Saccadic eye movement analysis as a measure of drug effects on human psychomotor performance

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1 Analysis of human horizontal saccadic eye movements can provide measurements of central nervous system depression and stimulation.

2 Effects on saccadic eye movements have been observed in normal volunteers with barbiturates, benzodiazepines, opiates and related compounds, carbamazepine, amphetamine and ethanol.

3 A suite of programmes have been developed to allow the generation, collection and analysis of saccadic eye movements using a CBM 3032, 8032 or BBC B microcomputer. The system allows almost continuous sampling and rapid analysis of movements.

Keywords eye movements saccades psychomotor testing benzodiazepines ethanol amphetamine microcomputers

Introduction

Aschoff (1968) first described the use of saccadic eye movements as a marker of drug induced central nervous system (CNS) depression. It is, however, only recently that advances in microelectronics have led to the development of simple, quick and robust methods of generating and analysing saccadic eye movements in man (Smith *et al.*, 1981; Marshall *et al.*, 1983).

Physiology of saccadic eye movements

Saccadic eye movements are rapid conjugate shifts of gaze, which can be produced by instructing a subject to follow a target made to jump instantaneously from one point to another. A typical horizontal saccade will start approximately 180 ms after the target movement (Baloh & Honrubia, 1976). Once the saccade is initiated the eyes accelerate rapidly to peak velocities that can exceed 600°/s, then decelerate to stop with the fovea on target. Normal subjects will on occasion miss the target either by under- or overshooting. This necessi-

tates a secondary corrective saccade (Westheimer, 1954; Hyde, 1959; Robinson, 1964; Weber & Daroff, 1971). The peak velocity of saccades increases with the amplitude of the movement, reaching a maximum at saccades of approximately 30° of angular movement (Baloh *et al.*, 1975b). These properties make saccades the fastest and best controlled movements of which the body musculature is capable (Fuchs & Kaneko, 1981). Control of saccadic eye movements is exerted by several central structures: parts of thalamus, large areas of cortex, the basal ganglia, the cerebellum and the superior colliculus. However, there are small groups of neurones in the brain stem, close to the oculomotor nuclei, that have discharge patterns which appear to be solely related to saccadic eye movements. It is thought that these neurones interact to form the immediate premotor machinery for saccade generation (Luschei & Fuchs, 1973; Keller, 1974).

The nerve impulses that generate the motoneurone discharge leading to a saccade originate in two types of neurone: burst neurones and tonic neurones. The former produce high fre-

quency bursts of action potentials that begin just before a saccade commences and end just prior to the eye landing on target. The duration of saccades increases linearly with the duration of the bursts. Pause neurones have a complimentary discharge pattern. When an animal fixates on a stationary target the pause neurones discharge at relatively regular rates. However, just before a saccade begins, the pause neurones show a marked reduction or pause in firing that lasts for the duration of the saccade. The length of this pause duration increases linearly with saccade duration. Electrical stimulation of pause neurones can prevent the occurrence of saccades, while still allowing smooth eye movements to occur. Keller (1974) suggested that pause neurones provided a powerful tonic inhibition to burst cells.

Tonic neurones discharge at regular rates which increase linearly with lateral eye displacement. The activity of these neurones combined with burst neurone activity has been used to explain the characteristics of moto-neurone discharge. The latter can be modelled by a pulse of firing which causes the eye to achieve rapid saccade velocities, and a step change in basal firing rate which holds the eye in the new lateral eccentric position. The pulse or burst of firing is produced by the burst cells while the step change is produced by the tonic cells (Luschei & Fuchs, 1972).

Robinson (1975) has described a neural control system for the generation of saccades. He proposed that the burst neurones are excited by some input proportional to the desired target position, and this causes the burst neurones to discharge at their maximum rate. The burst neurones are 'turned off' when the neural replica of eye position is equal to that of the target. As the burst neurones must have a low threshold to respond quickly and maximally, but must not respond to synaptic noise, they are suppressed by pause cells, so that just prior to and during a saccade the pause neurones are inhibited to allow a saccade to occur. An inhibitory feedback from the burst neurones prevents the pause neurones from firing before the end of a saccade.

