Saccades in progressive supranuclear palsy – maladapted, irregular, curved, and slow

Aasef G. Shaikh, MD, PhD1,2, Stewart A. Factor, DO3, and Jorge Juncos, MD3
1Department of Neurology, Case Western Reserve University, Cleveland, OH
2Daroff-Dell’Osso Ocular Motility Laboratory and Neurology Service, Louis Stokes Cleveland VA Medical Center, Cleveland, OH
3Department of Neurology, Movement Disorders Program, Emory University, Atlanta, GA

Abstract

Background and objectives—Slowed and curved rapid eye movements, saccades, are the well-known features of progressive supranuclear palsy (PSP). We hypothesized that the saccades in PSP are not only slow and curved, but they are also irregular and have timing deficits.

Methods—We tested this hypothesis in 12 patients with PSP by measuring vertical and horizontal visually guided saccades using a limbus tracker.

Results—Both, horizontal and vertical saccades were slow and had irregular trajectory and velocity profiles, but deficits were much more robust in vertical saccades. The irregularity in the saccade velocity was due to premature interruptions that either completely stopped the eyes, or moved the eyes at much slower velocity along or in the opposite direction of the ongoing saccade. The direction of the eyes’ trajectory was often changed after the interruption. We simulated a conductance based single-compartment model of the burst neurons embedded in local feedback circuit for saccade generation. This model mimicked anatomical and physiological realism, while allowing the liberty to selectively change the activation of individual burst neurons or the pause neurons. The PSP saccades were comparable to the simulations during reduced activity of the inhibitory and excitatory burst neurons.

Conclusion—PSP saccades are due to the paucity in burst generation at the excitatory and imprecise timing signal from the inhibitory burst neurons. Premature discharge of the inhibitory burst neuron further leads to breaks in the saccade trajectory, and maladaptive superior colliculus activity leading to aberrant saccades changing the intended trajectory of the ongoing saccade.
Keywords
parkinsonism; eye movement; brainstem; superior colliculus

Introduction
Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative conditions related to the abnormal accumulation of tau, the main constituent of the neurofibrillary tangles responsible for neuronal injury \(1^{–5}\). Typical clinical features of PSP include early postural instability, axial rigidity, bulbar defects and supranuclear gaze palsy \(6, 7\). Prominent autopsy changes in typical forms of PSP are found in substantia nigra pars compacta of basal ganglia, the subthalamic nucleus, the diencephalon, and the brainstem reticular formation \(8, 9\).

The eye movements can be important biomarkers of PSP. Clinically evident slowing of vertical saccades progress to vertical gaze limitation, which is a hallmark of PSP \(6, 7, 10–17\). The oblique saccades have the prominent curvature with relatively faster horizontal component distinguishing PSP from other forms of atypical parkinsonism and Parkinson’s disease \(14\). The curved trajectory of vertical saccades in PSP is called “round the houses sign” \(18\). While early cases of PSP present with hypometria of horizontal saccades, they get slower as the disease advances \(10\).

Conventionally the slowing of saccades in PSP is attributed to the decreases in peak saccade velocity due to degenerative loss of mesencephalic saccadic burst generators \(10\). Traditional literature suggested selective degeneration of the burst neurons responsible for vertical saccades from rostral interstitial medial longitudinal fasciculus (riMLF), while sparing of burst generators in paramedian pontine reticular formation (PPRF) leads to isolated vertical saccade slowing \(4, 10, 19, 20\). Involvement of the omnipause neurons (OPNs) from pontine reticular formation was considered less likely etiology, as the dysfunctional OPNs can equally impair both horizontal and vertical saccades \(21, 22\). We asked whether slowing of saccades occurs due to impaired burst generation due to the impairment in the function of excitatory burst neurons (EBNs), or it is due to disinhibition from loss of inhibitory burst neurons (IBNs). The burst neurons provide feedback to the superior colliculus. Therefore, we hypothesize that at least two additional phenomenology are involved in slowing of saccades. One mechanism includes inappropriately timed interruption of ongoing saccade that is followed by a catch-up saccade. The second mechanism is misdirection of the saccade trajectory and subsequent correction. Delineating the mechanisms of saccade abnormalities in PSP will facilitate development of the reliable and possibly prodromal disease markers that will help in the early differential diagnosis and quantify progression of illness in way not possible with traditional clinical scales.

