Comparison of the main sequence of reflexive saccades and the quick phases of optokinetic nystagmus

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Abstract

Background/aims—Abnormalities in the saccadic main sequence are an important finding and may indicate pathology of the ocular motor periphery or central neurological disorders. In young or uncooperative patients it can be difficult eliciting a sufficient number of saccades to measure the main sequence. It is often assumed that the quick phases of optokinetic nystagmus (OKN) are identical to saccades. If this were the case, it would be feasible to use OKN, an involuntary response that is easily evoked, as a simple way of eliciting many saccades. The aim of this study was to determine whether reflexive saccades and the quick phases of OKN are indeed identical, and whether OKN quick phases could have a clinical role in identifying patients with slow saccades.

Methods—OKN and reflexive saccades were recorded from 10 healthy adults using an infrared limbus eye tracker and bitemporal DC electro-oculography simultaneously. OKN was stimulated by rotating a full field patterned curtain around the subject at 10–50°/s. Reflexive saccades were elicited to red LED targets at 5–20° eccentricity.

Results—OKN quick phases tended to have a longer duration compared to saccades, but these differences were not significant. OKN quick phases had a slightly lower peak velocity compared to saccades, which was statistically significant ($p < 0.05$).

Conclusion—The main sequence for duration is the same for reflexive saccades and OKN quick phases. The main sequence for peak velocity is slightly faster for reflexive saccades than OKN quick phases, but the difference is unlikely to be of clinical significance. As an illustration of the potential of this technique, the authors demonstrate that OKN quick phases show similar slowness to saccades in a child with brainstem pathology caused by Gaucher disease type III. It is concluded that recording OKN may be a simple clinical means for approximating the main sequence.

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Both the duration and peak velocity of saccades can be characterised by their stereotypical relation with respect to saccade amplitude. This relation is known as the main sequence.^{1,2} For saccades above about 4°, duration increases linearly with amplitude. Linearity is lost at the larger amplitude end of the spectrum around 50°. Peak velocity also increases with amplitude but there is a progressive saturation beyond amplitudes of 20°, with asymptotic values of about 500°/s.³ Unlike the relation between duration and amplitude, that between peak velocity and amplitude is non-linear.

It is impossible to voluntarily alter the velocity of a saccade^{4,6} and thus significant slowing is regarded as a pathological sign.³ Slow saccades with a restriction of ocular motility usually reflect abnormalities in the ocular motor periphery, such as ocular muscle or ocular motor nerve paresis, or lesions of the medial longitudinal fasciculus. Conjugate slow saccades in patients with a full ocular range are usually caused by central neurological disorders.³ To identify patients with slow saccades it is preferable to record their main sequences for duration and peak velocity,⁷ and therefore it is necessary to elicit a large number of saccades over a range of amplitudes. This can be difficult to achieve in infants and uncooperative patients, or in patients who already have difficulty in triggering saccades. Indeed, in children with saccade initiation failure (SIF) (“ocular motor apraxia”), it is crucial to detect any slowing of saccades, as this can distinguish progressive neurological disease from the more benign classic congenital SIF (Cogan’s apraxia).⁸ In this study we investigated the possibility of measuring the speed of quick phases of optokinetic nystagmus (OKN) as a substitute for measuring saccade speed, as OKN is an involuntary behaviour that can be easily evoked from most patients, even in infancy.

Clinical and neurophysiological studies have indicated that horizontal saccades and the quick phases of vestibular and optokinetic nystagmus (OKN) have the same anatomical substrate in the paramedian pontine reticular formation (PPRF).^{9–13} Therefore, a priori, it seems plausible that saccades and quick phases should have similar speeds, and that a disease

