The effect of diabetes and ageing on the initiation of smooth pursuit eye movement

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Abstract

Aim: **To examine the initiation of smooth pursuit in a group of elderly, diabetic subjects, and to compare their performance with a group of age-matched non-diabetic subjects and a group of healthy young subjects.**
Methods: **Smooth pursuit was assessed quantitatively in 10 diabetic subjects (mean age 69.2 ± 6.8; range 58–80 years), 10 age-matched non-diabetic subjects (mean age 69.8 ± 5.2; range 64–81 years) and 10 healthy young subjects (mean age 21 ± 2.3; range 19–26 years), using infra-red oculography.**
Results: **Qualitatively, pursuit performance was similar in the healthy elderly, diabetic and young subjects. However, quantitatively statistical analysis indicated smooth pursuit latency was significantly higher in both elderly diabetic and age-matched healthy individuals when compared with healthy young individuals ($p < 0.0001$). Diabetes itself did not affect smooth pursuit latency for either leftward or rightward pursuit ($p > 0.05$).**
Conclusion: **Given that we have demonstrated there is no statistically significant difference in smooth pursuit latency between healthy elderly and diabetic elderly subjects, systemic disease in general does not appear to exacerbate the age-related alteration in pursuit we have previously reported. This result suggests that quantitative assessment of smooth pursuit might provide a means of assessing the general state of the cortex in elderly subjects.**

Key words: Ageing, Cortex, Diabetes, Pursuit

Introduction

Ageing alters processing in many areas of the brain and visual system, with neuroanatomical changes leading to behavioural changes in eye movement control.[1] As with other classes of eye movement, smooth pursuit (SP) has been reported to be modified by ageing.[2–5] However, much of the processing for pursuit is performed in cortical areas (including occipital, parietal and frontal cortices), and its dependence on a distributed cortical network means that SP is particularly sensitive to cortical insults.[6] It is therefore of limited value for localising cortical lesions. However, the corollary of this may be that SP could be useful for detecting diffuse or subtle cortical damage, and that appropriate measures of SP performance might provide a general indicator of 'cortical' health.

Past literature on the effects of ageing on SP is relatively sparse and somewhat contradictory, especially when compared with the number of studies on the effect of ageing on saccadic eye movements (see Davidson and Knox for full review[1]). It has been reported that the gain of SP is reduced in old age[2] and latency is increased.[3] However, the use of predictable target movements (either sinusoids or triangular waveforms) in these earlier studies makes it difficult to disentangle two distinct sets of neural processes: SP maintenance and initiation. Using the step-ramp paradigm[4] and taking measures to reduce anticipatory movements, it is possible to study SP initiation (its latency and gain) without prediction. Using this paradigm, the saccade that normally accompanies the beginning of SP can be delayed or abolished, allowing SP latency and initial velocity to be measured. In one small ageing study (5 subjects, mean age 67 years) in which ramps of this type were used, it was reported that elderly subjects had reduced eye acceleration and velocity but that there was no difference in SP latency.[5] This is somewhat surprising given that from the saccade results one might predict an increase in latency. However, measuring SP latency is not straightforward, and the combining of data for leftward and rightward pursuit responses can give misleading results.[7] We recently examined this issue and found that SP latency was consistently longer in elderly healthy subjects, although as a group their performance was more variable than that of younger subjects.[8]

Most such studies (including ours) have examined pursuit in elderly healthy subjects, i.e. those with no known health problem. Thus these results may not be typical of the ageing population as a whole and, more particularly, not typical of elderly patients presenting in orthoptic clinics. One issue that has yet to receive much attention is how disease in the elderly alters or exacerbates age-related alteration in function, including age-related changes in oculomotor function.

One disease prevalent in elderly individuals is diabetes mellitus, with 1 in 5 elderly adults living with diabetes.[9] While adults over 65 years comprise 12% of the

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population, they account for 41% of all diabetic patients.[9] There are two main types of diabetes: insulin-dependent diabetes mellitus (IDDM), also known as type 1, and non-insulin-dependent diabetes mellitus (NIDDM), also known as type 2.[10] The commonest form of diabetes in the elderly is NIDDM, with almost 50% of patients being over 60 years of age.[11] Despite the wealth of interest in diabetes-related ocular pathology, few studies have investigated the combined impact of diabetes and ageing on oculomotor control.[12] We have therefore examined the initiation of smooth pursuit in a group of elderly diabetic subjects and compared their performance with a group of age-matched non-diabetic subjects and a group of young subjects.