Methods
We measured eye movements in 4 age-matched healthy controls and 12 patients (6 men and 6 women, age range 50–74 years) with the clinical diagnosis of PSP using criteria defined by Litvan and colleagues \(6\). In addition, for the comparison of saccade velocity to amplitude...
relationship comparison, we also used normative data values collected from various subjects in our laboratory. History and examination included early falls, axial rigidity, convergence insufficiency, slow vertical saccades and slow or hypometric horizontal saccades. They all demonstrated a typical course with an average time from disease onset of 5.9±3.2 years. They all had limited to no response to levodopa and at the time of testing 9 were on levodopa therapy with a mean dose of 605±286 mg per day. The study and consent form were approved by The Emory Institutional Review Board. Each subject signed an IRB approved informed consent.

**Experimental setup**

We used limbus tracker to measure horizontal and vertical eye movements (Ober Jazz Novo, Ober Consulting, Poland). The apparatus tracked the corneal limbus and the position of both eyes producing a conjugate vector. The voltages generated by the sensor were digitized with a sampling rate of 1000 Hz. In vivo calibration was performed before each experimental session. The calibration used saccades made to target shifts of known distance. The data were further processed and analyzed with previously published techniques using custom software (Matlab®).

**Experimental protocol**

The subjects’ head was comfortably restrained with chin and forehead rest. The subjects were asked to look at the target projected straight-ahead or 5, 10, 20 or 30 degrees to the right and left and 5, 10, and 20 degrees up or down. The eye movements were simultaneously recorded.

**Analysis of saccades**

Eye position was differentiated and smoothed with a Savitzky-Golay filter (polynomial order: 3; frame length: 21) to compute eye velocity. Acceleration was measured by further differentiating and smoothing eye velocity with the same filter. The start of the saccade was determined when eye position shifted 2 degrees away from the steady baseline after the target shift. The end was when the eyes reached the new baseline. Breaks in the saccades were determined using the velocity trace. Matlab® toolboxes were used for the statistical analyses and curve fitting (Mathworks™, Natick, MA).

**Results**

Fig 1A–C depicts an example of normal visually guided saccade measured from a healthy subject. The saccade has high velocity and it is uninterrupted as evident from a single peak of the velocity profile (Fig 1B). The saccadic pathway follows a straight trajectory as evident in Fig 1C. Fig 1D–I depict examples of two vertical saccades from one PSP subject measured during the same experiment session. A small negative velocity deflection at the offset of saccade in normal subject depicts physiological drift. The first example of the vertical saccade illustrates four types of interruptions in its trajectory. One type (red arrow in Fig 1D) completely stops the eye movement. Complete cessation is also evident in the velocity trace (red arrow in Fig 1E). During second type of interruption of the vertical saccade (a blue arrow in Fig 1D) the eyes do not completely stop but move at much slower speed.
speed compared to the velocity of the preceding or subsequent segment of the saccade (blue arrow in Fig 1E). The third type of interruption results in slow eye movements in the opposite direction (green arrow Fig 1D, E). The second example of saccade in Fig 1G has fewer interruptions compared to example 1. However, the peak eye velocity is much lower (compare gray arrows in Fig 1E,H).

These examples of saccades in the subject with PSP are not only slow and interrupted, but they also had curved and irregular trajectories. For instance, in example 1 the initial saccade is upward and to the right (Fig 1F). After a halt (interruption, not seen in Fig 1F), the movement crosses the midline but overshoots to the left. After another interruption (not seen in Fig 1F) the series of subsequent eye movements bring the gaze to the destination (red dot in Fig 1F). The shape of trajectory in an example depicted in Fig 1F is curved suggesting “round-the-houses” sign. Curved paths are also seen example 2, but here the eyes make series of upward-rightward and upward-leftward movements to reach the target (Fig 1I). The trajectory in the example depicted in Fig 1I has the serpentine shape.

Interruptions and curvatures are also present in horizontal saccades (Fig 1J–L). The horizontal saccade described in Fig 1J shows two interruptions (red arrows, Fig 1J,K). During each break, the velocity reaches zero (red arrows Fig 1K), it is then followed by a catch-up saccade bringing the eyes to their destination. The curvature is also present in the horizontal saccade trajectory. In illustrated example, for rightward eye movements, the eyes first move to the right and down, and then to the right and up (Fig 1L). Such interruptions and curvatures of saccades were consistently seen in all subjects. Both phenomena are quantified in the next sections.

