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Speech biomarkers in Huntington disease: a cross-sectional study in pre-symptomatic, prodromal and early manifest stages

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Word count: 3499
Abstract count: 245
Running title count: 37
Number of references: 43
Number of tables/figures:4/2

Running title: Speech abnormalities across HD stages

Keywords: Huntington disease, prodromal biomarker; speech; hyperkinetic dysarthria; acoustic analysis.

Abstract

Background: Motor speech alterations are a prominent feature of clinically manifest Huntington disease (HD). Objective acoustic analysis of speech can quantify speech alterations. It is currently unknown, however, at what stage of HD speech alterations can be reliably detected.

Aim: We explored patterns and extent of speech alterations using objective acoustic analysis in HD and explored correlations to rater-assessed phenotypical features as well to biological determinants of HD.

Methods: Speech samples were acquired from 44 premanifest (29 pre-symptomatic and 15 prodromal) and 25 manifest HD gene expansion carriers, and 25 matched healthy controls. A quantitative automated acoustic analysis of 10 speech dimensions was performed.

Results: Automated speech analysis allowed to differentiate between HD and controls with an area under the curve of 0.74 for pre-symptomatic, 0.92 for prodromal, and 0.97 for manifest stages. In addition to irregular alternating motion rates and prolonged pauses seen only in manifest HD, both prodromal and manifest HD displayed slowed articulation rate, slowed alternating motion rates, increased loudness variability, and unstable steady state position of articulators. In premanifest subjects, speech alteration severity was associated with cognitive slowing ($r=-0.52$, $p<0.001$) and the extent of bradykinesia ($r=0.43$, $p=0.004$). Speech alterations correlated with a measure of exposure to mutant gene products (CAP scores; $r=0.60$, $p<0.001$).

Conclusion: Speech abnormalities in HD are associated with other motor and cognitive deficits and are measurable already in premanifest stages of HD. Therefore, automated speech analysis might represent a quantitative HD biomarker with potential for assessing disease progression.

Introduction

Huntington disease (HD) is a progressive autosomal dominant neurodegenerative disease caused by a cytosine-adenine-guanine (CAG) expansion in the huntingtin (*HTT*) gene (1). Expression of mutant huntingtin gene products results in neuronal dysfunction and premature brain atrophy (2), leading to characteristic motor signs regarded as important criterion for the clinical diagnosis of HD (3), and cognitive and behavioural abnormalities. No disease-modifying treatment is currently available although new therapeutic approaches aiming at lowing levels of mutant huntingtin gene products are currently in development and are being tested in randomized controlled clinical trials (3), (4). These steps towards disease-modifying therapies (DMTs) in HD emphasizes the importance of highly sensitive biomarkers that can quantify subtle disease-associated changes in early stages of HD, as interventions in early HD are likely more promising for the purpose of delaying disease progression (5). Neuroimaging, measurements of neurofilament light protein in blood and cerebrospinal fluid, quantitative motor and cognitive assessments are currently explored to have potential to serve as markers that precede the traditionally defined clinical onset of HD by many years (6), (5).

Speech represents one of the most complex, yet quantifiable motor functions sensitive to damage of neural circuits (7). Imprecise consonants, variable rates, mono-pitch, harsh voice and inappropriate silences are considered as distinctive characteristics of hyperkinetic dysarthria associated with chorea syndromes based on two independent perceptual studies using the Mayo Clinic dysarthria rating scale (8), (9). In addition, findings based on objective acoustic analysis disclosed increased phonatory instability (10), (11), subharmonics (12), (11), syllable repetition instability (13), (14) and intensity variability (15) in manifest HD. Many of these speech abnormalities are likely a reflection/manifestation of involuntary movement patterns that typically predominate in the initial and middle clinical stages of adult onset HD. However,

early on in the disease process abnormal patterns of voluntary movements such as subtle problems with planning, initiating, smoothly executing and terminating intended movements emerge in parallel (16). In addition, premanifest HD gene expansion carriers (HDGECs) perform significantly worse on a range of cognitive measures (5). How cognitive dysfunction and the voluntary motor abnormalities described above affect speech in premanifest stages of HD is not well established. Only a limited number of studies with relatively small group sizes (13), (17), (18), (19) sought to identify the patterns of subtle speech dysfunction in genetically confirmed prodromal HD and reported mostly phonatory and timing abnormalities. Possible speech abnormalities of HDGECs across the full spectrum of early HD (pre-symptomatic, prodromal, and early manifest), covering all stages of the newly proposed HD-Integrated Staging System (HD-ISS) (20) have not yet been investigated.

Methods

Study design

From 2020 to 2021, we enrolled HDGECs and healthy controls at the Huntington Center Ulm, Department of Neurology, Ulm University. All participants in the HD group underwent a genetic test confirming ≥ 36 CAG repeats in one of the *HTT* alleles. The exclusion criteria for HDGECs were history of communication or significant neurological disorders unrelated to HD, non-native German language speaker, and severe intellectual impairment that would interfere with study protocol. For healthy controls, exclusion criteria included a history of neurological or communication disorder and non-native German language speakers.

The clinical examination of HDGECs included demographics, medical history, past and current medication, Unified Huntington's Disease Rating Scale (UHDRS) total motor score (21) and Symbol Digit Modalities Test (SDMT) (22). The CAG-Age-Product (CAP) score was

calculated using the following formula: age x (CAG – 30)/6.49 (23). Years to disease onset (YDO) were estimated for participants with premanifest HD using the formula: 21.54 + exp(9.556 – 0.46 x CAG) (24).

HDGECs were divided into three groups: pre-symptomatic HD (preHD), prodromal HD (proHD), and manifest HD (mHD) based on the proposed criteria by Ross et al. (3). In the preHD group, gene carriers had diagnostic confidence level (DCL) equal 0 or 1 without presence of motor and cognitive signs and symptoms. In the proHD group, gene carriers had DCL 2 or 3 and presented with subtle motor signs, typically with some cognitive alteration compared to matched normal controls. In the mHD group, participants had DCL of 4 and were classified using the UHDRS Total Functional Capacity Rating Scale scores as early HD (score ≥ 7). In addition, following the publication of the HD-ISS (20), HDGECs were divided into four groups: Stage 0 (= far from onset with CAG ≥ 40 only), Stage 1 (= altered biomarkers of pathogenesis using striatal atrophy as landmark), Stage 2 (= displaying a clinical phenotype using Total Motor Score and SDMT as landmark), and Stage 3 (= displaying a decline in function using Total Functional Capacity and Independence Scale as landmarks).

The study was approved by the Ethics Committee of the University of Ulm, Germany (approval number: 381/18) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written, informed consent prior to their inclusion.

Speech recordings

The speech recordings were taken in a room with low ambient noise level with a professional head-mounted condenser microphone (Shure Beta 53, Illinois, United States) (25) . The audio data were sampled at 48 kHz with 16-bit quantization. There were no time constraints imposed upon the recordings. Each participant performed a sustained phonation of the vowel /a/ per one

breath for as long and steadily as possible, fast /ta/ syllable repetition for at least 5 seconds, and standardized reading passage composed of 199 words. Each task was performed twice.

