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Modulation of error-sensitivity during a prism adaptation task in people with cerebellar degeneration

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Hanajima R, Shadmehr R, Ohminami S, Tsutsumi R, Shirota Y, Shimizu T, Tanaka N, Terao Y, Tsuji S, Ugawa Y, Uchimura M, Inoue M, Kitazawa S. Modulation of error-sensitivity during a prism adaptation task in people with cerebellar degeneration. *J Neurophysiol* 114: 2460–2471, 2015. First published August 26, 2015; doi:10.1152/jn.00145.2015.—Cerebellar damage can profoundly impair human motor adaptation. For example, if reaching movements are perturbed abruptly, cerebellar damage impairs the ability to learn from the perturbation-induced errors. Interestingly, if the perturbation is imposed gradually over many trials, people with cerebellar damage may exhibit improved adaptation. However, this result is controversial, since the differential effects of gradual vs. abrupt protocols have not been observed in all studies. To examine this question, we recruited patients with pure cerebellar ataxia due to cerebellar cortical atrophy ($n = 13$) and asked them to reach to a target while viewing the scene through wedge prisms. The prisms were computer controlled, making it possible to impose the full perturbation abruptly in one trial, or build up the perturbation gradually over many trials. To control visual feedback, we employed shutter glasses that removed visual feedback during the reach, allowing us to measure trial-by-trial learning from error (termed error-sensitivity), and trial-by-trial decay of motor memory (termed forgetting). We found that the patients benefited significantly from the gradual protocol, improving their performance with respect to the abrupt protocol by exhibiting smaller errors during the exposure block, and producing larger aftereffects during the postexposure block. Trial-by-trial analysis suggested that this improvement was due to increased error-sensitivity in the gradual protocol. Therefore, cerebellar patients exhibited an improved ability to learn from error if they experienced those errors gradually. This improvement coincided with increased error-sensitivity and was present in both groups of subjects, suggesting that control of error-sensitivity may be spared despite cerebellar damage.

cerebellum; degenerative ataxia; cerebellar cortex

DAMAGE TO THE CEREBELLUM CAN profoundly impair the ability of the brain to adapt motor commands. For example, in humans and other primates, if a perturbation is applied to alter the sensory consequences of motor commands, the result is a large error. In healthy individuals, this error decreases in an exponential manner in subsequent trials. However, in people with cerebellar dysfunction, regardless of whether the perturbation is applied via prism glasses (Baizer et al. 1999; Martin et al. 1996; Weiner et al. 1983), visuomotor rotations (Izawa et al. 2012; Tseng et al. 2007; Werner et al. 2010;), or force fields (Criscimagna-Hemminger et al. 2010; Donchin et al. 2012; Maschke et al. 2004; Smith and Shadmehr 2005), the participants show marked impairments in their ability to adapt.

These previous studies have demonstrated that the human cerebellum plays an important role in the process of motor adaptation. However, an interesting possibility is that, in patients with cerebellar damage, adaptation can be aided if the perturbation is not imposed in full, but built up gradually over many trials (Criscimagna-Hemminger et al. 2010). In that work, the authors reported that patients with severe cerebellar degeneration had impairment in adapting their motor commands in response to a sudden perturbation. However, when the same magnitude perturbation was imposed gradually over many trials, the patients showed improvements. This result raised the possibility that in cerebellar degeneration, there may be a latent ability to adapt motor commands, particularly in scenarios in which the perturbation is imposed gradually.

In contrast to these results, in a visuomotor rotation paradigm, Schlerf et al. (2012) reported that individuals with cerebellar damage showed similar adaptation deficits in abrupt and gradual perturbation protocols. In a force field paradigm, Gibo et al. (2013) reported that the benefit from the gradual protocol was present in some reach directions, but not others. These contrasting results are puzzling, prompting us to reexamine this question.

In the present study we used prism adaptation (Welch 1978) in patients with cerebellar ataxia and asked whether adaptation was differentially affected in the abrupt and gradual protocols. We employed a novel paradigm that tightly controlled visual feedback during the movement, preventing within-trial corrections in response to the perturbation. This allowed us to measure trial-to-trial error-dependent learning and compare performance of the participants in the gradual and abrupt protocols.

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METHODS

Thirteen patients with cerebellar degeneration (7 men and 6 women; 62.8 ± 10.9 yr old, Table 1) and 13 age-matched healthy volunteers participated in this study (7 men and 6 women, 67.4 ± 5.2 yr old). All patients showed clinical cerebellar ataxia symptoms, namely ataxic gait, dysmetria, and decomposition in the limb movement, without any pyramidal signs or extrapyramidal symptoms. The motor symptoms were similarly observed on both sides. None of the patients showed intention tremor or diplopia. All patients could see the target, push the button, and reach for the target on the screen. Genetic analysis revealed that five patients were spinocerebellar ataxia type 31 (SCA31), and five patients were SCA6. Two patients had no genetic abnormalities for SCA1, SCA2, SCA3, SCA6, SCA31, or dentatorubural pallidoluysian atrophy. One patient had no available genetic analysis. All patients had cerebellar cortical atrophy with preserved deep nuclei in the brain magnetic resonance image. The severity of ataxia was rated using the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al. 1997). None of the healthy volunteers had a history of neurological disorders, neuropsychiatric disorders, brain injury, or stroke. All participants were right handed. Written informed consent was obtained from all subjects. The experiments were performed according to the Declaration of Helsinki; the procedures were approved by the Ethics Committee of the University of Tokyo (no. 2833). No side effects were noted in any individual.

Prism adaptation task. The participants were seated, facing a 17-inch CRT screen 250 mm from their eyes with their head restrained by a chin rest and a head band. The monitor was placed with its center at level to the eyes. The target of the reaching movements (5 mm, 1.1 degree, diameter circle superimposed on a 15 × 15 mm, 3.4 × 3.4 degree, cross) was presented at a random location within the target zone (40 mm radius circle, 9.2 degree radius, placed at the center of the screen). Participants were instructed to reach as fast and accurately as possible. Reach end (the position of touch on the screen) was detected by a touch sensor (ERTS1701, sampling frequency 100 Hz, resolution <0.05 mm; EIT, Tokyo, Japan) that covered the surface of the screen. The participants viewed the screen through a refractor, with two motor-driven wedge prisms, one for each eye (Fig. 1*A*). The refractor restricted the view of the screen within the visual field to ±30°. The refractor was designed to achieve a desired displacement of 0–30 diopter (D) (0–16.7°) in any direction by adjusting the angles of two 15-D wedge prisms with a command from a computer (Precision 370; Dell). The same prismatic deviation was applied to both eyes.

Liquid crystal shutters (PLATO; Translucent Technologies) were placed between the prisms and the eyes of the participants. The shutters opened at initiation of each trial, at which time a target (5-mm-diameter circle superimposed on a 15 × 15 mm cross) was presented at a random location (uniformly sampled from a circle of 40 mm radius, centered on the screen). At trial onset the participant's right index finger rested on a button positioned 300 mm below and 70 mm ahead of the subject's eyes in the midsagittal plane. Reach onset was detected when the finger lifted off the button. Reach end was detected when the finger touched the screen. The shutters closed at the release of the button (start of the reach) and then reopened at the touch of the screen (detected with a touch sensor). The shutters remained open for 300 ms, allowing the participants to see the final hand position with respect to the target (visual feedback was not available for some trials, termed VF− protocol, Fig. 1*A*). The participants were required to hold the final finger position for 1 s, after which a beep sounded, instructing them to return their finger to the starting position.

In summary, on any given trial the target position was selected at random. As the reach began, the shutters were closed, and visual feedback was removed. When the reach ended, the shutters opened for 300 ms, but the subjects were instructed to maintain finger position for 1 s, after which they heard a beep and returned their hand to the start location, thus preventing any form of within-trial error-correction.

To allow visual feedback of endpoint error, the shutters were kept open for 300 ms. We chose this period because an earlier set of experiments in healthy people (Kitazawa et al. 1995) had found that, as the shutter-opening period increased from 20 to 12,000 ms, there were no differences in the asymptotic error, as measured by the size of the aftereffect. However, as the shutter-opening period increased from 20 to 200 ms, the rate of learning increased, but then reached a plateau for shutter-opening periods that were longer than 200 ms. Therefore, we designed the current experiment based on these empirical data, allowing for the shutter glasses to remain open for 300 ms to allow exposure to the reach error.