Quantitative characteristics of saccade interruptions

We measured the ratio of the eye velocity during the interrupted segment and the peak velocity of the preceding saccade segment to quantitatively characterize the interruptions. The ratio would be zero in instances where the break led to a complete cessation of the eye movement. A non-zero value of the ratio suggested slow eye movement during the interruption. The positive value of the ratio meant that the slow eye movement was in the same direction as the ongoing saccade, while the negative value suggested slow eye movements in the opposite direction. In most instances the eyes did not completely stop during the interrupted segment. Instead they slowly moved in the direction of ongoing saccade or in the opposite direction. We chose to compute ratio instead of using absolute eye velocity during interruption for two reasons: 1) eye velocities are already slow in subjects of PSP, therefore it might be difficult to distinguish whether there was a further reduction in eye velocity during interruption. 2) The ratio would provide robust measure of change in the eye velocity during interruption compared to ongoing saccade. Fig 2 illustrates the summary of ratios. Each panel of the histogram in Fig 2A, C depicts summary from individual subjects for vertical and horizontal saccades respectively. The histograms represent that ratios in most instances were a non-zero value, and it spanned in positive and negative directions in all subjects. The histograms in Fig 2B, D depict the summary of ratios from all patients. The dashed line in Fig 2B, D graphically illustrates the mean value of the ratio. The range of covering 66% area under the curve was −0.42 through 0.05 for vertical saccades,
while it was −0.24 to −0.006 for horizontal. The mean vertical ratio was 0.01±0.014, while the horizontal ratio was 0.01±0.2. Comparison of distributions of ratios from horizontal and vertical saccades revealed statistical significance (Kolmogorov-Smirnov test, p < 0.001).

**Quantitative characteristics of saccade curvature**

We measured the change in the direction of saccade after the interruption to quantify curvatures and irregularity. We computed the differences in the directions of the trajectories of the saccades before and after the interruption. Fig 3 depicts the summary of the differences in the direction of the trajectories of saccade segments before and after the interruption. Each histogram in Fig 3A, C illustrates one subject; Fig 3A depicts vertical saccades; while the horizontal saccades are represented in Fig 3C. The mean of the difference in the direction of the trajectory was a non-zero value in all subjects. Fig 3B, D depicts the summary of all saccades from all subjects. The range of values encompassing 66% area under the curve was −141.1 degree to 63.1 degrees for vertical saccades, while it was −18.3 degree to 14.7 degrees for horizontal. The mean value of changes in the vertical saccade trajectory was −10.5±83.8 degrees, while it was −0.73±19.9 degrees for the horizontal. The comparison of histograms representing the distributions of the directional changes in the trajectories revealed statistical significance (Kolmogorov-Smirnov test, p < 0.001). These results suggest that interrupted saccades in PSP subjects were invariably misdirected and had to make multiple changes in the trajectory to reach the target of interest.

**Saccade amplitude to velocity relationship**

We then assessed the amplitude-to-velocity relationship (main-sequence) of vertical and horizontal saccades (Fig 4A,B). There were two components to this analysis as schematized in the inset of Fig 4B. In the first component, we compared desired saccade amplitude (‘Ad’ in the inset of Fig 4B; dots in Fig 4A,B) with the peak velocity (Vmax) during the entire gaze shift. The unique aspect of this analysis was that it asked whether “interrupted” saccade is comprised of multiple, sequential “normal” saccades, or it is pathologically interrupted one saccade. If they were multiple sequential small saccades with normal kinematic properties then we expect normal amplitude to velocity relationship upon comparing the velocity with amplitude of the each saccade segment. However, in that case main-sequence of peak velocity (which can be of any of the saccade segment) to desired amplitude would be abnormal, because segmented saccade is scaled for smaller amplitude. In contrast, if the saccade is “normal” in size but interrupted, then we would find increased velocity of segment of saccade for the amplitude of the given segment; however there will be normal peak velocity for the desired amplitude. Lastly, if the saccades are slow and interrupted, then it is expected to find slowing in case of both comparisons. The analysis compared the amplitude of segmented saccade (‘A1’ in the inset Fig 4B; open symbols in Fig 4A,B) with the corresponding velocity (V1). Fig 4A,B depicts the summary of main-sequence from 12 PSP patients. Colored dots in Fig 4A depict the main-sequence of the desired saccade amplitude, each color depicts one subject. Open symbols in Fig 4A illustrate the main-sequence of the segmented portions of the saccades. Black dashed lines represent the normative range. In all instances the filled data points depicting main-sequence of desired saccades fall below the normative range, while open symbols are below the normative values in PSP subjects # 1,2,7,8,10 and 11. We then performed two parts of main-sequence analysis
for horizontal saccades. Summary is depicted in Fig 4B. The main-sequence comparison of desired saccade (comparison of peak saccade velocity with the amplitude to the desired saccade) is illustrated with colored dots. Such symbols in all except #1, 4, and 9 fell below the lower range of normal. The open symbols depicting the comparison of the velocity of saccade segment with the amplitude of each segment fell within the normal range (between dashed lines) in all subjects (Fig 4B).

