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RESEARCH REPORT

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A loss of a velocity-duration trade-off impairs movement precision in patients with cerebellar degeneration

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Abstract

Current theories discussing the role of the cerebellum have been consistently pointing towards the concept of motor learning. The unavailability of a structure for motor learning able to use information on past errors to change future movements should cause consistent metrical deviations and an inability to correct them; however, it should not boost "motor noise." However, dysmetria, a loss of endpoint precision and an increase in endpoint variability ("motor noise") of goal-directed movements is the central aspect of cerebellar ataxia. Does the prevention of dysmetria or "motor noise" by the healthy cerebellum tell us anything about its normal function? We hypothesize that the healthy cerebellum is able to prevent dysmetria by adjusting movement duration such as to compensate changes in movement velocity. To address this question, we studied fast goal-directed index finger movements in patients with global cerebellar degeneration and in healthy subjects. We demonstrate that healthy subjects are able to maintain endpoint precision despite continuous fluctuations in movement velocity because they are able to adjust the overall movement duration in a fully compensatory manner ("velocity-duration trade-off"). We furthermore provide evidence that this velocity-duration trade-off accommodated by the healthy cerebellum is based on a priori information on the future movement velocity. This ability is lost in cerebellar disease. We suggest that the dysmetria observed in cerebellar patients is a direct consequence of the loss of a cerebellum-based velocity-duration trade-off mechanism that continuously fine-tunes movement durations using information on the expected velocity of the upcoming movement.

KEYWORDS

cerebellar ataxia, duration adjustment, motor noise, precision

Abbreviations: ADCA, autosomal dominant cerebellar ataxia; ARCA, autosomal recessive cerebellar ataxia; MCP, metacarpophalangeal joint; SAOA, sporadic adult onset ataxia; SCA, spinocerebellar ataxia.

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1 | INTRODUCTION

Contemporary discussions on the role of the cerebellum have revolved around the concept of motor learning, that is the improvement of motor behaviour based on the experience of past inadequacies (Albus, 1971; Ito, 1982; Marr, 1969). Motor learning should be fast, yet, a certain time of temporal integration ensuring the consistency and reliability of information on past behaviour is indispensable in order to avoid detrimental behavioural adjustments (Shadmehr, Smith, & Krakauer, 2010). This view of the role of the cerebellum that is based on a large body of physiological, theoretical and behavioural investigations is not least supported by the observation of various types of motor learning deficits in patients suffering from cerebellar disease (Donchin et al., 2012; Izawa, Criscimagna-Hemminger, & Shadmehr, 2012; Maschke et al., 2000; Therrien & Bastian, 2015). However, ataxia, characterized by dysmetria of movement as well as less smooth and deviant trajectories, is not readily understandable as a consequence of disturbed motor learning. The reason is that unlike motor learning, ataxia is instantaneous, changing the movement phenotype from one moment to the next or, to put it another way, it is a manifestation of increased motor noise. While attempts to lead ataxia back to biased internal models of movement kinematics or body dynamics (Bhanpuri, Okamura, & Bastian, 2014) thought to be optimized by learning, are able to account for consistent patient-specific aspects of the ataxic phenotype like target overshooting or in other patients target undershooting, they fail to explain the conspicuous increase in endpoint variability. We hypothesize that the increase in endpoint variability that characterizes cerebellar ataxia is the result of the inability of the diseased cerebellum to adjust movement duration such as to compensate changes in movement velocity that are consequences of a variety of noncerebellar influences ("velocity-duration trade-off"). To test this idea, we studied fast goal-directed finger movements in patients with global cerebellar degeneration and in healthy control subjects. We show that the dysmetria of cerebellar patients, the hallmark of their ataxia, is a direct consequence of the loss of a cerebellum-based velocity-duration trade-off mechanism that continuously fine-tunes movement duration using information on the expected velocity of the upcoming movement. In other words, rather than mediating behavioural

TABLE 1 Patients' details

	Sex	Age	Diagnosis	SARA scores	
				Total / 40	Task relevant / 12
P01	Male	27	[a]ARCA1 (with spasticity and polyneuropathy)	5	3
P02	Male	47	Cerebellar ataxia	7	2.5
P03	Male	53	SAOA	11	4
P04	Male	60	ADCA (excluded SCA1, 2, 3, 6, 7, 17)	6.5	2
P05	Male	63	ADCA (excluded SCA1, 2, 3, 6, 8, 10, 12)	10	3
P06	Male	59	SAOA (excluded SCA1, 2, 3, 6, 7, 17)	9	2.5
P07	Female	43	ADCA (excluded SCA1, 2, 3, 6, 7, 17)	5	2
P08	Female	60	ADCA (aetiology unknown)	15.5	6
P09	Female	53	Cerebellar ataxia	20.5	5.5
P10	Male	60	Cerebellar ataxia	5.5	2
P11	Female	56	ADCA type 3 (SCA1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 17, 27 excluded)	18	5
P12	Male	36	[a]ARCA (with pyramidal tract lesion)	10.5	3
P13	Male	32	ARCA	10	4
P14	Male	54	SAOA (SCA1, 2, 3, 6, 7, 8, 12, 14, 17, & FXTAS excluded)	10.5	3
P15	Female	52	SCA 14	12	4

Notes. Task relevant score is based upon the performance during tasks involving upper limb extremities.
ARCA: autosomal recessive cerebellar ataxia; ADCA: autosomal dominant cerebellar ataxia; SCA: spinocerebellar ataxia; SAOA: Sporadic adult-onset ataxia.
[a]Patients with additional noncerebellar damage.

adjustments based on a posteriori information, our findings suggest that an important aspect of cerebellar functioning, which is of utmost relevance for the ataxic phenotype, is the usage of a priori information.

2 | MATERIALS AND METHODS

2.1 | Participants

Fifteen healthy subjects (five females, 10 males, mean age: 51.6 years, range: 33–66 years) and 15 patients (five females, 10 males, mean age: 50.3 years, range: 27–63 years) suffering from different forms of global cerebellar degeneration (for details see Table 1) participated in the main experiment. Thirteen (five females, eight males, mean age: 53.2, range: 32–63 years) out of the 15 patients studied suffered from well-defined genetically determined variants of cerebellar degeneration and are addressed as the group of "cerebellar patients," compared with healthy controls. In these patients, a significant involvement of noncerebellar structures was excluded using standard clinical procedures and the data available from MRI scans and electrophysiological tests, noninvasive approaches that certainly do not exclude more subtle alterations at the microscopic level. The two other patients (P01, P12) had additional extracerebellar pathology and were therefore excluded from the group of cerebellar patients. Nevertheless, the data of patients P01 and P12 are presented in several figures, clearly separable from the other subjects as they may be of interest to those trying to better understand the specific incapacities resulting from such rare diseases. Another group of 10 healthy individuals (four females, six males, mean age: 55.4 years, range: 47–62 years) participated in a "feedback control" experiment. All participants were right-handed and not familiar with the experiment. All participants gave written consent and the Ethical Committee of the Medical Faculty and the University of Tübingen approved the study (verification/project number 413/2015BO2), which was conducted in accordance with the World Medical Association Declaration of Helsinki. Prior to the main experiment, all participants completed a detailed questionnaire exploring the medical history, physical and vocational as well as recreational interests. All patients were examined neurologically among others, carefully considering the items of the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hubsch et al., 2006).

