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Deficits of smooth pursuit initiation in patients with degenerative cerebellar lesions

Carsten Moschner,[1] Trevor J. Crawford,[2,3] Wolfgang Heide,[1] Peter Trillenberg,[1] Detlef Kömpf[1] and Christopher Kennard[3]

[1]*Department of Neurology, Medical University of Lübeck, Germany,* [2]*Department of Psychology, Lancaster University and* [3]*Division of Neuroscience and Psychological Medicine, Imperial College School of Medicine, London, UK*

Correspondence to: Dr Carsten Moschner, Department of Neurology, Medical University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany

Summary

It is well known that cerebellar dysfunction can lead to an impairment of eye velocity during sustained pursuit tracking of continuously moving visual target. We have now studied the initiation of smooth pursuit eye movements towards predictable and randomized visual step-ramp stimuli in six patients with degenerative cerebellar lesions and six age-matched healthy controls using the magnetic scleral search-coil technique. In comparison with the control subjects, the cerebellar patients showed a significant delay of pursuit onset, and their initial eye acceleration was significantly decreased. These cerebellar deficits of pursuit initiation were similarly found in response to both randomized and predictable step-ramps, suggesting that predictive input does not compensate for cerebellar deficits in the initiation period of smooth pursuit. When we compared initial saccades during smooth tracking of foveofugal and foveopetal step-ramps, the absolute position error of these saccades did not significantly differ between patients and controls. In fact, none of the patients showed any bias of the saccadic position error that was related to the direction or velocity of the ongoing target motion. This work presents further evidence that the effect of cerebellar degeneration is not limited to the impaired velocity gain of steady-state smooth pursuit. Instead, it prolongs the processing time required to initiate smooth pursuit and impairs the initial eye acceleration. These two deficits were not associated with an abnormal assessment of target velocity and they were not modified by predictive control mechanisms, suggesting that cerebellar deficits of smooth initiation are not primarily caused by abnormal information on target motion being relayed to the cerebellum.

Keywords: smooth pursuit; saccade; cerebellum; prediction; motion perception

Abbreviations: ASEM = anticipatory smooth eye movements; MST = medial superior temporal area; MT = middle temporal area; PRED = predictable step-ramp stimulus; RAND = randomized step-ramp stimulus; STEP = pure step stimulus

Introduction

Human subjects use smooth pursuit eye movements to stabilize the retinal image of a continuously moving target. In most recent models (see Keller and Heinen, 1991), smooth pursuit is driven by three distinct inputs: (i) a relatively direct retinal slip signal; (ii) an internal representation of target velocity in space, derived from processed visual and proprioceptive information (e.g. Robinson *et al*., 1986); and (iii) predictions of the future location of the target in space.

If a pursuit eye movement is triggered by a new and unexpected motion stimulus, two different periods of the pursuit response can by distinguished (Keller and Heinen, 1991). The earlier pursuit initiation period is mainly driven by the retinal slip signal that accelerates the eye into the direction of the ongoing target motion after a short time required for visuomotor processing. It takes another 80–100 ms before the internally generated feedback is provided to the system (Tychsen and Lisberger, 1986; Carl and Gellman, 1987), thus leading to the second period of the pursuit, which is often referred to as the period of *pursuit maintenance*. During this period, gaze velocity finally matches target velocity, thereby keeping the target image near the fovea. In between, small saccadic eye movements commonly correct for positional errors.

Predictive input becomes most effective during repeated presentation of regular target motion. For example, during pursuit maintenance of periodic stimuli, prediction adjusts the eye velocity gain and corrects for phase lags that are due to the delays required to process visual input (Becker and

Fuchs, 1985; van den Berg, 1988; Barnes and Asselman, 1991). Furthermore, prediction modifies pursuit initiation. In healthy human subjects, comparison of initial pursuit triggered by predictable and non-predictable step-ramp stimuli demonstrated that anticipation of the target shortens the latency between target onset and the start of the visually-guided smooth pursuit response (Kao and Morrow, 1994). In addition, there is an increase in the initial eye acceleration.

The present clinical study analysed effects of degenerative cerebellar lesion on smooth pursuit initiation. The important role of the cerebellum in maintaining smooth pursuit is well established. Diffuse lesions due to cerebellar degeneration lead to a significantly decreased eye velocity during tracking of periodic stimuli (Zee *et al*., 1976; Baloh *et al*., 1986; Moschner *et al*., 1994). Animal experiments and clinical studies revealed that these deficits are attributed to lesions of the flocculus/paraflocculus (Zee *et al*., 1981; Büttner and Waespe, 1984; Noda and Warabi, 1987; Stone and Lisberger, 1990; Krauzlis and Lisberger, 1991, 1996; Waespe, 1992) or the posterior vermis (Keller 1988; Suzuki and Keller, 1988*a*, *b*; Vahedi *et al*., 1995) and its projections to the dorsal fastigial nuclei (Büttner *et al*., 1994; Fuchs *et al*., 1994; Robinson *et al*., 1997). Some authors have suggested that cerebellar dysfunction primarily disturbs the closed-loop visual pathways that maintain pursuit while sparing predictive control mechanisms (Waterston *et al*., 1992).

Cerebellectomy leads to a complete abolition of smooth pursuit eye movements in monkeys (Westheimer and Blair, 1974), suggesting that the cerebellum is required to initiate smooth pursuit. Recently, two clinical studies have reported decreased eye velocities during the initial phase of non-predictive smooth pursuit, one in patients with disseminated cerebellar lesions of various aetiologies (Lekwuwa *et al*., 1995), the other in patients with more focal lesions of the cerebellar hemispheres (Straube *et al*., 1997). Their data suggest that initial eye acceleration is impaired in cerebellar patients compared with controls, but both studies were limited by the infrared-reflection oculography method which is of limited capability in the measurement of initial eye acceleration. Furthermore, they presented conflicting findings regarding the timing of pursuit onset elicited by unpredictable stimuli. Lekwuwa and colleagues (Lekwuwa *et al*., 1995) observed abnormally delayed smooth pursuit responses in their patients, whereas Straube and colleagues found normal pursuit latencies (Straube *et al*., 1997). It remains, therefore, unclear to what extent a cerebellar lesion affects the time required to initiate non-predictive smooth pursuit.

Lekwuwa and colleagues (Lekwuwa *et al*., 1995) additionally compared smooth pursuit towards predictable and non-predictable ramp stimuli. In cerebellar patients and healthy controls, the eye velocity during the first 100 ms of pursuit tended to be higher during predictable than during non-predictable stimulation, although in the former group this difference did not reach statistical significance. It remains uncertain whether cerebellar dysfunction spares the predictive control mechanisms of pursuit initiation.