Acoustic speech analysis

We selected 10 speech parameters representing distinct aspects of hyperkinetic dysarthria that are feasible to evaluated using quantitative objective acoustic analysis. These parameters correspond to the perceptual description of the main patterns of hyperkinetic dysarthria associated with chorea based on the Mayo Clinic dysarthria rating scale (8), (9), and were in addition tested in previous pilot studies on acoustic speech abnormalities in prodromal and manifest HD (9-17) (26).

Unstable steady state position of articulators was assessed using standard deviation of power spectral density (stdPSD), *harsh voice* via harmonics-to-noise ratio (HNR) and *pitch breaks* using the proportion of subharmonic intervals (PSI) via a sustained phonation paradigm. *Imprecise consonants* were assessed using the voice onset time (VOT), *slow alternating motion rates* were assessed using the diadochokinetic rate (DDKR), *irregular alternating motion rates* through diadochokinetic irregularity (DDKI), and *increased loudness variability* using standard deviation of speech intensity envelope (stdPWR) via the fast syllable repetition. *Prolonged pauses* using the duration of pause intervals (DPI), *monopitch* was assessed using standard deviation of pitch contour (stdF0) and *slow articulation rate* through the net speech rate (NSR) via reading passage.

Final speech values used for the statistical analysis were calculated as the mean of the two repetitions to provide greater speech assessment stability (25). A list of used parameters and their detailed description can be found in **Table 1**. Comprehensive algorithmic details on individual acoustic measures were reported previously (27). In addition, accuracy of the algorithms for the identification of temporal intervals, pitch sequences, and glottal cycles has

been thoroughly tested in previous studies (28), (27), (29). All analyses were performed in MATLAB® (MathWorks, Natick, MA).

Speech alteration severity analysis

The primary endpoint was the *composite dysarthria index* (CDI, representing the overall severity of speech alteration) which represents a combination of 10 acoustic speech parameters associated with hyperkinetic dysarthria in HD. Thereby, all 10 speech parameters were converted to z-scores using the mean and standard deviation of the control group. To ensure correct directionality, the z-scores were reversed for those measures in which lower raw scores were associated with greater severity in speech abnormalities (i.e., HNR, DDKR, stdF0, NSR). We estimated CDI as the mean value from 10 calculated z-scores.

In addition, we created a supporting, rater-based composite score to evaluate elements of speech that might not be captured by acoustic analysis called *perceptual dysarthria score* (PDS). The PDS was assessed by three independent Huntington specialists with several years of experience. The perceptual assessment was performed blindly on randomised audio data from all four participant groups using all vocal paradigms. The perceptual criteria for dysarthria outlined by Darley et al. (8) were used to judge the presence and severity of speech abnormalities. The PDS was ranked as: 0 = normal, 1 = slight abnormal signs with at least one distinctive speech dimension affected, 2 = mild dysarthria, 3 = moderate dysarthria, and 4 = severe dysarthria. We estimated the inter-rater reliability using the two-way mixed single score. Intra-class correlation reached a value of 0.75 (30) for Huntington specialists; thus, the final consensus PDS was calculated as the median value of three perceptual ratings.

Statistical Analysis

Given the large effect size (Cohen's f of > 0.4) observed for overall severity of speech alteration between HD patients and controls in a previous study (15) and considering an error probability of α set at 0.05 and a false negative rate β set at 0.2 (i.e., power of 0.8) for the CDI, the a-priori power analysis indicated a recommended minimum overall sample size of 73 for four groups (80 for five groups) (31).

As the Kolmogorov-Smirnov test showed that the acoustic features were normally distributed, we performed analysis of covariance (ANCOVA) with age set as covariate to evaluate group differences. We addressed multiple comparisons via Bonferroni adjustment and determined thresholds of $p<0.05$ for the primary endpoint CDI (and the PDS) and $p<0.005$ (0.05/10) for individual speech parameters. Post-hoc comparisons using Fisher least-squares differences were applied only for significant measures on the omnibus test.

Informed by primary hypothesis results, we performed a binary logistic regression followed by a leave-one-subject-out cross-validation to assess the ability of a combination of acoustic features to distinguish between groups (i.e., accuracy, sensitivity, and specificity). As an overall indication of diagnostic accuracy, we reported the area under the curve (AUC) obtained from the receiver operating characteristic curve. We iterated through all possible features combinations for the one yielding the highest AUC.

To provide further insights into the features of speech dysfunction in HD and minimize the possibility of Type I errors, speech performance was related to three representative clinical scales including chorea (chorea subscore, composed of the items of the UHDRS chorea subscale), bradykinesia (bradykinesia subscore, composed of the UHDRS finger taps, pronate-supinate hands, bradykinesia and rigidity subitems), and cognition (processing speed by SDMT) separately for premanifest (merged preHD and proHD groups) and manifest (mHD

group) stages. In addition, we explored the relationship between CAP scores and CDI, eliminating the need to bin participants into groups based on clearly defined but somewhat subjective and arbitrary criteria like DCL. Non-parametric Spearman partial correlation coefficient with age set as covariate was preferred due to violations of normality of clinical data in premanifest stages. The significance level was set at $p<0.05$ for the primary endpoint CDI (and the PDS) and at $p<0.005$ (0.05/10) for the individual speech parameters.

Results

Clinical data

A total of 69 HDGECs were included in this study, consisting of 29 preHD subjects (10 men) with mean age of 39.0 (SD 10.6, range 24-62) years, 15 proHD subjects (7 men) with mean age of 42.1 (SD 11.4, range 22-62) years, and 25 mHD subjects (10 men) with mean age of 47.3 (SD 12.5, range 22-76) years (**Table 2**). Out of 69 HDGECs, neuroleptics (Quetiapin, Olanzapin, Zyprexa, Promethazin, Aripiprazol, Sulpirid) were used by 4 mHD, 2 preHD, 1 proHD, antichoreas (Tetrabenazin, Tiaprid) by 5 mHD, and sedatives (Zopiclon, Zoldem) by 1 mHD and 1 preHD participants. In addition, a total of 63 HDGECs fulfilled the HD-ISS criteria, consisting of 7 Stage 0, 24 Stage 1, 10 Stage 2, and 22 Stage 3 subjects (**Table S1**); 3 cannot be classified by HD-ISS and 3 have a CAG below 40 and therefore HD-ISS does not apply. As a healthy control group, 25 participants (10 men) with mean age of 46.7 (SD 13.5, range 27-78) years were recruited.

Group differences

Compared to controls, CDI was larger in the groups of mHD ($p<0.001$) and proHD ($p<0.001$), but not in preHD ($p=0.30$) as a group (**Figure 1**). Similarly, PDS was more pronounced in the

groups of mHD ($p<0.001$) and proHD ($p=0.003$), but did not differ from controls in preHD as a group ($p=0.33$). The similar pattern of increasing CDI across stages 0-3 of HD-ISS was observed with trend toward significance between controls and Stage 1 ($p=0.09$) as well as significant differences between controls and Stage 2 or 3 ($p<0.001$) (**Figure S1**). Perceptual and acoustic speech severity analyses were strongly correlated (CDI vs. PDS: $r=0.77$, $p<0.001$).