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process causing a slowing of saccades should also lead to slowing of quick phases. A number of investigators have compared the main sequences for duration and/or peak velocity of saccades and quick phases of optokinetic or vestibular nystagmus (VN) showing some degree of similarity, but some inconsistencies have also been reported. Thus, in monkeys and cats it has been shown that spontaneous saccades and the quick phases of vestibular nystagmus, induced by rotation, share the same temporal characteristics.¹⁴⁻¹⁵ In humans, some studies have concluded that voluntary saccades, elicited to fixed targets in the light, are similar to OKN quick phases.¹⁶⁻¹⁹ In contrast, Henriksson *et al*²⁰ and Gavilán and Gavilán²¹ found some significant differences between these rapid eye movements. Both groups of investigators found that saccades had a significantly higher velocity (peak velocity measured by Henriksson *et al*; average velocity measured by Gavilán and Gavilán) than OKN quick phases. These discrepancies may reflect methodological differences. Some investigators have measured only duration, others only velocity (peak velocity or average velocity), and some both. Also different studies have compared the fast phases of nystagmus with voluntary saccades elicited under different condition (light and/or dark; eyes open/eyes closed). Further, different recording techniques (electro-oculography; infrared reflection) and signal processing may have produced different results.

In this study we re-examine this issue with the ultimate aim of being able to routinely measure the main sequence from OKN quick phases for clinical use. Here, we compare the peak velocity and duration main sequences of reflexive saccades with OKN quick phases in normal adult subjects in the light. We also compare two eye movement recording techniques used simultaneously, infrared limbal reflection (IR) and DC electro-oculography (EOG). IR was chosen because it is very accurate; however, it is cumbersome and of limited value in the paediatric clinical setting. In our paediatric eye movement laboratory we routinely use EOG, which is clinically practical for patients of all ages but not as accurate as IR. Before we could consider applying this technique for recording the main sequence in infants and children we felt that it was necessary to determine that both recording methods yielded similar results. Further, as discussed above, in the literature some investigators have reached opposing conclusions regarding whether saccades and quick phases are the same in humans. These discrepancies could be explained by the choice of recording technique. By using both infrared tracking and electro-oculography we controlled for this variable.

Finally, in the discussion we will illustrate the measurement of the main sequence with OKN from a child diagnosed with neuronopathic Gaucher disease (type III), a condition characterised by severe SIF and slow saccades.⁸

Methods

Ten healthy adult subjects aged between 25 and 48 years (mean 28.4 years) were recorded. None had a history of strabismus or any known neurological or ocular motor problems. Horizontal eye movements were measured using an infrared limbus eye tracker (Iris, Skalar Medical, Delft, Netherlands) and bitemporal DC electro-oculography (EOG) simultaneously. The infrared limbus eye tracker (IR) had a horizontal linear range of plus or minus 25° with an accuracy of 3 min arc. For the EOG recording, self adhesive silver/silver chloride electrodes were placed at the outer canthus of each eye, and a common mode reference electrode was sited at the mid-forehead. Subjects' heads were supported in a chin rest and the importance of keeping their heads still was stressed. Alertness was maintained by frequent verbal encouragement. Subjects were randomly assigned as to whether they had horizontal OKN or reflexive horizontal saccades tested first.

A full field, brightly coloured, patterned curtain was used as the horizontal optokinetic stimulus.²² This was rotated around the subject for a total time of 5 minutes. The curtain was rotated rightward and leftward at speeds of 10, 20, 30, 40 and 50°/s, for periods of 30 seconds each. The direction and speed of the stimulus was randomised. Subjects were instructed to look straight ahead and keep the curtain as clear as possible, but not to track any individual feature.

The stimulus for eliciting reflexive saccades consisted of red LEDs mounted on a black horizontal stimulus arc. Saccades of 5, 7.5, 10, 15, and 20° eccentricity, to the left and right were elicited. The order of target eccentricity was randomised and a total of 40 target illuminations (20 to the left and 20 to the right) were presented at each eccentricity, in a pseudo random order. As the peripheral target was illuminated the central target was extinguished simultaneously. Only centrifugal saccades were analysed.

Eye movements recorded using IR and EOG were digitised and sampled at 1090 Hz, then stored on digital audio tape. These eye position data were filtered using a zero phase low pass digital filter (3 dB point = 64 Hz), and differentiated to give an estimate of eye velocity. A saccade or OKN quick phase (fast eye movement (FEM)) was detected when the velocity was continuously above 100°/s for at least five points. The high threshold was chosen to avoid accidental detection of slow phases and to eliminate small corrective FEMs that we were not interested in. The peak velocity of each FEM was determined. FEM onset and offset were then defined as the last points either side of the peak velocity before which the velocity fell below 10°/s. On account of the higher level of associated instrument noise, the EOG data were refiltered (3 dB point = 30 Hz) before applying the above onset/offset detection algorithm. These points were used to calculate the amplitude and duration of the FEMs. Only FEMs with an amplitude >4°

were used for regression and statistical analysis, and eye movements to the right were examined independently from those to the left. All eye movements associated with blinks were rejected.