The experiment consisted of two sessions, with each session composed of three periods (Figs. 1*A* and 2). In each session there were two set breaks (Fig. 2, subplot on *top*). In the preexposure period (30 trials), the participant performed the reach with the prisms set to zero displacement. During the middle 10 trials of the preexposure period (from the 11th to the 20th trial), the shutters were kept closed even after the touch until the participants returned their finger to the starting position, which resulted in a short block during which no visual feedback regarding consequences of motor commands was available (VF− protocol). There was a set break (2.0 ± 1.5 min duration, mean ± SD) following the completion of the preexposure trials.

In the exposure block, the prisms displaced the visual field. Each participant was tested in two separate sessions, one within a gradual exposure protocol, and the other in an abrupt exposure protocol. In the abrupt protocol (Fig. 2*A*, plot on *top*), the participants performed 50 trials under visual displacement to the right or to the left by 43 mm in the horizontal direction (17 D, 9.8°). In the gradual protocol (Fig. 2*B*, plot on *top*), visual displacement was gradually increased from 0 to 43 mm (17 D) in 90 trials (from the 1st to the 90th trial), by a step of 17/90 D for each trial. In the last 10 trials of the exposure period (from the 91th to the 100th trial), visual displacement was kept constant at 43 mm.

The schedule of perturbations and the duration of the gradual protocol (exposure period) were set so that the integral of the perturbation over the block of trials was comparable to the integral of perturbation in the abrupt protocol: in the abrupt protocol, the integral of the perturbation was 43 mm × 50 trials = 2,150 mm/trial during the exposure block. In the gradual protocol, the integral of the perturbation was 43 × (90/2 + 10) = 2,365 mm/trial. The exposure lengths were designed in this way because earlier work had suggested that the size of aftereffects (in healthy individuals) depended on the cumulative exposure to the visual shift, irrespective of whether the displacement was introduced abruptly or gradually (Uchimura et al. 2011).

Table 1. *Patient characteristics*

	Age, yr	Gender	Diagnosis	ICARS	Disease Duration
	43	M	SCA6	9	4
	49	F	SCA6	20	5
	66	F	SCA6	51	27
	59	M	SCA6	55	5
	66	M	SCA6	66	16
	44	M	SCA31	5	3
	75	F	SCA31	71	23
	69	M	SCA31	72	7
	67	M	SCA31	75	7
	72	F	SCA31	46	3
	67	M	Sporadic	41	2
	66	F	Sporadic	69	39
	74	F	Not tested	29	5
Mean	62.8			46.8	11.2
SD	10.9			24.5	11.6

M, male; F, female; ICARS, International Cooperative Atexia Rating Scale; SCA, spinocerebellar ataxia.

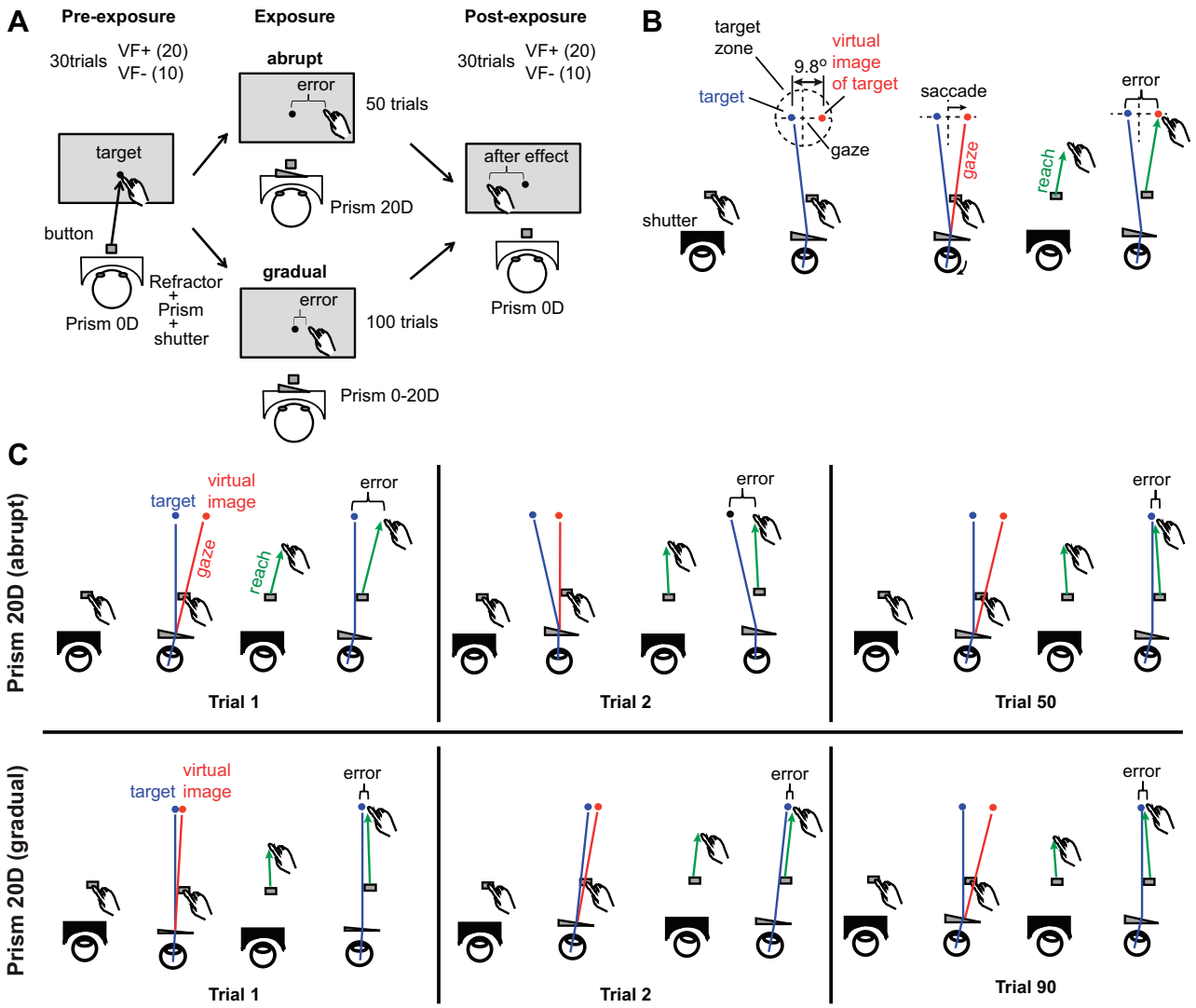

Fig. 1. Experimental protocol. *A*: one session consisted of three periods: preexposure (30 trials), exposure (50 or 100 trials), and postexposure (30 trials). A visual target appeared at random locations on a screen. Participants viewed the target through a refractor and reached for it by lifting their finger from a button and touching the screen. The views of the hand and the target were blocked during the reach by a pair of liquid crystal shutters that closed after the finger lifted off the button. On some trials, the shutters were reopened for 300 ms when the participants touched the screen (visual feedback on, VF+). On the other trial, the shutters remained closed even after the touch (visual feedback off, VF−). The refractor was equipped with two pairs of computer-controlled motor-driven wedge prisms, one pair for each eye. The prisms were rotated for a fixed period after each trial, to prevent the participants from judging whether the visual displacement was introduced or not from the sound of the motors. During the preexposure period, the prisms were positioned so that no visual displacement was introduced [0 diopter (D)]. During the exposure period, the displacement was fixed to 17 D in the abrupt protocol (50 trials, panel on *top*), or gradually increased from 0 to 17 D in 90 trials and continued for another 10 trials in a gradual protocol (panel on *bottom*). During the postexposure period, the visual displacement was set to 0 D again. *B*: the sequence of events that takes place during a single trial. As the trial begins the gaze is directed straight ahead. When the shutter opens, the light traveling from the target to the fovea (blue line) is distorted by the prisms. The distortion of the light makes the target appear in the location noted by the red dot (virtual image of target). To bring the virtual image of the target on the fovea, the subject makes a saccade to the right. The red line indicates the direction of gaze. In the naïve condition, the reach (green arrow) is in the same direction as the gaze. This results in endpoint error. *C*: the sequence of events that takes place during abrupt and gradual training protocols. At start of training, the reach and gaze angles are colinear. With training, the subject learns to rotate the angle of reach with respect to the angle of gaze, compensating for the distortion caused by the prisms.

