Cerebellar Involvement in Anticipating the Consequences of Self-Produced Actions During Bimanual Movements

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[3]*Integrative Biology and* [4]*Helen Wills Neuroscience Institute, University of California, Berkeley, California*

Diedrichsen, Jörn, Timothy Verstynen, Steven L. Lehman, and Richard B. Ivry. Cerebellar involvement in anticipating the consequences of self-produced actions during bimanual movements. *J Neurophysiol* 93: 801–812, 2005. First published September 8, 2004; doi:10.1152/jn.00662.2004. Anticipatory postural adjustments (APA) during bimanual actions can be observed when participants hold an object in one hand and then lift it with the other hand. The postural force used to hold the object is reduced in anticipation of unloading, indicating an accurate prediction of the change in load. We examined patients with unilateral or bilateral cerebellar damage as well as two individuals lacking the corpus callosum on the bimanual unloading task. The acallosal patients showed an intact APA, suggesting subcortical integration of motor signals for anticipatory adjustments during bimanual actions. Contrary to the hypothesis that the cerebellum is critical for predicting and compensating for the consequences of our actions, we found that the well-learned APA in this task was largely intact in cerebellar patients. However, cerebellar damage abolished short-term adaptation of the APA, and the patients were unable to acquire an APA in a similar but previously untrained situation. These results indicate that while over-learned anticipatory adjustments are preserved after cerebellar lesions, adaptation of this response and the acquisition of a novel coordination requires the cerebellum ipsilateral to the postural hand. Furthermore, this structure appears to be essential for the accurate timing of previously learned behaviors. The patients with cerebellar damage showed poorly timed adjustments with the APA beginning earlier than in healthy participants.

INTRODUCTION

To produce coordinated action, we must integrate movements across different parts of the body. In bimanual actions, the hands often assume asymmetric roles with one hand holding an object and the other performing manipulative functions (Guiard 1987). To provide stability, the postural hand needs to compensate for forces generated by the other hand (Witney et al. 2000). The unloading task has been used as a model to study interactions that occur when we manipulate an object with two hands (Dufosse et al. 1985; Hugon et al. 1982; Massion et al. 1999). In this task, participants support an object with one hand, *the postural hand*, by exerting an upward *postural force* to resist the *load force* of the object. When the object is unexpectedly lifted by an external force, the postural hand shows a rapid upward perturbation because it is still pressing against the object (Fig. 1*A*). In contrast, when the person picks up the object with the other hand, *the lifting hand*, the upward perturbation of the postural hand is greatly attenuated (Fig. 1*B*)

due to an anticipatory reduction of the postural force. Such a response is called an anticipatory postural adjustment (APA).

To ensure stability, the decrease in the postural force is scaled to the speed of the lifting action (Lum et al. 1992) and begins 50 ms before the load force is removed (Hugon et al. 1982). This tight coupling indicates that the nervous system is capable of anticipating and compensating for a perturbation in one hand that would be the result of a volitional action of the other hand. Thus the APA provides an example for the use of internal models in motor control (Wolpert et al. 1995). Various hypotheses have been proposed concerning the neural locus of this form of bimanual integration.

First, the APA may be generated by communication between cortical motor areas across the corpus callosum. At odds with this hypothesis is the finding that a patient with complete resection of the corpus callosum exhibited a normal APA (Viallet et al. 1992). Similarly, well-trained bimanual skills are preserved in callosotomy patients (Franz et al. 2000; Serrien et al. 2001).

A second hypothesis is that the commands to the two hands originate from a single hemisphere, most likely the one contralateral to the lifting hand. Thus the primary motor cortex contralateral to the postural hand should not play an active role in generating the APA. Contrary to this prediction, patients with motor cortex lesions in this hemisphere show abolished APAs, even though basic motor functions for the postural hand have recovered (Massion et al. 1999; Slijper et al. 2002; Viallet et al. 1992; but see Bennis et al. 1996). These results suggest that both hemispheres are needed to generate the control signals for the postural and lifting hands.

A third perspective emphasizes a critical role for subcortical mechanisms. An efference copy of the commands to the lifting hand might be relayed to a subcortical structure that modulates the commands to the postural hand, either directly via descending signals or indirectly by influencing activity in the cortex contralateral to the postural hand. The cerebellum has been hypothesized to be the locus of the computations required for the APA (Massion et al. 1999). This proposal is congruent with theoretical and empirical work suggesting that internal models of task dynamics are learned and stored in the cerebellum (Imamizu et al. 2000; Wolpert et al. 1998).

To investigate the role of the cerebellum in the acquisition and retention of bimanual anticipatory responses, we tested patients with either bilateral or unilateral cerebellar damage. To evaluate the role of direct communication between the
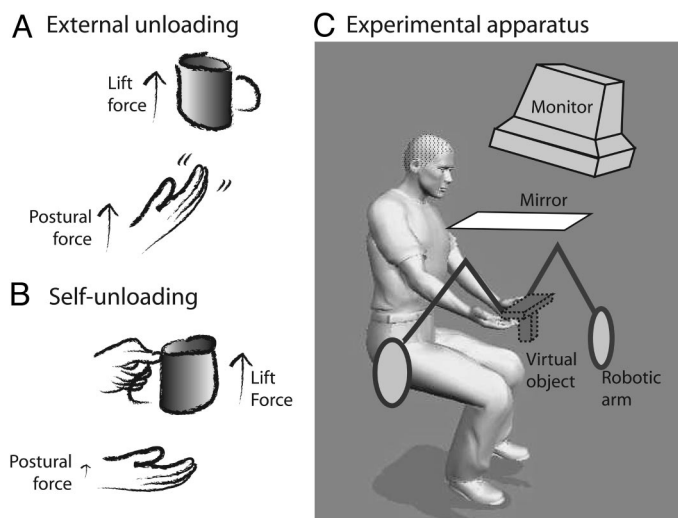

FIG. 1. Unloading task. *A*: when a supported object is lifted by an external force, the persistence of the postural force leads to an upward perturbation of the postural hand. *B*: when the person lifts the object with the other hand, the perturbation is attenuated by a reduction of the postural force, an anticipatory postural adjustment (APA). *C*: experimental setup. Viewed with stereo glasses, a virtual environment is displayed containing the object and spherical cursors representing the hand positions. Movement recording and force feedback are provided by 2 robotic arms.

cortical hemispheres, we also included two patients lacking the corpus callosum. Two versions of the unloading task were used: In *experiment 1,* we tested the over-learned situation in which one hand was used to lift an object supported by the other hand. We compared this self-unloading condition with an external unloading condition in which the object rose at an unpredictable time from the postural hand with a time course similar to the self-unloading condition. In *experiment 2,* we

tested a novel situation in which unloading from the postural hand was triggered by a button press with the other hand. Here, the APA is initially absent and can be acquired through learning.

METHODS

Participants

Seven patients with bilateral cerebellar atrophy and seven patients with unilateral lesions were tested in the first experiment. The atrophy group included individuals with genetic etiology (SCA2, SCA3, SCA6) and with unknown origin. Unilateral damage was due to either stroke or tumor with the neurological incident occurring between 3 and 12 yr prior to testing. The lesions were localized in the left or the right cerebellar hemisphere, and MRI evidence indicated the extension of the lesion into the deep cerebellar nuclei in three patients. All cerebellar patients underwent a neurological examination to assess the severity of cerebellar symptoms (Table 1). Patients with strong extra-cerebellar signs (weakness, rest tremor) were excluded from the study. One bilateral (*AC06*) and one unilateral patient (*LC06*) did not participate in the second experiment.

