



Reflexive and volitional saccadic eye movements and their changes in age and progressive supranuclear palsy

Isaac Hempstead Wright^a, Akila Sekar^a, Marte Theilmann Jensen^b, Megan Hodgson^b,
Matthew J. Bancroft^a, Nehzat Koochi^{a,c}, Andrew J. Lees^d, Huw R. Morris^b, Diego Kaski^{a,c,*}

^a Centre for Vestibular and Behavioural Neurosciences, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK

^b Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, UK

^c The Ear Institute, University College London, London, UK

^d Reta Lila Weston Institute of Neurological Studies, University College London, London, UK

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ABSTRACT

Background and objectives: Saccades, rapid movements of the eyes towards a visual or remembered target, are useful in understanding the healthy brain and the pathology of neurological conditions such as progressive supranuclear palsy (PSP). We set out to investigate the parameters of horizontal reflexive and volitional saccades, both visually guided and memory-guided, over a 1 min epoch in healthy individuals and PSP patients.

Methods: An experimental paradigm tested reflexive, volitional visually guided, and volitional memory-guided saccades in young healthy controls ($n = 14$; 20–31 years), PSP patients ($n = 11$; 46–75 years) and older age-matched healthy controls ($n = 6$; 56–71 years). The accuracy and velocity of saccades was recorded using an EyeBrain T2® video eye tracker and analyses performed using the MyEyeAnalysis® software. Two-way analysis of variance (ANOVA) was used to identify significant effects ($p < 0.01$) between young and older controls to investigate the effects of ageing upon saccades, and between PSP patients and age-matched controls to study the effects of PSP upon saccades.

Results: In both healthy individuals and PSP patients, volitional saccades are slower and less accurate than reflexive saccades. In PSP patients, accuracy is lower across all saccade types compared to age-matched controls, but velocity is lower only for reflexive saccades. Crucially, there is no change in accuracy or velocity of consecutive saccades over short (one-minute) timescales in controls or PSP patients.

Conclusions: Velocity and accuracy of saccades in PSP does not decrease over one-minute timescales, contrary to that previously observed in Parkinson's Disease (PD), suggesting a potential clinical biomarker for the distinction of PSP from PD.

1. Introduction

Saccades are rapid movements of the eyeballs towards a visual target, projecting it onto the fovea to bring it into focus. A well characterised brainstem motor network involving the superior colliculus and midline cerebellum promotes synchronous, congruent movements of both eyes to a visual target [1,2]. Although the low order neural substrates for horizontal saccades are well understood [3], the neural networks responsible for higher order control are less so.

Saccades can be reflexive towards a novel stimulus, voluntary towards a visual target, or memory-guided to a previously remembered

target [4], with each of these engaging different brain circuits [5,6]. Such saccades differ in several parameters including latency, velocity and amplitude [7–10], and while volitional control of saccadic eye movements is inherently complex [11], a detailed analysis of volitional versus reflexive saccades can provide insight into the neuroanatomical basis of different saccadic parameters and how higher-level brain centres encode these movements.

Saccades are not only useful in understanding the healthy brain, but also the pathology of neurological conditions. Progressive supranuclear palsy (PSP) is an atypical Parkinsonian disorder caused by the accumulation of tau in central nervous system cells [12,13]. Slow and small

Abbreviations: PSP, progressive supranuclear palsy; PD, Parkinson's Disease; FEFs, frontal eye fields.

* Corresponding author.

E-mail address: d.kaski@ucl.ac.uk (D. Kaski).

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saccades, predominantly in the vertical direction, are a defining clinical feature of PSP [14], caused by degeneration in brainstem areas that control eye movements [15,16]. Degeneration in PSP also occurs in brain regions concerned with high-level control of eye movements, such as the basal ganglia [17], resulting in wide-ranging, sometimes contradictory, effects on various eye movements [18–21]. A more comprehensive mapping of saccadic parameters in PSP will aid our understanding of disease pathology to improve diagnosis, which remains a significant unmet clinical challenge in the early stages of the disease [22–24].

The present study investigates horizontal reflexive and volitional saccades, both visually guided and memory-guided, in healthy individuals and PSP patients. Differences in saccadic parameters can illuminate how ageing selectively affects different brain networks while differences in PSP may offer novel clinical biomarkers for the disease.

