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Adaptive changes in responses to repeated locomotor perturbations in cerebellar patients

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Abstract This study examined the responses of cerebellar patients and a group of age- and sex-matched control subjects to repeated changes in treadmill speed in order to test whether cerebellar patients can adapt their gait to this type of perturbation and, if so, whether their responses are comparable to those of controls. While the subject walked on the treadmill, a perturbation consisting of a sudden slowing of the treadmill followed by a sudden increase back to the original speed was applied repeatedly at a specific time during the step cycle. Both the control subjects and cerebellar patients were able to compensate for the perturbations by minimizing their postural sway and changing step length. However, the nature of the compensatory changes in step length differed between these subject groups. Control subjects compensated for the perturbation by consistently using the same leg to initiate the response to the perturbation and by adapting a pattern of stepping such that the EMG characterizing the response occurred in a manner that was entrained to the timing of the normal locomotor cycle. In contrast, the patients, although undergoing modifications in step length, employed a much less consistent motor pattern from trial to trial than that of the normal subjects. An inconsistent pattern among their responses was apparent in both the analysis of stepping and in the EMG activity of the gastrocnemius and anterior tibial muscles. These results suggest that, although the cerebellar patients can adapt their behavior in response to locomotor perturbations, they do not establish a motor pattern comparable to that employed by normal subjects.

Key words Cerebellum · Locomotion · Perturbation · Adaptive process · Cerebellar patients

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Introduction

The cerebellum has been implicated in the modification of several different motor behaviors (see Bloedel and Bracha 1995 for a review). These include the vestibulo-ocular reflex (Lisberger 1988), the nictitating-membrane reflex (Irwin et al. 1992; Welsh 1992; Woodruff-Pak et al. 1993; Bloedel and Bracha 1995), gain adjustments required for visuo-motor tracking tasks (Miall et al. 1987; Ojakangas and Ebner 1992), force production (Gilbert and Thach 1977; Thach et al. 1992), prism adaptation (Beizer and Glickstein 1974; Weiner et al. 1983), and postural adjustment to platform perturbations (Nashner and Grimm 1978; Horak and Diener 1994). The cerebellum also is involved in the acquisition of novel volitional movements. Several recent positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies demonstrated the activation of cerebellar structures during the early acquisition period of a movement trajectory (Seitz et al. 1994), finger movement sequences (Seitz et al. 1990; Friston et al. 1992; Seitz and Roland 1992; Jenkins et al. 1994; Jueptner et al. 1997), and a visuo-motor transformation (Ebner et al. 1996). However, the exact mechanisms of the cerebellum's participation in modifying the central processes underlying the acquisition of these movements are still unknown. Recent studies using a behavioral paradigm in which cats learned novel patterns of complex forearm movements demonstrated that, although the cerebellum is not a critical storage site required for retaining the memory engram established during the learning of this behavior, it still likely participates in the acquisition of complex movements (Shimansky et al. 1994; Milak et al. 1995; Wang et al. 1997). In support of this view, patients with cerebellar lesions could improve their performance in a visuo-motor learning task involving the recall and tracing of memorized shapes. However, they could not attain the same level of performance as normal subjects (Timmann et al. 1996). These findings together with the recent data of Milak et al. (1995) and Wang et al. (1997) (see also Bloedel et al. 1996) suggest that, rather than serving as a critical storage

site, the cerebellum participates in specifying and/or selecting an effective motor pattern for executing the desired movement during the acquisition process (Milak et al. 1995).

Even though the cerebellum's involvement in regulating the coordination of locomotor behavior has been demonstrated in both clinical (Gilman et al. 1981) and laboratory studies (Armstrong 1986), the involvement of the cerebellum in generating responses to perturbations of on-going locomotion only recently has been explored. Neurons in the cerebellar nuclei were modulated when cats responded to the braking and resumption of treadmill movement (Schwartz et al. 1987). Increased complex spike discharge of Purkinje cells was observed during the same type of modification in treadmill speed (Kim et al. 1987; Lou and Bloedel 1992a) and in association with the displacement of ladder rungs (Andersson and Armstrong 1987). These complex spike responses were associated with alterations in the modulation of simple spikes in the same population of Purkinje cells (Lou and Bloedel 1992b). It is not known how this modulation contributes to the coordination of movements evoked by unexpected perturbations or to the acquisition of an effective adaptive response when the perturbation is applied in successive steps. The possibility that the cerebellum is important for the acquisition of adaptive changes in treadmill locomotion was emphasized recently by Yanagihara and Kondo (1996), who demonstrated that inhibition of nitric-oxide synthesis in the cerebellar cortex was associated with a decreased capacity to acquire imposed asymmetrical gait patterns.

To obtain insights into the types of compensatory changes to which the cerebellum contributes, the responses of cerebellar patients to repeated sudden changes in treadmill speed during locomotion were examined. The specific objective of the present study was to test the hypothesis that cerebellar patients can adapt their gait to a randomly applied perturbation of the step cycle, but that the adaptive strategies they employ are different than those of normal subjects. The selected patients had only minimal clinical signs related to locomotion. Consequently, it was possible to look for changes in patterns of adaptation to locomotor perturbations in a population of patients with minimal deficits in normal stepping. The results will show that cerebellar patients adapted their postural sway and step length to compensate for the perturbation. However, these patients employed a different motor pattern than normal subjects. Furthermore, the modulation of EMG activity in antagonistic pairs of leg muscles did not return to the near-normal temporal and amplitude characteristics observed in control subjects following adaptation. A preliminary study has been reported elsewhere (Rand et al. 1995).

Materials and methods

Subjects

Five patients having chronic, isolated cerebellar lesions and age- and sex-matched healthy controls were tested in the present study. This study was approved by the Institute's Internal Review Board overseeing the use of human subjects in research and ensuring that all studies are performed in accordance with the 1964 Declaration of Helsinki. A brief summary of the patients' clinical characteristics is shown in Table 1. Each had recovered from their cerebellar lesions sufficiently, so that only minimal signs of a clinical locomotor deficit were apparent in normal overground walking. None of the patients required a cane or walker, all could walk using a consistent, normally paced gait without falling, and all exhibited a very modest

Table 1 Summary of patients' clinical characteristics

Subject	Diagnosis	Radiological Findings	Deficits
Patient 1: male, 56 years	Left cerebellar cortex tumor (tumor and undersurface of the tentorium excised in 1988)	MRI: Large lesion of left intermediate and lateral cerebellar cortex secondary to removal of a large tumor (40×30 mm). Slight involvement of the left cerebellar nuclei.	Very mild gait ataxia. Also very mild ataxia and oscillations while pointing with his left arm.
Patient 2: male, 43 years	Left hemisphere dysplastic gangliocytoma (resected in 1991)	MRI: Lesion secondary to removal of a tumor (30×70 mm) involving the left hemisphere, midline and a small part of the right hemisphere.	Exhibited only mild gait ataxia at time of testing.
Patient 3: male, 53 years	Right cerebellar infarct with necrotic lesion (resected in 1995)	MRI: Lesion of the right cerebellar vermis and hemisphere which includes but extends beyond the distribution of the posterior-inferior cerebellar artery (PICA).	Mild dysmetria with right finger to nose and veers slightly to the right with mildly ataxic gait.
Patient 4: male, 44 years	Left cerebellar aneurysm (resected in 1993)	MRI: Post-clipping of a PICA aneurysm. Infarct in the cerebellar distribution of this artery. Cerebellar aneurysm (10×10 mm).	Mild ataxia of upper extremities (left greater than right) with a slightly ataxic gait.
Patient 5: female, 20 years	Pilocystic astrocytoma (resected in 1992)	MRI: Resection of large region of the inferior cerebellar vermis.	No upper extremity involvement. Slight gait ataxia with an occasional drift to the right while ambulating.

broad-based gait. The quality of the patient's locomotion was emphasized by the fact that all of them were able to walk on the treadmill at the same speed as the controls without any difficulty. All subjects signed a written consent prior to participating.

