Hereditary Cerebellar Ataxia Progressively Impairs Force Adaptation During Goal-Directed Arm Movements

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Maschke, Matthias, Christopher M. Gomez, Timothy J. Ebner, and Jürgen Konczak. Hereditary cerebellar ataxia progressively impairs force adaptation during goal-directed arm movements. J Neurophysiol 91: 230–238, 2004. First published September 17, 2003; 10.1152/jn.00557.2003. We investigated how humans with hereditary cerebellar degeneration [spinocerebellar ataxia (SCA) type 6 and 8, $n = 9$] and age- and sex-matched healthy controls ($n = 9$) adapted goal-directed arm movements to an unknown external force field. We tested whether learning could be generalized to untrained regions in the workspace, an aspect central to the idea of an internal model, and if any learning could be retained. After removal of the force field, SCA patients showed little or no learning-related aftereffects indicating that repeated force-field exposure never led to successful force compensation. In contrast, healthy control subjects quickly adapted their movements to the new force field. The difference in force adaptation was significant for movements to targets that required both the shoulder and elbow joint ($P < 0.001$). Moreover, the generalization of learned movements to targets outside the learned workspace was prevented by the cerebellar degeneration ($P < 0.01$). Retention of force adaptation was significantly lower in SCA patients ($P = 0.003$). The severity of ataxia in SCA patients correlated negatively with the extent of learning ($r = -0.84, P = 0.004$). Our findings imply that progressive loss of cerebellar function gradually impairs force adaptation. The failure to generalize learning suggests that cerebellar degeneration prevents the formation of an internal representation of the limb dynamics.

INTRODUCTION

Empirical evidence suggests that the human cerebellum plays a role in motor learning processes such as conditioning, habituation, and adaptation (Gerwig et al. 2003; Martin et al. 1996; Maschke et al. 2000a,b; Timmann et al. 2000; Weiner et al. 1983; Woodruff-Pak 1997). In addition, the cerebellum is said to be involved in the learning of complex skills as shown by many functional imaging and behavioral studies (Deuschl et al. 1996; Doyon et al. 2002; Flament et al. 1996; Friston et al. 1992; Imamizu et al. 2000; Miall et al. 2001; Nezafat et al. 2001; Penhune and Doyon 2002; Seitz and Roland 1992; Seitz et al. 1994; Topka et al. 1998b). However, the exact function of the cerebellum in implicit motor learning is still matter of debate. For example, system-theoretic approaches suggested that the acquisition of an internal model of the limb dynamics serves as the basis of skill learning (Kawato et al. 1987; Shadmehr and Mussa-Ivaldi 1994; Wolpert et al. 1995) and that the cerebellar cortex appears to participate in acquisition and storage of these internal models (Imamizu et al. 2000; Nezafat et al. 2001; Kawato and Gomi 1992; Kitazawa et al. 1998; Shadmehr and Holcomb 1997; Shidara et al. 1993; Wolpert et al. 1998). This claim for a prominent role of the cerebellum in sensorimotor learning is contrasted by recent evidence demonstrating that the cerebellum is important for the expression of an improved motor performance during skill learning but might not have been involved in the learning process itself (Seidler et al. 2002).

In light of this discussion, it is noteworthy that only a few studies investigated patients with cerebellar disorders during motor learning of novel situations such as throwing while looking through prisms (Martin et al. 1996; Weiner et al. 1983). While it seems that an intact cerebellar cortex is necessary for visuomotor adaptation, it remains unclear how adaptation to an unknown force field is mediated by the cerebellum. From an anatomical point of view, one may presume that the cerebellum plays a role in force adaptation given that the cerebellum receives major sensory input from the spinocerebellar tracts (Bloedel and Courville 1981; Bosco and Poppele 2001). Likewise, a recent imaging study in which subjects performed goal-directed arm movements in an external force field revealed an activation of the ipsilateral cerebellar cortex during the initial adaptation, whereas a region within the anterior cerebellar cortex showed a decrease in activity during long-term adaptation (Nezafat et al. 2001). These results hint at a cerebellar involvement during force adaptation.

