Binocular Discoordination Kinetic Features: A Novel Approach to Evaluate Neurodegenerative Diseases

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***Abstract*— Eye tracking has emerged as a promising technology to assess neurodegenerative diseases (NDs). Although existing literature has extensively explored the potential of eye tracking, there remains a gap in studying binocular coordination. In our study, we present an approach aimed at evaluating Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), and Parkinson's Disease (PD) through the assessment of binocular discoordination. We compare these cohorts with a healthy control group (CTL), and a neurodegenerative control group we have categorized as Parkinson's Disease Mimics (PDM). Our findings indicate that the ND groups demonstrated noticeably poorer binocular coordination functionality than the CTL group, characterized by significantly less convergence to the stimulus during the tests and greater kinetic differences in terms of eye movement velocity and acceleration between the two eyes. By automatically assessing binocular discoordination, our study gains insights into the potential of new features as possible biomarkers to support the diagnosis and monitor the progression of NDs. This novel approach provides a new means for early detection and evaluation of NDs, which may lead to improved patient care and management strategies.**

Keywords*— *Neurodegenerative disease, Alzheimer's disease, Parkinson's disease, eye tracking, binocular coordination

I. Introduction

Neurodegenerative diseases (NDs) occur when neurons lose function over time. The progressive damage to the brain and to the nervous system causes impairment in multiple ways. With a growing portion of the elderly population worldwide, NDs affect millions of people. It is expected that NDs will continue to affect an ever-increasing number of people in the near future [1], [2]. There exist many types of NDs, among which Alzheimer's Disease (AD) and Parkinson's Disease (PD) are the most prevalent types [3]. These diseases lead to cognitive and motor deficits as a result of the progressive deterioration of a shared brain region responsible for both cognitive and cortical motor control functions [4]. Consequently, people affected by NDs commonly experience impaired motor function, significantly impacting their overall quality of life.

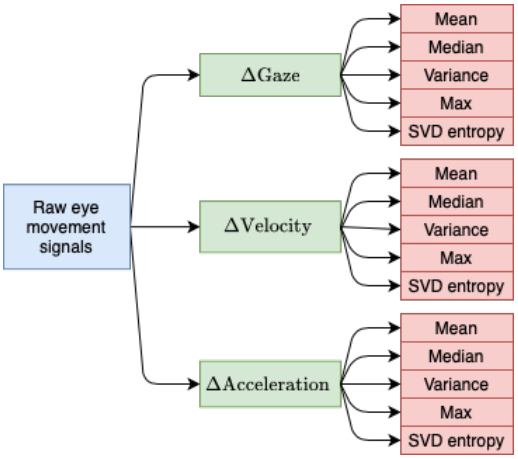

Figure 1. Block diagram of the main components of this study. Three time-series are first obtained from the raw signal. Five features are subsequently computed from each time-series.

The diagnosis of NDs presents a great challenge, even for highly skilled specialists. Existing gold standard diagnostic approaches, which may be effective for a broad spectrum of other diseases, often prove insufficient for efficiently diagnosing NDs [5]. Accurate diagnosis of neurodegenerative diseases normally takes months or years due to the complexity of their nature. One of the major research of interest in this field is to improve early detection methods [6], as early intervention could play a pivotal role in impeding the progression of NDs in the future and improve the quality of life of patients.

Eye movement is regulated by various regions of the brain and the neural system. Each eye movement engages multiple brain areas and neural circuits [7]. As NDs progress, distinct regions of the brain are affected differently, causing specific alterations in eye movement patterns. Large-scale studies have revealed a strong correlation between visual impairment and neurodegeneration of the brain [8]. Moreover, extensive research confirms that patients suffering from NDs experience a gradual decline in ocular functionality over time. The presence of abnormal ocular motor behavior offers an opportunity for early-stage evaluation of NDs [9].