The neurones involved in this complex system lie closely together and so it has proved impossible to test Robinson's model. Most of the electrophysiological work on this system has been carried out in monkeys and cats. For a more detailed review of the brain stem generation of saccadic eye movements the reader is referred to Fuchs & Kaneko (1981) and Robinson (1975, 1981).

In man saccadic eye movement analysis provides two types of measurement. Peak

saccade velocity and saccade duration are indicators of brain stem reticular formation function (Keller, 1974), while saccade reaction time is a marker of higher CNS function.

In our experience peak saccade velocity and saccade duration are very sensitive measures of CNS depression and have the advantage of being beyond voluntary control. Any attempt by the subject to slow his saccades will only decrease saccade amplitude, leaving the saccade amplitude : velocity relationship intact (Becker & Fuchs, 1970; Baloh *et al.*, 1975a).

Methods used for measuring eye movements

Several techniques for the measurement of drug effects on saccadic eye movements have been described (Smith *et al.*, 1981; Rothenberg *et al.*, 1981; Lehtinen *et al.*, 1979). These methods are largely based on the technique described by Baloh *et al.* (1975b) where the subject is instructed to follow the movements of a target presented to him on a television screen and the movement of his eyes monitored by recording the electro-oculogram (EOG). The movements of the target are determined by playing back data pre-recorded on one channel of a DC tape recorder while the EOG is recorded on a second channel. A mini-computer is used to analyse the data but before this can be done the analogue data from the tape must be converted into numerical form by digitization, which involves sampling the analogue signal at a fixed rate to produce a series of binary numbers proportional to the voltage of the analogue signal at each instant of sampling. The most used measure for the assessment of drug effects has been peak saccade velocity. However, computer analysis can extract many other parameters from the data, for example, saccade reaction time, duration, delay, peak acceleration, peak deceleration and measures of the accuracy of saccade.

We have recently developed The Cardiff Saccade Generation and Analysis System (CSGAAS) (Figure 1) based on inexpensive micro-computers (CBM 3032, 8032 & BBC Model B) (Marshall *et al.*, 1984). Saccades are generated by the computer moving a target spot on the screen of a 26" television monitor. Since the microcomputers used have video outputs (1v video, RGB or UHF) no special television or computer output circuitry is required. The memory mapped video display of these micro-computers simplifies the programming of the rapid changes of target position. The subject sits with his eyes 50 cm from the TV which

Figure 1 Block diagram of the Cardiff Saccade Generation and Analysis System (CSGAAS). The system illustrated used CBM computers. The latest version of the system uses the BBC microcomputer and does not require the 'video signal composition' component of the interface unit since the computer provides both composite video and RGB outputs either of which is suitable for direct connection to a TV monitor.

allows a maximum symmetrical target displacement of 40° . The eye-movements are monitored from the electro-oculogram measured between silver/silver chloride electrodes placed on the outer canthi of each eye. The signals from the electrodes are amplified by a differential DC amplifier and low-pass filtered (50 Hz, -3dB) before being digitized to 8-bit resolution at a sampling rate of 250 Hz and stored in the computer.

Sequences of up to 45 saccades each of predetermined displacement (10° – 40° in 5° steps) can be programmed. The interval between each successive saccade of a sequence can also be programmed. A long sequence of saccades can be broken up into periods with a rest interval

between each period (Figure 2). The first four saccades of each period are not collected to allow the subjects' responses to stabilise and the operator to compensate for any baseline drift caused by facial muscle movement of the electrodes during the rest period. We currently use two standard saccade sequences. The first (Figure 2) consists of 45 saccades divided into three 15 saccade periods which yields 10 saccades for analysis at each of 30° , 35° and 40° target displacement. The saccades are separated by equal 1.5 s intervals and the whole sequence takes 1 min 55 s to complete. The second sequence lasts only 25 s and consists of 15 saccades at 1.5 s intervals of which 11 are collected for analysis. On the completion of

Figure 2 A sample chart record of the EOG during a 45 saccade sequence. To minimise the effects of fatigue on subject performance, this long sequence is broken up into three equal 15 saccade periods. The first period consists of nine saccades at 40° and five saccades at 35° with one asymmetric saccade when the target displacement changed, which is not analysed. Similarly the second period consists of nine saccades at 35° and five at 40° and the third period of nine saccades at 40° and five at 30° . When the settling saccades, the first four of each period, are ignored this results in 10 analysable saccades at each of 40° , 35° and 30° .

each sequence the digitized EOG data is written to floppy disk for permanent storage prior to analysis.