Methods

With local ethics approval and informed consent, experiments were performed on 10 diabetic subjects aged 58–80 years (mean 69.2 ± 6.8 years; the 'diabetic' group), 10 age-matched non-diabetic subjects aged 64–81 years (mean 69.8 ± 5.2 years; the 'healthy elderly' group) and 10 healthy young subjects aged 19–26 years (mean 21 ± 2.3 years; the 'young' group). All subjects had good visual acuity in the left eye with or without necessary optical correction, normal ocular movements, no history of any condition likely to affect eye movement and were on no current medication known to affect the oculomotor system. All subjects were neurologically normal. In the diabetic group all subjects were under review of an ophthalmologist for annual visual screening checks and all were free from significant ocular pathology and had no history or symptoms of neurological disease. A thorough case history was undertaken for each diabetic subject to ascertain the duration and type of diabetes. This information was confirmed by accessing the subjects' medical records. Of the 10 diabetic subjects, 7 suffered from NIDDM and 3 had IDDM.

Stimuli

For the SP experiments, subjects viewed a visual display with their left eye at a distance of 57 cm with their right eye occluded. Visual stimuli were generated by a Visual Stimulus Generator 2/5 (Cambridge Research Systems, Rochester, UK); the fixation and SP targets were 0.3°×0.3° dark squares presented on a light background. The fixation target was presented in the centre of the display for a variable period (0.5–1.5 seconds). This variable fixation time introduced a temporal uncertainty into the task which prevented prediction and anticipation. SP latencies remained consistent with visually guided SP despite the apparently high level of spatial predictability and did not decrease as the experiment proceeded. The SP target appeared randomly 5° to the right or left of fixation and moved back through the centre of the display at 14°/second. This combination of step amplitude and target speed provided a high yield of trials in which the first oculomotor response was a smooth (as opposed to saccadic) eye movement (Fig. 1). Subjects were presented with runs of 96 trials consisting of sets of four tasks (always two leftward, two rightward), presented in random order. In each set of four, both gap[13] and non-gap tasks were presented. We report here only the data for the non-gap tasks, in which as soon as the fixation point was extinguished, the SP target appeared and moved.

Eye movement recording and analysis

Horizontal eye movement was recorded by means of an infra-red corneal reflection device (IRIS, Scalar Medical, Delft, The Netherlands), and the eye position signal digitised with 12-bit precision at 1 kHz using a CED μ1401 (Cambridge Electronic Design, Cambridge, UK). The eye position and a time marker of the appearance of the pursuit target were displayed on the computer screen; data from approximately 200 ms before to 800 ms after the appearance of the target were stored on disc for analysis off-line. Eye position traces were differentiated to yield traces of eye velocity. For each trial the two
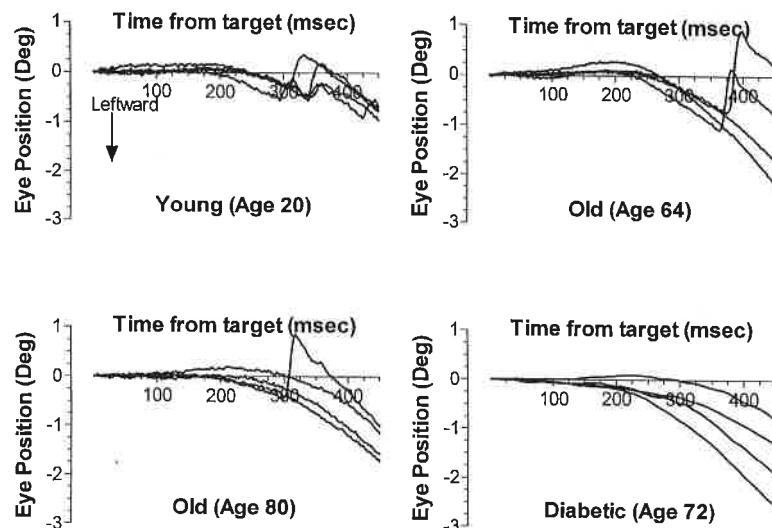

Fig. 1. Each plot shows raw eye position data for four trials in which the target stepped right and moved left. Note the substantial pre-saccadic SP, relatively stable fixation and qualitatively similar responses in all four subjects.

traces were displayed together. Leftward and rightward data were kept separate in order to identify any directional asymmetries in responses. SP latency was measured from the velocity traces using a regression technique.[14] A linear regression of velocity against time was first fitted through the data from approximately 50 ms before to 50 ms after the time of target appearance. A second regression was calculated over the initial, acceleration phase of the pursuit response. The calculated intersection between the two functions was taken to estimate the time of SP initiation.