2. Methods

2.1. Experimental paradigm

Our experimental paradigm tested reflexive horizontal saccades, volitional visually guided horizontal saccades, and volitional memory-guided horizontal saccades, as per [25]. For reflexive saccades, a 1° by 1° central fixation target appeared for variable amounts of time, followed by a 200 ms blank screen (a ‘gap’; see [26]), and then a target 20° to the left or right (Fig. 1A). Participants were instructed to fixate the targets as soon as they appeared by moving their eyes only, performing an array of leftward-guided and rightward-guided horizontal reflexive saccades over 50 s (Fig. 3, left column). Following this, the fixation target reappeared, and was subsequently replaced by two 20° left and right targets for another 50 s (with no gap; Fig. 1B), with participants instructed to look between them at will (Fig. 3, middle column). Finally, a blank screen was presented for another 50 s, with participants instructed to look between the points of the remembered targets (Fig. 1C; Fig. 3, right column). The paradigm was designed using the MeyeParadigm® software and displayed on an 11×19 inch computer monitor. Each participant performed one trial for each condition.

Eye movements were recorded using an EyeBrain T2® video eye tracker (suricog.fr). The eye tracker was placed over the participant’s head, 60 cm from the computer screen. Head movements were

minimised using a chin rest. The eye tracker was calibrated prior to each paradigm using thirteen reflexive saccades. Calibration was successful when the horizontal calibration percentage score for an eye was $\geq 90\%$.

2.2. Participants

We measured eye movements in 6 age-matched, healthy controls (4 women; age range 63–75 years) and 11 patients (3 women; age range 46–76 years) who had a clinical diagnosis of PSP according to MDS PSP criteria [27] and recruited from the UK-wide Progressive Supranuclear Palsy–Corticobasal Syndrome–Multiple System Atrophy (PROSPECT) study. In addition, we measured eye movements in 14 healthy young controls (8 women; age range 20–31 years). History and examination included early falls, axial rigidity, convergence insufficiency, slow vertical saccades, and slow or hypometric horizontal saccades. All participants demonstrated a typical course, with an average time from disease onset of 4.5 ± 3.1 years. They all had limited to no response to levodopa (L-DOPA) and, at the time of testing, five patients were on L-DOPA therapy: three at a dose of 25/100 mg (carbidopa/levodopa) three times per day, one at a dose of two 25/100 mg (carbidopa/levodopa) tablets five times per day, and one at doses of 50/12.5 mg and 100/25 mg (levodopa/benserazide) five times per day. One participant was additionally on ropinirole at a dose of 16 mg once daily. The study protocol and consent forms were approved by the UCL Queen Square Institute of Neurology research ethics committee.

2.3. Data analysis

Analyses were performed using MyEyeAnalysis® software. The amplitude traces produced by the software were examined for each eye and the less noisy eye was selected. Blinks were detected and removed by the software, and if a trace was noisy, it was Gaussian and median filtered. Saccades were detected using the in-built saccade detection tool and the output was manually inspected for quality.

As in other oculomotor studies of PSP [28], only the first saccade made was taken for analysis. In the reflexive epoch, only the first saccade of amplitude $>1^\circ$ occurring after the appearance of a target but before the appearance of the subsequent target was used in the analysis. Anticipatory saccades or error saccades made in the opposite direction to the target were not considered as they do not represent true visually