We quantified the main-sequence by measuring the goodness of fit to the equation: $V=K*A^L$. In this equation $V$ is peak saccade velocity, $A$ is saccade amplitude, two parameters $K$ and $L$ determine the amplitude dependence of the saccade velocity. This analysis was separately done for two types of comparison of the main-sequence for vertical and horizontal saccades. Supplementary Table 1 depicts the summary of results. We found weak correlation between the values of parameters $K$ and $L$ for the main-sequence relationship of desired as well as interrupted saccades in horizontal and vertical directions and the duration of PSP. For vertical saccades, we found the weak relationship between the disease duration and the value of parameter $K$ for both components of analyses (desired saccade component: $r^2=0.04$; segmented saccade component: $r^2=0.3$). The parameter $L$ weakly correlated with the disease duration in case of desired as well as interrupted saccade (desired: $r^2=0.4$; interrupted: $r^2=0.36$). There was no correlation between the disease duration and the parameters $K$ and $L$ for both components of analyses in horizontal saccades ($K$: desired saccade: $r^2=0.007$; segmented saccade: $r^2=0.04$; L: desired saccade: $r^2=0.004$; interrupted horizontal saccade: $r^2=0.0002$). These results suggested that degree of disease duration has no influence on the velocity of the interrupted saccade, suggesting that saccadic abnormalities are independent of disease progression as viewed by the traditional clinical rating scale.

**Amplitude to acceleration comparison**

In subsequent analysis, we compared amplitude dependence of peak vertical and horizontal saccade acceleration. As depicted in Fig 4C all data points (colored symbols) representing such relationship for vertical saccade in PSP subjects fell below the normative values (black symbols). Fig 4D illustrates the dependence of peak acceleration of horizontal saccade amplitude. All colored symbols depicting horizontal saccades in PSP subjects fell below the normative value (black symbols). Fig 4E, F illustrates the relationship of peak deceleration with vertical and horizontal saccade amplitudes respectively. In both comparisons, the data points depicting saccades from PSP subjects fell below the normative values illustrated with black data points. These results depict a reduction in the saccade acceleration and deceleration in horizontal and vertical axes.

**Discussion**

Slowing and curved trajectories are known features of saccades in PSP. We discovered that PSP saccades are not only slow and curved, but they are often interrupted and had irregular trajectories. We also found that kinematic properties of abnormal saccades do not correlate with the duration and severity of PSP. Latter discovery challenged predictions practiced in conventional clinical rating scales for PSP. Various
phenomenologies can explain abnormal features of visually guided saccades in PSP. We hypothesize that saccade slowing in PSP is due to involvement of inhibitory and excitatory burst neurons and it also affects the burst generator feedback system involving the superior colliculus. We predict a maladaptive firing in superior colliculus activity leading to abnormally directed saccade trajectory. It is also possible that with further progression of the disease there is involvement of the omnipause neurons (OPNs) leading to further impairment in saccade generation. We found an overlap between all three phenomenologies in our PSP patients.

**Impaired function of burst generators in PSP**

The rapid shift in the eye movements rely on abrupt increases in the excitability of the burst neuron due to sudden cessation of inhibition, i.e. the post-inhibitory rebound (PIR)\(^{22, 26–29}\). Two sources of sustained inhibitory influence are modulated via glycinergic inputs. The sustained activity of OPNs, one of the inhibitory sources, ceases at the time of desired saccade onset leading to an abrupt increase in EBN firing due to PIR\(^{22, 26–29}\). Simultaneously the activity of ipsilateral IBNs inhibits contralateral EBNs, hence preventing the activation of antagonistic eye muscles. However, malfunction of OPNs is less likely to cause saccade slowing, as they equally affect horizontal and vertical saccades, while PSP patients have prominent involvement of vertical saccades. Here we ask whether impaired inhibition through the IBNs or decreased excitation of EBNs cause slowing of the saccade.

