Abstract: One common finding in Huntington's disease (HD) is related to phonatory disruptions that can be perceptually characterized by harshness, strained-strangled voice quality, and pitch fluctuations. These alterations of voice occur mainly as a consequence of underlying involuntary contractions, variable muscle tone, or even tremor of laryngeal musculature. Recently, several new acoustic analysis methods have been introduced to capture different aspects of these phonatory abnormalities. In this report, we summarize objective acoustic metrics suitable for assessment of phonatory dysfunction and provide their classification accuracy in separation between patients with HD and healthy controls. For this purpose, data consists of 272 phonations collected from 34 individuals with HD and 34 healthy controls. As impairment of phonatory function in HD was found across all investigated measurements, voice analysis may potentially serve as a marker of disease progression.

Keywords: Huntington's disease, hyperkinetic dysarthria, dysphonia, acoustic analysis, classification.

I. INTRODUCTION

Huntington's disease (HD), which is caused by an expansion of the number of CAG repeats located on the short arm of chromosome 4 at 4p16.3 [1,2], is a chronic, degenerative, neuropsychiatric disorder, characterized by progressively increasing of choreiform movements. In the course of the illness, the patients with HD typically develop a distinctive alteration of speech termed as hyperkinetic dysarthria [3]. Hyperkinetic dysarthria in HD is mainly affected by the involuntary contractions of speech mechanism musculature, occurring mainly as a consequence of underlying choreatic movements. Such involuntary contractions of vocal muscles can especially transcend during speaking task such as sustained vowel phonation which demands stable coordination of the jaw, tongue, palate, and facial movements. Recently, we have introduced several metrics that were sensitive to differentiate between healthy and HD voices [4]. The aim of the current study was to review the most successful algorithms to capture phonatory dysfunction in HD and investigate their ability to predict HD membership.

II. METHODS

A. Data

The data for this study were collected as the part of the previous study [4]. From 2011 to 2012, a total of 34 Czech native participants (15 men and 19 women) with genetically verified HD were recruited. Their mean age was 45.2 ± SD 13.3 (range 23–67) years, mean age at HD onset was 39.3 ± 13.5 (14–62) years, mean disease duration 5.9 ± 3.1 (2–16) years, and average number of CAG triplet repeats 46.4 ± 5.8 (40–70). As a control group, 34 persons (15 men and 19 women) of comparable age, mean age 45.5 ± 13.6 (range 24–68) years, with no history of neurological or communication disorders were included. None of the participants had undergone voice therapy and all gave their consent to the vocal tasks and recording procedure. Every subject was instructed to perform sustained phonation of the vowel /a/ and vowel /i/, each one repeated two times.

B. Acoustic measurements

Acoustic analyses were performed using several phonatory measurements in order to investigate different aspects of speech in HD patients and controls. To assess airflow insufficiency, we examined maximum phonation time (MPT) [5], and MPT until the occurrence of the first voice break (MPTvb) [4]. To investigate aperiodicity, we evaluated number of voice breaks (NVB) and degree of voicelessness (DUV) [6]. With respect to irregular
vibrations of vocal folds, we extracted fundamental frequency variations (F0 SD) [7], recurrence period density entropy (RPDE) [8], and pitch period entropy (PPE) [9]. To examine signal perturbations, we investigated jitter and shimmer [6]. To capture problems with increased noise, we calculated harmonics-to-noise ratio (HNR) [6], and fluctuation analysis (DFA) [8]. Finally, we have also introduced new acoustic parameter related to articulation deficiency based upon mel-frequency cepstral coefficients (hereinafter, MFCC) [4], which was defined as the mean of the standard deviations of the 1st-12th MFCCs using the implementation of Brooke's Matlab toolbox [10].

C. Classification experiment

Each designed acoustic feature underwent classification experiment, where support vector machine (SVM) with Gaussian radial basis kernel was used to decide whether the speech performance belongs to HD or control speaker. The cross-validation scheme was applied where all data (136 phonations of HD patients and 136 phonations of controls) were randomly separated into training (80%) and testing (20%) subsets; the process of cross-validation was repeated 20 times for each parameter.

III. RESULTS

According to the SVM classifier, four metrics including MPT, MPT_{VB}, F0 SD, and MFCC achieved greater classification accuracy exceeding 80% in differentiation between HD and control speakers (Table 1). The best single parameter reflecting phonatory dysfunction in HD was found to be MPT_{VB} with classification accuracy of 89.4 ± 3.9% (sensitivity: 91.8 ± 4.9%; specificity: 87.9 ± 5.5%). This parameter represents sudden phonation interruptions and can be associated with motor impersistence, which is the inability to sustain certain simple voluntary act such as keeping the tongue protruded or maintaining a firm grip.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Classification score % (Mean ± SD)</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airflow insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPT</td>
<td>85.5 ± 4.6</td>
<td>3rd</td>
</tr>
<tr>
<td>MPT_{VB}</td>
<td>89.4 ± 3.9</td>
<td>1st</td>
</tr>
<tr>
<td>Aperiodicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVB</td>
<td>65.5 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>DUV</td>
<td>72.8 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>Irregular vibrations of vocal folds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0 SD</td>
<td>84.9 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>RPDE</td>
<td>79.9 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>PPE</td>
<td>68.5 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>Signal perturbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jitter</td>
<td>63.8 ± 5.8</td>
<td>10th</td>
</tr>
<tr>
<td>Shimmer</td>
<td>62.5 ± 5.9</td>
<td>12th</td>
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<tr>
<td>Increased noise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNR</td>
<td>62.9 ± 5.8</td>
<td>11th</td>
</tr>
<tr>
<td>DFA</td>
<td>66.1 ± 5.1</td>
<td>8th</td>
</tr>
<tr>
<td>Articulation deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFCC</td>
<td>88.8 ± 3.6</td>
<td>2nd</td>
</tr>
</tbody>
</table>