Alterations in the speech of HDGECs were observed for 6 out of 10 acoustic parameters (**Table 3, Video 1**). Compared to controls, the mHD group showed unstable steady state position of articulators (stdPSD: $p<0.001$), slow alternating motion rates (DDKR: $p<0.001$), irregular alternating motion rates (DDKI: $p<0.001$), increased loudness variability (stdPWR: $p<0.001$), prolonged pauses (DPI: $p<0.001$), and slow articulation rate (NSR: $p<0.001$). Comparing proHD and controls showed unstable steady state position of articulators (stdPSD: $p=0.01$), slow alternating motion rates (DDKR: $p=0.01$), increased loudness variability (stdPWR: $p=0.01$) and slow articulation rate (NSR: $p=0.009$). The group comparison between preHD and controls did not show individual acoustic parameters to differ significantly.

Sensitivity analysis

Contrasting mHD and controls, the best discrimination accuracy with AUC of 0.97 (accuracy 90%, sensitivity 92%; specificity 88%) was detected using a combination of five parameters including HNR, DDKR, stdPWR, stdF0 and NSR. For proHD compared to controls, the best discrimination accuracy (AUC of 0.92) was achieved using the parameters stdPSD and DDKI (accuracy 83%, sensitivity 85%; specificity 79%). To discriminate between preHD and controls, a combination of HNR and stdF0 yielded the best results with AUC of 0.74 (accuracy 60%, sensitivity 61%; specificity 60%).

Correlations between speech parameters, clinical characteristics and CAP scores

The severity of acoustic speech alteration as measured by CDI in premanifest stages (merged preHD and proHD groups) correlated with the bradykinesia subscore (r=0.43, p=0.004) and SDMT (r=-0.52, p<0.001) whereas CDI in manifest stages (i.e., mHD group) correlated with the chorea subscore (r=0.49, p=0.02), the bradykinesia subscore (r=0.57, p=0.005) and SDMT (r=-0.49, p=0.02). The same significant correlations were observed for the severity of the perceptual speech alteration measured using PDS (**Table 4**). Considering individual acoustic speech parameters, the highest correlations were found for the bradykinesia subscore with increased loudness variability in the premanifest HD group (stdPWR: r=0.52, p<0.001), with prolonged pauses in the mHD group (DPI: r=0.57, p=0.005) and with slow articulation rate in mHD group (NSR: r=-0.62, p=0.002) (**Table 4**). HDGECs with CAP scores of 100 and above (mean CDI 1.95, SD 1.01) compared to HDGECs with CAP scores below 100 (mean CDI 0.63, SD 1.00) showed more severe alterations (p<0.001); the correlation of CDI with CAP scores was also observed (r=0.60, p<0.001) (**Figure 2**).

Discussion

This study provides the first attempt to characterize speech alterations from pre-symptomatic to prodromal to early-stage manifest HD, comparing subjective perceptual analysis by experts head-to-head with objective acoustic analysis. Both types of analysis were mutually supportive in demonstrating dysarthria already in the prodromal stage of HD. Our classification analysis yielding an AUC of 0.74 suggest that subliminal speech abnormalities are already present in a pre-symptomatic stage of HD. The correlations observed with clinical, rater-based scales and with CAP-scores support the concept that objective acoustic analysis may be used to quantify alterations of brain structure and function driven by the progressive disease process in HD. The

results demonstrating graded alterations of speech in a stage-dependent manner are consistent with the notion that a fully automated speech assessment method has potential as quantitative marker of progression of HD, potentially informing future clinical trials aiming at disease modification. In addition, objective quantitative acoustic analysis may aid in refining the definition of landmarks for stage transition in HD (20).

In our study, the main speech dimensions affected in proHD were slow articulation rate, slow alternating motion rates, increased loudness variability and unstable steady state position of articulators. The ROC analysis yielded a very high AUC of 0.92 for the discrimination between proHD and controls, suggesting the presence of considerable speech alteration already before the emergence of motor signs currently widely accepted as criteria for a clinical diagnosis of HD (3). In agreement with the observations presented here, a previous study reported that trained listeners perceived subtle differences in proHD (19). While temporal abnormalities including slow articulation rate and slow alternating motion rates have already been reported in proHD (13), (17), (18), (19), to the best of our knowledge, increased loudness variability and unstable steady state position of articulators have not been described previously in proHD.

Increased loudness variability during the fast syllable repetition paradigm was found to be associated with the extent of bradykinesia in premanifest HD. A similar increased variability in the execution of movements in HD was observed in a range of motor tasks including tapping (32), grasping (33), tongue protrusion (5), gait (34), and reaching (35). Therefore, variability in the loudness of repetitive vocalization expands the family of more variable motor coordination parameters that appears to be a hallmark of HD (32). Unstable steady state position of articulators during sustained phonation has only been reported in manifest stages of HD and was associated with the occurrence of chorea (11). Although we did not find a definite clinical correlate for this speech phenomenon in our premanifest HD cohort, we suggest that unstable

articulatory stability might be considered as precursor of chorea as we observed a trend towards an association between unstable steady state position of articulators and chorea (p=0.04, uncorrected) in our manifest HD group.

For slowness of speech in premanifest HD we found a trend towards a correlation with bradykinesia (p=0.02, uncorrected) and cognitive decline measured by SDMT (p=0.009, uncorrected), a widely-used cognitive measure of processing speed known for its sensitivity in HD (36). This observation is in agreement with a recent report on proHD (19) and with a previous study showing a strong association between slowed articulation rate and processing speed decline in multiple sclerosis (37). Reduced speech rate has also been observed in idiopathic rapid eye movement sleep behaviour disorder (38), a special case of prodromal parkinsonism which is associated with a higher risk of cognitive impairment. Contrary to natural speech rate, reflecting a combination of speech motor execution and cognitive-linguistic processing, diadochokinetic rate measures the motor abilities of the speech articulators and reveals their movement limitations. We may hypothesize that slower alternating motion rates in our premanifest HD patients are mainly related to changes in voluntary motor control, which is partly supported by a trend towards a correlation to the bradykinesia subscore (p=0.02, uncorrected). A previous study showed that reduced maximum speed during oral diadochokinesis in multiple sclerosis was related to greater cerebellar atrophy (39). Since abnormal cerebellar volume has also been observed in early manifest HD (40), its contribution to slow oral diadochokinesis in our HD cohort may need to be considered, aside from the impact of marked basal ganglia dysfunction and of striatal atrophy .

An excellent AUC of 0.97 was observed for discriminating between early-stage HD and control speakers, confirming motor speech disorder as common though underappreciated manifestations of HD (15). Two additional speech abnormalities including irregular alternating motion rates and prolonged pauses were detected, which is well in agreement with previous

studies (15), (14), (13). Instability of syllable repetition appears to be influenced by chorea, which is not surprising as sudden choreatic movements may influence the timing of syllable production. On the other hand, prolongation of pauses in our mHD cohort likely reflect the extent of bradykinesia, and therefore might be linked to difficulties in the initiation of speech and inappropriate timing. In addition, some prolonged pauses might reflect the effects of chorea as well. For instance, chorea blocks/interrupts voluntary movement, or the speaker waits in anticipation of an abnormal movement or until the abnormal movement ceases. Overall, HD speech alterations appeared to develop in parallel with other motor abnormalities, which is in accordance with recent research demonstrating that acoustic speech features allowed the prediction of individual cognitive, motor, and functional scores (41). Interestingly, the perceptual analysis in mHD was more influenced by the extent of chorea than acoustic analysis. Probably, this is mainly caused by a bias in the perceptual analysis of experienced clinicians recognising specific effects involuntary movements on speech in HD patients.