Two patients lacking a corpus callosum were also tested. One patient was a 50-yr-old female who had undergone a callosotomy operation as part of her treatment for severe epilepsy seven years prior to testing. The other person was a 58-yr-old male with callosal agenesis. This condition was discovered during a medical examination related to headaches. Both patients report little or no difficulties with bimanual action in everyday life. The callosotomy patient participated in both experiments, whereas the patient with callosal agenesis was only tested in the second experiment. Eleven neurologically healthy participants were recruited to serve as controls for both experiments, matched on age, handedness, and education variables to the patients. All experiment and informed consent procedure had been approved by the University of California Berkeley Internal Review Board.

TABLE 1. *Participant demographic and neurological information*

	Demographics				Ataxia Rating					Lesion Description		
	Gender	Age	Years of Education	Handedness	PO (34)	LL (24)	LR (24)*	SP (8)	OM (6)	Etiology	Onset, yr	Location
Bilateral cerebellar degeneration group												
AC09	M	63	20	R	4	4	4	3	3	AT	5	
AC07	M	37	16	R	12	10	10	3	2	SCA2	13	
AC08	M	54	15	R	7	3	3	3	5	AT	12	
AC01	F	56	18	R	11	6	6	4	2	AT	4	
AC10	M	76	12	R	20	8	9	5	2	SCA6	42	
AC06	M	67	17	R	13	11	9	6	3	AT	41	
AC04	M	51	18	R	18	12	12	3	4	SCA3	13	
Mean		57.7	16.5		12	7.7	7.4	3.9	2.8		18.5	
Unilateral cerebellar lesion group												
LC01	M	53	13	R	2	7	0	2	0	Stroke	7	LH: I–VIIb
LC03	M	58	12	R	8	6	1	1	4	Tumor	12	LH: VIII, IX
LC07	M	57	11	L	8	7	1	5	3	Tumor	6	LH: I–IX, Dentate
LC05	M	47	18	L	11	0	13	4	4	Tumor	6	RH: VI–VIII
LC06	M	76	18	R	1	1	1	1	0	Stroke	11	RH: I–VIIb, Dentate
LC02	M	66	14	R	13	0	10	2	0	Stroke	12	RH: I–V, VI
LC04	M	45	18	L	3	0	11	1	4	Stroke	3	RH: I–IX, Dentate
Mean		58.2	14.4		6.3	8	0	2.1	2		8.1	
Control group												
Mean		57.2	15.5	(6 female, 5 male, 1 left-handed individual)								

Ataxia rating according to the International Cooperative Ataxia Rating Scale (Trouillas et al. 1997). *PO,* posture; *LL* and *LR,* limb ataxia left and right (including lower and upper limb); *SP,* speech disorders; *OM,* oculomotor disorders. The score that would indicate maximal impairment on each subtest is given in parenthesis. *SCA,* spinocerebellar ataxia genetic subtype; *AT,* atrophy of unknown origin; onset, years since onset of symptoms of since insult; *LH and RH,* left or right cerebellar hemisphere with extent of lesion indicated by Larsell-notation (see Schmahmann et al. 2000). *For the sake of a symmetric assessment of limb ataxia, the subtest 14 (drawing) was dropped from the evaluation.

Apparatus and stimuli

To manipulate the feedback to the postural and lifting hand independently, we used a virtual three-dimensional environment to simulate the unloading task (Fig. 1*C*). Visual and haptic feedback created a vivid impression of manual interactions with a real object. The participants were seated and looked downward into a mirror through which they viewed a 24-in computer monitor mounted above the mirror. The monitor displayed a virtual workspace ($40 \times 35 \times 26$ cm) that appeared to be located directly in front of the participants. The workspace contained a table-like object that consisted of a $20 \times 10 \times 2$-cm surface centered over a $4 \times 4 \times 7$-cm base.

An accurate haptic model of the virtual workspace was generated by the computer and updated at 1,000 Hz. Each index finger was linked to a robotic arm (PHANToM 3.0 System, SensAble Technologies) by a thimble-like interface. Position sensors in the robot arm tracked the location of the index fingers and two 0.8-cm spheres were displayed on the monitor at the corresponding location to provide visual feedback. The program calculated the forces exerted by the hands onto the virtual object at each update cycle, using a damped spring (2.5 N/m) with lateral frictional components as a surface model (Sensable Technologies 2004, p. 15). Stiffer surfaces cannot be simulated due to limitations in the PHANToM system. The object could only be moved in the vertical direction and had a weight of 0.5 kg in experiment 1 and 0.34 kg in experiment 2. By summing the forces acting on the object, the computer calculated the acceleration of the object, updated its position, and computed the resultant forces on the hands. These forces were applied to the hands by torque motors to create appropriate feedback. The visual feedback was calibrated to spatially match the force feedback, creating the impression of an interaction with a real object. Position data and applied forces were recorded at 200 Hz.

Experiment 1: natural unloading

A trial began with the participant lifting the object with the postural hand to a height of ~3–6 cm, and maintaining this posture for a variable period of time. This movement required that the elbow be flexed at ~90°. Participants wore a splint on each hand that immobilized the wrist and yoked the index and middle finger together. By restricting movements to elbow rotation, it was possible to compute the torque generated about the elbow via inverse dynamics.

In the *self-unloading* condition, participants positioned the lifting hand, with palm facing upward, below the object on the side opposite to the postural hand. The index and middle finger had to be within 3 cm of the object's lower surface but could not be in contact with the object. After a 1- to 2-s holding period, a tone signaled the participant to move this hand smoothly upward to lift the object off the postural hand to a height of ≥12 cm. The participant then had to lower the object back to the "floor" of the workspace to end the trial. Feedback was provided indicating the speed of the lifting action, calculated as the time from the moment the lifting hand touched the object until the object had reached a height of 12 cm. Because the size of the perturbation and the size of the APA depend critically on the speed of the unloading action, we decided to explicitly assess this relationship. Thus participants were instructed to lift the object at a range of different speeds across trials.

In the *external unloading* condition, the computer initiated the unloading without warning after a holding period of random duration (1–3 s). The computer simulated the upward force acting on the object to mimic the force generated by the lifting hand during natural unloading. The object was unloaded at three different speeds, chosen to encompass a range similar to that expected to be used by the participants in the self-unloading condition. The subjects were informed of the forthcoming speed on external-unloading trials.

One way to achieve postural stability would be to increase stiffness about the elbow by co-contracting the biceps and triceps (Biryukova

et al. 1999). While participants were instructed to avoid co-contraction, we also included randomly interspersed *catch trials* to explicitly test if participants adopted a co-contraction strategy. On catch trials, the participant would see the object being lifted (either as a result of their own action or from the external force), while the robotic device maintained a 4.9 N constant load force on the postural hand. During self-unloading the haptic feedback for the lifting hand was identical to normal trials. If participants were achieving stability by co-contraction, the postural hand should remain stable on catch trials; if participants generated an APA, the postural hand should exhibit a downward acceleration just prior to unloading. Once the object reached the ceiling of the workspace (500–600 ms after the start of unloading), the force applied to the postural hand was removed in a smooth fashion.