MPT = maximum phonation time, MPT_{VB} = maximum phonation time until first break, NVB = number of voice breaks, DUV = degree of voicelessness, F0 SD = variability of fundamental frequency, RPDE = recurrence period density entropy, PPE = pitch period entropy, HNR = harmonics-to-noise ratio, DFA = detrended fluctuation analysis, MFCC = mel-frequency cepstral coefficient.

Table 1: List of classification results of acoustic phonatory measures with mean and standard deviation (SD) values for differentiation between patients with HD and healthy controls.

strangled with irregular pitch fluctuations and arrests [5,11-13]. Considering main phonatory deficits in patients with HD revealed in this study from physiological point of view, we can hypothesize that (a) airflow insufficiency and aperiodicity reflected by sudden phonation interruptions are a consequence of choreic contractions, abnormal muscle tone, or hyper-adduction of vocal folds, (b) articulation deficiency is mainly caused by problems in coordination of articulators including misplacement of tongue, lips, jaw, and face, whereas (c) irregular vibrations of vocal folds manifested as pitch fluctuations occur as a consequence of inefficient nervous system control.

In fact, recognizing of specific signs of speech and voice disorders can provide important clues about the etiology of the disease, and may be useful in differential diagnosis [3,14,15]. Comparing the current finding of hyperkinetic dysarthria in HD patients to better described hypokinetic dysarthria in Parkinson’s disease (PD) patients, we can note several differences. Both hyperkinetic and hypokinetic dysarthrias manifest decreased quality of voice (breathiness, harshness, hoarseness) [16]. In contrast, the higher incidence of voice breaks seems to be more specific for hyperkinetic dysarthria. Slight misplacement of articulators during phonation captured by MFCC has also been shown in PD...
whereas parkinsonian patients do not manifest such marked pitch fluctuations as observed in HD subjects [7]. Table 2 summarizes main results for HD group and compares it to previous findings in PD group.

V. CONCLUSION

A precise description of vocal patterns may significantly contribute to existing assessment batteries for monitoring disease onset and progression, and may be beneficial in the differential diagnosis of movement disorders. In addition, a qualitative description of voice dysfunction may be helpful to gain better insight into the pathophysiology of the vocal mechanism. In practice, the measurement of speech is non-invasive, fast, easy to apply, and inexpensive. Future studies combining various aspects of voice may extend our knowledge to identify longitudinal changes of phonatory dysfunction in HD patients as well as in subjects at risk for HD.

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INTRODUCTION

Vocalization deficits are common in PD and several studies suggest voice impairments may actually precede the cardinal motor signs [1-5], making it an early marker of disease. These deficits can severely reduce the quality of life for patients. While sensorimotor and cranial sensorimotor deficits can be assessed in rodent models of PD by measuring the intensity and bandwidth of ultrasonic vocalizations (USVs), the use of these methods has been limited due to the complexity of vocalization analysis.

In this study, we used these methods to measure vocalization deficits relevant to PD in rodent models. We investigated the use of cranial sensorimotor function in the early, pre-motor signs of PD using ultrasonic vocalizations as a diagnostic and therapeutic tool.

METHODS

Animals:

Male PINK1 KO and DJ-1 KO rats were generated and maintained on a Long-Evans background strain by SAGE laboratories (Sigma-Aldrich). For the PINK1 experiment, the groups included PINK1 KO-HOM n=16, PINK1 KO-HET n=16, and WT n=16. For the DJ-1 experiment, homozygous (PINK1-HOM), PINK1-HET, and wild-type (WT) rat USVs were analyzed at 2, 4, 6, and 8 months of age.

For the DJ-1 experiment, homozygous (PINK1-HOM), PINK1-HET, and wild-type (WT) rat USVs were analyzed at 2, 4, 6, and 8 months of age. For the DJ-1 experiment, homozygous (PINK1-HOM), PINK1-HET, and wild-type (WT) rat USVs were analyzed at 2, 4, 6, and 8 months of age.

RESULTS

We have shown that cranial sensorimotor function can be assessed in rodent models of PD by measuring the intensity and bandwidth of ultrasonic vocalizations (USVs). These methods have excellent construct validity because they have a strong face validity, as they are similar to vocalization deficits observed in PD as well as deficits seen in the 6-OHDA and alpha-synuclein models of PD. The strength of these models is that they can be used to test the progression of PD over time, as deficits increase with age.

In mice, vocalization deficits have been implicated in PD pathology. We hypothesize that vocalization deficits in rodent models of PD may be due to a dysfunction and increased oxidative stress. Mitochondrial function is critical to PD pathology and has long been implicated in PD pathology. We have shown that PINK1 can function as a mitochondrial sensor for oxidative stress, and that PINK1 KO rats display vocalization impairments as well as potential therapeutic targets for PD.

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REFERENCES