Procedure

The experimental setup is shown in Fig. 1A. The subjects wore a harness and walked on a treadmill at a speed of 1.03 m/s (2.3 miles/h). To familiarize themselves with treadmill walking, the subjects walked on the treadmill for 5–10 min before the experiment. While walking, a perturbation was applied on an average of once every 12 step cycles. The number of step cycles between perturbations was varied pseudo-randomly between 9 and 15 step cycles. The perturbation consisted of a sudden slowing (S-Dec) of the treadmill followed by a sudden increase (S-Inc) up to the original speed (time course shown in Fig. 1B). The mechanical constraints of the treadmill system resulted in an asymmetrical change in treadmill velocity. This waveform was found to be optimal for generating a substantial gait modulation at the selected treadmill speed. For each subject, the duration of the perturbation from S-Dec to S-Inc was consistent throughout the experiment, and it was equal to one step-cycle duration × 1.4. This duration evoked an ample perturbation for the experiment without endangering the stability of the subject. The average perturbation duration used for all subjects was 1526 ms with a range of 1344–1598 ms. The lowest treadmill speed during the perturbation varied as a function of the perturbation duration used for a given subject. The average value across subjects was 0.27 m/s (0.6 miles/h) with a range of 0.13–0.56 m/s (0.3–1.2 miles/h). In the experiments reported here, all perturbations were applied at a specific time of the step cycle (P3), i.e., at approximately two thirds of the stance phase duration (see Fig. 1C).

To determine the perturbation timing in relation to the step cycle, displacement of the right knee angle was measured with an electrogoniometer. Step-cycle duration was measured between successive maximum knee flexions, and the mean step-cycle duration over 20 steps during normal, unperturbed stepping was calculated before the perturbation sessions were initiated. P3 corresponded to 55% of this mean step-cycle duration. Thirty of these fixed perturbations were applied in each of two sessions separated by a third session in which randomly timed perturbations were applied at different times of the step cycle: near the end of the swing phase (P1) and near the beginning (P2) and end (P4) of the stance phase (see Fig. 1C). These times corresponded to 1%, 15%, and 75% of the mean step cycle duration for P1, P2, and P4, respectively. Thirty perturbations (ten perturbations at each perturbation time) were applied in a pseudo-random order. Because the data from these trials did not add any additional insights, they have not been incorporated into the manuscript.

Body position during gait was recorded from the right side using an Optotrak 3D system (Northern Digital) positioned approximately 4 m from the treadmill. Infrared light emitting diodes (IREDS) were placed over the big toe, fifth metatarsal, heel, ankle, knee, thigh, hip, shoulder, neck, and upper back. Positions of the IREDS were sampled at a rate of 100 Hz. In addition, video recordings of gait movements were made from the right side using a video camera (Panasonic, 33 frames/s). In order to record the time of heel strike and toe lift off during gait, pressure sensitive devices (FSR model 302 C, Interlink Electronics) were placed under the big toe and heel of each foot as foot contact switches. EMG signals were recorded from the tibialis anterior (TA) and gastrocnemius (G) of both legs using bipolar surface silver/silver-chloride electrodes. The electrodes were placed 3 cm apart over the belly of each muscle. The EMG signal was amplified (bandwidth 30–3000 Hz), then rectified and filtered through a Paynter filter with a time constant of 50 ms. EMG signals and signals from the foot contact switches were sampled at 400 Hz.

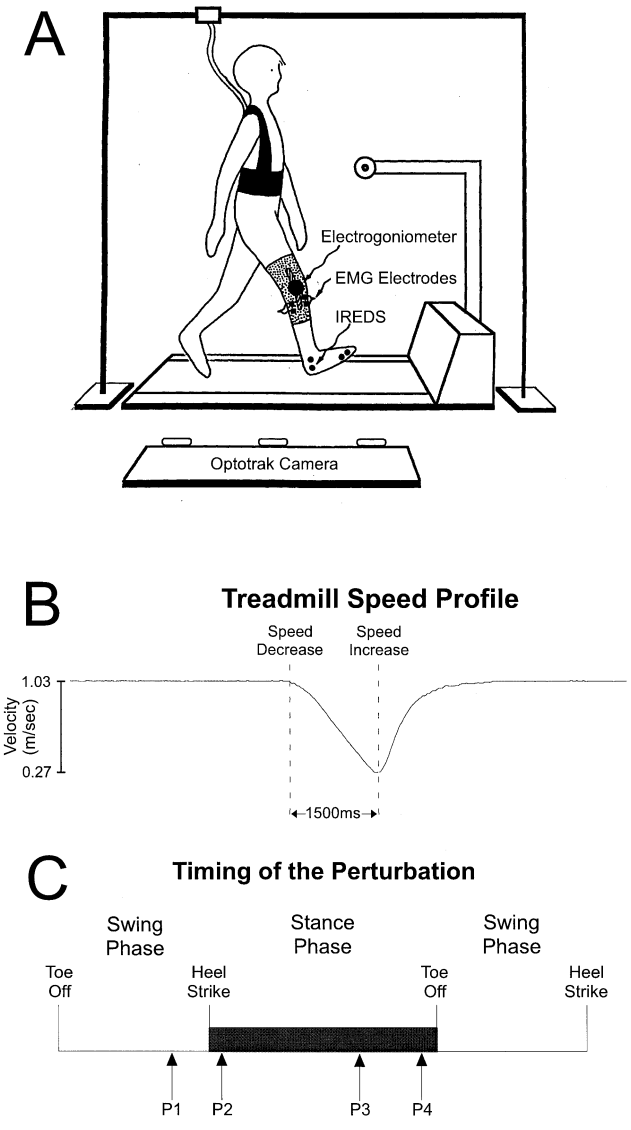

Fig. 1A–C Experimental setup. **A** The subject walked on the treadmill while an electrogoniometer monitored extension and flexion of the right knee joint. EMG electrodes were attached over the tibialis anterior and gastrocnemius muscles of both legs. Infrared light-emitting diodes (*IREDS*) were placed over the positions described in the text for 3D motion recording. **B** Treadmill speed profile. Each perturbation consisted of a decrease and subsequent increase in the treadmill speed. In this example, the speed decreased from 1.03 to 0.27 m/s (2.3–0.6 miles/h). This value varied as a function of the perturbation duration used for a given subject. **C** Timing of the perturbation. The perturbation was given at a specific time during the step cycle (*P3*) when perturbations were applied in the sessions employing nonrandomized stimuli, while for the randomly-timed perturbation sessions, the perturbation was applied at *P1*, *P2*, and *P3*

Data analysis

Responses in the two sessions with 30 fixed perturbations (P3) were selected for further analysis. Each step cycle was divided into a stance phase, defined as the period from heel strike to toe lift off, and a swing phase from toe lift off to heel strike. Adaptive changes of gait in response to the perturbation over the time course of the experiment were examined in terms of step length, postural sway, and EMG patterns. In order to analyze successive movements of

the lower extremities during ambulation, step length was measured from video recordings for each leg as the distance traveled in the sagittal plane during the swing phase. Specifically, step length of the right leg was defined experimentally as the distance from the heel on the left foot to heel strike of the right foot, and that of the left leg as the distance from the heel on the right foot to the heel strike of the left foot. The length of any steps taken backwards in response to the perturbation was assigned a minus value.

