Objective Assessment of Eye Alignment and Disparity-driven Vergence in Parkinson's Disease

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Abstract

Diplopia is a common non-motor symptom in patients with Parkinson's disease (PD) affecting 1/3rd of patients. We used high-resolution video-oculography to demonstrate that diplopia in PD arises from disruption of binocular co-ordination of eye movements. Using video-oculography we measured fixation eye movements, the angle and control of eye alignment and its correlation to convergence insufficiency in 13 PD patients and 6 healthy controls. We found that all PD patients had larger amplitude of fixational saccades with increased inter-saccadic drifts particularly of the non-fixing or non-viewing eye. Eye movement recordings suggest that the extent of eye alignment varies across PD subjects, 38% had good eye alignment and control under monocular and binocular viewing similar to controls (Group1). 62% of PD patients had increase in eye position difference, which was outside the threshold window of good alignment under monocular and binocular viewing (Group2 PD). PD subjects with good eye alignment were less likely to exhibit saccadic responses to disparity-driven vergence whereas those with poor control and worse eye alignment were more likely to exhibit saccadic responses with staircase saccades. A cohort of PD patients (Group2) exhibited pure vergence or combined vergence/saccade responses; they had deficits of both fusion initiating (prolonged latencies, reduced gain and peak vergence velocities) and fusion sustaining components (increased eye position variance). The results demonstrate that the vergence abnormalities in PD subjects systematically correlate with both the angle and control of eye alignment. Further, our data suggests an interaction between the vergence and saccade subsystems in PD patients. Abnormalities of vergence in PD may be the result of direct effects of the disease on vergence motor control, coupled with disturbances in the saccadic pathway indirectly leading to effects on vergence.

Introduction

Parkinson's disease (PD) is a neurodegenerative condition characterized by a host of motor and non-motor symptoms affecting about 10 million individuals worldwide. Visual impairments in PD are far more common than appreciated and include blepharospasm, dry eyes, reduced blinking, visual hallucinations, decreased visual acuity and contrast sensitivity [1–5]. On the oculomotor level, the deficits comprise of impaired saccades with increased saccadic intrusions causing difficulties in reading and scanning the environment [2, 6–9]. Studies have shown that 10-70% patients experience diplopia arising from convergence insufficiency (the disconjugate movement of the eyes elicited in response to target jump from far to near) which compromises depth perception [5, 8, 9]. There are two key sensory drives for inducing vergence a) binocular retinal disparity-driven vergence and b) monocular blur driven vergence. There are two key motor components to the vergence response a) fusion initiating component (the open loop or pulse like component that enhances early movement dynamics) and b) fusion maintenance component (driven by visual or internal feedback to bring the eyes accurately and maintain on the target) [10, 11].

Self-reported visual function and non-movement symptom questionnaires are frequently utilized to determine the risk and prevalence of diplopia [1, 12–16]. A few studies have characterized diplopia in PD using clinical ophthalmological and orthoptic tests and have reported significant association between convergence insufficiency and strabismus and severity of PD [2, 3]. However, clinical testing alone has several limitations including examiner variability and subjective assessment of strabismus control and vergence deficits. Video-oculography has been used to quantify eye misalignment in patients without neurologic diseases [17–19]. These studies have reported deficits that are frequently not recognized with standard clinical assessments such as variability of angle of eye misalignment under different viewing conditions also referred as incomitance of strabismus. Video-based infrared eye tracking is an objective method that has been used to quantify vergence abnormalities in childhood convergence insufficiency and brain injury from trauma or ischemia and neurodegenerative disorders[20–24]. We have previously shown that PD disproportionately affects disparity-driven vergence compared to age matched controls [25, 26]. These abnormalities are thought to reflect brainstem and cerebellar pathology affecting supra-nuclear gaze holding structures. None of the studies to date have quantified both eye alignment and vergence abnormalities in PD subjects using video-oculography. The purpose of the present study was three-fold a) to

quantify the control and angle of eye alignment in PD b) to quantify initiation and binocular coordination of the eyes during convergence eye movements and c) to examine a correlation between vergence deficits, eye alignment and severity of PD. We hypothesize that the extent of impairment of both vergence components would correlate with the angle and control of eye alignment under binocular viewing (tropia) and monocular viewing (phoria) in PD.

Methods

Study Participants & Experiment Protocol

We recruited 13 PD patients (ages: 50–70 years) and six age-matched healthy controls. The PD diagnosis was based on clinical impression and response to dopaminergic medications. The Cleveland Clinic Institutional Review Board approved the protocol and written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Table 1 depicts the summary of recruited subjects, their demographic information, and details of clinical ophthalmic and neurologic presentation. PD severity was assessed using the Motor Subscale (Part 3) of the Unified Parkinson Disease Rating Scale (UPDRS-III) [27]. These assessments were made without knowledge of the ophthalmological findings. The number of falls and duration of disease were documented.

Table 1: Demographic and clinical ophthalmic and neurologic details of PD patients.

Subject Group	Subject ID	Age	Sex	Ethnicity	Dominant hand/leg	Disease duration	Major complaint	Affected side	#Falls over last 6	UPDRS	Visual Acuity		Cover Test		NPC		
											OD	OS	Near	Distance	Pen (cm)	RAF (cm)	Diverging Eye
PD G1	PD01	76	M	White	R/R	11	Vision	R	7	51	20/25	20/30	4X(T)	Ortho	31	26	right
PD G1	PD02	53	M	White	R/R	5	Speech, balance	R	2	12	20/25	20/20	Flick X	Ortho	22	33	right
PD G1	PD03	52	M	White	R/R	12	Arm tremor	L	0	40.5	20/20	20/20	10-12X(T)	Ortho	60	36	right
PD G1	PD04	69	M	White	R/R	8	Pain on the left side	R	0	25.5	20/40	20/40	8-10X(T)	Ortho	24	24	right
PD G1	PD05	59	M	White	R/R	7	Memory, fatigue, tremor	R	4	30	20/20	20/20	8-10X(T)	Ortho	13	15	left
PD G2	PD06	71	M	White	R/R	21	Arm tremor	R	9	36.5	20/50	20/30	8X(T)	Ortho	30	27	left
PD G2	PD07	69	M	White	R/R	9	Tremor, leg weakness, sleep	L	4	48.5	20/20	20/20	15X(T)	FlickX	17.5	19.5	right
PD G2	PD08	69	M	White	R/R	10	Tremor, leg weakness, sleep	Bilateral	>20	35.5	20/50	20/30	4X(T)	Ortho	20	25.5	right
PD G2	PD09	64	M	White	R/R	18	Speech, handwriting	Bilateral	0	56	20/30	20/40	10X(T)	Ortho	28	23	left
PD G2	PD10	71	M	White	R/R	14	Hand tremor	L	>20	41	20/20	20/30	14X(T)	Ortho	30	33	left
PD G2	PD11	79	M	White	R/R	17	Hand tremor	Bilateral	2	54	20/25	20/25	9X(T)	Ortho	28	24	right
PD G2	PD12	64	M	White	R/R	10	Left hand tremor	L	>20	23.5			4X(T)	FlickX	24	20	right
PD G2	PD13	68	F	White	R/R	8	Hand tremor	R	3	30	20/30	20/25	8X(T)	Ortho	16	13	left