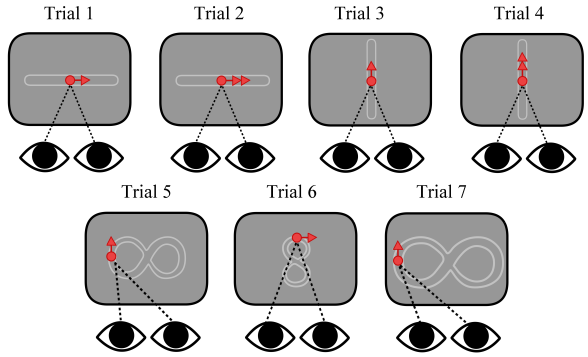

Figure 2. An illustration of the 7 trials considered in this study. Trial 1 and 2 had the same trajectory but different target velocities. Trial 3 and 4 had the same trajectory but different target velocities. Trial 5,6,7 are infinity patterns in different orientations with different amplitudes and target velocities.

The study of impaired eye movement as a means to aid in the diagnosis of NDs has been extensively explored in the existing literature. Frei et al. [10] conducted a systematic review encompassing 29 studies on smooth pursuit eye movement in PD, identifying valuable biomarkers such as directionality, speed, latency, accuracy, and saccadic movements for PD diagnosis. Additionally, common visual problems observed in PD include blurred vision, diplopia, abnormal eye alignment, and convergence insufficiency [11]. Similarly, individuals affected by AD experience comparable visual impairments during the course of the disease. Fernandez et al. [12] suggested that even patients in the early stages of AD exhibit a decrease in visual functionality, and this impairment could provide useful insight into the early detection of AD. Javaid et al. [13] also suggested that ocular motor impairment is a common symptom of AD, and eye tracking holds promise as a useful non-invasive approach for early detection. However, a substantial portion of the existing literature primarily focuses on saccadic or smooth pursuit eye movements of individual eyes. Even though some prior studies in the available literature focused on binocular vision impairment, the majority have concentrated solely on convergence insufficiency [11], [14], [15]. Consequently, the potential impairment of binocular coordination remains largely unexplored in the context of NDs.

In this work, a non-invasive eye tracking technique is employed to capture eye movement during 7 smooth pursuit trials. The collected raw eye movement data contains gaze coordinates from both eyes and their corresponding timestamps. After a pre-processing of the raw eye movement data, three main groups of time-series are obtained. These raw time-series encompass the difference between gaze locations, velocity, and acceleration of the two eyes at each timestamp. A summary of the main components of our study is illustrated in Figure 1. By analyzing these three time-series, this study aims to gain insights into the binocular discoordination associated with NDs and its potential as a source of diagnostic biomarkers.

II. Materials

II-A. Data set

In this work, our primary focus revolves around the examination of MCI, AD, and PD. In this study, we combine the MCI and AD into a single group (AD/MCI) as the MCI individuals have their cognitive impairment due to AD etiology. Additionally, we extend our study to encompass a collection of NDs that mimic Parkinsonian symptoms, and we categorize this group as PDM. To conduct our study, we gathered data from 89 subjects containing 107 recording sessions. Out of these sessions, 18 were follow-up recordings from subjects who were already part of our existing data set. All individuals affected by NDs were examined at Johns Hopkins Medicine, and all participants provided their informed consent. The data collection was approved by the Johns Hopkins Institutional Review Board. Sample size, sex, age distribution, and scores on the Montreal Cognitive Assessment (MoCA) for each group, Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)for the AD/MCI group, and Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) for the PD and PDM groups are reported in Table 1.

II-B. Data collection

The eye tracking data for this study was acquired using the EyeLink Portable Duo, developed by SR Research Ltd. The recording setup consisted of the aforementioned eye tracking device, an infrared flashlight, a computer to control the eye tracker, and a display used to present stimuli during the recording sessions. The display monitor had dimensions of 380×215 *mm* (1920×1080 pixels). The participants' heads were positioned 500 *mm* away from the top of the monitor. During the recording sessions, the head-free mode was employed, in which a sticker was attached to the middle of participants' foreheads to enable eye location. This mode was preferred in our experiment since it allows unrestricted jaw movement, whereas the head-fixed mode requires chin rests. This would affect the tasks in which the participants were asked to speak (although not pertinent to this study). The gaze coordinates were obtained by detecting the pupil and corneal reflex. The eye tracker operated at a sampling rate of 1000 *Hz*. Participants were instructed to maintain stable head positions throughout the experiment. Targets used in all tasks exhibited high contrast against the background color, and consistent brightness was maintained across both the screen and the environment lighting. Calibration was performed at the onset of each session. Additionally, before commencing each task, drift correction was performed to further increase the

Table 1. Demographic and disease severity statistics.