There was a set break (12.4 ± 17 s duration, mean ± SD) following the completion of the exposure trials. Participants were not informed of the set break, but just waited for the shutter to open while holding their finger on the starting button. The set break was just a few seconds longer than the mean intertrial interval during the exposure block. In this way, the break was equivalent to a longer than usual intertrial interval.

In the postexposure period (30 trials), the participant performed the task without visual displacement, resulting in reach errors that were considered aftereffects of adaptation. Visual feedback regarding consequences of the motor commands was not provided during the initial 10 trials of the postexposure period (VF−), but allowed in 20 trials thereafter (VF+).

Participants were randomly assigned to experience a rightward or a leftward visual field displacement. They experienced the same displacement in both the gradual and abrupt sessions. However, the first session was randomly assigned to be gradual or abrupt.

Data analysis. The mean horizontal reach error during the preexposure period across both sessions was regarded as a bias and was subtracted from the horizontal reach errors obtained during the exposure and postexposure periods. The resulting bias-free horizontal errors were then used for estimating the error during the exposure

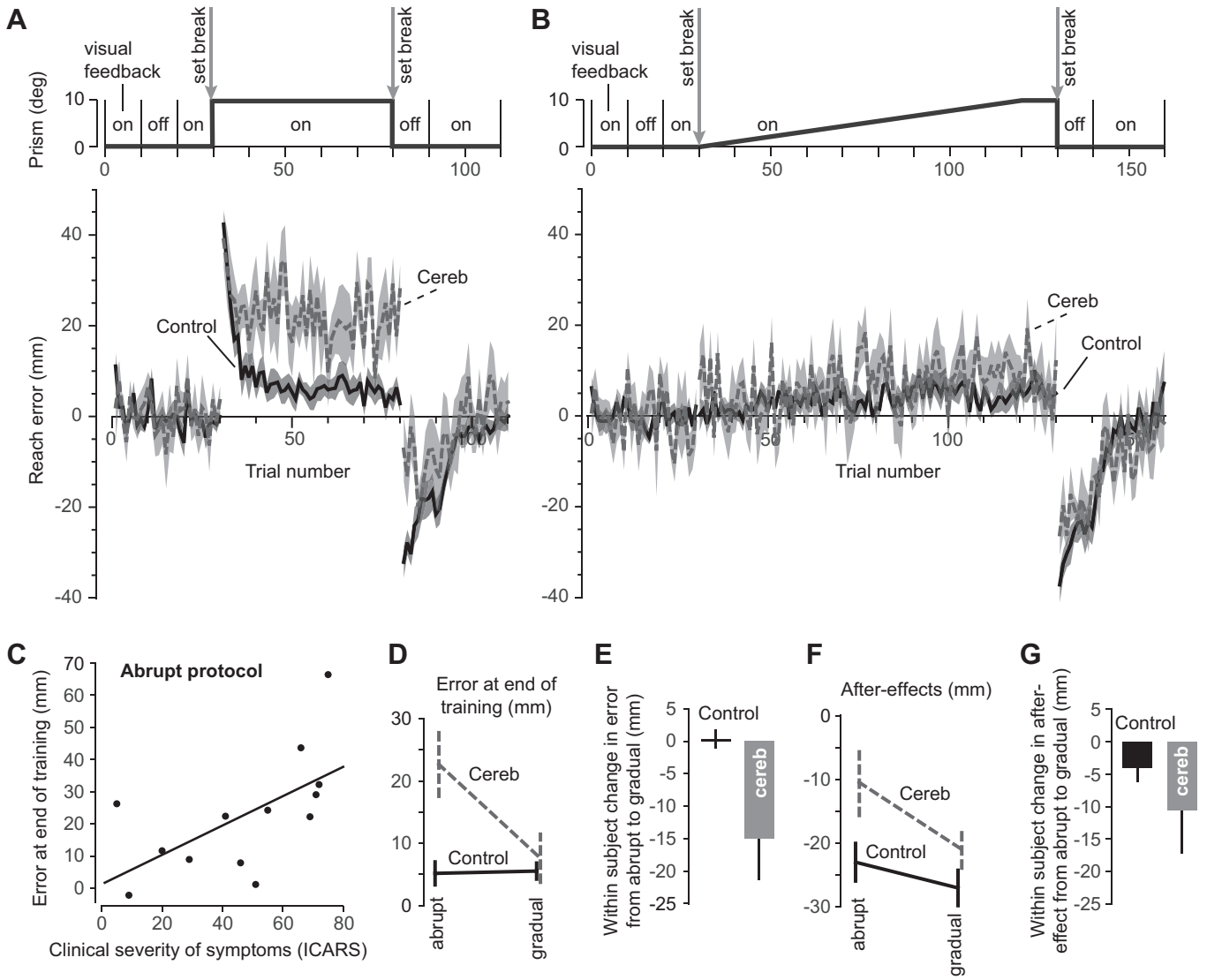

Fig. 2. Performance in the abrupt and gradual protocols. *A*: abrupt protocol. *Top*, prism-induced displacement schedule and the visual feedback schedule. *Bottom*, endpoint errors for the two groups of subjects. *B*: gradual protocol. The format is similar to *A*. Data are means ± SE. *C*: reach errors in the final 10 trials of the exposure period during the abrupt protocol for each subject in the cerebellar group are shown as a function of that subject's severity of symptoms [International Cooperative Ataxia Rating Scale (ICARS) score]. The correlation is significant ($P = 0.029$, $R = 0.60$). *D*: reach errors in the final 10 trials of the exposure period for each group in each protocol. *E*: within-subject change in the reach errors (final 10 trials of the exposure block) from the abrupt to the gradual protocol. Data are means ± SE. *F*: aftereffects, measured by the errors in the first 10 trials of the postexposure period, during which no visual feedback was available. *G*: within-subject change in the aftereffects from the abrupt to the gradual protocol (first 10 trials). Data are means ± SE.

period, and the size of the aftereffect in the postexposure period. The vertical component of the error was not analyzed because the visual displacement was applied in the horizontal direction, to the right or to the left.

We defined the asymptotic error during the exposure period as the average of errors in the last 10 trials (during these 10 trials the perturbation was the same in both the gradual and abrupt protocols). The asymptotic error was considered to reflect limitation in adaptation: a large asymptotic error remained when adaptation was impaired.

The aftereffects and the asymptotic errors were compared between the two groups, in the two protocols. For this comparison we used a 2×2 repeated-measures ANOVA, where we had two protocols (abrupt and gradual) and two groups of subjects (cerebellar and healthy). We followed up this omnibus statistic with a within-group post hoc analysis using *t*-tests.

Endpoint errors that were >90 mm were labeled as outlier and removed from analysis. This represented 25 out of 7,020 data points (<0.5% of the data), and was chosen because it represented two times the size of the perturbation.

To elucidate correlation between clinical symptoms and parameters of the prism adaptation, we performed correlation analysis between ICARS and parameters of the prism adaptation, namely the aftereffect and the asymptotic error in each protocol. All statistical analyses were conducted using R and Mathematica. Nonparametric comparisons were made using Wilcoxon signed-rank test when *t*-tests could not be used as the data violated assumptions of normality.

Estimating error-sensitivity and forgetting. Short passage of time produces forgetting in the memory that has been acquired during adaptation (Criscimagna-Hemminger and Shadmehr 2008). To measure this time-induced forgetting, we considered the reach errors at the end of the exposure period (final 2 trials) and the reach errors following the set break in the postexposure period (first 2 trials). If $r^{(n-1)}$ is the prism-induced perturbation for trial $n-1$, and $e^{(n-1)}$ is the reach error in that trial, then the forgetting due

to the set break can be estimated by the following expression $\{[r^{(n)} - e^{(n)}]/[r^{(n-1)} - e^{(n-1)}]\}$.

