Analysis of Interpretable Handwriting Features to Evaluate Motoric Patterns in Different Neurodegenerative Diseases

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***Abstract*— Clinicians currently use handwriting as one of the methods to establish the presence and monitor the progression of neurodegenerative diseases (NDs). While common handwriting evaluation methods are valuable means to detect fine motor and cognitive impairments associated with NDs, these are observer-dependent and subjective. In the present study, we analyzed a broad array of interpretable features, some proposed for the first time in this study, obtained from online handwriting data of participants with NDs and control subjects (CTRL). ND participants have Alzheimer's disease (AD), Parkinson's disease (PD), or Parkinson's disease mimics (PDM). Handwriting data from three different neuropsychological tasks was used: Copy Text task, Copy Cube task, and Copy Image task. Then, we arranged three complementary sets of features and conducted a statistical analysis to test their significance between groups. Overall results suggested that subjects with AD reported a significantly higher ($p < 0.05$) amount of data points and total duration with respect to the CTRL group in almost all the tasks under assessment. On the other hand, subjects with PD showed a significantly lower ($p < 0.05$) horizontal width (both on tablet and in the air). Even though the AD and PDM groups showed a significantly lower velocity and acceleration ($p < 0.05$), their number of inversions in velocity and acceleration was significantly greater ($p < 0.05$), which indicates disfluency in writing. The features that we have used were found to provide good results in differentiating the studied groups and could be considered as part of diagnostic tools for the assessment and monitoring of NDs in clinical trials.**

Keywords*— *neurodegenerative diseases, handwriting, copy tasks, interpretability, kinematics, micrographia..

I. Introduction

Neurodegenerative diseases (NDs) encompass disorders involving brain, nerves and spinal cord which develop later in life and are progressive. NDs are a major cause of death and disability worldwide [1]. Here, we focus on select NDs–Alzheimer's disease (AD) and Parkinson's disease (PD). The gold standard test for AD and PD necessitates pathological evidence of neurodegeneration, usually via autopsy. Both diseases take months or years for accurate diagnosis, resulting in uncertainty and undue burden on patients and their caregivers and delayed implementation of optimal treatment strategies. Various methodologies exist to assess NDs, and many approaches have been proposed to facilitate diagnosis. Specifically, many algorithms have been developed to assess a subject's gait to monitor symptoms or assess disease type or severity [2]. Acoustics is used to extract features across different types of speech tasks [3]. Algorithms for recognising facial expressions are being designed to identify the loss of verbal communication in ND subjects[4]. We propose a set of interpretable features that clinicians can use to back their findings while assessing patients with NDs. Handwriting has been used by doctors to examine a subject's motor and cognitive capabilities to determine cognitive and motor loss associated with ND. However, subjective observation of raw handwriting data may not represent a patient's exact condition. Hence, it becomes essential to extract detailed information in the form of features that can be used to objectively explain behaviors observed in the patients in both a cross-sectional and a longitudinal manner. In addition, many behaviors exhibited by these conditions are observable – like micrographia in Parkinsonian subjects. As a part of this study, we analyzed the online handwriting data from various subjects with different NDs, i.e., AD, PD, and PDM, along with controls (CTRL). We collected data from different handwriting tasks, extracted features, and conducted a statistical analysis to establish the significance of these features between groups.

II. Related Work

The literature concerning handwriting analysis in NDs includes two forms of handwriting data, online and offline. The former consists of time-series signals which capture the writing sequence, while the latter consists of static images. Online handwriting signals are typically captured by a digitizing tablet. By doing so, we can collect the following time sequences: x and y coordinates, in-air/on-tablet status, pressure, azimuth, and tilt. Previous studies have used handwriting data to identify dysgraphia, and classify the severity of PD symptoms [5, 6]. Kinematic features such as velocity, acceleration, and jerk were extracted, Our study focuses on online

Table 1. Demographic and disease severity statistics of the study population. We report sample size, age distribution and scores on the Montreal Cognitive Assessment (MoCA) for each experimental group. In addition, we report Clinical Dementia Rating scale Sum of Boxes (CDR-SB) for the AD group and Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) for the PD and PDM groups