UPDRS – Unified Parkinson’s disease Rating Scale; NPC – Near point convergence; OD – right eye; OS – left eye; XT: Exotropia

The ophthalmological examination comprised of best-corrected visual acuity (BCVA) at near with the Rosenbaum near vision chart at 30 cm, Simultaneous Prism Cover Test (SPCT) at distance and near, Prism and Alternate Cover Test (PACT) at distance and near and near point of convergence (NPC) measured with a Prince rule. We defined normal intact vergence

as a near point convergence (NPC) of less than 10 cm. Out of the 6 healthy age-matched controls, 5 had intact vergence whereas one control had mild increase in NPC at 14 cm. There were no differences in age (years) between controls versus PD subjects (Controls: 64.2 ± 2.59 , PD: 66.25 ± 8.32 , Mann Whitney U test $p=0.23$).

The subjects wore their corrective lenses for the experiments. A high-resolution video-based eye tracker (EyeLink 1000) was used as described previously to measure binocular horizontal and vertical eye positions simultaneously at 0.01° spatial and 500 Hz temporal resolution [28, 29]. Each subject's head was supported on a chin-rest. An infrared permissive filter was used to block visible light while allowing the non-viewing eye to be tracked. The study was done in two parts, one to analyze the dynamic vergence response and the other to analyze eye alignment. Convergence was quantified by placing LED targets at 20, 55, 150, and 240 cm distances along the sagittal plane and at the level of the eyes, presented as a step stimulus. The patient was instructed to try and focus on these targets using the viewing eye and avoid blinking when the step stimulus was switched back and forth between near and far target. The disparity-driven vergence response was recorded for both PD and age-matched healthy controls. The experiments done in binocular viewing condition with best-corrected vision facilitated measurement of disparity-driven vergence. The eye position data was further processed and analyzed with MATLAB (Mathworks, Natick, MA) using the algorithms prepared in our laboratory [17–20]. A 3-step calibration was performed: i.) Monocular calibration and validation of each eye was done using a 3-point constellation with best-corrected vision in a dark room at 55 cm in head fixed position; ii.) Monocular calibration (with only one eye viewing at a time) at LED targets placed on 2 isovergence angles at 20 and 150 cm for horizontal eye movements in transverse plane; On the circle close to the subject 3 LEDs were placed one at the center and the other two at $\pm 10^\circ$ and on the far circle 5 LEDs were placed one at the center and two at $\pm 10^\circ$ and $\pm 20^\circ$ and, iii.) Depth calibration for data recorded at each target distance (20, 55, 150 and 240 cm) to account for disparity [25]. For the vergence response tasks, as the LED target was turned on, the subject shifted their gaze at the corresponding target location and held there for five seconds. For the eye alignment tasks, the recordings were obtained under binocular viewing (BV) and monocular viewing (MV) conditions. The subject was instructed to look at the target at 55 cm continuously for 45s.

Data Analysis:

The calibrated eye position data were further processed and analyzed using MATLAB (Mathworks, Natick, MA). The eye positions were de-noised using Savitzky-Golay filter. The de-noised eye position signal was then differentiated to compute eye velocity.

Fixation characteristics and Eye Alignment Analysis:

Fixational saccades and square wave jerks/saccadic intrusions seen in control and PD subjects were identified using the clustering algorithm [30–33]. We pooled together the fixational saccades and saccadic intrusions as they share the same dynamic properties [31, 34–38]. We computed the frequency (Hertz) of fast FEMs as described in our previous work [39]. Drifts were defined as epochs between fixational saccades and saccadic intrusions as described previously [39]. The composite amplitude ($^\circ$) and median velocity ($^\circ/\text{s}$) of fast and slow FEMs for each eye was calculated as per equation (1.1). The fixation stability was quantified by calculating the bivariate contour ellipse (BCEA) encompassing 95% of fixation points [40–42].

$$\text{Composite} = \sqrt{(\text{Horizontal})^2 + (\text{Vertical})^2} \quad (1.1)$$

The eye position data was filtered with a moving average filter (window size 1.5s) to remove fast eye movements. The filtered data was then used to compute the horizontal and vertical eye positions for each eye. The difference in eye positions between the two eyes was used to calculate the eye alignment ($^\circ$). A histogram of composite eye alignment for each trial/subject was plotted and the 95% lower and upper bounds were computed.

The eye alignment angles were then clustered in 2D using Density Based Spatial Clustering and Application with Noise (DBSCAN) [43, 44] algorithm implementation on MATLAB. The selection of the DBSCAN algorithm was motivated by a desire to automatically detect and measure eye alignments in a way consistent with the judgements that a human would make without a priori knowledge of the number of unique alignments that a subject might exhibit during a session. During a relatively stable period of fixation, a greater number of points will accumulate in the same region of horizontal - vertical misalignment space, resulting in a higher density of data points. A density-based algorithm like DBSCAN can be tuned so that it classifies these dense areas as unique alignments while discarding the sparse areas representing transitions between stable alignments as noise without the need to specify a number of clusters. DBSCAN uses a minimum density level estimation with a radius determined interactively to be 0.05° and a core point threshold potential determined adaptively to be proportional to twice the expected number of points given an even distribution of points within 95% of the BCEA approximation or 40 (interactively determined), whichever is greater. The clustering algorithm parameters were chosen such that the eye trajectories arising from rapid disconjugate movements with quick changes in eye alignment were not sufficiently dense to join all of the clusters together but at the same time, not set the density threshold so high such that there were a large number of small clusters in the neighborhood. Clusters grow out from cores points (direct density reachable), which have more than a threshold number of points within their radius. If core points are direct density reachable, they were included in the original cluster and their cluster points were labeled as border points. After the initial clustering step, the clusters were then classified as being in “good” or “bad” alignment zones with good zones identified as per control performance. These good and bad clusters were further merged into super-clusters with the following criteria: 1) for good clusters, all good clusters were combined into one super cluster and 2) for bad clusters, the clusters with both horizontal and vertical means $< 2^\circ$ were merged together.