The present study seeks to systematically determine the dependency of adaptation of goal-directed arm movements to an unknown force field on the integrity of the cerebellum. We choose to investigate this paradigm in patients with spinocerebellar ataxia (SCA) type 6 and type 8. Both SCA types are genetically caused by trinucleotide repeat expansions and characterized as slowly progressive, pure, or predominately cerebellar ataxia (Day et al. 2000; Gomez et al. 1997). Autopsy studies have revealed intact dorsal columns and spinocerebellar tracts and nerve conduction studies have shown only a mild sensorimotor neuropathy in lower but not upper limb nerves in SCA6 (Gomez et al. 1997). Moreover, patients with SCA8 do not present signs of sensory nerve or tract involvement (Day et al. 2000). Thus proprioceptive arm afferents are intact in SCA6 (Bloedel and Courville 1981; Bosco and Poppele 2001).

The present study seeks to systematically determine the dependency of adaptation of goal-directed arm movements to an unknown force field on the integrity of the cerebellum. We choose to investigate this paradigm in patients with spinocerebellar ataxia (SCA) type 6 and type 8. Both SCA types are genetically caused by trinucleotide repeat expansions and characterized as slowly progressive, pure, or predominately cerebellar ataxia (Day et al. 2000; Gomez et al. 1997). Autopsy studies have revealed intact dorsal columns and spinocerebellar tracts and nerve conduction studies have shown only a mild sensorimotor neuropathy in lower but not upper limb nerves in SCA6 (Gomez et al. 1997). Moreover, patients with SCA8 do not present signs of sensory nerve or tract involvement (Day et al. 2000). Thus proprioceptive arm afferents are intact in SCA6 and SCA8 patients. Therefore possible adaptation deficits found in these patients would not be due to disturbed sensory input from the periphery. We hypothesized that SCA patients would exhibit difficulties in force-field adaptation, which could not be explained by motor control deficits alone. Furthermore,
if an intact cerebellum is essential for this form of adaptation then progressive cerebellar degeneration ought to lead to decreased learning, generalization, and retention.

**METHODS**

**Subjects**

Nine patients with degenerative cerebellar disorders (age 46.2 ± 7.5 (SD) yr, range 38–63 yr, 4 females, 5 males) and nine age- and sex-matched healthy control subjects (age 46.2 ± 7.1 yr, range 38–59 yr, 4 females, 5 males) with no neurological or general medical limitations participated. All patients were recruited from the cerebellar ataxia outpatient clinic at the University of Minnesota and were diagnosed as having a genetically defined spinocerebellar ataxia (SCA) either type 6 (n = 5) or type 8 (n = 4). They had a moderate to severe cerebellar ataxia based on the International Cooperative Ataxia Rating Scale of the World Federation of Neurology (WFN scale) (Trouillas et al. 1997). Main symptoms were gait and stance instability, limb ataxia predominantly involving the lower limbs, cerebellar dysarthria, and a variable severe cerebellar oculomotor dysfunction (gaze-evoked nystagmus, saccadic dysmetria). Neurological examination including sensory testing (vibration sense, light touch, pinprick sensation, and position sense at index finger and first toe) revealed no extracerebellar signs such as peripheral nerve disease or motor neuron involvement. All patients were right-handed based on results of the Edinburgh Handedness Inventory (Oldfield 1971). Eight control subjects were right-handed and one left-handed. Descriptive characteristics of patients are summarized in Table 1. All patients and healthy subjects gave informed consent. The study was approved by the institutional review board of the University of Minnesota.

**Experimental setup**

Subjects were asked to move a cursor (cross with a length of 0.5 cm) on a monitor screen (size: 30.8 × 23 cm) by moving a robot arm manipulandum with two translational degrees of freedom for elbow and forearm motion (Fig. 1A). The manipulandum control was implemented through a UNIX and PC workstation. During testing, subjects sat on a chair in front of the manipulandum. Shoulder straps restrained forward movements of the shoulders. The right shoulder was aligned with the starting circle on the screen and with the torque engines of the robotic arm. The distance to the manipulandum and chair height was individually adjusted to assure that the initial arm posture was almost identical for all subjects at the holding position (upper limb to forearm in clockwise direction; patients: 104.4 ± 2.8°, controls: 104.8 ± 1.5°).