One limitation of the current study is that the classification of participants in several groups based on criteria that imply judgement calls (e.g. DCL) raise the possibility of some questionable classifications of individual HDGECs. Nevertheless, applying a different staging system (ID-ISS) did not change the conclusion that the severity of speech alterations is stage dependent. In addition, the clear correlation of speech alterations with CAP scores stresses that the severity of speech alterations is to driven by a key biological parameter underlying disease progression. Also, some of the HDGECs studied here were subject to pharmacotherapy aiming at symptomatic relief using neuroleptics, antihyperkinetics and sedatives which may impact vocal performance. Finally, we did not collect subjective self-report of voice alterations (e.g., Voice Handicap Index (10)). Therefore, future studies are encouraged to investigate how the self-expressed awareness of change in speech is matched with clinical examination, formal perceptual analysis, and acoustic analysis in premanifest HD.

In conclusion, speech deficits are detectable already in premanifest stages of HD and are associated with other motor and cognitive deficits. Automated acoustic analysis provides an inexpensive, non-invasive way to assess HD repeatedly, without sophisticated technical equipment, that is scalable across languages (42). Future work should focus on extending our findings in a longitudinal design while correlating speech changes with brain structures by MRI.

Acknowledgements

Our study would not be possible without the vital contribution of the research participants. We thank all the people within the HD community who have contributed to our study.

Conflict of Interest

The authors have nothing to disclose.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Funding

This study was supported by the National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Funded by the European Union – Next Generation EU), Czech Ministry of Health (grants nr. MH CZ–DRO-VFN64165), Czech

Technical University in Prague (grant SGS "Biological Signal Analysis, Modelling, and Interpretation"), and Czech Ministry of Education - project Cooperatio LF1, research area Neuroscience. Several authors of this publication (AM, GBL) are members of the European Reference Network for Rare Neurological Diseases - Project ID No 739510.

Authors' Roles

Tomas Kouba was responsible for conception and execution of the research project; data analysis; design of the statistical analysis; and writing of the manuscript.

Wiebke Frank was responsible for conception, organization and execution of the research project and critique of the manuscript.

Tereza Tykalova was responsible for execution of the research project; review and critique of the manuscript.

Alzbeta Mühlbäck was responsible for execution of the research project; review and critique of the manuscript.

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G. Bernhard Landwehrmeyer was responsible for conception and execution of the research project; securing funding; review and critique of the manuscript.

Jan Rusz was responsible for conception and execution of the research project; design of the statistical analysis; securing funding; and writing of the manuscript.

References

(1) MACDONALD, M. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* [online]. 1993, **72**(6), 971-983 [cit. 2022-12-01]. ISSN 00928674. Dostupné z: doi:10.1016/0092-8674(93)90585-E

(2) BATES, Gillian P., Ray DORSEY, James F. GUSELLA et al. Huntington disease. *Nature Reviews Disease Primers* [online]. 2015, **1**(1), 10 [cit. 2022-12-01]. ISSN 2056-676X. Dostupné z: doi:10.1038/nrdp.2015.5

(3) ROSS, Christopher A., Ralf REILMANN, Francisco CARDOSO et al. Movement Disorder Society Task Force Viewpoint: Huntington's Disease Diagnostic Categories. *Movement Disorders Clinical Practice* [online]. 2019, **6**(7), 541-546 [cit. 2022-05-06]. ISSN 2330-1619. Dostupné z: doi:10.1002/mdc3.12808

(4) TABRIZI, Sarah J, Carlos ESTEVEZ-FRAGA, Willeke MC VAN ROON-MOM et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. *The Lancet Neurology* [online]. 2022, **21**(7), 645-658 [cit. 2022-12-01]. ISSN 14744422. Dostupné z: doi:10.1016/S1474-4422(22)00121-1

(5) TABRIZI, Sarah J, Douglas R LANGBEHN, Blair R LEAVITT et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *The Lancet Neurology* [online]. 2009, **8**(9), 791-801 [cit. 2021-12-15]. ISSN 14744422. Dostupné z: doi:10.1016/S1474-4422(09)70170-X

(6) SCAHILL, Rachael I, Paul ZEUN, Katherine OSBORNE-CROWLEY et al. Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington's disease Young Adult Study (HD-YAS): a cross-sectional analysis. *The Lancet Neurology* [online]. 2020, **19**(6), 502-512 [cit. 2021-12-15]. ISSN 14744422. Dostupné z: doi:10.1016/S1474-4422(20)30143-5

(7) *Duffy JR. Motor Speech Disorders: Substrates, Differential Diagnosis and Management*. 4th ed. St. Louis: Mosby, 2019. ISBN 9780323530545.

(8) DARLEY, Frederic L., Arnold E. ARONSON a Joe R. BROWN. Differential Diagnostic Patterns of Dysarthria. *Journal of Speech and Hearing Research* [online]. 1969, **12**(2), 246-269 [cit. 2022-01-25]. ISSN 0022-4685. Dostupné z: doi:10.1044/jshr.1202.246

(9) DIEHL, Sarah K., Antje S. MEFFERD, Ya-Chen LIN, Jessie SELLERS, Katherine E. MCDONELL, Michael DE RIESTHAL a Daniel O. CLAASSEN. Motor speech patterns in Huntington disease. *Neurology* [online]. 2019, **93**(22), 2042-2052 [cit. 2022-01-25]. ISSN 0028-3878. Dostupné z: doi:10.1212/WNL.0000000000008541

(10) VELASCO GARCÍA, María Jesús, Ignacio COBETA, Gonzalo MARTÍN, Hortensia ALONSO-NAVARRO a Félix Javier JIMENEZ-JIMENEZ. Acoustic Analysis of Voice in Huntington's Disease Patients. *Journal of Voice* [online]. 2011, **25**(2), 208-217 [cit. 2022-01-25]. ISSN 08921997. Dostupné z: doi:10.1016/j.jvoice.2009.08.007

(11) RUSZ, Jan, Jiří KLEMPÍŘ, Eva BABOROVÁ et al. Objective Acoustic Quantification of Phonatory Dysfunction in Huntington's Disease. *PLoS ONE* [online]. 2013, **8**(6) [cit. 2022-01-25]. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0065881

(12) RAMIG, Lorraine A. Acoustic Analyses of Phonation in Patients with Huntington's Disease. *Annals of Otology, Rhinology & Laryngology* [online]. 1986, **95**(3), 288-293 [cit. 2022-01-25]. ISSN 0003-4894. Dostupné z: doi:10.1177/000348948609500315

(13) KAPLOUN, L.R., J.H. SAXMAN, Paula WASSERMAN a Karen MARDER. Acoustic analysis of voice and speech characteristics in presymptomatic gene carriers of Huntington's disease: Biomarkers for preclinical sign onset?: Biomarkers for preclinical sign onset?. *Journal of Medical Speech-Language Pathology*. 2011, **19**, 49-63.