Category	Sample (n)	Age		MoCA		CDR-SB		MDS-UPDRS III	
		avg	range	avg	range	avg	range	avg	range
CTRL	36	66.57	26-94	25.50	16-30	–	–	–	–
AD	11	67.74	58-79	17.45	6-30	4.3	1.5-14	–	–
PD	29	67.74	41-86	25.90	21-30	–	–	22.65	5-52
PDM	9	54.55	27-74	24.73	19-30	–	–	22.5	14-30

handwriting for various tasks of varying complexity levels, including writing a sentence, copying a cube and, lastly, drawing a complex image. Yu et al. [7] attempt to explore the relationship between the clinical aspects and the motor impairments of PD subjects and essential tremors (ET). In this respect, they proposed a new feature called the ratio of deceleration phase (RDP). Thomas et al. [8] discussed fluency features of handwriting, which involve the number of inversions in velocity (NIV) and the number of inversions in acceleration (NIA) profiles in handwriting. For fluent writing, the velocity profile is a bell-shaped curve, while for dysfluent writing one can observe irregularities in the velocity and acceleration profiles. Most of the previous studies focused on analyzing a single ND and a unique neuropsychological task, while in this paper we present features that were significant in distinguishing between different NDs (i.e., AD, PD, PDM) and a CTRL population during the execution of three different tasks.

III. Materials

III-A. Data Set

The data set, NeuroLogical Signals (NLS), is an ongoing multi-modal corpus being collected by the authors of this study. It contains spoken responses, eye movement saccadometry, and handwriting data, among other modalities, collected during the execution of different neuropsychological tasks from CTRL and subjects with different NDs seen at University-based sub-speciality clinics. Clinical patients represent numerous NDs, including, but not limited to, PD, AD, and PDM. All patients were seen by physicians (specifically authors AB, EO, and RS) at Johns Hopkins Medicine and signed informed consent documentation. The handwriting data was collected on a Wacom One tablet with a 250 Hz sampling rate using the software Eye&Pen[9], which records time sequences of both the pen's tip position [x,y] coordinates and on-tablet pressure of the pen tip. The handwriting signals were then manually observed in Eye&Pen to ensure that the signals were properly recorded and the tasks were completed by the subject. Any beginning and ending segments of the recording where the participants were not performing the tasks were manually removed.

III-B. Subject Grouping

In the current study, we included individuals diagnosed with Clinically Established PD, AD, PDM and CTRL participants. The PDM group was comprised of persons whose former, provisional diagnoses included *Possible Parkinson Disease* before their diagnosis was clarified with subsequent testing and included conditions with varying degrees of motor Parkinsonism: Dementia with Lewy Bodies, Multiple System Atrophy, Tourette Syndrome, Dystonia, Spinocerebellar Ataxias and Wilson's disease. Table 1 contains the demographic and disease severity statistics of the different experimental groups.

III-C. Tasks

Handwriting data collected was time-series data for x, y, pressure and timestamp. The NLS data employed in this study contains three different kinds of handwriting tasks - the Copy Text (CT), Copy Cube (CC) and Copy

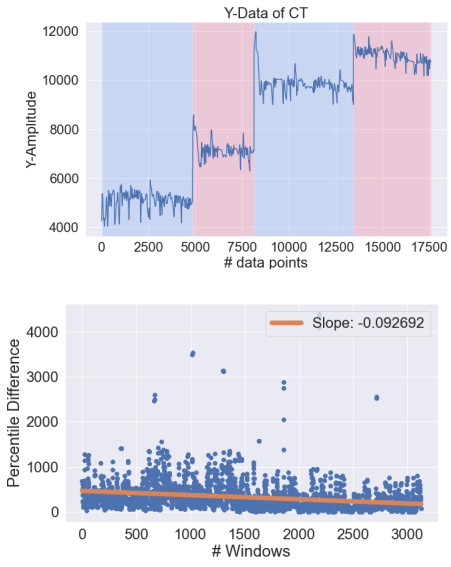

Figure 1. Coordinates of the y-axis for pen position while performing the CT task (top). Scatter plot of the percentile differences in a moving window ($size = 50$, $stepsize = 10$) of the y-axis coordinates, and, a linear regression of the percentile differences is also plotted (bottom)

