certain type of speaking task can exert significant influence on vowel articulation. Specifically, complex tasks such as monologue are more likely to elicit articulatory deficits in parkinsonian speech, compared to other speaking tasks.

5.9. Distinct patterns of imprecise consonant articulation among Parkinson's disease, progressive supranuclear palsy and multiple system atrophy (B1)

Authors and affiliations:

Tereza Tykalová[1], Jan Rusz[1,2], Jiří Klempíř[2,3], Roman Čmejla[1], Evžen Růžička[2]

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Journal, year of submission: Submitted to peer-reviewed journal, June 2016

Abstract:

Distinct speech characteristics that could help to differentiate between Parkinson's disease (PD), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are tenaciously explored. The aim of the current study was to investigate the patterns and degree of consonant articulation deficits across voiced and voiceless stop plosives in 16 PD, 16 PSP, 16 MSA and 16 healthy control speakers using objective acoustic measures. The extent of consonant articulation deficits was more profound in PSP and MSA than in PD, although slight deterioration of consonant articulation was also observed in PD as compared to healthy speakers. In particular, voiceless plosives were found to be more prolonged in both PSP and MSA compared to PD, while voiced plosives were revealed to be significantly shorter only in MSA as a consequence of damage to the cerebellar structures. Detailed speech analysis may be diagnostically helpful in distinguishing between PD and atypical parkinsonian syndromes.

6. Summary of the achieved results and their contributions to the aims of the doctoral thesis

In the following section, a brief list of the main results obtained along with their contributions to the goals of the doctoral thesis is provided. For more detailed discussion of results and their implications see the discussion sections of particular articles (A1-A8, B1). The results are organized according to the aims defined in chapter 3.

1) To objectively quantify the effect of neurological disorder on speech production.

   - *Using the appropriate speech parameters, methodology and evaluation criteria we managed to objectively quantify the effect of neurological disorder on speech production in PD (A2-A5, A8, B1), HD (A6, A7), APS (A5, B1) as well as CA (A1) patients. Furthermore, the combination of 4 dysphonia aspects enables the separation of HD patients from HC participants with the best classification performance of 94.1 ± 2.3 % (sensitivity of 95.1 ± 4.0 %; specificity of 93.2 ± 4.3 %) (A7). The differentiation among several types of parkinsonian disorders is also possible, as documented in our study (A5) where using objective speech measurements we were able to discriminate between APS and PD with 95.3 ± 6.4 % accuracy (sensitivity of 93.4 ± 8.7 %; specificity of 99.5 ± 4.1 %) as well as between PSP and MSA subjects with 75.2 ± 13.3 % accuracy (sensitivity of 74.3 ± 15.3 %; specificity of 81.2 ± 17.7 %) (A5).*

2) To design the feasible algorithms, methodologies or measurements that would be sensitive and accurate enough to capture pathological changes presented in particular speech dimensions.

   - *As a part of our research (A3, A5, A7, A8, B1) several innovative algorithms, methodologies and measurements were designed to allow the evaluation of all speech aspects necessary for precise assessment of hypokinetic, hyperkinetic, spastic and ataxic components of dysarthria. For instance, we designed the algorithm for evaluation of articulation deficiency based on mel-frequency cepstral coefficients (A7), the methodology for assessment of vowel articulation from non-standardized connected utterances such as monolog (A8), or the measurement titled Stress Pattern Index designed to mirror the effect of all distinct acoustic clues exploited during word-stress production (A3).*

3) To relate the potentially observed speech changes to overall motor performance or medication doses in order to provide deeper insight into the pathophysiology of speech disturbances.

   - *A number of correlations were found between clinical characteristics and speech parameters mainly in studies (A1, A2, A4-A7, B1). Considering PD, an adverse effect of prolonged dopaminergic therapy using L-dopa on speech fluency was found in PD patients after 3-6 years of taking medication (A2).*

On the other hand, we found improved or maintained speech performances (related mainly to consonant and vowel articulation, pitch variability and number of pauses) in two-thirds of those PD patients whereas speech deteriorated only in one-third; indicating general positive effect of long-term dopaminergic therapy on MSD in early stages of PD (A4). The extent of speech improvement correlated with L-dopa equivalent dose ($r = 0.66$, $p = 0.008$) as well as with reduction in principal motor manifestations based on the Unified Parkinson's Disease Rating Scale ($r = -0.61$, $p = 0.02$), particularly reflecting treatment-related changes in bradykinesia but not in rigidity, tremor, or axial motor manifestations (A4). Regarding HD, we observed that antipsychotic medication may induce excessive loudness and pitch variations and further exaggerated general problems with speech timing (A6).