To further clarify the mechanisms of cerebellar smooth pursuit disorders, we have investigated pursuit initiation in patients with cerebellar degeneration and age-matched healthy subjects with the high resolution magnetic scleral search-coil technique. A detailed analysis of pursuit parameters is reported: first, we have measured the latency of pursuit onset and the mean eye acceleration during the initiation period of pursuit. Initial eye acceleration was then compared with the peak eye velocity that was measured during the later maintenance period of pursuit when feedback control is established. Secondly, we have assessed the efficacy of predictive control in patients with cerebellar lesions by comparing initial pursuit eye movements towards predictable and non-predictable step-ramp target movements (Rashbass, 1961). Visually triggered smooth pursuit eye movements were analysed separately from possible anticipatory smooth eye movements that are generated prior to any actual target motion (Kao and Morrow, 1994).

A further analysis was conducted to detect a possible impairment of visual velocity perception as an underlying cause of a cerebellar pursuit deficit. Derived from a more general model on the dominant role of the cerebellum in time-dependent control functions (Ivry and Keele, 1989), it has been suggested that cerebellar lesions result in a decreased perception of visual target motion that, in turn, may contribute to the cerebellar impairment of smooth pursuit. This hypothesis was supported by previous reports on deficits in the correct velocity discrimination of slow visual motion stimuli (Ivry and Diener, 1991) and in the detection of motion direction (Nawrot and Rizzo, 1995) in patients with cerebellar lesions. An association of deficient visual motion perception and smooth pursuit impairment has been found in monkeys from experimental lesions involving the neocortical areas MT (middle temporal area) and MST (medial superior temporal area) (Newsome *et al*., 1985; Dürsteler and Wurtz, 1988), and in patients with unilateral cortical lesions that probably included the analogous regions in the human parieto-occipital cortex (Thurston *et al*., 1988; Barton *et al*., 1995, 1996; Heide *et al*., 1996). Some of these patients had increased position errors of the initial saccade while tracking step-ramp stimuli that started in the contralesional hemifield, whilst these same patients were able to generate normometric reflexive saccades to a step-target jump (Thurston *et al*., 1988; Heide *et al*., 1996). This saccadic position error to constantly moving targets was most likely related to a perceptual deficit based on the erroneous estimation of the visual target velocity prior to or during the preparation of the saccade (Keller and Johnsen, 1990; Gellman and Carl, 1991). All of these patients presented with associated deficits of pursuit initiation including a delayed onset and decreased acceleration. To identify a similar perceptual deficit in patients with cerebellar lesion, we analysed

Table 1 *Summary of clinical data*

	Patient number					
	1	2	3	4	5	6
Age (years)	48	59	30	32	65	35
Diagnosis	ADCA-I	ADCA-III	IDCA	IDCA	IDCA	FA
Duration of symptoms (years)	9	5	3	5	18	9
Clinical ratings						
Standing balance impairment	3	3	1	1	4	4
Gait ataxia	2	3	1	1	4	4
Upper limb ataxia	3	2	0	1	3	3
Lower limb ataxia	2	1	0	1	4	4
Upper and lower limb hypertonia	3	1	0	0	2	0
Postural tremor	2	1	0	1	1	2
Dysarthria	1	1	1	2	0	3
Ocular movement impairment	4	2	2	1	5	4

The clinical diagnoses included autosomal-dominant cerebellar atrophy of type I (ADCA-I) and type III (ADCA-III) based on the clinical classification of Harding and colleagues (Harding *et al*., 1984), idiopathic cerebellar atrophy (IDCA) and Friedreich's ataxia (FA) (see Harding *et al*., 1984; Hammans, 1996). The clinical ratings refer to a rating scale for cerebellar functions published by Wessel and colleagues (Wessel *et al*., 1995). For the first seven categories, scores range between 0 (no dysfunction) and 4 (disabling). The last category, ocular movement impairment, summarizes the results of various bedside tests of cerebellar oculomotor function (maximum score = 8).

additionally the position error of the first saccade towards foveofugal and foveopetal step-ramp targets.

Methods

Subjects

We studied six patients with a degenerative lesion of the cerebellum (mean age 44.8 ± 14.9 years) and six healthy control subjects (mean age 48. 2 ± 17.7 years). All participants had a visual acuity of 6 out of 9 or better and normal visual fields. They did not take any medication that is known to affect eye movements and all gave their informed written consent to participate in the study, which was approved by the ethics committees of the participating institutions. The diagnosis and clinical features of the patients are summarized in Table 1. All of them showed significant cerebellar atrophy on cranial CT or MRI scans. Otherwise, the diagnosis was based on the history and clinical features; genetical analysis was not available. Except for one patient (patient 1) with pathologically prolonged visually evoked potentials and increased limb reflexes, none of the patients showed extracerebellar signs.

Data recordings

In a darkened room, subjects were seated 1.5 m in front of a semi-translucent tangent screen with their head fixed. The target consisted of a red laser dot (diameter 5 mm) that was rear-projected and moved across the horizontal meridian by means of a low inertia two-axis mirror galvanometer. In step-ramp experiments, eye movements were recorded monocularly by a magnetic scleral search-coil system in 1.8 × 1.8 m field coils (CNC Engineering, Seattle, Wash., USA). Horizontal target and eye position signals were low-pass filtered by an analogue 4-pole Butterworth low-pass filter with a cut-off at 250 Hz (–3 dB), digitally sampled at 500 Hz and stored on a computer hard-disk. Additionally, the data were displayed online by a pen recorder to provide the experimenter with immediate feedback of the subject's performance.

Experimental paradigms

Subjects were instructed to follow the visual target as accurately and as quickly as possible. During each step-ramp trial, the target stepped away from centre position and then moved with a constant velocity of 10°/s or 20°/s either in the same direction as the step (foveofugal ramp) or in the opposite direction (foveopetal ramp) before it stepped back to centre position (Fig. 1). With foveofugal ramps, the step amplitude was always 3° and the ramp duration was 400 ms. With foveopetal ramps, the step size was adjusted to the ramp velocity so that the target crossed the centre position in 200 ms in order to facilitate pre-saccadic smooth pursuit by delaying the first saccade (Rashbass, 1961). We used a ramp velocity of 10°/s (step size 2°, ramp duration 1000 ms) or 20°/s (step size 4°, ramp duration 700 ms), whereby ramp velocity and the inter-trial interval of 1500 ms were kept constant during each sequence of step-ramps.