To quantify trial-by-trial learning from error, we analyzed the data using a state-space model of motor adaptation (Ethier et al. 2008; Smith et al. 2006). In this model, on trial n the participant is presented with a visual target at location $t^{(n)}$. Because of the effects of the prism, this location is perceived to be at $t^{(n)} + r^{(n)}$, as illustrated in Fig. 1, *B* and *C*. The subject produces a movement that results in the reach endpoint $u^{(n)}$. We measure the reach endpoint $u^{(n)}$ via the position of the finger on the touchscreen. If visual feedback is available, the participant observes the visual sensory consequence $y^{(n)}$, which is perturbed by the prisms by amount $r^{(n)}$:

$$y^{(n)} = u^{(n)} + r^{(n)} \quad (1)$$

The participant's motor command depends on the perceived location of the target, and his/her estimate of the perturbation, labeled as $x^{(n)}$. In addition, this command is corrupted by noise ε.

$$u^{(n)} = t^{(n)} + r^{(n)} - x^{(n)} + \varepsilon \quad (2)$$

If we assume that on each trial the subject predicts that the hand will land on target, then the sensory prediction error $e^{(n)}$ is the difference between the observed finger position $y^{(n)}$ and the observed target location $t^{(n)} + r^{(n)}$:

$$e^{(n)} = y^{(n)} - t^{(n)} - r^{(n)} \quad (3)$$

Equation 3 reduces to $e^{(n)} = r^{(n)} - x^{(n)} + \varepsilon$, which demonstrates that reach error on each trial is the expected value of the difference between the perturbation r and the subject's estimate of the perturbation x.

We represented the process of adaptation as trial-by-trial change in the participant's internal state as a function of the sensory prediction error:

$$x^{(n+1)} = ax^{(n)} + be^{(n)} \quad (4)$$

In the above equation a represents trial-to-trial retention, and b represents sensitivity to error. This equation defines a single-state model of adaptation in which the participant updates its estimate of the perturbation by learning from the sensory prediction error (Kitazawa et al. 1995; Kitazawa and Yin 2002; Thoroughman and Shadmehr 2000; Uchimura and Kitazawa 2013).

The complete state-space model consists of *Eqs. 3* and *4*. *Equation 3* is the "measurement" equation, and *Eq. 4* is the state-update equation. The measured variables are $u^{(n)}$ (finger position), $t^{(n)}$ (target position), and $r^{(n)}$ (prism displacement). The states $x^{(n)}$ are unknown. Furthermore, the parameters a (trial-by-trial retention) and b (error-sensitivity) are unknown. We assumed that the motor noise ε was normally distributed with mean zero and variance σ. To estimate σ, we used the variance in the subject's performance on the first 30 trials during which there were no perturbations.

We first focused on estimating the parameter a (trial-to-trial retention). To estimate this parameter, we considered the 10 trials in the postexposure period during which no visual feedback was available, thereby making $e^{(n)} = 0$ for these trials. For these 10 datapoints, we had the following set of equations:

$$x^{(n+1)} = ax^{(n)} \quad (5)$$

In the above equations the measured variables are $u^{(n)}$ and $t^{(n)}$, variance of the noise ε is known from prior measurements (as described above), the hidden states $x^{(n)}$ are unknown, and the objective is to estimate the parameter a. We solved this problem by using expectation maximization, as described in Shadmehr and Mussa-Ivaldi (2012). In this approach, we begin with an arbitrary guess for a, and then use a Kalman filter to estimate the hidden state for each trial from the observed motor commands on that trial. After completion of this step, we use our estimate of hidden states to compute an estimate of a:

$$\hat{a} = \frac{\sum_{n=1}^{N} \hat{x}^{(n)}\hat{x}^{(n+1)}}{\sum_{n=1}^{N} \left(\hat{x}^{(n)}\right)^2} \quad (6)$$

We then repeat these two steps until $\hat{a}$ converged (in our case, around 200 sweeps of the postexposure aftereffect data).

We used a bootstrapping technique, sampling from each population in each protocol at random, with replacement, to acquire a population- and protocol-specific estimate of mean and SD for a. We then used this group- and protocol-specific estimate of a to estimate for each subject in each protocol their subject- and protocol-specific error-sensitivity b.

To estimate the error-sensitivity parameter b, we followed the following procedures (Herzfeld et al. 2014b; Marko et al. 2012). We used *Eqs. 1* and *2* to rewrite *Eq. 3*:

$$e^{(n)} = r^{(n)} - x^{(n)} + \varepsilon^{(n)} \quad (7)$$

We then computed the retention-weighted change in error from one trial to the next:

$$e^{(n+1)} - ae^{(n)} = r^{(n+1)} - ar^{(n)} - \left(x^{(n+1)} - ax^{(n)}\right) + \eta \quad (8)$$

In the above equation, η is a noise variable related to ε. The above equation can be simplified:

$$e^{(n+1)} - ae^{(n)} = \left(r^{(n+1)} - ar^{(n)}\right) - be^{(n)} + \eta \quad (9)$$

By inserting $\hat{a}$ in the above equation, the only unknown parameter is b, which represents error-sensitivity. For each subject in each protocol we measured error $e^{(n)}$ in all exposure and postexposure trials in which visual feedback was available, and then used linear regression (with one parameter to fit in the above equation) to estimate $\hat{b}$. The result was an estimate of error-sensitivity for each subject in each protocol. The term $e^{(n+1)} - ae^{(n)} - [r^{(n+1)} - ar^{(n)}]$ represents learning from error in trial n.

RESULTS

In the preexposure period, the baseline patterns of reaching in the cerebellar group were more variable than the control group. We found that the SD of reach error was significantly larger in the cerebellar group than in healthy volunteers (Mann-Whitney, $P = 0.00033$). Furthermore, the mean reaction time was longer in the cerebellar group (abrupt, 590 ± 200 ms; gradual, 590 ± 190 ms) than the control group (abrupt, 350 ± 94 ms; gradual, 410 ± 150 ms). Movement durations were also longer in the cerebellar group (abrupt, 830 ± 390 ms; gradual, 930 ± 510 ms) than in the control group (abrupt, 390 ± 82 ms; gradual, 410 ± 110 ms).

Prism adaptation. When the prism-induced perturbation was introduced abruptly (Fig. 2*A*), it resulted in large reach errors (first trial, 42.4 ± 3.1 mm in the healthy group and 38.9 ± 6.2 mm in the cerebellar group). These initial errors were similar in the two groups (*t*-test, $P = 0.63$). In healthy volunteers, the errors decreased with trials and returned to near baseline levels. However, in the cerebellar group the errors persisted. To statistically compare performance of the two groups in the abrupt protocol, we binned the data by five trials and performed a repeated-measures ANOVA with cerebellar and control as the between-subject group factor and trial during the exposure period as the within-subject repeated measure. We found a significant effect of group [$F(1,24) = 6.9$, $P = 0.015$], a significant effect of trial [$F(9,216) = 6.3$, $P = 0.012$], and a significant trial by group interaction [$F(9,216) = 3.37$, $P = 0.0007$]. The interaction statistic, coupled with similar starting

point of errors at the onset of the exposure period, indicated that in the abrupt protocol the cerebellar group was impaired in their ability to adapt their motor commands to the imposed perturbation. Indeed, the severity of the clinical symptoms correlated with the size of the errors at the end of the exposure period [last 10 trials, $F(1,11) = 6.32$, $P = 0.029$, $R = 0.60$, Fig. 2*C*].

In contrast, when the prism was introduced gradually (Fig. 2*B*), by the end of the exposure period (final 10 trials) the errors in the two groups appeared comparable. A repeated-measures ANOVA with cerebellar vs. control as the group effect, and trial as the within-subject repeated measure, produced no significant effect of group [$F(1,24) = 0.41$], no significant effect of trial [$F(19,456) = 2.43$], and no significant trial by group interaction [$F(19,456) = 0.95$, $P = 0.52$]. Furthermore, the severity of the clinical symptoms no longer correlated with the size of errors at the end of the exposure period [last 10 trials, $F(1,11) = 0.51$, $P = 0.49$, $R = -0.21$]. Therefore, whereas the performance of the cerebellar participants was impaired in the abrupt protocol, their performance in the gradual protocol appeared similar to controls.