4) To critically discuss the revealed findings in the context of wide state-of-the-art.

- *Our findings especially contribute to clarification of previously published, highly inconsistent findings related to effect of long-term usage of dopaminergic medication on dysfluency (A2) as well as related to effect of dopaminergic medication of speech production in general (A4). With respect to dysfluency, we suggested based on our results that not only too high but also extremely low levels of dopamine may lead to different forms of dysfluent events including vocal blocks, prolongations and repetitions (A2). Regarding the effect of L-dopa on speech production in PD, we revealed that after initiation of therapy the speech is improved, however it is slightly continuously deteriorated within following several years, presumably due to disease progression (A4). Finally, we also unified the previous ambiguous findings related to duration of voice onset time, a commonly used parameter for evaluation of consonant articulation, as we suggested the potential relationship between increased/decreased values of voice onset time and particular voice onset time category (B1).*

5) To determine specific dysarthric patterns and estimate their reliability in differentiating between PD, PSP and MSA patients.

- *We found that PD speakers manifest pure hypokinetic dysarthria, whilst MSA speakers demonstrate predominant ataxic dysarthria and PSP speakers show severe deficits in both hypokinetic and spastic elements of dysarthria (A5). Moreover, the combination of five deviant speech dimensions (harsh voice, inappropriate silences, slow alternating motion rates, excess intensity variation and excess pitch variation) was able to separate PD from APS with a very high classification accuracy 95.3 ± 6.4 % (A5). Furthermore, the four deviant speech dimensions including harsh voice, fluency, slow rate and vocal tremor were able to discriminate PSP and MSA subjects with 75.2 ± 13.3 % accuracy (A5). From single parameters, consonant articulation of voiceless plosives turned out to be*

the best for separation of APS from PD ($p < 0.001$) and consonant articulation of voiced plosives for differentiation between MSA and PSP ($p < 0.01$) (B1).

6) To search for possible early markers of PD that would separate HC speakers from de-novo PD patients.

   - *Using measurement of vowel articulation elicited from the speaking task of monologue, we were able to differentiate between controls and de-novo PD patients with classification accuracy up to 80 % (A8). Furthermore, we found a reduced ability to expressed contrastive word-stress in these patients (A3).*

7) To design innovative measurement that would reflect the effect of all main acoustic cues exploited during stress production.

   - *A novel measurement termed Stress Pattern Index was designed and proved its feasibility for evaluation of prosodic changes in untreated de-novo PD patients (A3).*

8) To design methodology for evaluation of imprecise vowel articulation based on spontaneous speech such as monologue.

   - *An innovative 6-step methodology for vowel selection from spontaneous speech and determination of formant frequencies from these vowels was established (A8). The methodology was tested for measurement reliability and showed to have high intra- as well as inter-judge reliability ($r = 0.93$-0.99, $p < 0.001$). Although it has been originally designed based on de-novo PD patients database (A8), it has also been successfully used for evaluation of imprecise vowel articulation in MSA, PSP, HD and CA patients (A1, A5, A6).*

9) To investigate the effect of different speaking tasks on assessment of vowel articulation.

   - *Four speaking tasks including sustained phonation, sentence repetition, reading passage and monologue were compared in order to test their suitability for capturing subtle alterations in vowel articulation of de-novo PD patients (A8). In summary, sustained phonation was found to be inappropriate speaking task for investigation of deficits in vowel articulation in early PD (A8). Contrary, monolog was the most sensitive in differentiating between controls and de-novo PD patients with high classification accuracy up to 80 % (A8).*

10) To examine the effectiveness of a 2-week intensive coordinative motor training on speech production in CA patients.

   - *We found that 12-day rehabilitative program had a mild beneficial effect on speech in CA patients (A1). Immediately after the last training session, slight improvements in overall speech performance were evident in all 10 patients (A1). Furthermore, follow-up assessment performed 4 weeks later revealed that speech improvements were maintained in 90 % of the patients (A1).*

7. Conclusion

Using innovative methods of acoustic analysis it is possible to objectively quantify the effect of different neurological disorders on speech production in patients with various medical diagnoses and disease severities. In particular, we were able to assess a number of speech aspects belonging to different dysarthria subtypes including hypokinetic, hyperkinetic, ataxic and spastic in subjects with PD, HD, MSA, PSP and CA. Furthermore, we managed to detect subtle speech changes related to articulation and contrastive stress production in untreated de-novo PD patients, i.e. patients recorded at the time of the diagnosis before the symptomatic treatment was established. Based on our findings and since each neurologic disease affects speech in a manner that reflects its localization and underlying pathophysiology, we believe that recognition, evaluation and classification of speech disturbances can significantly contribute to early and correct diagnosis of the particular disorder.