Results

Smooth pursuit latency

Qualitatively, SP performance was similar between healthy elderly, diabetic elderly and healthy young subjects. There was no evidence of either marked inability to perform the tasks, or an increase in fatiguability or distractibility in either of the elderly groups. Although these factors were not measured, there was no apparent qualitative difference between groups at this level (Fig. 1).

Individual latencies for the young group ranged from 129 ± 28 ms (mean $\pm$ SD) to 191 ± 54 ms for leftward SP and from 128 ± 25 ms to 185 ± 63 ms for rightward SP. The mean latency was 162 ± 17 ms for leftward SP and 157 ± 18 ms for rightward SP. In the healthy elderly group, latencies ranged from 175 ± 30 ms to 365 ± 77 ms for leftward SP and from 168 ± 37 ms to 276 ± 90 ms for rightward SP. The mean latency was 210 ± 27 ms for leftward SP and 209 ± 37 ms for rightward SP. The range for the elderly diabetic group was 169 ± 32 ms to 257 ± 65 ms for leftward SP and from 178 ± 29 ms to 254 ± 74 ms for rightward SP. The mean latency was 217 ± 29 ms for leftward SP and 210 ± 27 ms for rightward SP.

We analysed these data using ANOVA, with age group ($\times 3$) and direction ($\times 2$) as factors. Overall, there was a statistically significant modulation in SP latency ($F_{5,54} = 10.5$; $p < 0.0001$). Post-hoc tests with Newman–Keuls statistics revealed a statistically significant difference in latency between the young group and both

the healthy elderly ($p < 0.0001$) and the diabetic elderly groups ($p < 0.0001$). There was no statistically significant difference between the two elderly groups ($p = 0.7$). Direction had no statistically significant effect on the data ($p = 0.8$).

We further examined the effect of age and diabetes on SP latency by plotting the individual subject means against subject age (Fig. 2). Given that there was no statistically significant difference in latency between the two elderly groups, these were combined for this analysis. While we found a statistically significant correlation between age and SP latency for leftward ($r^2 = 0.5$) and rightward ($r^2 = 0.47$) SP, there also was a considerable degree of overlap between the two groups. However, SP latency does not appear to decline progressively with age as there was no statistically significant correlation between ageing and SP latency for leftward and rightward pursuit, for either the healthy elderly or the diabetic elderly groups (Fig. 3). Fig. 3 also demonstrates the significant overlap between the healthy elderly and diabetic elderly groups.

Although diabetes itself does not appear to influence latency, the length of onset did appear to have an effect. The mean latency was lower in the subjects with a longer duration of diabetes. There was a negative correlation between duration of diabetes and latency for leftward and rightward direction but this only reached statistical significance for leftward SP ($r^2 = 0.47$; Fig. 4).

The mean SP latency was calculated for both the IDDM (mean 196.7 ± 16.1 ms) and NIDDM (mean 216.01 ± 29.4 ms) groups. Using a two-tailed t-test, there was no statistically significant difference in SP latency between the groups ($t = 2.3$; $p > 0.05$) for either leftward or rightward pursuit.

Discussion

In general, the clinical assessment of SP is purely qualitative, with the clinician observing the smoothness of pursuit as the patient tracks a slow-moving target. On a qualitative level, our results demonstrated that neither
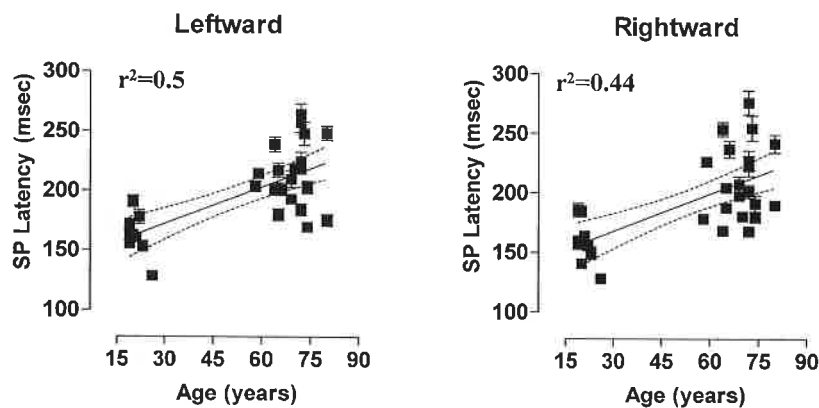