The weighted mean characteristics of clusters in bad alignment zones was calculated to further understand and quantify the impaired alignment. Using equation 1.1, composite values were calculated for each of the newly formed bad super-clusters (n) means ($Composite_n$). Then, the amount of time associated with each of these bad super-clusters (T_n) was calculated as a fraction (FT_n) of the total time (T_{total}), as described in equation 1.2. Using the results from equations 1.1 and 1.2, the cluster composite ($ClusterComposite_n$) was calculated as per the time spent for each of the clusters as described in equation 1.3. Finally, the weighted mean of all the bad super-clusters was determined using equation 1.4.

$$FT_n = T_n / T_{total}$$

$$[T_{total} = T_1 + T_2] \quad (1.2)$$

$$ClusterComposite_n = Composite_n * FT_n \quad (1.3)$$

$$Mean_{weighted} = (\sum ClusterComposite_n) * T_{total} / 1000 \quad (1.4)$$

Vergence responses:

Vergence eye movement responses that were contaminated by blinks were rejected. From the two individual calibrated eye positions, we calculated the conjugate saccade signal $[(left\ eye + right\ eye)/2]$ and the disconjugate vergence signal $(left\ eye - right\ eye)$. We have previously shown that the PD patients exhibited the following strategies: Strategy 1: Pure vergence (pure disconjugate movements with no saccades), Strategy 2: Vergence-Saccade (disconjugate followed by conjugate movement), Strategy 3: Saccade-Vergence (conjugate movement followed by disconjugate response) Strategy 4: Saccadic response (conjugate response only with absence of disconjugate component) to accomplish disparity-driven vergence tasks [25]. Strategy 5: Repeating combinations of saccade and vergence components to accomplish gaze shift (5A: Initial

vergence component with interspersed saccades following & 5B: Staircase starting with saccade with interspersed small vergence sections).

We devised customized scripts per the following criteria to analyze vergence responses. Saccadic parameters were computed using Engbert algorithm. The detected events were verified interactively.

Fusion Initiating Component:

1. Latency: In the fusion-initiating component, vergence latency was determined as the time when the eyes shifted position 0.5° away in opposite directions from the steady baseline after the target shift with an increase in vergence eye velocity above a threshold of $5^\circ/\text{sec}$. Saccade latency was determined as the initiation time of first saccade detected by Engbert's algorithm [45] after target jump with both eyes moving in the same direction (conjugate component change of minimum 0.5°).
2. Gain: Vergence gain was determined as the ratio between change in vergence amplitude (LE-RE) and actual vergence demand. Positive values correspond to a net convergence movement and negative values correspond to a net divergence movement. Vergence amplitude was determined as the change between position at start of fusion-initiation (latency) and start of fusion-sustaining component. The fusion-sustaining component was defined as the time during which the vergence velocity dropped to below $5^\circ/\text{sec}$ and extending till the end of the trial. Micro and macro-saccadic intrusions such as square wave jerks were excluded from fusion-sustaining component. Saccade amplitudes were obtained from Engbert's algorithm.
3. Peak Velocity: Vergence peak velocity of the disconjugate fusion initiating component was defined as the maximum velocity during the excursion and measured in $^\circ/\text{sec}$. Saccade peak velocity was defined as the maximum velocity observed during the periods of conjugate movements and were obtained from Engbert's algorithm.

Fusion sustaining component: Variance of vergence was computed between the end of fusion-initiating component when the velocity fell below $5^\circ/\text{sec}$ till the end of the trial, which is the fusion-sustaining component. Micro and macro-saccadic intrusions such as square wave jerks were excluded from fusion-sustaining component.

Statistical Analysis: The statistical analysis was performed using SPSS. FEM characteristics (frequency and median composite amplitude of fast FEMs and median composite velocity and variance of slow FEMs) of subjects with PD were compared to controls using unpaired t tests. We analyzed the 95% upper and lower bound of histograms of eye alignment and composite weighted mean of eye alignment per the time spent in a given cluster using two-way repeated-measures ANOVA (one within- viewing conditions and one between subjects Factor-Groups 0-2). Normality of data was evaluated using the Kolmogorov–Smirnov test. For all the tests, the Levene's test and the Mauchly's test of sphericity indicated that the assumption of homogeneity of variance and sphericity were met. Post-hoc analyses were conducted on significant main effects and interactions using Bonferroni correction. Chi square tests were used to analyze the strategies employed in response to disparity-driven vergence task across groups. Fusion initiating vergence gain defined as disconjugate amplitude/vergence demand) and fusion sustaining vergence (variance of vergence while fixing on the target) were analyzed using a one-way ANOVA. All statistical tests had a critical alpha value of 0.05. Mann-Whitney U test was used to compare the age between controls versus PD subjects and the UPDRS scores, disease duration and number of falls between PD Groups 1&2.

Results

We tested the hypothesis that degree of ocular misalignment is directly correlated with the extent of vergence impairment in PD patients. We describe fixation characteristics and eye alignment and vergence responses separately in the

subsequent sections. There are at least three characteristic properties of vergence eye movements that bear a positive correlation to the control and angle of eye alignment as shown in our results.

Fixation Characteristics and Eye alignment:

We evaluated the eye positions traces obtained under MV and BV in healthy age-matched control subjects. We computed the 95th percentile of horizontal and vertical eye position difference of control subjects to be 3.4° and 1.8° respectively. Thus, a window of 3.5° horizontally and 2° vertically was chosen as a threshold of good eye alignment. PD subjects were characterized based on eye alignment into two groups: Group1: Eye alignment was similar to control subjects and within the determined threshold in MV and BV conditions ($n=5$) for 50% or more time. Group2: Eye alignment was above the threshold for >50% of the time in MV ($n=8$).