**TABLE 1. Basic characteristics of patients**

<table>
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<th>N</th>
<th>Age</th>
<th>Sex</th>
<th>Handedness*</th>
<th>Walking Aid</th>
<th>Disease, yrs</th>
<th>WFN</th>
<th>Posture and gait</th>
<th>Upper limb ataxia</th>
<th>Lower limb ataxia</th>
<th>Speech</th>
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m, male; f, female; * according to the Edinburgh Handedness Score (range 20 (right handed) to −20 (left handed)) (Oldfield, 1971); † SCA, spinocerebellar ataxia; ‡ WFN score, World Federation of Neurology Ataxia Score (total score: Range 0–100, the higher the score, the more severe the ataxia) (Trouillas et al. 1997).

**Procedure**

The paradigm consisted of a center-out task to selected targets. Subjects had to bring the cursor within a starting circle (Ø 2 cm; Fig. 1B). Once the cursor was within the starting circle, its color turned to yellow, and a smaller target (Ø 0.5 cm) appeared in yellow. The disappearance of the starting circle and the change of the target color to green represented the go signal. Subjects were instructed to move the cursor fast, accurate and in a straight line to the target at either 45 or 90° or to 0, 30, 60, 120, and 150°. The path length from the starting circle to each of the targets was 10 cm on the monitor (Fig. 1B). The experiment was divided into five blocks each consisting of 120 trials (Fig. 1C). Within each block the targets were presented in a pseudo-randomized order. In the first block, subjects learned to move to the two targets with no external force present (baseline condition). During the next three blocks, a velocity-dependent force field was produced through the torque motors of the manipulandum. The force field was defined as (F = force applied on the handle, v = resulting velocity)

\[
F = B \cdot v \quad \text{where} \quad B = \begin{bmatrix} 0 & 13 \\ -13 & 0 \end{bmatrix} \text{N/s/m}
\]

In the adaptation (block 2), generalization (block 3), and retention conditions (block 4), unperturbed trials, so called catch trials, were interspersed every 10th trial. These catch trials produced a displacement of the movement in the opposite direction of the displacement observed in perturbed trials and were used to obtain a measure for the degree of learning related aftereffects. During the second and fourth block, catch trials were performed to either 45 or 90° targets. In contrast, during the third block (generalization condition), catch trials consisted of movements to 0, 30, 60, 120, and 150°. After the generalization condition, subjects had a 3-h lunch break before the start of block 4 (retention condition). The fifth and last block tested the unperturbed performance to targets used to test generalization (i.e., 0, 30, 60, 120, and 150° targets).

**Data analysis**

The position and velocity of the manipulandum handle in the transverse plane were recorded for each trial and subsequently analyzed using Matlab and SAS. To obtain spatial information of the trajectories the maximal perpendicular displacement (YDmax) in the y direction for each trial was calculated. Therefore the time-position series of each trial to the 45° target was rotated by 45° to align the x axis to the 45° target. Cerebellar patients are known to produce large endpoint errors due to their intention tremor and dysmetria. To avoid erroneous amplification of the YDmax by these endpoint errors, we...
Adaptation to a velocity-dependent force field

RESULTS

Only analyzed the first 75% of the individual trial length, which represented the major portion of the transport phase. To provide information about the time course of learning, we calculated an adaptation index (AI) (Criscimagna-Hemminger et al. 2003), which combined the mean of the YDmax of 10 successive perturbed trials to one target (i.e., 45 or 90°) and the YDmax of one catch trial to the same target, which was interspersed in these 10 trials

\[
AI = \frac{YDmax_{CatchTrial}}{YDmax_{CatchTrial} + \text{meanYDmax}_{PerturbedTrials}}
\]