In the *predictable step-ramp condition* (PRED), a sequence of seven identical steps to the right was followed by seven identical steps to the left and the ramp was always directed foveopetally (see example in Fig. 1A). Since we were interested in the effect of target predictability, the first trial to each direction was discarded. In the *randomized step-ramp condition* (RAND), the direction of steps and ramps

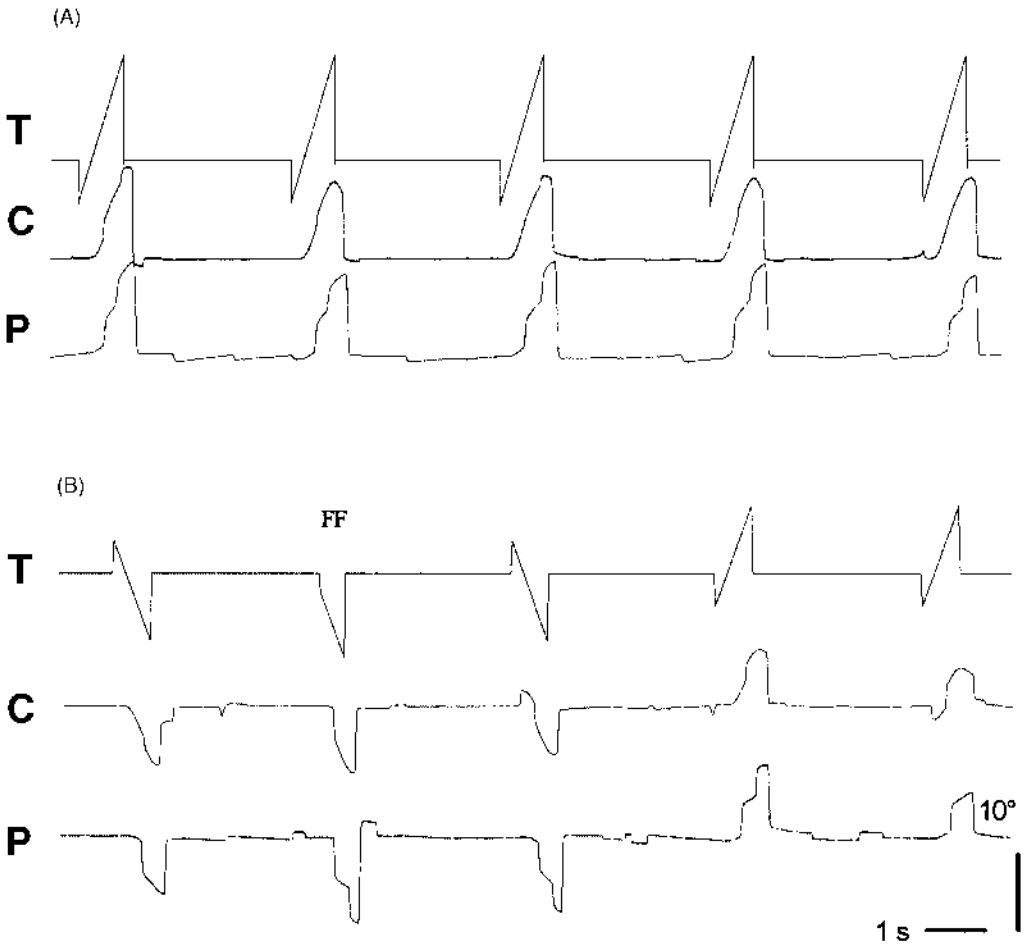

Fig. 1 Examples of smooth pursuit responses to (**A**) a predictable sequence of step-ramps where the ramp was directed rightwards and (**B**) a randomized sequence of foveofugal and foveopetal step-ramps in both directions. The traces show the target position (T), the eye movement of a control subject (C) and patient 3 with a cerebellar lesion (P). When a subject made an initial saccade towards the step direction (as the control subject did in **B**), the response was discarded from statistical analysis of smooth pursuit parameters. FF in **B** refers to an example of foveofugal step-ramps where the initial saccade precedes smooth pursuit.

varied independently in a balanced pseudo-random order, thus including foveofugal and foveopetal ramps in equal numbers (Fig. 1B).

In the third condition, *pure step condition* (STEP), the target stepped between centre position and eccentric horizontal positions at $\pm 7.5°$ and $\pm 15.0°$ without any ramp target motion in between. Target steps were presented sequentially in a balanced pseudo-random order. The STEP condition was exclusively used to evaluate accuracy and latency of non-predictive, visually-guided saccades towards a peripheral target position that remained stationary during the preparation of the saccade. For this condition, we used an infrared light eye-tracking device (Skalar, Delft, The Netherlands) instead of the magnetic search-coil system.

Data analysis

Further analysis was performed off-line using an interactive eye movement analysis software. To derive eye velocity, the eye position data were differentiated after being smoothed using a digital filter (weighted moving average: damping of –0.42 dB below 5 Hz, at least –26 dB above 40 Hz). Saccades were identified on the basis of velocity and acceleration criteria (eye velocity $>35°/s$; eye acceleration $>1000°/s^2$). In step-ramp experiments, pre-saccadic smooth pursuit was minimal during foveofugal step-ramps, so the analysis of smooth eye movements was restricted to foveopetal step-ramps.

The acceleration of a possible anticipatory smooth eye movement (ASEM) was detected by the slope of a linear regression line that was fitted to a 180 ms-segment of velocity data starting 80 ms prior to ramp onset (Fig. 2). A second regression line was fitted to the 60 ms-segment that followed the point where the eye velocity exceeded the range of the first regression line by >3 SD (see Carl and Gellman, 1987; Kao and Morrow, 1994). The time of the visually triggered pursuit onset was then defined by the time point where the two regression lines crossed. The eye acceleration during