(14) SKODDA, Sabine, Uwe SCHLEGEL, Rainer HOFFMANN a Carsten SAFT. Impaired motor speech performance in Huntington's disease. *Journal of Neural Transmission* [online]. 2014, **121**(4), 399-407 [cit. 2022-01-25]. ISSN 0300-9564. Dostupné z: doi:10.1007/s00702-013-1115-9

(15) RUSZ, Jan, Jiří KLEMPÍŘ, Tereza TYKALOVÁ, Eva BABOROVÁ, Roman ČMEJLA, Evžen RŮŽIČKA a Jan ROTH. Characteristics and occurrence of speech impairment in Huntington's disease: possible influence of antipsychotic medication. *Journal of Neural Transmission* [online]. 2014, **121**(12), 1529-1539 [cit. 2022-01-25]. ISSN 0300-9564. Dostupné z: doi:10.1007/s00702-014-1229-8

(16) THOMPSON, P.D., A. BERARDELLI, J.C. ROTHWELL, B.L. DAY, J.P.R. DICK, R. BENECKE a C.D. MARSDEN. THE COEXISTENCE OF BRADYKINESIA AND CHOREA IN HUNTINGTON'S DISEASE AND ITS IMPLICATIONS FOR THEORIES OF BASAL GANGLIA CONTROL OF MOVEMENT. *Brain* [online]. 1988, **111**(2), 223-244 [cit. 2022-12-01]. ISSN 0006-8950. Dostupné z: doi:10.1093/brain/111.2.223

(17) VOGEL, Adam P., Christopher SHIRBIN, Andrew J. CHURCHYARD a Julie C. STOUT. Speech acoustic markers of early stage and prodromal Huntington's disease: A marker of disease onset?. *Neuropsychologia* [online]. 2012, **50**(14), 3273-3278 [cit. 2022-01-25]. ISSN 00283932. Dostupné z: doi:10.1016/j.neuropsychologia.2012.09.011

(18) SKODDA, Sabine, Wenke GRÖNHEIT, Carsten LUKAS, Barbara BELLENBERG, Sarah M. VON HEIN, Rainer HOFFMANN a Carsten SAFT. Two different phenomena in basic motor speech performance in premanifest Huntington disease. *Neurology* [online]. 2016, **86**(14), 1329-1335 [cit. 2022-01-25]. ISSN 0028-3878. Dostupné z: doi:10.1212/WNL.0000000000002550

(19) CHAN, Jess C.S., Julie C. STOUT, Christopher A. SHIRBIN a Adam P. VOGEL. Listener Detection of Objectively Validated Acoustic Features of Speech in Huntington's Disease. *Journal of Huntington's Disease* [online]. 2022, **11**(1), 71-79 [cit. 2022-08-01]. ISSN 18796397. Dostupné z: doi:10.3233/JHD-210501

(20) TABRIZI, Sarah J, Scott SCHOBEL, Emily C GANTMAN et al. A biological classification of Huntington's disease: the Integrated Staging System. *The Lancet Neurology* [online]. 2022, **21**(7), 632-644 [cit. 2022-12-01]. ISSN 14744422. Dostupné z: doi:10.1016/S1474-4422(22)00120-X

(21) Unified Huntington's disease rating scale: Reliability and consistency. *Movement Disorders* [online]. 1996, **11**(2), 136-142 [cit. 2022-05-06]. ISSN 0885-3185. Dostupné z: doi:10.1002/mds.870110204

(22) SMITH, A. The Symbol-Digit Modalities Test: A neuropsychologic test of learning and other cerebral disorders. *Learning Disorders: Special Child Publications*. 1968, **1968**(3), 8.

(23) WARNER, John H., Jeffrey D. LONG, James A. MILLS, Douglas R. LANGBEHN, Jennifer WARE, Amrita MOHAN a Cristina SAMPAIO. Standardizing the CAP Score in Huntington's Disease by Predicting Age-at-Onset. *Journal of Huntington's Disease* [online]. 2022, **11**(2), 153-171 [cit. 2022-11-05]. ISSN 18796397. Dostupné z: doi:10.3233/JHD-210475

(24) LANGBEHN, Douglas R., Michael R. HAYDEN a Jane S. PAULSEN. CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* [online]. 2010, **153**(2), 397-408 [cit. 2022-05-06]. ISSN 15524841. Dostupné z: doi:10.1002/ajmg.b.30992

(25) RUSZ, Jan, Tereza TYKALOVA, Lorraine O. RAMIG a Elina TRIPOLITI. Guidelines for Speech Recording and Acoustic Analyses in Dysarthrias of Movement Disorders. *Movement Disorders* [online]. 2021, **36**(4), 803-814 [cit. 2021-10-17]. ISSN 0885-3185. Dostupné z: doi:10.1002/mds.28465

(26) RUSZ, Jan, Carsten SAFT, Uwe SCHLEGEL, Rainer HOFFMAN, Sabine SKODDA a Pedro GONZALEZ-ALEGRE. Phonatory Dysfunction as a Preclinical Symptom of Huntington Disease. *PLoS ONE* [online]. 2014, **9**(11) [cit. 2022-07-22]. ISSN 1932-6203. Dostupné z: doi:10.1371/journal.pone.0113412

(27) HLAVNIČKA, Jan. *Automated analysis of speech disorders in neurodegenerative diseases*. Prague, 2018. Ph.D. Thesis. Czech Technical University.

(28) HLAVNIČKA, J., R. ČMEJLA, J. KLEMPÍŘ, E. RŮŽIČKA a J. RUSZ. Acoustic Tracking of Pitch, Modal, and Subharmonic Vibrations of Vocal Folds in Parkinson's Disease and Parkinsonism. *IEEE Access*. 2019, **7**, 150339-150354. ISSN 2169-3536. Dostupné z: doi:10.1109/ACCESS.2019.2945874

(29) HLAVNIČKA, Jan, Roman ČMEJLA, Tereza TYKALOVÁ, Karel ŠONKA, Evžen RŮŽIČKA a Jan RUSZ. Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. *Scientific Reports* [online]. 2017, **7**(1), 10 [cit. 2022-05-06]. ISSN 2045-2322. Dostupné z: doi:10.1038/s41598-017-00047-5

(30) CICCHETTI, Domenic V. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment* [online]. 1994, **6**(4), 284-290 [cit. 2022-11-05]. ISSN 1939-134X. Dostupné z: doi:10.1037/1040-3590.6.4.284

(31) FAUL, Franz, Edgar ERDFELDER, Albert-Georg LANG a Axel BUCHNER. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods* [online]. 2007, **39**(2), 175-191 [cit. 2022-05-06]. ISSN 1554-351X. Dostupné z: doi:10.3758/BF03193146

(32) BECHTEL, N., R. I. SCAHILL, H. D. ROSAS et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. *Neurology* [online]. 2010, **75**(24), 2150-2160 [cit. 2022-08-01]. ISSN 0028-3878. Dostupné z: doi:10.1212/WNL.0b013e3182020123

(33) GORDON, Andrew M., Lori QUINN, Ralf REILMANN a Karen MARDER. Coordination of Prehensile Forces during Precision Grip in Huntington's Disease. *Experimental Neurology* [online]. 2000, **163**(1), 136-148 [cit. 2022-08-01]. ISSN 00144886. Dostupné z: doi:10.1006/exnr.2000.7348

(34) RAO, Ashwini K., Lisa MURATORI, Elan D. LOUIS, Carol B. MOSKOWITZ a Karen S. MARDER. Spectrum of gait impairments in presymptomatic and symptomatic Huntington's disease. *Movement Disorders* [online]. 2008, **23**(8), 1100-1107 [cit. 2022-08-01]. ISSN 08853185. Dostupné z: doi:10.1002/mds.21987