After a brief familiarization phase (16 trials), participants completed 12 test blocks with a fixed order of 2 external, 4 self-unloading, 2 external, and, finally, 4 self-unloading blocks. The postural hand alternated between blocks and the starting hand was counterbalanced between subjects. Each block consisted of 24 trials, 6 of which were randomly selected to be catch trials.

Measured variables and inverse dynamics

Figure 2 shows example traces from one control participant in the external and self-unloading conditions. Lift and load force were recorded by the computer. Velocity and acceleration traces were obtained by numerical differentiation of the position signal and subsequent smoothing with a Gaussian kernel of 22 ms full width at half maximum.

Separate traces are shown for normal and catch trials. The lift force (Fig. 2*A*) represents the force applied to the object by the participant's lifting arm (self-unloading) or by the computer (external unloading). The load force on the postural hand (Fig. 2*B*) decreased correspondingly until the object detached from the postural hand ~40 ms after lifting began. On catch trials, the load force on the postural arm remained constant across the trial.

On normal trials, the reduction in load force led to a smaller upward acceleration of the postural hand (Fig. 2*C*) in the self-unloading condition compared with that in the external unloading condition. On catch trials, we observed a downward acceleration of the postural hand during the interval when a reduction in load force would be expected. This shows that participants actively reduced the postural force in the self-unloading condition rather than adopt a strategy of achieving stability by co-contraction

On catch trials, the downward acceleration of the postural hand is directly related to the postural force, i.e., the force produced by the muscles around the elbow joint of the postural arm (Diedrichsen et al. 2003; Lum et al. 1992). In contrast, on normal trials, the upward acceleration not only depends on the postural force but also on the rate at which the load is removed. Perturbations may have been smaller in self-unloading trials than in the external condition because the load force decreased more slowly. To account for variations in unloading speed, we used inverse dynamics to estimate the postural force.

For simplicity, we based this analysis on the forces at the connection point between the hand and robotic device, rather than on joint torques. Because the angle of the elbow joint varied only over 6° (~5 cm at fingertip), the relation between the elbow torque and resultant forces at the hand was approximately linear. The goal was to estimate the force produced by the participant's postural arm (F_{po}) using the measured load force applied to the postural hand by the PHANToM arm (F_{load}), the hand velocity ($\dot{x}$), and acceleration ($\ddot{x}$). The gravitational force on the hand (F_g) was essentially constant within the small range of angular motion, and was subsumed into the postural force. The postural force can be calculated as

$$F_{po} = -F_{load} + v\dot{x} + m\ddot{x}$$

We ignored the viscosity of the elbow joint (v), because this factor is likely low, given maximal resultant velocities during the first 50 ms of
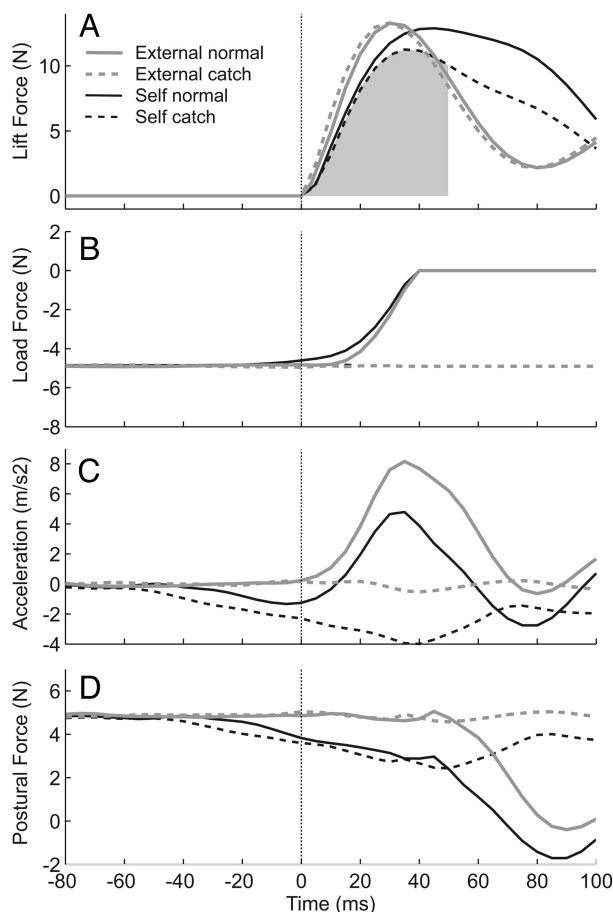
FIG. 2. Dynamics of self-unloading and external unloading in neurologically healthy participants. Example traces are shown, aligned to when the lift force is applied to the object. *A*: lift force is generated by the participant's lifting arm in the self-unloading condition or simulated in the external unloading condition. The integral over the first 50 ms—the initial impulse to the object (▨)—is taken as a measure of lifting speed. *B*: load force decreases until the object loses contact with the postural hand. On catch trials, the simulated force on the postural hand remains constant at −4.9 N. *C*: upward acceleration of the postural hand is smaller on self-unloading trials compared with external unloading trials. On self-unloading catch trials, a downward acceleration is observed. *D*: using load force and hand acceleration, the force generated by the postural hand can be estimated. The reduction in postural force is evident ~30–40 ms prior to unloading.

0.1 m/s (Latash and Gottlieb 1991). When estimating the inertia of the arm (*m*), one has to consider the possible dependence on the position and load of the elbow joint and the considerable internal inertia of the PHANToM device itself (Diedrichsen 2003). To arrive at an estimate that is valid for our situation, we used the data from the external-unloading condition. Because the exact time of unloading in this condition was not predictable for the subject, it was expected that the postural force would remain constant until feedback processes caused a reaction to the perturbation. While monosynaptic spinal reflexes can lead to measurable EMG activity as fast as 25 ms after a perturbation, measurable forces due to spinal reflexes are typically not apparent until after 50 ms. Thus over this time window, we predicted that the relation between the load force and acceleration of the hand would be linear with a slope of $1/m$. Moreover, the slope should be independent of unloading speed. Both the linearity and constant slope predictions were confirmed. The estimate of *m* was then used to calculate F_{po} in the self and external-unloading conditions.

The estimate of postural force (Fig. 2*D*) showed an anticipatory reduction in the self-unloading but not in the external unloading condition. This was the case for both normal and catch trials. No

difference between the postural force on normal and catch trials was evident until ~50 ms after unloading. At this time, reflexive mechanisms reduced the upward force generated by the postural hand on normal trials (Houk and Rymer 1981).

We restricted our analysis to the feed-forward component of the postural command. As a measure of the APA magnitude on each trial, we calculated the difference between the force required to hold the object (4.9 N) and the average postural force calculated over the initial 50 ms after the beginning of unloading. We also calculated the *lifting impulse*, the integral of the lift force over the same time interval, as a measure of lifting speed (shaded area in Fig. 2*A*).

Experiment 2: button-triggered unloading

As in the previous experiment, the participants held an object with the postural hand; however, object unloading was now triggered by a button press with the index finger of the contralateral hand. The virtual response button (4 × 3 × 2 cm) was positioned on the workspace floor, 14 cm lateral to the object. The button could be depressed over a distance of 2 cm and was simulated with a spring stiffness of 1.76 N/cm.