To test the influence of OPNs, IBNs, and EBNs in the makeings of slow and irregular saccades we simulated the conductance-based single-compartment neuromimetic model of the burst generators within a local feedback loop model of saccades\(^{27}\) and compared the outcome with data from our PSP patients. Yellow box in Figure 5 depicts the architecture of conductance-based model of saccade generation. The technical details of this model were previously published\(^{27, 28}\).

Normal membrane properties and profile of ion channel expression in the model simulated normal saccade as depicted in the first column from the left. Blue and light blue plots depict normal eye position and eye velocity, while black trace depicts biphasic acceleration and deceleration profile during simulated saccades. Such kinematic properties of normal saccade are supported by temporally precise activation of inhibitory and excitatory burst neurons (green and red traces).

The second column from the left in Fig 5 depicts an example of simulated saccade when inhibition to the burst neurons was reduced (as expected from reduced function of OPNs). The simulated saccade was irregular (blue and light blue traces), and there was a reduction in peak velocity (light blue trace), peak acceleration (black trace), maximal deceleration (black trace). Disruption of the firing synchrony and absence of abrupt change in the firing rate suggesting the lack of PIR. Simulated features matched with the characteristics of saccades in PSP. As previously suggested the OPN mediated mechanism of the slow saccade is less likely as the pause neurons equally affected horizontal and vertical saccades\(^{10}\). We also found more substantial impairment of the vertical saccade generation.
The third column from the left in Fig 5 illustrates an example of saccade generated when the inhibitory influence of the IBN was reduced. Resultant saccade had reduced peak velocity (light blue trace) and irregular trajectory (dark blue trace), but there is no reduction in peak acceleration or deceleration (black traces). There was an abrupt increase in neural firing, but the density of neural discharge is reduced, hence suggestive of the weak PIR. The features of such simulated saccades are comparable to visually-guided saccades in PSP, with an exception of lack of change in peak acceleration.

The fourth column from the left in Fig 5 depicts an example of simulated saccade when the EBN gain was reduced. The resultant saccade was slow, had reduced acceleration and deceleration; however, unlike PSP, the trajectory was regular. The simulated neural response had PIR, but it was weak as suggested by the lack of burst in neural spikes.

These simulations suggest that prominently slow and irregular vertical saccades are consistent with combined involvement of the excitatory and inhibitory burst neurons. The deficits are not due to OPN involvement at least early in the disease course. However, progressive OPNs degeneration in advanced disease will have a synergetic effect on saccade slowing. These predictions of our analysis of saccades and neuromimetic model are consistent with the histopathologic reports. A handful of investigations documented involvement of mesencephalic reticular formation in PSP. Hence greater slowing of vertical saccades in PSP is likely to be consistent with decreased function of excitatory and inhibitory burst neurons in riMLF, however, as disease progresses there is additional involvement of the pause neurons causing further deficit in horizontal burst neurons and enhancing the slowness of vertical saccades. Indeed, a study measuring cell count from RIP, the anatomical location of the OPNs, revealed evidence of neuronal loss.

We also suggest that reversal in saccade direction can be induced by poorly synchronized IBNs and inadequate inhibition imposed by these neurons. Latter phenomenon can lead to weak PIR and emergence of the oscillations. Although such oscillations are seen in patients, they are much less robust compared to model simulation. We anticipate two potential causes for this finding. 1) the model is simulated with one set of neurons; while in real biological system (such as in PSP patient) the response is further shaped by ensemble firing response from group of neurons; and this activity is further smoothened by elastic plant dynamics, hence causing robustness of the oscillations. 2) When reduced and activity of IBNs is combined with that of EBNs and OPNs, latter as part of broader degenerative involvement, we would expect less robust oscillations but pronounced slowing.

