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Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction

C. Helmchen, A. Hagenow, J. Miesner, A. Sprenger, H. Rambold, R. Wenzelburger,[1] W. Heide and G. Deuschl[1]

Department of Neurology, University of Luebeck,
[1]Department of Neurology, University of Kiel, Germany

Correspondence to: Professor Dr Christoph Helmchen, Department of Neurology, University of Luebeck, Ratzeburger Allee 16023538, Luebeck, Germany
E-mail: helmchen_ch@neuro.mu-leubeck.de

Summary

Experimental and clinical data indicate that the cerebellum is involved in the pathophysiology of advanced stages of essential tremor (ET). The aim of this study was to determine whether a dysfunction also affects cerebellar structures involved in eye movement control. Eye movements of 14 patients with ET and 11 age-matched control subjects were recorded using the scleral search-coil technique. Vestibular function was assessed by electro-oculography. Eight ET patients had clinical evidence of intention tremor (ET_{IT}); six had a predominantly postural tremor (ET_{PT}) without intention tremor. ET patients showed two major deficits that may indicate cerebellar dysfunction: (i) an impaired smooth pursuit initiation; and (ii) pathological suppression of the vestibulo-ocular reflex (VOR) time constant by head tilts ('otolith dumping'). In the step ramp smooth pursuit paradigm, the initial eye acceleration in the first 60 ms of pursuit generation was significantly reduced in ET patients, particularly in ET_{IT} patients, by ~ 44% (mean 23.4°/s^2) compared with that of control subjects (mean 41.3°/s^2). Subsequent steady-state pursuit velocity and sinusoidal pursuit gain (e.g. 0.4 Hz: 0.90 versus 0.78) were also significantly decreased in ET patients, whereas pursuit latency was unaffected. The intention tremor score correlated with the pursuit deficit, e.g. ET_{IT} patients were significantly more affected than ET_{PT} patients. Gain and time constant (τ) of horizontal VOR were normal, but suppression of the VOR time constant by head tilt ('otolith dumping') was pathological in 41% of ET patients, particularly in ET_{IT} patients. Saccades and gaze-holding function were not impaired. The deficit of pursuit initiation, its correlation with the intensity of intention tremor, and the pathological VOR dumping provide additional evidence of a cerebellar dysfunction in the advanced stage of ET, when intention tremor becomes part of the clinical symptoms, and point to a common pathomechanism. The oculomotor deficits may indicate an impairment of the caudal vermis in ET.

Keywords: cerebellum; essential tremor; eye movements; intention tremor

Abbreviations: ET = essential tremor; ET_{IT} = essential tremor with intention tremor; ET_{PT} = essential tremor with postural tremor; ITS = intention tremor score; PT = postural tremor; VOR = vestibulo-ocular reflex; τ = time constant of VOR

Introduction

The pathophysiology of essential tremor (ET) is still unclear. Since the inferior olive is one of the main sites for suspected lesions in ET, one experimental approach is to investigate the function of its efferent projections, i.e. the olivo-cerebellar pathways. If the lesion-induced oscillating activity of the inferior olive is transmitted to the cerebellum, as suggested by the harmaline animal model of ET (Wilms *et al*., 1999), it might affect the normal functioning of cerebellar feed-forward functions involved in executing rapid and smooth eye movements. Clinically, some patients with essential tremor show an intention tremor in addition to postural tremor (Deuschl *et al*., 1998). Recent clinical and electrophysiological studies revealed signs of cerebellar dysfunction in arm movements (Deuschl *et al*., 2000; Köster *et al*., 2002) and gait (Singer *et al*., 1994; Stolze *et al*., 2001) of ET patients. This intention tremor cannot be clinically distinguished from the classic intention tremor in cerebellar disorders. Kinematic studies of arm movements in a reach and grasp task in ET patients showed cerebellar dysmetria, possibly indicating that the cerebellum plays a role in ET (Deuschl *et al*., 2000).

Table 1 *Clinical features of ET patients*

	Essential tremor with postural tremor							Essential tremor with intention tremor									
Patient number:	3	5	9	10	11	12	17	1	2	4	6	7	8	13	14	15	18
Age (years)	70	34	25	44	43	43	52	68	71	65	81	66	58	66	57	64	24
Sex	M	M	F	M	F	F	F	M	M	F	M	M	M	F	M	M	F
Disease duration (years)	11	25	9	23	28	6	10	40	7	47	74	26	9	33	43	45	17
ITS	2	2	1	1	1	2	0	4	4	3	4	3	3	4	4	3	3
Head tremor	Yes	Yes	0	0	No/yes	No	0	0	0	0	0	Yes	No	Yes/no	0	0	0
Family history	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–
Alcohol*	NT	+	–	+	+	+	–	+	NT	–	+	+	+	+	+	–	+
Propranolol**	NT	–	NT	+	+	+	NT	+	NT	+	+	–	+	+	NT	+	–
Drugs	Prim.	No	No	Met.	No	No	No	Prim.	No	No	No	No	Prop.	Met.	Met.	No	No

ITS = intention tremor score (sum of both hands, see Subjects and methods); Prim. = primidone; Met. = metoprolol; Prop. = propranolol; – = negative; + = positive, i.e. improvement of ET by alcohol or propranolol; *tremor improves on alcohol; **tremor improves on propranolol; NT = not tried.

Methodologically, kinematic analyses of arm and hand movements may be contaminated by various types of tremor (postural, simple kinetic, intention tremor). Although cerebellar dysmetria in ET patients is probably not secondary to tremor components (Deuschl *et al*., 2000), we sought highly reliable clinical parameters that (i) can be recorded with great accuracy; (ii) cannot be disturbed by hand tremor artefacts; and (iii) potentially indicate cerebellar region-specific dysfunction. We therefore recorded eye movements in ET patients, which are known to indicate cerebellar dysfunction, and tried to correlate them with the clinical intention tremor components. The absence of eye movement disorders had been used to distinguish the cerebellar dysfunction in ET patients from that of patients with cerebellar degeneration (Deuschl and Bain, 1998). However, we will show that distinct eye movement disorders in ET patients probably indicate cerebellar dysfunction although they are not obvious during clinical bedside testing.

Subjects and methods

Subjects

Seventeen outpatients with ET (seven women, 10 men; age range 24–81 years, mean 54.8 ± 16.7 years) were examined. The age at onset of the disease varied, ranging from 7 to 64 years (mean 27.6 ± 17.3 years), and disease duration was 6–74 years (mean 26.7 ± 18.6 years). Fourteen patients reported a family history (Table 1). Six of the patients were on anti-tremor agents (e.g. β-blocker, primidone). Eleven of 17 ET patients responded to alcohol consumption. Seven of the patients showed head tremor. None of them had a history of any other neurological disease apart from ET. All patients had a neurological examination and were also examined clinically to determine tremor scales (see below). Except for two cases (patients 1 and 3, who were on primidone), ET patients did not take any medication known to affect eye movements. All patients fulfilled the diagnostic criteria of classic ET as defined by the consensus statement of the Movement Disorder Society (Deuschl *et al*., 1998). Besides a neurological examination, the patients also underwent a standardized assessment of clinical features of the tremor and eye movements. The patients were compared [clinically, electro-oculography (EOG), scleral search-coil recordings] with a group of 11 (six women, five men) age-matched healthy subjects (mean age 56.6 years, range 31–74 years).