Table 2. Summary of the features per each analysis type

Analysis Type	Features
Writing	Horizontal (on-tablet) (width [mm], height [mm], length [mm], duration [s], orientation [radians]), Pressure (μ), Data duration ratio, Horizontal (in-air) (width [mm], height [mm], length [mm], Duration [s], Orientation [rad]), Total duration [s], CISP [(mm/s)]
Kinematic	Speed [mm/s], Velocity [(mm/s)] (μ, σ), Horizontal velocity [(mm/sec)] (μ, σ), Vertical velocity [(mm/s)] (μ, σ), Acceleration [(mm/s^2)](μ, σ), Horizontal acceleration [(mm/s^2)](μ, σ), Vertical acceleration [mm/s^2](μ, σ), jerk [mm/s^3](μ, σ), Horizontal jerk [mm/s^3](μ, σ), Vertical jerk [(mm/s^3)](μ, σ), Horizontal normalized jerk (HNJ) (μ, σ), Vertical normalized jerk (VNJ) (μ, σ), Angular velocity [(rad/s)]
Fluency and Micrographia	Number of Inversions in Velocity (NIV), Number of Inversions in Acceleration (NIA), Ratio of Deceleration Phase (RDP), Micrographia (MSlope)

Image (CI) tasks. In the CT task, subjects were asked to write a paragraph that is shown to them. The CT task can be used to assess how a subject is performing in writing a mixture of complex sentences or letters for an extended period of time. We hypothesized that this task could produce features that were indicative of motor-related factors which can be correlated clinically. In the CC task, subjects were asked to draw a cube. A three-dimensional structure such as a cube can help in screening the visual construction abilities of the subjects-a component of the Montreal Cognitive Assessment screening test (MoCA)[10]. In the CI task, subjects were asked to draw a complex image. Some details of the figure might be missed by people with cognitive impairments, including visuospatial abilities, attention, motor planning, working memory and executive functions generally. This task is similar to Rey–Osterrieth complex figure [11] albeit with some modifications. Although the CI task is focused on analyzing cognitive functioning, it was also helpful to reveal motor impairment.

IV. Methods

In this study, we first extracted different features encoding motoric and cognitive information. Then, we performed a statistical analysis to determine which of these features provides a better differentiation between the four experimental groups under assessment.

IV-A. Feature Extraction

A Matlab library of functions and scripts for handwriting feature extraction [12] designed in the Brain Diseases Analysis Laboratory (BDAL) at the Brno University of Technology was applied. This library was designed for digital biomarker feature extraction. Moreover, we designed new sets of features and included them along with the features from BDAL and categorized all together into 3 different types of analysis: writing analysis, kinematic analysis, fluency analysis and micrographia. These features are presented below and summarized in Table 2 along with their respective unit of measurements.

The writing analysis was meant to asses subjects' writing abilities. Its set of features includes the amount of data (AOD) used, pressure (μ), total duration of writing (TD), height (H), length (L), width (W), number of changes in x (NCX) and y (NCY), the relative number of changes in x (RNCX) and y (RNCY), writing tempo (WT), tremor (T), speed frequencies (SF), and Composite Index of Speed and Pressure (CISP) [13]. The height, width and length-related features are further divided into in-air and on-tablet features. This analysis was performed on all three tasks. The features proposed by us within this analysis were AOD and pressure (μ). Where AOD represents the amount of data a subject uses to complete a task, pressure (μ) is the average pressure applied on the tablet over the entire task.

The kinematic analysis assesses a subject's fine hand motor function. Features extracted included: writing speed, velocity, horizontal velocity, vertical velocity, acceleration, horizontal acceleration, vertical acceleration, jerk, horizontal jerk, vertical jerk, horizontal normalized jerk (HNJ), vertical normalized jerk (VNJ), angular velocity[14]. Apart from speed, since these features are not scalar values but vectors, we also calculated the mean of each and performed the analysis on all the three tasks.

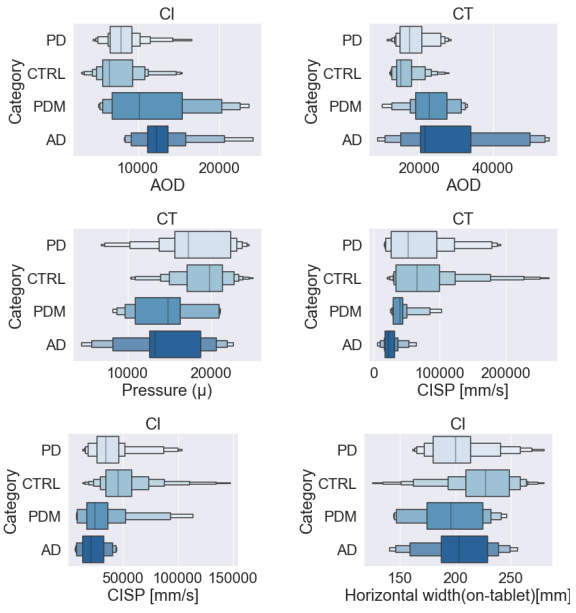

Figure 2. Categorical plots reporting some of the significant features ($p < 0.05$) from the writing analysis