**Superior colliculus activation and maladaptive changes in saccade trajectory**

Hypothetically directional changes in the saccade trajectory can be described by stimulation of the superior colliculus fixation zone during the ongoing saccade. Our findings resembled the saccades that were interrupted in primates by selective stimulation of the fixation zone of the superior colliculus. The stimulation of the rostral pole of the superior colliculus in non-human primates causes the significant deviation in the trajectory of the ongoing saccade. The random trajectory of the redirected saccades in the subjects with PSP leads to curvature of ongoing vertical saccade and suggesting premature activation of the fixation zone of the superior colliculus in these patients. One hypothesis is that the inhibitory
burst neuron responsible for the vertical saccades are first affected in PSP. Due to the degenerative insult, the burst neurons discharge spontaneously and out of synchronization (Fig 5, simulations). Such discharge pattern of the IBNs during the ongoing saccade is not only inferred as a signal to pause the OPNs, but it is also forwarded in the feedback circuit to the superior colliculus \(^{35}\). The consequence is undesired activation of the collicular fixation zone leading to redirected saccades in an arbitrary direction. Such maladaptive process involving the circuit of abnormally firing IBNs and maladaptively compensating superior colliculus results in slow, interrupted, and curved saccades in PSP.

We emphasize that the saccades in PSP are interrupted but not hypometric. There is a fundamental difference between hypometria and interrupted saccades. Inappropriate scaling of saccades, often a result of cerebellar deficits, cause hypometria. On the contrary, we propose that interruptions, in patients with PSP, are due to abnormal function of the pontine-mesencephalic saccade generation network and subsequent maladaptive process at the level of tectum.

We used the corneal curvature tracker that measures the position of both eyes and yields the conjugate eye position vector. Therefore it can be speculated that the observed irregularity in eye position during saccade is the product of disconjugacy between two eyes. This possibility is unlikely because of two compelling reasons: (1) saccades in PSP are not disconjugate\(^{10, 11, 14, 15, 36, 37}\), and (2) the previous studies utilizing the gold standard search coil techniques and measuring the position of only one eye also revealed such irregularities in their vertical saccade trajectories (see Fig 1A,B,D of Schneider et al\(^{15}\) and Fig 1 Bhidayasiri, et al\(^{10}\)). These previous studies were aimed at entirely different experimental question and did not have a mention or the analysis of irregularity and curvatures in the saccade trajectory. We conclude that curvatures and irregularity are the physiological phenomenon.

In summary, our results suggest that slow eye movements in PSP is not an exclusive consequence of the decreased saccadic velocity, but it is also due to curved and irregular trajectory and interruptions in ongoing saccade. We also found that saccade curvature is not merely due to mismatch in the velocity of horizontal and vertical saccade components (horizontal being faster), but it is due to aberrant activation of saccades in random trajectory after an interruption. We further propose that irregularities and slowing could be due to impaired function of EBNs and IBNs; while impaired function and lack of IBNs’ timing leads to maladaptive process involving the premature activation of the superior colliculus.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

**Funding support:** Aasef Shaikh was supported by Dystonia Medical Research Foundation Clinical Fellowship Award, and Dystonia Coalition/Dystonia Medical Research Foundation Career Development Award.

Aasef Shaikh was supported by Dystonia Medical Research Foundation Clinical Fellowship Award, and Dystonia Coalition/Dystonia Medical Research Foundation Career Development Award (NIH U54 TR001456).
Bibliography