Figure 1 shows the horizontal and vertical eye position traces obtained under BV and MV from PD subjects. The top panel is an example from a control subject with good eye alignment where the right and left horizontal and vertical eye position traces are very close together during BV and MV conditions. The fixational saccades occur at a frequency of 1-2/sec (Figure 1A red arrow). Figure 1D shows an instance of inter-saccadic drift (inset: black arrow). The middle panel is an example from a PD subject in Group1 with good eye alignment where the right and left horizontal and vertical eye position traces are very close together during BV and MV conditions. The inset in (B) demonstrates a square wave jerk. The bottom panel is an example from a PD subject in Group2- notice that the subject initially had good eye alignment with right eye drifting to the right by 6° (suggestive of exotropia) during BV and the left eye drifting to the left by 6.2° under MV condition. Fixational saccades (FEMs) identified using the clustering algorithm were pooled together for each subject and studied with respect to frequency of and amplitude between PD ($n=13$) and controls ($n=6$) under each viewing condition (BV and MV). In agreement with previous studies[34], there was no difference in the frequency of fixational saccades with increased amplitude of fixational saccades in PD subjects than controls. The frequency of fixational saccades in PD subjects were similar to controls (BV: PD = 2.2 ± 0.5 Hz, Controls = 2.0 ± 1 Hz, unpaired t-test $p=0.34$, and MV: PD = 2.4 ± 0.5 Hz, Controls = 1.9 ± 0.7 Hz, unpaired t-test: $p=0.09$). The amplitude of fixational saccades was analyzed in both fixing (FE) and non-fixing eye (NFE) and found to be higher in PD subjects than controls (Table 2). We also analyzed the frequency of square wave jerks (SWJ-defined as two consecutive saccades of same amplitude but opposite direction, separated by a short interval, approx. 200ms) and found it to be similar in PD subjects and controls (BV: PD = 0.4 ± 0.1 Hz, Controls = 0.3 ± 0.06 , unpaired t-test $p=0.18$, and MV: PD = 0.37 ± 0.06 Hz, Controls = 0.38 ± 0.12 Hz, unpaired t-test: $p=0.38$). We studied the SWJ amplitude in both FE and NFE. The amplitude of SWJ in PD subjects was higher than controls (Table 2). Besides abnormalities of fixational saccades, PD subjects had increased eye position variance and composite eye velocity particularly for non-viewing and non-fixing eye during inter-saccadic drifts than controls (Table 2).

Table 2
Fixation Eye Movement Characteristics under monocular and binocular viewing in controls and PD subjects.

	BV			MV		
	Control	PD	p-value (T-test)	Control	PD	p-value (T-test)
Fixational saccade amplitude (FE) (°)	0.4 ± 0.1	0.85 ± 0.48	0.0001	0.7 ± 0.37	0.88 ± 0.5	0.0001
Fixational saccade amplitude (NFE) (°)	0.68 ± 0.33	0.84 ± 0.48	0.01	0.78 ± 0.37	0.87 ± 0.49	0.49
SWJ amplitude (FE) (°)	0.4 ± 0.16	0.64 ± 0.24	0.01	0.42 ± 0.2	0.66 ± 0.32	0.03
SWJ amplitude (NFE) (°)	0.39 ± 0.12	0.64 ± 0.27	0.007	0.46 ± 0.12	0.65 ± 0.33	0.04
Inter-saccadic drift eye position variance (FE) (°)	0.002±0.001	0.008±0.006	0.004	0.002±0.001	0.007±0.007	0.016
Inter-saccadic drift eye position variance (NFE) (°)	0.003±0.001	0.008±0.008	0.015	0.002±0.000	0.006±0.005	0.011
Composite velocity (FE) (°/sec)	0.41±0.15	0.82±0.34	0.000	0.44±0.017	0.91±0.43	0.002
Composite velocity (NFE) (°/sec)	0.43±0.16	0.86±0.31	0.000	0.49±0.21	0.92±0.43	0.004
(Mean ± SD);						
FE: Fixing eye; NFE: Non-fixing eye						

Figure 2 depicts the right and left eye positions (black= viewing/fixing and gray =non-viewing/non-fixing eye) obtained from one control and one subject from each PD Groups (1&2) under BV (top panel) and MV (middle panel). The bottom panel plots the histogram and 95% upper and lower bounds of the histogram of composite eye position differences of the right and left eye for each subject under BV (green) and MV (purple) conditions. We pooled the 95% upper and lower bound histogram values of all 3 groups (Table 3) across BV and MV. There was a statistically significant difference for the 95% lower-bound limit across the viewing conditions with increased eye misalignment under MV than BV for all groups particularly for subjects in Group2: [Main effect ($F(1,16)=9.8$, $p=0.006$, $\eta_p^2 = 0.38$), with a statistically significant interaction between viewing conditions and the 3 groups [Interaction ($F(2,16)=6.7$, $p=0.007$, $\eta_p^2 = 0.45$) and pairwise comparison Controls vs. Group2: $p=0.019$. There was no statistically significant difference for the 95% upper-bound limit across the viewing conditions [Main effect ($F(1,16)=2.6$, $p=0.12$, $\eta_p^2 = 0.14$) with no interaction between viewing conditions and the 3 groups [Interaction ($F(2,16)=0.82$, $p=0.45$, $\eta_p^2 = 0.09$].

Table 3
Eye alignment under monocular and binocular viewing in controls and PD subjects.

	Control		PD G1		PD G2	
	OU	OD	OU	OD	OU	OD
Composite Lower Bound (°)	0.92±0.95	0.29±0.29	0.63±0.49	1.99±1.79	1.40±2.28	3.98±1.37
Composite Upper Bound (°)	2.79±1.08	3.26±2.05	2.07±0.79	6.08±4.78	6.08±4.78	6.61±1.16
GoodTime (%)	69.05±27.24	81.12±16.62	76.22±24.39	56.57±33.17	98.16±0.71	0.06±0.09
CompWtdMean(deg ² s)	0.5±0.54	0.338±0.51	0.08±0.22	65.40±87.67	40.84±28.13	82.81±74.57
CompLowerBound – Composite minimum value of spread; CompUpperBound – Composite maximum value of spread; GoodTime % – total percentage of time when both eyes were well aligned; CompWtdMean – Composite mean of clusters of difference of eye positions with respect to time attributed to the particular cluster; OU – Binocular viewing; OD – Monocular viewing (right eye).						

Figure 3 demonstrates the application of DBSCAN and our clustering approach graphically on the eye alignment obtained under BV (Figure 3A-H: BV) and MV (Figure 3I-P: MV) from a PD subject in Group2. Figure 3A&I depict the horizontal(x-axis) and vertical(y-axis) eye positions of the right eye and left eye. Figure 3B&J represent the time series of horizontal, vertical and composite eye positions (equation 1.1) of the right and left eye in BV (B) and MV (J). Figure 3C&K depict the difference in eye position in horizontal (x-axis) and vertical (y-axis) plane while Figure 3D&L show the time series representation of horizontal, vertical and composite difference in eye positions in BV (Figure 3C&D) and MV (Figure 3K&L). Notice the eyes are well aligned under BV whereas there is a marked increase in difference of eye position differences under MV.

To analyze the control and angle of eye alignment within each trial we evaluated the following parameters obtained after running the DBSCAN, which allowed identification of the clusters within and outside the threshold window. On initial application of DBSCAN on eye position difference, we get 4 clusters in BV and 24 clusters in MV, depicted as difference in eye position in horizontal and vertical direction with cluster core points shown in black 'X's in BV (Figure 3E) and MV (Figure 3M); and represented as a time series of difference in eye positions in horizontal and vertical planes as well as the composite difference in BV (Figure 3F) and MV (Figure 3N). Note, in BV, Figure 3E&F show the 4 clusters in varying shades of green, signifying good alignment whereas in MV, Figure 3M&N show the 24 clusters in varying shades of red and brown signifying bad alignment (outside the determined threshold window). Points not part of any cluster i.e., are not density reachable from any core points were depicted as gray sections and arise from rapid eye movements.