Table 3. Pairwise Kruskal–Wallis H test results for statistically significant features ($p < 0.05$) from the writing analysis

Writing Analysis				
Task	**Sample** (n)		p-**value**	**AUROC**
	1	**2**		
AOD				
CT	CTRL ($n = 36$)	AD ($n = 10$)	0.03	0.78
	CTRL ($n = 36$)	PDM ($n = 9$)	0.03	0.80
CI	CTRL ($n = 36$)	AD ($n = 11$)	0.001	0.87
	PD ($n = 29$)	AD ($n = 11$)	0.003	0.85
Pressure (μ)				
CT	CTRL ($n = 36$)	AD ($n = 10$)	0.046	0.75
	CTRL ($n = 36$)	PDM ($n = 9$)	0.04	0.78
CISP [(mm/s)]				
CT	CTRL ($n = 36$)	AD ($n = 10$)	< 0.001	0.88
	CTRL ($n = 36$)	PDM ($n = 9$)	0.047	0.74
	PDM ($n = 9$)	AD ($n = 10$)	0.02	0.81
	PD ($n = 28$)	AD ($n = 10$)	0.02	0.76
CI	CTRL ($n = 36$)	AD ($n = 11$)	< 0.001	0.86
	CTRL ($n = 36$)	PDM ($n = 9$)	0.02	0.75
	CTRL ($n = 36$)	PD ($n = 29$)	0.01	0.68
	AD ($n = 11$)	PD ($n = 29$)	0.02	0.75
Horizontal Width (on-tablet)				
CI	CTRL ($n = 36$)	PD ($n = 29$)	0.02	0.71
Horizontal Width (in-air)				
CI	CTRL ($n = 36$)	PD ($n = 29$)	0.02	0.72
Total Duration				
CI	CTRL ($n = 36$)	AD ($n = 11$)	0.001	0.83
	PD ($n = 29$)	AD ($n = 11$)	0.004	0.83

The fluency analysis was meant to assess the ease in performing a handwriting task. Several measures can be used to define fluency, such as the NIV, NIA, and RDP. NIV and NIA are the number of local extrema in the velocity and acceleration profiles [8]. Micrographia is a symptom commonly found in PD, but also in AD, in which handwriting gets smaller and cramped [15] as a sentence or a paragraph is written–the pathophysiology of this is debated and may be mediated by different factors in PD (i.e.*bradykinesia*) than AD [16].

Micrographia is common but not universal in PD, but noted in 50-60% of the population [17]. To analyze micrographia, we propose a new feature to selectively characterize this condition in subjects with NDs. We did so by measuring the amplitude in the *y*-axis data and tracking if it is decreasing along the end of the task. This feature was developed uniquely for the CT task. Figure 1 (top) represents the data along Y-axis for the the subject's task. We created a moving window of size 50 samples with a step size of 10 samples which moves through the entire data along Y-axis and calculates the difference between the 90^{th} and 10^{th} percentile of the amplitudes in each window. This helps in ignoring the outliers in the data. A scatter plot of these differences is plotted and then a linear line is fitted to regress these points as shown in the Figure 1 (bottom). The slope of this line is used as a feature for micrographia, and we named this feature as *MSlope*.

IV-B. Statistical Analysis

We applied our feature extraction pipeline using the techniques introduced in Section IV-A. Then, we conducted pair-wise Kruskal–Wallis H-tests for each family of features to determine if there were any statistically significant differences between experimental groups per each feature. The Kruskal-Wallis test is a non-parametric test whose null hypothesis is that the mean ranks of the groups are the same. To control for false discovery rate (FDR), we applied Benjamini–Hochberg correction to each pair-wise comparison for each family of features [18]. The error rate, α was set to 0.05. For each significant comparison, we report the corresponding $p-value$ and the area under the ROC curve (AUROC), as a criterion to measure the feature's discriminative ability [19].

V. Results and Discussion

Results for each of the three types of analysis conducted (i.e., writing, kinematic, fluency and micrographia) are summarized in Tables 3, 4, 5 respectively, and commented separately in the sections below. Features not reported in Tables 3, 4, 5 did not result to be significant between any pair.