To directly compare the performances of each participant in the two perturbation protocols we performed a two-way repeated-measures ANOVA. In this test we had cerebellar and control groups as the between-subject factor, and protocol (gradual and abrupt) as the within-subject factor, with the outcome measure being the reach error during the last 10 trials of exposure (the trials for which the perturbation was the same in the two protocols). The data that were submitted to this test are shown in Fig. 2*D*. We found a significant effect of group [$F(1,12) = 7.59$, $P = 0.017$], a significant effect of protocol [$F(1,12) = 4.97$, $P = 0.045$], and a significant group by protocol interaction [$F(1,12) = 6.97$, $P = 0.021$]. The group effect suggested that, in general, the cerebellar subjects had larger errors compared with control. The protocol effect suggested that, in general, at the end of the gradual protocol the errors were smaller than in the end of the abrupt protocol. However, the critical statistic is the interaction, which suggested that the cerebellar group preferentially benefited from the gradual protocol.

To explore this result further, we compared the within-subject change in errors from the abrupt to the gradual protocol (final 10 trials of exposure). The results are shown in Fig. 2*E*. We found a significant difference between groups (Mann-Whitney, $P = 0.0048$), with the cerebellar group showing a larger reduction in endpoint errors from abrupt to gradual compared with the control group. Indeed, we found that in the cerebellar group 11 out of the 13 participants had a smaller error in the gradual protocol compared with the abrupt protocol (signed-rank test, change in error from the last 10 trials in the abrupt to gradual, $P = 0.012$). In comparison, in the control group 6 out of 13 participants had a smaller error in the gradual protocol (signed-rank test, change in error from the last 10 trials in the abrupt to gradual, $P = 0.944$). In the control group, the asymptotic errors were similar in the two protocols, whereas for the cerebellar group, these errors were significantly smaller in the gradual protocol.

In summary, whereas in the abrupt protocol the cerebellar group was impaired in their ability to adapt their motor commands, in the gradual protocol the performance of this group significantly improved, exhibiting levels of performance that were not different from control. A within-subject analysis revealed that at the end of the exposure period in the gradual protocol the cerebellar subjects produced significantly smaller errors than in the abrupt protocol, suggesting that the cerebellar group benefited from the gradual schedule of perturbations.

Aftereffects. Following the exposure block the perturbation introduced by the prisms was removed, and we measured the resulting aftereffects. In the first 10 trials of this postexposure block the visual feedback that subjects would normally receive at the completion of their reach was withheld. This allowed us to measure the resulting aftereffects while preventing the learning that would usually take place following the visual feedback associated with the aftereffects. To compare the aftereffects in the two groups, we began with the abrupt protocol and performed a repeated-measures ANOVA that focused on the first 10 trials of the postexposure block (bin size of 5 trials, Fig. 2*A*). We found a significant effect of group [$F(1,24) = 4.48$, $P = 0.04$]. This result implied that, following the abrupt protocol, the cerebellar group exhibited smaller than normal aftereffects.

We next compared the aftereffects of the two groups in the gradual protocol. We applied a repeated-measures ANOVA that again focused on the first 10 trials of the postexposure block (bin size of 5 trials, Fig. 2*B*). In contrast to the abrupt protocol, we now found no effect of group [$F(1,24) = 0.33$, $P = 0.57$], suggesting that in the gradual protocol the aftereffects in the cerebellar group were comparable to normal.

To compare the aftereffects for each subject in the two perturbation protocols, we performed a two-way repeated-measures ANOVA. In this test we had cerebellar and control groups as the between-subject factor, and protocol (gradual and abrupt) as the within-subject factor, with the outcome measure being the aftereffects during the first 10 trials of postexposure. The data that were submitted to this test are shown in Fig. 2*F*. We found a significant effect of group [$F(1,12) = 5.40$, $P = 0.038$], and a marginal effect of protocol [$F(1,12) = 4.26$, $P = 0.061$]. The main effect of group implied that the aftereffects in general were larger in the control group. The main effect of protocol implied that the protocol had a marginal effect on the aftereffects. To quantify this effect further, we measured the within-subject change in the aftereffects from the abrupt to the gradual protocol (Fig. 2*G*) and found that in both groups the aftereffects were generally larger following the gradual protocol. In particular, for the cerebellar group the aftereffects early in the postexposure block were larger in the gradual protocol [first 3 postexposure blocks, within-subject comparison of abrupt and gradual, paired t-test, $t(12) = 2.4$, $P = 0.033$].

In summary, the aftereffects were smaller than normal in the cerebellar group following the abrupt protocol, but were not different from normal following the gradual protocol. The gradual protocol coincided with a significant increase in the size of aftereffects in the cerebellar group of participants.

Retention after passage of time. We considered two possible mechanisms with which the cerebellar patients may have improved their ability to adapt to the perturbations. One mechanism was via improved trial-to-trial retention (maintaining more of the memory that was acquired from one trial to the next). Another mechanism was via improved sensitivity to error (learning more from the error that was experienced). We performed a set of analyses to ask which of these two mech-

anisms may have been responsible for the changes in performance that we had observed in the gradual protocol.

There was a set break (12.4 ± 17 s duration, mean ± SD) following the completion of the exposure trials. This passage of time allowed us to ask what fraction of the memory that had been acquired during the exposure period was expressed following the set break. The duration of the set break was not different in the two groups (9.5 ± 5.7 s in the control group, 15.3 ± 23 s in the cerebellar group; Mann-Whitney, $P = 0.49$). The duration of the set break was also not different in the two protocols (within-subject comparison of the set break durations in each protocol, $P = 0.22$ in the control group, $P = 0.15$ in the cerebellar group). We estimated the fraction of the acquired memory that was expressed following the set break by computing the within-subject ratio of the aftereffects in the first two trials of the postexposure period to the errors in the last two trials of the exposure period (see METHODS). The results are shown in Fig. 3*A*. We found ~80% retention in both groups of participants following the abrupt protocol, and a trend toward better retention in the control group following the gradual protocol. However, statistical analysis did not reveal a significant difference between groups or protocols (2-way repeated-measures ANOVA, no main effects or interactions). Therefore, about 80% of the memory that had been acquired during exposure was expressed following a brief passage of time in the subsequent aftereffects. This fraction was comparable between the two groups, and not different in the two protocols.

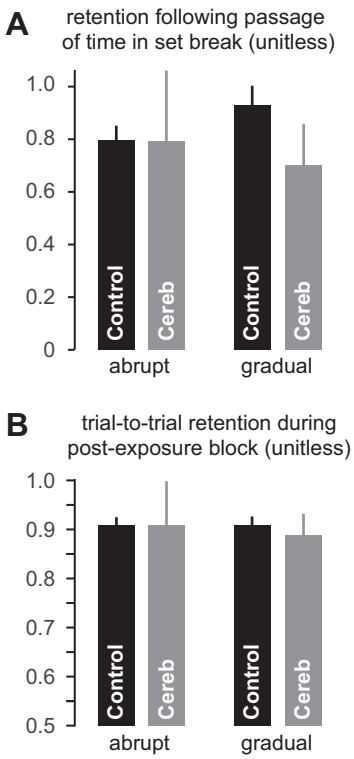

Fig. 3. Measures of retention of motor memory in the two protocols. *A*: percentage of memory retained following passage of time in the set break between the exposure and postexposure blocks. The plot shows the within-subject ratio of the aftereffects in the first 2 trials of the postexposure period to the errors in the last 2 trials of the exposure period (see METHODS). *B*: trial-to-trial retention parameter a (*Eq. 5*), as estimated by analysis of the first 10 trials in the postexposure period during which no visual feedback was provided.

Learning from error. To better understand why the cerebellar group learned better in the gradual protocol (as evidenced by the smaller errors at the end of exposure block), we quantified learning from error on a trial-by-trial basis for each subject. For this analysis we considered the error in each trial $e^{(n)}$, and the change in motor command $u^{(n)}$ (finger position on the screen) from that trial to the next. This allowed us to estimate parameter a, representing trial-to-trial retention, and parameter b, representing sensitivity to error (*Eq. 4*).

To estimate the trial-to-trial retention parameter a, we focused on the first 10 trials in the postexposure period during which no visual feedback was provided. This was critical, since it allowed us to eliminate the effects of parameter b from the state-space model (*Eq. 5*). The results, displayed in Fig. 3*B*, suggested that trial-to-trial retention was not different between groups, and was reproducible across the protocols. This was an independent confirmation of our earlier results (Fig. 3*A*) in which we had found that retention, as measured during passage of time during the set break, was comparable in the two groups.