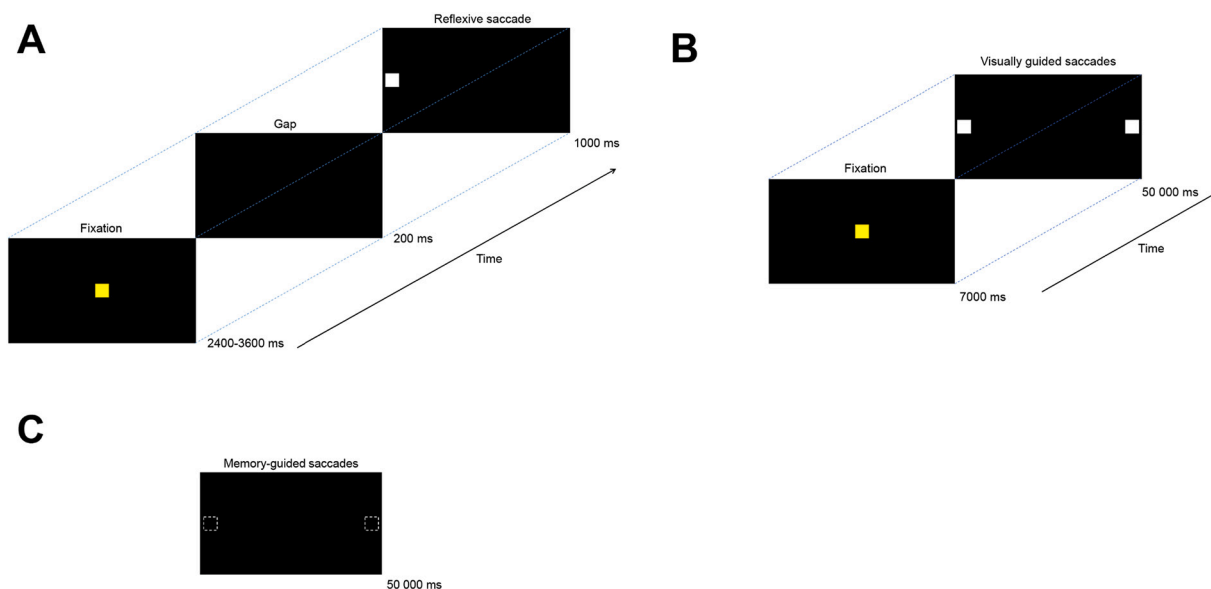


Fig. 1. Experimental paradigm for A: Reflexive saccade task. Example shows a leftward guided reflexive saccade. B: Volitional visually guided saccade task. Visual targets (white squares) to the right and left of the screen were presented simultaneously and remained for the duration of the trials. C: Volitional memory-guided saccade task. Dashed boxes indicate imagined targets on blank screen. Target size not to scale.

guided reflexive saccades. Additionally, only reflexive saccades made directly from the fixation point to a target were included, to avoid any amplitude bias introduced by failure of PSP patients to reach the fixation target before appearance of the subsequent target.

In the volitional epoch, the start point of an attempted saccade was taken as the first saccade performed in the correct direction relative to a target after reaching the maximum amplitude in the direction of the opposite target, and of amplitude $>1^\circ$. Only these saccades were used in the analysis. In this way, for volitional saccades, the first attempted saccade made from one target to the other was taken for analysis.

Amplitude and peak velocity of saccades were selected for analysis. Amplitude was converted to accuracy, calculated as the difference between the measured saccade amplitude and the target eccentricity. The amplitude and velocity of saccades is known to scale via a non-linear relationship known as the ‘main sequence’ effect, whereby larger amplitude saccades have greater velocity [29]. To account for the confounding effect of amplitude on saccadic velocity [30], a main sequence curve was fitted (Fig. 2), via the procedure and equations outlined in [25]. Separate curves for young and older controls were generated to account for the effect of ageing on the main sequence effect. Residual amplitude-corrected velocity was then calculated as the difference between any given data point and the appropriate main sequence curve (for young controls, the curve generated from younger controls, and for age-matched controls and PSP patients the curve generated from age-matched controls). These amplitude-corrected values were then used for all further analysis.

After these manipulations, the data was divided into two groups. The first group included all healthy controls, young and old, to investigate the effects of ageing on saccades, while the second group included PSP patients and age-matched controls to study the effects of PSP on saccades. Two-way analysis of variance (ANOVA) was used to identify significant effects ($p < 0.01$). Post-hoc testing was performed with Tukey’s Honestly Significant Difference test, accounting for multiple comparisons. Statistical tests were performed using RStudio Version 1.3.1093.

3. Results

Overall, there were noticeable differences in the eye movements of healthy individuals and PSP patients. Representative traces (Fig. 3) show that the saccades of healthy individuals (top row) are large, rapid