Because a total of 10 trials to each target were interspersed in the second block (adaptation condition) and in the fourth block (retention condition), 10 AIs were obtained for each target. An analysis of covariance (ANCOVA) was separately performed for each target with AI (1st and 5th AI of the adaptation and retention) as the dependent variable (group = between-subjects factor, mean peak velocity of a bin of 10 successive trials as covariate). The perpendicular displacement of catch trials to targets used to test the ability to generalize learning was compared with the baseline performance of the last 16 movements to these targets obtained in baseline trials in the patient group demonstrating a higher variability and pronounced endpoint errors (Fig. 2C). However, the patient with severe ataxia exhibited a higher variability and pronounced endpoint errors (Fig. 2C). When exposed to a force field, hand-trajectory formation of all subjects was immediately affected demonstrating a right- and downward deviation. While the control subject straightened his trajectories during subsequent trials, both patients showed a decomposed movement with little or no signs of straightening in successive trials regardless of the severity of their ataxia (Fig. 2, D–F).

This assessment is corroborated by data demonstrating learning-related aftereffects, which were obtained during interspersed catch trials (null field) during the adaptation block. While the catch trials of the representative control subject showed a pronounced upward displacement with respect to the baseline, catch trial displacement of both patients fell within their baseline displacement range (Fig. 2, A–C). Group data showed that during force trials the mean maximal perpendicular displacement (YDmax) in the downward direction was significantly higher in cerebellar patients, revealing that their trajectory formation was more affected by the force field. However, during catch trials, the mean YDmax in the upward direction was not significantly different from the mean YDmax obtained in baseline trials in the patient group demonstrating a failure to show an aftereffect (Fig. 3A).

To quantify the degree and the time course of learning, we computed an adaptation index (AI) for bins of 10 successive trials that was based on the maximal perpendicular displacement of the catch and perturbed trials (formula see METHODS). Values for AI ranged between 0 and 1, with a higher value indicating a stronger adaptation. For 45° movements, the AI of the control group rapidly increased from the first to the second bin with a persisting, slighter increase to the end of the adaptation (Fig. 4A). In contrast, cerebellar patients showed a decrease from the first to the second bin and only a slight decrease from the second to the third bin.
increase from the second to the fifth bin (Fig. 4A). Even after accounting for differences in movement velocity between subjects, the two groups showed significant differences in learning during the adaptation block (group × bin interaction effect: *P < 0.001 for 2 group × 2 bin ANCOVA with maximal peak resultant velocity of each bin as covariate). Velocity-adjusted means of the AI were significantly higher in the last bin compared with the first bin in control subjects but not in

![Graph](image-url)

**FIG. 2.** Representative examples of trajectories to 45° of 1 control subject and 2 cerebellar patients. A–C: baseline performance. Superimposed trajectories of catch trials obtained during the adaptation block were deviated in an upward direction in the control subject (A) but were situated in the range of baseline trajectories in both cerebellar patients (B and C). D–F: adaptation to force field. G–I: retention of force adaptation.

**FIG. 3.** Group data of the maximal perpendicular displacement (YDmax) of trials of the baseline block and force trials and catch trials of the adaptation block. A: mean ± SE of YDmax to 45°. Both controls and patients revealed a pronounced negative (downward) displacement in force trials, which was significantly higher in patients (*, *P < 0.001). In contrast, controls showed a prominent positive (upward) displacement during catch trials indicating a strong aftereffect. In cerebellar patients, the YDmax of catch trials was significantly lower and did not exceed the extent of the upward displacement during baseline trials demonstrating the impairment of force adaptation. B: mean ± SE of YDmax to 90°. The difference between the positive displacement during catch trials between controls and patients was less pronounced in movements executed to 90°.
cerebellar patients (control group means: 0.35 vs. 0.71, patient group means: 0.45 vs. 0.33). The amount of learning expressed through the AI at the end of the adaptation block (5th bin) correlated negatively with the severity of ataxia measured on the WFN ataxia scale ($r = -0.84$, $P = 0.004$; Fig. 5). In contrast, disease duration was not correlated with the AI of the fifth bin ($r = 0.001$, $P > 0.5$). Moreover, the resultant peak velocity, time-to-peak velocity and 75% movement time were not significantly correlated with the AI of the fifth bin. This demonstrates that differences between groups in hand velocity and, consequently, in the velocity-dependent perturbation force could not account for differences in learning. Peak velocities of patients and controls are shown in Fig. 6. Kinematic variables are summarized in Table 2.