2.2 | Experimental setup

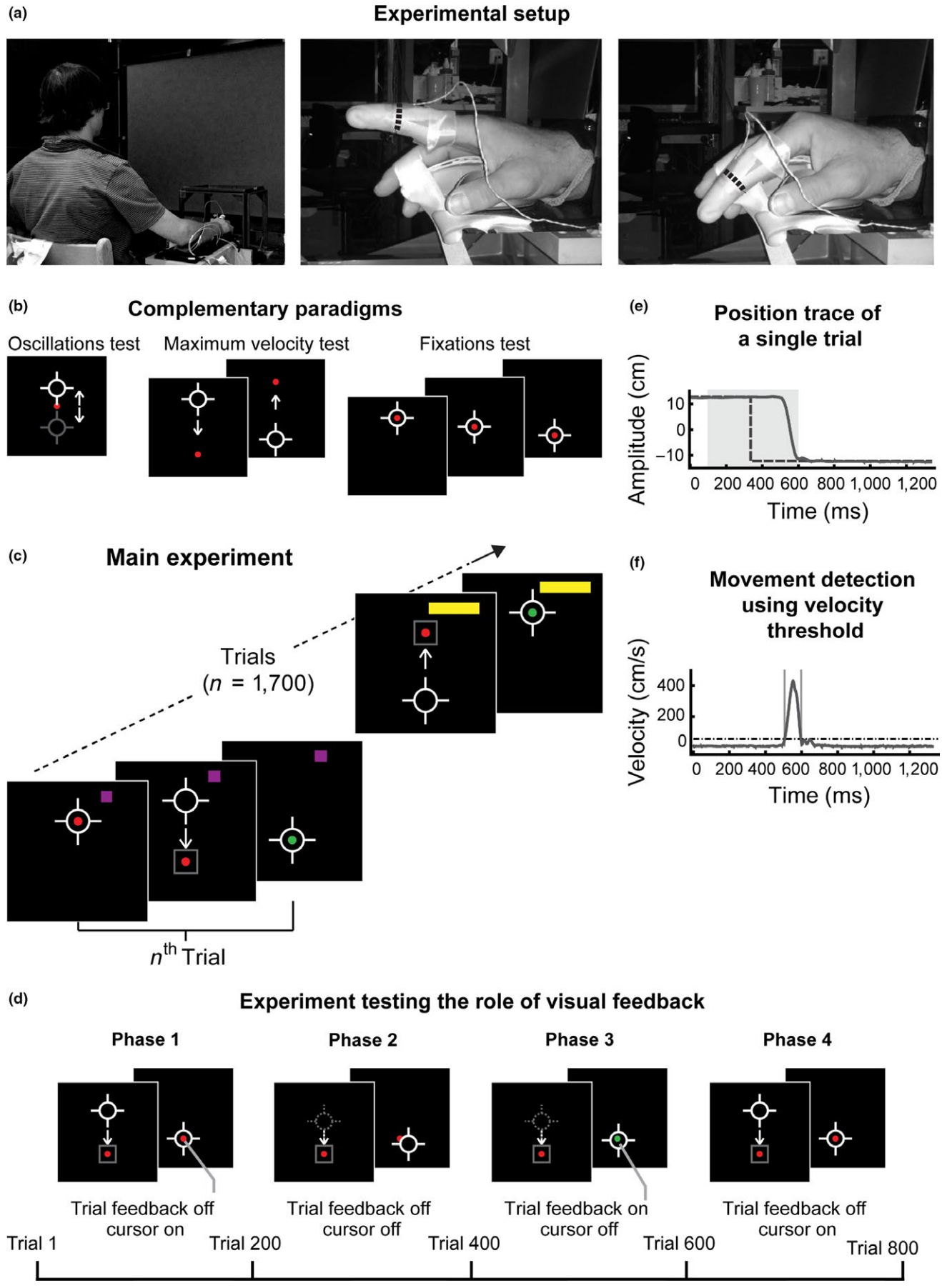
Subjects were seated comfortably in an upright position on a chair fixed in front of a large screen (width: 160 cm, height: 120 cm) such that the distance between the eye and the screen was approximately 150 cm with the sagittal body axis aligned with the mid-line of the screen. To ensure maximum comfort during the experiment, the subjects' head was not fixed and adopted a convenient position with their right arm on a forearm rest with the hand and the index finger pointing forward (Figure 1a). In order to prevent relevant arm movements during experiments, the forearm and hand/wrist were secured to the rest by Velcro fasteners. As we were interested in fast index finger movements about the finger's base joint (=metacarpophalangeal joint, MCP joint), we blocked significant movement contributions of the two distal finger joints by splinting the index finger distal of the MCP joint using a finger-shaped cast made out of lightweight thermoplastic material. The position of the distal phalanx was measured using the search coil technique by attaching a magnetic search coil (Bechert & Koenig, 1996) to the finger cast axially around the distal phalanx (Figure 1a), sampling the coil signal at a resolution of 1 kHz.

In-house software (NREC), running on a Linux PC (http://nrec.neurologie.uni-tuebingen.de) was used for data collection, stimulus presentation and operations control. All visual stimuli were projected onto the tangent screen by an NEC GT2150 LCD projector (60 Hz, 1280 × 1024 pixels).

2.3 | The main behavioural paradigm

In the main experiment, subjects had to execute rapid, alternating extension and flexion movements of the index finger about the MCP joint needed to keep a white cross-hair shaped cursor (diameter: 4 cm), representing the fingertip's vertical and horizontal position, within a target zone centred on a red dot target (diameter: 1.7 cm), projected onto the screen. The target appeared first in a start position in the screen centre and next jumped unpredictably to one of the two new positions, above and below the start position, respectively, and

FIGURE 1 Experimental setup and paradigm used for measuring fast finger movements. (a) A healthy participant seated comfortably on a chair (left) placed in front of a large projection screen with his right (=preferred) hand resting on a customized ergonomic "mouse" allowing up (mid) and down (right) index finger movements. The index finger was stabilized using a cast. A search coil was placed axially around the middle phalanx, as shown by the dotted black line. (b) Complementary behavioural paradigms. (c) The main behavioural paradigm consisted of 1,700 trials that lasted for around 37 min. (d) Experiment for testing the role of cursor feedback. (e) Position trace during a single downward trial (solid dark grey line). The target jump (dashed grey line) times were randomized within a time window (shaded region) of 100–600 ms from the onset of the trial. (f) Movement onset detection (vertical grey lines) was based on a velocity threshold (horizontal dashed line) of 50 cm/s. Velocity profile (solid dark grey line) of the index finger during a downward movement


(a)
Experimental setup
(b)
Complementary paradigms
Oscillations test
Maximum velocity test
Fixations test
(c)
Main experiment
Trials
(n = 1,700)
nth Trial
(d)
Experiment testing the role of visual feedback
Phase 1
Phase 2
Phase 3
Phase 4
Trial feedback off
cursor on
Trial feedback off
cursor off
Trial feedback on
cursor off
Trial feedback off
cursor on
Trial 1
Trial 200
Trial 400
Trial 600
Trial 800
(e)
Position trace of
a single trial
Amplitude (cm)
10
0
−10
0 200 400 600 800 1,000 1,200
Time (ms)
(f)
Movement detection
using velocity
threshold
Velocity (cm/s)
400
200
0
0 200 400 600 800 1,000 1,200
Time (ms)

from there alternated between the two. The two target positions were: up: $x = 0$ cm, $y = +12.5$ cm; down: $x = 0$ cm, $y = -12.5$ cm). With a distance between the MCP joint and the screen centre of 110 cm, the 25 cm jump of the target between its two positions evoked an angular rotation of approximately 60° about the MCP joint.

The index finger's resting position was aligned with the middle of the screen in a way that the MCP joint had to be rotated by comparative amounts up and down from the resting position in order to reach the two vertical targets. In order to exclude the possibility that precision might be achieved by merely flexing or extending the index finger to its maximum rotation limit, the amount of angular rotation needed in either direction was kept significantly smaller than the maximal rotation possible. Although all experiments were conducted in a dark room, the weak screen backlight might have allowed some subjects to obtain visual feedback on their moving finger. This is why we used an occluder that prevented watching the hand.