To quantifiably compare saccade and quick phase dynamics, for each subject regressions were fitted to the duration and peak velocity main sequences for saccades and for OKN quick phases (Fig 1), and the slope and intercept values were used for statistical purposes. The relation between peak velocity and amplitude is not a linear one (Fig 1B) and therefore a logarithmic (base 10) plot (Fig 1C) was constructed for each subject, before performing linear regressions. This process is equivalent to a power law fit.

Statistical analysis was unaffected by choice of logged or unlogged slope and intercepts. For clarity, unlogged values are shown throughout the paper.

The slope and intercept values of the linear regressions are co-dependent; higher regression slopes are associated with lower regression intercepts. Thus, in order to determine if there were statistical differences between saccades and OKN quick phases, it was necessary to use a multivariate analysis of variance (MANOVA), taking the slope and intercept as the independent variables. Statistical significance is assumed at a $p=0.05$ level throughout.

Results

Our saccadic data lie within previously reported ranges. For the saccadic duration-amplitude main sequences recorded by IR we report individual values for the slope that ranged from 1.51 to 3.10 ms/deg (mean 2.10 ms/deg) and an intercept that ranged between 20.15 and 31.35 ms (see Table 1). In the literature reported individual values for the slope range from 1.5 to 3 ms/deg (with means clustered between 2 and 2.7 ms/deg) and intercept values typically range from 20 to 30 ms.^{5 7 23 24} Also the main sequence relation that we found between saccade peak velocity and amplitude is quite typical of that which has been reported previously.^{1 25 26} Our OKN measures were also similar to those reported in the literature,^{27 28} with a typical decrease in slow phase velocity gain (from values up to 0.87) with increasing optokinetic stimulus velocity.

COMPARISON OF FEMS RECORDED USING THE INFRARED LIMBUS EYE TRACKER

The duration of saccades and OKN quick phases differed slightly, but were not statistically different (see Table 1, Fig 2A). For a given amplitude, OKN quick phases tended to have a longer duration compared with saccades.

There were also differences in the peak velocity of saccades and OKN quick phases (see Table 1, Fig 2B). Statistical testing demonstrated that unlike for duration these differences were significant. For a given amplitude, OKN quick phases tended to have a lower peak velocity compared to saccades. There were some idiosyncratic differences

between eye movements to the right and those to the left. However, these differences were not statistically significant.

COMPARISON OF FEMS RECORDED USING ELECTRO-OCULOGRAPHY

As with the data recorded by IR, the differences in the duration-amplitude main sequences of saccades and quick phases were not significantly different. Similarly, as with the peak velocities recorded using IR, the differences between the peak velocity-amplitude main sequences of

Figure 1 Typical saccadic main sequences for duration and peak velocity. These plots were derived from saccades recorded from subject 6 using infrared limbal reflection. (A) Scatter plot for saccadic duration versus saccadic amplitude. Linear regression line for saccadic amplitudes $>4^\circ$ also shown. (B) Plot demonstrating the non-linear relation between saccadic peak velocity (PV) and saccadic amplitude (A). Curve fitted according to $PV = I \cdot S^{\log 4}$, where I and S are unlogged values of the linear regression intercept and slope for log PV versus log A. (C) Logarithmic plot of PV versus A, for saccadic amplitudes $>4^\circ$. Linear regression line also shown.