Clinical scores

For intention and postural tremor rating we used a modification of the clinical tremor rating scale (rates 0–3) of Fahn and colleagues (Fahn *et al*., 1993). The upper limb on each side was rated. Intention tremor, as defined in the consensus statement of the Movement Disorder Society (Deuschl *et al*., 1998), is present if the tremor amplitude increases during visually guided movements toward a target, provided that a position-specific tremor and a postural tremor at the end of the movement is excluded, and if the amplitude fluctuates significantly when approaching the target. To rate the intention tremor, the terminal period of the finger-to-nose test was evaluated: 0 = no intention tremor; 1 = probable intention component; 2 = definite intention component; 3 = functionally incapacitated due to intention tremor. Taking the uni- versus bilateral tremor involvement into account, we computed a score for the intention tremor of each hand, subsequently termed the intention tremor score (ITS) [e.g. a probable (score = 1) intention component in both hands yielded 2 points on the ITS].

In addition, subjects were evaluated for resting tremor and postural tremor (Deuschl *et al*., 2000). None had resting tremor. Postural tremor (PT) was examined with respect to disability, i.e. we examined patient ability to hold a glass of water: 0 = no tremor visible; 1 = slight tremor, but no water is spilled; 2 = spills some water, but <30%; 3 = spills >30% of the water.

Tremor rating and ET subgroups

Patients who showed a definite intention tremor on at least one hand (rating score of 2 unilaterally) were classified as 'essential tremor with intention tremor' (ET_{IT}) (n = 10). Patients with a postural tremor of the hands without definite intention tremor (rating 0 or 1 uni- or bilaterally, with 1 indicating only a probable intention tremor) were classified as 'essential tremor with predominantly postural tremor' (ET_{PT}) (n = 7). None of the control subjects showed any form of tremor.

Eye movement recordings

Eye movements were recorded with the magnetic scleral search-coil system and direct current (DC) EOG. EOG was used in particular to investigate optokinetic nystagmus and vestibularly elicited eye movements [vestibulo-ocular reflex (VOR) gain, time constant].

Scleral search-coil

Eye movements were recorded by a search-coil system (2 m^3; CNC Engineering, Seattle, WA, USA) with standard annulus search coils (Skalar, Delft, The Netherlands). Search coil recordings were approved by the ethical committee of the medical faculty of the University of Luebeck. All subjects signed an informed consent statement, which was obtained in accordance with the Declaration of Helsinki. Data were stored in binary format at 500 Hz sampling rate on the recording PC (personal computer) by an ADC (analogue digital converting) device (PCI 6170; National Instruments, Munich, Germany). The stimulus was a red laser dot (diameter of 0.1°) presented on a translucent screen (Marata screen) in a completely darkened room. The laser dot was moved by two galvanometer scanners (GSI Lumonics, Munich, Germany), driven by an analogue output card in the stimulus PC (AT-AO6/10; National Instruments, Munich, Germany). The subject was seated in a comfortable wooden chair with the head fixed in a head-holding device and the chin resting on a chin rest bar. In addition, head movements were recorded with a search coil mounted to the forehead to account for possible head movement components. The eye-to-screen distance was 140 cm. After the cornea was desensitized by a local anaesthetic (oxybuprocaine, Conjucain®, Mann, Berlin, Germany), the scleral search-coil was placed in the right eye. Eye movements were calibrated by an *in vivo* calibration as described previously (Rambold *et al*., 2001, 2002*a*).

Electro-oculography

Vestibular and optokinetic nystagmus were examined using conventional EOG (Heide *et al*., 1999). Subjects were seated in a darkened room on a vestibular chair with their head in the centre of a hemispheric white screen (distance 0.9 m). Horizontal eye movements were recorded using DC EOG by means of four electrodes: one each placed on the outer canthi of the eyes, the other two vertically above and another below one eye. The signals were amplified and low-pass filtered with a cut-off frequency of 70 Hz.

Experimental paradigms and data analysis

Smooth pursuit eye movements, saccades, optokinetic nystagmus, gaze-holding function and horizontal VOR were investigated.

Paradigms in scleral search-coil recordings

Step ramp paradigm. To investigate initial smooth pursuit eye movements, subjects performed two sequences of 28 horizontal step ramp stimuli in accordance with the Rashbass paradigm. Each sequence consisted of 10 foveopetal pursuit ramps (3° step, opposite to ramp direction, 15°/s ramp velocity, duration 800 ms) to either side and four foveofugal ramps in the same direction as the step (3° step, 15°/s ramp velocity, duration 800 ms) in both directions. The stimuli were presented in a random order. To prevent anticipatory effects, the duration of fixation before each trial was varied from 1500 to 2000 ms.

Pursuit eye movements were analysed offline using an interactive program. Pursuit eye position was filtered by a 3rd order polynomial smoothing filter (Savatzky-Golay filter; Orfanidis, 1995) and differentiated. Saccades were excluded from the pursuit velocity data and the data were interpolated linearly (Moschner *et al*., 1999). Latency, initial acceleration, steady-state velocity and the position error of the first saccade in the step ramp smooth pursuit response were analysed.

For the analysis of initial smooth pursuit and its latency, all trials with saccades in the initial phase were excluded. The initial acceleration of smooth pursuit was calculated as reported elsewhere (Carl and Gellman, 1987; Moschner *et al*., 1999). We used eye acceleration in the first 60 ms to characterize the initial phase of the smooth pursuit response (Carl and Gellman, 1987; Moschner *et al*., 1999), since averaging eye acceleration in the entire open-loop period may not reveal subtle deficits in pursuit acceleration (Takagi *et al*., 2000). Initial eye acceleration was quantified by a linear regression of the velocity trace. The linear regression started when eye velocity exceeded its SD during fixation by 3.2-fold. The initial eye acceleration was computed by regression of the following 60 ms (Fig. 1). The onset of the smooth pursuit response was defined by the intersection of the regression line with the mean of pursuit eye velocity during fixation. The latency of pursuit initiation was defined as pursuit onset minus stimulus onset. To determine smooth pursuit latency, each individual trial was analysed separately.

To analyse the potential effects of deficient motion perception on initial pursuit acceleration, we calculated the position error of the first saccade elicited by the step ramp stimulus as the difference between eye position at the end of

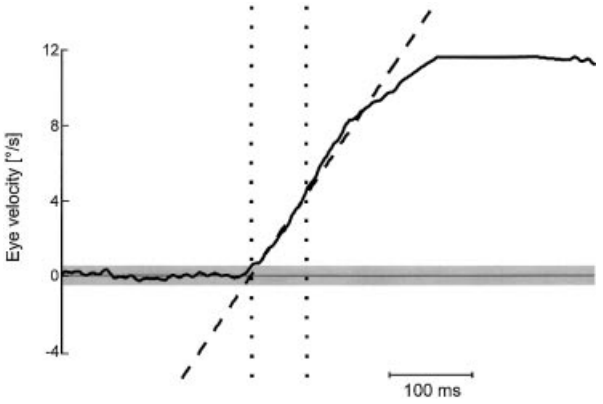

Fig. 1 Analysis of the initial pursuit response in a normal subject during a horizontal step ramp stimulus. Solid line: eye velocity trace; grey zone: 3.2 × SD of eye velocity during fixation; dashed line: first order regression line of eye velocity in the first 60 ms after eye velocity exceeded the grey zone; vertical dotted lines: begin and end of the 60 ms interval for the analysis of initial pursuit response. Positive and negative values (ordinate) indicate rightward and leftward eye movements, respectively.

the first saccade and the target (Moschner *et al*., 1999). Pathological motion perception was assumed when position errors deviated significantly from those of the control subjects. Mean eye velocity during pursuit maintenance (steady-state velocity) was measured in each individual trial, in intervals of 200 ms at 400, 600 and 800 ms after the onset of the ramp. Maximum steady-state velocity was defined by the maximum of all three intervals.

Sinusoidal smooth pursuit paradigm. The frequency dependence of smooth pursuit was tested in a sinusoidal smooth pursuit paradigm of 0.2 and 0.4 Hz (15° amplitude). After desaccadation, the eye velocity signal was fitted by a Marquard-Levenberg method (Borse, 1997), using nine cycles of smooth pursuit. The gain was calculated by the ratio of eye velocity to target velocity and the phase difference, by target phase minus eye velocity phase.