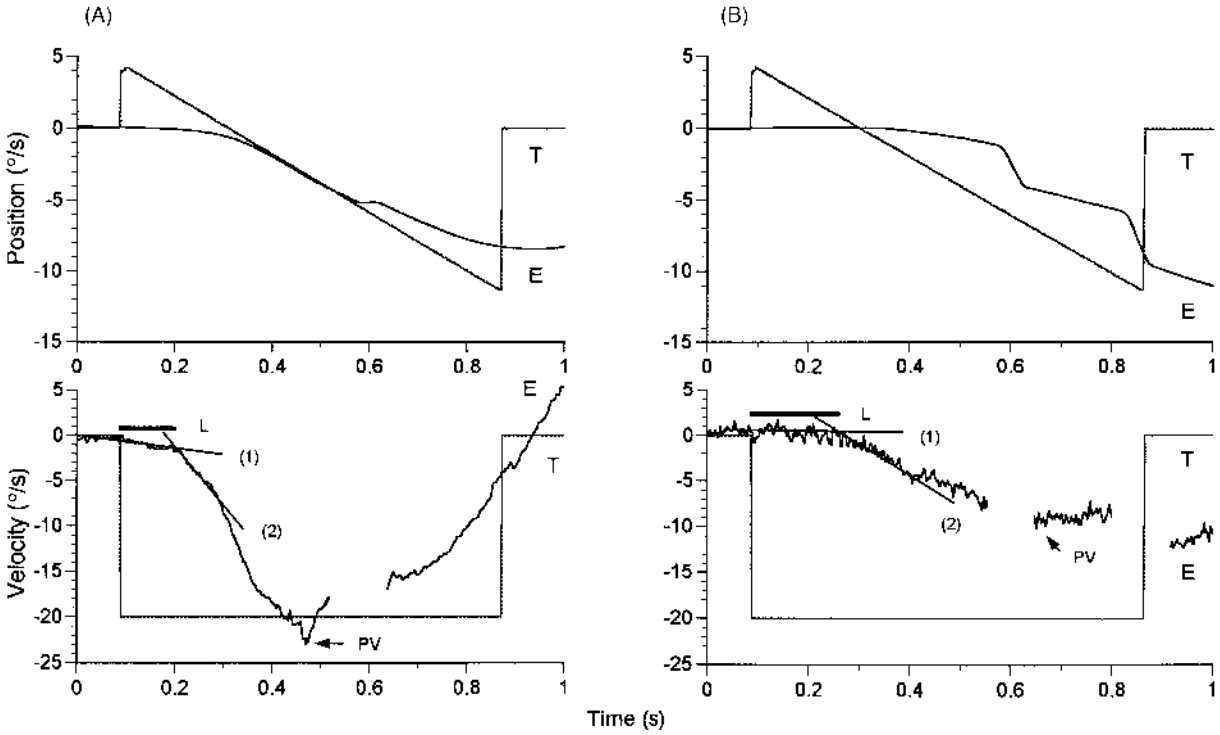

Fig. 2 Examples of single smooth pursuit responses triggered by a predictable step-ramp stimulus (**A**) in a control subject and (**B**) in a cerebellar patient. The upper traces show the position of eye (E) and target (T); the lower traces represent the corresponding velocity signals. The slope of the first regression line (1) describes any anticipatory eye acceleration, the slope of the second line (2) the initial acceleration of visually triggered pursuit. The length of the thick line represents pursuit latency (L) and the arrow the time of peak eye velocity (PV). The patient shows an increased latency and a decreased initial acceleration when compared with the control subject. In this example, only the control subject demonstrates a small anticipatory eye acceleration.

pursuit initiation was represented by the slope of the second regression line. A trial was excluded from analysis of smooth eye movements if saccades occurred during these two measurement intervals. Between 9 and 18% of trials were thus rejected. Furthermore, we measured the peak eye velocity during pursuit maintenance that was reached in a 400 ms epoch starting 150 ms after smooth pursuit onset. In each subject, at least eight step-ramp trials were analysed for each target condition and stimulus velocity.

To detect possible deficits of motion perception, we analysed separately the latency and position error of the first saccades that were triggered either by foveopetal step-ramps, foveofugal step-ramps or by pure step displacements of 7.5° (STEP condition). The position error of the saccade was the difference between eye and target position at the end of the saccade. Some degree of saccadic hypometria was regularly found in our group of healthy controls and can be considered a physiological phenomenon (Bötzel *et al*., 1993). Therefore, we defined a normative range for the final position error based on the data in the control group (normal range = mean position error ± 2 SD). The relative frequency of hypo- and hypermetric saccades in patients was determined with reference to this normative range.

The data have been submitted to a three-way analysis of variance (ANOVA) with a between group factor (two levels, controls versus patients) and two repeated measures, target predictability (two levels, PRED versus RAND) and ramp velocity (two levels, 10°/s versus 20°/s). A further within group two-way ANOVA was conducted to determine the within group effects of target velocity and predictability. We adopted the 0.05 significance level.

Results

We did not find a significant effect of target direction for any of the measured parameters when we compared responses to the right and to the left side. We therefore pooled the responses from both sides for these data analyses.

Latency of smooth pursuit initiation

The mean latency of smooth pursuit onset was always prolonged in patients compared with healthy controls [$F(1,11) = 27.7$, $P < 0.001$] (Fig. 3A). This effect was more pronounced in the PRED compared with the RAND condition [$F(1,11) = 13.3$, $P < 0.01$]. The ramp velocity did not significantly affect smooth pursuit latency [$F(1,11) = 0.6$, $P = 0.45$]. When both groups were analysed separately, the effect of target predictability on pursuit latency was highly significant only in healthy controls [$F(1,5) = 56.1$, $P < 0.005$]. In patients, however, pursuit latency was not significantly shorter in the PRED condition compared with

