doi:10.1093/brain/awr009 Brain 2011: 134; 879–891 | 879

BRAIN
A JOURNAL OF NEUROLOGY

Differences in saccade dynamics between spinocerebellar ataxia 2 and late-onset cerebellar ataxias

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The cerebellum is implicated in maintaining the saccadic subsystem efficient for vision by minimizing movement inaccuracy and by learning from endpoint errors. This ability is often disrupted in degenerative cerebellar diseases, as demonstrated by saccade kinetic abnormalities. The study of saccades in these patients may therefore provide insights into the neural substrate underlying saccadic motor control. We investigated the different extent of saccade dynamic abnormalities in spinocerebellar ataxia type 2 and late-onset cerebellar ataxias, genetically undefined and with prevalent cerebellar atrophy. Reflexive and voluntary saccades of different amplitude (10°–18°) were studied in seven patients with spinocerebellar ataxia 2, eight patients with late-onset cerebellar ataxia and 25 healthy controls. Quantitative analysis of saccade parameters and measures of saccade accuracy were performed. Detailed neurological, neurophysiological and magnetic resonance imaging assessment was obtained for each patient. Genetic and laboratory screening for spinocerebellar ataxias and other forms of late-onset cerebellar ataxias were also performed. A lower peak saccade velocity and longer duration was observed in patients with spinocerebellar ataxia 2 with respect to those with late-onset cerebellar ataxia and controls. Unlike subjects with spinocerebellar ataxia 2, patients with late-onset cerebellar ataxia showed main sequence relationships to similar saccades made by normal subjects. Saccades were significantly more inaccurate, namely hypometric, in late-onset cerebellar ataxia than in spinocerebellar ataxia 2 and inaccuracy increased with saccade amplitude. The percentage of hypometric primary saccades and of larger secondary corrective saccades were consistently higher in late-onset cerebellar ataxia than in spinocerebellar ataxia 2 and controls. No other significant differences were found between groups. Two different mechanisms were adopted to redirect the fovea as fast and/or accurately as possible to peripheral targets by the two groups of cerebellar patients. Patients with spinocerebellar ataxia 2 maintained accuracy using slow saccades with longer duration. This reflects prevalent degenerative processes affecting the pontine burst generator and leading to saccade velocity failure. On the other hand, patients with late-onset cerebellar ataxia reached the target with a number of fast inaccurate, mostly hypometric saccades. Different degrees of cerebellar oculomotor vermis involvement may account for differences in optimizing the trade-off between velocity and accuracy in the two groups. In addition, as suggested by spinocerebellar patients having slow saccades that are no longer ballistic, visual feedback might be continuously available during the movement execution to guide the eye to its target.

Received September 23, 2010. Revised November 29, 2010. Accepted December 23, 2010

Keywords: saccade dynamics; accuracy; degenerative cerebellar diseases; spinocerebellar ataxia type 2; late onset cerebellar ataxia
Abbreviations: ICARS = international cooperative ataxia rating scale; SCA2 = spinocerebellar ataxia type 2

Introduction

Saccades are stereotyped eye movements used in repositioning the fovea over regions of interest (Leigh and Zee, 2006). To serve vision optimally, saccades must be simultaneously fast and accurate (Kowler and Blaser, 1995; Ramat *et al*., 2007). However, since the high speed of saccades excludes any correction by visual feedback, their accuracy is ensured by an efferent copy of ongoing motor commands (forward model) (Robinson, 1975; Wolpert *et al*., 1995; Optican, 2005) that allows the motor commands themselves to be monitored by predicting the sensory effects of the current movement and its trajectory to be corrected (Quaia *et al*., 2000). In the optimal control theory framework (Todorov, 2005), motor commands tend to minimize specific costs of the saccade system related to low vision for target eccentricity and endpoint variability due to signal-dependent noise (Harris and Wolpert, 1998). In this model, faster saccades are generated by higher motor commands that in turn determine greater noise, producing higher endpoint variability; on the contrary, slow movements are more accurate at the expense of taking longer with poor vision (Harris and Wolpert, 1998). To overcome this cost, the saccadic system has developed mechanisms to optimize the trade-off between duration and accuracy (Harris and Wolpert, 2006; van Beers, 2008). Another possible optimal strategy to catch the target as fast as possible is to undershoot it, making subsequent corrective saccades toward the same direction (Harris, 1995). This well established phenomenon occurs in normal subjects when target displacement is $>10^{\circ}$ and saccades undershoot it by $\sim$10% (Becker and Fuchs, 1969; Henson, 1978). The cerebellar oculomotor vermis is considered a crucial structure, where saccadic signals are rapidly regulated and adapted to maintain accuracy (Hopp and Fuchs, 2004; Catz *et al*., 2005; Chen-Harris *et al*., 2008, Kojima *et al*., 2010). Familial or sporadic degenerative cerebellar diseases affecting this structure lead to persistent dysmetria (Zee *et al*., 1976*b*; Moschner *et al*., 1994). Thus, the study of saccadic eye movements in these patients may provide insights into the definition of cerebellar functions. In some cases, however, neurodegenerative processes affecting the cerebellum also induce slow saccades. The study of patients with slow saccades offers the unique opportunity to consider an alternative hypothesis regarding how the saccadic subsystem can maintain accuracy using visual feedback. Previous studies on patients with slow saccades, (Zee *et al*., 1976*a*; MacAskill *et al*., 2000) have suggested that normal saccades are only open-loop because they are too fast to be modified in flight by visual feedback. In reality, when saccades last more than 100 ms, as in case of patients with spinocerebellar ataxia type 2 (SCA2), visual information may be used to get them on the target (closed-loop). This implies that the saccadic system could continuously acquire visual references on target position that may be used in monitoring the current eye displacement and adjusting it. This mechanism becomes available when saccades are slow enough to be modified in flight by visual feedback.

Autosomal dominant SCA2 is a genetic neurodegenerative disorder mainly affecting the brainstem, cerebellum and cerebral cortex, due to CAG trinucleotide repeat expansion (Geschwind *et al*., 1997). Oculomotor disorders in these patients characteristically include a substantial reduction in saccade velocity. Previous reports indicate that slowing of saccades runs parallel to disease progression, CAG trinucleotide repeat expansion and is also observed in pre-symptomatic subjects (Velázquez-Pérez *et al*., 2009). Reduced accuracy has also been observed in these patients (Buttner *et al*., 1998).

Besides SCA2, late-onset cerebellar ataxia with undefined genetic mutations but clinical and MRI evidence of isolated cerebellar atrophy including midline structures, may also show abnormalities in saccade dynamics (Kerber *et al*., 2005).

The aim of this study was to quantify and compare saccade dynamics in seven patients with SCA2 and eight patients with late-onset cerebellar ataxia. We tested the hypothesis that main sequence relationships optimize the trade off between speed and accuracy in these two degenerative diseases. Alternatively, but not mutually exclusive, we also consider the visual feedback as a possible mechanism maintaining saccade accuracy only in patients with slow saccades. Finally we suggest that abnormalities in saccadic parameters differ between the two groups of patients according to specific anatomical substrate.

Materials and methods

Patients and controls

Seven patients with genetically confirmed SCA2 (four males, three females), mean age 44.1 years (range 28–65 years), and eight patients with late-onset cerebellar ataxia (five males, three females), mean age 50.8 years (range 39–63 years) were enrolled in the study. All patients underwent complete neurological and neuro-ophthalmological examination. International Cooperative Ataxia Rating Scale (ICARS) (Trouillas *et al*., 1997) was scored at the moment of neurological examination and brain MRI. All patients underwent the recommended clinical protocol for ataxias, including genetic and laboratory testing when pertinent. In patients with late-onset cerebellar ataxia, Friedreich ataxia, fragile X-premutation, ataxia-telangiectasia, ataxias associated with mutation of aprataxin, senataxin or sacsin, metabolic causes of ataxia such as abetalipoproteinemia, vitamin E deficiency, late-onset Tay–Sacs disease, cerebrotendinous xanthomatosis, and other causes of recessive ataxias were ruled out, as well as autosomal dominant spinocerebellar ataxias due to *de novo* mutations. Demographic and clinical data of these patients are reported in Table 1. The control group consisted of 25 healthy age-matched subjects (11 males, 14 females) of mean age 43.2 years (range 30–68 years). Exclusion criteria for control subjects included any history of neurological or eye problems, toxic or drug abuse and current pharmacological treatment for neurological or eye diseases. All subjects gave their informed consent and the study was approved by the Regional Ethics Committee.