We cluster all the good alignment (horizontal and vertical eye position difference that falls *within* the threshold window) into one big super cluster as represented in Figure 3G and Figure 3H (time series representation of horizontal, vertical and composite difference in eye positions), obtained in BV. Conversely, as found in MV, we grouped the bad alignment (horizontal and vertical eye position difference that falls *outside* the threshold window) clusters together if the difference in horizontal and vertical means of the clusters were < 2° resulting in two super-clusters, as depicted in Figure 3O ((horizontal and vertical eye position difference) and Figure 3P (time series representation of horizontal, vertical and composite difference in eye positions). The super-cluster means of the eye alignment outside the threshold window during MV for brown cluster were 6.26° (horizontal) and -1.17° (vertical) with time spent as 10.06 sec and pink cluster were 6.46° (horizontal) and -3.34° (vertical) with time spent as 27.08 sec. We computed the weighted mean (Mean_{Weighted}) per the time spent in each cluster (equations 2.1-2.4), which was 224.7 in this particular example.

Figure 4 describes the mean cluster locations as identified after initial application of DBSCAN (similar to Figure 3E and Figure 3M above) as well as the time spent in that region. The different marker shapes correspond to the different groups

(Circles = Controls, Squares = PD Group1, and Diamonds = PD Group2). The size of the markers describes the time spent within that cluster. We further classify these clusters into super clusters as those within vs. outside the threshold window as described in Figure 3. We then compute the weighted mean of composite eye alignment in each super-cluster per the time spent in the super-clusters for each subject under MV and BV conditions. We pooled the values of all 3 groups across BV and MV conditions (Table 3). The weighted mean were greater under MV for PD subjects [Main effect ($F(1,16)=4.5$, $p=0.04$, $\eta_p^2 = 0.22$), with no statistically significant interaction between viewing conditions and the groups [Interaction ($F(2,16)=1.3$, $p=0.29$, $\eta_p^2 = 0.14$)].

Fusion initiating and fusion sustaining vergence:

Figure 5A, B and C shows a representative sample of the convergence response (green trace), conjugate response (cyan), right (blue) and left (magenta) eye and target positions (solid and dotted lines respectively) obtained from Controls and PD Groups 1&2. The control subject had a robust convergence response (gain = 1.0, peak velocity = $122.37^\circ/\text{sec}$) with the right and left eyes moving in opposite directions (disconjugate response) as expected with a latency of 200 msec. The subject was able to maintain both eyes on the target (fusion sustaining component) indicated by the black dots on the convergence (green) trace with a variance of 0.04° . PD Group1 subject had an impaired vergence response (gain = 0.67, peak velocity = $48.3^\circ/\text{sec}$, latency = 412 msec) with the left eye moving to the right however the right eye showed an initial conjugate response, moving toward the right before correcting itself resulting in minimal net displacement of the right eye and there was slightly increase in variance (0.17°) on the target during the fusion sustaining component. PD Group2 subject had very minimal vergence response (reduced gain: 0.16 and reduced peak velocity: $39.5^\circ/\text{sec}$) with an initial conjugate movement of both eyes to the left (red arrow) with a subsequent slow movement of the left eye to the right while the right eye was on the target for a brief duration (black bracket) resulting in prolonged latency (610 msec) which was followed by the right eye moving back to the left and increased eye position variance during fusion sustaining component (0.25°). Recall that in such trials the target LEDs were along the midline and a pure vergence (disconjugate) movement was required. Yet, there are considerable conjugate movements.

Figure 6 depicts the distribution of different strategies recruited in order to perform gaze shift in BV. In Figure 6A, we found that all control subjects were successful in performing vergence eye movements as pure vergence or vergence initiation followed by saccade whereas, PD Group1 subjects (Figure 6B) used saccades as well as a combination of saccade (conjugate) and vergence (disconjugate) eye movements apart from pure vergence movements to perform gaze shift. In Figure 6C, we found that PD Group2 subjects had substantially less disconjugate eye movement and mostly showed conjugate gaze shifts. Chi-Square test statistics showed a significant difference in strategy recruitments between groups (χ^2 p value= 2.26^{-12}).

Figure 7 describes the latencies observed across all subjects in Control (black circles), PD Group1 (green squares) and PD Group2 (red diamonds). For each gaze shift, we recorded the strategy recruited to perform the gaze shift as well the corresponding latency of each type of eye movement associated with the strategy recruited to perform the gaze shift. For non-combination gaze shift strategies, i.e., pure vergence or pure saccade, an arbitrary value of 2.5 was assigned to the non-participating type of eye movement in order to emphasize the difference between physiological values. Therefore, we see that most control subjects performed pure vergence movements and are clustered on the top-left corner of the graph. Some controls and Group1 PD subjects performed a combination of movements (vergence followed by saccade). We saw PD Group1 present predominantly in pure-vergence and vergence-saccade and a few instances of saccade-vergence strategy with prolonged net latencies. In the bottom-right corner, we predominantly see PD Group2, mostly performing pure saccades or saccade-vergence with very high vergence component latency.

Unpaired t-test was conducted to understand the relationship between latencies of controls and PD groups. For pure vergence gaze shifts, latencies of controls ($0.26s \pm 0.07$) were found to be significantly lower than PD Group1 ($0.45s \pm$

0.28; T-test: $p=0.006$). In vergence-saccade type gaze shifts, controls ($0.29s \pm 0.08$; T-test: $p=0.006$) and PD Group1 subjects ($0.27s \pm 0.09$) had comparable latencies (non-significant $p\text{-value}=0.7$). Group 2 subjects were not used for statistical analysis due to the small number of trials where they exhibited pure vergence or vergence-saccade strategies. Latencies of saccade-vergence type of gaze shift were compared for PD Group1 ($0.47s \pm 0.11$) and PD Group2 ($0.51s \pm 0.14$) and no significant difference was found ($p=0.5$). None of the controls exhibited SV strategy and were excluded from this analysis. PS strategy was seen only in Group2 subjects. Latencies from staircase-type strategies (Strategy 5) were also excluded from statistical analysis. In case of saccade staircase, both PD Groups 1&2 had the same number of occurrences and in vergence staircase, there were limited but similar number of occurrences.