V-A. Writing Analysis

The categorical plots reported in Figure. 2 represent the significant features ($p < 0.05$) from the writing analysis. First, the AOD was significantly greater relative to the CTRL group ($p < 0.05$) for AD and PDM groups in the CT task, and for PD and AD groups in the CI task.

Table 4. Pairwise Kruskal–Wallis H test results for statistically significant features ($p < 0.05$) from the kinematic analysis

Kinematic Analysis [14]				
Task	**Sample** (n)		p-**value**	**AUROC**
	1	**2**		
Velocity (μ)				
CI	CTRL ($n = 36$)	AD ($n = 11$)	< 0.001	0.89
	PD ($n = 29$)	AD ($n = 11$)	0.004	0.88
CT	CTRL ($n = 36$)	PDM ($n = 9$)	0.04	0.80
Acceleration (μ)				
CI	CTRL ($n = 36$)	AD ($n = 11$)	0.01	0.80
	CTRL ($n = 36$)	PDM ($n = 9$)	0.02	0.86
	PD ($n = 29$)	PDM ($n = 9$)	0.025	0.90
	PD ($n = 29$)	AD ($n = 11$)	0.01	0.83
CC	PD ($n = 15$)	AD ($n = 14$)	0.01	0.85
Horizontal normalized jerk (HNJ) (μ)				
CI	CTRL ($n = 36$)	AD ($n = 11$)	0.001	0.83
	PD ($n = 29$)	AD ($n = 11$)	0.01	0.76
CT	PDM ($n = 9$)	CTRL ($n = 36$)	0.046	0.76
CC	PD ($n = 15$)	AD ($n = 14$)	0.005	0.89
Vertical normalized jerk (VNJ) (μ)				
CI	CTRL ($n = 36$)	AD ($n = 11$)	0.001	0.83
	PD ($n = 29$)	AD ($n = 11$)	0.01	0.75
Speed				
CI	CTRL ($n = 36$)	AD ($n = 11$)	< 0.001	0.91
	PD ($n = 29$)	AD ($n = 11$)	0.004	0.86
CT	CTRL ($n = 36$)	PDM ($n = 9$)	0.046	0.80

Table 5. Pairwise Kruskal–Wallis H test results for statistically significant features ($p < 0.05$) from the fluency analysis and micrographia

Fluency Analysis and Micrographia				
Task	**Sample** (n)		p-**value**	**AUROC**
	1	**2**		
NIV acceleration				
CT	CTRL ($n = 36$)	AD ($n = 10$)	0.02	0.76
	CTRL ($n = 36$)	PDM ($n = 9$)	< 0.001	0.80
NIV velocity				
CT	CTRL ($n = 36$)	AD ($n = 10$)	0.02	0.78
	CTRL ($n = 36$)	PDM ($n = 9$)	< 0.001	0.81
MSlope				
CT	CTRL ($n = 36$)	AD ($n = 10$)	0.0457	0.74
	CTRL ($n = 36$)	PDM ($n = 9$)	0.003	0.85
	CTRL ($n = 36$)	PD ($n = 28$)	0.02	0.64

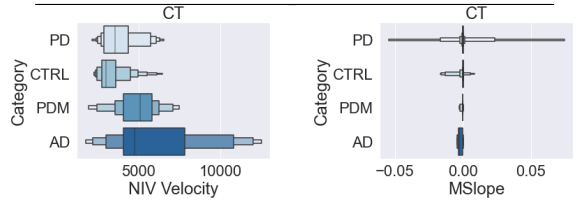

Figure 4. Categorical plots reporting some of the significant features ($p < 0.05$) from the fluency analysis and micrographia

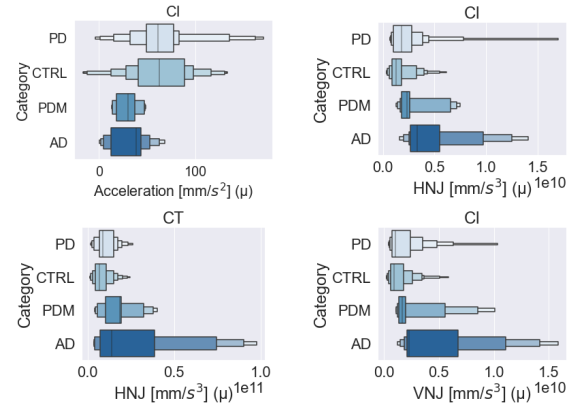

Figure 3. Categorical plots reporting some of the significant features ($p < 0.05$) from the kinematic analysis