For each trial, two measurements of postural sway, defined as the displacement of the upper body as a consequence of angular motion of the trunk, were made. Maximum range of anterior-posterior sway in the sagittal plane and maximum range of medio-lateral sway in the transverse plane were measured as the change in distance between the back IRED and the IRED on the hip within each respective plane. The zero position was the distance between these IREDs in each plane with subjects in the standing position. Anterior-posterior sway and medial-lateral sway were measured within four different time windows: 1–500 ms before the perturbation, during the perturbation (S-Dec to S-Inc), 1–500 ms after, and 501–1000 ms after the perturbation. For EMG analysis, burst duration of the right TA muscle and its onset latency from the perturbation onset (S-Dec) were measured.

Statistical analysis

To assess whether features of the *unperturbed* locomotion of the control and patient groups were different, the length of the step before the S-Dec of the perturbation, designated the control step, and the anterior-posterior sway distance occurring 1–500 ms before S-Dec were measured for each trial. Differences between the control and patient groups for the step length and the sway distance were evaluated statistically using an analysis of variance (ANOVA, group vs. trial).

To compare differences in performance during unperturbed and perturbed locomotion, the averages of both step length and sway distance were calculated for the last ten control steps preceding S-Dec. This average sway-distance measurement was compared with that during the step after S-Inc for the first ten trials using the *t*-test. Similarly, the average control values of step length were compared with those for the first step after S-Dec during the first ten trials, again using the *t*-test.

The progressive changes in postural sway occurring during the responses to the perturbation were determined using a regression analysis for both the patient and control groups. For this purpose, the sway occurring 1–500 ms after the S-Inc were averaged for each trial across subjects. In addition, the average of the first and last ten trials were calculated and compared using the *t*-test. In the analysis of step length, a regression analysis over all trials was performed on the following data, averaged across the subject groups: the first right step of controls occurring after S-Dec, the first right step of patients after S-Dec, the first left step of patients after S-Dec. Because the control subjects quickly adopted a strategy in which no step with the left leg occurred before S-Inc, a regression analysis of this step comparable to that used to analyze the left step of patients could not be undertaken. In addition, the averages of the first and last ten trials were compared for each data set using the *t*-test. The difference in the strategy employed by the patients and controls was assessed statistically by comparing the percent of subjects in each group exhibiting a step with the left leg between S-Dec and S-Inc during the first and last 15 trials, again using the *t*-test.

EMG data were analyzed by measuring time of onset of each burst-like activation relative to the initiation of the perturbation as well as the duration of the activity for each of five successive activations of the right TA muscle: EMG 1 – one activation prior to S-Dec, EMG 2 – first activation between S-Dec and S-Inc, EMG 3 – second activation (if present) between S-Dec and S-Inc, EMG 4 and EMG 5 – first and second activation following S-Inc. The Levene test was used to ascertain the homogeneity of variance for: (1) measurements of EMG onset between the first and last ten trials in the two subject groups, and (2) measurements of EMG duration between subject groups. In addition, the average EMG onset and the average duration for EMGs 1–5 were compared between subject groups using the *t*-test. The significance level used for discussion of all data was $P \leq 0.05$.

Results

Modulation of stepping

Both the cerebellar patients and normal controls were able to maintain their ambulation on the treadmill throughout the experiment with no difficulty. For both groups, the unperturbed (control) step length was consistent throughout the experiment, and the average values were very comparable across as well as within groups. Mean length of the unperturbed step with the right leg over the last 30 trials was 528 mm for the patients and 554 mm for the control subjects. Similarly, that of the left leg was 527 mm for the patients and 552 mm for the control subjects. An ANOVA with repeated measures (groups by trials) revealed that there was no difference between the subject groups for unperturbed stepping for both legs [right leg: $F(1,8)=2.35$, $P>0.05$; left leg: $F(1,8)=2.34$, $P>0.05$)]. A comparison of the right- and left-leg step lengths in the same group of subjects was not done because of the possible error in absolute measurements of these distances due to the error introduced by recording images from one side and measuring the steps using a two dimensional video screen, even though a compensatory algorithm was employed to minimize this effect. The lack of this comparison does not affect the interpretation of the data, since all conclusions are based on relative changes in specific measurements characterizing the movement and/or EMG pattern of a given extremity.

Adaptive changes in the step length in response to the perturbation were observed for both the cerebellar patients and control subjects. To illustrate these changes, results from one cerebellar patient and its age-matched control are plotted in Fig. 2. The step length of the right leg (A and C) and the left leg (B and D) is plotted for each subject against the trials for steps during each of five successive epochs: one step before (control), one step during (perturbed step), and three steps after (post-step 1, 2, 3) the perturbation. Similar to the other control subjects, this one quickly adapted a strategy in which only a step with the right leg was taken during the perturbation. A step with the left leg occurred only in the first few trials. In addition, step length during post-step 1 approached that during unperturbed (control) locomotion (see also post-steps 2 and 3). The control subject definitely recovered from the perturbation by post-steps 2 and 3, as indicated by the near normal step lengths occurring well before the 60th trial. In contrast, the patient displayed a tendency to step with both legs during the perturbation over the 60 trials, and the length of the step with the left leg was quite variable. In the initial trials, there was a tendency for the patient actually to step backwards slightly with the left leg in the initial trials (D), a tendency which was not present across the group of subjects (see Fig. 3