The "Main Experiment" (Figure 1c) required participants to execute long series (~1,700 trials; ~37 min) of fast and precise vertically alternating index finger movements. Each trial lasted approximately 1,300 ms and the target jump times were selected randomly from a variable time window of 100–600 ms from the trial onset to avoid movements based on intuition (Figure 1e). We placed an invisible squared window (4×4 cm) comparable in size to the diameter of the circular ring of the moving cross-hair pointer around the target. The finger movement had to place the cursor into the confines of this window to count as successful. To make sure that the executed movements were fast, we chose a time window of 300 ms that opened 150 ms after the target jump. Any movements executed earlier than the onset of the window or later than 300 ms after the onset, were considered "too early" and "too late" movements, respectively. Only if the movements were fast and precise the target dot turned green, indicating a successful trial. To keep participants motivated throughout the experiment, a horizontal "performance bar" was displayed at the top right corner of the screen that increased in length with every successful trial. Since there was no reference to the maximum length of the bar, no exact estimates of task duration could be inferred from its length. However, near the end of the task, the colour of the bar changed from purple to yellow followed by a beep sound, alarming that only 10% trials were left to finish the task. No other communication was allowed during the experiment.

2.4 | Complementary behavioural paradigms

Before the main experiment, we carried out a series of three short tests (Figure 1b). The first test was the "oscillations test" in which participants were asked to execute rapid, unguided vertically oscillating movements for 10 s, around a red target dot (diameter: 1.7 cm) displayed in the middle of the screen but without an endpoint target. The purpose of this task was to measure the maximum oscillation frequency of the index finger. To this end, subjects were free to choose the movement amplitudes ensuring the highest possible movement frequency. In the second test, the "maximum velocity test," subjects had to execute very fast movements (60 trials; trial duration: 1,400 ms) between two vertically alternating targets. As the main interest of this experiment was to measure the maximum finger velocity possible, precision was not enforced although feedback on the finger position was provided. Finally, in the third test, the "fixation test," subjects had to fixate each of the three target positions (in the order centre: $x = 0$ cm, $y = 0$ cm; up: $x = 0$ cm, $y = +12.5$ cm and down: $x = 0$ cm, $y = -12.5$ cm) with the cursor for 10 s (see Supporting Information Appendix S1 for results).

2.5 | Data analysis

We performed the analysis offline using scripts written in MATLAB (MATLAB, The MathWorks Inc., MA). First, we smoothed the vertical and horizontal components of the finger position records (sampled at a rate of 1 kHz) using a Savitzky–Golay filter (Savitzky & Golay, 1964) (bin size = 10 samples; polynomial degree = 3, derivative = 1), based on a chosen order of derivative. Instantaneous finger velocity and acceleration were derived from the finger position data (Figure 1e). Detection of (primary) finger movements (Figure 1f) was based on a lenient velocity threshold of 50 cm/s that was chosen to eliminate the corrective (secondary) finger movements that resulted from overshooting or undershooting of the cursor relative to the desired target location. We calculated movement amplitude as the absolute difference of vertical finger position at the time of movement onset and offset and duration as the time between on- and offset. Movements lasting for 80–300 ms within an amplitude range of 10–35 cm only were considered for analysis. A significance level of $p < 0.05$ was adopted for statistical interpretations.

3 | RESULTS

3.1 | Main task

The idea behind the "main task" was to scrutinize the relationship between movement velocity and duration on a trial-by-trial basis. Since the peak velocity of a movement is a very sensitive marker of trial-to-trial fluctuations in velocity, we focused our analysis mainly on the peak velocity of finger movements. To examine this relationship, we asked all participants to make long series of fast and precise alternating movements of the index finger of their preferred hand in order to move the cursor up and down such as to achieve the desired target locations displayed on the monitor. We observed

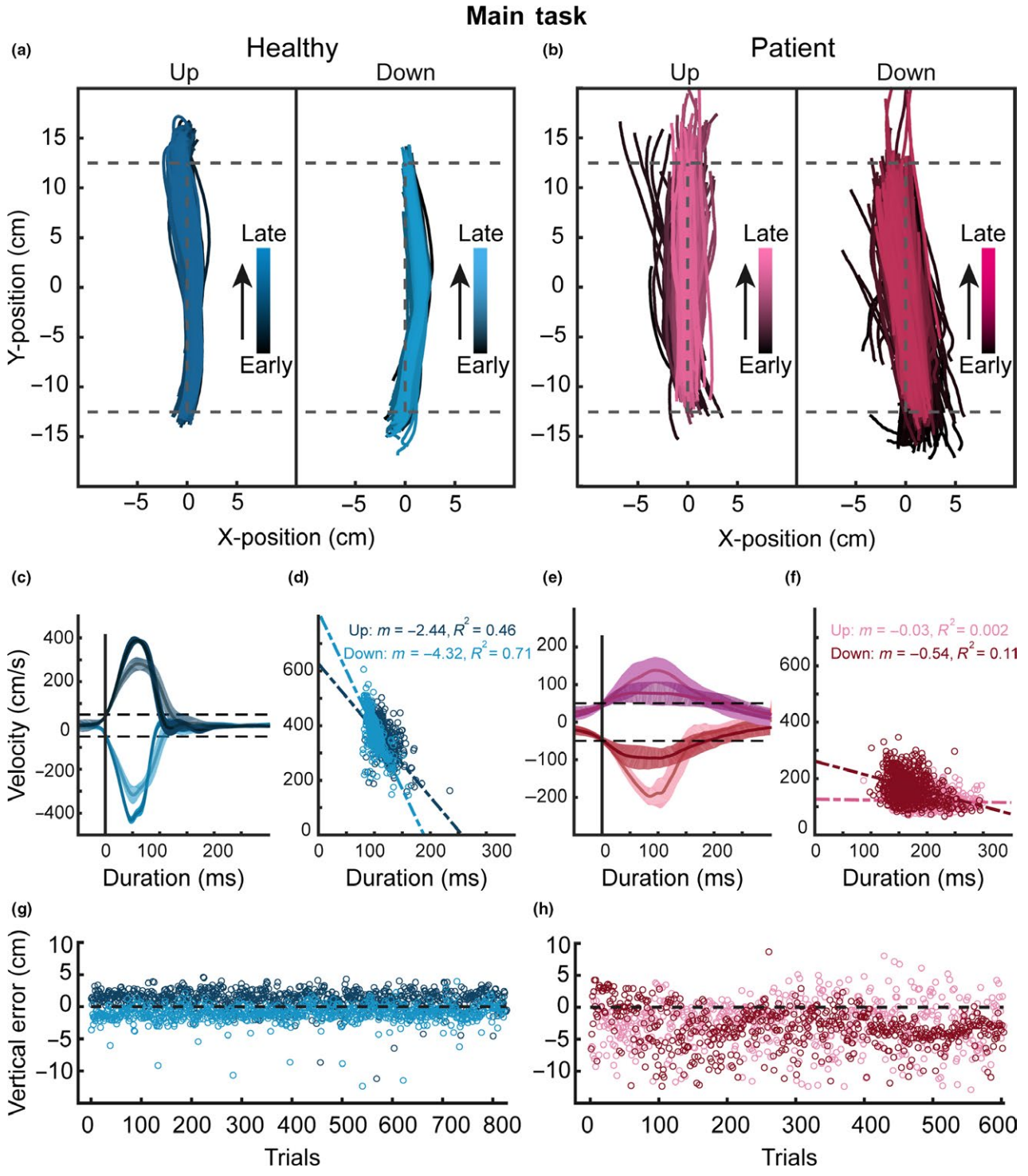


FIGURE 2 Endpoint precision, movement velocity and movement duration in exemplary subjects. (a,b) Movement trajectories of an exemplary healthy subject and cerebellar patient respectively. (c, e) Mean and standard error of mean (*SEM*) of the velocity trace for up and down finger movements with higher and lower peak velocity (100 trials each). (d, f) Velocity-duration trade-off in the healthy subject and patient, respectively, represented by the dashed regression lines fitted to the peak velocity and duration of all up and down trials. Slopes of regression, healthy: $m_{up} = -2.44$; $m_{down} = -4.32$; patient: $m_{up} = -0.03$; $m_{down} = -0.54$. (g, h) Endpoint errors in the up and down movements of the healthy subject and cerebellar patient

that the movement trajectories of the index finger of single healthy participants (Figure 2a) showed much less variability in their general pattern than those of single cerebellar patients (Figure 2b). We also found that individual healthy subjects were able to compensate for changes in the movement velocity (Figure 2c) by making fine adjustments in movement

duration; lower velocity movements were accompanied by higher movement durations and vice-versa. Such clear compensatory adjustment of movement duration in response to changes in peak velocity of finger movements was clearly not seen in individual cerebellar patients (Figure 2e).