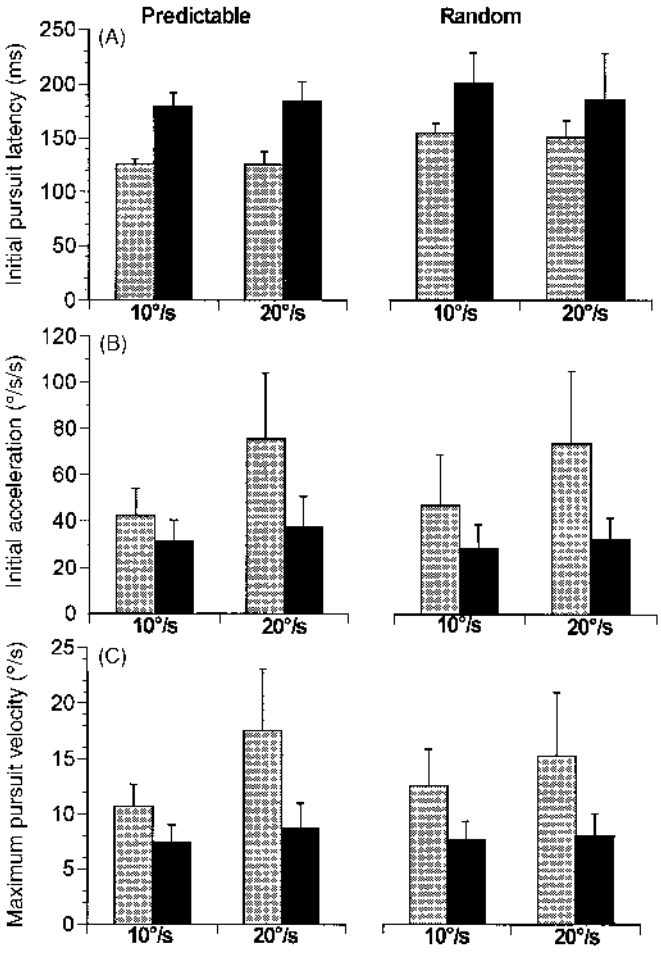

Fig. 3 Histograms to show (**A**) mean latency, (**B**) mean eye acceleration of the initial smooth pursuit response, and (**C**) the later peak eye velocity, in the group of control subjects (stippled columns) and patients (black columns). Error bars represent 1 SD.

the RAND condition [$F(1,5) = 1.4$, $P = 0.3$]. Individual mean latencies in control subjects varied between 119 ms and 140 ms in the PRED condition, and increased to between 136 ms and 168 ms in the RAND condition, which is within the range that has been previously reported in healthy subjects (Carl and Gellman, 1987; Kao and Morrow, 1994).

Initial acceleration of smooth pursuit eye movements

As shown in Fig. 3B, the mean initial eye acceleration, averaged during the first 60 ms of visually guided smooth pursuit, was decreased in patients compared with controls [$F(1,11) = 7.2$, $P < 0.05$]. Initial eye acceleration increased with faster ramp velocities [$F(1,11) = 32.4$, $P < 0.001$] and the ANOVA revealed a significant interaction between group factor and ramp velocity [group × velocity: $F(1,11) = 16.7$, $P < 0.005$], i.e. the difference between patients and controls was accentuated at faster target velocities (see Fig. 3B). A separate analysis within each group revealed a ramp velocity-dependent increase of initial eye acceleration in controls [$F(1,5) = 26.2$, $P < 0.005$] and to a lesser extent in patients [$F(1,5) = 7.6$, $P < 0.05$]. There was no significant effect of target predictability on initial eye acceleration in controls [$F(1,5) = 0.2$, $P = 0.7$] or patients [$F(1,5) = 2.6$, $P = 0.2$]. When we compared initial eye acceleration for PRED and RAND trials for each patient separately (Wilcoxon rank test for two related samples), none of the patients showed a significant increase of initial acceleration in PRED trials compared with corresponding RAND trials. However, in both groups, patients and controls, the mean eye acceleration was quite variable among individuals. In healthy controls, individual mean eye acceleration ranged between 43 and 128°/s^2 when triggered by predictable step-ramps, and between 44 and 124°/s^2 when triggered by randomized stimuli of 20°/s ramp velocity, which is in line with previous results (Kao and Morrow, 1994). In cerebellar patients, the corresponding individual mean eye acceleration did not exceed 59°/s^2 in the PRED condition and 44°/s^2 in the RAND condition.

Peak eye velocity during the maintenance period of pursuit

After initiation, smooth pursuit continued for several hundred ms before it stopped due to the end of the ongoing ramp target motion (Fig. 2). The peak eye velocity was always reached after more than 125 ms, thus representing a measure of velocity gain in the maintenance period of smooth pursuit. Generally, this peak eye velocity was impaired in patients compared with controls [$F(1,11) = 11.6$, $P < 0.01$] (Fig. 3C). This group difference increased with increasing ramp velocities [group × velocity: $F(1,11) = 8.1$, $P < 0.05$], similar to the group difference in initial eye acceleration. Peak eye velocity did not generally increase with higher target predictability in controls [$F(1,5) = 0.7$, $P = 0.4$] or patients [$F(1,5) = 0.1$, $P = 0.7$].

Anticipatory smooth eye movements

Occasionally, significant ASEM occurred in controls and patients with anticipatory eye accelerations reaching 25–40°/s^2, predominantly in PRED trials (see Fig. 2A), but on average, the individual anticipatory eye acceleration did not exceed 5°/s^2. There was only one control subject in whom mean anticipatory eye acceleration reached 5.8°/s^2 in RAND trials and 8.7°/s^2 in the PRED condition. Mean anticipatory eye acceleration was slightly higher in controls than in patients, but this group difference was insignificant [$F(1,11) = 2.6$, $P = 0.1$]. In both groups, the average anticipatory accelerations were too small and too variable to reveal any difference between the PRED and RAND conditions.

Latency of the first saccade to step-ramp and pure step displacements

With foveofugal step-ramps, which were presented only in the RAND condition, mean initial saccade latency was

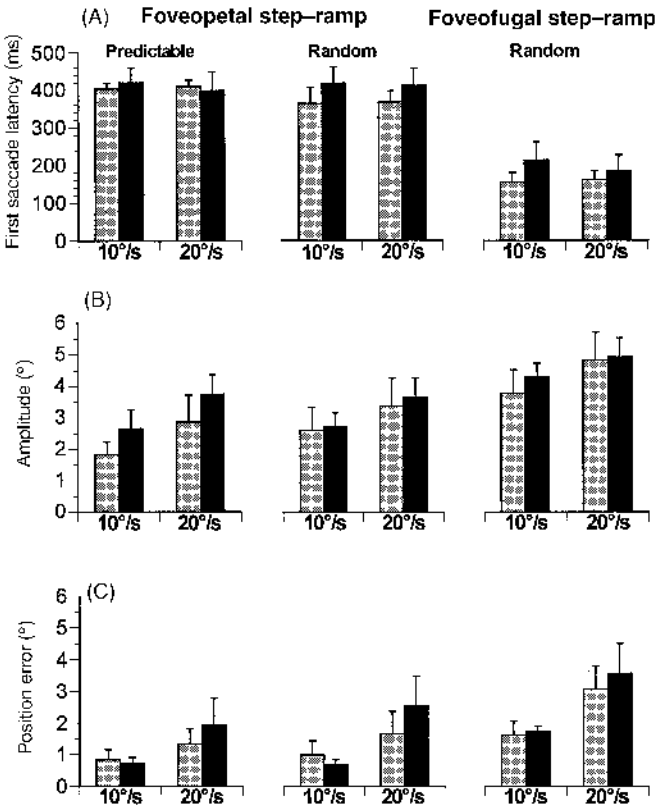

Fig. 4 Histograms to show (**A**) mean latency, (**B**) mean amplitude, and (**C**) mean absolute value of the position error of first saccades during foveopetal step-ramps (PRED and RAND condition) and foveofugal step-ramp movements (RAND condition only). In foveopetal step-ramp trials, mean saccade amplitudes of patients (black columns) tend to be slightly increased compared with controls (stippled columns); none of the measurement conditions revealed any significant difference between the two groups. Error bars represent 1 SD.

not different from visually-triggered saccades to pure step displacements [$F(1,11) = 0.2$, $P = 0.7$]. This was due to the fact that they were triggered by the initial step-displacement, thereby preceding any significant smooth pursuit eye movement (Gellman and Carl, 1991). The latency of non-predictive, initial saccades to foveofugal step-ramps (Fig. 4A) or pure steps did not significantly differ between controls and patients [$F(1,11) = 0.9$, $P = 0.3$].