For movements executed to the 90° target, the AI was lower in cerebellar patients, but the difference at the end of the adaptation was not significant (Fig. 4B). Adjusted means of the AI were 0.39 (1st bin) and 0.51 (last bin) for control subjects and 0.44 (1st bin) and 0.37 (last bin) for cerebellar patients ($P > 0.05$). The difference of the mean YDmax during catch trials between patients and controls was smaller in movements to the 90° target compared with the difference obtained in 45° movements (Fig. 3B). The AI of movements to the 90° target at the end of the adaptation block did not correlate with the WFN ataxia scale ($r = 0.14$, $P > 0.05$).

**Generalization of learning**

After the adaptation condition, the ability to generalize the adapted movement to five different targets outside the learned...
workspace was tested (generalization condition). Control subjects revealed prominent after-effects to targets near to the trained workspace, i.e., to the 60° and in a lesser amount to the 30° target (Fig. 7) as expressed by the perpendicular displacement adjusted to the baseline performance to these targets. After-effects to targets decreased with further distance (0, 120, and 150°). In contrast, cerebellar patients did not exhibit clear differences between movements to targets used during the adaptation block and targets presented during the generalization block (Fig. 7). The difference between SCA patients and control subjects was statistically significant (P < 0.01).

Retention of force adaptation

After a consolidation block, subjects had a break of 3 h before beginning with the second portion of the experiment that tested the retention of force adaptation. Exemplar trajectories of a control subject and two patients are shown in (Fig. 2, D, G, E, F, H, and I). The group analysis revealed intact retention in the control group but reduced or absent retention in the cerebellar group. Mean AI of the first bin of retention block was higher than the mean AI of the first bin of the adaptation block in control subjects for movements to the 45° target (control group means: 0.36 vs. 0.59), whereas in cerebellar patients an inverse relationship was obtained (patient group means: 0.46 vs. 0.21; Fig. 4A). This difference was significant (ANCOVA: group × bin interaction effect: P = 0.003).

In contrast, the AI at the beginning of the retention appeared to be similar between control subjects and cerebellar patients to the 90° target (Fig. 4B). The mean AI of the first bin of the retention block was higher than the first bin of the adaptation block in both groups [control group means: 0.37 vs. 0.55, patient group means: 0.44 vs. 0.53; P > 0.05 (ANCOVA)].

**DISCUSSION**

This study explored whether the adaptation to unknown external forces relies on the integrity of the cerebellum. We exposed patients with a genetically defined degeneration of the cerebellum to a velocity-dependent unknown force field during the execution of volitional arm movements. The main results of this study are 1) SCA patients were impaired in force adaptation, 2) progression of cerebellar ataxia significantly correlated with the impairment of learning, 3) healthy subjects but not SCA patients generalized learning to untrained workspace, and 4) in SCA patients, the retention of learning was impaired for movements to the 45° target, but less affected for simple horizontal movements (90° target).