Category	Sample (n)			Age		MoCA		CDR-SB		MDS-UPDRS III	
	tot	female	male	avg	range	avg	range	avg	range	avg	range
CTL	33	14	19	66.30	34-94	26.24	16-30	–	–	–	–
AD/MCI	17	13	3	71.44	58-84	21	2-30	2.5	2.5-2.5	–	–
PD	23	13	10	65.96	41-82	26.23	23-30	–	–	31	10-58
PDM	16	9	7	57.44	31-77	24.4	18-29	–	–	24.33	14-42

accuracy of the eye movement data captured during the experiments.

II-C. Trials

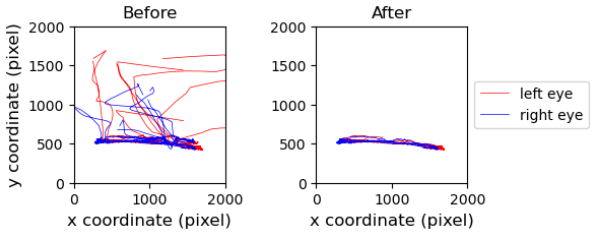

Figure 3. An illustration of the gaze path before and after data cleaning of patient NLS_019 in trial 1.

In this study, we considered 7 smooth pursuit trials, as depicted in Figure 2. The participants were instructed to follow a red dot (target) that is 22 pixels in diameter. The target moved in 7 different trajectories across the 7 trials. 2 trials with horizontal lines, 2 trials with vertical lines, and 3 trials with infinity patterns. The movement pattern was sinusoidal, to avoid abrupt changes in direction and speed. Each trial lasted 18 s. The trials are as follows:

1) Horizontal pursuit 1: The target moved horizontally and parallel to the x-axis at a frequency of 0.2 Hz and an amplitude of 14°.
2) Horizontal pursuit 2: The target moved horizontally and parallel to the x-axis at a frequency of 0.4 Hz and an amplitude of 14°.
3) Vertical pursuit 1: The target moved vertically and parallel to the y-axis at a frequency of 0.2 Hz and an amplitude of 8°.
4) Vertical pursuit 2: The target moved vertically and parallel to the y-axis at a frequency of 0.4 Hz and an amplitude of 8°.
5) Infinity pattern 1: The target moved in an infinity pattern with frequency of 0.2 Hz and amplitude of 12° in the x-axis and frequency of 0.4 Hz and y amplitude of 6°. in the y-axis
6) Infinity pattern 2: The target moved in an vertical infinity pattern with frequency of 0.4 Hz and amplitude of 3° in the x-axis, and frequency of 0.2 Hz and amplitude of 6° in the y-axis.
7) Infinity pattern 3: The target moved in an infinity pattern with frequency of 0.1 Hz and amplitude of 18° in the x-axis and 0.2 Hz and amplitude of 8° in the y-axis.

III. Methods

III-A. Data preparation

Typically, eye movement analysis involves the examination of four primary eye movements: blinks, saccades, smooth pursuit, and fixations. However, in this particular study, the focus is solely on the smooth pursuit eye movements. The reason for this choice is that smooth pursuit eye movements are particularly relevant to the investigation of convergence and kinematic differences between the two eyes. During the smooth pursuit trials, there is consistently a moving target on the screen through the entire trial and there are no sudden changes in the target location and velocity, which could lead to saccades. This makes them suitable for the purposes of this study. The raw data consists of records of the target position on the screen (stimulus) and the associated gaze separately. In order to capture the eye movement at the onset and the end of the trials, the recording session begins before the target appears and ends after the target disappears. As a consequence, there are intervals with no target on the screen, causing the participants' eyes to wander. A data preprocessing step is performed in this study to remove the wandering that is outside of the recording session, as shown in Figure 3. This is performed by trimming the recording session to have the same onset and ending timestamp as the target appearance and disappearance. This procedure is applied consistently to all trials across all participants. Lastly, blinks and saccades are removed using the algorithm suggested by Li et al [16]. We analyze 4 different segments - the entire 18-second recording session, the first 6-second segment, the middle 6-second segment, and the last 6-second segment.