The velocity-duration trade-off suggested by the movement trajectories shown in Figure 2a,b is captured by the significant negative slope (m) of the regression lines fitted to plots of peak velocity as a function of movement duration for the two subjects shown in Figure 2d,f. The notion of a disturbed velocity-duration relationship in the patient is supported by two facts disclosed by Figure 2f. Firstly, the quality of the linear fit was poorer in the patient as indicated by significantly smaller coefficients of determination (R^2), (healthy: $R^2_{up} = 0.46$, $R^2_{down} = 0.71$; patient: $R^2_{up} = 0.002$, $R^2_{down} = 0.11$). Secondly, the slope of the regression line was significantly lower in the patient, both for up and for down finger movements (Figure 2d, healthy: $m_{up} = -2.44$; $m_{down} = -4.32$; Figure 2f, patient: $m_{up} = -0.03$; $m_{down} = -0.54$), indicating that a much smaller fraction of the endpoint error that would otherwise result from changes in velocity was compensated in the healthy subject. Consequently, the patient's finger movement trajectories were less smooth and less precise as documented by a larger mean absolute deviation of the finger endpoint from the target and a significantly larger variability of movement endpoints (Figure 2h). The patient not only lacked the high-quality velocity-duration trade-off presented by the healthy subject but in general exhibited smaller movement velocities. However, independent of the clear performance differences between the patient and the control subject, both demonstrated faster downward than upward movements (Figure 2d,f, Supporting information Figure S2a,b). The features distinguishing the exemplary patient and control subject also differentiated the two groups. Healthy participants (Figure 3a,b) had significantly more negative (steeper) values of m (healthy subjects: mean $m_{up} = -1.89$, mean $m_{down} = -2.53$; patients: mean $m_{up} = -0.68$, mean $m_{down} = -0.73$; Wilcoxon rank-sum test, up movements: $z = -4.24$, $p = 2.26 \times 10^{-5}$, down movements: $z = -3.92$, $p = 9.02 \times 10^{-5}$) as well as significantly larger coefficients of determination (healthy subjects: mean $R^2_{up} = 0.5$, mean $R^2_{down} = 0.52$; patients: mean $R^2_{up} = 0.22$, mean $R^2_{down} = 0.13$; Wilcoxon rank-sum test, up movements: $z = 3.41$, $p = 6.52 \times 10^{-4}$; down movements: $z = 4.01$, $p = 6.13 \times 10^{-5}$).

3.2 | Slopes for a matched range of speeds

Since the distribution of the peak velocities of finger movements (Figure 3c, all trials, up and down pooled) of the

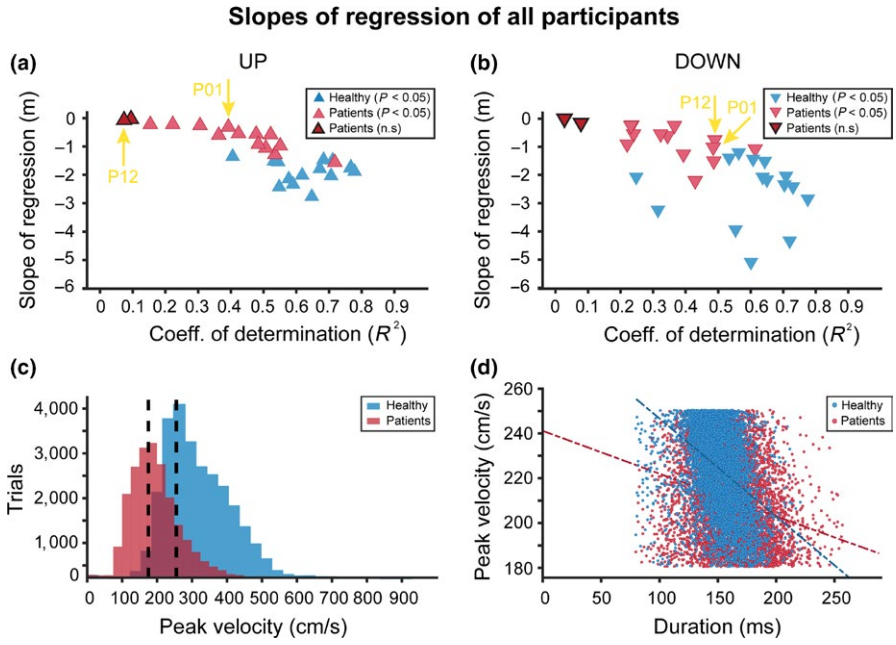


FIGURE 3 Analysis of relationship of movement velocity and movement duration. (a, b) Slopes of regression (m) of movement velocity as function of movement duration for individual subjects as function of associated coefficient of determination (R^2) for up and down finger movements, respectively. Healthy subjects: solid blue triangles; cerebellar patients: solid red triangles. Yellow arrows indicate the patients (P01 and P12) with additional noncerebellar damage (not included in statistical analysis). (c) Peak velocity distribution for all movements (up and down combined) pooled across all healthy subjects and cerebellar patients. Equal numbers of samples were drawn at random from a matched range of peak velocities (180–250 cm/s, dotted black lines) to compute the regression of peak velocity as function of movement duration shown in panel D. (d) Slopes of regression for matched range peak velocities in healthy subjects ($m = -0.44$, $p = 9.53 \times 10^{-234}$, R^2=0.16) and patients ($m = -0.19$, $p = 2.13 \times 10^{-79}$, $R^2 = 0.06$)

cerebellar patients was shifted relative to one of the healthy participants (on average 38.12% lower in patients, Wilcoxon rank-sum test: $z = 130.62$, $p = 0$), one might argue that the poor relationship between movement duration and peak velocity observed in the patient group is an artefact of their lower velocity finger movements rather than a true group difference. To address this objection we restricted the regression analysis to a fixed range of peak velocities (180–250 cm/s) covering the velocity distributions of both groups, drawing at random equal numbers of trials for both groups in order to compute the velocity-duration regressions. Even within this small range of matched velocities, the slopes of regression lines for healthy participants ($m_{\text{healthy}} = -0.44$, $p = 9.53 \times 10^{-234}$) were higher and the corresponding coefficients of determination ($R^2_{\text{healthy}} = 0.16$) larger than in the cerebellar patients ($m_{\text{patients}} = -0.19$, $p = 2.13 \times 10^{-79}$,