(35) SMITH, Maurice A., Jason BRANDT a Reza SHADMEHR. Motor disorder in Huntington's disease begins as a dysfunction in error feedback control. *Nature* [online]. 2000, **403**(6769), 544-549 [cit. 2022-08-01]. ISSN 0028-0836. Dostupné z: doi:10.1038/35000576

(36) HEIM, Beatrice, Marina PEBALL, Carsten SAFT, Sarah Maria HEIN, Philipp ELLMERER, Johanna Maria PIATER, Klaus SEPPI a Atbin DJAMSHIDIAN. Time will tell: Decision making in premanifest and manifest Huntington's disease. *Brain and Behavior* [online]. 2020, **10**(11), 10 [cit. 2022-08-01]. ISSN 2162-3279. Dostupné z: doi:10.1002/brb3.1843

(37) FRIEDOVA, Lucie, Jan RUSZ, Jiri MOTYL et al. Slowed articulation rate is associated with information processing speed decline in multiple sclerosis: A pilot study. *Journal of Clinical Neuroscience* [online]. 2019, **65**(65), 28-33 [cit. 2022-08-01]. ISSN 09675868. Dostupné z: doi:10.1016/j.jocn.2019.04.018

(38) ILLNER, Vojtěch, Tereza TYKALOVÁ, Michal NOVOTNÝ, Jiří KLEMPÍŘ, Petr DUŠEK a Jan RUSZ. Toward Automated Articulation Rate Analysis via Connected Speech in Dysarthrias. *Journal of Speech, Language, and Hearing Research* [online]. 2022, **65**(4), 1386-1401 [cit. 2022-08-01]. ISSN 1092-4388. Dostupné z: doi:10.1044/2021_JSLHR-21-00549

(39) RUSZ, Jan, Manuela VANECKOVA, Barbora BENOVA et al. Brain volumetric correlates of dysarthria in multiple sclerosis. *Brain and Language* [online]. 2019, **194**(194), 58-64 [cit. 2022-08-01]. ISSN 0093934X. Dostupné z: doi:10.1016/j.bandl.2019.04.009

(40) WOLF, Robert Christian, Philipp Arthur THOMANN, Fabio SAMBATARO, Nadine Donata WOLF, Nenad VASIC, G. Bernhard LANDWEHRMEYER, Sigurd Dietrich SÜßMUTH a Michael ORTH. Abnormal cerebellar volume and corticocerebellar dysfunction in early manifest Huntington's disease. *Journal of Neurology* [online]. 2015, **262**(4), 859-869 [cit. 2022-08-01]. ISSN 0340-5354. Dostupné z: doi:10.1007/s00415-015-7642-6

(41) RIAD, Rachid, Marine LUNVEN, Hadrien TITEUX et al. Predicting clinical scores in Huntington's disease: a lightweight speech test. *Journal of Neurology* [online]. 2022, **2022**(1), 10 [cit. 2022-08-01]. ISSN 0340-5354. Dostupné z: doi:10.1007/s00415-022-11148-1

(42) RUSZ, Jan, Jan HLAVNIČKA, Michal NOVOTNÝ et al. Speech Biomarkers in Rapid Eye Movement Sleep Behavior Disorder and Parkinson Disease. *Annals of Neurology* [online]. 2021, **90**(1), 62-75 [cit. 2022-08-17]. ISSN 0364-5134. Dostupné z: doi:10.1002/ana.26085

Figure legends

Figure 1. Results of acoustic and perceptual severity of speech alteration.

Legend: Group differences with **p < 0.01, ***p < 0.001, whereby the symbols represent mean values and error bars represent standard deviation of the mean. preHD = pre-symptomatic HD gene expansion carriers, proHD = prodromal HD gene expansion carriers, mHD = manifest HD gene expansion carriers.

Figure 2. Correlation analysis between acoustic severity of speech alteration and CAP scores.

Legend: The performance of healthy controls using two standard deviations is depicted by a shaded area. CAG = cytosine-adenine-guanine.

Video legends

Video 1. Composition of audio examples of representative speech abnormalities in patients with manifest HD.

Table 1. Overview of used acoustic features.

Speech dimension	Acoustic feature (unit)	Definition	Hypothesized pathomechanism
Sustained phonation			
Unstable steady state position of articulators	stdPSD (dB)	Standard deviation of power spectral density, defined as the mean value of the standard deviations of different frequency banks.	Involuntary movements cause unstable articulatory stability.
Harsh voice	HNR (dB)	Harmonics-to-noise ratio, defined as the amplitude of noise relative to tonal components.	Reduced rate of airflow and improper control of vocal folds cause increased turbulent noise.
Pitch breaks	PSI (%)	Proportion of subharmonic intervals, defined as the ratio of subharmonic intervals per total duration of all voiced segments.	Asymmetry of vocal fold cycles.
Syllable repetition			
Imprecise consonants	VOT (ms)	Voice onset time, defined as the length of the consonant from initial burst to vowel onset.	Slowing of lip and tongue movements.
Slow alternating motion rates	DDKR (syll/s)	Diadochokinetic rate, defined as the number of syllable vocalizations per second.	Reduced ability of articulatory movements.
Irregular alternating motion rates	DDKI (ms)	Diadochokinetic irregularity, defined as the standard deviation of the time difference between two following syllables.	Inappropriate timing of speech movements.
Increased loudness variability	stdPWR (dB)	Standard deviation of power, defined as the standard deviation of speech intensity envelope.	Inappropriate coordination of speech organs leading to unstable loudness of individual syllables.
Reading passage			
Prolonged pauses	DPI (ms)	Duration of pause intervals, defined as the median length of pause intervals.	Difficult initiation speech and inappropriate timing lead to prolonged pause intervals.
Monopitch	stdF0 (semitones)	Pitch variability, defined as the standard deviation of pitch contour.	Reduced amplitude of vocal cord movements leads to glottal incompetence.
Slow articulation rate	NSR (syll/s)	Net speech rate, defined as the total number of syllables divided by the total duration of speech after removal of pauses.	Impaired control of orofacial muscles leads to a decrease in speech rate.

Table 2. Clinical characteristics of HD gene expansion carriers.

Clinical variable	Controls (n = 25)	preHD (n = 29)	proHD (n = 15)	mHD (n = 25)
Male sex	n = 10	n = 10	n = 7	n = 10
Age (years)	46.7 ± 13.2	39.0 ± 10.6	42.1 ± 11.4	47.3 ± 12.5
CAG	n/a	42.3 ± 2.0	44.3 ± 3.6	45.4 ± 4.4
CAP	n/a	72.7 ± 16.1	87.1 ± 11.4	104.8 ± 11.4
YDO	n/a	12.8 ± 9.5	4.4 ± 6.1	n/a
DCL	n/a	0.14 ± 0.34	1.6 ± 1.2	4.0 ± 0
Total functional capacity	13 ± 0	12.9 ± 0.4	12.3 ± 1.1	11 ± 1.6
UHDRS total motor score	0.0 ± 0.0	0.8 ± 1.4	5.3 ± 4.9	25.2 ± 13.7
UHDRS bradykinesia subscore	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 0.8
UHDRS chorea subscore	0.0 ± 0.0	0 ± 0	0.7 ± 1.0	6.7 ± 4.0
SDMT	53.0 ± 11.2	53.7 ± 12.4	45.4 ± 10.3	27.1 ± 10.5

Data are the mean ± SD (range).

n/a = not applicable, preHD = pre-symptomatic HD gene expansion carriers, proHD = prodromal HD gene expansion carriers, mHD = manifest HD gene expansion carriers, CAG = cytosine-adenine-guanine, CAP = CAG-Age-product (age x [CAG – 30] / 6.49), DCL = diagnostic confidence level, UHDRS = Unified Huntington's Disease Rating Scale, YDO = Years to disease onset (21.54 + exp(9.556 – 0.46 x CAG)), SDMT = Symbol Digit Modalities Test.