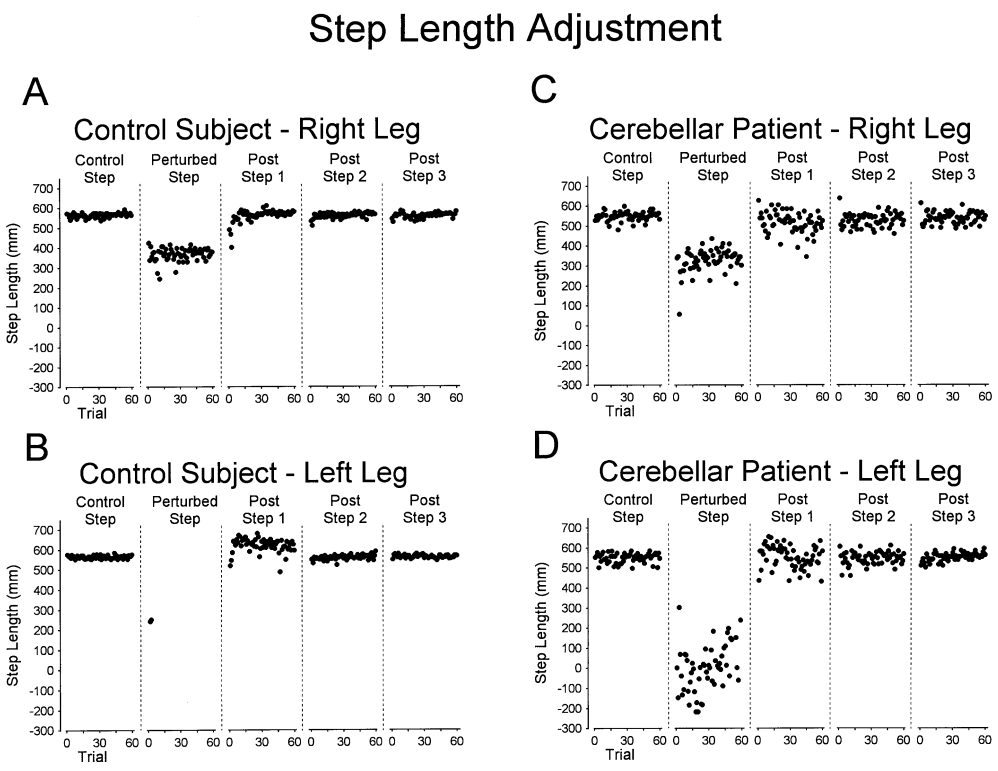

Fig. 2 Examples of the changes in step length with the right and left leg produced by a cerebellar patient (**C** and **D**) and an age- and sex-matched control (**A** and **B**). Each large plot consists of separate small plots indicating the change in step length over the 60 trials for the indicated steps. The step length of the right leg is plotted against the trial number for each of five steps: one step before (*Control Step*), one step during (*Perturbed Step*), and three steps after (*Post Step 1, 2, 3*) the perturbation

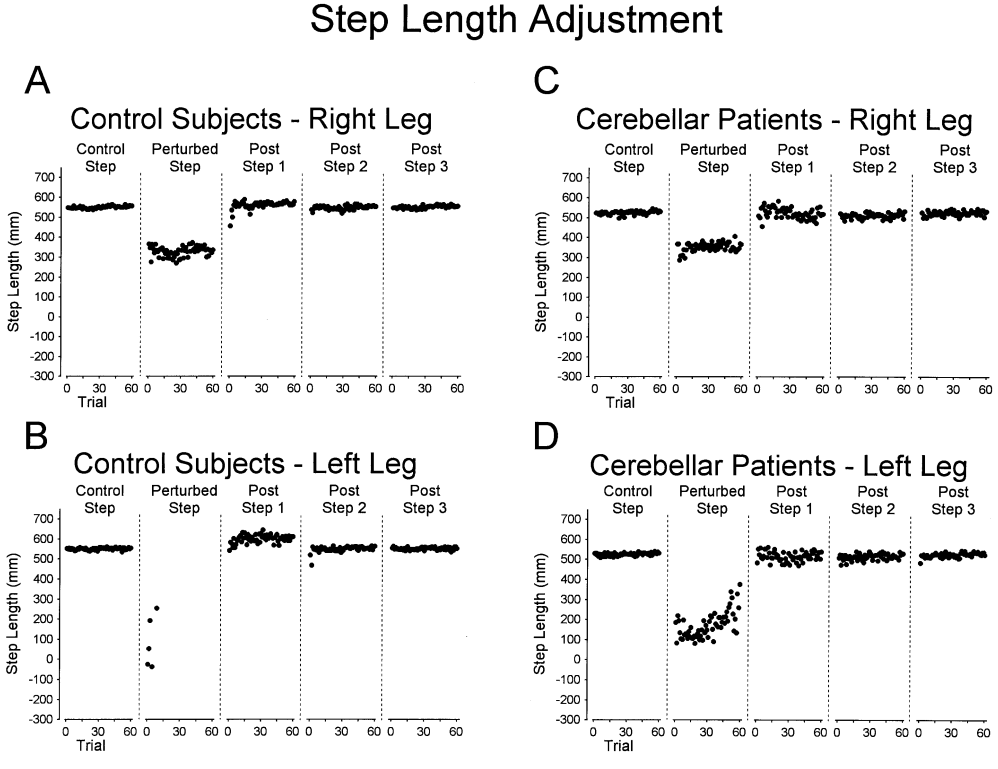

Fig. 3A–D Adaptive changes in step length in response to repeated locomotor perturbations – group data. Mean length of steps with the right and left leg for all control subjects (**A** and **B**) and cerebellar patients (**C** and **D**) is plotted against trial number. Formats of the plots are the same as in Fig. 2

for group data). Consistent with the analysis of the group data (see below), the length of the step with the left leg increased slightly across the 60 trials. Notice also that the step length on the right during post-step 1 was quite variable for the patients.

Comparable plots for the group data are shown in Fig. 3. For each group, these data were obtained by averaging measurements for all subjects in the group across each successive trial. As a group, control subjects showed very little change in the length of steps with the right leg

(A) and a tendency to delay the completion of any full step with the left leg during the perturbation (B). This strategy permitted these subjects to "step through" the perturbation using a locomotor pattern which was temporally comparable to that occurring during unperturbed locomotion. Fortuitously, all subjects in the control and patient group responded to the onset of the perturbation with a step of the right leg. Similar to the controls, patients' steps with the right leg changed very little during the perturbation (C). However, they continued to step with the left leg throughout this period, and the steps with the left leg were initially very small, becoming progressively longer across the 60 trials (D). Both groups showed virtually no changes during post-steps 2 and 3.

Over the first ten trials, an average of all control subjects for the perturbed step with the right leg was 333 mm and was 546 mm for the control step. The difference between these two values was statistically significant ($P \leq 0.001$). There was no significant difference between the values during the first and the last ten trials (330 mm) of the perturbed step for the controls, based on the *t*-test analysis ($P > 0.05$). The linear regression analysis of the control group's stepping data during the perturbed step across the 60 trials indicated that there was no significant trend in measurements of the right-leg step length (correlation coefficient: $r=0.16$, $P > 0.05$, slope=0.24) as the task was practiced. A comparable analysis for the left-leg step length could not be done because steps were not taken with this extremity in the perturbed step period during later trials.

For the cerebellar patients, the average step with the right leg following perturbation over the first ten trials was 328 mm and was 521 mm for the control step. The difference between these two values was statistically significant ($P \leq 0.001$). There also was a significant difference between the values during the first and the last ten trials (354 mm) of the perturbed step, based on the *t*-test analysis ($P \leq 0.05$). The linear regression analysis of the right-leg step length indicated that there was a significant positive trend across trials for the patient group (correlation coefficient: $r=0.35$, $P \leq 0.007$, slope=0.45).

Similar, but more dramatic effects were observed for the length of steps with the left leg in the patient group. There was a significant positive relationship between this measurement during the perturbation and the trial number, and the slope of this relationship was appreciably greater than that found for the steps with the right leg (correlation coefficient: $r=0.64$, $P \leq 0.001$, slope=2.41). In addition, the difference between the left-leg step length in the first ten trials and last ten trials (averages were 146 mm vs. 259 mm, respectively) was significant ($P \leq 0.001$).

The critical difference in strategy with regard to step length between the patients and controls is shown in Fig. 4. This plot shows the percent of subjects in each group that employed a step with the left leg during the perturbation period (between S-Dec and S-Inc). Notice that, whereas the percent of patients stepping with the left leg during this period didn't change markedly over the 60 trials, there was a clear decrease in the percentage among the control group. The average percent (98.7%) for stepping with the left leg of the first 15 trials did not differ significantly from that (93.3%) of the last 15 trials for the patient group (*t*-test: $P > 0.05$), while the average percent (44.0%) of the first 15 trials for the control group was significantly higher than that (22.7%) of the last 15 trials (*t*-test: $P \leq 0.001$). Finally, across all 60 trials, there also was a significant difference between the two groups (*t*-test: $P \leq 0.001$).