Table 1 Main sequence parameters recorded using infrared limbal reflection

Subject	Duration-amplitude relation								Peak velocity-amplitude relation							
	Saccades				OKN quick phases				Saccades				OKN quick phases			
	Right		Left		Right		Left		Right		Left		Right		Left	
	S ms/°	I ms	S ms/°	I ms	S ms/°	I ms	S ms/°	I ms	S	I	S	I	S	I	S	I
1	1.54	30.79	1.55	31.35	1.68	30.82	1.97	30.82	4.57	87.10	4.47	87.10	4.57	72.44	5.62	57.54
2	3.10	22.33	2.18	25.79	2.87	28.31	2.34	27.65	2.19	144.54	3.24	112.20	3.47	81.28	4.68	72.44
3	1.81	23.43	2.04	26.04	1.62	26.47	1.89	28.21	3.98	97.72	3.72	93.33	4.17	89.13	4.90	70.79
4	2.31	28.76	2.02	30.41	2.36	30.81	3.02	29.36	3.72	87.10	3.47	97.72	5.01	60.26	5.33	58.88
5	1.97	27.25	1.77	24.06	2.54	24.10	2.73	20.79	3.63	89.13	3.47	114.82	3.63	87.10	2.88	120.23
6	1.94	25.95	1.51	28.52	1.62	29.90	1.65	27.09	3.89	97.72	4.27	93.33	6.17	60.26	4.90	79.43
7	1.73	27.18	2.04	24.30	1.64	26.21	1.49	28.86	3.02	125.89	3.47	109.65	5.01	72.44	5.37	67.61
8	2.22	21.97	2.13	20.82	1.88	23.47	2.21	20.97	2.51	141.25	2.88	141.25	3.02	114.82	3.34	120.23
9	3.03	20.15	1.94	29.67	3.18	21.72	2.23	27.75	2.82	109.65	3.39	102.33	3.24	87.10	4.17	77.62
10	2.62	25.34	2.43	22.56	2.71	22.19	1.96	22.61	2.69	117.49	3.72	97.72	2.95	102.33	3.89	97.72
Mean	2.23	25.32	1.96	26.35	2.21	26.40	2.15	26.41	3.30	109.76	3.61	104.95	4.12	82.72	4.51	82.25

The slope (S) and intercept (I) values for the duration-amplitude (D-A) relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope and intercept values for the peak velocity-amplitude (PV-A) relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°, such that PV = I.S^{logA} (see Methods and Fig 1B, C).

Figure 2 Scatter plot of the saccadic and OKN quick phase main sequences for duration (A) and for peak velocity (B) for a typical subject (subject 9). Data recorded using infrared limbal reflection.

saccades and quick phases recorded by EOG were significantly different (Table 2). The main sequence parameters for duration and peak velocity recorded using EOG were

compared to those recorded using IR. No statistical differences were found. The similarities are illustrated by comparing confidence regions for each recording device (Fig 3). The ellipses represent 95% confidence bounds on the probability that the population mean slope and intercept lie within and are centred on the group means (see Tables 1 and 2). Greater intersubject variability is reflected in larger confidence regions.

Discussion

Statistical analysis demonstrated that the saccadic main sequence for duration was not significantly different from the OKN quick phase main sequence for duration. In animals it has been demonstrated that the duration-amplitude main sequence for spontaneous saccades is the same as that for VN quick phases.^{14 15} It has also been shown that both spontaneous saccades and the quick phases of VN are similarly affected by light and darkness. Three studies have compared the duration-amplitude main sequences of saccades and OKN quick phases in humans,^{16 19 29} and concluded that they were similar. Mackensen and Schumacher¹⁶ tested only two subjects, but concluded that the duration-amplitude main sequences of these FEMs were the same. They also noted that the intrasubject differences were quite marked and that there were differences between FEMs made to the right compared to the left. We also noted large intrasubject differences and for individual subjects there were also directional differences. Jürgens *et al*^{19 29} compared optokinetic quick phases to voluntary saccades. They found that the duration-amplitude main sequences for these two FEMs scattered around the same regression line. Our results support their findings and suggest that measurement of the OKN quick phases duration-amplitude main sequence in infants or uncooperative patients could be used clinically to assess the functioning of the saccade system.

We found that OKN quick phases tended to have a lower peak velocity compared to reflexive saccades. The fact that we found differences between the peak velocities of these FEMs but no differences in the duration may imply that