To start each trial, the index and middle index and middle fingers of the postural hand were used to lift the object. Given that unloading always occurred at a fixed speed (and thus we did not have to use inverse dynamics to assess the unloading response), we did not splint the fingers together in experiment 2 to allow for more natural movements. Nonetheless, participants were instructed to use both fingers when lifting the object and to keep the fingers fully extended during lifting. In the button-press condition, a tone sounded after a holding period of 2 s. On the button press, the computer simulated unloading in a stereotypic fashion. In the external unloading condition, the object rose off the hand after an unpredictable interval (200–1,200 ms), chosen to span the range of latencies in the button-press condition.

In both conditions, unloading occurred in an invariant manner, decreasing the load force on the postural hand over 200 ms in a roughly linear manner. Thus in this experiment, the change in acceleration of the postural hand provided a stable measure of the change in the feed-forward command. As a result, it was not necessary to employ inverse dynamics and movements of the postural and lifting arms could be unconstrained around the elbow, wrist and fingers. As a measure of the perturbation of the postural hand, relatively uninfluenced by feedback processes, we used the acceleration averaged over the time interval from 25 ms before to 50 ms after the button press.

At the end of the trial, feedback was provided, indicating the amount of movement of the postural hand in millimeters. Participants were instructed to minimize this value without co-contraction.

Occasionally, participants would adopt a strategy in which they lowered the postural hand around the same time as the button press. This was monitored by the experimenter and actively discouraged. Trials in which the postural hand achieved a downward acceleration of 0.4 m/s^2 50 ms before the button press were discarded.

The experiment consisted of five phases. An initial baseline phase of two blocks, each composed of 15 external unloading trials, was followed by a pretraining phase of four blocks, each composed of 15 button-press trials. The postural hand alternated between blocks. The learning phase consisted of 8 blocks of 24 button-press trials with the postural hand fixed for all of the blocks. The posttraining phase was identical to the pretraining phase and the experiment ended with a final baseline phase. In all of the blocks except the learning phase, 4 of 15 trials were randomly selected to be catch trials. Catch trials were not included in the learning phase because pilot work indicated that they significantly slowed the acquisition of the button-press triggered APA.

The dominant hand was used as the postural hand for the split-brain, callosal agenesis, and bilateral cerebellar degeneration patients. This role assignment was chosen because pilot studies with healthy control participants showed that learning occurred more rapidly when

the dominant hand was used as the postural hand than when the nondominant hand served as the postural hand. The unilateral patients were initially tested with their ipsilesional hand serving as the postural hand. They returned 2–4 mo later for a second session in which their contralesional hand served as the postural hand. Seven of the 11 control participants were also tested in a second session. For these seven, the order in which the dominant and nondominant hands served as the postural hand was matched to that of the unilateral patients.

RESULTS

Experiment 1

APA SCALING AND MAGNITUDE IN CONTROL PARTICIPANTS. Figure 3*A* shows the mean postural force for normal and catch trials, split by whether the lifting speed was slow, medium or fast (*top*) and a scatter plot of the lifting speed and the average reduction in postural force (*bottom*). The results demonstrate that the APA strongly depended on the speed at which the object was lifted: the larger the initial force impulse generated to lift the object, the larger the APA. This relationship was also observed on catch trials, indicating that the dependency was caused by the coordination of neural feed-forward commands rather than by the physical linkage of the hands through the object (Lum et al. 1992). As a measure of the *scaling* relationship, we used the correlation coefficient between the change in postural force and the lifting impulse. The scaling was present in each control participant (mean correlation = −0.64; range = [−0.76; −0.48]).

This dependence has to be taken into account to arrive at a measure for the overall *magnitude* of the APA. This becomes especially important in the study of neurological populations because patients often show a general slowing of movement (McNaughton et al. 2004). Thus a reduced APA could be due to its dependency on movement speed rather than a specific deficit in anticipatory control (Viallet et al. 1987). Although on average the patients were not slower than the control participants, the unloading speed varied substantially between participants and, within participants, between the two hands. To account for these differences, we calculated a regression line of the change in postural force and the lifting impulse. In contrast to the regression used to assess the scaling relationship, we constrained the intercept in this analysis to be zero. This resulted in a slope coefficient that reflects the magnitude of the APA independent of the speed of the lifting action and the strength of the scaling relationship. Figure 4a shows the slope coefficients for the left and right hands of the control participants.

Preserved APA after callosotomy and cerebellar lesions

The pivotal observation that a bimanual APA in the unloading task is preserved after the resection of the corpus callosum is based on a report involving a single participant (Viallet et al. 1992). Given this, we tested a second split-brain patient. Replicating the results from the previous study, the callosotomy patient clearly exhibited an APA on normal and catch trials (Fig. 3*B*). The magnitude of the APA was in the range of control participants (Fig. 4*A,* white circles). Furthermore, the magnitude of the APA was scaled to movement speed. The scaling was normal when the left hand served as the postural hand ($r = -0.53$). The correlation was lower when the right

hand served as the postural hand ($r = -0.27$), perhaps due to the fact that the range of lifting speeds was severely restricted. Nonetheless, both correlation coefficients were significant, indicating that the APA was not only preserved in this patient but that it was appropriately scaled on a trial-to-trial basis.

To compare the bilateral cerebellar patients with the control group, we performed a group × hand repeated-measures ANOVA. Three planned comparisons were performed for the unilateral cerebellar patients: the within-subject contrast between ipsi- and contralesional hands and the between-subject contrast of ipsilesional hand versus control performance and contralesional hand versus control performance. Because the ipsilesional hand was dominant in half the cases, we averaged control performance for this comparison over dominant and nondominant hands. Unexpectedly, the APA was also preserved in patients with bi- and unilateral cerebellar lesions. A reduction of postural force occurred on normal and catch trials during the self-unloading condition (data from two characteristic patients are shown in Fig. 3, *C* and *D*). The magnitude of the APA for the bilateral cerebellar patient group (Fig. 4*A*), as measured by the slope of the regression line relating the change in the postural force and lifting impulse, was comparable to the control group, $F(1,16) = 0.12$, $P = 0.73$. In terms of scaling of the APA, we found slightly reduced correlation coefficients between the lifting impulse and the APA magnitude compared with controls, $F(1,16) = 8.03$, $P = 0.012$. These correlations, however, were still significant in every patient (average $r = -0.47$, range = [−0.65; −0.13]).

The unilateral cerebellar patients provided the opportunity to compare situations in which the ipsilesional (ataxic) or the contralesional (normal) hand served as the postural effector. The magnitude of the APA did not differ significantly between these two situations, $t(6) = 1.58$, $P = 0.16$. In a direct comparison of this group with the control participants, neither hand showed an impairment in the APA [ipsilesional: $t(16) = 1.24$, $P = 0.23$; contralesional: $t(16) = 0.09$, $P = 0.92$]. The correlation coefficients between lifting speed and the postural force were negative for all participants, indicating a preserved scaling relationship. The correlation when the ipsilesional hand was postural ($r = -0.44$, range = [−0.59; −0.36]) was slightly lower than when the contralesional hand was postural ($r = -0.66$, range = [−0.79; −0.46]). While this difference was not significant, $t(6) = 1.90$, $P = 0.106$, only the ipsilesional hand showed a significant difference compared with the control participants, $t(16) = 4.20$, $P < 0.001$.