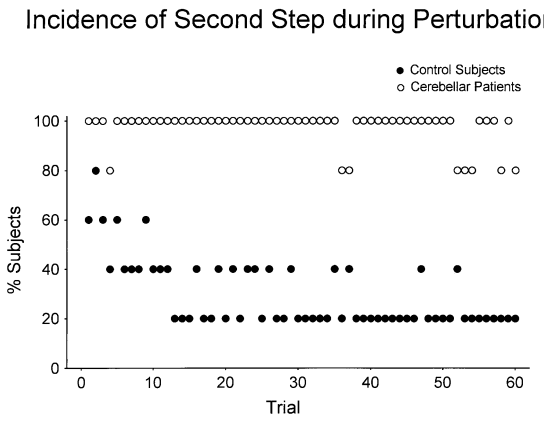

Fig. 4 Incidence of a second step between speed decrease and speed increase for all control subjects and cerebellar patients. Incidence is expressed as the percent of the patients in each group initiating a second step, defined as lifting of the toe from the treadmill surface at the conclusion of the stance phase. As indicated in the text, all patients in both groups undertook all second steps with the left leg

In summary, the analysis of step length demonstrates that cerebellar patients show an adaptive change that was most dramatically characterized by the change in the length of the step made with the left leg during the 60 trials. Furthermore, they did not display the primary adaptive strategy employed by the control subjects, who quickly acquired the tendency to step only with the right leg during the perturbation period.

Modulation of sway

An examination of the control steps revealed that the average unperturbed (control) anterior-posterior sway distances for both groups were fairly similar. Mean sway distance of the last 30 trials was 31 mm for normal controls and 50 mm for the patients. An ANOVA with repeated measures (groups by trials) revealed that there was no difference between the two groups [$F(1,8)=0.77$, $P > 0.05$].

In response to the perturbation, anterior-posterior postural sway was adjusted over the time course of the experiments in both control subjects and patients. As examples, Fig. 5 illustrates the postural adjustment of one cerebellar patient (B) and the age- and sex-matched control subject (A). The sway distance is plotted against the trials for four periods: 1–500 ms before the perturbation (control), during the perturbation, 1–500 ms after (Post-Perturb. 1) and

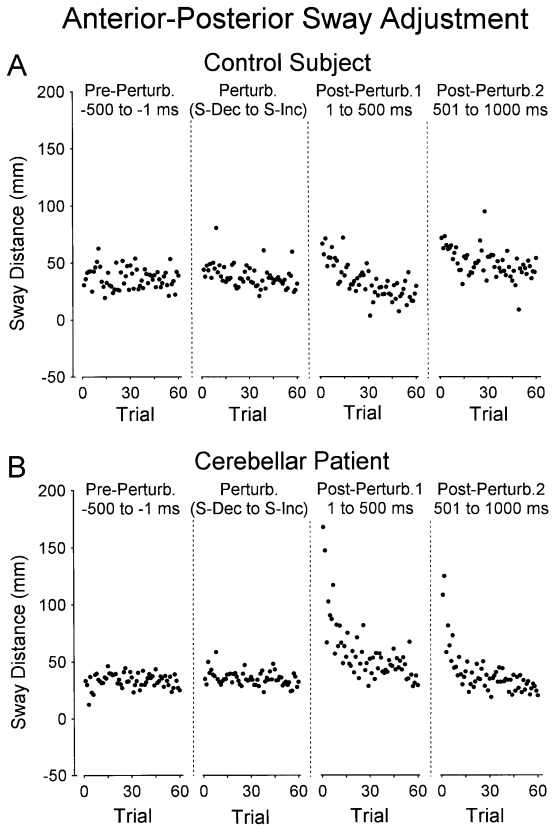

Fig. 5 Examples of the changes in anterior-posterior sway by an age- and sex-matched control subject (**A**) and a cerebellar patient (**B**). Comparable to the plots of step length in Figs. 2 and 3, each large plot consists of separate small plots indicating the change in sway over the 60 trials for the indicated periods. The sway distance is plotted against the trial number for each of four periods: 1–500 ms before the speed decrease (*S-Dec*) of the perturbation (*Pre-Perturb.*), during the perturbation (*S-Dec to S-Inc*), 1–500 ms, and 501–1000 ms after the speed increase (*S-Inc*) of the perturbation (*Post-Perturb. 1* and *2*, respectively)

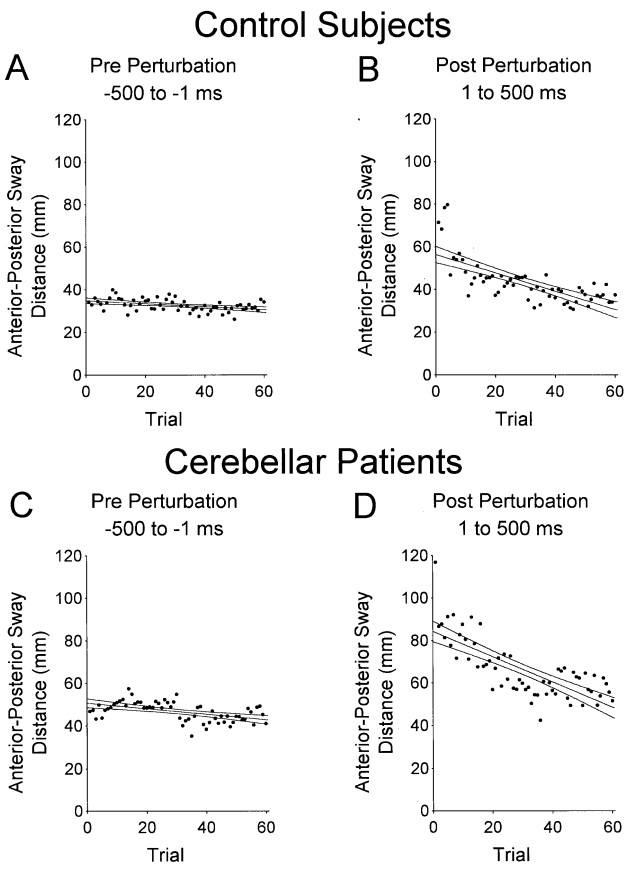

Fig. 6A–D Adaptive changes in postural sway in response to repeated perturbations – group data. Mean anterior-posterior sway distance for all control subjects (**A** and **B**) and all cerebellar patients (**C** and **D**) is plotted against the trial number. Values obtained for 1–500 ms before the speed decrease of the perturbation are presented in panels **A** and **C**, values obtained for 1–500 ms after the speed increase are shown in panels **B** and **D**. The sway distance after the speed increase of the perturbation (**B**) decreased significantly for both the control group (linear regression analysis: r=0.72, P≤0.001, slope=–0.43) and the cerebellar patient group (r=0.75, P≤0.001, slope=–0.60). *Solid lines* above and below the linear-equation line indicate the 95% confidence interval

501–1000 ms (Post-Perturb. 2) after the perturbation. The control subject (A) increased sway distance transiently in the post-perturbation periods and quickly resumed a normal degree of sway. For the cerebellar subject (B), anterior-posterior sway became larger and much more variable immediately after the perturbation began, being particularly marked in the post-perturbation periods 1 and 2. The lengthened sway distance decreased gradually and finally returned to near-normal values as more perturbations were experienced. Clearly, both the cerebellar patient and control subject could acquire adaptive changes in their postural sway as they compensated for the perturbation.