Leftward

Rightward

Fig. 2. SP latency plotted against age, for all subjects. Points are the individual means ($\pm$SE). Lines are pooled linear regressions ($\pm$95% confidence intervals). The r^2 value given for both leftward and rightward pursuit represents the statistically significant correlation between SP latency and age.
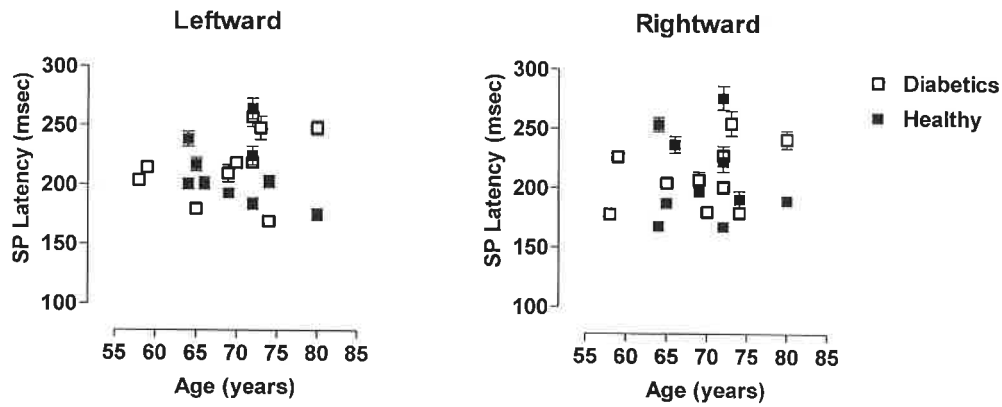
Leftward   **Rightward**

Fig. 3. SP latency plotted against age, for the healthy elderly and diabetic elderly subjects. Points are the individual means (±SE). There was no statistically significant correlation between SP latency and age for either the diabetic or the healthy elderly group.

ageing nor diabetes had an effect on pursuit performance in comparison with healthy young individuals. There was no evidence of either marked inability to perform the tasks, or an increase in fatiguability or distractibility in either of the elderly groups.

However, on a quantitative level there are statistically significant differences between the SP of elderly and young individuals. The results showed that SP latency was statistically significantly higher in healthy elderly individuals compared with healthy young individuals for both directions of SP ($p < 0.0001$). This increase in latency could be due to increased processing time at any or all stages from sensory transduction of the motion stimulus to the final behavioural output. The effective stimulus for SP is visual motion, though not necessarily target motion, on the perifoveal retina. Motion information originating in retinal photoreceptors, projecting via the magnocellular layers of the lateral geniculate nucleus and primary visual cortex, is extracted and analysed by extrastriate cortical area V5. Many studies suggest that the ability of elderly subjects to detect and respond to visual motion is reduced compared with younger controls.[15] While direct extrapolation is difficult, this sensory decline could account for a substantial proportion of the absolute increase in pursuit latency we observed.

It could be argued that the group of healthy elderly individuals participating in our study were not representative of a typical ageing population as they were all very fit, free from systemic disease and very well motivated to take part in the study. To address this, we tested a group of age-matched individuals with diabetes. Our results showed that there was no statistically significant difference in SP latency between the healthy elderly and the diabetic elderly subjects for leftward or rightward pursuit. Thus this particular systemic condition does not alter or interact with the age-related decline in SP performance we have observed. This is an important finding. Given the distributed cortical network that SP is dependent upon, it might be suggested that performance on SP tasks might provide a useful index of cortical function. If this is the case, then it appears that the diabetic subjects we examined were ageing no better or worse than their healthy counterparts.