Table 1 Demographic, clinical, genetic and MRI findings of patients with SCA2 and late-onset cerebellar ataxia (LOCA)

Subject	Gender/age	Age at onset	CAG repeats	ICARS	MRI
SCA2-1	F/47	37	20–41	48	Global brainstem and cerebellar atrophy
SCA2-2	M/28	25	21–39	36	Ponto-cerebellar atrophy
SCA2-3	M/65	48	19–36	35	Ponto-cerebellar atrophy
SCA2-4	M/33	23	22–43	37	Ponto-cerebellar atrophy
SCA2-5	F/35	24	21–40	23	Hemispheric cerebellar and pontine atrophy
SCA2-6	M/36	17	23–42	56	Global brainstem and cerebellar atrophy
SCA2-7	M/65	50	37–39	36	Global brainstem and cerebellar atrophy
LOCA-1	M/41	25		38	Olivo-cerebellar atrophy
LOCA-2	M/39	24		45	Global cerebellar atrophy
LOCA-3	F/56	43		38	Cerebellar/vermian atrophy
LOCA-4	M/56	20		27	Global cerebellar atrophy
LOCA-5	F/55	54		23	Global cerebellar atrophy
LOCA-6	F/44	16		71	Cerebellar/vermian atrophy
LOCA-7	M/53	44		34	Cerebellar/vermian atrophy
LOCA-8	M/63	59		41	Olivo-cerebellar hypometabolism (PET)

F = female; M = male.

Equipment and eye movement recording

Patients and controls performed horizontal saccades in response to a visual target. Eye movements were recorded using an ASL 504 eye-tracker device (Applied Science Laboratories, Bedford, MA, USA). Stimulus was generated by a microcomputer-controlled LCD stimulator. An interactive programme was used for eye calibration, based on nine static points disposed in central, horizontal, vertical and oblique position on the screen. Horizontal and vertical gaze positions were recorded during the experiment. Data was sampled at a frequency of 240 Hz and stored in binary digital form with 16-bit resolution in a personal computer.

The visual stimulus was presented on a 31 × 51 cm LCD screen (frame rate 60 Hz) having a resolution of 1024 × 768 pixel at a distance of 72 cm from the subject's eyes. The visual target was a red dot (luminance 63 cd/m^2) with diameter subtending a visual angle of 0.4°, presented on a black background (luminance 2.5 cd/m^2). In order to minimize head perturbations, subjects' heads were immobilized by a bite bar and chinrest. All recordings were conducted in complete darkness binocularly, measuring one eye.

Experimental design

We focused our interest on saccadic parameters (refer to 'Saccadic parameters and statistical variables' section) and their relationships in order to test significant differences between the two groups of cerebellar patients. To account for cortical deficits that may alter the premotor command for saccade execution, antisaccades (voluntary saccades) were also investigated. Thus we performed prosaccade tests and antisaccade tests at different amplitudes of the target.

In the prosaccade test (reflexive saccades), after the central fixation point was switched off, the visual target appeared to the right or left in an unpredictable manner without 'gap' periods. When possible, subjects performed three different experiments, usually on different days. Each test consisted in a sequence of 20–40 or 60 trials. The target randomly jumped at four possible locations (10° and 18° of amplitude) in the horizontal plane. The target was presented at a time interval of 1500–2000 ms. Subjects were instructed to make a saccade as fast and as precisely as possible towards the target.

In the antisaccade test, we followed the same protocol as for prosaccades, except that subjects were instructed to direct the gaze in the opposite direction to the target, making a saccade of the same amplitude (10° and 18°).

Saccadic parameters and statistical variables

We determined the traditional descriptive parameters (Becker, 1991) of saccade dynamics for the initial saccade (first saccade performed after target presentation). Saccade duration, amplitude, peak velocity, latency and gain were assessed for all identified saccades. Saccade duration was the time interval between the start and the end of the movement, a velocity threshold of 10°/s was used to determine the starting and ending times of saccades; saccade amplitude was the difference, in degrees of visual angle, between eye position at the start and end of the saccade; peak saccade velocity was the maximum eye velocity, in degrees of visual angle/second, of a saccade; saccade latency was the time delay between target presentation and saccade onset; saccade gain was the ratio of the initial saccade amplitude to target distance. We also evaluated mean saccade velocity as the ratio of saccade amplitude to duration. To better examine the skew of velocity waveform, the ratio between peak velocity and mean velocity (Q) was also calculated (Kumar *et al*., 2005).

Since estimation of saccade gain may suffer from error cancellation due to the occurrence of hypometric and hypermetric saccades in individual subjects, we obtained a more accurate estimation of saccade dysmetria by measuring both accuracy, using the absolute error (α) and variance of saccade sizes. The absolute error was defined as the modulus of the angular distance between target position (T) and final eye position of the initial saccade (A): $\alpha = |T - A|$. Finally, we assessed the percentage of primary hypermetric and hypometric saccades corrected by a secondary corrective saccade after a latency of ~100–150 ms (Leigh and Zee, 2006).

The variables analysed statistically were the means and sample variances of all saccadic parameters mentioned above, which were calculated for each experiment of each patient.

Signal processing

Post-processing analysis was conducted off-line using a semi-automatic detection algorithm. Identification of a saccade and calculation of related parameters were performed using an automatic algorithm based on threshold detection of velocity. Blinks were deleted from horizontal and vertical eye position signals according to a numeric threshold and the data removed were replaced by a linear interpolation. Recorded data were filtered using a third-order Butterworth low-pass digital filter with −3 dB attenuation at 25 Hz cut-off frequency. No appreciable effects of the signal processing were noted between filtered and original data signals. Eye velocity was obtained using an eight-point central difference derivative algorithm which has a bandwidth >70 Hz at a digitization frequency of 240 Hz (Inchingolo and Spanio, 1985). Saccades with a latency of <100 ms were regarded as anticipatory or spontaneous and excluded. Finally, saccades with a direction of >30° with respect to the horizontal plane were also excluded. The number of saccades that did not meet one or more of these criteria was 5–10% in healthy subjects. The automatic selection of each saccade was corrected interactively if necessary. The interactive mode was also used to identify the initial saccade and corrective saccades.

For each group we assessed the relation between the main sequence of peak velocity versus amplitude and duration versus amplitude using the well known linear relationships for saccades under 20°. The main sequence of peak velocity versus amplitude was also fitted using the exponential model (Leigh and Zee, 2006), where the asymptotic peak velocity (V_{max}) and the angle constant shaping the exponential rise (C) were estimated by an iterative procedure using the non-linear regression method of Levenberg–Marquardt. The iterative procedure converged and was stopped when no appreciable difference (<1%) in V_{max} and C between steps N and N-1 were observed. To determine the accuracy of models on the entire dataset, model prediction was evaluated using percentage root mean square error, where large values of this parameter indicated poor fit. The dispersion of peak velocity data were measured as median absolute deviation in subsets of overall tested amplitudes. The considered subsets were constant intervals of equal amplitude in each group.

For the antisaccade test we also calculated the directional error of voluntary saccades, defined as those initially directed towards the target.

Saccade detection and parameter estimate algorithms were performed using Matlab software, version 7 (The MathWorks Inc., Natick, MA, USA).