We chose to use an equal interval between saccades because our early results indicated that the interval between saccades could significantly affect the dynamics of the saccades. The 1.5 s interval chosen was designed to be sufficiently short to prevent loss of concentration between saccades and hence a startle response on the next saccade but not so short that the subject is driven by the rapid regular movements of the target and begins to anticipate them. The use of a microcomputer to generate the target displacement and digitize the EOG data simultaneously has several advantages besides cost. The operator is not bound by a pre-recorded experiment but can easily change any of the saccade generation parameters during a recording session. The intermediate tape recording of the EOG data and the inevitable introduction of noise into the signal that this process introduces is avoided. The data is available for immediate analysis after collection which allows data to be analysed before the patient is released.

Saccade analysis is carried out in two stages. First the raw data is recovered from the floppy disk and each saccade in the sequence is analysed separately. The first and second derivatives (velocity and acceleration respectively) are calculated at each sampled point (Figure 3) and then the actual amplitude of the saccade, the delay between target movement and the start of the eye movement, the peak velocity, the peak acceleration, the peak deceleration, the duration of the movement and the accuracy in terms of percent overshoot and/or undershoot are extracted. The programme recognises eight conditions which would invalidate the analysis. If one of these conditions is detected the saccade is rejected from the analysis and an error number indicating the reason for rejection printed. Since the target displacement of each saccade is pre-programmed the EOG for each saccade can be calibrated by observing the signal before target movement and at a time after movement when the eyes will have fixed on the new position of the target. This saccade by saccade calibration ensures that changes in electrode characteristics will be compensated.

The final stage of the analysis involves the calculation of the values of each parameter at a fixed saccade amplitude by fitting quadratic functions or straight lines through the actual saccade angle versus each of the other parameters in turn using the method of least squares. The influence of outliers is minimised by carrying out each fit twice and weighting the

Figure 3 Computer printout of a portion of the computer sampled data for a single saccade. The top panel shows the digitised EOG data which measures eye position. Each symbol represents the magnitude of the EOG at the instant of sampling. There is an interval between samples of 4 ms. The data on the lower two panels is derived from the digitised EOG by numerical differentiation. The middle panel shows the first derivative which gives the eye velocity at each instant of sampling. The lower panel is the second derivative of the EOG which gives the acceleration of the eyes at each sampled point.

second fit with $1/(1.64)^2$ if the residual is within the 90% probability region or with the reciprocal of the square of the number of s.d.s from the fitted line if it is outside this range. This reduces the influence of outliers without giving undue weight to points which were close to the first fit. The value of each parameter at saccade angles of 30°, 35° and 40° is calculated by interpolation.

Some normative data from our experiments are shown in Table 1.

Results of studies on eye movements

Benzodiazepines

The effects of diazepam on saccadic eye movements were first reported by Aschoff (1968)

Table 1 Normative data from 12 subjects were measured on two occasions separated by at least 1 week. Measurements were started at 09.00 h on each occasion. Each sequence of stimulation consisted of 11 saccades at 35°. Five sequences were measured on each occasion. The data presented is peak velocity in °/s for a displacement of 35°. The range, the mean, the standard deviation (s.d.) and the coefficient of variation (CV%) for each subject on each occasion is shown.