Saccade paradigm. Subjects performed horizontal saccades of 10 and 20° to either side, starting from gaze straight ahead, i.e. 10 centrifugally and 10 centripetally. Centrifugal and centripetal saccades were investigated since saccade dysmetria is more likely to appear in centripetal saccades (Helmchen *et al*., 1994*b*). The paradigm was randomized for the order of saccade appearance (direction and amplitude) and for the intersaccadic interval, i.e. the fixation duration of the target varied from 1000 to 1600 ms in order to exclude anticipatory latency effects. The 10 and 20° saccades were analysed separately. Saccades were filtered by a 100 Hz Gaussian filter (–3dB) and detected automatically using peak velocity (20°/s) and acceleration criteria (Rambold *et al*., 2002*a*). Anticipatory and spontaneous saccades were excluded by filtering only saccades with a latency between 80 and 530 ms. All computerized saccade detections were controlled and adjusted manually if required. Saccade amplitude gain was calculated as the ratio between the amplitudes of the primary saccade and target displacement. We used the comparison of: (i) saccadic amplitude gain; (ii) frequency of dysmetric saccades; and (iii) the position errors and the number of corrective saccades between patients and control subjects to determine saccadic dysmetria (Bötzel *et al*., 1993; Moschner *et al*., 1994; Wessel *et al*., 1998). Dysmetria was considered pathological if the primary saccade had an amplitude gain of <0.85 (hypometria) or of >1.0 (hypermetria) (Bötzel *et al*., 1993; Moschner *et al*., 1994; Wessel *et al*., 1998). This analysis was performed for each subject and the mean results are given for each group (control, ET patients; see Results). In the next step, the frequency of dysmetric saccades was calculated for each subject in per cent of the total number of visually guided saccades. Pathological dysmetria was assumed when the frequency of hypometric or hypermetric saccades exceeded 23% (Wessel *et al*., 1998). The pattern of corrective (primary, secondary, tertiary) saccades was considered as pathological if the number, amplitude and/or direction of corrective saccades was significantly different from that of the control subjects.

Spontaneous nystagmus and gaze-holding function. Spontaneous nystagmus was examined with the eyes closed and in darkness (30 s). Fixation nystagmus was tested with eyes opened during fixation in the 'gaze straight ahead' position. Gaze-holding nystagmus was tested during at least 30 s of sustained fixation of vertical and horizontal eccentric laser targets. Rebound nystagmus was assessed in the gaze straight ahead position after prolonged periods of eccentric fixation.

Paradigms in EOG

To investigate the VOR, the vestibular chair was rotated, in the dark, (i) sinusoidally and (ii) with a constant chair velocity around an earth vertical axis as described previously (Wessel *et al*., 1998). VOR gain was calculated by the ratio of the fastest slow phase velocity of vestibular nystagmus to chair velocity. For sinusoidal stimulation, a frequency of 0.2 and 0.33 Hz with a ±90°/s chair peak velocity after an initial acceleration of 90°/s^2 was used. After vestibular stimulation with constant chair velocity (90°/s) for at least 2 min, post-rotatory nystagmus was analysed after sudden deceleration (from 90°/s^2 to 0°/s^2) of the chair within 1 s to characterize the velocity storage mechanism. It was determined with the head in an upright position by the time constant (τ) of the decay of the post-rotatory vestibular nystagmus (Heide *et al*., 1999), defined as a decay of 37% of maximum slow phase velocity of post-rotatory vestibular nystagmus.

The VOR suppression (attenuation of the post-rotatory nystagmus) by fixation of a head-stationary target was calculated by the reduction in VOR gain. Pathological VOR suppression was assumed when the sinusoidal VOR gain could not be suppressed below 0.12 (Heide *et al*., 1999). In addition, VOR tilt suppression (i.e. 'dumping' of its time constant) was induced by a head tilt of 90° forward off the

vertical axis of rotation ('otolith dumping') 4 s after the chair stopped rotating. It was measured as a reduction of the time constant of post-rotatory nystagmus compared with trials without head tilts (Heide *et al*., 1988; Wessel *et al*., 1998). Dumping was considered normal, if the time constant (τ = decay of post-rotatory slow phase velocity by 37%) after head tilt was reduced to <70% of the time constant of post-rotatory VOR without head tilt (Wessel *et al*., 1998). Under normal circumstances the discharge (dumping) of the velocity storage mechanism of the VOR by otolith input (head tilt) is thought to be a cerebellar sign of the nodulus and caudal vermis (Waespe *et al*., 1985; Heide *et al*., 1988). For a better comparison, we compared the otolith dumping effect in ET patients with five patients (aged 33–69 years) with cerebellar lesions in the midline vestibulo-cerebellum (Heide *et al*., 1988).

Horizontal optokinetic nystagmus (OKN) was elicited by 60°/s and 90°/s full-field stimulation (constant velocity) generated by random light dots moving horizontally as described previously (Wessel *et al*., 1998). The gain was calculated as the ratio of peak slow phase velocity to stimulus velocity.

Statistical analysis

The univariate analysis of variance (ANOVA) was used to compare the groups. In case of a significant influence of the group factor on the dependent variables, *post hoc* comparisons were computed using Bonferroni's test. The level of significance was set at $P < 0.05$ unless stated otherwise. For correlation analysis we used Pearson's test. Normal distribution was shown in all experimental data by using the Shapiro–Wilk test.

Results

Clinical tremor scores

Clinical examination of the patients showed no rest tremor. Postural tremor was found in all 17 patients. Sixteen had probable or definite intention tremor in at least one hand; six had a probable intention tremor, while 10 had a definite intention tremor (Table 1).

The two ET subgroups, ET_{PT} ('essential tremor with predominantly postural tremor'; $n = 7$) and ET_{IT} ('essential tremor with definite intention tremor', i.e. rating score of at least 2 unilaterally; $n = 10$), showed significant differences in the following aspects: ET_{IT} patients were older (62.0 ± 14.9 versus 44.4 ± 14.2 years in ET_{PT}) and had a longer history of ET (34.3 ± 20.4 versus 16.0 ± 9.0 years in ET_{PT}); however, there was no difference in age at disease onset. Age did not significantly differ between ET_{IT} patients and control subjects. Furthermore, ET_{IT} patients not only had a higher ITS [3.63 ± 0.52 (ET_{IT}) versus 1.17 ± 0.75 (ET_{PT}), $P < 0.01$], but also a higher postural tremor score [1.6 ± 0.52 (ET_{IT}) versus 1.0 ± 0.58 (ET_{PT})]. The ITS of each patient did not differ by more than one point in the right compared with the left hand.

Head tremor was found in four ET_{PT} patients and in three ET_{IT} patients. There was a positive family history in all seven ET_{PT} patients and in eight out of 10 ET_{IT} patients (Table 1). Five ET patients (one ET_{PT} and four ET_{IT} patients) had been examined by quantitative accelerometry previously (Deuschl *et al*., 2000). One clinical investigator (C.H.) was blinded for the previous accelerometry results, but all of those five patients were clinically assigned to the appropriate ET_{IT} and ET_{PT} patient groups.

On clinical neuro-ophthalmological examination, seven out of 17 patients had cogwheel horizontal smooth pursuit eye movements. Otherwise the patients did not show oculomotor abnormalities.