Statistical analysis

Differences in variables between patient and control groups were analysed by ANOVA and *post hoc* multiple pairwise group comparison with Bonferroni correction, where a statistical significance of 95% was considered. In particular we compared means and variances of all saccadic parameters (duration, amplitude, peak velocity, mean velocity, latency, gain, absolute error, Q-ratio). We also estimated the percentage of total corrected initial saccades, and hypermetric and hypometric initial saccades followed by corrective saccades, with respect to the total number of saccades, and compared these percentages between groups, after testing for normality of data distribution by the Lilliefors test (Lilliefors, 1967). Spearman correlation coefficients were estimated and Mann–Whitney U-test was used for non-parametric data. Friedman test and Dunn *post hoc* multiple comparison test were used to analyse differences in dispersion of saccadic parameters among groups.

All statistical computations and regression of the data were performed using Statistical Package for the Social Sciences software, version 10 (SPSS Inc., Chicago, IL, USA).

Results

Clinical and magnetic resonance imaging data

Demographic data, ICARS score, number of CAG repeats for patients with SCA2 and MRI findings are shown in Table 1. All patients with SCA2 were previously diagnosed by molecular analysis demonstrating abnormal CAG expansion (Pareyson *et al*., 1999); the triplet repeat cut-off number qualifying for diagnosis was 34 CAG on one allele. The mean number of triplet repeats of our patients was 40 ± 3. Five patients were part of a study of quantitative MRI analysis (Della Nave *et al*., 2008). All these patients showed progressive gait and trunk ataxia associated with slow saccades, dysarthria, tremor and peripheral neuropathy. None had gaze-evoked nystagmus at examination. Dividing the ICARS score into four ranges of increasing cerebellar deficit, we found one patient very mild (score 0–25), five patients mild (score 25–50), one patient moderate (50–75 score) and no patient severe (score 75–100). MRI examination showed cerebellar grey matter atrophy including cerebellar vermis and hemispheres, sparing lobules I, II, VII and Crus II, VIII and X, and atrophy of middle cerebellar peduncle and dorsal pons. The ventral pons and olivary region were spared as well as the supratentorial compartment. All patients with late-onset cerebellar ataxia presented with variable ataxia, gait unbalance, dysarthria and MRI evidence of selective cerebellar atrophy involving midline structures and olives; three subjects had gaze-evoked nystagmus, no extracerebellar signs were observed. Using the above division of the ICARS score, we found one patient very mild (score 0–25), six patients mild (score 25–50), one patient moderate (score 50–75) and no patient severe (score 75–100). ICARS scores of patients with SCA2 and patients with late-onset cerebellar ataxia were not correlated with saccade parameters tested at 10°. When we compared ICARS score with saccade parameters tested at 18° we found that in patients with SCA2, ICARS was significantly correlated with mean velocity (inverse correlation; $P = 0.04$) and duration (direct correlation; $P = 0.02$) whereas in patients with late-onset cerebellar ataxia, ICARS was correlated with amplitude (inverse correlation; $P = 0.008$), gain (inverse correlation; $P = 0.008$) and absolute error (direct correlation; $P = 0.004$).

Prosaccade results

Significant differences in saccade duration, peak velocity and mean saccade velocity were found between the two groups of patients (Table 2). Saccade duration was significantly longer in patients with SCA2 than in patients with late-onset cerebellar ataxia (10°: $P < 0.05$, 18°: $P < 0.05$) and controls (10°: $P < 0.05$, 18°: $P < 0.05$) for 10° and 18°. No significant differences in duration were found between patients with late-onset cerebellar ataxia and controls. Peak velocity was significantly lower in patients with

Table 2 Significant data of traditional saccade parameters

	Mean of saccadic parameters				Variance of saccadic parameters			
	Duration	Peak velocity	Mean velocity	Amplitude	Duration	Peak velocity	Mean velocity	Amplitude
Control								
10°	(48 ± 4) ms[a]	(378 ± 47)°/s[a]	(202 ± 24)°/s[a]	(10.1 ± 0.5)°	8 (6–10) ms[b,d]	46 (33–56)°/s[b,d]	30 (27–39)°/s[b,d]	0.8 (0.7–1.2)°[b,d]
18°	(66 ± 5) ms[a]	(501 ± 72)°/s[a]	(268 ± 33)°/s[a,c]	(18.2 ± 1.1)°[c]	11 (9–13) ms[b]	66 (57–79)°/s[b,d]	40 (31–45)°/s[b,d]	1.1 (1.0–1.8)°[b,d]
SCA2								
10°	(145 ± 80) ms[a,e]	(170 ± 76)°/s[a,e]	(82 ± 33)°/s[a,e]	(10.0 ± 0.9)°	26 (17–38) ms[b,f]	27 (20–47)°/s[b,f]	12 (10–20)°/s[b,f]	1.6 (1.1–2.0)°[b]
18°	(207 ± 133) ms[a,e]	(229 ± 117)°/s[a,e]	(166 ± 57)°/s[a,e]	(18.4 ± 0.9)°[e]	27 (16–35) ms[b,f]	38 (22–68)°/s[b,f]	18 (10–27)°/s[b,f]	2.3 (1.8–2.8)°[b,f]
LOCA								
10°	(45 ± 6) ms[e]	(379 ± 95)°/s[e]	(201 ± 49)°/s[e]	(9.4 ± 2.8)°	10 (9–13) ms[d,f]	79 (61–122)°/s[d,f]	50 (41–63)°/s[d,f]	1.9 (1.6–2.5)°[d]
18°	(68 ± 20) ms[e]	(449 ± 121)°/s[e]	(225 ± 57)°/s[c,e]	(14.9 ± 3.5)°[c,e]	14 (9–24) ms[f]	96 (82–123)°/s[d,f]	56 (45–72)°/s[d,f]	3.3 (2.4–3.8)°[d,f]

Mean (mean and SD) and variance (median and interquartile range, SD values are shown) of saccade parameters estimated for all saccades in each experiment. Duration, peak velocity, mean velocity and amplitude of 10° and 18° saccades for healthy controls, patients with SCA2 and late-onset cerebellar ataxis (LOCA). Statistically non-significant parameters are not shown.
Statistical significance ($P < 0.05$) of comparisons between:
a Controls and SCA2 (Anova and Bonferroni correction).
b Controls and SCA2 (Kruskal–Wallis H-test and Mann–Whitney U-test).
c Controls and LOCA (Anova and Bonferroni correction).
d Controls and LOCA (Kruskal–Wallis H-test and Mann–Whitney U-test).
e SCA2 and LOCA (Anova and Bonferroni correction).
f SCA2 and LOCA (Kruskal–Wallis H-test and Mann–Whitney U-test).

SCA2 than in patients with late-onset cerebellar ataxia (10°: $P < 0.001$, 18°: $P < 0.001$) and controls (10°: $P < 0.001$, 18°: $P < 0.001$). No significant differences in saccade velocity and mean saccade velocity were evident between patients with late-onset cerebellar ataxia and controls. Mean saccade velocity was significantly lower in patients with SCA2 than late-onset cerebellar ataxia (10°:$P < 0.001$, 18°: $P < 0.001$) and controls (10°: $P < 0.001$, 18°: $P < 0.001$). Differences in amplitude of initial saccades were observed in the three groups, however they did not reach significance at 10° ($P > 0.05$), whereas amplitude was significantly lower in patients with late-onset cerebellar ataxia than SCA2 ($P < 0.05$) and controls ($P < 0.05$) for 18°. The Q-ratio (peak velocity/mean velocity) was significantly greater in patients with SCA2 than late-onset cerebellar ataxia ($P = 0.006$) and controls ($P = 0.001$), for only 10° saccades (for 10°, SCA2: 2.1 ± 0.2; late-onset cerebellar ataxia: 1.9 ± 0.1; control: 1.9 ± 0.1. For 18°, SCA2: 2.0 ± 0.1; late-onset cerebellar ataxia: 2.0 ± 0.2 and control: 1.9 ± 0.1) (Fig. 1).