To assess group effects related to compensatory changes in sway, the average anterior-posterior sway distance across all subjects within each group was plotted for each of the 60 trials for the control period (A and C) and post 1- to 500-ms period (B and D) in Fig. 6. These plots illustrate that the patients as a group showed an increased sway in the post 1 to 500 ms period in the early trials followed by a progressive decrease to near-normal levels (D). The average of all cerebellar patients over the first 10 trials (88 mm) for the post 1 to 500 ms period was significantly larger than that (48 mm) for the preceding control period (t-test, P≤0.001). The linear regression analysis also revealed a significant negative relationship between the sway distance in the post 1 to 500 ms period and the trial number (correlation coefficient: r=0.75, P≤0.001, slope=–0.60). This inference is also supported by the fact that the values for all cerebellar patients over the last ten trials (57 mm) was significantly different from that over the first ten trials (88 mm; t-test, P≤0.001) for the same period. Although the sway distance approached near-normal levels at the end of the post 1 to 500 ms period, the average of the last ten trials of the post 1 to 500 ms period still showed a significant difference from the average for the comparable trials of the control period (45 mm; t-test, P≤0.001).

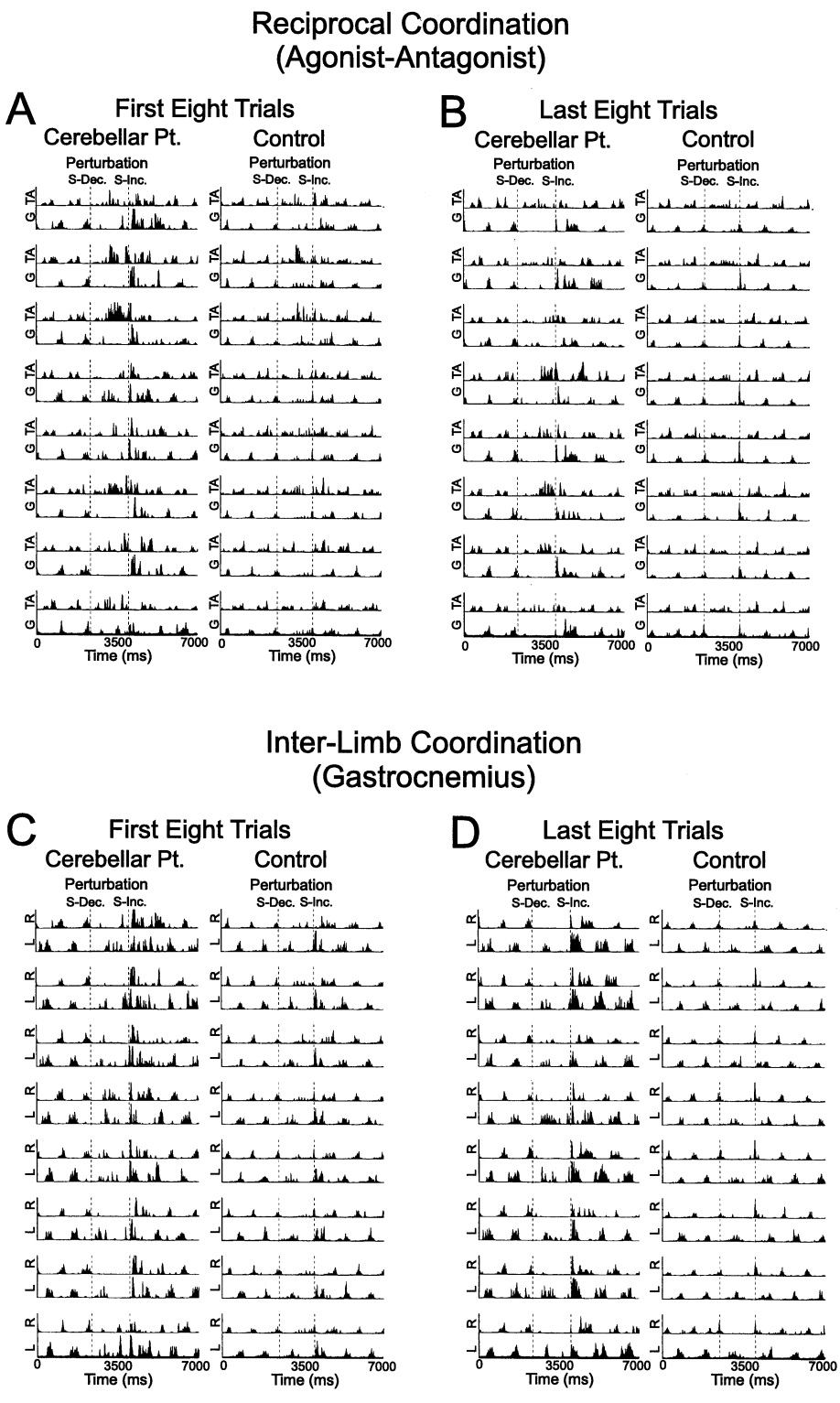

Fig. 7 Examples of the EMG patterns from the first eight trials (**A** and **C**) and the last eight trials (**B** and **D**). EMG signals are plotted against time. Examples of the reciprocal activation of tibialis anterior (*TA*) and gastrocnemius (*G*) muscles of the right leg are shown in **A** and **B**, and examples of inter-limb coordination of the G muscles in **C** and **D** (*L* left, *R* right). *Vertical dashed lines* in the figure indicate the times of the speed decrease (*S-Dec*) and speed increase (*S-Inc*) of the perturbation

These trends seen in the cerebellar patient group were similar to those of the control group. The control subjects as a group showed a larger sway distance at the beginning of the post 1 to 500 ms period (Fig. 6B) than the control period (Fig. 6A). The average values for the control subjects over the first ten trials (61 mm) of the post 1 to 500 ms period was significantly larger than that (35 mm) for the control period (*t*-test, $P \leq 0.001$). A negative relationship between the sway distance during the post 1 to 500 ms period and the trial number was significant statistically (correlation coefficient: $r=0.72$; $P=0.001$; slope= –0.43), and the average for all control subjects over the last ten trials (37 mm) in the post 1 to 500 ms period was significantly different from that (61 mm) of the first ten trials (*t*-test, $P \leq 0.001$). As seen in Fig. 6B, the sway distance in the post-perturbation period became very close