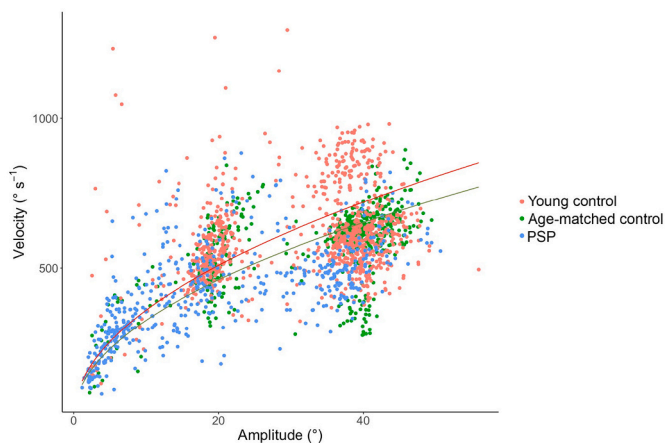


Fig. 2. Main sequence effect. Saccadic velocity versus amplitude for all saccades measured across the different study groups (red dots indicate young controls, green age-matched controls, and blue PSP patients). Red curve indicates model of main sequence for young controls and green curve for older controls, calculated as in [25] (see Methods). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and generally reach the target within one or two saccades, with no obvious change between each stage of the paradigm. In PSP patients (Fig. 3, bottom row), on the other hand, saccades are substantially smaller, often taking three or four saccades to get close to the target, with this effect most obvious in the volitional stages of the paradigm. Reflexive saccades in PSP are also noticeably slower than in controls. These saccades display a ‘staircase effect’, with multiple small saccades chained together to reach the target, as is commonly reported in Parkinsonian conditions including PSP [31,32].

In healthy individuals, accuracy varied significantly with saccade type (ANOVA, $F(2,1404) = 8.96, p = 10^{-4}$), with visually guided and memory-guided saccades less accurate than reflexive saccades across age groups, by 1.64° ($p = 0.003$) and 2.10° ($p = 10^{-4}$) respectively (Fig. 4A). Velocity also varied significantly between saccade types (ANOVA, $F(2,1404) = 138, p < 2 \times 10^{-16}$), with visually guided saccades 132° s^{-1} and memory-guided 136° s^{-1} slower than reflexive saccades across age groups (Fig. 4B), both significant at $p < 10^{-7}$. No significant differences were identified in accuracy or velocity between visually and memory-guided saccades, nor between young and older controls. Overall, therefore, volitional saccades are slower and less accurate than reflexive saccades across age groups.

In the PSP group, accuracy varied significantly with group, saccade type and their interaction (ANOVA, group: $F(1,1042) = 262$ and type: $F(2,1042) = 49.2$, both $p < 2 \times 10^{-16}$; and group:type: $F(2,1042) = 16.4, p = 10^{-7}$). Each saccade in PSP patients was significantly less accurate than the corresponding saccade in age-matched controls. The difference was -5.72° for reflexive ($p = 3 \times 10^{-4}$), -13.1° for visually guided ($p < 10^{-7}$), and -15.8° for memory-guided saccades ($p < 10^{-7}$; Fig. 4C), suggesting that volitional saccades are worst affected. As with age-matched controls, in PSP volitional saccades were also less accurate than reflexive saccades, by 9.94° and 13.0° for visually guided and memory-guided saccades respectively, both at $p < 10^{-7}$ (Fig. 4C). Overall, therefore, while the accuracy of all saccades is impaired in PSP, volitional saccades appear to be worst affected, with the relationship between reflexive and volitional saccades enhanced.

Velocity also varied significantly with saccade type and the interaction of group and saccade type (ANOVA, type: $F(2,1042) = 81.4, p < 2 \times 10^{-16}$; group:type: $F(2,1042) = 4.62, p = 0.01$). In PSP patients, only reflexive saccades had significantly lower velocity compared to age-matched controls ($-48.5^\circ \text{ s}^{-1}, p = 0.01$; Fig. 4D), suggesting reflexive velocity is most affected in PSP, in contrast to the findings on accuracy. Similar to the findings with accuracy, however, the bias towards reflexive saccades remains, with volitional visually guided saccades $81.8^\circ \text{ s}^{-1}$ slower and volitional memory-guided saccades $79.4^\circ \text{ s}^{-1}$ slower than reflexive saccades, both at $p < 10^{-7}$ (Fig. 4D). As with controls, no significant differences were identified in accuracy or velocity between visually and memory-guided saccades. We found no significant difference in the frequency of saccades during the volitional epoch between PSP patients and age-matched controls (ANOVA, $F(1,15) = 0.477, p = 0.5$).

Fig. 5 shows the same data as in Fig. 4 but plotted over time, showing accuracy and velocity of consecutive saccades in each stage of the paradigm. None of the slopes is significantly different from 0 (t -test) at $p = 0.01$ (Fig. 5). To account for individual bias introduced by collapsing the data points, we also calculated these slopes for each individual PSP patient. Where accuracy was concerned, 10 out of 11 patients had no significant upward or downward slope at $p = 0.01$. One patient did, however, show a highly significant downward slope ($-0.290^\circ \text{ s}^{-1}, p = 7 \times 10^{-8}$), but only during the final stage of testing (memory-guided saccades). Where velocity was concerned, 11 out of 11 patients showed no significant upward or downward slope at $p = 0.01$ in any of the stages.