We next measured the distribution of errors during the exposure period for each subject in each protocol. The resulting probabilities are shown in Fig. 4, *A* and *B*. As expected, the error distribution had a smaller mean in the gradual protocol (because the mean perturbation as measured over all trials was smaller in the gradual protocol). However, the critical question was whether learning from error was different.

For each subject in each protocol we measured error in each trial, $e^{(n)}$, and then computed learning that resulted from that error. To compute learning from error, we used *Eq. 9* to estimate $be^{(n)}$ via the quantity $e^{(n+1)} - ae^{(n)} - [r^{(n+1)} - ar^{(n)}]$. We used the group- and protocol-specific estimate of $\hat{a}$, focusing on the data during the exposure period, as well as during the postexposure periods for trials in which error feedback was provided (that is, VF+ trials). We have plotted learning from error as a function of error for two representative subjects in Fig. 4*C*. The slope of the resulting single-parameter line is an estimate of error-sensitivity, i.e., $\hat{b}$ (fit statistics: control subject, abrupt, $P < 0.0001$; gradual, $P < 0.0001$ and cerebellar subject, abrupt, $P = 0.022$; gradual, $P < 0.0001$). Next, in each protocol we computed the pair [error, learning from error] for all perturbation trials in all subjects and fitted a single-parameter line to the resulting data, as shown in Fig. 4*D*. Once again the fit statistics were highly significant (in all cases $P < 10^{-5}$). The slope of the data appeared larger in the gradual protocol than in the abrupt protocol for both groups of subjects. To improve visualization of the data, we binned the error space for each subject and then computed an across-subject mean and SE statistic on the pair [error, learning from error]. The results are shown in Fig. 3*E*, which hinted that error-sensitivity had increased from the abrupt to the gradual protocol.

We proceeded to quantify error-sensitivity $\hat{b}$ for each subject in each protocol. To do so, we computed the error and learning-from-error data for each trial and then fitted the resulting data for each subject to *Eq. 9*. In the gradual protocol, the fit was significant for all subjects at $P < 0.001$. This implies that $\hat{b}$ was significantly different from zero in all control and cerebellar subjects in the gradual protocol. In the abrupt protocol, the fit was significant for all but one control subject at $P < 0.05$. In the abrupt condition, the fit was not significant for seven cerebellar subjects, implying that $\hat{b}$ was not significantly dif-

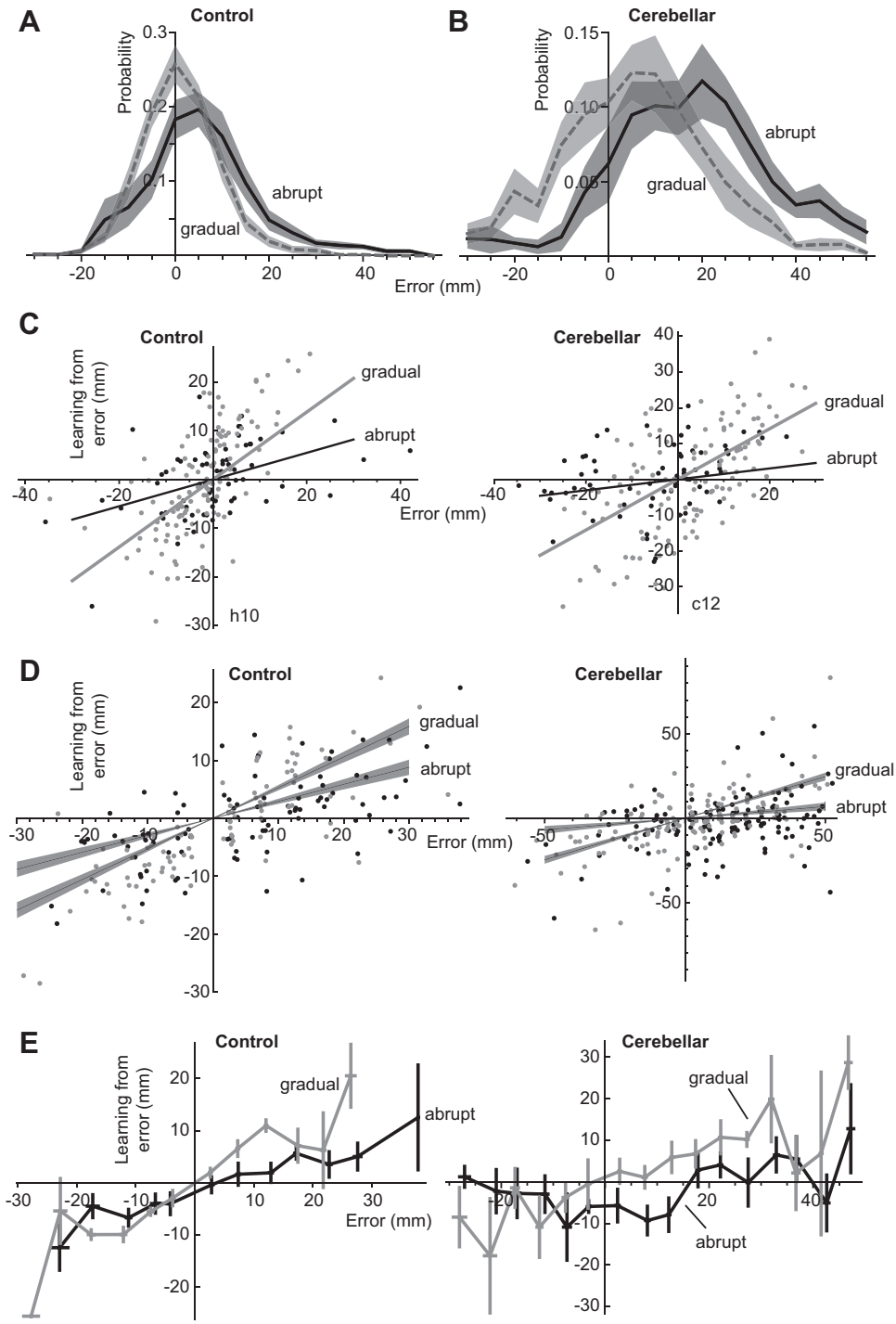

Fig. 4. Measures of error, and learning from error, in the two protocols. *A* and *B*: distribution of errors experienced in the exposure block in the control and cerebellar groups. *C*: error and learning from error for each VF+ trial in the exposure and postexposure blocks in two representative subjects. A single-parameter line was fitted to each dataset (fit was significant at $P < 0.0001$ for all conditions except cerebellar abrupt, in which case $P = 0.022$). The slope of each line is error-sensitivity $\hat{b}$. *D*: data for all VF+ trials in the exposure and postexposure blocks in all subjects in each protocol were fitted to a single-parameter line (fit was significant at $P < 0.0001$ for all conditions). The ±95% confidence regarding the slope parameter is plotted at the gray region around the line. For ease of display, the data for each subject were binned in bins of 5-mm error size and are displayed as a single dot for each bin. *E*: for each subject, the errors experienced in each VF+ trial, and the corresponding learning from error (exposure and postexposure blocks), were averaged in error bins of 5 mm to form within-group distribution of error and learning from error. Error bars are SE.

ferent from zero for these subjects in the abrupt protocol. This later result is consistent with the observation that cerebellar subjects in general had difficulty learning from error in the abrupt condition. The resulting distribution of sensitivity to error term $\hat{b}$ is shown in Fig. 5*A*. A repeated-measures ANOVA with protocol-type as the repeated measure (abrupt and gradual), with the outcome measure of error-sensitivity $\hat{b}$, produced a significant main effect of group [$F(1,24)=7.07$, $P = 0.014$], and a significant main effect of protocol [$F(1,24) = 60.1$, $P < 0.0001$], but no significant interaction. The significant main effect of group indicates that the cerebellar group exhibited a lower error-sensitivity than the control group. The main effect of protocol indicates that both groups exhibited increased error-sensitivity in the gradual protocol. The within-subject change in error-sensitivity from the abrupt to the gradual protocol is summarized in Fig. 5*B*. The amount of increase in error-sensitivity from abrupt to gradual was significant in each group (control, $t = 7.6$, $P < 10^{-5}$; cerebellar, $t = 4.0$, $P = 0.0018$), and not different between the two groups ($t = 1.42$, $P = 0.17$). The amount of increase in error-sensitivity in the cerebellar group did not correlate with severity of the symptoms [$F(1,11) = 0.02$, $P = 0.89$].