Overall, the cerebellar patients exhibited an APA of normal magnitude during bimanual coordination. The scaling relationship was also preserved for both bi- and unilateral patients, although it was slightly attenuated in the latter group when these patients used the ipsilesional hand as the postural hand.

Abnormal timing of the APA after cerebellar lesions

For each hand, we determined the onset of the APA by calculating when the average change in postural force had reached 20% of the total change measured in the interval from 0 to 50 ms. For control participants, the APA began 45 ms prior to unloading; for the callosotomy patient, the onset time was slightly earlier (65 and 85 ms). In contrast, the bilateral cerebellar patients showed a substantially earlier onset (Fig. 4*B*). A repeated-measures ANOVA for control and bilateral
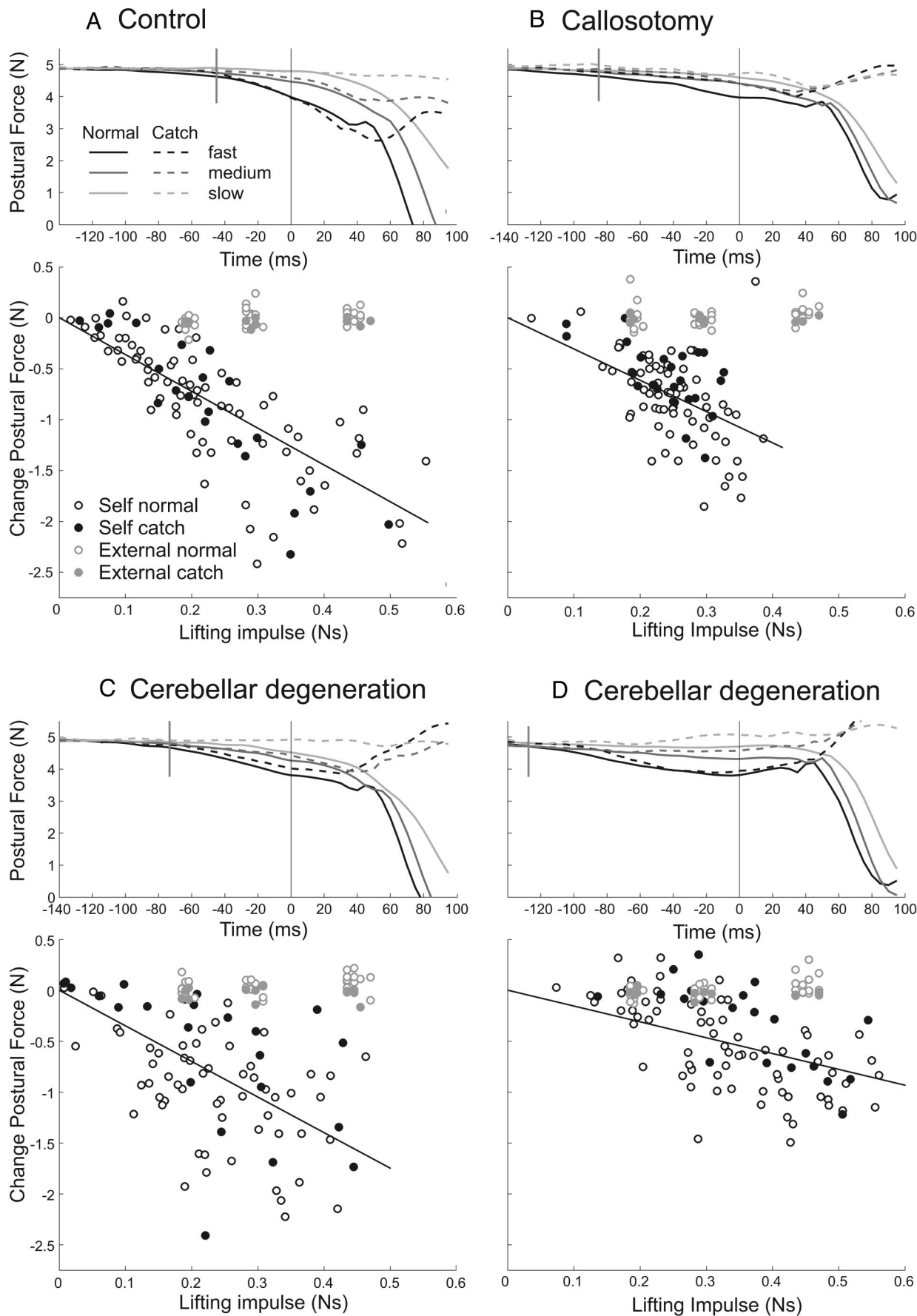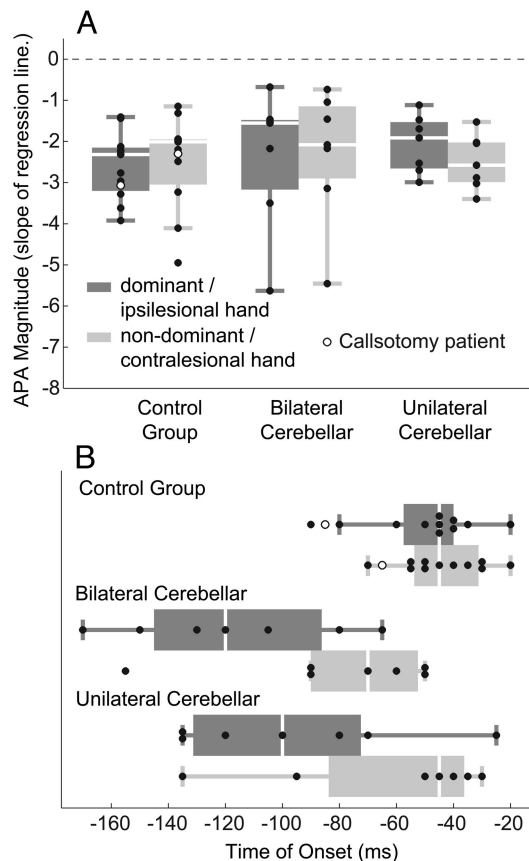
FIG. 4. While the magnitude of the APA in the self-unloading task is preserved, the response is initiated earlier in cerebellar patients. *A*: measure for the magnitude of the APA is based on slope of the regression line in Fig. 3. Each dot represents this measure for an individual participant, and the results for the callosotomy patient are shown as white circles within the control group. The white lines indicate the median, the boxes the 25th–75th percentile and error bars span from the minimal to maximal value, excluding values that are >2.5 SD from the mean. For control participants, callosotomy patient and bilateral cerebellar patients the results are split by when the dominant or nondominant hand serves as postural hand, and for unilateral patients when the ipsi- or contralesional serves as postural hand. *B*: onset of the reduction in postural force relative to the onset of lift force.

cerebellar group revealed a main effect of group, $F_{(1,15)} = 20.85$, $P < 0.001$. The APA onset was also earlier for both control and bilateral groups when the nondominant hand served as the postural hand, $F_{(1,15)} = 13.49$, $P = 0.002$.

For the unilateral patients, the difference between the hands was not significant, $t(6) = 1.52$, $P = 0.178$, due to large intersubject variability. Compared with control participants, however, APA onset was significantly earlier for the ipsilesional hand, $t(16) = 3.68$, $P = 0.002$ but not for the contralesional hand, $t(11) = 1.14$, $P = 0.269$. Thus both cerebellar groups showed an earlier onset of the APA than healthy control participants when an ataxic limb was used to support the object.