Additionally, acoustic analyses of MSD can provide more insights into underlying pathophysiology of such diseases as clearly documented in our study focused on evaluation of speech dysfluencies in PD, where the hypothesis about the connection of stuttering-like behaviour with reduced level of dopamine within the basal ganglia circuit has been at least partially supported.

Finally, accurate evaluation and monitoring of speech abnormalities may be helpful in assessment of treatment efficiency, providing feedback to patients during speech therapy or assist clinicians in making different management decisions. With respect to this goal, we also performed some preliminary experiments as a part of this thesis as we assessed the effect of motor coordinative training in CA patients.

8. Future work

Future research should confirm our previous findings, extend and validate the reliability of algorithms, methodologies and measurements applied for acoustic analysis and further test the potential of objective speech evaluation to serve as a tool for establishing of early diagnosis, separating between different neurological diseases with similar initial clinical symptoms or providing feedback to patients and clinicians during speech therapy.

It would be desirable to verify our previous findings using large homogenous databases, ideally accompanied by other clinical examinations such as functional magnetic imaging resonance or positron emission tomography, since most of our studies (A1-A5, A8, B1) have rather character of pilot studies with datasets counting 10-25 subjects in each patient's group. The large sample sizes would further allow splitting of patients into more specific groups, for instance, according to predominance of motor manifestations (PD tremor dominant vs. PD akinetic-rigid dominant) or disease subtypes (MSA-cerebellar type vs. MSA-parkinsonian type). Research based on such databases is likely to significantly contribute mainly to our knowledge regarding underlying speech-related pathophysiologic mechanisms of studied disorders.

In classical study by Duffy (1), the classification of dysarthria subtypes (ataxic, spastic, hypokinetic, hyperkinetic vs. flaccid) was based on perceptual evaluation of more than 50 different distinguishing speech aspects. However, we are currently capable to precisely objectively quantify only a small proportion of them. Thus, it is necessary to further extend, optimise and validate the existing algorithms and methodologies for evaluation of particular speech aspects and to develop novel acoustic measurements for speech aspects whose evaluation is currently based solely on perceptual methods.

As an example, the speech dimension of reduced stress might be used. Recently, the ability to express word-stress was assessed mainly by perceptual assessments (1) while it has been already shown that changes in expression of word-stress can also been captured by acoustic parameters such as modification of pitch, intensity or duration (74, 75). As a part of this thesis, a novel measurement termed Stress Pattern Index which mirrors the alterations in all these prosodic parameters was designed and proved to be suitable for evaluation of reduced stress in untreated de-novo PD patients (A3). Yet, the feasibility of this measurement needs to be tested for patients with lower or more severe speech severity as well as for different CNS disorders where the disturbed ability to express linguistic stress might be anticipated. In addition, the acoustic analyses are currently only partially automated as they still demand manual control of process. It would be also useful to manage to evaluate the ability to express word-stress from some non-specialized speaking task such as monologue.

To ensure that the measured speech alterations in particular subject are genuinely the result of underlying neuropathological processes, it is essential to know what effect might have the second repetition of speaking task by same person (test-retest) on measurement of individual speech aspect and in what range the performance of HC speakers might be expected. To this extent, the longitudinal studies, monitoring and recording the same patients for several years, should be carried out to test the sensitivity of acoustic measurements and to confirm the previously observed trend in worsening of speech performances due to disease progression. Furthermore, the acoustic investigation of speech performances using large

dataset of HC speakers should be performed to define the effect of age and gender on particular speech parameters. In fact, the natural changes of voice and speech performances in HC population are presented as a consequence of normal aging process due to changes in anatomy and physiology of the speech mechanism, reduced sensory feedback or decreased speed/accuracy of motor control (76, 77). However, such changes are not pathological in its origin and their effects have to be known and well-defined.