Table 2 Main sequence parameters recorded using electro-oculography

Subject	Duration-amplitude relation								Peak velocity-amplitude relation							
	Saccades				OKN quick phases				Saccades				OKN quick phases			
	Right		Left		Right		Left		Right		Left		Right		Left	
	S ms/°	I ms	S ms/°	I ms	S ms/°	I ms	S ms/°	I ms	S	I	S	I	S	I	S	I
1	1.50	28.00	1.71	27.19	1.68	30.72	1.78	29.42	4.47	89.13	4.27	95.50	4.47	64.57	5.62	63.10
2	2.57	19.43	2.46	23.08	3.22	19.63	3.43	19.95	2.04	138.04	3.02	114.82	3.16	79.86	4.07	75.86
3	2.27	16.44	2.33	16.24	2.97	17.83	2.83	18.34	3.89	104.71	3.72	97.72	4.27	91.20	4.47	79.43
4	2.18	27.12	2.39	27.80	2.69	28.35	3.25	26.07	3.63	85.11	3.63	91.20	4.47	64.57	4.90	56.23
5	1.71	27.19	1.63	26.85	2.39	26.32	2.48	28.87	4.27	79.43	3.16	102.33	3.72	74.13	3.16	102.33
6	1.92	25.34	1.58	28.60	1.63	26.85	2.13	23.43	3.72	91.20	3.98	97.72	5.62	53.70	5.37	70.79
7	1.96	26.97	2.05	26.47	1.97	25.80	2.42	27.20	3.09	128.82	3.24	117.49	4.57	79.43	5.01	68.79
8	1.85	21.67	1.78	18.38	2.17	19.00	2.10	15.71	2.57	141.25	2.69	131.83	3.02	117.49	3.02	120.50
9	2.86	18.50	2.35	26.01	3.34	21.15	3.26	18.61	2.51	117.49	3.09	107.15	2.82	91.20	3.24	79.43
10	2.30	19.11	2.44	18.59	2.43	19.51	2.53	19.73	2.24	134.90	2.88	114.82	2.57	97.72	3.72	91.20
Mean	2.11	22.98	2.07	23.92	2.45	23.52	2.62	22.73	3.24	111.01	3.37	107.06	3.87	81.39	4.26	80.77

The slope (S) and intercept (I) values for the duration-amplitude (D-A) relation were obtained from a linear regression of the main sequence for duration for amplitudes >4°. The slope and intercept values for the peak velocity-amplitude (PV-A) relation were obtained from a linear regression of the logged main sequence for peak velocity for amplitudes >4°, such that PV = I.S^{logA} (see Methods and Fig 1B, C).

reflexive saccades and OKN quick phases have slightly different shaped trajectories (this is currently under investigation). In the literature OKN quick phases in humans have variously been reported to have a lower peak velocity than saccades,²⁰ lower peak velocity at greater amplitudes (>20°) than saccades,¹⁷ or indistinguishable from saccades.^{16–19, 29} The different conclusions reached may be partly explained by exactly what type of saccade was used for comparison. The peak velocity of saccades differs depending on the type of saccade elicited (in the light or dark, reflexive or voluntary). Indeed, it is believed that the neural mechanisms generating reflexive and voluntary saccades are at least partially different,³⁰ and this could result in them having different dynamics. Erkelens and Hulleman³⁰ attempted to determine the neural mechanisms controlling reflexive and voluntary saccades by looking at the effects of lesions. They concluded that voluntary saccades are most probably generated via the frontal eye field

Figure 3 Illustration of bivariate confidence regions comparing results recorded using infrared limbal reflection, and those recorded using electro-oculography. Ellipses show 95% confidence regions for the population slope and intercept of the duration (A, B) and peak velocity (C, D) main sequence parameters. (A, C) Saccades. (B, D) OKN quick phases.

pathways, whereas collicular pathways seem to be more important in the control of reflexive saccades. Also the peak velocities of saccades differ depending on the direction of the saccade. For example, it is well documented that centripetal saccades have faster kinematics than centrifugal saccades.^{26 31–35} In our experiment we compared reflexive centrifugal saccades with OKN quick phases. We chose to do this because quick phases are essentially centrifugal movements since they not only reset the eyes but also move the eyes in an anticomensatory direction (that is, in the opposite direction to stimulus movement, “contraversion”).³⁶ A further consideration is the fact that in humans the OKN response differs depending on the attentional state of the subject. Depending on the instructions given by the investigators, subjects can assume different attitudes towards an optokinetic stimulus. Ter Braak³⁷ distinguished between “look-OKN” and “stare-OKN.” Stare-OKN is obtained by instructing the subject to look passively at the stimulus, without any deliberate attempt to pay attention to specific