Impaired short-term plasticity

All groups showed a downward perturbation of the postural hand on catch trials, the clearest indication of an APA. An intriguing form of short-term plasticity was evident after these catch trials. Figure 5 shows the magnitude of the APA on normal trials as a function of whether the trial occurred before or after a catch trial. The magnitude of the APA for the control group was significantly reduced after a catch trial, $F_{(1,10)} = 40.48$, $P < 0.001$. This effect was not the result of participants choosing to lift the object at a slower speed after a catch trial: the average unloading impulse was identical before and after catch trials, $F_{(1,10)} < 0.01$. Indeed, it is unlikely that this effect results from any conscious strategy, as participants were often unaware of the inclusion of catch trials. Rather the transient reduction likely reflects short-term plasticity in the controller of the APA. The APA returned to baseline after three normal unloading trials.

The adjustment of the APA after a catch trial was absent in the bilateral degeneration group, $t(6) = 0.52$, $P = 0.66$. When the unilateral patients used their contralesional hand to support the object, the short-term plasticity effect was clearly present, $t(6) = 3.84$, $P = 0.009$ and comparable in magnitude to that found for the controls. In contrast, no adjustment was evident when the ipsilesional hand was used to support the object, $t(6) = 1.77$, $P = 0.128$. The callosotomy patient also exhibited normal short-term plasticity after catch trials (reduction of 0.1 N on either hand after a catch trial).

These findings provide evidence that the downward perturbation on catch trials leads to an immediate adjustment of the gain of the APA. The results from the patients suggest that this short-term plasticity does not require an intact corpus callosum but is dependent on the integrity of the cerebellar hemisphere ipsilateral to the postural hand.

Experiment 2

ABOLISHED LEARNING IN CEREBELLAR PATIENTS. The self-unloading condition is a behavior that is over-learned in adults given that it approximates the situation where we transfer objects from one hand to the other. The APA in this task is acquired in late childhood (Schmitz et al. 2002) and, as such, it was well established in the cerebellar patients prior to the onset of their pathology. The absence of short-term plasticity, however, led us to hypothesize that the cerebellum would be necessary to acquire an APA in a novel coordination task. To test this prediction, participants were tested on a novel bimanual task in which an APA could be learned (Diedrichsen et al. 2003).

Participants held an object with one hand and pressed a button with the other hand. This button press triggered the unloading of the virtual object in a stereotypical fashion (Fig. 6A). In the pretest phase, the upward perturbation of the postural hand was nearly as large as the upward perturbation

FIG. 3. Time course of the APA and scaling with the speed of the lifting action. *A*: data from 1 control participant. *Top*: the postural force in self-unloading trials, aligned to the start of lift force (0 ms). The data were split 3 ways for each participant into fast, medium, and slow trials based on the size of the initial lifting impulse. Both normal and catch trials show a reduction of the postural force beginning 50 ms before start of the lift force. *Bottom*: the scaling relationship between the lifting impulse and the change in postural force and a common regression line for normal and catch self unloading trials (the intercept was fixed to 0 for the computation of APA magnitude). *B*: callosotomy patient shows an overall preservation of the APA. *C* and *D*: 2 patients with cerebellar degeneration also show intact coordination, but the onset of the reduction occurs earlier than in control participants. In all 4 cases, the nondominant hand lifted the object and the dominant hand assumed the postural role.
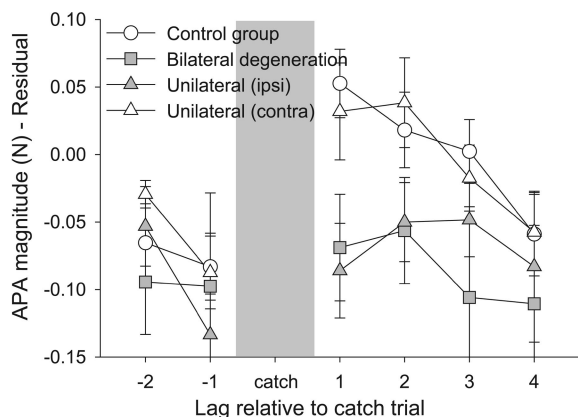
FIG. 5.   Cerebellar patients fail to exhibit transient reduction in the APA after catch trials. As a measure of the APA magnitude, adjusted for the speed of the unloading action, residuals from the regression of the postural force onto the unloading impulse are used (Fig. 3, *bottom*). Positive residuals indicate a smaller than expected APA. Mean data are shown for normal trials before (−2, −1) and immediately after (1–4) a catch trial (0). This form of short-term plasticity is absent for either hand in the bilateral group (data are averaged over 2 hands) and when the unilateral patients use their impaired, ipsilesional hand as the postural hand.

when the unloading was externally triggered (Fig. 6*B*). After 180 trials in which unloading was triggered by a button press, the upward perturbation was significantly reduced compared with the pretest amplitudes. In addition, a downward perturbation was observed on the posttraining catch trials.

In terms of the average traces, most of the learning-related changes occurred after unloading had begun. Thus the learned

FIG. 6.   Button-triggered unloading experiment. A: an object is held with 1 hand and unloading is triggered by a button press of the other hand. *B*: average acceleration traces of the postural hand. Normal control participants show a reduction in upward acceleration from pre- to posttest on normal trials (—) and a downward deflection on catch trials (- - -), indicative of the acquisition of an APA. *C*: bilateral cerebellar patients fail to acquire the APA in this novel context, whereas the callosotomy patient (*D*) and the callosal agenesis patient did learn.

response appears to be less anticipatory than during natural unloading (e.g., compare Figs. 2 and 6). This difference may be due to the fact that the simulated time course for unloading following the button presses spanned almost 200 ms, whereas unloading was generally much faster during self-unloading (e.g., <40 ms for some participants). We had initially used a time course that more closely approximated that observed during self-unloading. However, we found that learning was quite poor for the given amount of training. It is likely that the delayed APA for the button press condition is related to the slower time course for unloading here. Nonetheless, the learned response had a clear anticipatory component as evidenced by the fact that we observed the presence of a downward perturbation on catch trials. We also restricted our quantitative analysis to a time window of 25 ms before to 50 ms after the start of unloading. We found a significant change between the pre- and posttest phases for both normal, $t(10) = -3.39$, $P < 0.007$, and catch trials, $t(10) = -7.04$, $P < 0.001$. Individual learning scores, determined as the change in acceleration between pre- and posttest calculated over this time window are shown in Fig. 7. These scores were averaged over normal and catch trials; however, comparable results were obtained when each were analyzed separately.

Patients with bilateral cerebellar lesions (Fig. 6*C*) failed to exhibit evidence of learning in either normal or catch trials. The learning scores were not significantly different from zero, $t(5) = 0.33$, $P = 0.75$. The unilateral patients were tested twice, holding the object with either their ipsilesional or contralesional hand. As a group, the unilateral patients failed to learn when the ipsilesional hand supported the object, $t(5) = -0.16$, $P = 0.873$, but exhibited significant learning when the contralesional hand supported the object, $t(5) = -2.39$, $P = 0.043$.