Subject	First occasion				Second occasion			
	Range	Mean	s.d.	CV%	Range	Mean	s.d.	CV%
1	388–429	417	16.6	3.98	404–545	455	62.6	13.76
2	384–417	405	13.0	3.20	442–460	454	7.3	1.62
3	339–380	362	14.9	4.10	380–429	408	20.4	5.0
4	415–541	485	48.2	9.9	510–589	545	30.6	5.62
5	441–470	457	11.6	2.54	385–416	402	11.3	2.8
6	489–543	523	22.6	4.32	467–478	474	6.0	1.27
7	423–469	439	18.1	4.12	379–430	395	26.8	6.78
8	474–529	518	25.7	4.96	466–513	501	21.2	4.23
9	563–581	571	7.1	1.23	541–635	549	37.4	6.4
10	583–615	596	12.0	2.02	609–639	613.2	4.1	0.63
11	483–500	487	8.5	1.74	488–498	493	4.2	0.86
12	500–553	517	27.5	5.32	462–518	490	23.0	4.69
Mean of all subjects		481.3		3.95		484.5		3.63
s.d.		69.0		2.28		69.5		2.27
CV%		14.33				14.34		

who gave 5–10 mg intravenously to 12 healthy subjects. He obtained a dose-related reduction in the velocity of 20° saccades associated with a decrease in accuracy through undershooting and prolonged reaction time. Subsequently diazepam has been used orally in eye movement studies (Gentles & Llewellyn-Thomas, 1971; Brand *et al.*, 1974; Rothenberg & Selkoe, 1981; Bittencourt *et al.*, 1981a). When given orally diazepam reduces saccade velocity and prolongs duration of the movement, but no change in reaction time or accuracy has been reported.

We have recently examined the effects of 5 mg of diazepam given intravenously to 12 healthy drug free subjects and have seen a marked decrease in peak saccade velocity and increases saccade duration. In addition, a very striking decrease in accuracy was seen, resulting from undershooting of the eye on the target. This latter change followed a different time course from the other effects, peaking within the first minute and decaying to placebo levels within 30 min whereas peak saccade velocity and saccade duration deteriorates more slowly and changes persisted for over 1 h. It is probable that central levels of diazepam rise too slowly when the drug is given orally for this hypometric effect to be seen.

Tedeschi *et al.* (1984) compared the rate of entrance of two benzodiazepines into the CNS following intravenous administration. Dia-

zepam and lorazepam were compared using the method of Smith *et al.* (1981). Their results showed that diazepam produces its peak effect most rapidly while lorazepam, a less lipid soluble drug, is relatively slow in onset (Figure 4).

Numerous other benzodiazepines have been shown to produce a fall in saccade velocity and prolongation of duration (see Table 2).

The development of tolerance and cross tolerance to benzodiazepines has been a subject of much interest, and because saccadic eye movements are so sensitive to benzodiazepines they provided an ideal technique with which to examine the phenomenon. Griffiths *et al.* (1983) investigated the effects of chronic administration of nitrazepam (long elimination half-life) and temazepam (short elimination half-life) on normal subjects and showed that the residual performance impairment produced by nitrazepam on the first day of treatment had disappeared by day 6, despite much higher serum concentrations (Figures 5 and 6). Temazepam on the other hand produced no residual effects on day 1 but by day 6, with slightly higher serum concentrations, a significant performance impairment was seen. This would suggest tolerance had occurred to nitrazepam, possibly by desensitization of the benzodiazepine receptor, but not to temazepam. One explanation for this difference might be that the receptors in the central nervous system are

Figure 4 Peak saccade velocity (degrees/s) against time (min) for (a) 2 mg intravenous lorazepam and (b) 5 mg intravenous diazepam. In both cases ● is the active treatment and ○ is placebo.

exposed for much longer periods to a high concentration of nitrazepam, giving more opportunity for tolerance to develop.

Following on from this study we investigated cross tolerance between nitrazepam and diazepam, using three treatment regimes: (i) nitrazepam 10 mg nightly for 6 days followed by a challenge dose of 10 mg of diazepam on the morning of day 7, (ii) placebo nightly for 6 days followed by 10 mg of diazepam, and (iii) nitrazepam 10 mg for one night only, followed by 10 mg of diazepam. The saccade velocity results are shown in Figure 7. Pre-diazepam there was no significant difference between

treatments. However, after 10 mg diazepam had been given a significant difference between placebo treatment and 1 night's nitrazepam pretreatment developed. Conversely the 6 nights' pretreatment with nitrazepam failed to show a significant difference from placebo + diazepam. Diazepam was more potent in reducing peak saccade velocity after 1 night's pretreatment than on its own. However, after 6 nights pretreatment (with serum concentrations of nitrazepam almost twice those after only 1 night's nitrazepam) diazepam produced a smaller decrease in velocity than on its own. This suggests that at these doses, some degree of cross tolerance between diazepam and nitrazepam exists.