Foveopetal step-ramps extended the period of smooth pursuit prior to the first saccade (Rashbass, 1961; Gellman and Carl, 1991). We observed this normal effect in both patient and control groups, irrespective of target predictability. In foveopetal step-ramp trials we have limited the analysis of saccadic accuracy to those saccades starting after smooth pursuit onset. These saccades represent so called 'catch-up saccades' that correct for eye position errors during the ongoing smooth pursuit. Their mean latency ranged between 360 and 420 ms (Fig. 4A), at a time when the target had already crossed the centre position. The latency of these catch-up saccades did not, again, differ between patients and controls [$F(1,11) = 1.6$, $P = 0.2$] indicating that patients were not delayed in the initiation of saccades during ongoing target motion.

Amplitude and final position error of first saccades

In both groups the amplitude of first saccades towards unpredictable, foveofugal step-ramps increased with increasing ramp velocities [$F(1,11) = 33.8$, $P < 0.001$], as one would expect if the perception of the ramp target motion during the latency period of the saccade was intact. With foveofugal step-ramps, patients and controls showed similar amplitudes of initial saccades. [$F(1,11) = 0.3$, $P = 0.6$] (Fig. 4B). During the ongoing smooth pursuit of foveopetal step-ramps, there was a trend towards slightly larger catch-up saccades in patients compared with controls as one would expect due to their pursuit impairment, but this trend was statistically insignificant [$F(1,11) = 2.5$, $P = 0.2$].

Importantly, the absolute error of eye position at the end of the saccade did not significantly differ between patients and controls, either during presentation of foveofugal [$F(1,11) = 0.3$, $P = 0.6$] or foveopetal step-ramps [$F(1,11) = 1.2$, $P = 0.3$] (Fig. 4C), although, with higher ramp velocities (20°/s) there was a slight trend towards larger absolute errors in the patient group (Fig. 4C). We tried to clarify whether this trend was due to a general cerebellar dysmetria of saccades, or due to a deficient perception of ramp velocity. First, we measured the frequency of increased position errors in each individual patient with respect to a normative error range during step-ramp presentation (Table 2). In three patients, there was a considerable number of dysmetric first saccades (patients 1, 3, 6). However, the patients' dysmetria was not systematically related to the relative direction of the ramp motion (foveopetal versus foveofugal). For example, patients showed no consistent hypometria of the initial saccades during foveofugal ramps as would be predicted if patients were generally underestimating ramp velocity. Secondly, we measured the individual patients' frequency of dysmetric saccades in the STEP condition using a similar normative range as a reference (Table 2). In line with the previous literature, the distribution between hypermetric and hypometric saccades varied inter-individually among the cerebellar patients (e.g. Zee *et al*., 1976; Baloh *et al*., 1986; Moschner *et al*., 1994). Comparison of this distribution in the same patient often revealed no consistent pattern between step-ramp trials and pure step trials. However, in those patients with a considerable amount of dysmetric saccades in step-ramp trials (patients 1, 2, 3, and 6) a similar, or even higher, percentage frequency of dysmetric saccades was found in response to pure step displacements (Table 2). Thus, their amount of saccadic dysmetria in the step-ramp trials might just reflect a general cerebellar deficit in the adjustment of saccade amplitude.

In summary, the following converging evidence undermines abnormal motion perception as a convincing

Table 2 *Percentage frequency of abnormal position errors of first saccades towards step-ramps and pure step displacements*

Patient number	Foveofugal step-ramps				Foveopetal step-ramps				Pure steps, no ramp; step size = 7.5°	
	Hypo.	Hyper.	Hypo.	Hyper.	Hypo.	Hyper.	Hypo.	Hyper.	Hypo.	Hyper.
1	39	11	14	0	7	29	29	15	11	67
2	0	0	0	0	0	7	11	0	16	24
3	0	18	0	14	0	25	7	27	3	34
4	0	0	0	0	0	6	0	0	24	40
5	0	0	0	0	0	0	8	0	–	–
6	25	0	0	0	0	25	7	27	8	84
Ramp velocity	10°/s		20°/s		10°/s		20°/s			
Normal range	–2.68 to –0.40°		–6.12 to –0.24°		–1.83 to +0.24°		–3.63 to –0.51°		–0.80 to +0.38°	

Normal ranges refer to the average final position error ±2 SD in the control group. Negative final position errors represent undershooting saccades (hypo. = hypometric), and positive values overshooting saccades (hyper. = hypermetric) with respect to synchronous target position; data given as percentage frequency. Patient 5 did not participate in the STEP task.

account of the smooth pursuit dysfunction in the cerebellar patients: (i) the saccadic latency in step-ramp trials was not prolonged in patients compared with controls; (ii) the patients' absolute position error of first saccades was similar to that of controls; (iii) their amplitude of first saccades increased with increasing ramp velocities; and (iv) their saccadic dysmetria during step-ramp trials was not related to the relative direction of the ramp motion.

Discussion

The major findings of this study can be briefly summarized: (i) patients with cerebellar degeneration demonstrated an abnormal decrease of eye acceleration during the first 60 ms of smooth pursuit; (ii) their smooth pursuit initiation was abnormally delayed; (iii) the predictive shortening of pursuit latency that was found in controls was not present in these patients; and (iv) the position error of first saccades towards a step-ramp target displacement was not significantly different between patients and controls. These points are now discussed in more detail.