Learning of a bimanual APA without corpus callosum

Previous studies have indicated that patients lacking a corpus callosum are unable to acquire novel bimanual skills (Franz et al. 2000; Preilowski 1972). Given this, we hypothesized that these patients would fail to learn the APA in the
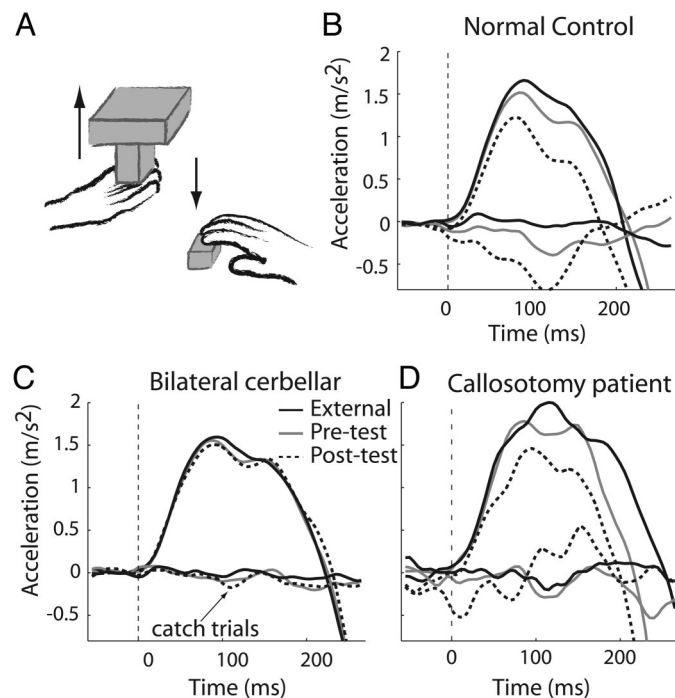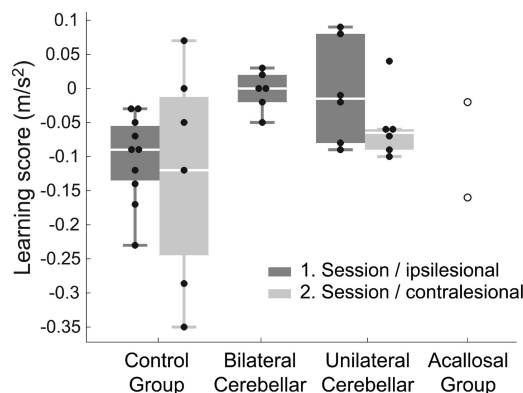

FIG. 7.   Summary of learning effects in the button-triggered unloading experiment. A learning score was defined as the difference between the acceleration on the pre- and posttraining blocks, averaged across catch and normal trials. Individual scores are presented as dots. (For other graphical conventions see Fig. 4.) For unilateral patients, the ipsilesional hand was used as the postural hand in the 1st session and contralesional hand in the 2nd session. A subset of controls was tested in a second session with the order of hands matched to the unilateral group on an individual basis.

button-triggered condition. To our surprise, the callosotomy patient developed an APA in this novel task with a reduction of the upward acceleration from pre-to posttest (Fig. 6D). The patient with callosal agenesis showed a reduced perturbation after learning. However, this reduction and the downward acceleration on catch trials were only evident 100 ms after unloading. Thus the learning score for this individual was close to zero (Fig. 7). However, when considering the acceleration over a longer time window ($-25-125$ ms), learning was significant for both patients [$F(1,33) = 5.49$, $P = 0.025$, and $F(1,53) = 5.28$, $P = 0.026$]. Thus patients without a corpus callosum could learn the task to some degree, however, only the callosotomy patient showed an unambiguous anticipatory component.

DISCUSSION

Previous studies have generally focused on how the cerebellum contributes to the coordination of movements about a single joint (Hore et al. 1991), across joints within a single limb (Bastian et al. 1996; Hore et al. 2002), or between movements of the head and eye (Lisberger 1988; Sparks and Barton 1993). The present study provides new evidence concerning the role of the cerebellum in bimanual coordination. Based on previous theoretical and empirical work, one might assume that the cerebellum would be essential in the generation of the anticipatory postural adjustment observed in the unloading task (Kawato et al. 2003; Massion et al. 1999). Contrary to that hypothesis, the basic features of the APA were intact in patients with either bilateral cerebellar degeneration or focal, unilateral lesions. The patients showed a clear reduction in postural force prior to unloading, and the APA was scaled to the speed of the lifting action.

Given that the APA was well established prior to the onset of cerebellar pathology in the patients (Schmitz et al. 2002), the results indicate that after a long period of consolidation, the integration of the bimanual commands is in large part independent of the cerebellum. It is, of course, possible that the preserved APA is dependent on the function of residual cerebellar tissue. However, the degree of degeneration was extensive in many of the bilateral patients and three of the unilateral patients had complete or partial damage to the deep cerebellar nuclei. Yet we found no systematic effect between the extent or location of the lesion and the magnitude of the APA.

These results suggest that extracerebellar sites may be the critical locus of the long-term memory trace underlying the APA. Subcortical targets of cerebellar efferent projections, the red nucleus or the reticular formation, have been implicated in postural control (Prentice and Drew 2001). The memory could also be neo-cortically mediated, with subcortical structures involved in the control of the timing and scaling of the anticipatory response.

Our findings appear to contradict various reports of impaired anticipatory behaviors subsequent to cerebellar damage. For example, patients with cerebellar lesions fail to show a normal anticipatory adjustment in grip force when lifting or moving an object (Babin-Ratte et al. 1999; Muller and Dichgans 1994; Nowak et al. 2002; Serrien and Wiesendanger 1999). However, similar to our findings, the basic pattern of the anticipatory response was intact in these studies. The patients increased grip force prior to displacing the object. The impairments were instead evident in the abnormal timing of the adjustment or in a failure to appropriately scale the responses.

In contrast to the striking preservation of the APA during self-unloading, the present study demonstrates that the cerebellum is essential for two forms of learning that is dependent on the integration of bimanual signals. First, the control participants showed a transient reduction of the APA after catch trials. At first glance it might seem surprising that such an over-learned response would be modified so readily in healthy participants. However, aiming movements, another highly practiced skill, exhibit a similar adaptation rate when performed in novel dynamic environments (Shadmehr and Mussa-Ivaldi 1994; Thoroughman and Shadmehr 2000). It appears that the nervous system constantly fine tunes actions as a way to adapt to changes in the environment. Unlike the controls, the cerebellar patients did not show this adaptation when the postural hand was ipsilateral to the cerebellar lesion. These same deficits were observed in the patients with unilateral lesions but only when the ipsilesional, affected hand was used as the postural hand. Thus the results extend the domain of cerebellar learning beyond tasks involving single-limb movements (Maschke et al. 2004; Smith 2001) or visuo-motor adaptation (Lisberger 1988; Martin et al. 1996; Sparks and Barton 1993). Our findings are consistent with other studies showing that patients with cerebellar lesions fail to modify anticipatory responses based on previous experience or based on explicit knowledge about an upcoming perturbation (Horak and Diener 1994; Lang and Bastian 1999, 2001; Timmann et al. 2000).