Ethanol

Ethanol has been shown to affect saccadic eye movements by many groups (Lehtinen *et al.*, 1979; Baloh *et al.*, 1979; Bittencourt *et al.*, 1981b; Tedeschi *et al.*, 1983d; Jantti *et al.*, 1983). All groups reported a decrease in velocity and in some cases an increase in duration. One group (Jantti *et al.*, 1983) reported a change in reaction time following intravenous ethanol. They demonstrated a biphasic effect of ethanol on reaction time, since 15 min after the start of infusion a decrease in saccade reaction time was seen.

Saccadic eye movements have also been used to evaluate ethanol-drug interactions: ethanol + tetrahydrocannabinol (Baloh *et al.*, 1975) ethanol + meptazinol (Tedeschi *et al.*, 1984). In the latter study meptazinol and ethanol were shown not to have a synergistic effect since performance decrement due to ethanol was not enhanced by the meptazinol pretreatment. Unpublished studies from our laboratory have shown that dextropropoxyphene also does not significantly enhance the effect of ethanol on eye movements, although it markedly increases

Table 2 Studies demonstrating a reduction in peak saccadic velocity by benzodiazepines (other than diazepam).

Chlordiazepoxide	30 mg oral 25 mg i.v.	Gentles & Llewellyn-Thomas (1971) Tedeschi <i>et al.</i> (1983c)
Temazepam	20 mg oral 20 mg oral	Bittencourt <i>et al.</i> (1981a) Griffiths <i>et al.</i> (1983)
Flurazepam	15 mg oral	Bittencourt <i>et al.</i> (1981a)
Nitrazepam	5 mg oral 10 mg oral	Bittencourt <i>et al.</i> (1981a) Griffiths <i>et al.</i> (1983)
Desmethyldiazepam	10 mg oral	Bittencourt <i>et al.</i> (1981a)
Clonazepam	1 mg oral	Bittencourt <i>et al.</i> (1981a)

Figure 5 Nitrazepam (10 mg, ▲), temazepam (20 mg, ●) and placebo (■) were given nightly for 6 days. On the first and the sixth night peak saccade velocity was measured at 22.00 h (time of drug intake), 23.00, 07.00 and 10.00. Significant performance impairment (between drug and placebo) occurred with nitrazepam on day one at 23.00 h and 07.00 h and with temazepam on day 6 at 23.00 h. Eight subjects took part in the study. * $P < 0.05$.

the depressant effect of ethanol on respiratory drive. Baloh *et al.* (1975) in a complex study of varying concentrations of tetrahydrocannabinol and ethanol concluded that the eye movement effects of the latter overshadowed those of tetrahydrocannabinol.

Barbiturates and non-barbiturate anticonvulsants

Bittencourt (1981) observed a significant decrease in peak saccadic velocity at 4 and 8 h after 1000 mg of carbamazepine was given to five healthy subjects. In the same experiment no effect was produced by single oral doses of phenytoin (500 mg and 1000 mg) carbamazepine (400 mg) and sodium valproate (600 mg) when compared with placebo. Phenobarbitone was not investigated. However, in a later study (Tedeschi *et al.*, 1983b) oral amylobarbitone sodium (200 mg) was shown to produce a decrease in peak saccade velocity which was maximum at 2 h and was still significantly different from placebo at 6 h. The maximum impairment of eye movement performance ranged between 25–29%.

Figure 6 Serum concentration (mean $\pm$ s.d.) data for Figure 5. Nitrazepam can be seen to have accumulated over the 6 day period, while temazepam had not.