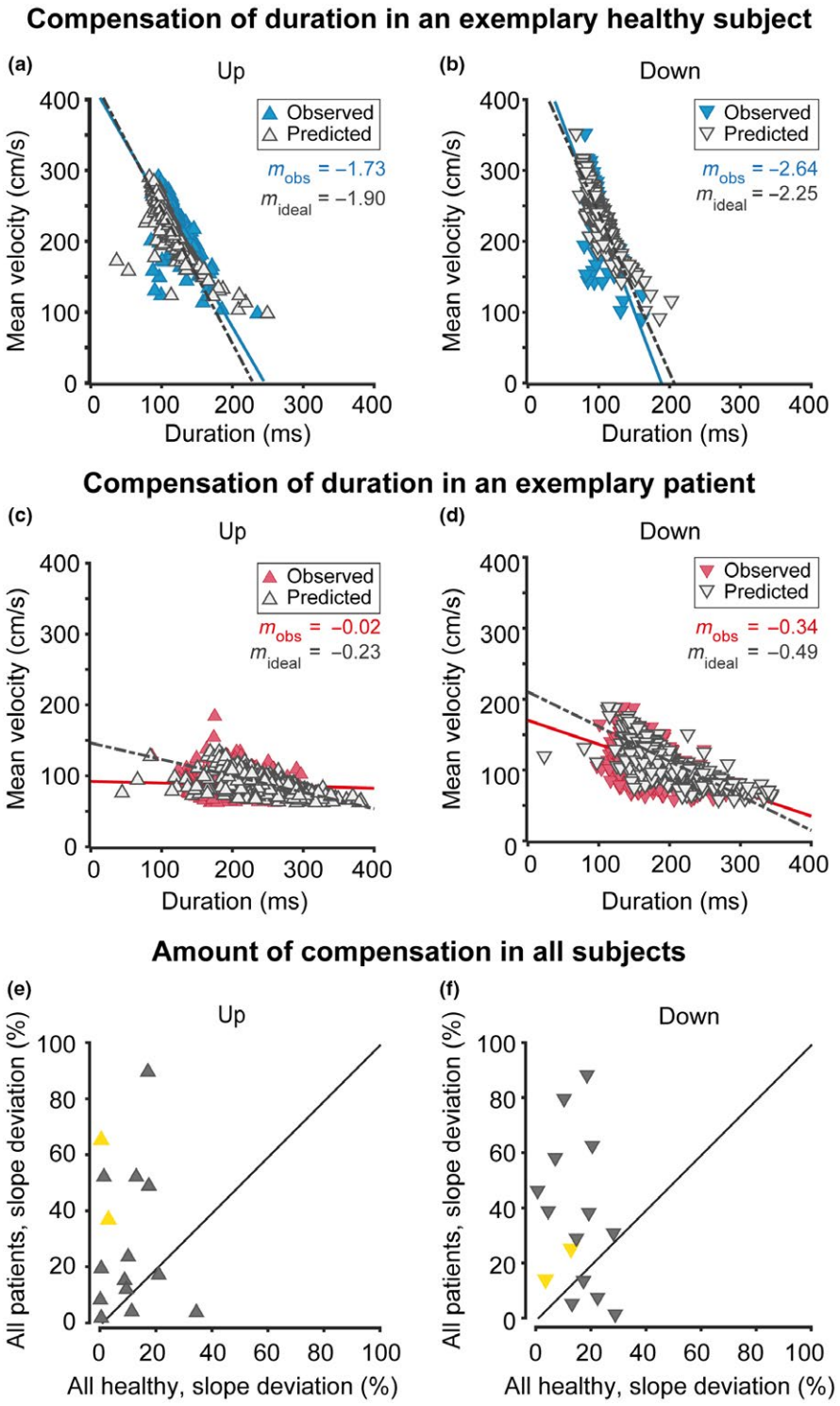


FIGURE 4 Analysis of duration compensation of velocity fluctuations. (a-d) Plots of mean velocities as function of observed durations and ideal durations (see main text for explanation) respectively, for the two exemplary subjects (a, b healthy subject; c, d patient) for up and down movements. Scatter plots and resulting regressions for observed durations are distinguished by colour (red for patients, blue for healthy subjects) from those for ideal durations (light grey). (e, f) Plots of slope deviation coefficients of patients as a function of coefficients of healthy controls. Note that patients exhibited significantly larger slope deviations than healthy subjects (healthy subjects: mean $m_{\text{deviation up}} = 9.9\%$, mean $m_{\text{deviation down}} = 14.75\%$, patients: mean $m_{\text{deviation up}} = 26.73\%$, mean $m_{\text{deviation down}} = 38.47\%$; Wilcoxon rank-sum test, up movements: $z = -2.03$, $p = 0.04$; down movements: $z = -2.40$, $p = 0.01$). Yellow triangles indicate the patients (P01 and P12) with additional noncerebellar damage (not included in statistical analysis)

$R^2_{\text{patients}} = 0.06$, Figure 3d). Finally, although patients' peak velocities were on average slower, measures of velocity variability were not different between groups *SD*, mean $SD_{\text{healthy}} = 60.1$, mean $SD_{\text{patients}} = 54.48$, Wilcoxon rank-sum test, $z = -0.88$, $p = 0.38$). On the other hand, a closer look at the plots of peak velocity as function of duration (Figure 3d) reveals that patients exhibited a larger variability in their movement durations (mean $SD_{\text{healthy}} = 18.84$, mean $SD_{\text{patients}} = 31.74$, Wilcoxon rank-sum test, $z = 4.33$, $p = 1.49 \times 10^{-5}$), ultimately responsible for the poor relationship between movement duration and peak velocity.

3.3 | Quality of velocity-duration trade-off

We next tried to assess the ability of the velocity-duration trade-off to ensure endpoint precision on a trial-to-trial basis. A perfect velocity-duration trade-off would keep the endpoint error zero despite fluctuations in movement velocity when deploying appropriate movement duration. We estimated this ideal movement duration (D_{ideal}) in single trials using the relation,

$$D_{\text{ideal}} = A_{\text{zero}-error}/V \quad (1)$$

where "*V*" is the mean velocity of finger movements and "$A_{\text{zero-error}}$" is the distance between the target and the vertical finger position at the onset of the movement that is, the amplitude required for zero error. We used the mean velocity of individual trials to estimate D_{ideal} rather than peak velocity because it provides a more accurate measure of the consequences of fluctuations in instantaneous velocity for the resulting movement amplitude than peak velocity. We then regressed mean finger velocity as a function of D_{ideal} to compute the ideal slope (m_{ideal}) of the velocity-duration relationship and then compared the slope (m_{ideal}) of the regression line with the slope (m_{observed}) of the regression of mean velocity as a function of observed movement duration. To this end, we calculated a slope deviation coefficient $m_{\text{deviation}}$ expressing how much the observed slope deviated from the predicted one, the latter warranting optimal compensation of velocity fluctuations, according to

$$m_{\text{deviation}} = (m_{\text{ideal}} - m_{\text{observed}})/m_{\text{ideal}} \times 100 \quad (2)$$

The deviation coefficient was clearly smaller in the exemplary healthy individual (Figure 4a,b) ($m_{\text{deviation up}} = 9\%$, $m_{\text{deviation down}} = 17\%$) than in the exemplary patient (Figure 4c,d, $m_{\text{deviation up}} = 91\%$, $m_{\text{deviation down}} = 31\%$). In general, healthy subjects exhibited significantly smaller slope deviations than patients (healthy subjects: mean $m_{\text{deviation up}} = 9.9\%$, mean $m_{\text{deviation down}} = 14.75\%$, patients: mean $m_{\text{deviation up}} = 26.73\%$, mean $m_{\text{deviation down}} = 38.47\%$; Wilcoxon rank-sum test, up movements: $z = -2.03$, $p = 0.04$; down movements: $z = 2.40$, $p = 0.01$), the patients displayed a clear inability to compensate fluctuations in movement velocity paralleled by larger slope deviations that underlies the loss of movement precision in patients (Figure 4e,f).

3.4 | Loss of vigour and hypometria in cerebellar patients

Despite the long and exhausting session it was quite surprising to see that none of the healthy participants showed "fatigue" or loss of their vigour of movement in the main task, in the sense of a gradual steady decline in peak velocity of the finger movements over time. This is the conclusion suggested by comparing the mean peak velocity, duration and amplitude of finger movements (up and down pooled), averaged across all healthy participants (Figure 5 aI,bI,cI) for trials in the early (first 120 trials), late (120 trials before time alarm, i.e. a tone and change in colour of performance bar indicating that 90% of the experiment had been completed) and last (120 trials after time alarm) phase of the main experiment. This comparison showed no significant difference between the three phases (one-way ANOVA for repeated measures, $F = 0.09$, $p = 0.91$). On the other hand, cerebellar patients exhibited a consistent drop (Figure 5 aII) in movement vigour between the early and the late phase (one-way ANOVA for repeated measures, $F = 9.49$, $p = 9.19 \times 10^{-4}$; early vs. late, *t* test: $t = 3.05$, $p = 0.01$). Even the alarm signal indicating 90% task completion did not seem to boost peak velocities (late vs. last, *t* test, $t = 1.31$, $p = 0.22$). As the task difficulty was not adjusted for the patients' group, one potential factor that could possibly account for this loss of movement vigour in patients might have been a decline in motivation over the course of the task. We captured the quality of task performance by gauging the number of successful trials (score) and the instantaneous ratio (ΔS) of successful trials relative to trials executed as proxy of motivation. Both groups exhibited an increase in the number of successful trials (Figure 5 dI,dII) from the early phase (after the first 120 trials: $\text{score}_{\text{healthy}} = 107$, $\text{score}_{\text{patients}} = 70.54$) till the end of the last phase (120 trials after alarm: $\text{score}_{\text{healthy}} = 1{,}444.3$, $\text{score}_{\text{patients}} = 566.54$). Yet, as indicated by the numbers presented, this accumulation was generally slower in patients. Moreover, it took place at a constant rate only in healthy controls. However, in cerebellar patients the quality of task performance (ΔS) declined gradually in the course of the experiment, paralleling the decline in peak velocity. This decline in the vigour of finger movements over trials in the patient group remained uncompensated for duration (Figure 5 bII, one-way ANOVA for repeated measures, $F = 1.99$, $p = 0.16$; early vs. late, *t* test, $t = -1.76$, $p = 0.1$), causing the movement amplitudes to gradually fall short of the desired target location more and more (Figure 5 cII, one-way ANOVA for repeated measures, $F = 7.25$, $p = 0.003$;