Although it is widely accepted that diabetes is a significant risk factor for lowering visual acuity[16,17] and contributing to cranial nerve palsies,[18] the literature on the effect of diabetes on eye movement is relatively sparse. It has been suggested that saccade latencies are increased in diabetic patients.[19] This was recently confirmed by Alessandrini *et al.*,[12] who investigated whether a correlation existed between saccade latency
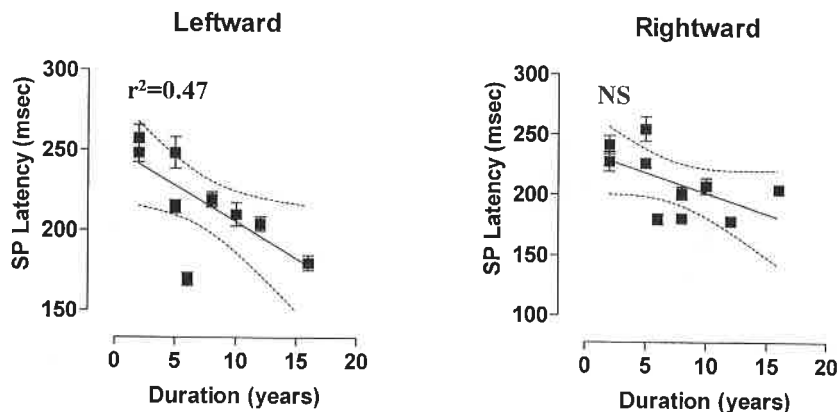
Leftward   **Rightward**

Fig. 4. SP latency plotted against the duration of diabetes (years). Points are the individual means (±SE) and lines are pooled linear regressions (±95% confidence intervals). There is a statistically significant correlation only for leftward pursuit, shown by the r^2 value. There was no statistically significant correlation (NS) for rightward pursuit.

and visual pathway function in diabetic subjects. Their study used electronystagmography (ENG) to assess saccades, and confirmed higher latencies in young diabetic subjects (mean age 25.7 ± 8.7 years) compared with age-matched non-diabetic controls. Using visual evoked potentials to assess visual pathway function, they found that this was also impaired in the diabetic group, although the impairment showed no correlation with the saccade impairment, suggesting that the latter cannot be exclusively ascribed to the dysfunction observed in the visual pathways. The authors suggest that the increase in saccade latency in IDDM subjects could be ascribed to diffuse neuronal involvement.[12] This finding is in agreement with past literature, which suggests that the radiological appearance of the diabetic brain reflects a process of accelerated ageing, with more pronounced cerebral atrophy in diabetic subjects than in age-matched controls.[20–22] The finding of no alteration in SP latency in diabetics is therefore interesting as it may suggest that this accelerated ageing does not affect the cortical areas controlling pursuit but does involve structures controlling saccades, such as subcortical areas. It may also be possible that SP latencies would be high in young diabetics compared with age-matched controls, and therefore it would be worth investigating SP latency in different age groups of subjects with and without diabetes. One could suggest that the reason for the increase in latencies in previous studies but not in ours is related to the type of diabetic subjects tested. Both Alessandrini *et al.*[12] and Virtaniemi *et al.*[19] investigated eye movement in IDDM subjects, but the majority of subjects in our present study (7 of 10) suffered from NIDDM. However, this seems unlikely, as there was no statistically significant difference in SP latency in the NIDDM subjects in our study compared with the IDDM subjects. This finding is supported by several studies investigating electrophysiological changes in diabetic brains, as all found similar changes in IDDM and NIDDM subjects.[23,24] Additionally, a recent study found that IDDM and NIDDM subjects exhibited similar, significant deficits in gaze-holding in the darkness, small changes in vestibulo-ocular reflexes (VOR) and a decrease in opto-kinetic reflexes (OKR).[25]

Many of the ocular pathologies linked to diabetes, such as retinopathy[26–28] and cataract,[29] appear to correlate with the duration of diabetes. We found that although diabetes itself did not appear to affect SP, there was a negative correlation between duration of diabetes and SP latency, i.e. latency appeared to reduce as duration of diabetes increased (Fig. 4). This correlation was present for both leftward and rightward direction, but only reached statistical significance for leftward SP ($r^2 = 0.47$). This finding is slightly surprising because in related pathologies such as diabetic retinopathy, the prevalence of disease increases with the duration of diabetes. A recent study by Florkowski *et al.*[28] revealed that the mean time for retinopathy to develop decreases by 14% (95% CI 10–17%) for each year after disease onset. Our results suggest that SP latencies are not affected in a similar way by duration of the disease and are actually lower in the individuals with the longest duration of disease for leftward and rightward SP.

Conclusion

Diabetes does not appear to exacerbate the age-related alteration in SP we have previously reported,[8] as demonstrated by the lack of any statistically significant differences in SP latency between healthy elderly and diabetic elderly subjects. This result suggests that quantitative assessment of pursuit might provide a means of assessing the general state of the cortex in older subjects, even in the presence of systemic disease.

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