III-B. Feature extraction and analysis

Three time-series related to binocular discoordination are derived from the data: 1): Difference between gaze locations of the two eyes (Δ Gaze). This time-series is calculated as the Euclidean distance between the gaze locations of the two eyes at any given timestamp. 2) Difference in eye velocity at each timestamp (Δ Velocity).

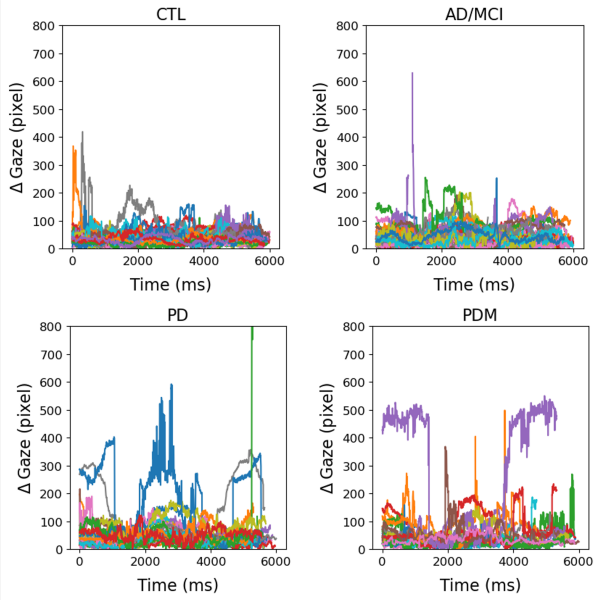

Figure 4. An example of Δ Gaze of the four groups with respect to time. Different colors indicate different participants in their respective group. The CTL group shows lower gaze distance between eyes.

This time-series is generated by initially computing the finite difference of the gaze location with $\Delta t = 1$ ms for both eyes. Following this, the Euclidean norm of the difference between the two eyes' velocity vectors is calculated at any given timestamp. 3) Difference in eye acceleration at each timestamp (Δ Acceleration). This time-series is generated by initially computing the finite difference of the eye velocity with $\Delta t = 1$ ms for both eyes. Following this, the Euclidean norm of the difference between the two eyes' acceleration vectors is calculated at any given timestamp. An example of Δ Gaze for the four cohorts is provided in Figure 4. Subsequently, five features are calculated for each of these time-series: mean, median, variance, max, and singular value decomposition entropy (SVD entropy). The complexity measurement, SVD entropy, is included to capture the more irregular binocular coordination behavior often observed in patients with NDs. The higher this value, the more complex the time-series, as more orthogonal vectors would be needed to explain it. These features are calculated for four different segments: the entire 18-second recording session, the beginning 6-second segment, the middle 6-second segment, and the last 6-second segment respectively. The goal is to evaluate if the beginning, central, or ending parts of the trials contain more information than the rest. For instance, the beginning of the trial contains the segments related to eye movement initiation, which can be important to detect PD as movement initiation is sometimes impaired in people with PD. At the same time, some participants with NDs could be more easily impacted by fatigue at the end of the trials, and the resulting features could provide higher differentiation with the control group.