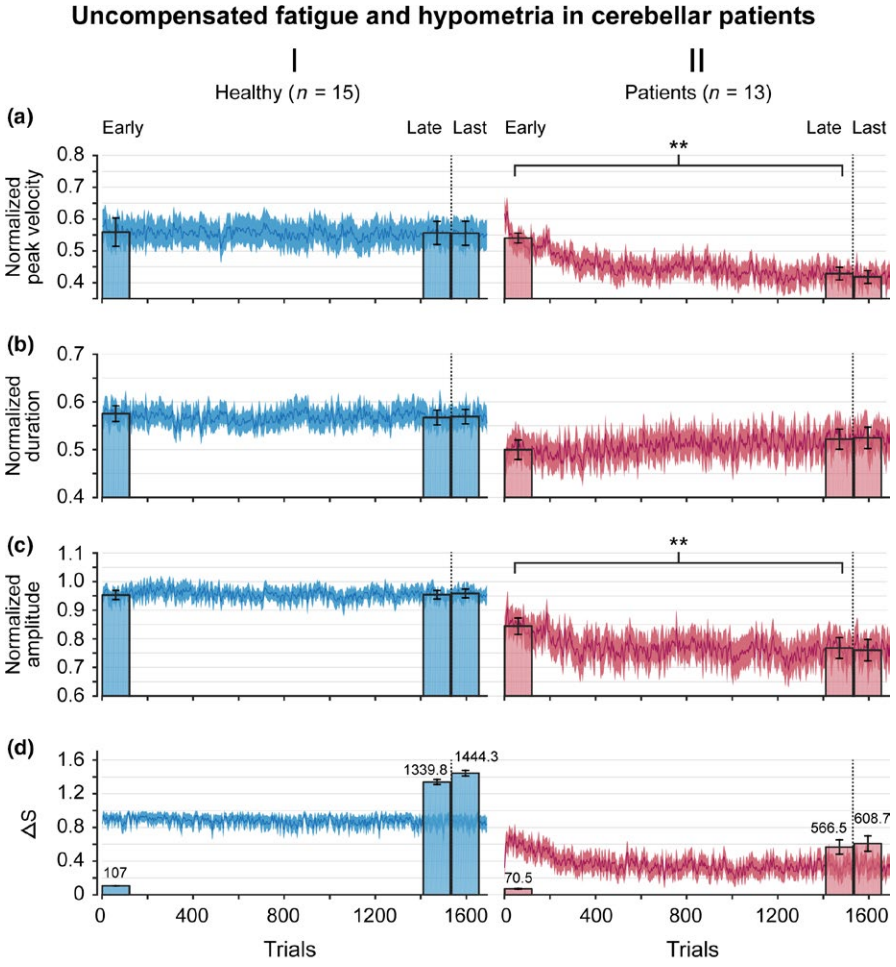


FIGURE 5 Movement velocity, amplitude, duration and task performance as a function of trial number. (aI, bI, cI, aII, bII, cII) Plots showing the mean (±*SEM*) of the normalized peak velocity, duration and amplitude of finger movements (up and down combined) of all healthy participants (blue traces) and patients (red traces) respectively, during the main task. The bars represent the mean (±*SEM*) of the respective kinematic parameter of trials during the "early" (first 120 trials), "late" (120 trials before alarm signal, as indicated by the dotted black line) and "last" phase (120 trials after alarm) of the main task. (dI, dII) The absolute mean score of all healthy participants (blue bars) and cerebellar patients (red bars), respectively, at the end of early, late and last phase of the main task. The average (±*SEM*) instantaneous ratio (ΔS) of successful trials relative to executed trials of all healthy participants and cerebellar patients is shown by the blue and red traces, respectively

early vs. late, *t* test, $t = 2.63$, $p = 0.02$), a condition usually referred to as "hypometria."

3.5 | Experiment testing the role of feedback

The findings reported before suggest that finger movements of healthy controls and patients are subject to velocity fluctuations. Moreover, they indicate that it requires a healthy cerebellum to ensure that the fluctuations are not translated into endpoint errors. This is achieved by an appropriate adjustment of movement duration. Does this adjustment depend on the visual feedback of the ongoing finger movement? This seemed highly unlikely, given the fact that the overall movement duration was usually less than 170 ms (mean + *SD*: 172.9), that the minimal latency of visual feedback would hardly fall below 100 ms and that at least a few 10 ms would be required to capture the initial finger velocity and, based on it, to predict the landing point. Hence, the presence or absence of visual information should if anything impact the final phase of the movement and thereby modulate the overall trajectory. In order to find out if the visual feedback modulated the final movement phase, we tested a new group of 10 naïve healthy right-handed participants in a variant of the main experiment, in which we manipulated not only the availability of visual feedback but also the availability of performance feedback (Figure 1d). This feedback control experiment comprised of four phases, each phase consisting of 200 trials. Participants were instructed to make fast and precise movements. During all four phases, unlike the main experiment, subjects did not see any cumulative score (performance bar) capturing the evolution of the experiment. Although in phase one and phase four cursor feedback on the actual finger position was available, this cursor feedback was partially removed in the second and third phase of the experiment by blanking the cursor during mid-flight as soon as the movement velocity exceeded a threshold of 10 cm/s. The cursor reappeared 500 ms after the detected movement onset, that is well after the completion of a normal movement, which typically took 114.2 (mean-*SD*) to 172.9 (mean + *SD*) ms. Only during the third phase, performance feedback after each trial, indicated by the change of the target colour, was delivered. Had there been an influence of cursor feedback or performance feedback on movement trajectories, one would have expected changes of the typically smooth and continuous, almost bell-shaped velocity profiles of movements (Figure 6) when comparing those in phase one with those during the second or the

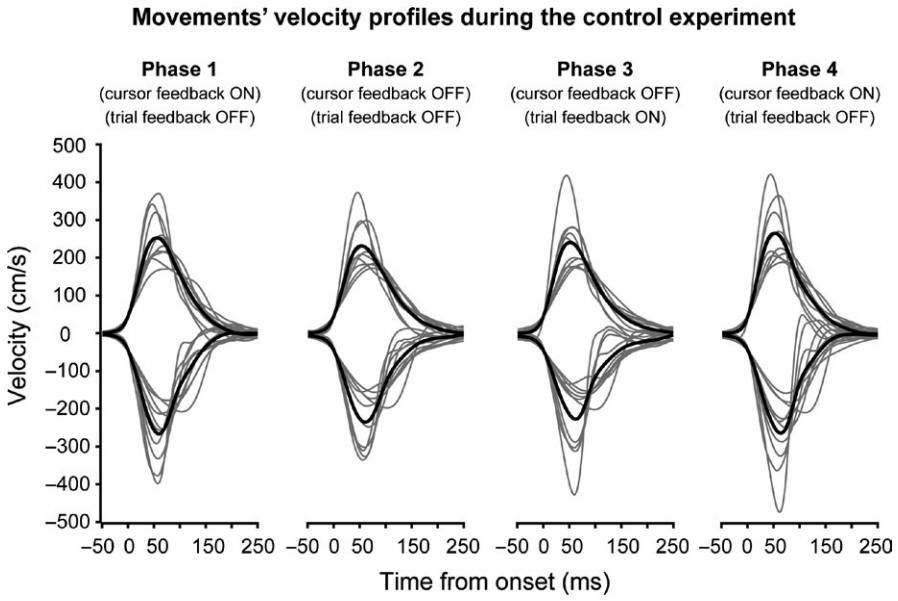


FIGURE 6 The role of cursor feedback. Mean velocity profiles of all up and down movements in healthy control subjects (solid grey lines) during the four phases of control task. Black solid traces indicate the mean of all velocity profiles of up and down finger movements during the four phases. There was no influence of the cursor feedback on the shape of movement velocity profiles