Second, cerebellar patients also failed to learn to produce an APA when unloading was triggered through a button press of the other hand. The button-triggered unloading task was created to be similar to the natural unloading condition yet still require learning of a bimanual coordination pattern within a novel context. However, there are some notable differences between the two tasks. First, for learning to occur within a single training session, it was necessary to slow the time course of unloading in the button-pressing condition. We assume this contributed to the fact that the onset of the APA was delayed. Second, whereas movements were restricted to rotation about the elbow joint in experiment 1, participants were able to move their fingers and wrist in experiment 2. Given reports that cerebellar lesions produce marked impairments on tasks requiring coordination across multiple joints (Bastian et al. 1996), it is possible that this difference contributed to the failure of the patients to exhibit learning in experiment 2. However, it is important to recognize that both the natural unloading and the button-press conditions involve coordination across multiple joints given that the tasks involve two hands. Combined with the clear impairment of adaptation in experiment 1, these learning deficits are consistent with the hypothesis that the cerebellum is necessary for plasticity of this form of bimanual coordination.

While the basic pattern of the APA during natural unloading was preserved in the patients with cerebellar lesions, the timing of the response was disturbed. For healthy controls, the reduction in the postural force was observed $\sim 30-60$ ms before the lifting hand began to unload the object. For the cerebellar patients, the onset of the APA was considerably earlier, beginning >100 ms prior to the unloading action for many patients. Cerebellar dysfunction has been associated with temporal ab-

normalities in many tasks, ranging from repetitive movements about a single joint (Ivry and Keele 1989) to the complex temporal coordination required across joints in tasks such as throwing (Timmann et al. 1999). Congruent with previous results (Serrien and Wiesendanger 2000), our study suggests a similar loss in temporal coordination when the two hands have to achieve a common goal.

There exists intriguing parallels between the current results and findings on the cerebellar role in eyelid conditioning. While lesions to the cerebellar cortex impair the conditioning of an eyelid response to a new stimulus, a previously conditioned eyelid response is preserved (Bracha et al. 1997; Woodruff-Pak et al. 1985). As with the APA studied here, the adaptive timing of the response is impaired and the response is initiated too early (Koekkoek et al. 2003; Perrett et al. 1993). Other studies show that when participants are instructed to lift both arms as fast as possible to a horizontal position, the movement is preceded by a forward shift of the center of gravity to counter the perturbations of stance resulting from the inertial forces of the limb. This form of an APA is also initiated early in patients with cerebellar damage (Diener et al. 1989).

The premature onset of the unloading APA could reflect a safety strategy: reducing the postural force early increases the likelihood that the APA is initiated prior to the unloading even if the timing is inaccurate. Yet there is a potential cost to prematurely initiated APAs. If the postural force is reduced too soon, the object may be dropped. Given this, we suggest that the early onset of the APA in cerebellar patients reflects a general mechanism by which the intact cerebellum ensures accurate timing across different joints and modalities. Activity in the deep cerebellar nuclei may reflect the components of an action (Thach et al. 1992). Inhibition from the Purkinje cells of the cerebellar cortex is used to optimize the response: the release of inhibitory input allows the response components to be initiated at the right moment in the course of an action. When the cerebellar cortex is damaged, the action components are still triggered, but the insertion of adaptive delays is abolished. According to this hypothesis, the cerebellar cortex coordinates action not by actively introducing new movement components, but by sculpting the preexistent response (Medina et al. 2000; Thach et al. 1992).

To our surprise, the callosotomy patient learned to make an APA when a button-press triggered unloading and showed intact short-term plasticity during self-unloading. This result is at odds with previous results indicating that the corpus callosum is essential for the acquisition of novel bimanual skills (Franz et al. 2000; Preilowski 1972). This discrepancy may result from differences in the tasks. Callosotomy patients failed to acquire skills that involved volitional gestures with each hand (e.g., tying a hook to a fishing line), whereas in the task studied here, only one hand moved actively while the other provided a postural function. This suggests that the integration of volitional commands to both hands into a novel unitary bimanual action may require the corpus callosum, whereas the acquisition and adaptation of an APA produced by a postural hand may not. However, the onset of the acquired postural adjustment was delayed in the individual with callosal agenesis compared with the control participants, indicating that the corpus callosum may play some role in the learning of the anticipatory response.

Intact learning without the corpus callosum would require that a subcortical locus integrates the efference copy of the forthcoming lifting action with an error signal from the postural hand. This structure could then modify the motor command to the postural hand to minimize the perturbation. While it appears that the cerebellum is the site of this integration, we can only offer a few speculations concerning how the neural signals required for bimanual coordination are brought together in the cerebellum. One possibility is that communication occurs between the two halves of the cerebellar cortex. Some parallel fibers do cross the cerebellar midline; however, such fibers are not long enough to connect the two cerebellar hemispheres (Mugnaini 1983).

Alternatively, inputs from the cortex to the cerebellum may be bilateral. Studies using retrograde labeling techniques in cats and rhesus monkeys have provided evidence that ~10% of pontine neurons project bilaterally to the cerebellar hemispheres (Brodal and Jansen 1946; Brodal 1980; Rosina and Provini 1984). A recent physiological study supports the idea that bilateral pontine projections may be functionally relevant. Simple spike activity in the lateral cerebellum is observed during unimanual movements with either limb, and in fact, the activity level in many of these cells is similar for ipsi- and contralateral movements (Greger et al. 2004). It is unclear if olivary inputs also project bilaterally. Nonetheless, if we assume the climbing fiber pathway conveys information regarding the perturbation of the postural hand, it is not essential that these signals be available to both sides of the cerebellum. Rather contralateral mossy fiber projections could be used to facilitate the volitional movement and ipsilateral mossy fiber projections could be used to modify the output from the cerebellum ipsilateral to the postural hand. Following this hypothesis, the hemisphere of the cerebellum ipsilateral to the postural hand would be the site of plasticity for learning and adjusting APAs during bimanual actions.

Indeed, short-term plasticity and learning of the button press-linked APA were completely abolished when unilateral patients supported the object with the ataxic, ipsilesional hand. Furthermore, when they lifted the object with the ataxic hand, short-term plasticity was preserved. Ironically, all of the unilateral patients found the latter configuration to be much harder because they had to use their ataxic hand to perform the overt action.

The results in the button-triggered unloading experiment were more mixed: although half of the patients showed significant learning when their contralesional hand held the object, the other half did not. The reason for this inconsistency remains to be determined. The contribution from the damaged side of the cerebellum to the volitional action might have provided a noisy input for the generation of an APA. In addition, the patients found it difficult to press the button with their ataxic, ipsilesional hand. This may have led them to direct more attention to the button-press component of the task and this might have reduced the rate of learning (Lang and Bastian 2002).

In summary, our results provide a novel view of the functional role of the cerebellum in bimanual coordination. While the cerebellum does not appear to be necessary for the overlearned APA in the bimanual unloading task, our results suggest an essential role for the cerebellum in short-term modifications of this well-learned behavior and in the acquisi-

tion of a new form of bimanual coordination. Furthermore, the ipsilateral cerebellum appears to play a role in the temporal organization of this predictive response. At a more general level, our results are congruent with a hypothesis of cerebellar function that has emerged from the study of a variety of behaviors. It indicates that the cerebellum plays a crucial role in the adaptive timing of neural activation patterns and the capability for rapidly modifying these patterns based on interactions with the environment (Mauk et al. 2000).

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