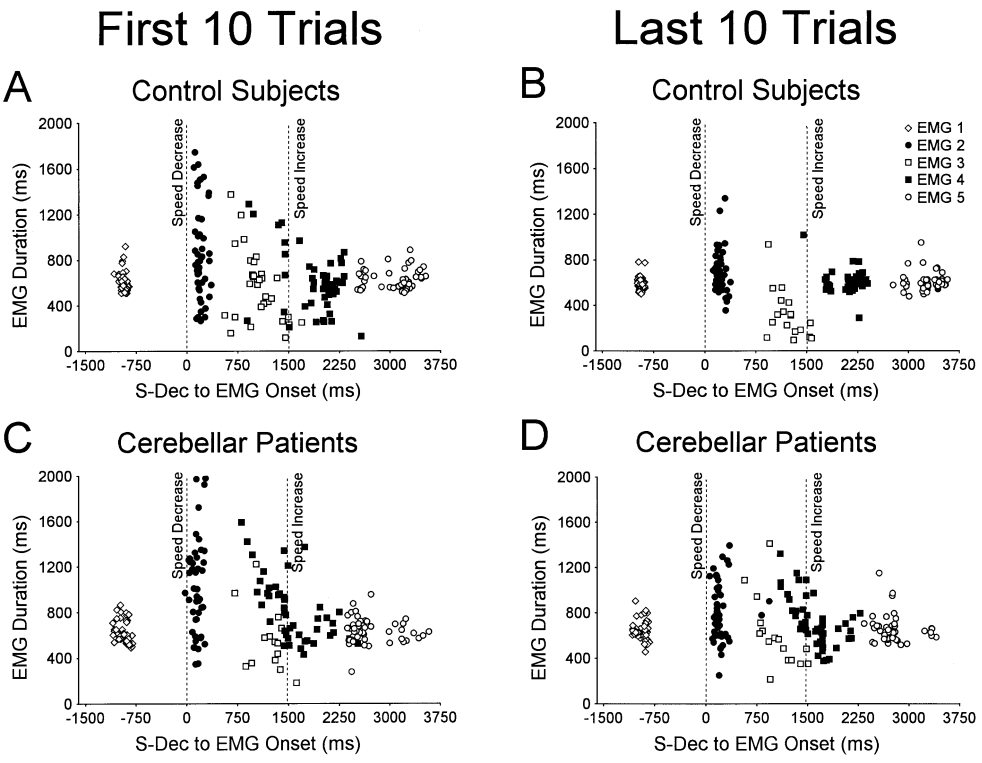

Fig. 8A–D Adaptive changes in the tibialis anterior EMG of the right leg across all subjects. The measurements corresponding to five successive EMG responses of this muscle are indicated with separate symbols as *EMG 1* through *EMG 5*. The plot contains all values obtained for all subjects in each group over the indicated trials. The tibialis anterior EMG burst is plotted against its onset latency relative to perturbation onset (*S-Dec*). Negative values indicated that the onset of the EMG burst preceded perturbation onset. Values from the first ten trials are presented in **A** for the age- and sex-matched control subjects and in **C** for the cerebellar patients. Values from the last ten trials are shown in **B** for the control subjects and in **D** for the cerebellar patients

to control values in the later trials. However, the average value for the last ten trials of the post 1 to 500 ms period (37 mm) showed a significant difference from that of the control period (32 mm) (*t*-test, $P \leq 0.01$).

We also measured medial-lateral sway distance in analyzing postural sway. However, modifications of this measurement were minimal, and the results were highly variable among the subjects. Thus, no meaningful insights were obtained from these data.

In summary, these data illustrate that the normal group and the patient group both showed clear adaptive changes in anterior-posterior sway. The increased sway distance observed in the early trials was reduced to near-normal levels as subjects in both groups compensated for the perturbations. However, the sway distance in the post-perturbation period did not reach control values after 60 trials for either group.

Modification of EMG activity

In order to characterize the changes in EMG patterns in the lower limb muscles, EMG patterns from the earliest trials were compared with those of the latest trials. Figure 7 shows typical examples of reciprocal activation of tibialis anterior (TA) and gastrocnemius (G) muscles of the right leg (A and B) and examples of inter-limb coordination of the G muscle (C and D) during the first and last eight perturbation trials from the same 60 trial session. In the control steps before the onset of the perturbation in each trial, both the cerebellar patient and the control subject showed similar EMG patterns. TA was mainly active during the swing phase with a two-peak activity pattern, one around toe lift off and the other just before heel strike. G showed activity during the stance phase with a single peak appearing during mid-stance. These EMG patterns for both muscles are consistent with previous studies of normal human locomotion (Dietz et al. 1981; Kameyama et al. 1990). When the perturbation was applied, the control subject showed some variability in the EMG patterns during the early trials but was able to re-establish near-normal patterns with minimal variability in amplitude and duration in the latest trials. In contrast, the cerebellar patient displayed a large variability in EMG onset, amplitude, and duration throughout the set of trials, indicating an inability to establish a near-normal gait pattern by the end of the block of 60 trials. Notice also that the cerebellar patient never lost the tendency to activate both Gs when the treadmill resumed.

To illustrate further the differences between the two groups of subjects in terms of modifications in EMG patterns, the duration of each subject's TA EMG activation is plotted in Fig. 8 against its onset latency relative to perturbation onset (S-Dec). For the control subjects (A and B), the duration and onset latency of the EMG burst were very consistent during the control steps (prior to the perturbation). However, during the first ten trials (A), the variability of the duration and latency measurements increased substantially in response to the perturbation. However, by the last ten trials (B), this variability had decreased, with the duration of EMG activity approaching that during the control step (preceding perturbation onset).

The cerebellar patients (Fig. 8C and D) also showed consistent EMG-burst durations and onset latencies during control stepping. Similar to the control subjects, the

Table 2 *t*-test comparison of onset times between patient and control groups

	EMG 1	EMG 2	EMG 3	EMG 4	EMG 5
First 10 Trials	p≤0.673	p≤0.001	p≤0.390	p≤0.001	p≤0.001
Last 10 Trials	p≤0.798	p≤0.635	p≤0.035	p≤0.001	p≤0.001

Table 3 Levene-test comparison of variances for EMGs 1–5 between patient and control groups

	EMG 1	EMG 2	EMG 3	EMG 4	EMG 5
First 10 Trials	p≤0.251	p≤0.672	p≤0.760	p≤0.985	p≤0.773
Last 10 Trials	p≤0.009	p≤0.009	p≤0.265	p≤0.001	p≤0.137

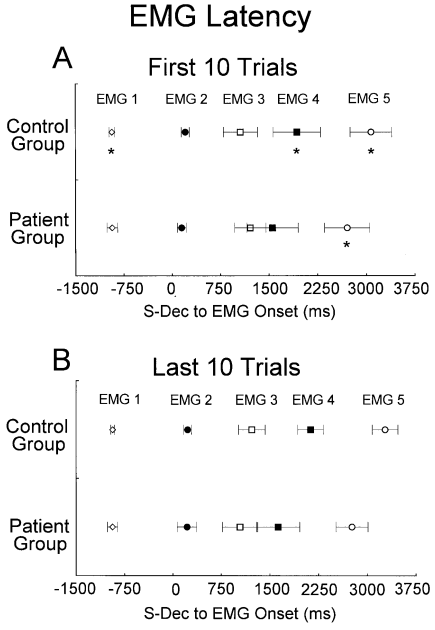

Fig. 9 Plots of the mean onset latencies for five successive bursts of tibialis anterior EMG activity (*EMG 1* through *EMG 5*) during the first (**A**) and last (**B**) ten trials for both subject groups. Onset time is expressed on the abscissa relative to the time of speed decrease (*S-Dec*). *Error bars* indicate the standard deviation. Symbols for the EMG responses are based on the same key shown in Fig. 8. The variances of the measurements indicated with the *star* in **A** were not homogeneous with those of the comparable measurements in **B** at a significance level of $P \leq 0.05$, based on the Levene test for homogeneity of variances. Pertinent *t*-test data are shown in Table 2