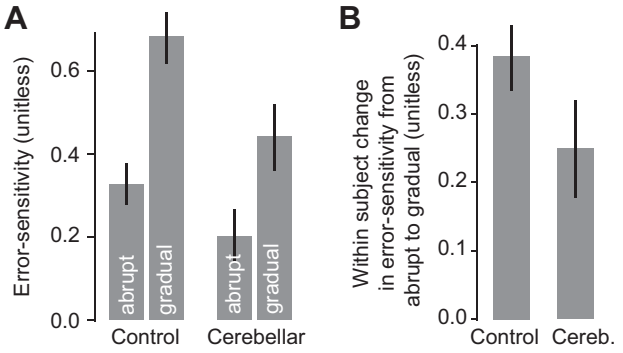

Fig. 5. For each subject, the errors experienced in each trial, and the corresponding learning from error, were fitted to a single parameter linear function. The slope of this linear function is error-sensitivity parameter $\hat{b}$. *A*: distribution of error-sensitivity in each group and each protocol (mean ± SE). *B*: within-subject change in error-sensitivity from the abrupt to the gradual protocol. Data are means ± SE.

In summary, trial-by-trial analysis suggested that the gradual protocol produced an increase in the amount that subjects learned from error, enhancing error-sensitivity in both groups of participants.

A recent theory provides a potential mechanism with which the brain may modulate error-sensitivity (Herzfeld et al. 2014b). In that theory, repetition of similar errors produces an increase in error-sensitivity. This theory explains that, in the gradual condition, the increased error-sensitivity is due to the repeated and extended exposure to the same errors (note that there are two times as many trials in the gradual protocol compared with the abrupt protocol). It also predicts that, even in the abrupt condition, error-sensitivity should be somewhat higher near the end of training compared with early training. We tested this idea in the control group in the abrupt condition by computing error-sensitivity during early trials (*trials 10-30* of the exposure period) and during late trials (*trials 30-50* of the exposure period). We found an increase in error-sensitivity from early to late (9 out of 13 subjects showed an increase, mean within-subject change 0.0288 ± -0.042), but this change did not reach significance.

Confounding variables. The participants experienced the same perturbation on two separate sessions. While we randomized the order of the perturbation protocols (abrupt and gradual), we wondered whether the second experience of the perturbation affected performance.

A within-subject comparison of the endpoint errors (final 10 trials) from the first and second sessions found no significant changes in the control group (*t*-test, $P = 0.22$), and no significant changes in the cerebellar group (signed-rank test, $P = 0.58$). This implied that if the protocols were masked, then simply performing the task for a second time produced no detectable changes in errors as measured at the end of the exposure period. Similarly, a within-subject comparison of the aftereffects (first 10 trials) from the first and second sessions found no significant change in the control group (*t*-test, $P = 0.3$), and no significant change in the cerebellar group (signed-rank test, $P = 0.78$). Finally, we performed a within-subject comparison of error-sensitivity parameter *b*. We found a slight decrease in this parameter from *session 1* to *session 2* (i.e., less learning from error on *session 2*), although this change was not significant (cerebellar group, paired *t*-test, $P = 0.62$; control group, paired *t*-test, $P = 0.17$).

Our measure of retention following passage of time in the set break used the average of the first two trials in the postexposure period. This has the advantage of reducing the effects of noise, but the disadvantage of underestimating retention because of the effects of trial-to-trial decay in the postexposure period. An independent method that can check our results is to compare the value of retention estimated via trial-by-trial analysis (Fig. 3*B*) with the value estimated from the passage of time (Fig. 3*A*). The set break was approximately two times as long as the time between two consecutive trials (12.4 ± 17.2 vs. 5.4 ± 1.5 s, mean ± SD). Therefore, we would expect that the passage of time estimate of retention to be approximately equal to the loss that is accumulated following two consecutive trials in the postexposure period. This is remarkably consistent with what we found: data in Fig. 3*B* are approximately the square root of the data in Fig. 3*A*, despite the fact that the two groups of estimates were derived from very different methods of analysis.

DISCUSSION

We measured performance of people with cerebellar ataxia in a reaching task in which they viewed the target and the visual consequences of their motor commands through computer-controlled prism glasses. As they reached to the target, we employed shutter glasses to prevent visual feedback, eliminating the within-movement visually triggered correction. Therefore, the prism glasses allowed us to control the magnitude of the perturbation on each trial over a continuous range, and the shutter glasses allowed us to measure learning from error on each trial.

We found that, when the perturbation was imposed abruptly, the cerebellar group was impaired in their ability to learn from the resulting errors. They showed greater than normal errors at the end of the exposure block, and smaller than normal aftereffects in the postexposure block. This impairment correlated with severity of clinical symptoms. When the perturbation was imposed gradually, their performance improved significantly and approached that of healthy controls, resulting in a reduction in the reach errors during the exposure block, and an increase in the aftereffects during the postexposure block.

Using a state-space model of adaptation we performed a trial-by-trial analysis of behavior, estimating learning from error, as well as retention due to passage of time and trial. We found that, whereas retention due to passage of time or trial was not different in the two groups, and was not affected by protocol, error-sensitivity was increased from the abrupt to the gradual protocol, as measured via the slope of the relationship between error, and trial-to-trial learning from error. Thus, our work has produced the following results: *1*) in a classic prism-adaptation paradigm for which cerebellar damage is known to produce profound impairments, we find that gradual imposition of the perturbation leads to improved performance, and *2*) this improved performance is due to upregulation of error-sensitivity, i.e., how much the brain learns from a given error.

Effect of gradual and abrupt protocols. The impairments that we observed in the abrupt protocol reproduced results of a number of previous prism adaptation studies (Martin et al. 1996; Milder and Reinecke 1983; Weiner et al. 1983). Although lesions in these previous studies were not necessarily

restricted to the cerebellum, all patients studied here had pure cerebellar type deficits with little involvement of other systems: SCA6 is characterized mainly by degeneration of Purkinje cell in the superior parts of the vermis and hemispheres (Ishikawa et al. 1999; Sasaki et al. 1998; Takahashi et al. 1998), and SCA31 also results mainly in degeneration of Purkinje cells (Niimi et al. 2013; Seidel et al. 2012), although regions other than the cerebellar cortex may also be affected in SCA6 or SCA31 (Seidel et al. 2012; Wang et al. 2010). The present results expand previous findings by suggesting that Purkinje cell dysfunction leads to impairments in prism adaptation in humans. The results also agree with nonhuman studies that reported impairments in prism adaptation in response to abrupt introduction of visual displacement after lesions in the cerebellar cortex (Baizer et al. 1999; Norris et al. 2011).

Our critical observation was that performance of the patients benefited from the gradual protocol. This conclusion was based on two separate measures, errors at the end of the exposure block and aftereffects at the start of the postexposure block. Our finding are consistent with an earlier study that used force-field perturbation tasks and found that performance of the cerebellar patients was impaired in the abrupt protocol, but less affected in the gradual protocol (Criscimagna-Hemminger et al. 2010). Our results, however, stand in contrast to a study that found similar impairments in the gradual and abrupt protocols in a visuomotor rotation task (Schlerf et al. 2012). Gibo et al. (2013) observed improvements in the gradual protocol, but only for some directions of reaching.

An important difference between our study and most previous studies that have compared abrupt and gradual protocols is that we used a technique (shutter glasses) to prevent within-movement correction due to sensory feedback. This may be critically important, since movement trajectory is affected both by the ability of the nervous system to learn from errors that were observed in the previous trials, termed trial-to-trial learning, and respond to errors that are sensed in the current trial, termed within-trial response to error (Ahmadi-Pajouh et al. 2012; Franklin et al. 2007; Kimura et al. 2006; Kimura and Gomi 2009; Wong et al. 2009). Some studies suggest that the human motor cortex may play an important role in learning to modulate the within-trial response to error (Kimura et al. 2006), although disruption of the human cerebellum also reduces the gain of this feedback pathway (Herzfeld et al. 2014a). Here, by eliminating this within-trial feedback, we were able to precisely measure learning from error on each trial. In our sample of patients we found impairments in the abrupt protocol, but significant improvements in the gradual protocol.