Table 3. Results of individual acoustic speech parameters.

Speech feature	controls	preHD	proHD	mHD	ANCOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p-value	Post-hoc significance (least-squares difference)
stdPSD (dB)	1.9 ± 0.4	2.0 ± 0.4	2.3 ± 0.5	2.8 ± 0.7	< 0.001	controls < mHD***, controls < proHD*, preHD < mHD***, proHD < mHD**
HNR (dB)	21.2 ± 3	20.8 ± 2.7	21.4 ± 3.3	19.5 ± 2.8	0.02	
PSI (%)	5.6 ± 12.6	3.9 ± 8	3.3 ± 4.8	6.9 ± 14.8	0.85	
VOT (ms)	26.0 ± 5.2	27.0 ± 7.5	27.5 ± 7.6	30.8 ± 7.6	0.10	
DDKR (syll/s)	6.7 ± 1	6.6 ± 0.8	6.0 ± 0.9	4.6 ± 1.1	< 0.001	controls > mHD***, controls > proHD*, preHD > mHD***, proHD > mHD***
DDKI (ms)	22.6 ± 15.0	25.6 ± 15.7	40.1 ± 18.0	82.5 ± 51.0	< 0.001	controls < mHD***, preHD < mHD***, proHD < mHD***
stdPWR (dB)	2.2 ± 0.7	2.4 ± 1.0	3.2 ± 1.1	3.8 ± 1.9	< 0.001	controls < mHD***, controls < proHD*, preHD < mHD***
DPI (ms)	140 ± 36	141 ± 41	155 ± 35	210 ± 87	< 0.001	controls < mHD***, preHD < mHD***, proHD < mHD*
stdF0 (semitones)	2.9 ± 0.9	2.5 ± 0.9	2.3 ± 0.8	2.3 ± 0.7	0.09	
NSR (syll/s)	5.0 ± 0.6	4.9 ± 0.7	4.4 ± 0.7	3.9 ± 0.8	< 0.001	controls > mHD***, controls > proHD**, preHD > mHD***, preHD > proHD*, proHD > mHD*

*p < 0.05, **p < 0.01, ***p<0.001.
preHD = pre-symptomatic HD gene expansion carriers, proHD = prodromal HD gene expansion carriers, mHD = manifest HD gene expansion carriers, stdPSD = Standard deviation of power spectral density, HNR = Harmonics-to-noise ratio, PSI = Proportion of subharmonic intervals, VOT = Voice onset time, DDKR = Diadochokinetic rate, DDKI = Diadochokinetic irregularity, stdPWR = Standard deviation of power, DPI = Duration of pause intervals, stdF0 = Pitch variability, NSR = Net speech rate, ANCOVA = Analysis of covariance

Table 4. Correlations between speech and clinical metrics for premanifest and manifest stages of HD separately.

Deviant speech dimension (acoustic feature)	Chorea subscore (UHDRS) €	Bradykinesia subscore (UHDRS) £	Cognitive decline (SDMT)
Premanifest HD (n = 44)#			
CDI	0.26 (0.097)	**0.43 (0.004)**	**-0.52 (<0.001)**
PDS	0.28 (0.071)	**0.44 (0.004)**	**-0.49 (0.001)**
stdPSD	0.05 (0.743)	0.17 (0.281)	-0.33 (0.034)
HNR	0.09 (0.594)	0.24 (0.132)	-0.17 (0.294)
PSI	0.05 (0.738)	0.06 (0.722)	0.02 (0.916)
VOT	-0.39 (0.010)	-0.12 (0.443)	0.01 (0.974)
DDKR	-0.13 (0.419)	-0.34 (0.029)	0.28 (0.074)
DDKI	0.04 (0.805)	0.37 (0.017)	-0.30 (0.050)
stdPWR	0.36 (0.019)	**0.52 (<0.001)**	-0.32 (0.038)
DPI	0.38 (0.013)	0.27 (0.090)	-0.21 (0.169)
stdF0	-0.05 (0.735)	0.02 (0.888)	0.13 (0.409)
NSR	-0.32 (0.038)	-0.35 (0.024)	0.40 (0.009)
Early-stage manifest HD (n = 25)			
CDI	**0.49 (0.021)**	**0.57 (0.005)**	**-0.49 (0.021)**
PDS	**0.72 (<0.001)**	**0.73 (<0.001)**	**-0.58 (0.004)**
stdPSD	0.43 (0.044)	0.34 (0.121)	-0.33 (0.138)
HNR	-0.24 (0.282)	0.13 (0.580)	-0.10 (0.675)
PSI	0.39 (0.077)	0.21 (0.345)	-0.34 (0.119)
VOT	0.08 (0.713)	0.21 (0.343)	-0.33 (0.131)
DDKR	-0.14 (0.537)	-0.39 (0.072)	0.44 (0.042)
DDKI	0.52 (0.013)	0.44 (0.042)	-0.53 (0.010)
stdPWR	0.23 (0.298)	0.27 (0.232)	-0.19 (0.397)
DPI	0.10 (0.653)	**0.57 (0.005)**	0.02 (0.946)
stdF0	0.17 (0.452)	0.05 (0.844)	0.04 (0.861)
NSR	-0.37 (0.093)	**-0.62 (0.002)**	0.20 (0.381)