Increased cerebellar degeneration progressively impairs force adaptation

Results of the present study underline the role of the human cerebellum in adaptive processes as shown by studies investigating prism adaptation in patients with cerebellar lesions (Martin et al. 1996; Weiner et al. 1983) and complement results of animal experiments (Baizer and Glickstein 1974; Baizer et al. 1999). Thus it appears that the cerebellum is not only necessary for a visually driven adaptation but also involved in adaptive processes that rely to a larger extent on proprioceptive signals. Our finding of an impaired force adaptation in cerebellar patients further corroborates recent research showing that a decline in movement errors during early force adaptation is associated with a decrease in blood flow of the ipsilateral posterior cerebellar cortex (Nezafat et al. 2001). However, from results of a recent fMRI study, it was argued that the cerebellum contributes to motor performance but not to motor learning itself (Seidler et al. 2002). Against the background of this finding, one may speculate that the impaired force adaptation of cerebellar patients in the present study merely represents performance deficits. Obviously, our patients exhibited kinematic deficits, as shown by decomposed movements, larger endpoint errors, low movement velocities and longer movement times (Table 2, Fig. 2). Such low velocities translated into smaller forces at the handle. In healthy individuals, lower perturbation forces lead to faster adaptation. This was not observed in our patient group. On the contrary, although generally exposed to smaller forces, learning was not accelerated but revealed clear kinematic deficits and had a longer time course. Hence, we here saw learning deficits that cannot solely be explained by deficits in motor performance. The view that the cerebellum is indeed involved in motor adaptation and not only important for the expression of learning is supported by

*Fig. 7. Generalization. Control subjects showed prominent aftereffects to 60° and to a lesser extent also to 30°, indicating that they were able to generalize learning. In contrast, the lack of aftereffects in cerebellar patients to targets used in generalization reflected the patient’s failure to acquire an internal model of the limb dynamics.*
the fact that infarction of the territory of the posterior inferior artery (PICA) did prevent adaptation of movements to the wearing of prisms (Martin et al. 1996). Interestingly, PICA infarction is not accompanied by a relevant ataxia of arm movements. In contrast, patients with severe ataxia due to ischemic stroke within the territory of the superior cerebellar artery (SCA) were still able to adapt to prisms. This dichotomy suggests a functional compartmentalization of adaptation and motor control processes in the human cerebellum.

The progression of cerebellar ataxia quantified by the WFN ataxia scale was highly correlated with a progressive failure of force adaptation. Given that the clinical worsening of the disease signals a progressive Purkinje cell loss, our data show that cerebellar degeneration progressively impairs the ability of humans to adjust motor commands to changes in the environmental forces. Our finding that force adaptation was not abolished in patients with less severe ataxia but was massively impaired in those patients with a higher WFN ataxia score (Fig. 5) becomes plausible, if one considers that those areas that are active during force adaptation (cerebellar cortex of the posterior lobe and lateral cerebellum) (Nezafat et al. 2001) only show mild to moderate Purkinje cell loss in SCA 6 patients (Gomez et al. 1997). Future studies should clarify whether this paradigm is suitable to detect subtle cerebellar dysfunctions in asymtomatic SCA gene carriers and may serve as a surrogate paradigm to detect subtle cerebellar dysfunctions in the human cerebellum.

As a final point, the incompete force-adaptation in cerebellar patients cannot easily explain, why the adaptation index in the cerebellar group dropped off after the first bin, while it rose in the control group. One may argue that cerebellar patients might have had a higher and more sustained co-contraction during the first movements resulting in a higher AI in the initial bin of the present study. Recent studies suggested that co-contraction might be accompanied by a reduction of perturbing effects of external forces resulting in an increased accuracy (Thoroughman and Shadmehr 1999). Others revealed that co-contraction decreases perturbations caused by joint interaction torques (Gribble and Ostry 1998). This led to the assumption that co-contraction might be used by the nervous system as a strategy to improve limb movement accuracy (Gribble et al. 2003). Against this background it might be speculated that cerebellar patients used a higher co-contraction to decrease perturbations and that this co-contraction declined in successive trials of the second bin due to fatigue or lack of attention. However, EMGs were not recorded, and, thus the question of a possible influence of co-contraction remains open.