Opiate and related compounds

Rothenberg *et al.* (1980) reported that oral methadone decreased the accuracy of saccadic eye movements (from increased undershooting) and increased their reaction time; they did not see a decrease in peak saccade velocity or increase in saccade duration. Their interpretation of this data was that methadone was affecting specific sensory rather than motor components of saccadic response. More recently Richens *et al.* (1983) compared the effects of intramuscular papaveretum (20 mg) with intramuscular meptazinol (100 mg) on saccadic eye movements. Unlike Rothenberg *et al.* (1980) they reported a highly significant decrease in peak saccadic velocity with both these opiate or opiate-like compounds (Figure 8). Tedeschi *et al.* (1984d) demonstrated that

Figure 7 Seven volunteers received either 6 nights of nitrazepam (10 mg, ●) or 6 nights of placebo (▼) or 1 night of nitrazepam (10 mg, ■). These pretreatments were all followed by oral diazepam (10 mg). Peak saccadic velocity following diazepam ingestion is shown in Figure 7. The asterisks marked against the ■ symbols represent significant differences from ▼; those against the ● symbols represent significant differences from ■. There were no significant differences between placebo and 6 nights' nitrazepam pretreatment.

* $P < 0.05$, ** $P < 0.01$.

Figure 8 The effects of intramuscular meptazinol (100 mg, ●) and intramuscular papaveretum (20 mg, ■) on peak saccade velocity (°/s) 1 h and 3 h after administration compared with placebo (○) (reproduced from Richens *et al.* (1983) with permission).

* $P < 0.001$.

meptazinol given orally (200 mg 3 hourly for four doses) did not significantly affect saccadic eye movements. Recent studies (unpublished) in our laboratory have shown that oral dextropropoxyphene (65 mg) produces a significant reduction in peak saccade velocity when compared with placebo but failed to change saccade reaction time.

Hence it would seem likely that the potent opiate compounds, methadone and papaveretum, can affect both specific sensory and motor components of saccadic eye movements, while dextropropoxyphene and meptazinol only alter motor components.

The differences between Rothenberg's studies and ours are probably due to different methods. In our studies the technique of Marshall *et al.* (1984) was used, which has been optimized to detect changes in velocity and duration of eye movements.

Amphetamine

Single oral or intravenous doses of dextro amphetamine sulphate 15 mg and placebo were given to volunteers in a study carried out by Tedeschi *et al.* (1983). Saccadic eye movements were measured at intervals of up to 1 h (intravenous route) and 6 h (oral route) after drug administration. Amphetamine produced no significant effects on saccadic eye movements after oral administration. However, when given parenterally it abolished the effect of fatigue on peak saccade velocity (Figure 9) and duration, and significantly shortened saccade reaction time in comparison with placebo.

Correlations between eye movements and other variables

Assessment of correlations between saccadic eye movements and other measures of psychomotor performance or serum drug concentrations are infrequent in the literature. There is evidence that negative linear correlations exist between peak saccade velocity and the serum concentrations of temazepam, diazepam and nitrazepam (Bittencourt, 1981). After nitrazepam and diazepam the same author reported relatively strong linear correlations between peak saccade velocity and subjective ratings of wakefulness and co-ordination, while after placebo temazepam, flurazepam and desmethyldiazepam a linear relationship was not observed. Bittencourt *et al.* (1981b) in another study examining the effects of ethanol observed a

Figure 9 Peak saccade velocity, before and after an intravenous injection of (+)-amphetamine, 15 mg (○) and placebo (●). Each value is the mean of six observations $\pm$ s.d.

significant correlation between blood ethanol levels and peak saccade velocity. Jantti *et al.* (1983), giving ethanol by infusion, noticed significant correlations between subjective feelings of drunkenness and mean saccade velocity duration and reaction time.

Conclusion

Saccadic eye movement analysis provides a novel method of psychomotor assessment. Independent groups have reported that eye

movements are sensitive to a wide range of drugs. They can be frequently and quickly measured without exhausting the subjects taking part, and, once initiated, are beyond voluntary control provided that the angular movement does not exceed 60°. An important use of saccadic eye movement analysis is in following the time course of drug action. When used in conjunction with other tests of psychomotor performance and cognitive function, a comprehensive profile of a drug's CNS effects and duration of action can be produced.

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