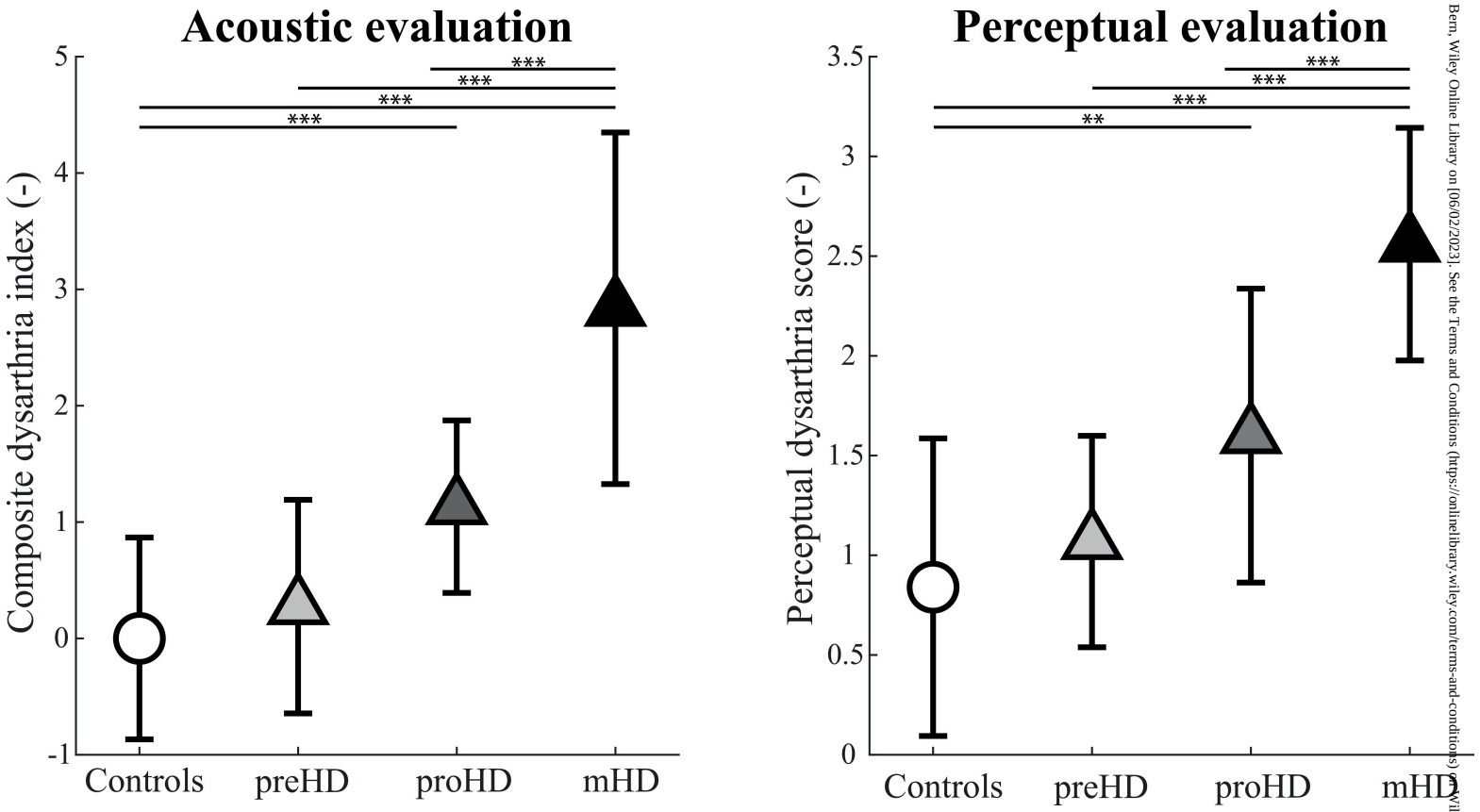
Data are represented by correlation coefficient *r* (p-value). Bold values indicate significant differences with p<0.05 for primary endpoints (CDI and PDS) and p<0.005 for individual acoustic parameters.

Premanifest HD group was defined as joint pre-symptomatic and prodromal HD groups.

€ Chorea subscore (ranging from 0 to 28) was composed from the items of the chorea subscale

£ Bradykinesia subscore (ranging from 0 to 4) was composed of the finger taps, pronate–supinate hands, bradykinesia and rigidity subitems.

CDI = composite dysarthria index, PDS = perceptual dysarthria score, stdPSD = Standard deviation of power spectral density, HNR = Harmonics-to-noise ratio, PSI = Proportion of subharmonic intervals, VOT = Voice onset time, DDKR = Diadochokinetic rate, DDKI = Diadochokinetic irregularity, stdPWR = Standard deviation of power, DPI = Duration of pause intervals, stdF0 = Pitch variability, NSR = Net speech rate, SDMT = Symbol Digit Modalities Test.



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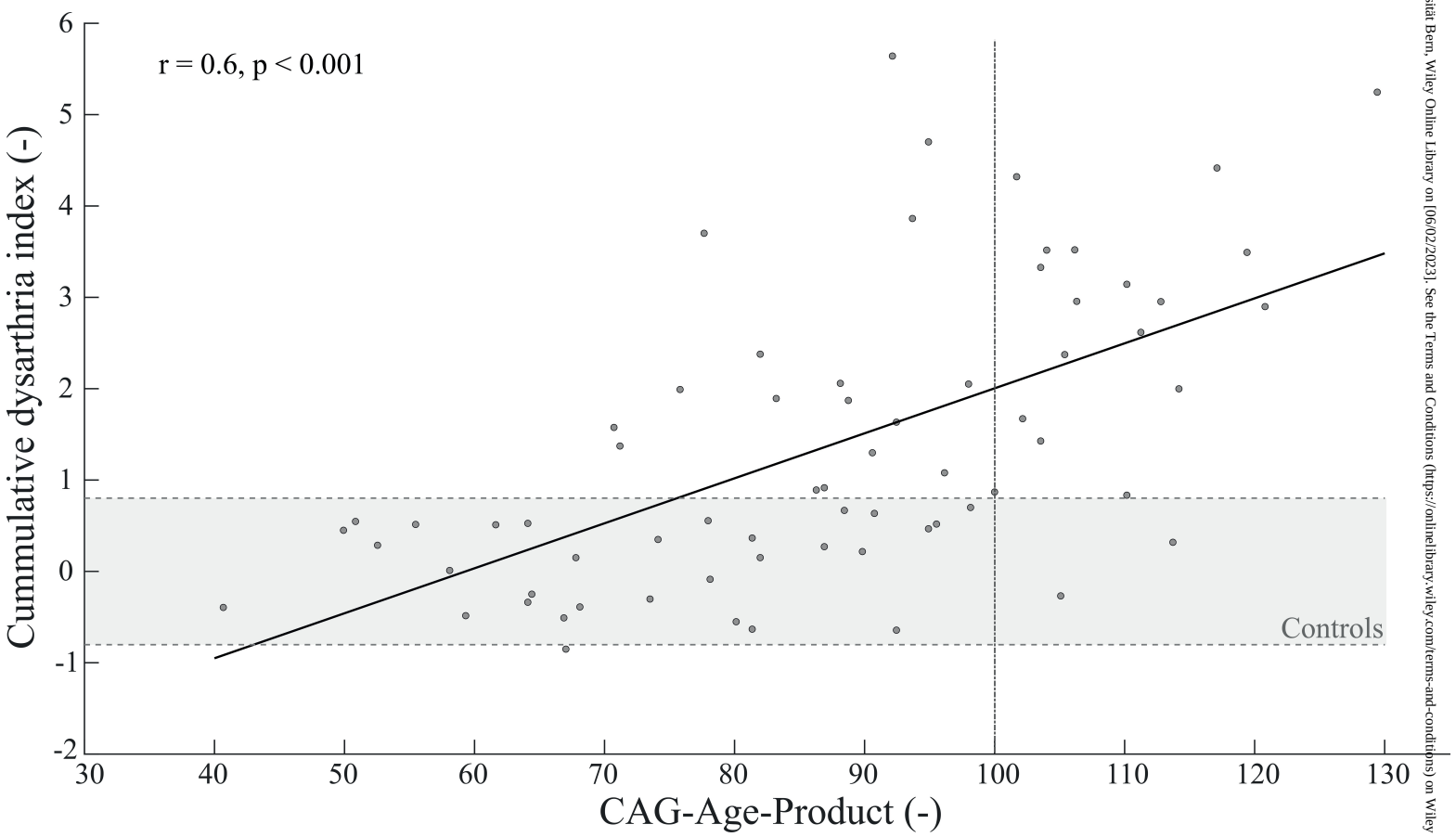

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