Learning does not generalize to untrained workspace in SCA patients

Recent research on goal-directed action in humans led to the hypothesis that the brain uses a neural representation of the limb-dynamics as controllers for feedforward motor control (Jordan et al. 1994; Kalveram 1992; Kawato et al. 1987; Lackner and Dizio 1994; Shadmehr and Mussa-Ivaldi 1994; Shidara et al. 1993; Wolpert and Kawato 1998; Wolpert et al. 1995). Such representations, so-called inverse dynamics models, transform the kinematic data of a movement plan into the required limb dynamics. In contrast, a forward dynamics model calculates joint kinematics on the basis of a given set of dynamics. Evidence for the presence of an inverse model of the limb dynamics arose from studies investigating force-field adaptation in healthy human subjects (e.g., Shadmehr and Mussa-Ivaldi 1994). Characteristic features of the arm trajectories that were indicative of an underlying inverse dynamics model were 1) learning-related after-effects (i.e., overshoot in the opposite direction after removal of the force-field) and 2) generalization of learning to untrained workspace. Such generalization of learning would be absent in a system that associates limb position with experienced force in a simple look-up table. In the present study control subjects presented learning-related after-effects and were able to generalize learning to targets they never trained before. This finding is consistent with the notion that control subjects acquired an inverse motor model of the limb dynamics. However, learning was not universal given that the learning related aftereffects were not found over the entire arm’s workspace, but decayed with distance from the perturbed locations. Our result that force-adaptation only partially extends to untrained portions of the workspace in healthy subjects is in line with the findings of a previous study (Gandolfo et al. 1996).

In contrast to control subjects, patients’ failure to adapt and to exhibit generalization implies that the acquisition or modification of these inverse dynamics models is impaired in cerebellar disease. This finding in humans complements previous results from animal, computational and functional imaging studies suggesting that the cerebellum plays a role in acquisition of an inverse dynamic model (Imamizu et al. 2000; Kawato and Gomi 1992; Kitazawa et al. 1998; Nezafat et al. 2001; Shadmehr and Holcomb 1997; Shidara et al. 1993).

Retention of learning is differentially impaired in SCA patients

Cerebellar lesions impair the retention of simple forms of motor learning such as long-term habituation of reflexes in humans (Maschke et al. 2000a). Here cerebellar patients demonstrated a reduced or even absent retention of force adaptation. However, it is noteworthy, that the patients revealed an impaired retention largely for the 45° movements, while demonstrating an improved adaptation during recall for 90° movements (increase in AI values from the 5th to the 6th bin). In a similar force adaptation paradigm, long-term recall resulted in a shift of activations from prefrontal regions to dorsal premotor and posterior parietal structures demonstrating that extracerebellar regions are engaged in the retention of force adaptation. However, this activation shift was accompanied by activations within the anterior cerebellar cortex indicating that the retention of force adaptation relies on a network of cerebellar and extracerebellar structures (Nezafat et al. 2001; Shadmehr and Holcomb 1997). Following this line of thinking, retention might have been mediated by parts of the cerebellum that store limb dynamics for 90° but not for 45° movements, although our data cannot speak conclusively to such claim. In addition, one may argue that movements to the 90° target resembled more single-joint movements given that subjects mainly had to rotate their shoulder to reach the target, whereas 45° movements required both shoulder rotation and elbow extension.
Furthermore, previous studies that employed a similar force-adaptation paradigm have revealed that healthy humans generally exhibit accelerated learning to the 90° target (Shadmehr and Mussa-Ivaldi 1994). This might indicate that this phenomenon is not particular to the cerebellar group and that the difference in adaptation of movements to 45° and 90° observed in cerebellar patients cannot be solely understood as a motor deficit due to cerebellar dysfunction. Knowing that cerebellar patients have difficulties in compensating the interaction torques arising during multi-joint motion (Bastian et al. 1996, 2000; Goodkin et al. 1993; Topka et al. 1998a), the seemingly simpler 90° movement might have required lower computational demands in motor control mechanisms resulting in an enhanced opportunity for adaptation and retention.

Collectively, results of the present study provide strong evidence that motor adaptation to unknown external forces relies on the integrity of the cerebellum. The decrease in adaptive ability was nearly linearly related to the extent of cerebellar degeneration.

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REFERENCES