third phase. To detect such changes, we fitted the velocity profile of each trial of all participants by a modified Gamma distribution (Van Opstal & Van Gisbergen, 1987) in order to detect phase-dependent changes in the properties of the fit. The Gamma distribution is given by

$$v(t) = \alpha * [t/\beta]^{\gamma-1} * \exp[-t/\beta] \ldots t \geq 0; \beta > 0; \gamma \geq 1 \quad (3)$$

where $v(t)$ is the movement velocity profile, α and β are scaling constants for velocity and duration, respectively, and γ is the shape parameter that determines the degree of asymmetry to compute skewness ($2/\sqrt{\gamma}$). Gamma functions were able to accommodate the mild deviation from a perfectly symmetric bell-shaped profile, due to the profiles′ slightly steeper ascent than descent. The resulting fits of the velocity profiles of up and down movements were characterized by goodness of fit measures (R^2) typically exceeding 0.94 (median R^2_{up}: Phase 1–4: 0.98, 0.98, 0.98, 0.98 respectively; median R^2_{down}: Phase 1–4: 0.94, 0.92, 0.89, 0.92 respectively), without a significant difference of R^2 and the skewness measure between phase one and phase two (two-way repeated measure ANOVA with the two factors phase and movement direction (i.e. up and down) and post-hoc Tukey-Kramer comparisons between phases with corrections for multiple comparisons; phase 1 vs. 2: skewness, $p = 0.37$; R^2, $p = 0.23$; phase 1 vs. 3: skewness, $p = 0.31$, R^2, $p = 0.09$, tested for multiple comparisons) indicating that there were neither qualitative nor quantitative differences in the shapes of velocity profiles. These results clearly suggest that the selection of movement durations appropriate for the peak velocity reached cannot be based on visual feedback, that is an a posteriori assessment of the velocity reached. Rather they suggest that the system uses a priori knowledge on future peak velocity in order to preselect appropriate movement durations.

4 | DISCUSSION

The aim of this study of fast goal-directed index finger movements was to extend our understanding of the role of the cerebellum in ensuring movement precision. Our results clearly demonstrate that the cerebellum achieves the desired accuracy despite continuous fluctuations in movement velocity by adjusting movement duration accordingly. This precise velocity-duration trade-off depends on the integrity of the cerebellum. This conclusion is based on the fact that patients suffering from a global malfunction of the cerebellum due to degeneration, although in general moving more slowly, exhibit similar variability of finger movement velocities, clearly indicating that this variability is a consequence of extra cerebellar influences. Yet, unlike healthy subjects, the patients are no longer able to deploy compensatory movement durations, an inability that leads to a loss of endpoint accuracy, in other words to dysmetria. This dysmetria is supplemented by less smooth trajectories that often show deviations from a simple "bell-shaped" velocity profile, the manifestation of deviant trajectory components and a relative slowness of movements, problems that in sum make up the cerebellar ataxia of movement.

4.1 | Deviant movement velocities in cerebellar patients

Slower velocities as exhibited by our patients are in accordance with previous observations (Hallett, Shahani, & Young, 1975; Topka, Konczak, Schneider, Boose, & Dichgans, 1998; Wild, Klockgether, & Dichgans, 1996) on the consequences of cerebellar disease. Slower movements could be a useful strategy to cope with the inability

to precisely control movement duration, the key functional disturbance unravelled by this study. The logic here is that the endpoint error resulting from not stopping the movement at the right point in time will decrease with the velocity of the movement. The fact that patients were not only slower in the main task but also in the "maximum velocity task" (see Supporting information Appendix S1), unlike the main task not emphasizing precision, does not necessarily invalidate this interpretation. The reason is that even in the maximum velocity task (Supporting information Figure S2), patients and healthy subjects were still surprisingly accurate. This may suggest that a nonadmitted strategy, ensuring precision, may have still influenced the behaviour. However, a potential alternative—a link to deficiencies of action value assessment—is suggested by a closer look at longer-term velocity changes in the course of the experiment.

It is well established that fast goal-directed eye movements, saccades, when carried out repetitively at short intervals, exhibit a gradual decline in their peak velocity (Bahill & Stark, 1975). This loss of saccadic vigour is a consequence of cognitive fatigue, in particular, a gradual loss of motivation to look at a target that becomes less and less rewarding, rather than a reflection of changes of the oculomotor plant due to usage (Prsa, Dicke, & Thier, 2010; Schmidt, Abel, Dell'Osso, & Daroff, 1979). Against the backdrop of these findings on saccades, we had expected to observe analogous changes in this study of fast finger movements. However, although movement velocity varied in both groups to a similar extent, only the patients showed a consistent decline in movement velocity or fatigue. We suggest that the slower movement velocities of cerebellar patients may be the consequence of lower motivation already early in the experiment and a continuing decline in motivation in its further course. This seems plausible as the subjective load of a task demanding precision must be much higher for subjects suffering from ataxia. The gradual drop in the quality of task performance (ΔS) over the course of the experiment exhibited by the patients (Figure 5 dII) is in line with the assumption of relative overstraining and increasing exhaustion during the experimental session.

4.2 | A cerebellar velocity-duration trade-off ensuring endpoint precision

Subjects in both groups exhibited trial by trial differences in movement velocity. Yet, only healthy subjects were able to compensate differences in velocity by appropriate changes in movement duration to a large extent, thereby substantially narrowing the scatter of finger cursor endpoints around the target. The absence of appropriate duration adjustments in patients clearly indicates that the velocity-duration trade-off is based on cerebellar machinery. Is the choice of appropriate movement duration based on feedback on movement velocity? The fact that the omission of visual feedback did not affect movement trajectories at all (Figure 6), clearly argues against a role of vision in guaranteeing it in healthy subjects. Since the patients were characterized by severe impairments of their velocity duration trade-off, a control experiment trying to assess if visual feedback is needed to implement a trade-off, missing in the patients, seemed inappropriate and was therefore skipped. However, one might argue that the patients–other than healthy controls–might resort to the cursor feedback to mitigate their deficit to some extent. We cannot exclude this possibility with certainty, given the lack of data from the control experiment. Notwithstanding the possibility of different strategies in the two groups, it is safe to conclude that visual feedback of the cursor cannot account for the deteriorated velocity-duration trade-off found in patients. Although a role of cursor feedback within a given trial is not supported by the control experiment, it does not question an important role of feedback in the optimization of an internal model improving the precision of future trials in a feed-forward manner. Indeed patients may exhibit insufficient optimization. This is suggested by the fact that they —unlike healthy subjects— exhibited a gradual decline of their movement amplitudes in the main experiment, compatible with an inability to use error information delivered by the cursor feedback.

With the qualification that the results from the control experiment do not rule out that the velocity-duration trade-off involves much more instantaneous proprioceptive feedback, they might suggest namely that the cerebellum uses a priori information on the velocity of the upcoming movement in order to prepare appropriate movement duration already before movement onset. Such a pre-formed velocity-duration trade-off will only be possible if a reliable estimate of the upcoming velocity is available and it will only be a viable solution if velocity fluctuations cannot be simply avoided from the outset.