4. Discussion

This study investigated horizontal saccadic parameters across young

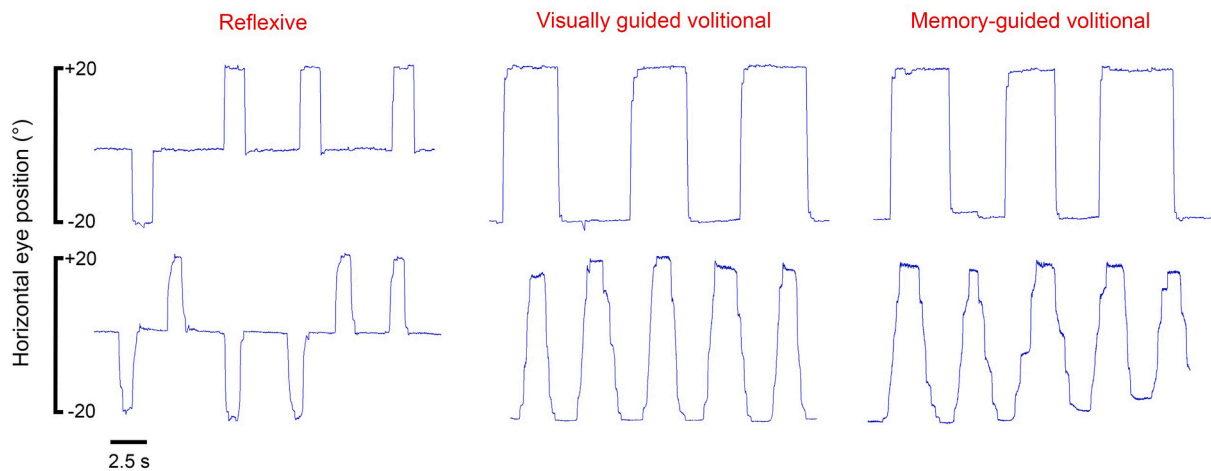


Fig. 3. Representative saccade traces for controls and PSP patients. Top row: Sections of representative saccade amplitude traces (blue lines) over time for healthy controls, with examples from each of the three stages of the paradigm (red text). Positive amplitude values indicate eye movement in one direction and negative values in the opposite direction, relative to the centre of the screen/fixation point (0°). Bottom row: Sections of representative saccade amplitude traces over time for PSP patients, with examples from each of the three stages of the paradigm (red text). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