Eye movement recordings

The scleral search-coil technique was used to investigate horizontal pursuit eye movements, randomized visually guided saccades, and impairment of gaze-holding function in 14 ET patients (six ET_{PT}, eight ET_{IT}) and 10 healthy subjects. In one patient (number 13), initial smooth pursuit acceleration was too poor (too many saccades and blinks during pursuit onset) for an appropriate analysis criterion. In three (one ET_{PT}, two ET_{IT}) of all 17 patients, search-coil recordings could not be obtained (e.g. the patients refused to allow them); eye movements were thus recorded by EOG only. These data were included only in the analysis of the VOR. Since there were generally no significant directional effects in all experimental paradigms, the amplitude-matched data were pooled, unless stated otherwise.

Smooth pursuit eye movements

Mean latency of smooth pursuit onset in the step ramp paradigm in ET patients (169.4 ± 20.5 ms) did not differ from that in the controls (168.60 ± 15.5 ms), nor in the ET subgroups (ET_{PT}: 155.3 ± 11.6 ms; ET_{IT}: 181.5 ± 18.9 ms). The initial eye acceleration in the first 60 ms of smooth pursuit eye movements in the step ramp paradigm was significantly decreased in patients (mean eye acceleration ± SD: 33.6 ± 15.0°/s^2) compared with that of our (mean 41.3 ± 20.2°/s^2) and other control subjects (Kao and Morrow, 1994; Moschner *et al*., 1999). Examples of individual ET_{PT} and ET_{IT} patients are shown as eye position traces with respect to the target displacement (Fig. 2) and as eye velocity traces (Fig. 3). Both show smooth pursuit deficits not only in the maintenance (steady-state velocity) phase, but also in the initial phase of smooth pursuit acceleration. In the comparison of ET subgroups, ET_{IT} patients (mean 23.4 ± 9.0°/s^2) showed a significantly (~ 50%) lower initial pursuit acceleration than ET_{PT} patients (mean 45.5 ± 11.5°/s^2) and control subjects (Figs 3 and 4). The peak of steady-state eye velocity was significantly decreased in ET patients (9.18 ± 2.6°/s) compared with the control subjects (11.7 ± 2.2°/s) and was

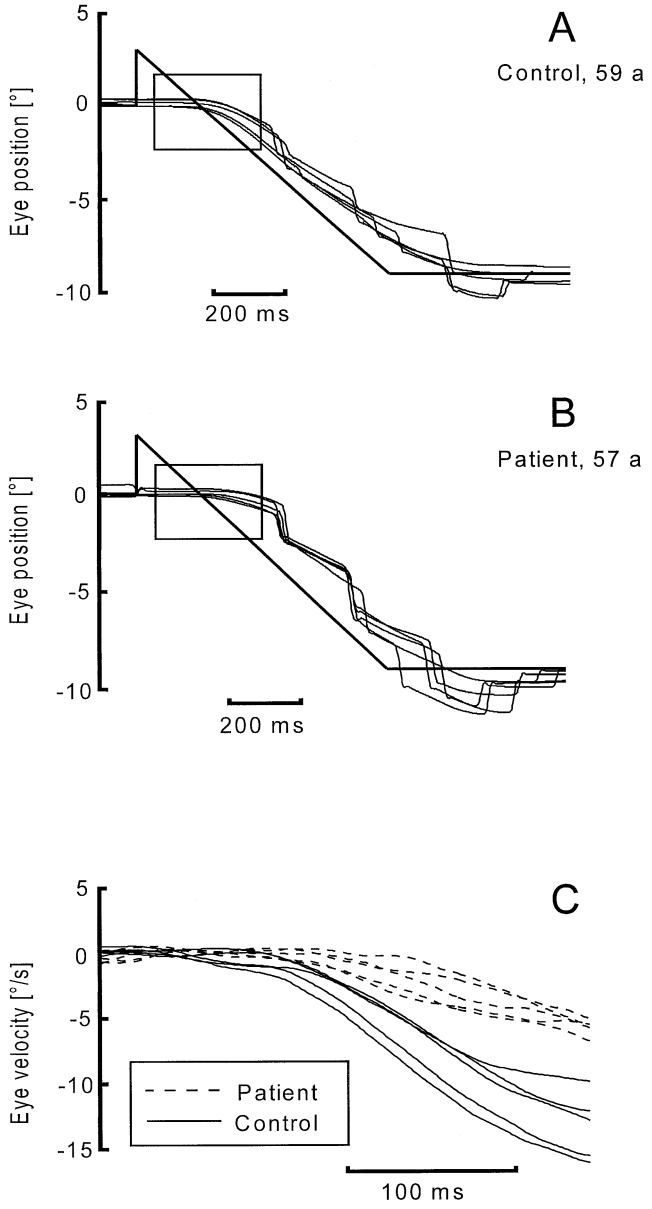

Fig. 2 Horizontal eye position (**A** and **B**) and velocity (**C**) during the step ramp paradigm. Original single eye movement traces are superimposed in a control subject (**A**) and an ET_{IT} patient (**B**). The target is represented by the thick solid line. The initial smooth pursuit response (boxes) in (**A**) and (**B**) is magnified in (**C**) and shown as velocity traces. Note the decreased initial smooth pursuit eye velocity in the patient (dashed line) when compared with the control (solid lines). Positive and negative values (ordinate) indicate rightward and leftward eye movements, respectively.

significantly lower in ET_{IT} (7.98 ± 1.6°/s) than in ET_{PT} patients (10.6 ± 2.9°/s) (Fig. 5A). The initial eye acceleration correlated positively with the peak steady-state eye velocity ($P < 0.01$) in healthy subjects ($r = 0.92$) and in ET patients (ET_{PT}: $r = 0.84$; ET_{IT}: $r = 0.66$). Horizontal sinusoidal smooth pursuit showed a significantly lower velocity gain of ET_{IT} patients compared with the control group, i.e. 0.90 versus 0.98 for 0.2 Hz and 0.75 versus 0.90 for 0.4 Hz ($P < 0.01$; Fig. 5B). The gain of the ET subgroups did not differ significantly among themselves. Visual fixation suppression of the sinusoidal VOR was impaired in five patients (one ET_{PT} and four ET_{IT} patients). Those four ET_{IT} patients with an impaired VOR suppression during visual fixation (mean gain 0.14) also showed a low sinusoidal pursuit gain (0.73).

When impaired smooth pursuit was compared with clinical data there was a negative correlation of the ITS with initial pursuit acceleration (Spearman Rho correlation coefficient: $r = –0.58$, $P < 0.05$) and peak eye velocity ($r = –0.56$, $P < 0.05$), i.e. the more intention tremor the patients showed, the more impaired was initial eye acceleration (Fig. 6A) and peak pursuit velocity (Fig. 6B).

To determine whether the initial pursuit acceleration deficit is secondary to an impaired motion perception in ET patients, the position error of the first saccade elicited by the step ramp stimulus was investigated. There were no significant differences between patients and controls with respect to: (i) amplitude (ET patients: 2.13 ± 0.5°; controls: 2.31 ± 0.8°); (ii) latency (ET patients: 227 ± 33.9 ms; controls: 239 ± 37 ms); or (iii) position errors (ET patients: 1.27 ± 0.7°; controls: 0.87 ± 0.4°) of the initial saccade while tracking the step ramp stimulus, in particular in foveofugal saccades. This indicates that ET patients show no deficit in taking into account the target velocity when programming the saccade, i.e. they probably do not have a perceptual deficit of target motion.

Saccades

Since centripetal and centrifugal saccades did not show significant differences with respect to saccadic latency, gain and peak velocity, they were pooled for further analysis. There were no significant differences between ET patients and control subjects with respect to the latency of saccade onset, gain and peak velocity (Table 2), either in 10 or 20° saccades. The subgroups (ET_{PT} versus ET_{IT}) did not reveal any significant differences either.