Could it be that oculomotor disturbances associated with cerebellar degeneration might explain the poor task performance observed in our patients? In an attempt not to overstrain our subjects, in particular the patients, we had refrained from implementing an explicit control of eye movements. Albeit, one can be certain that the occurrence of the peripheral target triggered a sequence of covert and overt shifts of attention to the target, followed by the finger movement only a few tens of milliseconds later. Hence, the planning of the next finger movement would be dependent on the vision of a target appearing optimally at 10° eccentricity and because of likely dysmetria a bit off, for example at 9 or 11° of eccentricity in the patients. The differences in visual resolution within the range of eccentricities mentioned are probably too small to expect qualitative differences in performance and/

or the selection of strategies differing between two groups. Moreover, also later corrections of dysmetric primary saccades based on secondary saccades would be too late to influence the finger movement. In sum, we suggest that the alterations of the patients′ finger movements are not a consequence of altered eye movements. Rather we would argue that the two motor systems share a common deficiency, namely the lack of an appropriate velocity-duration trade-off.

In previous work on saccadic adaptation of cerebellar patients we demonstrated that the inability of patients to use error feedback to up-regulate their saccade amplitudes was a direct consequence of the failure to adjust saccade durations (Golla et al., 2008). Electrophysiological work on saccadic adaptation of experimental animals suggests that a Purkinje cell simple spike signal controls the adjustment of saccade duration (Catz, Dicke, & Thier, 2008; Thier, Dicke, Haas, & Barash, 2000). Assuming a generic role of the Purkinje cell simple spike firing patterns, the duration adjustment limitations exhibited by the patients in our previous work on eye movements and this study of fast finger movements may be a direct consequence of a loss of the Purkinje cell simple spike control signal that is able to make use of information on the velocity of the ongoing movement.

5 | CONCLUSION

This study has established that the dysmetria of fast finger movements, a central aspect of the ataxia of cerebellar patients, is a direct consequence of the loss of a cerebellum-based velocity-duration trade-off mechanism that fine-tunes movement durations based on information on the expected velocity of the movement. Arguably, deficient temporal control might also explain other aspects of movement deficiencies exhibited by cerebellar patients usually captured by the term ataxia.

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CONFLICT OF INTERESTS

The authors have no conflicts of interests to declare.

DATA ACCESSIBILITY

As our data are collected from human subjects, it has still to be discussed with the local Ethics Committee which form is most suitable for public availability.

AUTHOR CONTRIBUTIONS

Akshay Markanday, Julian Messner and Peter Thier designed the experiments and worked on the manuscript. A. M. and J. M. conducted the experiments. J. M. collected the clinical data and A. M. performed the data analysis. Both, A. M. and J. M. contributed equally to this project.

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REFERENCES

Albus, J. S. (1971). A theory of cerebellar function. *Mathematical Biosciences*, *10*, 25–61. https://doi.org/10.1016/0025-5564(71)90051-4

Bahill, A. T., & Stark, L. (1975). Overlapping saccades and glissades are produced by fatigue in the saccadic eye movement system. *Experimental Neurology*, *48*, 95–106. https://doi.org/10.1016/0014-4886(75)90225-3

Bechert, K., & Koenig, E. (1996). A search coil system with automatic field stabilization, calibration, and geometric processing for eye movement recording in humans. *Neuro-Ophthalmology*, *16*, 163–170. https://doi.org/10.3109/01658109609009677

Bhanpuri, N. H., Okamura, A. M., & Bastian, A. J. (2014). Predicting and correcting ataxia using a model of cerebellar function. *Brain*, *137*, 1931–1944. https://doi.org/10.1093/brain/awu115

Catz, N., Dicke, P. W., & Thier, P. (2008). Cerebellar-dependent motor learning is based on pruning a Purkinje cell population response. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 7309–7314. https://doi.org/10.1073/pnas.0706032105

Donchin, O., Rabe, K., Diedrichsen, J., Lally, N., Schoch, B., Gizewski, E. R., & Timmann, D. (2012). Cerebellar regions involved in adaptation to force field and visuomotor perturbation. *Journal of Neurophysiology*, *107*, 134–147. https://doi.org/10.1152/jn.00007.2011

Golla, H., Tziridis, K., Haarmeier, T., Catz, N., Barash, S., & Thier, P. (2008). Reduced saccadic resilience and impaired saccadic adaptation due to cerebellar disease. *European Journal of Neuroscience*, *27*, 132–144.

Hallett, M., Shahani, B. T., & Young, R. R. (1975). EMG analysis of patients with cerebellar deficits. *Journal of Neurology, Neurosurgery and Psychiatry*, *38*, 1163–1169. https://doi.org/10.1136/jnnp.38.12.1163

Ito, M. (1982). Cerebellar control of the vestibulo-ocular reflex–around the flocculus hypothesis. *Annual Review of Neuroscience*, *5*, 275–297. https://doi.org/10.1146/annurev.ne.05.030182.001423

Izawa, J., Criscimagna-Hemminger, S. E., & Shadmehr, R. (2012). Cerebellar contributions to reach adaptation and learning sensory

consequences of action. *Journal of Neuroscience*, *32*, 4230–4239. https://doi.org/10.1523/JNEUROSCI.6353-11.2012

Marr, D. (1969). A theory of cerebellar cortex. *Journal of Physiology*, *202*, 437–470. https://doi.org/10.1113/jphysiol.1969.sp008820

Maschke, M., Drepper, J., Kindsvater, K., Kolb, F. P., Diener, H.-C., & Timmann, D. (2000). Involvement of the human medial cerebellum in long-term habituation of the acoustic startle response. *Experimental Brain Research*, *133*, 359–367. https://doi.org/10.1007/s002210000417

Prsa, M., Dicke, P. W., & Thier, P. (2010). The absence of eye muscle fatigue indicates that the nervous system compensates for non-motor disturbances of oculomotor function. *Journal of Neuroscience*, *30*, 15834–15842. https://doi.org/10.1523/JNEUROSCI.3901-10.2010

Savitzky, A., & Golay, M. J. (1964). Smoothing and differentiation of data by simplified least squares procedures. *Analytical Chemistry*, *36*, 1627–1639. https://doi.org/10.1021/ac60214a047

Schmidt, D., Abel, L. A., Dell'Osso, L. F., & Daroff, R. B. (1979). Saccadic velocity characteristics: Intrinsic variability and fatigue. *Aviation, Space and Environmental Medicine*, *50*, 393–395.

Schmitz-Hubsch, T., du Montcel, S. T., Baliko, L., Berciano, J., Boesch, S., Depondt, C., … Fancellu, R. (2006). Scale for the assessment and rating of ataxia: Development of a new clinical scale. *Neurology*, *66*, 1717–1720. https://doi.org/10.1212/01.wnl.0000219042.60538.92

Shadmehr, R., Smith, M. A., & Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Annual Review of Neuroscience*, *33*, 89–108. https://doi.org/10.1146/annurev-neuro-060909-153135

Therrien, A. S., & Bastian, A. J. (2015). Cerebellar damage impairs internal predictions for sensory and motor function. *Current Opinion in Neurobiology*, *33*, 127–133. https://doi.org/10.1016/j.conb.2015.03.013

Thier, P., Dicke, P. W., Haas, R., & Barash, S. (2000). Encoding of movement time by populations of cerebellar Purkinje cells. *Nature*, *405*, 72–76. https://doi.org/10.1038/35011062

Topka, H., Konczak, J., Schneider, K., Boose, A., & Dichgans, J. (1998). Multijoint arm movements in cerebellar ataxia: Abnormal control of movement dynamics. *Experimental Brain Research*, *119*, 493–503. https://doi.org/10.1007/s002210050365

Van Opstal, A. J., & Van Gisbergen, J. A. (1987). Skewness of saccadic velocity profiles: A unifying parameter for normal and slow saccades. *Vision Research*, *27*, 731–745. https://doi.org/10.1016/0042-6989(87)90071-X

Wild, B., Klockgether, T., & Dichgans, J. (1996). Acceleration deficit in patients with cerebellar lesions. A study of kinematic and EMG-parameters in fast wrist movements. *Brain Research*, *713*, 186–191. https://doi.org/10.1016/0006-8993(95)01514-0

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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