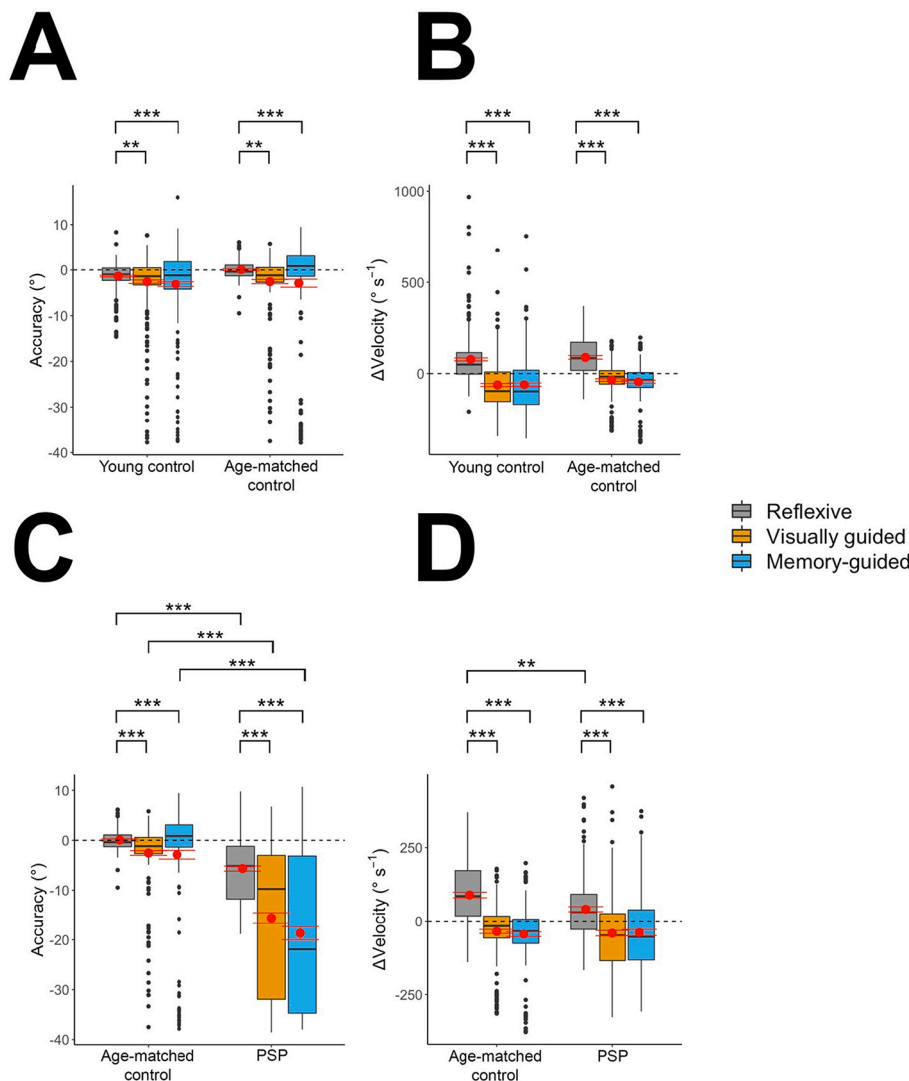


Fig. 4. Accuracy and velocity of horizontal saccades in healthy individuals and PSP. A: Accuracy of reflexive, visually guided and memory-guided horizontal saccades in young and age-matched controls. B: Amplitude-corrected velocity of reflexive, visually guided and memory-guided horizontal saccades in young and age-matched controls. C: Accuracy of reflexive, visually guided and memory-guided horizontal saccades in age-matched controls and PSP patients. D: Amplitude-corrected velocity of reflexive, visually guided and memory-guided horizontal saccades in age-matched controls and PSP. Red dots and whiskers indicate mean and standard error of the mean, respectively. Black horizontal lines indicate (from top to bottom) the upper quartile, median and lower quartile respectively, and black dots indicate any values which fall outside 1.5 times the interquartile range above or below the upper or lower quartiles. Asterisks denote significant differences per Tukey's test at $p < 0.01$ (**), and $p < 0.001$ (***). Note that when this analysis was performed on the uncollapsed data set (i.e., each individual contributing only one data point for each saccade type, calculated as the mean accuracy/velocity of all their saccades of that type), the trends largely remained. In controls, volitional saccades were still slower and less accurate than reflexive saccades ($p < 0.05$), and no effect of ageing was identified. In PSP, accuracy was reduced across all saccade types compared to age-matched controls, and volitional saccades were also less accurate than reflexive across groups ($p < 0.05$). As in the main analysis, no significant difference was found in voluntary saccade velocity between PSP patients and age-matched controls, and volitional saccades were again found to be slower than reflexive across groups ($p < 0.1$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