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List of author's publications

Publications related to the thesis

A. Publications in journals with impact factor (accepted articles)

(A1) Tykalová T, Pospíšilová M, Čmejla R, Jeřábek J, Mareš P, Rusz J. Speech changes after coordinative training in patients with cerebellar ataxia: a pilot study. Neurological Sciences. 2016;37:293-296. [17 %]

(A2) Tykalová T, Rusz J, Čmejla R, Klempíř J, Růžičková H, Roth J, Růžička E. Effect of dopaminergic medication on speech dysfluency in Parkinson's disease: a longitudinal study. Journal of Neural Transmission. 2015;122:1135-1142. [14 %]

(A3) Tykalová T, Rusz J, Čmejla R, Růžičková H, Růžička E. Acoustic Investigation of Stress Patterns in Parkinson's Disease. Journal of Voice. 2014;28:129.e1-129.e8. [20 %]

(A4) Rusz J, Tykalová T, Čmejla R, Klempíř J, Růžička E. Effects of dopaminergic replacement therapy on motor speech disorders in Parkinson's disease: a longitudinal follow-up study on previously untreated patients. Journal of Neural Transmission. 2016;123:379-387. [20 %]

(A5) Rusz J, Bonnet C, Klempíř J, Tykalová T, Baborová E, Novotný M, Rulseh A, Růžička E. Speech disorders reflect differing pathophysiology in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Journal of Neurology. 2015;262: 992-1001. [13 %]

(A6) Rusz J, Klempíř J, Tykalová T, Baborová E, Čmejla R, Růžička E, Roth J. Characteristics and occurrence of speech impairment in Huntington's disease: possible influence of antipsychotic medication. Journal of Neural Transmission. 2014;121: 655-664. [14 %]

(A7) Rusz J, Klempíř J, Baborová E, Tykalová T, Majerová V, Čmejla R, Růžička E, Roth J. Objective Acoustic Quantification of Phonatory Dysfunction in Huntington's Disease. PLoS One. 2013;8: e65881. [13 %]

(A8) Rusz J, Čmejla R, Tykalová T, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Imprecise vowel articulation as a potential early marker of Parkinson's disease: Effect of speaking task. Journal of the Acoustical Society of America. 2013;134: 2171-218. [11 %]

B. Publications in journals with impact factor (submitted articles)

(B1) Tykalová T, Rusz J, Klempíř J, Čmejla R, Růžička E. Distinct patterns of imprecise consonant articulation among Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Submitted to peer-reviewed journal, June 2016. [20 %]

C. Publications excerpted in Web of Science or Scopus

(C1) Tykalová T, Čmejla R, Růžička E, Rusz J. Comparison of developmental and neurogenic stuttering. In 9th International workshop on models and analysis of vocal emissions for biomedical applications. Firenze: Universita degli Studi, 2015: 125-128. [25 %]

D. Other publications

(D1) Tykalová T, Rusz J, Čmejla R, Růžička E. Využití akustických analýz pro hodnocení hlasu a řeči u Huntingtonovy choroby. In 22nd Annual Conference Proceedings Technical Computing Bratislava 2014.Praha: Humusoft, 2014. [25 %]

(D2) Tykalová T, Rusz J, Čmejla R: Formantové charakteristiky během vyjádření důrazu u Parkinsonovy nemoci. In 21th Annual Conference Proceedings Technical Computing Prague 2013. Praha: Humusoft, 2013. [33 %]

(D3) Tykalová T. Acoustic Investigation of Emotions in Parkinson's Disease. In POSTER 2013 - 17th International Student Conference on Electrical Engineering. Prague: Czech Technical University, 2013. [100 %]

(D4) Tykalová T, Rusz J, Čmejla R, Růžičková H. Acoustic Analysis of Stress Pattern in Parkinson's disease. In Czech-German Workshop on Speech Pathology and Biological Signals - Proceedings. Prague: CTU, Faculty of Electrical Engineering, Department of Circuit Theory, 2012: 64-66. [25 %]

(D5) Tykalová T, Rusz J, Čmejla R, Růžičková H. Akustické analýzy důrazu u Parkinsonovy nemoci. In Sborník 85. akustického semináře. Praha: Nakladatelství ČVUT, 2012: 65-70. [25 %]

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(D8) Rusz J, Klempíř J, Baborová E, Tykalová T, Majerová V, Čmejla R, Růžička E, Roth J. Acoustic Findings of Voice Disorders in Huntington's Disease Compared to Parkinson's Disease. In Models and analysis of vocal emissions for biomedical applications: 8th international workshop. Florencie: Universita di Firenze. 2013;8: 11-14. [14 %]

(D9) Rusz J, Tykalová T, Čmejla R, Růžičková H. Artikulace samohlásek u Parkinsonovy nemoci. In Novinky ve foniatrii. Praha: Nakladatelství Galén, 2012: 121-123. [25 %]

(D10) Rusz J, Novotný M, Tykalová T. Akustické analýzy řeči u Parkinsonovy nemoci. In Sborník 85. akustického semináře. Praha: Nakladatelství ČVUT, 2012: 45-50. [33 %]