Figure 2A shows the main sequence relationship between duration and amplitude using the linear model; Fig. 2B reports the main sequence of peak velocity versus amplitude fitted using the exponential model. Controls showed an asymptotic peak velocity of 645.1 ± 16.3°/s and a constant C of the exponential rise of 11.8 ± 0.6 (percentage root mean square error of the fit = 17%), patients with late-onset cerebellar ataxia showed an asymptotic peak velocity of 671.9 ± 26.8°/s and a constant C of the exponential rise of 11.7 ± 0.9 (percentage root mean square error of the fit = 33%) and patients with SCA2 showed an asymptotic peak velocity of 440.6 ± 73.4°/s and a constant C of the exponential rise of 16.6 ± 4.7 (percentage root mean square error of the fit = 89%). Amplitude was significantly correlated with peak velocity in controls ($P < 0.001$), patients with late-onset cerebellar ataxia ($P < 0.001$) and patients with SCA2 ($P < 0.001$). Data of controls and patients with late-onset cerebellar ataxia were well represented by the linear and exponential models, whereas data of patients with SCA2 were poorly represented by both proposed models. A significant difference in dispersion of peak velocity, at tested intervals of saccade amplitude, was found among groups ($P = 0.02$); the difference was significantly greater for patients with SCA2 with respect to normal subjects (Fig. 3).

Significant differences in saccade gain were found between the two groups of patients ($P < 0.05$) and between late-onset cerebellar ataxia and controls ($P < 0.05$) only for 18° of saccade amplitude. No significant difference in gain was found between SCA2 and controls.

Significant differences in saccade accuracy were found between the two groups of patients (10°: $P < 0.001$; 18°: $P < 0.05$) and between patients with late-onset cerebellar ataxia and controls (10°: $P < 0.001$; 18°: $P = 0.001$). We found a higher absolute error of primary saccades in late-onset cerebellar ataxia (10°: 2.92 ± 0.76°; 18°: 4.77 ± 2.66°) than patients with SCA2 (10°: 1.44 ± 0.39°; 18°: 2.05 ± 0.55°) and controls (10°: 0.81 ± 0.29°; 18°: 1.35 ± 0.53°) (Fig. 4A). Eye position error increased with increasing target distance. The box and whisker plots in Fig. 5 illustrate the absolute error of all trials in each group for 10° and 18° of target distance. Absolute error was significantly correlated with target distance in controls ($P < 0.001$), patients with SCA2 ($P = 0.005$) and patients with late-onset cerebellar ataxia ($P = 0.026$). The comparison of the median values relating absolute error to target distance, showed a similar increasing trend in the three groups, however, patients with late-onset cerebellar ataxia had a much larger median value than patients with SCA2 and controls for 10° saccades. Comparing 10° and 18° saccades, we found an increase in absolute error from 0.65° to 1.18° in controls ($P < 0.001$), from 1.36° to 1.66° in SCA2 ($P = 0.005$) and from 2.78° to 3.55° in late-onset cerebellar ataxia ($P < 0.001$). Figures 6A and B show the mean absolute error as a function of mean saccade amplitude and mean peak velocity, respectively, for each group. In all groups the mean absolute error

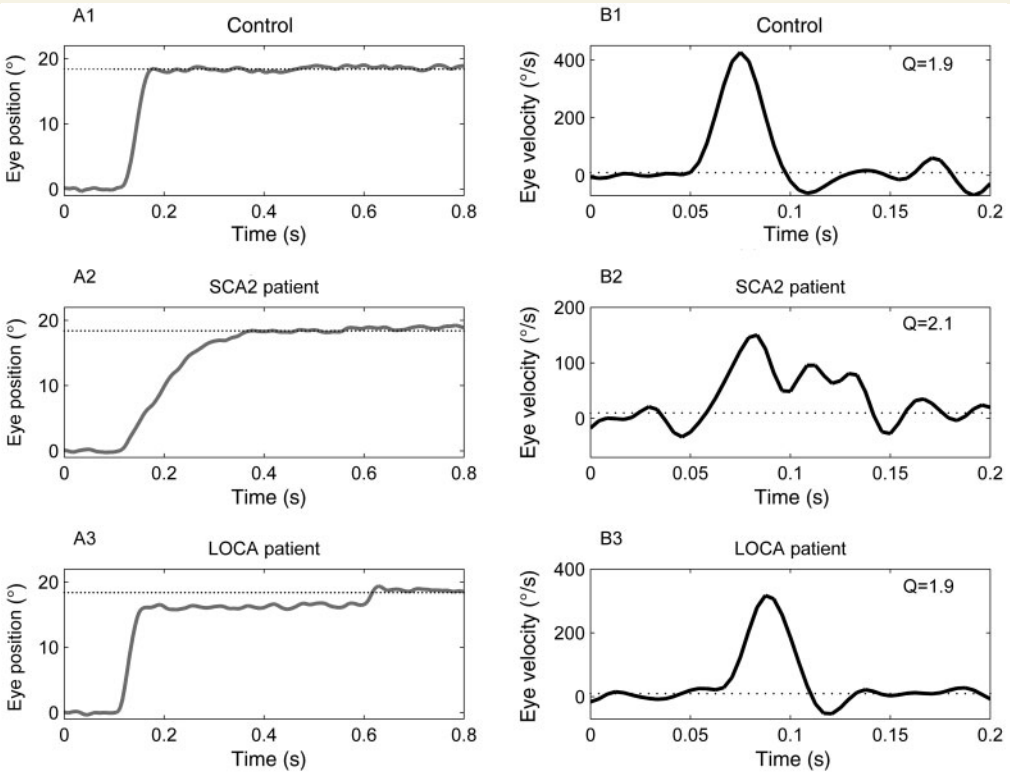

Figure 1 (**A**) An example of recorded data of 18° horizontal saccade made by (**A1**) a healthy control (**A2**) a patient with SCA2 and (**A3**) late-onset cerebellar ataxia (LOCA). Position records are shown. The broken line shows target position and the grey line, eye position. (**B**) Plot of velocity for 10° horizontal saccades of (**B1**) a healthy control, (**B2**) a patient with SCA2 and (**B3**) late-onset cerebellar ataxia (LOCA). Q-ratio between peak saccade velocity and mean saccade velocity is shown for represented data. The broken line shows threshold of velocity.

increased with increasing mean amplitude and mean velocity of saccades.

Significant differences in variance of saccade amplitude for both distances were found between cerebellar patients and controls (10°: $P \leqslant 0.001$, 18°: $P \leqslant 0.001$) (Table 2). The variance of saccade amplitude was greater in patients with late-onset cerebellar ataxia (10°: 1.85 ± 0.86°; 18°: 3.27 ± 1.35°) and patients with SCA2 (10°: 1.60 ± 0. 89°; 18°: 2.29 ± 1.06°) than normal subjects (10°: 0.79 ± 0.52°; 18°: 1.06 ± 0.87°) for all tested saccade amplitudes. The variance of saccade amplitude was different between late-onset cerebellar ataxia and SCA2 only for 18° ($P < 0.05$).

In order to further investigate saccadic dysmetria, all amplitudes were pooled by group. The first comparison of amplitude distribution showed a single peak at saccade amplitude 10° in controls. SCA2 showed a similar distribution trend but with a triple peak centred around 10° and distributed equally below 8.4° and above 12°. Patients with late-onset cerebellar ataxia showed a more widely spread trend that formed a smoother curve with a long tail and many more saccades with amplitude above the target and peak centred around 7.6–8.4° (Fig. 7A–C). Similar distribution was observed for 18° (Fig. 7–F). The percentage of saccades undershooting the target at 10° of ∼10% (1°) was 14% in controls, 27% in patients with SCA2 and 51% in patients with late-onset cerebellar ataxia; the percentages were 13% in controls, 14% in patients with SCA2 and 58% in patients with late-onset cerebellar ataxia for a target distance of 18° (undershoot of ∼1.6°).

The total number of primary saccades corrected with a secondary corrective saccade (Fig. 4B) was greater in patients with late-onset cerebellar ataxia than patients with SCA2 and controls. In particular, the number of corrected hypermetric primary saccades was greater in patients with late-onset cerebellar ataxia (10°: 0.105; 18°: 0.107) and SCA2 (10°: 0.130; 18°: 0.117) than controls (10°: 0.006; 18°: 0.006). The number of corrected hypometric primary saccades (Fig. 4C) was much higher in patients with late-onset cerebellar ataxia (10°: 0.405; 18°: 0.459) than with SCA2 (10°: 0.155; 18°: 0.297) and controls (10°: 0.239; 18°: 0.285).