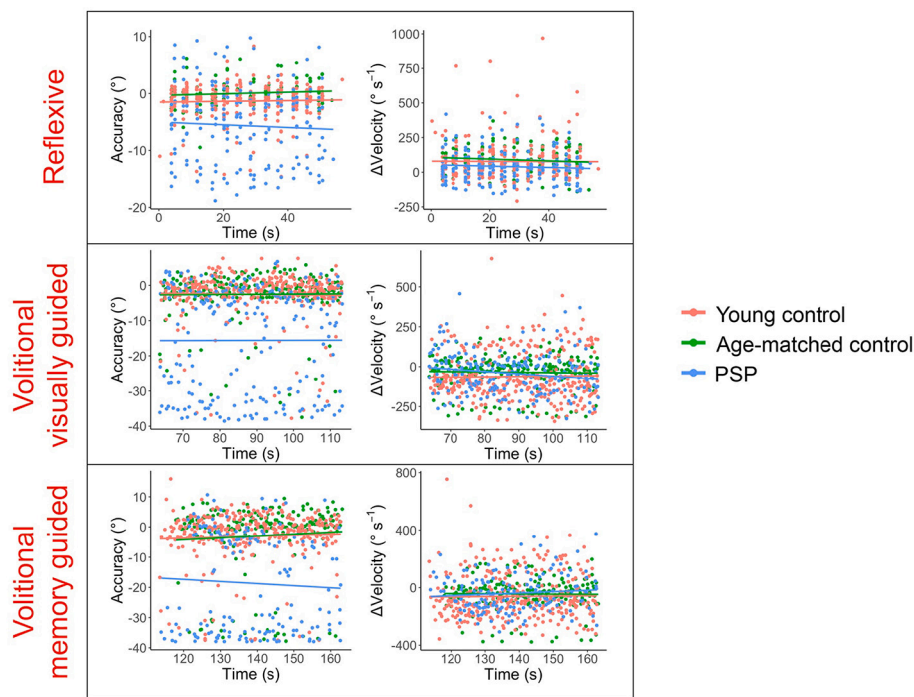


Fig. 5. Accuracy and velocity of consecutive saccades over time during each stage of the paradigm in healthy individuals and PSP. Accuracy (left column) and amplitude-corrected velocity (right column) of reflexive (top row), volitional visually guided (middle row) and volitional memory-guided (bottom row) horizontal saccades over time in young controls (red dots), age-matched controls (green dots) and PSP patients (blue dots). Solid lines indicate linear models fitted to young control data (red lines), age-matched control data (green lines) and PSP patients (blue lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and older controls, and in patients with PSP. We identified distinct differences in the generation of reflexive and volitional saccades across groups, adding to the range of oculomotor findings in PSP.

The increased accuracy and velocity of reflexive compared to volitional saccades is an intriguing finding; given that it occurs in both young and older healthy individuals and remains even in PSP patients, it appears to be a robust feature of the oculomotor system. While reflexive saccades with ‘gaps’ are known to occur with decreased latency relative to those where the fixation and eccentric targets are present on the screen simultaneously (‘overlap’ conditions; [7,26,33]), our results indicate this reflexive enhancement extends to velocity and amplitude. While previous work shows that saccades to visual targets are faster than saccades without visual targets [9,34], to our knowledge the specific effect of volition on saccadic velocity has not been reported in this way. Some evidence that reflexive visually guided saccades are of especially high velocity may be reflected in the finding that reflexive saccades are quicker than another kind of involuntary eye movement, optokinetic nystagmus (OKN) [35], and may suggest an inherent velocity bias towards reflexive saccades, although other work indicates this may also be the case for volitional saccades [36]. Overall, therefore, previous research is inconclusive when it comes to the parametrics of volitional and reflexive eye movements, and our novel finding offers a starting point for a renewed appraisal.

Given that reflexive saccades are well-placed to quickly shift attention to a potential threat, it is plausible that there would be an evolutionary advantage to executing these more quickly and accurately than volitional saccades. In support of this, visual neurons in the lateral intraparietal area/parietal eye field [37], an area associated with reflexive saccades [6], respond preferentially to saccades made to behaviourally salient stimuli [38], suggesting reflexive saccades may have adapted to the perception of salient or threatening stimuli. However, when human subjects were placed in a threatening scenario (a large height), reflexive saccades were no quicker or more accurate than baseline [39], arguing against such a role for reflexive saccades, at least one in which reflexive velocity is dynamically modulated in response to postural threat.

The lack of an effect of ageing on accuracy or velocity in healthy controls is of interest given previous work that suggests the oculomotor

system deteriorates with age [40,41]. The lack of obvious change in the present study might indicate these types of saccade are relatively robust to age-related oculomotor deterioration, though equally may reflect the heterogeneity of age-related neurodegeneration across the population [42].

The consistent lack of difference in velocity or accuracy between visually-guided and memory-guided saccades across all groups indicates that, at least where these parameters are concerned, these two types of saccade are indistinguishable. While there are other characteristics by which these saccades could be defined, it is striking that the two saccades with volitional components are similar to each other but different from reflexive saccades. Grouping saccades by reflexiveness or volition therefore appears to be a valid characterisation and lends support to the notion that distinct cortical pathways exist for the generation of either reflexive or volitional saccades.

Moreover, given that saccades made to a remembered target were no less accurate than to a visual target, inferences can be made about the high level of accuracy of visual memory and subsequent visuomotor transformations. Previous work suggests that complex circuitry involving both frontal and parietal cortices facilitates this visuomotor transformation [4,43,44]. Our data provides direct evidence for its remarkable accuracy, paving the way for more detailed analysis of these two types of saccade to shed light on the underlying circuitry. Additionally, that this effect remains even in PSP patients may also indicate that this specific cortical circuitry is relatively unaffected by PSP pathology.