Publications not-related to the thesis

E. Publications in journals with impact factor

(E1) Rusz J, Hlavnička J, Tykalová T, Bušková J, Ulmanová O, Růžička E, Šonka K. Quantitative assessment of motor speech abnormalities in idiopathic rapid eye movement sleep behaviour disorder. Sleep Medicine. 2016; 19:141-147. [14 %]

F. Other publications

(F1) Tykalová T, Hlavnička J, Macáková M, Baxa M., Čmejla R., Motlík J., Klempíř J., Rusz J. Grunting in a Genetically Modified Minipig Animal Model for Huntington's Disease: a Pilot Experiments. In The 3rd Conference on Animal Models for Neurodegenerative Diseases - proceedings book. Praha: ČLS JEP, 2015;78: 2S61-2S65. [13 %]

(F2) Tykalová T, Rusz J, Čmejla R. Využití transgenních mini-prasátek jako modelu pro studium Huntingtonovy nemoci. In V. Letní doktorandské dny 2015. Praha: ČVUT FEL, Katedra teorie obvodů, 2015: 59-62. [33 %]

(F3) Čmejla R, Rusz J, Bauer L, Lustyk T., Nejepsová M, Novotný M., Sedlák J., Stráník A., Tykalová T. Analýza patologického hlasu a řeči v laboratoři SAMI ČVUT. In Novinky ve foniatrii. Praha: Nakladatelství Galén, 2012: 28-30. [11 %]

Appendix

Due to publisher rights, the publications of this cumulative doctoral thesis are not included in its electronic version. Please find the abstracts and full articles in the internet using website of our research group http://sami.fel.cvut.cz/publication.htm or the following URLs.

Study (A1)
Tykalová T, Pospíšilová M, Čmejla R, Jeřábek J, Mareš P, Rusz J. Speech changes after coordinative training in patients with cerebellar ataxia: a pilot study. Neurological Sciences. 2016;37: 293-296.
http://link.springer.com/article/10.1007%2Fs10072-015-2379-7

Study (A2)
Tykalová T, Rusz J, Čmejla R, Klempíř J, Růžičková H, Roth J, Růžička E. Effect of dopaminergic medication on speech dysfluency in Parkinson's disease: a longitudinal study. Journal of Neural Transmission. 2015;122: 1135-1142.
http://link.springer.com/article/10.1007%2Fs00702-015-1363-y

Study (A3)
Tykalová T, Rusz J, Čmejla R, Růžičková H, Růžička E. Acoustic Investigation of Stress Patterns in Parkinson's Disease. Journal of Voice. 2014;28: 129.e1-129.e8.
http://www.sciencedirect.com/science/article/pii/S0892199713001379

Study (A4)
Rusz J, Tykalová T, Čmejla R, Klempíř J, Růžička E. Effects of dopaminergic replacement therapy on motor speech disorders in Parkinson's disease: a longitudinal follow-up study on previously untreated patients. Journal of Neural Transmission. 2016;123:379-387.
http://link.springer.com/article/10.1007%2Fs00702-016-1515-8

Study (A5)
Rusz J, Bonnet C, Klempíř J, Tykalová T, Baborová E, Novotný M, Rulseh A, Růžička E. Speech disorders reflect differing pathophysiology in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. Journal of Neurology. 2015;262: 992-1001.
http://link.springer.com/article/10.1007%2Fs00415-015-7671-1

Study (A6)
Rusz J, Klempíř J, Tykalová T, Baborová E, Čmejla R, Růžička E, Roth J. Characteristics and occurrence of speech impairment in Huntington's disease: possible influence of antipsychotic medication. Journal of Neural Transmission. 2014;121: 655-664.
http://link.springer.com/article/10.1007%2Fs00702-014-1229-8

Study (A7)
Rusz J, Klempíř J, Baborová E, Tykalová T, Majerová V, Čmejla R, Růžička E, Roth J. Objective Acoustic Quantification of Phonatory Dysfunction in Huntington's Disease. PLoS One. 2013;8: e65881.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0065881

Study (A8)
Rusz J, Čmejla R, Tykalová T, Růžičková H, Klempíř J, Majerová V, Picmausová J, Roth J, Růžička E. Imprecise vowel articulation as a potential early marker of Parkinson's disease: Effect of speaking task. Journal of the Acoustical Society of America. 2013;134: 2171-218.
http://scitation.aip.org/content/asa/journal/jasa/134/3/10.1121/1.4816541

Study (B1)
Tykalová T, Rusz J, Klempíř J, Čmejla R, Růžička E. Distinct patterns of imprecise consonant articulation among Parkinson's disease, progressive supranuclear palsy and multiple system atrophy. June, 2016.
Since the study (B1) *has not been accepted for final publication yet, it can be found only in paper version of doctoral thesis.*