The saccadic position error (difference of target position to eye position after the first saccade) was not significantly different in patients and controls for 10° (ET patients versus control: 0.04 ± 0.02° versus 0.04 ± 0.02°) and 20° saccades (ET patients versus control: 0.02 ± 0.01° versus 0.02 ± 0.02°). There were no subgroup differences (ET_{PT} versus ET_{IT}) for 10 and 20° saccades. Frequency and amplitude of corrective saccades (secondary and tertiary on- and off-saccades; Bötzel *et al*., 1993) did not differ between patients and control subjects. The frequency of tertiary off-saccades was normal (<10%; Bötzel *et al*., 1993), and there was no significant difference between ET patients (6.1%) and controls (4.0%). The frequency of dysmetric saccades did not differ between ET patients and controls for neither hypermetric nor hypometric saccades: according to the frequency criteria of dysmetria (>23%; see Subjects and methods), 16% of ET patients had hypometric saccades, while 20% of control subjects had hypometric saccades.

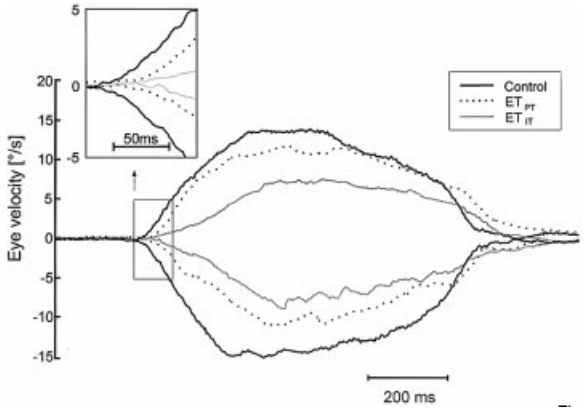

Fig. 3 Horizontal velocity profiles of smooth pursuit eye movements to the right (positive) and to the left (negative) during the step ramp paradigm of an ET_{PT} patient (dotted trace), an ET_{IT} patient (grey solid trace) and a control subject (solid black trace). In the magnified view (inset) there is a clear divergence of eye velocity traces already in the initial smooth pursuit acceleration phase. Positive and negative values (ordinate) indicate rightward and leftward eye movements, respectively. Unlike the mean latencies of all subgroups, which did not differ, these examples show small differences in latencies.

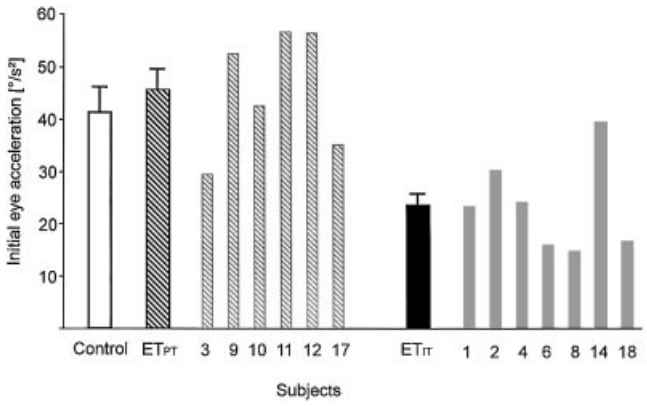

Fig. 4 Initial acceleration of smooth pursuit eye movements in the first 60 ms of the step ramp paradigm for the subgroups: control subjects (open bar), and ET_{PT} (hatched bars) and ET_{IT} (black/grey bars) patients. The thin bars indicate median values of initial eye acceleration of single patients (numbers are given below the column). Thick bars in bold contrast show the mean of those median values for each group with standard errors. Initial eye acceleration was significantly lower in ET_{IT} patients when compared with ET_{PT} patients and controls.

Spontaneous nystagmus and gaze-holding function

No patient showed a spontaneous nystagmus (>5°/s slow phase velocity). Gaze-holding function was not impaired, i.e. there was no gaze-evoked nystagmus. Neither was there rebound or periodic alternating nystagmus.

Vestibulo-ocular reflex (VOR)

VOR was investigated in 17 patients with essential tremor (seven ET_{PT} and 10 ET_{IT} patients) and 11 healthy control subjects. The mean VOR gain showed no significant differences between ET patients (0.77 ± 0.16) and control subjects (0.85 ± 0.12) during either sinusoidal or vestibular ramp stimulation. Neither was VOR gain in the ET subgroups significantly different (ET_{PT}: 0.72 ± 0.16; ET_{IT}: 0.80 ± 0.15). Dumping of the VOR time constant by head tilts ('otolith-dumping'; see Methods) was pathological in ET patients; the VOR time constant (τ) without head tilt (13.9 s) was diminished on average to only 70.1 ± 14.8% of VOR time constant with head tilt (9.75 s), which was significantly less diminished than in the control subjects (14.9 to 8.46 s; reduction to 56.8 ± 3.9%). This deficit was particularly evident in the ET_{IT} patients who were on the average unable to reduce the VOR time constant (14.1 s to 11.2 s; 79.4 ± 13.0%) (Fig. 7), whereas the ET_{PT} patient group (13.69 s to 8.52; 62.9 ± 13.2%) did not show significant differences to healthy control subjects (57.8 ± 3.9%). Accordingly, the mean reduction of the time constant after head tilt was shorter in ET_{IT} patients (3.45 ± 1.7 s) compared with ET_{PT} patients (5.17 ±1.9 s) and control subjects (6.14 ± 1.14 s). Evaluation of single subjects showed a normal dumping to <70% of the time constant without head tilt in four of seven ET_{PT} patients and in three of 10 ET_{IT} patients, while none of the healthy control subjects failed to dump the VOR time constant. For better comparison, the deficient otolith dumping effect was added in five patients (aged 33–69 years) with cerebellar lesions in the midline vestibulo-cerebellum (Heide *et al*., 1988) (Fig. 7A and B, right side), who were virtually unable to reduce the post-rotatory time constant, i.e. they could not discharge the velocity storage mechanism.

Optokinetic nystagmus

The gain of horizontal optokinetic nystagmus examined with a 60°/s stimulus (control: 0.95 ± 0.07; ET: 0.88 ± 0.15) and 90°/s (control: 0.81 ± 0.18; ET: 0.70 ± 0.19) stimulus was not significantly impaired in ET patients. Subgroup comparison did not show any significant difference either (60°/s: ET_{PT} 0.92 ± 0.11, ET_{IT} 0.85 ± 0.17; 90°/s: ET_{PT} 0.75 ± 0.18, ET_{IT} 0.67 ± 0.20).

Discussion

This is the first study to show oculomotor deficits in patients with essential tremor. Several lines of evidence from animal (Wilms *et al*., 1999), physiological (Deuschl *et al*., 2000; Stolze *et al*., 2001; Köster *et al*., 2002) and imaging (Colebatch *et al*., 1990; Jenkins *et al*., 1993; Wills *et al*., 1994; Pagan *et al*., 2002) studies pointed to a cerebellar role in ET. Thus, the aim of this study was to look for cerebellar eye movement disorders in patients with essential tremor that might help to characterize their cerebellar dysfunction. Our main findings were two distinct oculomotor deficits, which are assumed to be of cerebellar origin: (i) decreased initial