Amplitude of corrective saccades was greater in patients with late-onset cerebellar ataxia (10°: 3.41 ± 1.09; 18°: 4.85 ± 2.77) than with SCA2 (10°: 2.30 ± 0.30; 18°: 2.37 ± 0.97) and controls (10°: 1.86 ± 0.80; 18°: 2.35 ± 0.93; $P < 0.05$). The occurrence of more than one corrective saccade was also higher in patients with late-onset cerebellar ataxia.

Antisaccades

In order to evaluate cortical involvement that may contribute to altering the premotor command for saccade execution, voluntary saccades were measured in all subjects and the directional error of

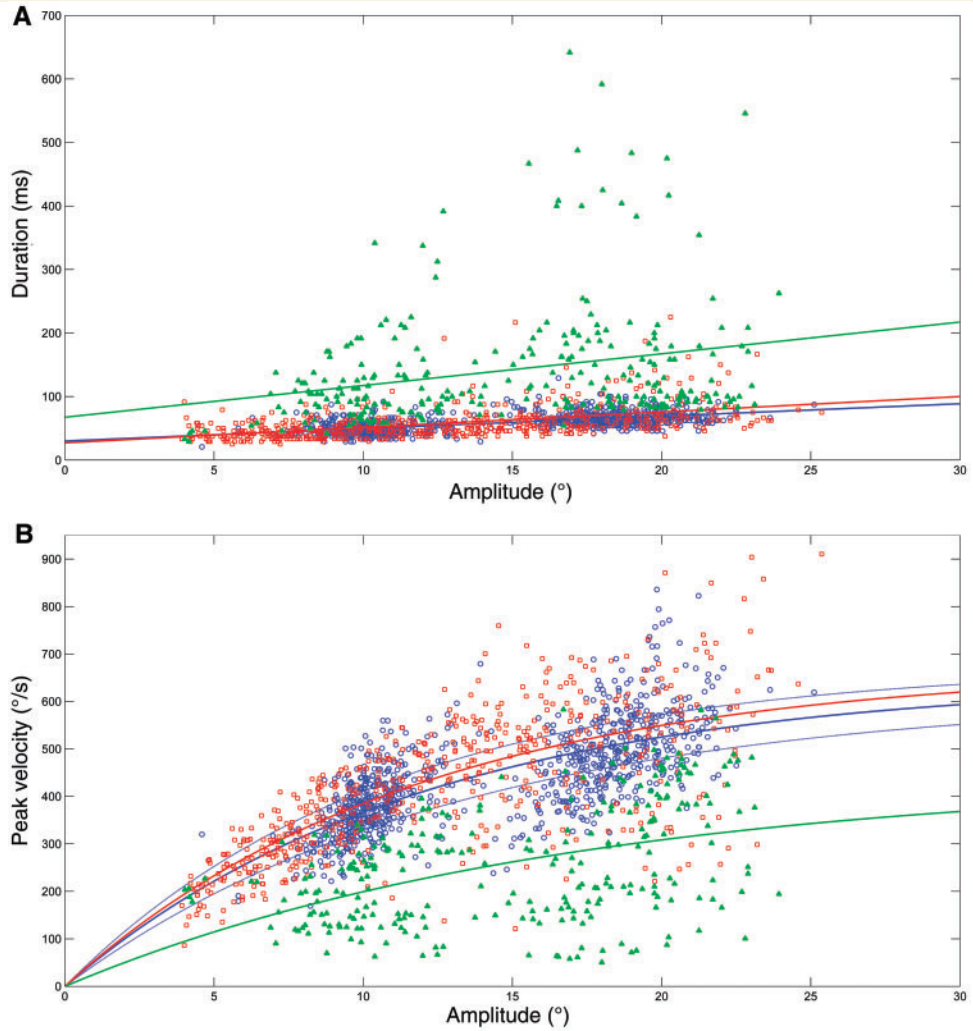

Figure 2 Plot of main sequence relationships. Data points are saccades of healthy subjects (open circle blue), patients with SCA2 (filled triangle green) and late-onset cerebellar ataxia (LOCA) (open rectangle red). The coloured curves were fitted to the respective data. (**A**) Plot of duration versus amplitude of saccades. The data was fitted using the linear polynomial equation. (**B**) Plot of peak velocity versus amplitude of saccades. The data was fitted using the exponential equation $V_{peak} = V_{max}\,[1 - e^{(amplitude/C)}]$, where V_{max} is asymptotic peak velocity and C is the angle constant shaping the exponential rise. The 95% prediction bounds for healthy subjects are indicated (broken curve).

antisaccades was examined. Patients with SCA2 ($3 \pm 0.20\%$, range 10–0%) and late-onset cerebellar ataxia ($16.66 \pm 3.86\%$, range 50–0%) did not show many more volitional saccades with wrong direction than controls ($12.56 \pm 1.66\%$, range 50–0%).

Discussion

The main result of this study into differences in saccade dynamics in two distinct degenerative diseases involving the cerebellum, showed impairment of saccade velocity without loss of accuracy in patients with SCA2 and better preserved velocity but significant inaccuracy in patients with late-onset cerebellar ataxia. The percentage of dysmetric saccades followed by more than one corrective saccade was significantly lower in patients with SCA2 than in patients with late-onset cerebellar ataxia. Similar to the controls, the former showed absolute error that increased with target eccentricity, whereas the latter failed to minimize endpoint error even at lower amplitudes (Fig. 5). Overall, these results suggest that patients with spinocerebellar ataxia still compensated for saccade slowing in order to reach the target correctly, whereas patients with late cerebellar ataxia did not. Two alternative, but not mutually exclusive hypotheses have been considered and are discussed below, in order to interpret the saccadic behaviour of these two groups of cerebellar patients and summarize possible mechanisms by which the saccadic system maintains accuracy.

Recent application of the optimal control framework, based on maximization of motor performance (Todorov and Jordan, 2002; Shadmehr and Krakauer, 2008), to saccadic eye movements, suggested that main sequence and trajectory optimize the trade-off between saccade duration and minimum distance between saccade endpoint and target (Harris and Wolpert, 2006;