Table 2. Kruskal-Wallis H test results with Benjamini–Hochberg correction method of all significant features ($p < 0.05$)

Trial	Feature	Pair	p-value
Δ Gaze			
1	Variance	CTL-AD/MCI	0.02
		CTL-PD	0.01
		CTL-PDM	0.006
	Max	CTL-PDM	0.003
7	Variance	CTL-AD/MCI	0.003
	Max	CTL-AD/MCI	0.005
Δ Velocity			
1	SVD entropy	CTL-PD	0.002
		CTL-PDM	0.007
		AD/MCI-PD	0.001
		AD/MCI-PDM	0.008
7	Max	CTL-AD/MCI	0.007
Δ Acceleration			
1	Max	CTL-PDM	0.008
		AD-PDM	0.01
	SVD entropy	CTL-PDM	0.002
		AD-PDM	0.003

Following this, Kruskal-Wallis H test [17] with $\alpha = 0.05$ was conducted against a null hypothesis that the median ranks of the groups are equal, and Benjamini–Hochberg correction method [18] is applied to control the false positive rate. The p-values were computed using the Python package developed by Charlier et al. [19].

IV. Results and Discussion

In this section, we report the results for the middle 6-second segment as this is the segment that yielded the most significant difference among the four groups. The middle 6-second segment yielded a total of 15 significant features (p<0.05), while similar but fewer significant features were yielded when considering other segments. The first 6-second segment yielded 9 significant features (p<0.05), the last 6-second segment yielded 7 significant features (p<0.05), and the entire 18-second segment yielded 4 significant features (p<0.05). We hypothesize that this is because participants of all groups require time to start following the target in the first 6-second segment and experience eye fatigue in the last 6-second segment. These factors could impact the eye movements of the participants in all four groups similarly.

The boxplots reported in Figure 5 represent all the significant features (p<0.05). CTL participants exhibited better binocular coordination functionality, demon-

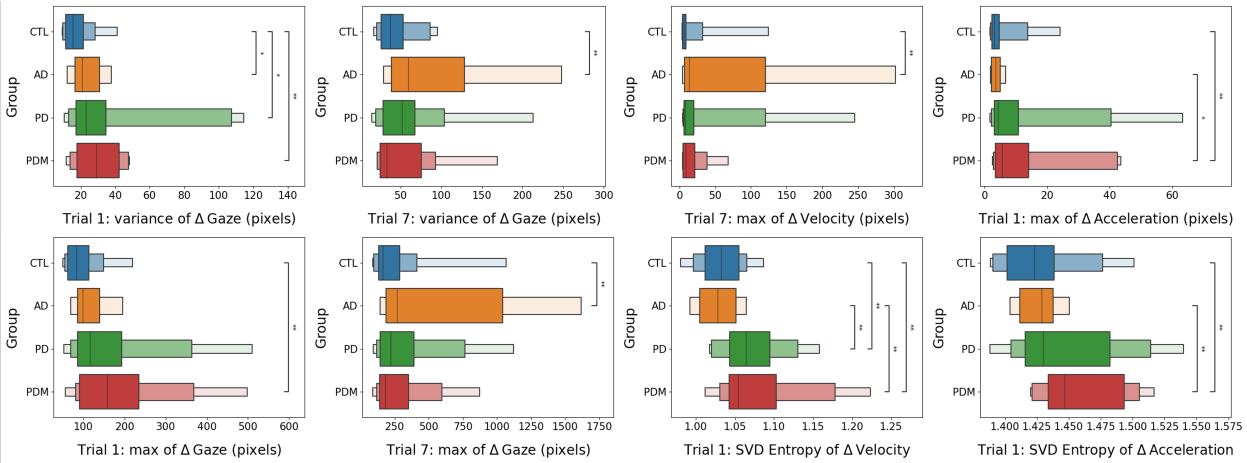

Figure 5. Boxplots of all significant features.
"Asterisks" indicate significance levels: ∗: 0.01 < p <= 0.05, ∗∗: 0.001 < p <= 0.01, ∗∗∗: p <= 0.001

strated by shorter gaze distances, and less difference in velocities and accelerations of the two eyes. Overall the CTL group had a lower mean, median, variance, and max in Δ Gaze, Δ Velocity, and Δ Acceleration. These findings suggest that CTL participants showed better ability during the trials to maintain their eyes converged and move synchronously. Conversely, participants with NDs presented with greater difficulty in maintaining convergence and with a higher degree of kinematic differences between eyes. The behavior of these features in the CTL group was also notably less irregular when compared with the ND groups. This is shown by significantly lower SVD entropy values. This result suggests that CTL participants experienced fewer ocular tremors and displayed less jaggedness in their eye movement time-series. Since SVD entropy serves as a measure of the complexity or irregularity of time-series, these results suggest that CTL participants had smoother and more regular eye movements compared to the ND groups. This may imply better overall eye coordination and stability in the CTL group during the smooth pursuit eye movement tasks.