CTRL subjects usually needed less AOD to complete a given task than subjects with NDs. This phenomenon may be driven by motoric and cognitive impairments resulting in subjects' hesitation and repetition while writing. Second, the pressure (μ) applied by subjects with NDs was significantly smaller ($p < 0.05$) than CTRL group. Third, CISP were significantly smaller for the AD and PDM groups ($p < 0.05$) relative to PD and CTRL groups. To conclude, the horizontal width was significantly smaller ($p < 0.05$) for the PD group than for the CTRL group, while the total time to complete the task was significantly greater for the AD group ($p < 0.05$) with respect to the PD and CTRL groups. We suspect this discrepancy may be due to overall cognitive impairment in the AD cohort compared to PD, which has a longer disease course and heterogeneous degree of cognitive involvement.

V-B. Kinematic Analysis

The categorical plots reported in Figure. 3 represent the significant features ($p < 0.05$) from the kinematic analysis. The mean velocity was significantly lower ($p < 0.05$) in CI task for the AD group with respect to CTRL and PD, as well as for PDM with respect to CTRL in the CT task. The mean acceleration of PDM was significantly smaller ($p < 0.05$) than that of the other groups. Moreover, HNJ worked well across all three tasks, as it shows significant differences between CTRL vs AD, PD vs AD pairs in the CI task, CTRL vs PDM in the CT task and PD vs AD in the CC task. VNJ worked equally well in differentiating the CTRL vs AD groups and PD vs AD groups. The writing speed was significantly lower ($p < 0.05$) in both CI and CT tasks for the AD and PDM groups compared to PD and CTRL groups. It is important to note that most of the features from the kinematic analysis have good AUCROC scores, which indicates the overall effectiveness of this set of features in differentiating between groups.

V-C. Fluency Analysis and Micrographia

The categorical plots reported in Figure. 4 represent the significant features ($p < 0.05$) from the fluency analysis and micrographia. Subjects with PDM and AD had a significantly greater NIV and NIA ($p < 0.05$) compared to the other two groups though they exhibited less velocity and acceleration Figure. 3. This indicates that these groups were very dysfluent in writing. Further, in the *MSlope* categorical plot in Figure. 4, PD subjects have values far less than zero compared to other groups which indicates micrographia in handwriting, and it shows significant differences between the CTRL group from all the three PD, AD and PDM groups, as evidenced by the p-values indicated in Table 5.

When compared to psychometric testing, handwriting alone has a large number of pre-procedural process issues - concept formulation, praxis development, execution and error detection that disturb the normal execution of handwriting. Alongside, in PD, the severity of micrographia is modulated by the time since dopamine replacement therapy dosing and specific subtype of PD more than overall PD disease severity. Additionally, our PD cohort had a wide age distribution and far less cognitive impairment, which may be protective against micrographia.

VI. Conclusions and Future work

This study analyzes handwriting features that provide good differentiation between several groups of NDs.

While being interpretable and objective, these features can be helpful for clinicians in diagnosing NDs. The three sets of features employed in this study encoded motoric and cognitive functions of handwriting. They can be used to assess the motor and cognitive impairments caused by NDs.

In the writing analysis, subjects with AD reported a significantly higher AOD, and total duration with respect to the CTRL group in almost all the tasks under assessment. On the other hand, subjects with PD had a significantly lower horizontal width (both on-tablet and in-air) while the PDM group had a significantly lower AOD and pressure (μ). In the kinematic analysis, subjects with AD and PDM reported a significantly lower velocity, acceleration and speed and a significantly greater HNJ with respect to the other groups. In addition, in the fluency analysis, NIV acceleration and NIV velocity were significantly greater for the PDM and AD groups, while the MSlope was significantly greater for AD with respect to the CTRL group. Regarding the employed tasks, the CC task provided less information to differentiate groups than the CT or CI tasks, probably because it is a much simpler task and requires less time and complexity to be completed. The study is an analysis of a corpus-in-progress and, as such, is limited by the subjects to date recruited. We continue our efforts to balance experimental groups and further refine the cohorts therein to be more representative of the entirety of the PD, PDM, and AD spectrum. The ultimate goal of this study is to leverage the features presented in this work within a machine learning framework, with the intent to support the development of diagnostic tools meant to perform a precise assessment of NDs and monitor their progression in time.

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