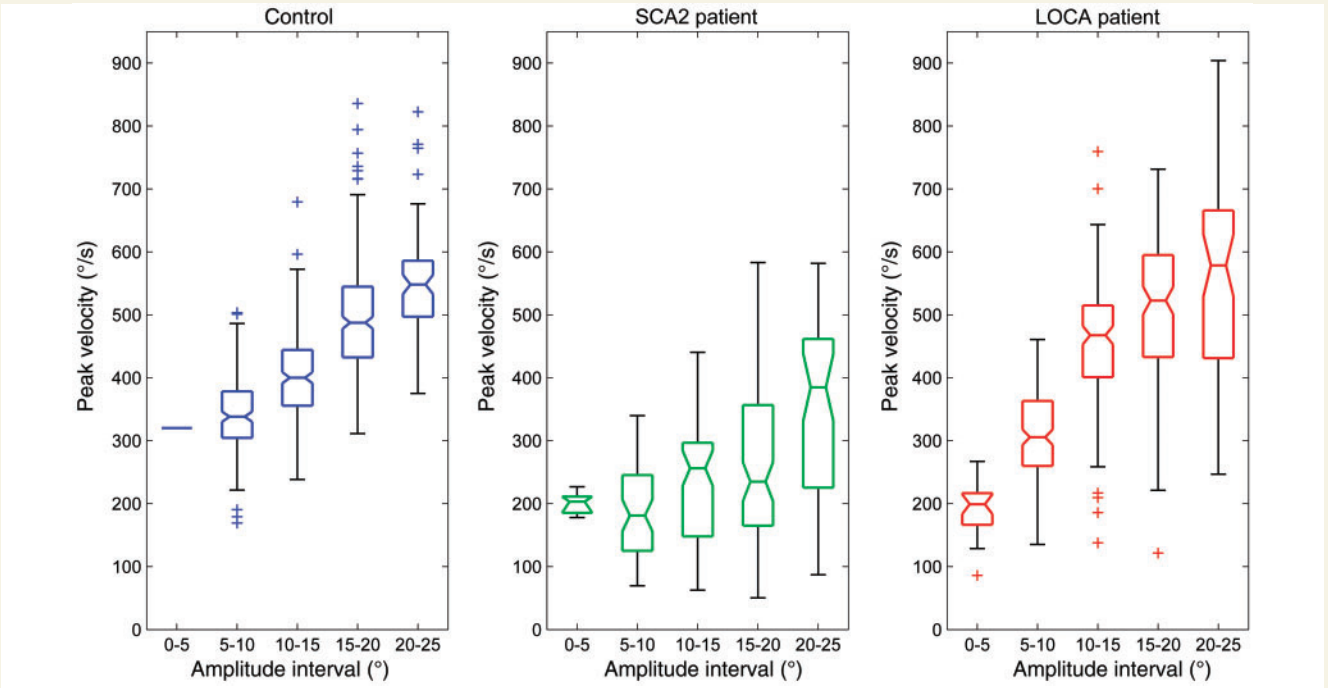

Figure 3 Summary of peak velocity versus five amplitude intervals of all tested saccade amplitudes. The size of each amplitude interval is 5°. The box and whisker plots show the peak velocity for each amplitude interval of all saccades in healthy subjects (blue), patients with SCA2 (green) and late-onset cerebellar ataxia (LOCA) (red). The horizontal bar in each box represents the median, lower and upper quartile (straight lines) values of peak velocity. The notches represent the 95% confidence interval around the median. The whiskers represent the distribution. The outliers (+) are shown.

van Beers, 2008). This theory assumes that the signal of motor command is perturbed by noise, which is proportional to signal amplitude. Quick movements are therefore induced by larger command signals, which are affected by greater noise, and pay the cost of large endpoint variability. Thus a compromise between speed and accuracy of saccades is essential to minimize the cost of motor-signal-dependent noise (Harris and Wolpert, 1998). According to this theory our patients showed that absolute error increased in larger saccades of all groups, indicating, as a general principle, that higher motor signals producing larger and faster saccades may be affected by greater noise. Unlike patients with spinocerebellar ataxia, however, who proved able to minimize endpoint variability by adapting their main sequence to each amplitude, patients with late-onset cerebellar ataxia could not compensate, since they were unable to optimize the speed-accuracy trade-off particularly for 18° saccades. Moreover, the main sequence of patients with SCA2 showed poor fit as peak velocity does not increase linearly with amplitude. They nevertheless maintained accuracy by increasing duration. This could be interpreted as a limitation imposed by the degenerative process that mainly affects the saccade burst generator in these patients. Conversely the main sequence of patients with late-onset spinocerebellar ataxia is closer to normal subjects.

Based on the results of saccade dynamics and considering the anatomical substrate of the degenerative processes, patients with late-onset cerebellar ataxia could adopt saccade undershooting as alternative optimal strategy to catch up with the target as fast as possible (Harris, 1995; van Opstal and Goossen, 2008). Indeed the phenomenon of saccade undershoot (~10%) is a well established normal strategy for rapidly assessing the nature of a peripheral target eluding foveation (Henson, 1978; Kapoula and Robinson, 1986). Actually, these patients are unable to control saccade size since they make more hypometric saccades followed by secondary saccades with amplitudes close to the initial saccades. More specifically, the number of saccades undershooting or overshooting the target was different in the two groups for each amplitude. The percentage of saccades undershooting the target at 10° and the amount of undershoot was higher in late-onset cerebellar patients. The difference between groups increased with larger eccentricity. This observed saccadic behaviour is similar to the 'range effect' of habitually made saccades, first described in normal subjects when target position appeared in succession and was characterized by the bias of some saccades to catch or overshoot the near and undershoot the far position (Kapoula and Robinson, 1986). The range effect indicates that oculomotor performance is more efficient when the eye makes movements of small amplitude around its primary position, where discrimination of an object is quite good.

The cerebellum is thought to be implicated in optimization of the duration-accuracy trade-off in order to minimize saccade endpoint variability (Golla *et al*., 2008; Izawa *et al*., 2008; Xu-Wilson *el al*., 2009). This is obtained by monitoring the dynamic error signal (the difference between the desired endpoint and current eye position) and modulating motor command of upcoming

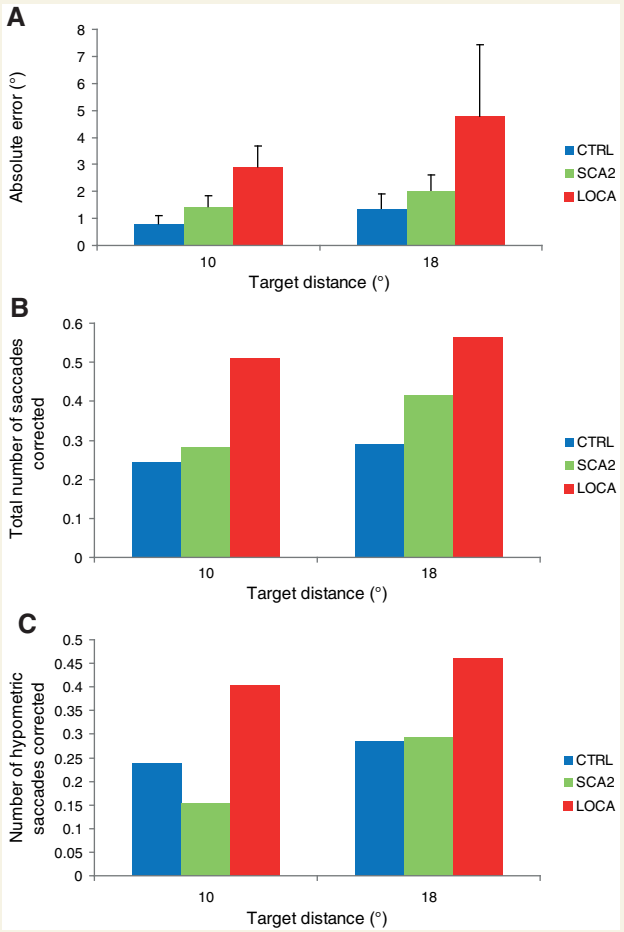

Figure 4 Saccade accuracy of healthy controls (CTRL) and patients with SCA2 and late-onset cerebellar ataxia (LOCA). Values of 10° and 18° prosaccade tests. (**A**) Absolute error of the initial saccade. Error bars represent the standard deviation. (**B**) Total number of saccades corrected by a corrective saccade. (**C**) Number of hypometric saccades corrected by a corrective saccade.