Figure 8A depicts the vergence amplitudes (x-axis) and the corresponding peak velocity (y-axis) during the fusion initiation phase across all groups – Controls (black circles), PD Group1 (green squares) and PD Group2 (red diamonds). We see that there are more vergence data points for control subjects which is in-line with our observation of strategy recruitment (Figure 6). In PD Group1, we see a number of trials with a high vergence amplitude and corresponding velocities. PD Group2 shows a severely compromised vergence response in line with our earlier observation. The line of best-fit had slopes (95% confidence interval) as follows – Controls: 11.52 (95% CI: 9.18 to 13.87), PD Group1: 5.89 (95% CI: 4.9 to 6.89), and PD Group2: 6.165 (95% CI: 3.49 to 8.83). The slopes were found to be significantly different ($F=10.01(77)$, $p<<0.01$). Figure 8B shows the saccade amplitude (x-axis) and the corresponding peak velocity (y-axis) during the fusion initiation phase across all groups for each eye (LE-filled, RE-open). We see again that controls are fewer in number and of lower amplitude whereas both PD Group1&2 show a more defined saccadic response with associated peak velocities. The line of best-fit had slopes (95% confidence interval) as follows – Controls: 84.86 (95% CI: 70.78 to 98.94), PD Group1: 28.92 (95% CI: 24.86 to 32.97), and PD Group2: 29.31 (95% CI: 24.86 to 32.97). The slopes were found to be significantly different ($F=11.77$ (458), $p<<0.01$). Thus, the peak velocities of convergence and saccadic components are reduced in PD subjects compared to controls [46].

Figure 9 summarizes the box and whisker plots of fusion initiating vergence gain (left panel) and fusion sustaining eye position variance (right panel) across all Controls (gray), PD Group1 (green) and PD Group2 (red). Table 4 describes mean and standard deviation found in gain and variance across all 3 groups. Overall mean gain for controls was found to be significantly different from PD Groups 1&2 (one-way ANOVA: $p<<0.01$, $F(2,95) = 32.5$). Post-hoc analysis of vergence gains showed significant difference between Control and PD groups as a whole (PD Group1 $p<0.01$; PD Group2 $p<0.01$). Variance for controls was also found to be significantly different from PD Groups 1&2 (one-way ANOVA: $F(2,74)=7.1$, $p=0.001$). Post-hoc analysis of fusion sustaining variance component showed significant difference between Control and PD Group2 (PD Group2 $p=0.002$) but not PD Group1.

Table 4
Vergence parameters in controls and PD subjects.

	Control	PD G1	PD G2
Gain (fusion-initiating component)	0.92±0.15	0.64±0.29	0.36±0.37
Variance (°) (fusion-sustaining component)	0.09±0.09	0.18±0.26	0.69±1.06
(Mean ± SD)			

We examined the severity of neurologic disease in Group1 versus Group2 PD subjects. We found the UPDRS-III scores were slightly worse in Group2 (Group1: 31.8 ± 14.8 , Group2: 40.6 ± 11.5 , $p=0.3$), with longer disease duration in Group2 (Group1: 8.6 ± 2.8 years, Group2: 13.3 ± 4.8 years, $p=0.1$) and greater number of falls in Group2 (Group1: 2.6 ± 2.9 , Group2: 9.7 ± 8.8 , $p=0.1$). Considering that the mean disease duration of both PD groups is high, we did not see a statistical difference in corresponding UPDRS values between the two groups, which is in line with observations by Repka et. al.[3]

Discussion

Oculomotor abnormalities are frequently seen in PD [1–5, 47]. Majority of the studies describe saccadic and gaze holding abnormalities in PD. These include increased frequency and amplitude of saccadic intrusions and square wave jerks [38, 39, 48–50]. Patients with PD have increased saccadic latencies, hypometric, slow and staircase saccades and more frequent errors during anti-saccade tasks [7, 39, 46, 50–53]. A handful of studies have quantified vergence in PD and have reported increased latency with variable effects on convergence velocity and gain [25, 54]. Ocular misalignment is described as both a consequence of convergence insufficiency [3, 47] as well as a more nuanced subcortical deficit in Parkinson's disease and are correlated with disease severity [2, 55, 56].

We quantified the fixation eye movements, eye alignment and vergence abnormalities in PD subjects. In our study, all PD patients exhibited increased near point of convergence (NPC > 10 cm) and 70% of subjects had intermittent exotropia at near of > 4 Prism diopters on clinical testing. Eye movement recordings suggest that the extent of eye alignment varies across PD subjects. 38% of PD subjects had good eye alignment under MV and BV similar to controls (Group1). 62% of PD patients had increase in eye position difference which was outside the threshold window of good alignment under MV and/or BV (Group2 PD). Eye movement recordings also show that the control of eye alignment varies across PD subjects. Group2 PD subjects had substantially lower time when the eyes were well aligned under BV with resultant increase in weighted means of eye alignment. PD subjects in Groups 2 had reduced time of good eye alignment with substantially higher weighted means of eye alignment under MV. All PD patients had larger amplitude of fixational saccades. We have previously parsed the fast and slow FEMs and have reported FEM abnormalities that correlate with the strabismus angle and extent of binocular function deficits in patients without neurologic disorders [30, 57–60]. We found that the inter-saccadic drift velocities and amplitude of fixational saccade increased as a function of control and angle of eye alignment. Similar to prior studies, PD patients in our cohort exhibited prolonged disparity-driven vergence latencies. Saccadic responses have been previously reported in response to pure vergence stimuli in control subjects and patients with traumatic brain injury [10, 11, 61]. PD subjects with good eye alignment were less likely to exhibit saccadic responses to disparity-driven vergence whereas those with poor control and worse eye alignment were more likely to exhibit saccadic responses with staircase saccades to pure symmetrical step stimuli located at different initial vergence angle. Group2 PD patients who exhibited pure vergence or combined vergence/saccade responses to disparity-driven vergence exhibited deficits of both fusion initiating (prolonged latencies, reduced gain and peak vergence velocities) and fusion sustaining components (increased eye position variance).

Fixation, Saccades, Vergence and Saccade vergence interactions: Insights from non-human primate (NHP) studies

NHP studies have provided important insights into the neural circuitry of fixation eye movements, saccades and vergence. The neural circuitry of saccades comprises of frontal eye fields, basal ganglia, superior colliculus and brainstem. NHP studies have shown that the larger visually guided saccades are generated by a spatially encoded saccadic command from the caudal superior colliculus [62–69]. The brainstem saccade generators provide the pulse signal and comprise of the two mutually inhibiting groups of neurons in the brainstem: excitatory burst neurons (EBN) and inhibitory burst neurons (IBN) [34, 70] and the omnipause neurons (OPNs) [51, 71]. The OPN fire at a constant rate between the saccades and they cease their inhibitory discharge to the EBN and IBN completely during saccades. The neural integrator converts the pulse (velocity) signal into the step (position) of innervation. The motor neurons combine the pulse and step signal to generate the temporally encoded saccadic response. The fixational saccades and visually guided saccades are thought to be an oculomotor continuum and share the same neural circuitry as visually guided saccades [30, 31, 34, 62, 72]. The fixational saccades are triggered by circuits formed by the rostral superior colliculus [72] and brainstem saccade generators [34, 73, 74].