features. Stare-OKN has a low gain, low amplitude, and frequent quick phases.³⁸ In contrast, look-OKN is elicited by instructing the subject to track single details in the moving stimulus. The OKN exhibited has a high gain, large amplitude slow phases, and infrequent quick phases.³⁸ Becker³⁹ suggested that the quick phases of look-OKN could conceivably resemble goal directed saccades, whereas the quick phases of stare-OKN, which do not profit from the selection of identified visual targets, may be slower. We attempted to elicit stare-OKN by instructing our subjects to look straight ahead and keep the curtain as clear as possible but to not track any individual target. Therefore, Becker’s argument may explain why we found that the peak velocities of reflexive saccades were higher than the quick phases of OKN. However, we did not really know the mental set of the subjects and the OKN elicited was most probably a mix of look-OKN and stare-OKN.

Another consideration is the range of amplitudes that are compared. Henriksson *et al*²⁰ found that the differences between the peak velocities of saccades and OKN quick phases were more pronounced at greater amplitudes. Dichgans *et al*¹⁷ found that the differences between the peak velocities of saccades and OKN quick phases were statistically significant only at amplitudes greater than 20° (and only to the left). This may explain why investigators who compared only a limited range of amplitudes (Mackensen and Schumacher¹⁶ 0–20°; Sharpe *et al*¹⁸ 0–10°) found no differences in the peak velocities of saccades and OKN quick phases. We limited comparisons to amplitudes between 4–25°, because of the restrictions in the linear range of the IR eye tracker.

The peak velocity differences that we found are slight enough that it seems unnecessary to hypothesise separate neural circuits for the generation of these two types of rapid eye movements. The small differences may only indicate that rapid eye movements are initiated in the same neural circuits but in slightly different ways.

The duration values we obtained using EOG were in good agreement with those recorded using IR, although scatter was greater, owing to the increased noise inherent in the EOG measurement technique. Bahill *et al*¹⁰ established their normative database of saccadic durations using IR. Compared with other laboratories where EOG had been used, Bahill and co-workers’ data coincided reasonably well (see Becker³⁹). On the other hand, Baloh *et al*⁷ using EOG, reported much larger values for saccadic durations. However, this is probably not because they used EOG, but was more likely the result of their signal processing.

We also found that the peak velocity main sequence parameters for saccades and OKN quick phases were similar whether recorded using IR or by EOG. In the literature saccadic peak velocities recorded using IR^{2 25} are comparable with EOG studies.^{7 39} Clearly different from most other work is the normative database of Bahill *et al*,⁴⁰ with its extremely

Figure 4 The OKN main sequences for duration (A) and peak velocity (B) of a patient with Gaucher disease type III and an age matched control.

large peak velocities. However, these differences are unlikely to be attributable to the use of IR reflection, but rather because they eliminated any saccades that were noticeably slower than optimum, as conceivably affected by "fatigue." Our results, together with those discussed above, confirm that, in the clinical setting, it is suitable to use EOG to measure the duration and peak velocity of saccades and OKN quick phases.

To illustrate the usefulness of this technique we examined a child with Gaucher disease type III (GD III) and a child that was age matched. Where it has been possible to assess horizontal saccades in children with GD III they have been reported as slow.⁸ It is very important to recognise slow saccades in these patients since in the presence of otherwise normal ocular motility and range, slow saccades in association with saccade initiation failure (seen in all GD III patients) indicates severe brainstem disease. We recorded eye movements using bitemporal EOG and used the same protocol for eliciting OKN as above. The data were analysed in the same way, although the threshold for peak velocity was reduced to 10°/s. In the child with GD III, OKN quick phases had a longer duration and lower peak velocity compared with the age matched control (Fig 4). Statistical analysis demonstrated that the differences in the OKN quick phases between the patient and control were highly significant. Additional clinical studies are needed; however, this finding suggests that measuring OKN quick phases may be a simple means for approximating the main sequence and thus a useful clinical tool for identifying brainstem pathology. Furthermore, OKN is an involuntary response that is easily elicited and thus the greatest use of this technique would be in young or uncooperative patients in whom it would be impossible to determine a saccadic main sequence. Also, the simplicity of OKN testing would permit serial recordings giving objective measurement of disease progression. Currently it is not known which conditions are associated with slow saccades in infants and children; however, this technique gives us the opportunity to examine this.

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