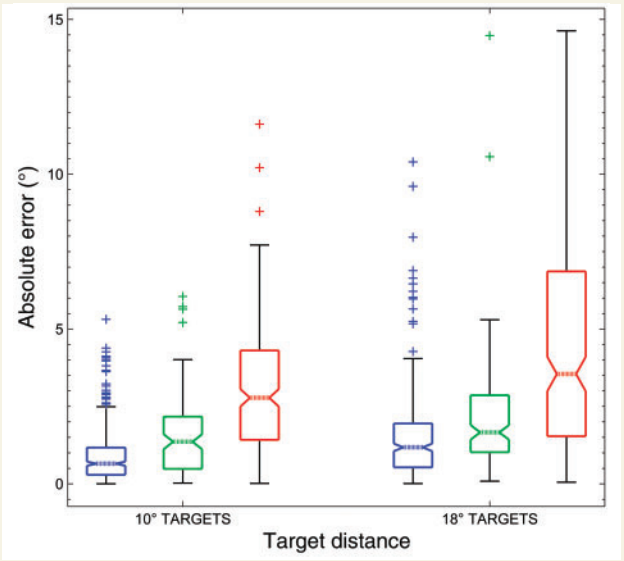

Figure 5 Summary of absolute error of all trials for target distance. The box and whisker plots show the errors of all saccades in healthy subjects (blue), patients with SCA2 (green) and late-onset cerebellar ataxia (red) for values of 10° and 18° targets. The horizontal bar in each box represents the median (broken line), lower and upper quartile (straight lines) values of absolute error. The notches represent the 95% confidence interval around the median. The whiskers represent the distribution. The outliers (+) are shown.

saccades by internal feedback or learning from endpoint error (Joiner and Shelhamer, 2009; Xu-Wilson *et al*., 2009). Significant advances in understanding neural substrate and mechanisms of saccadic motor control have been made in recent years. Several lines of evidence suggest that the superior colliculus, cerebellum and brainstem participate in a loop necessary for online correction of saccade amplitude and its rapid adaptation (Robinson *et al*., 1993; Takagi *et al*., 1998; Iwamoto and Yoshida, 2002; Robinson *et al*., 2002). The signal generating a saccade of specific speed and amplitude (displacement command) comes from the superior colliculus (Goossens and van Opstal, 2006; van Opstal and Goossens, 2008) and goes to the pontine burst generator via a direct pathway (Büttner-Ennever, 2008) and indirectly through the cerebellar oculomotor vermis (Scudder *et al*., 2002; Fujita, 2005; Iwamoto and Kaku, 2010) that receives mossy fibres from the nucleus reticularis tegmenti pontis, conveying motor command for saccades of any given vector and climbing fibres from the inferior olives carrying an error signal (Hopp and Fuchs, 2004; Azizi, 2007). Cerebellar oculomotor vermis output goes to the caudal fastigial nucleus directly to the contralateral pontine burst generator (Scudder *et al*., 1996; Scudder and McGee, 2003; Kojima *et al*., 2008, 2010) and indirectly, via basal ganglia and thalamus, to cortical areas (that in turn modulate subsequent superior colliculus activity). The direct pathway is thought to be critical for modulating short-term saccade accuracy, whereas the indirect pathway could participate in a more enduring resiliency of saccade trajectories due to remapping of the target (Chen-Harris *et al*., 2008; Soetedjo *et al*., 2009). According to this scheme, the saccade-related cerebellum controls accuracy, probably monitoring motor command via a forward model (Robinson, 1975; Wolpert *et al*., 1995; Quaia *et al*., 1999) in which internal feedback of motor command (efference copy) corrects for anticipated errors by rapid modifications of saccade duration (Chen-Harris *et al*., 2008). Although the size and direction of position error are sent to the cerebellum by the superior colliculus as an efference copy (Takeichi *et al*., 2007; Soetedjo *et al*., 2008, 2009), the caudal fastigial nucleus and cerebellar oculomotor vermis (lobules VI and VII) are necessary for error correction and rapid adaptation (Golla *et al*., 2008; Tian *et al*., 2009). In this respect, the cerebellar oculomotor vermis contains a high density Purkinje cell-discharging saccade-related simple spike burst (Marr 1969; Albus, 1971), the timing variations of which may be used to fit saccade duration into adequate amplitude (Noda and Fujikado 1987; Fuchs *et al*., 1993; Scudder, 2002; Hopp and Fuchs, 2004; Catz *et al*., 2005, 2008). Actually, differences observed in our

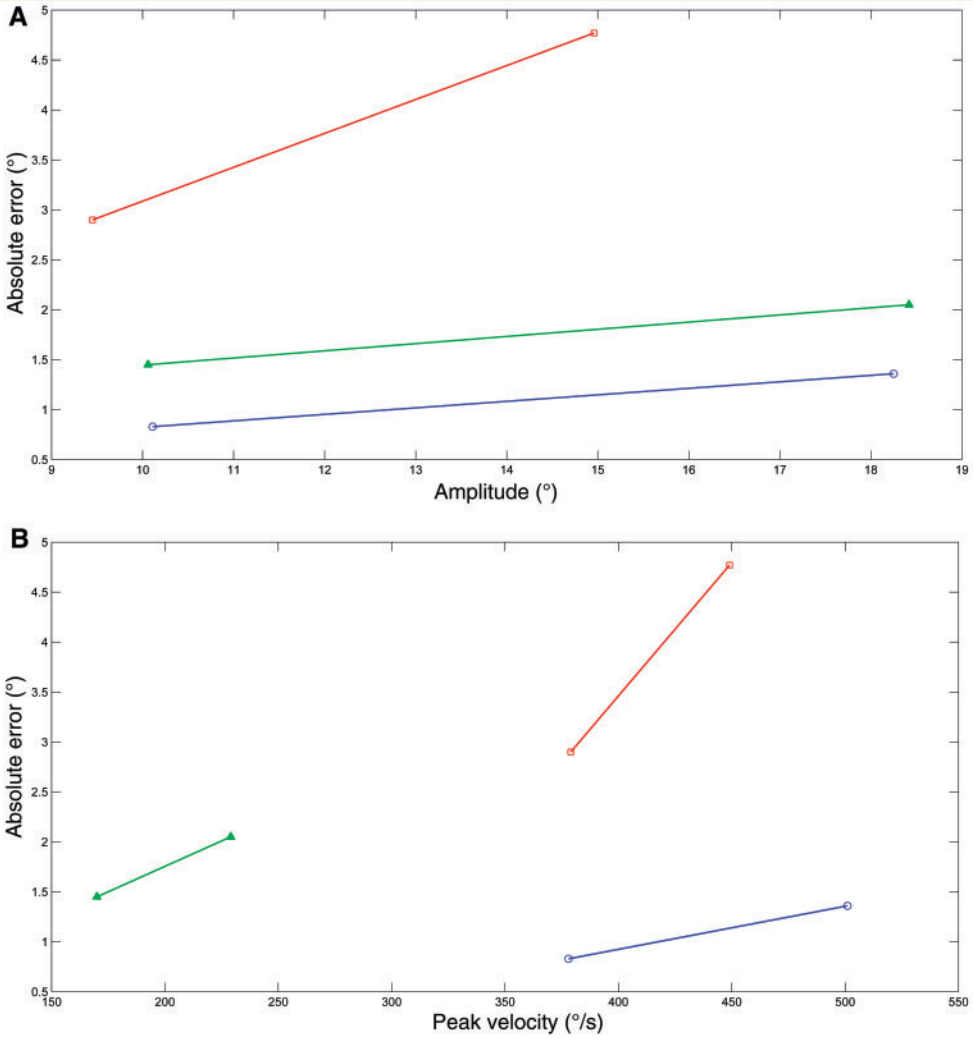

Figure 6 Relationships between mean absolute error, amplitude and peak velocity for saccades in healthy subjects (blue lines), patients with SCA2 (green lines) and late-onset cerebellar ataxia (red lines). (**A**) Mean absolute error as function of mean amplitude of saccades. (**B**) Mean absolute error as function of mean peak velocity of saccades.

groups may be explained by prevalent localization of the degenerative process at different levels of this neural substrate. Post-mortem studies of patients with SCA2 have shown diffuse brainstem and cerebellar atrophy, followed by progressive atrophy of the cerebral cortex, particularly the fronto-temporal areas (Estrada *et al*., 1999). Involvement of the middle cerebellar peduncles, basis pontis and cerebellar hemispheres is particularly evident in these patients (Geiner *et al*., 2008). Prominent involvement of brainstem structures has also been emphasized by pathological evidence of diffuse involvement of cranial nerve nuclei from midbrain to medulla (Gierga *et al*., 2005). However, these anatomical findings concern advanced cases with diffuse degenerative processes, whereas our patients were only moderately or mildly affected. Moreover, MRI studies documented a substantial reduction in dorsal pontine and cerebellar hemisphere volumes in our patients. These data suggest that pontine nuclei, namely the pontine burst generator and ponto cerebellar connections, are affected earlier in patients with SCA2, whereas functional effects of cerebellar oculomotor vermis disruption could be prominent later. Another possibility is that the signal for saccade generation is reduced due to progressive loss of collicular afferents to pontine burst neurons. Finally, loss of premotor command, itself due to degenerative processes affecting frontal eye fields, may cause slow saccades in spinocerebellar patients. The patients reported here, however, did not show any MRI evidence of involvement of cortical frontal areas and the percentage directional error of their voluntary saccades was within the normal range. Thus the slow saccades observed in our patients with SCA2 seemed mainly related to pontine burst generator functional loss (Büttner-Ennever and Horn, 1997), more specifically, these patients showed a severe reduction of pontine excitatory burst neurons in post-mortem studies (Geiner *et al*., 2008) although other cells of this circuit accounting for slowing saccades, namely omnipause neuron, may be involved into in the neurodegenerative process (Evinger *et al*., 1982). In this respect, the poor fit of main sequences observed in these patients may underlie an early