Our finding that saccades are hypometric and slower in PSP is in keeping with previous literature on horizontal saccades in PSP [20,28,45], which has been attributed to decreased firing of excitatory burst neurons in the brainstem [45]. The finding that volitional saccade accuracy appears to be disproportionately affected in PSP, however, implies a selective cortical impairment of volitional saccade generation networks, such as the frontal eye fields (FEFs; [46]), rather than a more universal inhibition of all saccades caused by brainstem nuclei degeneration. Imaging has shown activity decreases in the FEFs and basal ganglia in PSP [20], both areas implicated in the volitional control of saccades [46,47], supporting the notion that degeneration in cortical pathways rather than brainstem nuclei may contribute to oculomotor

deficits in PSP and may preferentially impair volitional saccades. However, in contrast, other work suggests that volitional saccades are under more efficient control than reflexive saccades in PSP [18]. Whether this accuracy impairment is truly specific to volitional saccades in PSP remains to be fully elucidated, but our preliminary results may offer an interesting starting point.

Contrastingly perhaps, we also show that the velocity of reflexive saccades degrades in PSP compared to age-matched controls, but the velocity of volitional saccades is unchanged, suggesting instead that reflexive saccade pathways, for example those through the parietal cortex, may be worse affected in PSP, with volitional pathways preserved. Other work has reported reductions in amplitude but not velocity of vertical volitional saccades in PSP, similar to the present study, though contrastingly also found reductions in horizontal volitional velocity, but not amplitude [20]. One possible conclusion from these apparently conflicting results is that the amplitude and velocity commands for different saccades are produced independently and in spatially segregated areas in cortex, resulting in differential effects of cortical degeneration on accuracy and velocity. Degenerative impairment of the reflexive amplitude and velocity pathways and volitional amplitude pathway, but preservation of the volitional velocity pathway, could explain our results in PSP. While this seems improbably specific, the complexity of the networks involved in voluntary saccade generation [48] may make them especially prone to diffuse, seemingly contradictory effects in degeneration, especially in a disease with such heterogeneous pathology and phenotype as PSP [24,49], a notion supported by the considerable degree of variation in the amplitudes of volitional saccades in PSP reported here (Fig. 4C).

The lack of change over time in saccadic velocity and accuracy is, however, a more robust finding, and is encouraging in the search for novel biomarkers of Parkinsonism. Recent preliminary work by our group identified saccadic bradykinesia and hypometria in Parkinson's Disease (PD) that worsens over one-minute timescales during consecutive volitional saccades [25], in contrast to the findings in PSP reported here. While one individual with PSP did show a similar progressive decrease in saccadic amplitude during the memory-guided epoch, given this occurred in the final stage of testing and did not occur in any of the other participants, nor indeed in this participant in the other, earlier stages of the paradigm, we wonder whether this reflects fatigue. Nevertheless, a fuller characterisation of this effect in a greater sample of PSP patients is necessary to verify the validity of this potential biomarker.

It has been speculated that the progressive decrease in velocity and amplitude of movements over time in PD is the result of deficits in short-term plasticity in primary motor cortex (M1), with a lack of synaptic facilitation resulting in reduced firing rates and smaller movements over time [50]. In PSP, on the other hand, some evidence suggests plasticity is increased, with a transcranial magnetic stimulation study finding greater input-output relationships in M1, attributable to enhanced cortical plasticity [51]. We speculate that this enhanced plasticity could serve to maintain oculomotor firing rates and saccadic parameters in PSP over short time frames. Whatever the cause, the consistent lack of decrease in amplitude or velocity over time in the present study suggests that a simple reflexive, voluntary or memory-guided paradigm (all of which are easy to perform at the bedside) could represent a useful biomarker for PSP versus PD.

In conclusion, our results, in addition to novel findings on the differences between reflexive and volitional saccades, offer evidence of an important pathological distinction between PSP and PD, and may hold promise in the search for novel biomarkers to distinguish between these two diseases. Our findings, however, remain preliminary, with a major limitation being the small sample size. Furthermore, we did not record oculomotor data from patients with PD in this study, and whilst we compare findings from patients with PSP and PD, using data previously acquired using an identical paradigm, the two studies did not use the same oculographic device or analysis. Future work should therefore aim

to more comprehensively map oculomotor parameters in both PSP and PD patients, exploring a wider array of parameters, such as saccade frequency or curvature of saccade path, in the hope of identifying reliable oculomotor differences between these two diseases. If such an approach proved fruitful, it could be extended to other neurological disorders to provide possible oculomotor biomarkers for diagnosis and disease progression.

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