Difference between the gradual and abrupt protocols. In a visuomotor reach adaptation paradigm, there are changes in the excitability of the human cerebellum during an abrupt protocol, but these changes are smaller in the gradual protocol (Schlerf et al. 2012). Disruption of the human motor cortex impairs adaptation in the force field paradigm during an abrupt protocol, but the same disruption appears to spare adaptation during a gradual protocol in force fields (Orban de Xivry et al. 2011) and visuomotor rotations (Hadipour-Niktarash et al. 2007). The state of the human motor cortex and the corticospinal network, as measured by motor-evoked potentials, changes during adaptation in a force field paradigm with an abrupt protocol, but not with a gradual protocol (Orban de Xivry et al. 2013). These results do not, at present, describe a clear picture of what roles the cerebellum and the motor cortex may play in learning to compensate for perturbations during abrupt and gradual protocols. However, it is clear that the neural systems that are engaged during adaptation in the abrupt protocol differ from those engaged in the gradual protocols.

A recent report demonstrated that the history of past errors affects how much the brain learns from error: if the recent history includes errors that are correlated in time, error-sensitivity is upregulated, resulting in greater learning (Herzfeld et al. 2014b). Our results here suggest that the gradual protocol tends to upregulate error-sensitivity.

There are often oculomotor deficits in patients with cerebellar damage that affect their ability to saccade to a target (Barash et al. 1999; Xu-Wilson et al. 2009). In the task that we examined, could oculomotor deficits play a role in the differential performance in the abrupt and gradual protocols? At trial onset we presented a target at a randomly selected location. This ensured that at trial onset saccade requirements did not differ between the two protocols. When the hand touched the screen, signaling end of the reaching movement, we opened the shutters and allowed visual feedback. We assumed that this visual feedback (distance of the finger from the fovea) would serve as an error signal. However, soon after opening of the shutter subjects may saccade to place the image of their finger on the fovea. This saccade would necessarily be larger when the prism-induced perturbations were large (abrupt protocol), that is, at end of the reaching movement saccades were likely a function of error size, which was smaller in the gradual condition. There is some evidence that learning is not only a function of the error itself, but is also affected by the corrective saccade that is generated in response to the error (Wallman and Fuchs 1998). Therefore, if cerebellar patients were impaired in making corrective saccades, this may have partly contributed to their reduced learning from error in the abrupt condition.

Neural basis of control of error-sensitivity. Errors that are deemed to be costly produce greater learning than errors that are deemed less costly (Trent and Ahmed 2013). From a theoretical perspective, one way with which modulation of error-sensitivity may take place is via probability of complex spikes (Marko et al. 2012). The complex spikes encode error (Kitazawa et al. 1998), and drive cerebellar learning (Gilbert and Thach 1977; Ito 2001; Kobayashi et al. 1998; Medina and Lisberger 2008). The complex spikes are produced by inputs to Purkinje cells from the inferior olive. We speculate that error-sensitivity during adaptation may be controlled via inputs to the inferior olive from other structures. Altering the strength of these inputs to the inferior olive can modulate error-sensitivity, i.e., control how much the cerebellum learns from a given error. Indeed, recent results suggest that learning from error depends on the intensity (or duration) of complex spikes in the cerebellar Purkinje cells (Yang and Lisberger 2014).

For example, in a task where motor commands are followed by visual error (not unlike the errors produced in our task here), subthreshold stimulation of the superior colliculus following completion of the movement can drive trial-to-trial changes in motor commands, changes that resemble normal adaptation (Soetedjo et al. 2009). That work suggests that stimulation of the superior colliculus encodes an error-like signal, which then engages the inferior olive, resulting in complex spikes that drive learning in the cerebellum. Activity in the superior

colliculus can be modulated by inputs from the cerebral cortex and the basal ganglia, which in turn can alter the strength of inputs to the inferior olive. In this way, the brain may have a mechanism in place to control how much the cerebellum learns from a given error.

This view predicts that, whereas learning from error is impaired in cerebellar damage, control of error-sensitivity may be spared, that is, cerebellar damage may limit the number of Purkinje cells that are available for participation in learning, but the ability to control the input to the inferior olive may allow modulation of the complex spikes that drive learning in the existing Purkinje cells. The fact that in the gradual protocol we observed a tendency toward increased error-sensitivity in both groups of subjects appears consistent with this view.

Dissociation between deficits in prism adaptation and severity of cerebellar ataxia. The classic cerebellar motor symptoms are loss of already acquired overtrained motor performances such as postural disturbance, limb ataxia, dysarthria, oculomotor disturbances, and others. ICARS evaluates the degree of these disturbances as a whole. In the present study we found that ICARS was positively correlated with the size of error at the end of the abrupt protocol (but not for the gradual protocol). This result is in contrast to an earlier paper that examined prism adaptation in the abrupt protocol (Martin et al. 1996) where no correlations were found between clinical scores and adaptation. In that paper, the discrepancy was explained by the difference in the lesioned sites in the cerebellum. Patients with a lesion in the territory of the posterior inferior cerebellar artery had impaired prism adaptation even though they had little or no ataxia. In contrast, patients with a lesion in the territory of the superior cerebellar artery showed ataxic symptoms but preserved adaptation. Thus, the locus of the damage to the cerebellum may produce differential effects on ataxia and reach adaptation. The fact that our participants suffered from cerebellar degeneration, which tends to have a global effect compared with cerebellar stroke, may account for the fact that adaption deficits were correlated with clinical deficits.

Limitations. Our study design required examination of the participants during two sessions. We tested them on the same perturbation two times, but randomly assigned them to the abrupt or gradual protocols on their first session. This allowed for a within-subject within-perturbation comparison of adaptation in the gradual and abrupt protocols. Alternatively, we could have tested the participants on two different perturbations. Such a between-perturbation study design suffers from the problem that the brain may learn one perturbation better than another (Gibo et al. 2013), irrespective of whether it is imposed gradually or abruptly. However, our approach suffers from the potential problem that the brain may relearn better the second time it experiences a perturbation. To check for this, we compared endpoint errors from the first and second session and found no significant differences due to session in either of the two groups. However, once the sessions were labeled as abrupt or gradual, then differences in performance emerged in the cerebellar group.

We used shutter glasses to strictly control availability of visual information to the participants, but this came with the disadvantage that we could not readily measure their eye movements. Because visual information regarding placement of the hand with respect to the target at reach end is the basis of learning in our task, oculomotor behavior of the patients may have provided further clues regarding why they appeared to learn better in the gradual protocol.

In summary, we designed a prism adaptation experiment in which errors were available only at the conclusion of the movement, preventing within-movement response to sensory feedback. This allowed us to measure trial-by-trial learning from error, and forgetting due to passage of time and trial. We observed unimpaired forgetting due to passage of time or trial in the cerebellar patients. Furthermore, we observed that, while damage to the human cerebellum resulted in impairments in learning from error in response to the abruptly introduced perturbation, the impairment was significantly reduced when the same perturbation was imposed gradually. This improvement coincided with an increase in error-sensitivity, that is, an upregulation of how much the brain learned from a given amount of error in the gradual protocol. The increase in error-sensitivity was present in both the patient group and the healthy group of participants, suggesting that control of error-sensitivity may be spared in cerebellar degeneration.

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DISCLOSURES

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Author contributions: R.H., R.S., M.I., and S.K. conception and design of research; R.H., S.O., R.T., Y.S., T.S., N.T., M.U., M.I., and S.K. performed experiments; R.H., R.S., S.O., R.T., Y.S., T.S., N.T., M.U., M.I., and S.K. analyzed data; R.H., R.S., S.O., Y.T., Y.U., M.U., and S.K. interpreted results of experiments; R.H., R.S., and S.K. prepared figures; R.H., R.S., Y.T., M.U., and S.K. drafted manuscript; R.H., R.S., S.T., Y.U., and S.K. edited and revised manuscript; R.H., R.S., S.T., Y.U., and S.K. approved final version of manuscript.

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