Across all three ND groups, significant differences were observed when compared with the CTL group. Specifically, In trial 1 and trial 7, the variance of Δ Gaze allowed for significant differentiation between CTL and AD/MCI groups (p<0.05). This indicates that the CTL group exhibited more consistent and coordinated eye movements with less spread-out Δ Gaze values, suggesting that they were better at maintaining eye convergence during the smooth pursuit tasks compared to the AD/MCI group. Additionally, in trial 7, the max of Δ Gaze also provided significant differentiation (p<0.01) between CTL and AD/MCI, suggesting that the CTL group showed fewer large deviations between the gaze locations of the two eyes during this trial. Moreover, in trial 1, the variance of Δ Gaze and the SVD entropy of Δ Velocity provided significant differentiation between CTL and PD groups (p<0.05). This indicates that the PD group displayed more frequent inconvergence and less smoooth, more irregular eye movements with more spread-out Δ Gaze values than the CTL group, probably caused by ocular tremors, which is a common symptom of PD [20]. It is worth noting that in addition to differentiating NDs from CTL, our results further demonstrated the potential to differentiate between NDs. Namely, AD/MCI from PD in trial 1 by the SVD entropy of Δ Velocity and Δ Acceleration, and by the max of Δ Acceleration. AD/MCI from PDM in trial 1 by the SVD entropy of Δ Velocity. We hypothesize that the presence of tremors and other motor impairments could increase the SVD entropy in participants with PD or PDM in comparison to AD and CTL groups

In the first 4 trials, we only observed a significant differences between groups in trial 1. Compared to trials 2 and 4, the target in trial 1 had a lower frequency. This suggests that CTL participants also exhibited poor binocular coordination ability as the gaze speed increased and the scale of the target path decreased. This is consistent with the results observed in the last three infinity pattern trials. We only observed significant differences in trial 7, in which the target had the largest amplitude of range of motion and a small frequency. This indicates that participants of all groups experienced challenges in binocular coordination when the target movement range was small or the frequency was high.

V. Conclusions and Future Work

In this study, we collected eye movement data with the primary objective of distinguishing between healthy participants and those afflicted with various NDs. The goal is to address the absence in the existing literature related to the area of binocular discoordination impairments in multiple NDs. Through applying statistical analysis to the eye movement data, we determined a

set of features that could be employed as potential biomarkers for evaluating NDs. Initially, our algorithm removes instances of blinks and saccades and isolates an approximate 6-second segment from the raw eye movement data while performing smooth pursuit tasks. Following this, three time-series — Δ Gaze, Δ Velocity, and Δ Acceleration — are computed. For each of these time-series, five features are then calculated. Statistical test results suggest that both the AD/MCI and the PD groups are found to have a significant deviation from the CTL. The AD group demonstrated higher variance and max of Δ Gaze and Δ Velocity. The PD group demonstrated a higher variance of Δ Gaze and SVD entropy of Δ Velocity. Our study further demonstrated the ability to differentiate between AD/MCI and PDM, AD/MCI, and PD by the SVD entropy of Δ Velocity and Δ Acceleration and the max of Δ Acceleration.

In the future, to enhance the robustness and generality of our study, we plan to include more participants to build a more balanced data set in terms of age, sex, and number of patients in each group. Additionally, we plan to explore additional features for binocular discoordination, especially new complexity measurements. By investigating more novel eye movement features, we can gain a deeper understanding of the importance of binocular coordination impairments in NDs. The finding of our study highlights how binocular discoordination could serve as a useful biomarker for evaluating NDs.

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