Fig. 1.
Examples of visually guided saccades from healthy subject and PSP patient. In first row of subplots the eye position is plotted on the y-axis while x-axis depicts corresponding time in seconds. Black line depicts vertical eye position, while green trace illustrates horizontal eye position. Grey dashed line is a baseline depicting straight-ahead position, while blue dashed line depicts the position of the target (desired eye position). Arrows depict interruption in ongoing saccades. Blue arrow illustrates one type of interruption where the eyes continue to move at slower velocity during interruption, green arrow depicts slower eye movement in the opposite direction, while red arrow illustrates cessation of eye movement during interruption. Panel A illustrates normal visually guided vertical saccade from a healthy subject. Panels D,G depict two examples of visually guided vertical saccades from the same PSP subject is illustrated. Panel J depicts eye positions during horizontal saccade. Middle row of subplots depict eye velocity. Panel B depicts eye velocity of normal visually guided saccade recorded from the healthy subject, while panels E,H depict vertical eye velocity during vertical saccade in PSP. Green line in panel K illustrates normal horizontal eye velocity during horizontal saccade in PSP. In these subplots the eye velocity is plotted on y-axis while x-axis illustrates corresponding time. Red arrow illustrates interruption in saccade when eye velocity was zero, green arrow is when eyes moved at slower velocity in the opposite direction, blue arrow is when eyes moved in the same direction at slower velocity. The bottom row of the subplots depict trajectories of horizontal and vertical saccades. Panel C depicts normal saccade from the healthy subject, panel F,I depicts vertical saccade in PSP, and panel L is horizontal saccade in PSP. Green dot is start point, red dot is stop point, while grey dashed line is the desired path of an eye movement. Vertical saccades have curved and serpentine path depicting the clinical phenomenon of “round the houses” sign. Similar curvature is present in horizontal saccade as well, but it is much less robust.
Fig. 2.
Summary of ratio of eye velocity during interruption and saccade segment of interrupted horizontal and vertical saccades in PSP. Panel on the left (A,B) depict vertical saccade, while that on the right (C,D) illustrate horizontal saccade. Histograms in inset (A,C) of each panel depict individual patient labeled from P1 (patient 1) through P12 (patient 12). The main figure in the bottom panel (B,D) illustrated cumulative summary of ratio from all subjects. Ratio near zero suggests that eyes movements completely paused during interruption; while positive value of the ratio depicts slow eye movement in the same direction as saccade. Negative value suggests slow eye movement in the opposite direction. X-axis depicts bins of ratio, while y-axis is number of incidences in the given bin. Tall dashed line depicts mean, while short dashed line is median value.
Fig. 3.
Summary of change in angle of trajectory after interruption of horizontal and vertical
saccades in PSP. Panel on the left (A,B) depict vertical saccade, while that on the right (C,D)
illustrates horizontal saccade. Histograms in inset of each panel (A,C) depict individual
patient labeled from P1 (patient 1) through P12 (patient 12). The main histogram (B,D) in
the bottom panel illustrated cumulative summary of change in trajectory angle from all
subjects. Angle of zero suggests no change in saccade trajectory after the interruption, while
the non-zero value suggests a change in the trajectory. X-axis depicts bins of trajectory
angles, while y-axis is number of incidences in the given bin. Tall dashed line depicts mean,
while short dashed line is the median value.
Fig. 4.
Comparison of saccade velocity and corresponding amplitude in main sequence analysis for vertical (A) and horizontal (B) saccades. Saccade velocity is plotted on y-axis while x-axis depicts saccade amplitude. Each color depicts one subject, each symbol depicts one saccade. Filled symbols depict the relationship of peak saccade velocity with the desired amplitude of saccade, while open symbols show the relationship between the amplitude of the broken segment of the saccade and corresponding velocity. Dashed black lines are normative range. Comparison of the saccade acceleration and corresponding amplitude for vertical and horizontal saccades are depicted in panels (C,D); while panels (E,F) depict such comparison for saccade deceleration. Acceleration or deceleration is plotted on y-axis, while corresponding amplitude is on the x-axis. Each color depicts one subject, while each symbol is one saccade. Black symbols illustrate data from normal subjects. Inset of panel B schematizes analysis scheme. Green arrow depicts segmented saccade, A1 is the amplitude of segmented saccade, while V1 is corresponding velocity. The red arrow depicts desired saccade amplitude with an amplitude of Ad. Vmax is maximal velocity during entire saccade.
Fig. 5.
Yellow box depicts architecture of neuromimetic model for saccade generation. Each units, labeled EBN and IBN comprised of membrane kinematics as reported in Miura and Optican 2006 and Shaikh, et al., 2007. The red arrows depict inhibitory (glycinergic) connections, while green arrows are excitatory connections. IBN: inhibitory burst neurons, EBN: excitatory burst neuron, OPN: omnipause neuron, VI: abducens nucleus, III: oculomotor nucleus. Simulation of this model in normal subjects is depicted in the first panel titled “normal”. Dark blue lines depict simulated saccade position, light blue lines are saccade velocity, while black traces are eye acceleration. Green lines are spikes of ipsilateral EBN, while red spikes are ipsilateral IBN. Dashed vertical line depicts onset of saccade. It is normal for EBN and IBN are inactive and abruptly burst at the onset of saccade. Second panel depicts slowing of saccade velocity due to reducing OPN activity in the model. In addition there is lack of abrupt change in EBN or IBN discharge. Third panel depicts model simulation of slow and decreased acceleration of saccade when IBN activity is reduced in the model. Saccades also have irregular trajectory (dark blue line). The neural spikerate of IBN and EBN abruptly increase but there is much less dense spike activity suggesting weak neural burst. Such abrupt firing but weak burst is also present when the EBN gain was reduced, resultant simulated saccades were slow, and it had reduced acceleration, but the trajectory was not irregular.