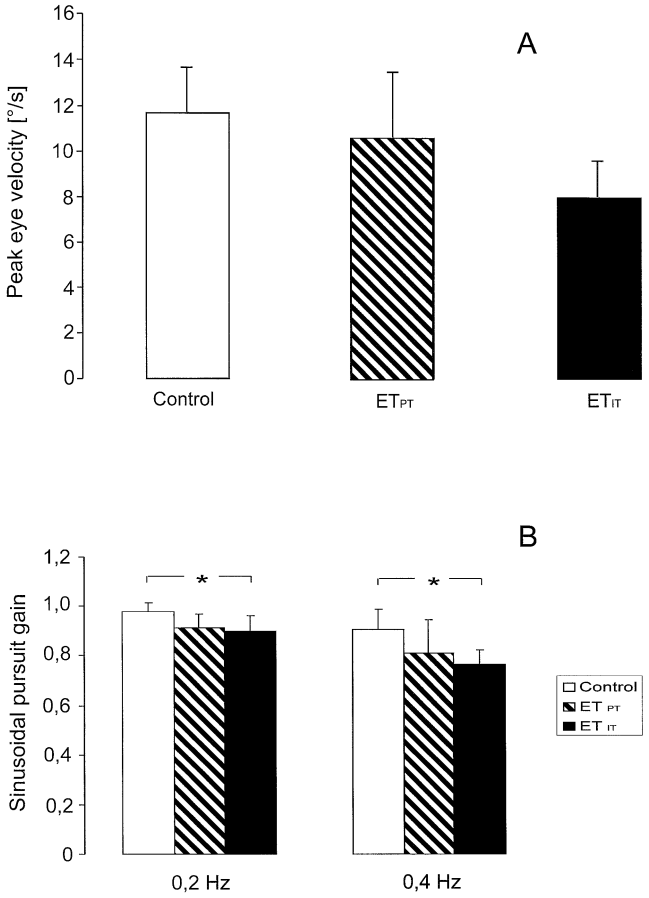

Fig. 5 (**A**) Means (+SDs) of peak steady-state velocity (V_{max}) of smooth pursuit eye movements in the step ramp paradigm are given for healthy control subjects (open bar), and ET_{PT} (hatched bar) and ET_{IT} (black bar) patients. Eye velocity was significantly decreased in ET_{IT} patients compared with controls and ET_{PT} patients. (**B**) Mean sinusoidal smooth pursuit gain for different (0.2 and 0.4 Hz) stimulus velocities for control subjects (open bars), ET_{PT} patients (hatched bars) and ET_{IT} patients (black bars). $^*P < 0.05$.

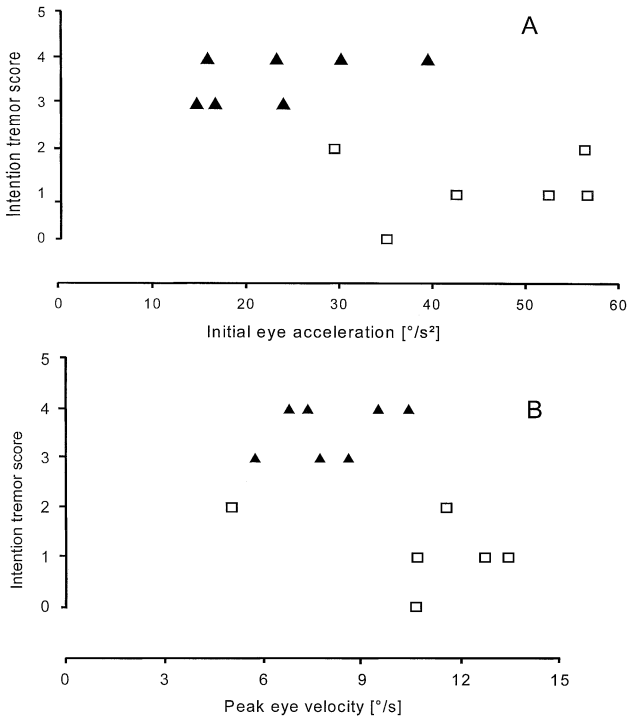

Fig. 6 Relation of initial eye acceleration (**A**) and peak velocity (**B**) of smooth pursuit eye movements (abscissa) to clinical intention tremor score (ITS) for both ET subgroups; ET_{IT} patients (filled triangles) and ET_{PT} patients (open squares). Initial eye acceleration and peak eye velocity decreases with increasing ITS.

pursuit acceleration (Straube *et al*., 1997; Moschner *et al*., 1999); and (ii) deficient capacity to discharge the velocity storage mechanism, i.e. the impaired vestibulo-cerebellar function to reduce the time constant of post-rotatory vestibular nystagmus by head tilts (Hain *et al*., 1988; Heide *et al*., 1988; Wessel *et al*., 1998). The pursuit deficit is of clinical significance since it is related to the amount of intention tremor, suggesting that progressive ET involves the cerebellum in the natural course of the disease (Deuschl *et al*., 2000). Thus, cerebellar dysfunction in ET does not only involve the cerebellar control of arm (Deuschl *et al*., 2000; Köster *et al*., 2002) and leg movements (Stolze *et al*., 2001), but also of oculomotor and vestibular function (this study), of which the latter can at least in part be localized to midline (vermal) cerebellar structures. Although these oculomotor deficits can usually not be detected by clinical neurologists, they might shed light on the pathophysiology of ET. Therefore the oculomotor deficits will be discussed in the light of their localizing value and potential implications for the pathomechanism of essential tremor.

Smooth pursuit deficits

Smooth pursuit eye movements consist of an initial acceleration phase and a maintenance phase with steady-state velocity. The initial phase represents the first 60 ms of eye acceleration (open-loop period), which is largely driven by retinal slip. In the maintenance phase, gaze velocity reaches target velocity via a closed-loop visual pathway. ET patients in our study showed impairment of both smooth pursuit initiation and maintenance, whereas the latency of pursuit onset was not affected. Smooth pursuit initiation impairment that has a normal latency is unlikely to be of cortical (e.g. parieto-occipital) origin (Heide *et al*., 1996) and can also not be explained by attentional deficits.

An impaired perception of visual target motion is also unlikely to account for the impairment of pursuit acceleration in our ET patients. There were no significant differences in amplitude, latency or position errors of the initial saccade between patients and controls while tracking the step ramp stimulus, nor in foveopetal or in foveofugal saccades. Increased saccadic position errors of initial pursuit without evidence of large amplitude saccadic dysmetria is thought to reflect impaired estimation of visual target velocity (Heide *et al*., 1996). This has also been shown in some cerebellar

Table 2 *Latency, gain and peak velocity of 10 and 20° horizontal saccades of control subjects, ET_{IT} patients and ET_{PT} patients*

	Control	ET_{PT}	ET_{IT}
Latency (ms)			
10°	229.9 ± 16.2	207.0 ± 45.5	244.4 ± 55.6
20°	237.3 ± 20.4	208.2 ± 31.8	258.3 ± 61.1
Gain			
10°	0.96 ± 0.02	0.96 ± 0.03	0.96 ± 0.02
20°	0.99 ± 0.02	0.98 ± 0.02	0.99 ± 0.02
Peak velocity (°/s)			
10°	310.9 ± 35.9	288.0 ± 24.3	283.2 ± 35.8
20°	409.5 ± 43.2	380.2 ± 32.3	356.7 ± 84.6

There were no significant differences between patients and control subjects.

patients (Nawrot and Rizzo, 1995; Moschner *et al*., 1999). However, even normal motion perception and normal latency eventually do not completely exclude cortical dysfunction. Impaired smooth pursuit eye movements can also be caused by pontine lesions, but neither the clinical examination nor the oculomotor findings pointed to a pontine dysfunction.

There is a known age-dependency of smooth pursuit eye movements, which also holds for the open-loop phase (Morrow and Sharpe, 1993). This is compatible with our results demonstrating that ET_{PT} patients showed a better initial pursuit acceleration compared with the two other groups of older subjects, i.e. ET_{IT} patients and controls. Thus, we cannot rule out that the difference between ET_{PT} patients and controls is age dependent. However, there was no statistically significant difference in age between ET_{IT} patients and controls, yet they showed a significant difference in initial pursuit acceleration. Thus, we believe that this effect is specifically related to essential tremor and probably reflects cerebellar dysfunction.