Deficits of pursuit initiation after cerebellar degeneration

First, our patients with cerebellar degeneration demonstrated an abnormal decrease of eye acceleration during the initial 60 ms of smooth pursuit. Initial eye acceleration shows a significant inter-subject variability, even in healthy humans (Carl and Gellman, 1987; Kao and Morrow, 1994). After the first 20 ms of pursuit, it generally increases with greater velocities of the continuous target motion (Lisberger *et al*., 1981; Tychsen and Lisberger, 1986). This effect might have contributed to our observation that pathological impairment of initial acceleration in patients increased with higher ramp velocities, similar to the patients' impairment of peak eye velocity during maintenance of smooth pursuit. A failure to adequately increase initial eye acceleration and the later eye velocity as ramp velocities increase would hypothetically be generated if there was an abnormal saturation in the pathways processing target velocity. If this were the case in cerebellar patients, one would expect their acceleration and peak velocity deficits to occur only above some ramp velocity threshold. However, previous studies in cerebellar patients that have utilized a wider range of stimulus velocities to evaluate pursuit initiation (Lekwuwa *et al*., 1995; Straube *et al*., 1997) and sustained smooth pursuit of periodic stimuli (Waterston *et al*., 1992) failed to establish such a stimulus velocity threshold. Instead, they found a significant decrease of the patients' eye velocity at all target velocities. Thus, cerebellar deficits of initial eye acceleration or steady-state velocity gain cannot be attributed to an abnormal velocity saturation alone.

It is likely that the underlying degenerative pathology in our patients affected various areas of the cerebellum. Consequently, we are unable to identify a specific anatomical structure in the cerebellum, the damage of which was responsible for this deficit of initial pursuit acceleration. However, when we compared eye acceleration during pursuit initiation with the peak velocity during pursuit maintenance, the individual deficits of both parameters were quite proportional in each patient, suggesting that deficits during the two different periods of pursuit control are caused by similar pathophysiological mechanisms. This hypothesis is further supported by experimental studies in primates that have demonstrated pursuit-related activity in the same cerebellar regions during initiation and maintenance of pursuit. These areas include the floccular and paraflocculer regions (Stone and Lisberger, 1990) as well as the oculomotor vermis (Suzuki and Keller, 1988*b*; Krauzlis and Miles, 1998). However, in human patients, decreased velocity of ipsilateral initial pursuit has been reported recently after observations that lateral lesions of the cerebellar hemispheres seem to spare these midline areas (Straube *et al*., 1997). This suggests that other more lateral projections participate in the control

of smooth pursuit initiation, although they have not yet been clearly identified.

In addition to the decreased initial acceleration, we found an abnormal delay of pursuit onset in cerebellar patients, as previously described by Lekwuwa and colleagues (Lekwuwa *et al*., 1995) for smooth pursuit triggered by pure ramp stimuli. In the current study, mean latency of smooth pursuit to non-predictable step-ramps was significantly prolonged in patients compared with controls. Although we have used a relative velocity threshold to determine the pursuit onset, this abnormal delay was not a secondary effect of the decreased initial acceleration since we found no positive correlation between initial acceleration and latency of pursuit in our patients ($P > 0.2$, linear correlation analysis using Pearson's coefficient). Furthermore, this delay of pursuit onset in patients cannot simply be related to non-specific effects, such as inattention or general cognitive impairment, because these effects would also be expected to prolong the patient's latency of first saccades which were measured in the same experiments yet remained within normal ranges. Obviously, cerebellar degeneration can extend the processing time required to initiate smooth pursuit. On the other hand, patients with focal lesions of cerebellar hemispheres had shown a decreased initial pursuit velocity without a significant delay of pursuit onset (Straube *et al*., 1997). In this earlier study, the cerebellar midline structures most commonly associated with the initiation of pursuit, especially the oculomotor vermis (Suzuki and Keller, 1988*b*), were relatively spared. These areas should be affected in our patients because they showed atrophy of these midline cerebellar structures on CT or MRI scans. It is, therefore, possible that more lateral hemispheric projections of the cerebellar cortex participate only in the control of pursuit velocity, whereas the midline cerebellum additionally controls the timing of pursuit onset.

Effect of prediction on cerebellar deficits of pursuit initiation

Visually-guided, initial smooth pursuit is, in part, controlled by predictive mechanisms that modify the response to a future target movement based on the perception of previous target presentations (Boman and Hotson, 1988; Kao and Morrow, 1994; Barnes *et al*., 1997). Our study confirms that predictive step-ramp stimulation generates a shorter latency of the smooth pursuit response than non-predictive stimulation in healthy human subjects (Kao and Morrow, 1994). Furthermore, we have now demonstrated that a similar predictive shortening of pursuit latencies is not present in cerebellar patients. Their mean pursuit latency was not modified by different levels of target predictability. In our study, randomization in the RAND condition was restricted to the direction of step and ramp stimulus components, whereas target onset remained constant in both the PRED and RAND conditions. It seems that healthy humans can use the predictive information on target direction and velocity to improve the anticipatory programming of the smooth pursuit response. In cerebellar patients this predictive enhancement is less effective than in healthy humans, so their pathologically delayed latency of pursuit initiation remains unchanged by target predictability.

In line with this, higher target predictability also did not compensate for the impairment of initial eye acceleration in our cerebellar patients. In healthy humans, Kao and Morrow (Kao and Morrow, 1994) observed a predictive enhancement of initial eye acceleration only when ramp velocities exceeded 30°/s, but not with the lower velocities of 10 and 20°/s used in our study. Our results in healthy controls were consistent with their observations because we were unable to demonstrate a significant predictive enhancement of initial eye acceleration with these lower ramp velocities in the control group when we compared the PRED and RAND conditions.

Since it is well known that the ability to generate fast smooth pursuit eye movements is generally impaired in most cerebellar patients (e.g. Zee *et al*., 1976; Baloh *et al*., 1986; Moschner *et al*., 1994), we have studied the possible predictive compensation of some cerebellar deficit of pursuit initiation at these lower stimulus velocities. If cerebellar lesions had left predictive control of smooth pursuit intact, we should have found some predictive enhancement of the patients' initial eye acceleration during presentation of highly predictable step-ramps. Instead, the pathological difference between initial eye acceleration of cerebellar patients and controls remained significant in the PRED condition, similar to the findings in the RAND condition. None of the patients showed any predictive enhancement of initial eye acceleration in the PRED condition compared with the RAND condition.