The cells within the rostral superior colliculus have also been shown to modulate vergence [69, 75–79]. The midbrain houses the neurons located in the mesencephalic reticular formation, in a region called supra-oculomotor area (SOA),

which are critical to control vergence position [80–82] and vergence velocity [83]. These neurons project to the ocular motor neurons innervating slow extraocular muscle fibers [81, 84, 85]. According to the Dual Mode model, the transient (open loop) fusion initiating component of the vergence system quickly facilitates the movement of the eyes to fuse a binocular target (driven by the peak velocity), while the fusion sustaining (feedback-closed loop) component reduces the error between the current position of the eyes and the target (determined by the accuracy) [86–89]. The SOA receives inputs from the deep cerebellar nuclei namely the fastigial nucleus and the interpositus nucleus.

Fixation, Saccade and Vergence Abnormalities in Strabismus: Insights from NHP and Human Studies:

Strabismus or eye misalignment interferes with visual-motor coordination of eye movements, resulting in disconjugate and cross-axis eye movements during visually guided saccades, variable and subnormal vergence responses, and fixation instability [30, 90–93]. Human and NHP studies have shown that the increased fixation instability arises due to abnormal vergence with resultant alterations of physiologic fixational eye movements (FEMs) [18, 28, 94–97].

NHP studies have also provided important insights into the neural correlates of oculomotor abnormalities observed in strabismus. Electrical micro-stimulation of the superior colliculus in strabismic NHPs has shown to evoke disconjugate saccades (both in direction and amplitude). [68] Neurons within the supra-oculomotor area, which encodes vergence responses in normal animals, were found to encode horizontal misalignment in strabismic monkeys [94, 98, 99]. The cells within the rostral superior colliculus have also shown to carry signals related to horizontal eye misalignment and fixation preference in strabismic NHPs [65, 66, 69].

Eye alignment, Fixation and Vergence Abnormalities in Parkinson's Disease: Common Neural Basis:

PD is a progressive neurodegenerative disorder caused due to degeneration of dopaminergic projections between the substantia nigra pars compacta (SNpc) and the remaining basal ganglia circuitry. Previous studies in PD patients have demonstrated widespread cortical hypometabolism and disrupted sensorimotor connectivity in the frontal and parietal regions [100, 101]. Cholinergic degeneration in PD affects the basal forebrain, nucleus basalis of Meynert and rostral brainstem structure called pedunculopontine nucleus. There is increasing evidence that subthalamic nucleus, one of the key regions demonstrating abnormal neural discharge in PD has visuo-oculomotor neurons [102]. The eye movement cells in monkeys and human PD subjects were primarily in the ventral portion of the subthalamic nucleus (STN) and comprised 20% of the share [102–106]. They receive inputs from the prefrontal association cortex [107], the frontal eye field (FEF) [108, 109] or the supplementary eye field (SEF) [108]. Human and non-human primate physiologic and anatomic studies suggest that STN plays a role in processing information related to eye movements [102, 103]. The oculomotor neurons in STN in PD patients showed task specific responses to cued versus self-paced saccades, responded to both passive limb movement and voluntary eye movement and scanning eye movements. There is increasing anatomic and neurophysiologic evidence that STN is connected with brainstem and cerebellar circuitry- particularly areas intricately involved with driving vergence and strabismus. Two possible pathways via which STN could modulate vergence are 1) The pathway involves the substantia nigra pars reticulata (SNr) - one of the output stations of the basal ganglia [110–112]. The SNr neurons have inhibitory connections with the superior colliculus (SC), but preceding saccade generation the SC is disinhibited through caudate-mediated inhibition of SNr [113, 114]. Inactivation of SNr neurons using muscimol has shown to disrupt fixation with increase saccades in monkeys, cats and rats [115–117]. SNr also receives inputs from the STN and projects to the SOA via superior colliculus [118]. Thus, impairment in SNr output as seen in PD could affect vergence. The second pathway directly involves the cerebellum [119]. This pathway involves subthalamo-ponto-cerebellar projections to the deep cerebellar nuclei via precerebellar pontine nuclei [120]. Further downstream from the subthalamo-ponto-cerebellar projections, the cerebello-pontine fibers connect the deep cerebellar nuclei to the strabismus angle sensitive neurons in SOA [94, 99, 121].

Debates exist in the literature concerning the neural control of binocular coordination of eye movements [122–124]. Previous studies have demonstrated complex, nonlinear interactions between the saccade (conjugate) and vergence

(disconjugate) subsystems [53, 125]. Although saccadic and vergence eye movements are thought to be generated by different neural subsystems, the occurrence of a saccade during a vergence movement increases vergence velocity [126]. Also, Collewijn et al have shown that for saccades that occur during vergence, the peak velocity of the saccades is reduced and the saccadic duration is increased [127]. Studies have shown that the crux of the interaction between saccades and vergence movements is within the OPN. Electrical micro-stimulation of the OPNs have shown to increase the tonic inhibition of vergence and saccadic velocity neurons slowing both the vergence and saccade components [128–130]. Thus, the release of OPN inhibition during a saccade allow the vergence velocity neurons to fire more vigorously thereby increasing the vergence velocity. The motor-neurons receive both a saccadic pulse-step signals and the vergence velocity and vergence position signals. Thus, the occurrence of a horizontal saccade during a vergence movement, results in combination of the vergence and saccadic signals producing a net pulse-step signal which is larger in one eye than the other resulting in saccades of unequal size.

Our study is the first to utilize video-oculography to quantify the angle and control of eye alignment and its correlation to convergence insufficiency frequently seen in PD patients. The results demonstrate that the vergence abnormalities in PD subjects systematically correlate with both the angle and control of eye alignment. The target stimuli within our study were pure, symmetrical disparity step stimuli located at different initial vergence angles (i.e. looking at targets located along the midline) with no retinal stimulation to the saccadic system. Yet, saccades were observed, especially within the slower vergence responses. We speculate, based upon the neurophysiology studies, that the responses to symmetrical vergence stimuli (along midline) will evoke the near response cells [131, 132] and when the vergence velocity is below a preferred threshold, a saccade may be initiated by (1) the excitation of burst neurons, (2) the inhibition of OPNs or (3) both the excitation and inhibition of burst neurons and OPNs. Our data support an interaction exists between the vergence and saccade subsystems in PD patients. Thus, abnormalities of vergence in PD may be the result of direct effects of the disease on vergence motor control, coupled with disturbances in the saccadic pathway indirectly leading to effects on vergence. Future neurophysiology and behavioral studies are needed to further understand the interaction between saccade and vergence eye movements. Further studies on early-stage and pre-symptomatic PD subjects are also needed to determine if vergence abnormalities and strabismus can serve as a biomarker of the disease.