The cerebellum is crucial for smooth pursuit eye movements. Indeed, cerebellectomy abolishes them (Westheimer and Blair, 1974; Burde *et al*., 1975). At least two main cerebellar structures participate in the generation of smooth pursuit eye movements forming two parallel pathways: (i) the flocculus/parafloccculus (Zee *et al*., 1981; Stone and Lisberger, 1990; Rambold *et al*., 2002*b*); and (ii) the vermal lobules VI,VII and the uvula (Heinen and Keller, 1996) with the underlying deep cerebellar nuclei (Suzuki and Keller, 1988). However, lesions of neither structure alone can fully account for the loss of smooth pursuit eye movements after cerebellectomy.

The maintenance of a constant pursuit velocity is primarily subserved by the flocculus (Stone and Lisberger, 1990). The fastigial nuclei (Robinson *et al*., 1997) and the posterior vermis (Ohtsuka and Enoki, 1998; Takagi *et al*., 2000) participate in direction-specific smooth pursuit initiation and maintenance (Krauzlis and Miles, 1998). Magnetic stimulation of the posterior vermis in human subjects increases (ipsilaterally) or decreases (contralaterally) both initial

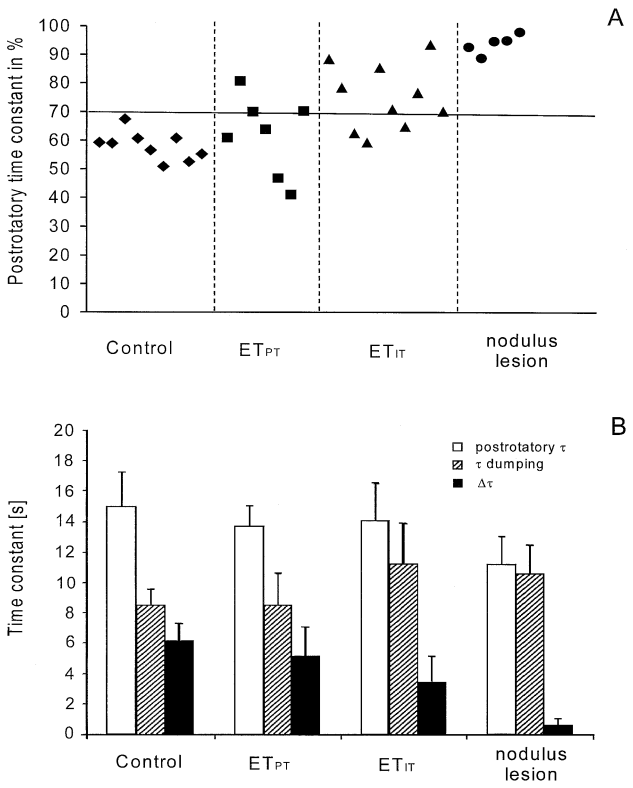

Fig. 7 Reduction of post-rotatory vestibular time constant(s) by head tilts ('otolith dumping') shown in four groups: healthy control subjects (filled diamonds), ET_{PT} patients (filled squares), ET_{IT} patients (filled triangles) and patients with cerebellar vestibulo-cerebellar (nodulus) lesions (filled circles) (Heide *et al*., 1988). (**A**) The post-rotatory time constant with head tilt is shown as a percentage of the post-rotatory time constant without head tilt. A pathological 'dumping' was assumed when the time constant could not be reduced by head tilts below 70% (horizontal line). (**B**) The time constants of post-rotatory nystagmus (s) are shown (+SDs) with (hatched bars) and without head tilt (open bars) for each of the four groups. The differences of post-rotatory time constants with versus without head tilt are shown as black bars. Note that ET_{IT} patients, and in particular patients with vestibulo-cerebellar lesions (nodulus), cannot dump the time constant sufficiently.

acceleration and steady-state pursuit velocity (Ohtsuka and Enoki, 1998). Therefore initial pursuit deficits have been proposed to indicate cerebellar dysfunction (Straube *et al*., 1997; Takagi *et al*., 2000), and the posterior vermis/fastigial nucleus complex probably plays a major role.

A few previous clinical studies have implicated diffuse (Lekwuwa *et al*., 1995; Moschner *et al*., 1999) or circumscribed (Straube *et al*., 1997) cerebellar lesions in the impairment of initial pursuit acceleration. However, only some of the focal cerebellar lesions (Straube *et al*., 1997), causing impaired initial pursuit acceleration, are involved the midline vermal cortex. Moreover, lesions of the oculomotor vermis (lobules VI,VII) should also have led to saccade dysmetria (Ritchie, 1976; Sato and Noda, 1992; Ohtsuka and Enoki, 1998; Takagi *et al*., 1998, 2000; Barash *et al*., 1999), but we did not find this (see below).

Saccades

A hallmark of cerebellar saccadic dysfunction is saccadic dysmetria (Bötzel *et al*., 1993). It is largely controlled by saccade-related neurons in the posterior vermis (Sato and Noda, 1992; Helmchen and Büttner, 1995) and fastigial nuclei (Fuchs *et al*., 1993; Helmchen *et al*., 1994*a*). Accordingly, lesions of the oculomotor vermis (Sato and Noda, 1992; Vahedi *et al*., 1995; Takagi *et al*., 1998) and fastigial nuclei (Robinson *et al*., 1993) cause direction-specific saccade dysmetria.

Since abnormal olivocerebellar neural rhythmicity, which is thought to be transmitted to the cerebellar Purkinje cells and the deep cerebellar nuclei (Lamarre, 1995), is a probable pathomechanism in ET, saccade dysmetria may also be caused by lesions affecting the afferent cerebellar projections in the brainstem. Impaired climbing fibres in the medullary brainstem at the level of the inferior olive, e.g. in Wallenberg's syndrome, may cause deficient climbing fibre input to the cerebellar Purkinje cells, leading to direction-specific saccadic dysmetria (Helmchen *et al*., 1994*b*) by increased inhibition (inactivation) of the fastigial nuclei.

Although we considered all criteria of saccadic dysmetria together (see Subjects and methods; Bötzel *et al*., 1993), we did not find significant dysmetria in ET patients, nor in ET_{PT} or ET_{IT} patients. This was independent of the direction and amplitude of the saccade. Since the saccade system is constantly recalibrated by the cerebellar cortex (Barash *et al*., 1999), saccade dysmetria can be a transient sign and may be absent in patients with chronic cerebellar disease (Fetter *et al*., 1994; Moschner *et al*., 1994).

Vestibulo-ocular reflex, velocity storage mechanism and gaze-holding function

The vestibulo-cerebellum controls and adjusts the gain of the VOR. It may be increased in patients with cerebellar lesions (Baloh *et al*., 1975; Baloh and Demer, 1993), but we did not find this. Accordingly, we did not find dynamic signs of a vestibular imbalance, i.e. vestibular spontaneous nystagmus. Another vestibulo-cerebellar function, in particular of the caudal vermal lobules, uvula and nodulus, is the capacity to discharge the velocity storage mechanism by otolith input (Schrader *et al*., 1985; Waespe *et al*., 1985). This is detected by the reduction of the time constant of the post-rotatory VOR following head tilts (Han *et al*., 2001). Patients with lesions of the vestibulo-cerebellum show impaired tilt suppression of the VOR (Hain *et al*., 1988; Heide *et al*., 1988). In contrast to the normal tilt suppression in all our control subjects, only two ET patients with intention tremor were able to produce a sufficient tilt suppression. Since ET_{PT} patients were much less affected than ET_{IT} patients, the impaired VOR tilt suppression by head tilts is a sensitive sign of cerebellar (uvula/nodulus) dysfunction in the advanced stage of ET. However, this deficit was incomplete when compared with patients with cerebellar lesions affecting the vestibulo-cerebellum (uvula/nodulus) (Heide *et al*., 1988) (Fig. 7). Uvula and nodulus lesions may also elicit periodic alternating nystagmus (Waespe *et al*., 1985), which we did not find. Finally, the cerebellum, particularly the flocculus, contributes to the gaze-holding function, i.e. cerebellar lesions may reduce the time constant of the slow phase of gaze-evoked nystagmus to 2 s (Optican and Robinson, 1980). The absence of gaze-evoked nystagmus in our ET patients argues against any considerable dysfunction of the flocculus.