Analogous results were found when we analysed the peak eye velocity during maintenance of smooth pursuit. In controls, target predictability did not lead to a statistically significant increase of peak eye velocity, although the data given in Fig. 3C suggest such an effect of target predictability at higher ramp target velocities which accords with the observation of Kao and Morrow (Kao and Morrow, 1994). This trend was not noted in the patients, and the patients' peak eye velocity remained impaired compared with controls, irrespective of the target predictability. Again, the inefficient predictive enhancement during both periods of smooth pursuit in the patient group was not solely due to a pure velocity saturation effect, because the patients showed at least some increase of initial eye acceleration and peak eye velocity with the higher target velocity of 20°/s in both the PRED and RAND conditions.

Our study has, therefore, revealed evidence that predictive control mechanisms based on repetitive presentation of constant target motion do not compensate for any of the cerebellar deficits of smooth pursuit, including the delayed onset, the decreased eye acceleration during pursuit initiation and the decreased peak eye velocity during maintenance of smooth pursuit. This challenges a previous observation by Waterston and colleagues (Waterston *et al*., 1992) who have

described an intact predictive control of smooth pursuit in cerebellar patients. However, these authors have looked at maintained pursuit while tracking the predictable and non-predictable sum of sine stimuli, whereas our study was focused on smooth pursuit in response to step-ramps. It may be that different predictive mechanisms are activated during these different types of pursuit tracking.

Furthermore, our results do not necessarily mean that predictive control of step-ramp pursuit is completely abolished in cerebellar patients. It is possible that in our patients, although the cerebellum receives predictive input from higher cortical areas, it is unable to transform this information into a more effective smooth pursuit motor output.

Although our study was mainly focused on smooth pursuit, we were able to observe some ASEM in both controls and patients. Both types of smooth eye movements, ASEM and smooth pursuit, probably share a common predictive control mechanism that uses stored information from previous target presentations (Boman and Hotson, 1988; Kowler, 1989; Kao and Morrow, 1994; Barnes *et al*., 1997). The generation of slow ASEM in some of our cerebellar patients suggests that predictive input to their cerebellum is not completely cancelled. The frequency and eye acceleration of ASEM was surprisingly low, even in healthy controls, when compared with the prior studies using predictable step-ramps (Kao and Morrow, 1994). Two factors, longer inter-trial intervals and slightly modified verbal instructions, could have contributed to this different anticipatory behaviour of healthy subjects in the current study. Low frequency of ASEM in controls made the analysis of ASEM an insensitive behavioural parameter to detect gradual cerebellar deficits of predictive pursuit control. As a result, the group difference of mean anticipatory eye acceleration between patients and controls was insignificant. In a previous study in which ASEM were more readily elicited, patients with cerebellar degeneration had significantly slower ASEM than healthy controls (Moschner *et al*., 1996). Thus, there is experimental evidence that cerebellar deficits of smooth pursuit occur independent of any output from predictive systems that participates in the control of smooth eye movements. Again, it seems that whatever the extent of the predictive cerebellar input is, it cannot be used functionally to overcome delays in pursuit initiation, and the attenuation of eye velocity and acceleration.

Assessment of target velocity

Studies in monkeys (Keller and Johnsen, 1990), healthy humans (Gellman and Carl, 1991) and patients with parieto-occipital lesions (Thurston *et al*., 1988; Heide *et al*., 1996) have shown that accurate saccades towards a continuously moving target require accurate perception of target velocity. Consequently, the assessment of saccadic accuracy during tracking of step-ramp stimuli provides a valid, indirect measure of motion perception in a velocity range in which patients with cerebellar lesions show a significant deficit of smooth pursuit.

Previous studies on motion perception deficits in cerebellar patients found either increased performance variability in a phi-movement, velocity comparison task (testing the ability to perceive a closely-spaced sequence of discrete target jumps as a continuous smooth movement) or impaired ability to detect a global motion vector in a stochastic motion display (Ivry and Diener, 1991; Nawrot and Rizzo, 1995). These abnormalities were observed at very low stimulus velocities of less than 5°/s suggesting that cerebellar lesion may slightly increase the velocity threshold that is required to correctly detect a directed target motion. They do not necessarily represent a global motion perception deficit. In patients with latent and congenital nystagmus, it is likely that motion perception thresholds are increased in order to adapt to retinal slip errors caused by the pathological nystagmus (Dieterich and Brandt, 1987; Shallo-Hoffmann *et al*., 1996). Most patients with cerebellar degeneration acquire some type of abnormal nystagmus, such as downbeat nystagmus or gaze-evoked nystagmus (Zee *et al*., 1976; Baloh *et al*., 1986; Moschner *et al*., 1994). Hypothetically, increased velocity-detection thresholds in these patients could simply represent a similar adaptive mechanism to reduce oscillopsia.

The current analysis of saccadic accuracy while tracking step-ramps now shows that motion perception at higher velocity ranges is not impaired in cerebellar patients compared with healthy controls, irrespective of whether the saccade was initiated before any significant smooth pursuit (foveofugal step-ramp), or after pursuit onset (foveopetal step-ramps). It was not surprising that at least some of our patients showed a certain amount of saccadic dysmetria compared with healthy subjects. It is known from animal experiments that midline cerebellar structures, especially oculomotor vermis and caudal fastigial nuclei, control the adjustment of saccade size (Keller, 1989; Büttner and Straube, 1995) and saccadic dysmetria is a common feature of degenerative cerebellar disease (Zee *et al*., 1976; Baloh *et al*., 1986; Moschner *et al*., 1994). Even in the patients with increased saccadic dysmetria, we found no systematic bias related to the direction or the velocity of the ramp target motion. Thus, it is unlikely that patients with degenerative cerebellar lesions have any impairment of motion velocity perception that is relevant to the generation of smooth pursuit. This leads to the hypothesis of correct information on the velocity of the target motion that is relayed to the cerebellum. Here, cerebellar degeneration causes a disturbed transformation of this information into the correct motor command that finally drives initial smooth pursuit eye movements. In contrast, the very similar deficits of pursuit initiation, i.e. delayed onset and decreased initial acceleration, found in patients with lesions of the parieto-occipital cortex (Thurston *et al*., 1988; Heide *et al*., 1996) are probably more related to a perceptual deficit because in these patients the analysis of catch-up saccades during step-ramp responses has revealed a clearly impaired assessment of target velocity.

These different observations in patients with cortical and cerebellar lesions further support current models of pursuit control that are based on animal experiments (e.g. Keller and Heinen, 1991). These models locate the cerebellum further 'downstream' in the hierarchy of the neuronal network that controls smooth pursuit. This downstream location of the cerebellum could also explain why prediction does not correct effectively for the cerebellar deficits of smooth pursuit.

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