Declarations

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Author contributions:

Study design: PG, AGS, FFG; Experiment design: PG, JMM, JJ, AGS, FFG; Data acquisition: PG, SBB, AGS, CWK, FFG; Data analysis: PG, FFG; Statistical analysis: PG, FFG; Manuscript drafting: PG, AGS, FFG; Manuscript editing: all authors.

Data availability statement:

The data generated and/or analyzed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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Competing interests:

The authors declare no competing interests.

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Figures

Figure 1

shows the sample eye position traces of right and left eye in horizontal and vertical plane (y-axis in degree) with respect to time (x-axis in seconds) of three PD subjects during gaze fixation task. RH-blue, RV-green, LH-red and LV-cyan. Left panel (A, B, C) shows binocular viewing eye alignment and right panel (D, E, F) shows monocular viewing eye alignment. A&D represent the eye alignment of a Control subject that showed consistently good alignment in both BV (A) and MV(D). B&E: Gaze fixation in a PD patient with consistently good alignment in both BV (B) and MV(E). (B) (E). C&F: Gaze fixation in a PD patient that showed that showed worsening control in the latter part of the trial in BV (C) and bad alignment MV (F).

Figure 2

Top panel shows the sample binocular viewing eye positions of viewing (black) and non-viewing (gray) eye along horizontal (x-axis) and vertical (y-axis). Middle panel shows the sample monocular viewing eye positions of viewing (black) and non-viewing (gray) eye along horizontal (x-axis) and vertical (y-axis). In control and PD G1, we see the viewing and non-viewing eye position cloud tightly packed. Under PD G2, we see the clouds close together though with a higher degree of spread than PD G1 in the top panel; whereas PD G2 in the middle panel shows the two eye clouds much farther apart. Under PD G3, we see a bigger spread of the eye clouds than PD G1 and PD G2 in BV (top panel) and we see a larger spread

of the eye positions as well as the two clouds being far apart in MV (middle panel). Bottom panel the spread of eye position difference (x-axis) along with the frequency (y-axis) of difference position occurrences in BV (green) and MV (purple) for control, PDG1, PDG2 and PDG3 samples shown in top and middle panel as histograms.

Figure 3

demonstrates the application of DBSCAN and clustering approach graphically on the eye alignment obtained under BV (Fig 3 A-H) and MV (Fig 3 I-P) from a PD subject. A&I depict the horizontal(x-axis) and vertical(y-axis) eye positions of right eye (blue) and left eye (red). B&J represent the time series of horizontal, vertical and composite eye positions of RE and LE in BV (B) and MV (J). C&K depict the difference in eye position in horizontal (x-axis) and vertical (y-axis) plane while D&L show the time series representation of horizontal, vertical and composite difference in eye positions in BV (C&D) and MV(K&L). E&M show application of DBSCAN resulting in 4 clusters in good alignment (shades of green) under BV (E) and 24 clusters in bad alignment (shades of red and brown) under MV (M), depicted as difference in eye position in horizontal and vertical direction with cluster core points shown in black 'X's; F&N show clusters represented as a time series of difference in eye positions in horizontal and vertical planes as well as the composite difference in BV (F) and MV (N). G&H

show a single super cluster of good alignment eye clusters found in E combined (horizontal and vertical eye position difference - G) and time series representation of horizontal, vertical and composite difference in eye positions (H), under BV. O&P show grouped bad alignment clusters found in M together if the difference in horizontal and vertical means of the clusters were < 2° resulting in two super-clusters, as depicted in O (horizontal and vertical eye position difference) and time series representation of horizontal, vertical and composite difference in eye positions (P).

Figure 4

shows cluster means generated using DBSCAN algorithm for each participant in BV (left) and MV (right). Marker shape corresponds to different patient populations as per our criteria: Circles: Controls (n = 6), Squares: PD Grp1 (n = 5), Diamonds: PD Grp2 (n = 8). Colors correspond to different subjects: Cooler colors (blues and greens) correspond to good alignment; Warmer colors (yellows and browns are indicative of bad alignment). Marker size is indicative of time spent in that region.

Figure 5

shows individual eye traces during dynamic gaze shift and post-dynamic fixation (Blue: Right eye, Magenta: Left Eye) in each group difference between the two eyes, i.e., vergence is shown in green and the dashed section depicts the brief period of fixation after gaze shift. Conjugate response depicted in cyan. A to C: Shows the fusion initiation and fusion sustaining (dashed section). Triangle represents peak velocity location during fusion initiation. Star represents movement initiation (latency). In PD G1 (B) we see a gaze shift with initial saccade followed by corrective vergence as described in Saccade-Vergence strategy (denoted by red arrow). In PD G2 (C), Black arrow shows conjugate (saccade response) and red arrow shows vergence response (delayed due to conjugate movement of the eyes).

Figure 6

depicts the distribution of different strategies recruited in order to perform gaze shift in BV. In Fig 6A, all control subjects were successful in performing vergence eye movements as pure vergence (PV) or vergence initiation followed by saccade (VS) whereas, PD G1 subjects (Fig 6B) used saccades as well as a combination of saccade (conjugate) and vergence (disconjugate) eye movements apart from pure vergence movements to perform gaze shift (PV, VS, SV & staircase). In Fig 6C, PD G2 subjects had substantially less disconjugate eye movement and mostly showed conjugate gaze shifts (PS, SV, Staircase).

Figure 7

shows a logarithmic plot of latencies found in each gaze shift broken down into the corresponding latency of each type of eye movement associated with the strategy recruited to perform the gaze shift across Controls (black circles) and PD Groups 1 (green squares) and 2 (red diamonds).

Figure 8

depicts the amplitudes (x-axis) and the corresponding peak velocity (y-axis). during the fusion initiation phase across all groups – Controls (black circles), PD Group1 (green squares) and PD Group2 (red diamonds). A. Shows vergence amplitude on x-axis. B. Depicts saccade amplitude vs peak velocity of each individual eye (LE-filled, RE-open).

Figure 9

shows summary box and whisker plots showing the overall gain (left) and fusion sustaining eye position variance (right) across Controls (gray) PD G1 (green) and PD G2 (red).