Pathophysiology of essential tremor

The pathophysiological research of ET is presently concentrating on the cerebellum, and many lines of evidence are now supporting a cerebellar dysfunction. The two oculomotor deficits described in this study are among the most recent arguments for such an abnormality. The impairment of smooth pursuit eye movements is even strengthening such a relation as we found a correlation between the initial pursuit acceleration deficit and the clinical ITS. The latter is considered the clinical hallmark for a cerebellar-like tremor. This correlation may indicate a similar pathophysiological background. This supports the hypothesis that intention tremor in ET patients is one of several cerebellar signs to probably indicate advanced stages of ET. Thus, we propose that not only arm and leg movements (dysmetria, intention tremor), but also smooth pursuit eye movements, constitute signs of cerebellar dysfunction in the advanced stages of ET. This correlation not only suggests a pathophysiological link between both systems (arm and eye movements), but it may also be helpful since the kinematic analysis of dysmetric arm movements may be contaminated by the tremor components that can be excluded by eye movement recordings. Our data strongly support the assumption that ET_{PT} and ET_{IT} patients constitute a continuum of the same disease (Deuschl *et al*., 2000), which may exert cerebellar (vermal) signs in the late stage that cannot be distinguished from patients with nodulus lesions (Fig. 7).

The common hypothesis about the pathomechanism of ET involves an abnormal olivocerebellar rhythmicity (Deuschl and Elble, 2000) and this may cause signs of cerebellar dysfunction. The climbing fibres originate from the inferior olive, travel through the inferior cerebellar peduncle, and terminate in the ipsilateral cerebellar cortex and cerebellar nuclei. In the animal model of ET, harmaline-induced tremor (Lamarre and Mercier, 1971; Elble, 1998), the cerebellar cortex and the deep cerebellar nuclei synchronously show a similar oscillation (Wilms *et al*., 1999). To ensure the accuracy of movements, the cerebellum is crucially involved in acceleration and deceleration. Thus, a pathological olivocerebellar oscillation may in particular lead to a pathological acceleration or deceleration of movements, affecting not only arm movements (Deuschl *et al*., 2000), but also eye movements as seen in the initial pursuit acceleration of our ET patients.

The termination of the climbing fibres responsible for this pursuit deficit remains to be determined. Cooling of the inferior olive results in suppression of the activity in the deep cerebellar nuclei (Benedetti *et al*., 1983). Thus, lesions or the inactivation of climbing fibres in the inferior olive might elicit oculomotor deficits resembling deep cerebellar nuclei inactivation, e.g. saccadic dysmetria (Helmchen *et al*., 1994*b*), which we did not find. Some mossy fibres that enter the cerebellar peduncle at the level of the inferior olive travel to the flocculus and paraflocculus through the inferior peduncle (Langer *et al*., 1985), but there were no signs of floccular dysfunction (gaze-evoked nystagmus) in our ET patients. Most recently, experimental ventral paraflocculus lesions have been shown to affect not only smooth pursuit maintenance, but also initial pursuit acceleration during open-loop pursuit tracking (Rambold *et al*., 2002*b*). Thus, parafloccular dysfunction in our ET patients may be a possible explanation.

Straube and coworkers found initial smooth pursuit deficits in patients with lesions in the cerebellar hemispheres and the interpositus nuclei, whereas the flocculus and paraflocculus were not involved (Straube *et al*., 1997). This agrees with some experimental animal stimulation studies (Ron and Robinson, 1973; Robinson and Brettler, 1998). The lateral cerebellar hemispheres are thought to be involved in the control of the accuracy of limb movements (Bastian and Thach, 1995), but it remains to be shown whether the initial pursuit deficit and the intention tremor and arm dysmetria in ET patients reflect a common cerebellar hemispheric lesion site. Additional evidence in favour of a hemispheric lesion site comes from recent spectroscopy findings in ET patients showing neurochemical abnormalities in the cerebellar hemispheres (Louis *et al*., 2002; Pagan *et al*., 2002). This is of localizing significance since previous imaging data pointing to hyperactive states of the cerebellum by PET (Colebatch *et al*., 1990; Jenkins *et al*., 1993; Wills *et al*., 1994) could not identify specific regional abnormalities within the cerebellum.

In summary, neither the oculomotor vermis (lobulus VI/VII) and underlying fastigial nucleus, nor the flocculus and paraflocculus, nor the cerebellar hemispheres alone can explain both the smooth pursuit deficit with intact saccades and the deficient tilt suppression of the VOR (pathological 'VOR dumping') together. In contrast, the cerebellar structure that could elicit both deficits in ET patients is the caudal vermis (uvula, nodulus): first, the uvula receives climbing and mossy fibre afferents supplying signals for visual motion processing that are important for the generation of smooth pursuit. These projections come from the dorsolateral pontine nuclei, and travel through the inferior olive to the paraflocculus and uvula (Glickstein *et al*., 1994) and may carry the pathological oscillatory signal supected in ET. Secondly, uvula lesions elicit profound smooth pursuit deficits, including impairment of initial eye velocity (Heinen and Keller, 1996), and a pathological 'VOR dumping' (Waespe *et al*., 1985; Heide *et al*., 1988). Thirdly, caudal vermis lesions do not impair saccades. Taking all these lines of converging aspects together the caudal vermis seems to play a critical role in the oculomotor disorders found in ET patients.

The cerebellar hypothesis of ET is now based on a number of observations. Arm movements (Deuschl *et al*., 2000; Köster *et al*., 2002), leg movements (Stolze *et al*., 2001) and eye movements (this paper) show a cerebellar-like abnormality in advanced ET. The timing of arm muscle activity shows a delay of the second agonist muscle (Britton *et al*., 1994) and this feature is more pronounced in patients with ET_{IT}, which probably reflects a disturbed cerebellar timing function in ET (Köster *et al*., 2002). Cerebellar hypermetabolism is reversed with reduction of ET during alcohol consumption (Boecker *et al*., 1996) and this effect is probably mediated by an effect on the central oscillator (Zeuner *et al*., 2002). The improvement of ipsilateral ET after a cerebellar stroke (Dupuis *et al*., 1989; Nagaratnam and Kalasabail, 1997) and the improvement of ET by cerebellar stimulation, either by direct magnetic stimulation (Gironell *et al*., 2002) or indirectly by deep brain (ventrolateral thalamic) stimulation of cerebello-thalamic afferent fibres (Zackowski *et al*., 2002), are further arguments favouring a critical role for the cerebellum in producing or suppressing ET. Further studies can now be based on a more solid hypothesis and will include more detailed imaging techniques.

In conclusion, our data support the assumption that cerebellar (uvular) dysfunction occurs in advanced stages of ET, particularly in ET_{IT} patients. The oculomotor signs (pursuit deficit and impaired discharge of the velocity storage mechanism) have previously not attracted much attention (Stolze *et al*., 2001), since they are clinically difficult to examine and usually require advanced eye movement recording techniques. The correlation of cerebellar intention tremor with the oculomotor deficits in ET implies an inherent relationship between both parameters that might be used as a marker for progress of the disease in ET patients. However, our study cannot answer the question of whether cerebellar signs of eye and arm movement impairment reflect the oscillatory olivocerebellar activity in advanced stages of the disease or whether the cerebellum itself participates in the pathogenesis of ET.

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