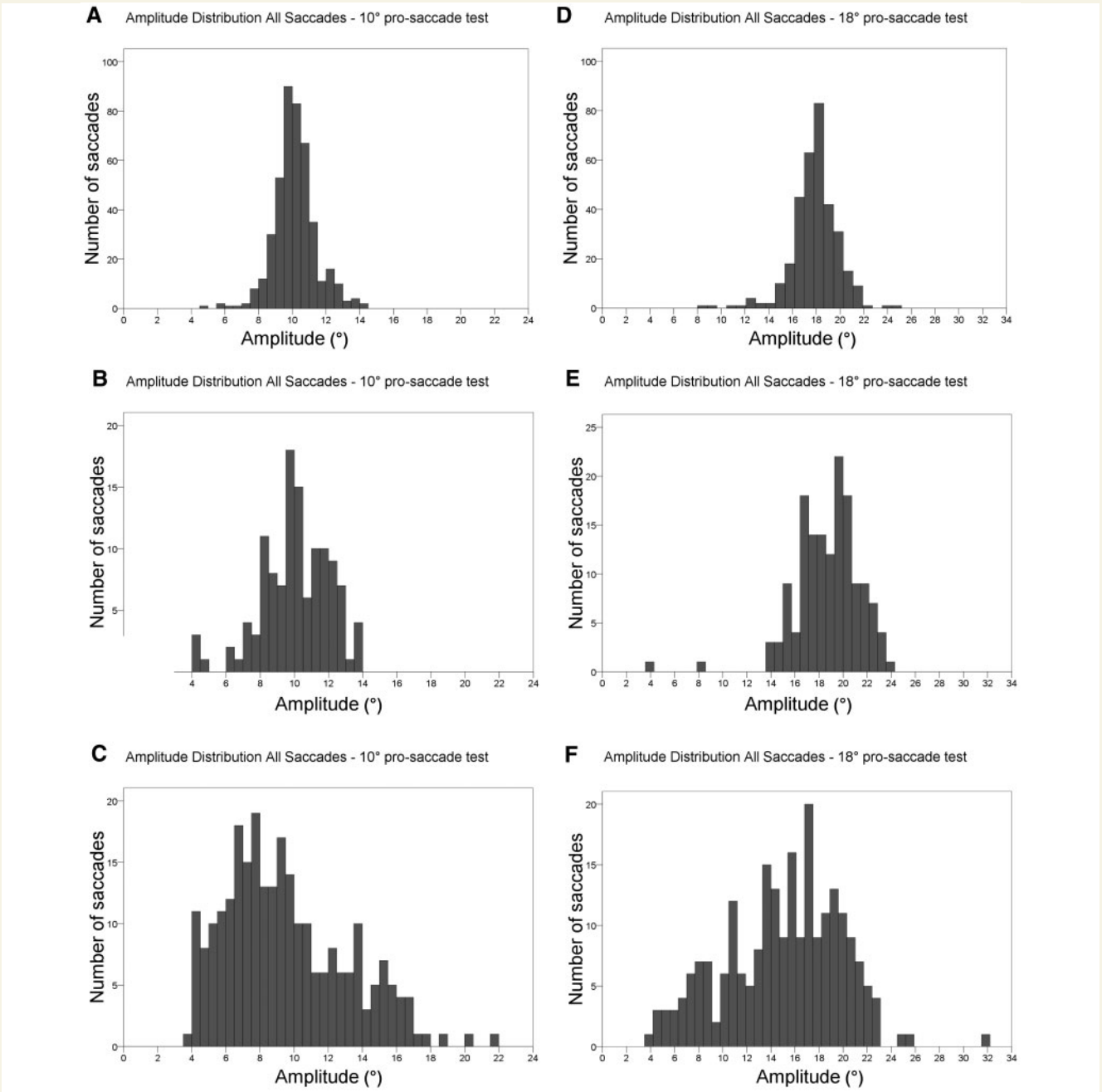

Figure 7 Amplitude distribution of horizontal saccades for 10° prosaccade test of (**A**) healthy subjects, (**B**) patients with SCA2 and (**C**) late-onset cerebellar ataxia and for 18° prosaccade test of (**D**) healthy subjects, (**E**) patients with SCA2 and (**F**) late-onset cerebellar ataxia.

'saturation' of burst neuron firing rate in the pons due to degenerative process. This concept agrees with the widely assumed notion of non-linearity of the main sequence related to an intrinsic velocity threshold limit of pontine burst generator (Scudder *et al.*, 1996). It could also be that signal-related noise and movement end-point variability is lower in these patients, depending on reduced activity (namely loss) of burst neurons. This could allow saccades to be more accurate. On the other hand, prominent impairment of the cerebellar oculomotor vermis and caudal fastigial nucleus could explain the prevailing alteration of saccade accuracy (hypometria) in patients with late-onset cerebellar ataxia (Takagi *et al.*, 1998; Catz *et al.*, 2005; Soetedjo and Fuchs, 2006) (Fig. 5).

In reality another possible interpretation of these data comes from a previous study on a few patients with slow saccades (Zee *et al.*, 1976*a*; MacAskill *et al.*, 2000). These authors showed that slow saccades can be modified in flight in response to intra-saccadic target displacement (target displaced after saccade onset), suggesting that, when saccade duration is longer than visual reaction time (~100 ms), visual feedback is continuously

available to guide the eye on its target. It has also been demonstrated that in-flight saccadic modifications can occur even when conscious awareness of the displacement is prevented, indicating that the oculomotor system might use sensory visual information not available to conscious awareness. This mechanism could play a relevant role in our patients with SCA2 but would not be expected to be the case in late-onset cerebellar patients for whom the saccade duration is shorter than the visual sensory input being processed. In accordance with the assumption that the burst neurons of patients with spinocerebellar ataxia 2 are damaged or lost, that they probably are firing as fast as they can and that there is no ability to modulate their discharge rate, visual feedback might be the emerging mechanism by which the saccadic system is kept accurate. This mechanism might explain the poor fitting of the main sequence (Fig. 2) and the significant difference in peak velocity spreading observed in our spinocerebellar patients with respect to normal subjects (Fig. 3). At the same time the continuous flow of visual information related to target position during saccade execution enables these subjects to optimize their accuracy.

Finally the results of our study indicate that ICARS scores correlated differently with saccade dynamic parameters in the two groups. In particular, higher ICARS was inversely correlated with measures of velocity in patients with SCA2 and measures of accuracy in patients with late-onset cerebellar ataxia. These differences may help in addressing diagnosis and following clinical outcome.

In conclusion, our study into differences in saccade dynamics between patients with SCA2 and patients with late-onset cerebellar ataxia suggests that at least two solutions may be adopted by the brain to make the saccadic subsystem efficient for vision. The first one uses an accurate-low speed visually driven system, compatible with brainstem burst generator failure; the second one adopts a less accurate, hypometric but high speed saccadic system compatible with cerebellar oculomotor vermis-caudal fastigial nucleus dysfunction.

Acknowledgements

We thank the patients and their families, who willingly gave their time, and continue to support our research. We wish to thank Stefano Ramat for his critical comments and the reviewers for their constructive suggestions.

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