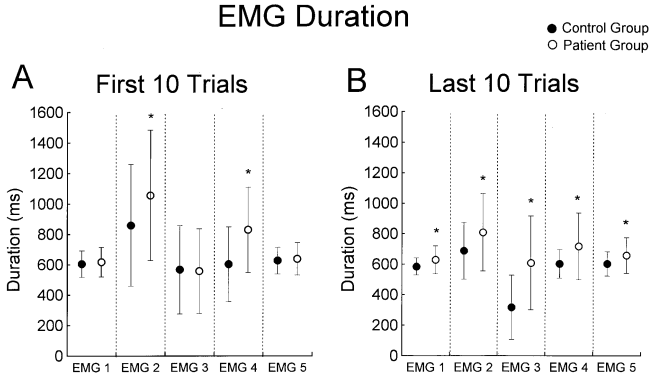

Fig. 10A, B Plots of the mean durations of the same EMG responses (*EMG 1–5*) whose onset latencies were assessed in Fig. 9. *Error bars* show the standard deviations. *Starred values* indicate that the means for the control and patient groups were significantly different for the EMG response indicated below on the abscissa (*t*-test: $P \leq 0.05$). Levene tests for the homogeneity of variances are shown in Table 3

patients' EMG bursts in response to the perturbation were quite variable over the first ten trials (C). However, in contrast to the control subjects, the large range of duration of the patients' TA EMG activity during and immediately following the perturbation in the first trials persisted into the last ten trials (D). Furthermore, the onset time of EMG-3 and EMG-4 activations continued to be variable throughout the 60 trials. The extent to which the variance of onset times changed with practice was statistically assessed using the Levene test for the homogeneity of variances. This was done by comparing variances for the onsets of EMGs 1–5 during the first and the last ten trials. The starred values in Fig. 9A indicate the EMG responses for the patients and for the controls, which showed a significant change in variances when the task was practiced. The variance of the EMG 1, EMG 4, and EMG 5 onsets for the control subjects significantly decreased (Levene test: $P \leq 0.05$) from the first to the last ten trials. In contrast, for the patients, the variances of the EMG onset measurements changed significantly only for the last response of the sequence, EMG 5. Note also that the onset times of the EMG responses occurred at appreciably more consistent intervals than those of the patients, particularly in the last ten trials. In contrast, the distributions of the onset times of the EMG 3 and 4 responses in the patients overlapped even after practicing the task (Fig. 9B). These onset times for EMGs 1–5 are compared statistically in Table 2. Note that the onset times differ significantly between the two groups for EMGs 3–5.

In a final analysis, the durations of EMGs 1–5 were compared between the control and patient groups. As shown in Fig. 10A, the durations of EMGs 2 and 4 increased in the patient group when they were first confronted with the perturbation (first ten trials), and the means of these responses for the two groups were significantly different (*t*-test: starred in Fig. 10A). However, after practice (during the last ten trials), the duration of each EMG response was significantly longer for the patients than for the controls (*t*-test: starred in Fig. 10B). Comparing the variances of the duration measurements using the Levene test (Table 3) revealed that, although there were no significant differences between the variances of the duration measurements during the first ten trials, those characterizing the EMG 1, EMG 2, and EMG 4 measurements of the patients and controls during the last ten trials were significantly different. These tests and those performed on the measurements of the comparable onset times (Fig. 9; Table 2) indicate that the variability of the patients' responses was substantially greater than that of the responses of the age- and sex-matched controls.

Discussion

The purpose of the present study was to test whether cerebellar patients can adapt their gait to sudden perturbations of treadmill speed during treadmill locomotion. The data indicate that cerebellar patients were able to compensate for this perturbation by modifying postural sway and step length, but in a manner different from that of normal subjects. Furthermore, patients did not modify the EMG activity of the G and TA over successive perturbations in the same way as normal subjects.

Difference in strategies employed by cerebellar patients and normal subjects

Although both cerebellar patients and normal subjects underwent progressive changes in their responses to the perturbation over the 60 trials of the experiment, there were substantial differences in the strategies employed by the two groups in generating the corrective responses. The age- and sex-matched controls rapidly modified their responses to the perturbation, so that the step with the left leg following the perturbation did not actually occur until after S-Inc (Figs. 2 and 3). In contrast, cerebellar patients uniformly stepped with the left leg before S-Inc throughout the 60 trials, and they dramatically increased the length of this step as the task was practiced.

One of the clearest differences between the adaptation of the patients and control subjects was reflected in the EMG activity of the TA and GA during the experiment. Normal subjects modified the duration as well as the pattern of EMG burst as they practiced (Figs. 7–10). The duration of the bursts in the early part of the response (EMGs 2 and 3) decreased, and their onset occurred in a near-normal gait-like pattern, which was particularly well developed by the last ten trials (Fig. 9B), suggesting that these subjects acquired the capacity to "walk through" the perturbation using a reciprocal pattern of the G and TA muscles (Fig. 7). In contrast, the considerable variability of both the onset and duration of the patients' EMG responses persisted throughout the 60 trials (Figs. 8–10). Furthermore, they consistently displayed longer burst durations than the controls, and they were never able to establish the locomotion-like regularity of onset times observed for the age- and sex-matched normal subjects.

The basis for the abnormal motor patterns in cerebellar patients

The unique compensatory motor pattern used by cerebellar patients was not due to a general abnormality in the synergy of their normal locomotor cycle. These patients were able to produce consistent, normal EMG patterns during control locomotion, indicating that their coordination of the spatio-temporal synergy required for unperturbed locomotion was well regulated. Furthermore, their initial step to the perturbation appeared to be unrelated to the side of lesion, since all patients in this group initiated their response with the same leg independent of the lesion's location. However, it is possible that their response to the perturbation could be related to the dysmetria observed by others when cerebellar patients attempted to scale their responses to perturbations of a platform while standing (Horak and Diener 1994). In these experiments, hypermetric leg and paraspinal EMG responses were observed when cerebellar patients with anterior lobe pathology responded to forward body sway induced by backward platform displacement (Horak and Diener 1994). Animal studies also have demonstrated that cooling or lesioning the vermal zone or paravermal zone of the cerebellar cortex resulted in hypermetria during stepping, even in the absence of perturbations (Udo et al. 1976, 1979a,b, 1980; Chambers and Sprague 1955a,b; Yu and Eidelberg 1983). Although the deficits reported in the present study would not be classified as hypermetria, a general deficit in scaling may be the basis for some of the variability in the patients' responses.

Based on the recent study of Shimansky et al. (1995) (see also Bloedel et al. 1996), the unusual motor pattern employed by cerebellar patients may in part reflect an abnormality in the on-line processing of responses to peripheral stimuli. They reported that, during inactivation of the anterior and posterior interposed and dentate nuclei, cats could compensate for predictable perturbations of reaching movements, but not for unpredictable perturbations when only on-line cues regarding the perturbation were available. In contrast, the functionally intact cats could compensate under both conditions. These findings indicate that the animals with the inactivated cerebellar nuclei learned strategies which could be implemented at motor set but not those requiring on-line processing of sensory inputs evoked by the perturbation. Since in the present experiments the trials in which the perturbations were applied were unknown to the subjects, it is quite feasible that their incapacity to develop the normal compensatory responses to the perturbation also might reflect inadequate on-line processing of incoming sensory information.

An impaired ability of cerebellar patients to process kinesthetic information has been demonstrated recently (Grill et al. 1994; Shimansky et al. 1997). In one of these experiments, the cerebellar patients showed a deficit in perceiving two-dimensional irregular shapes based on only kinesthetic cues and in discriminating them from a reference shape (Shimansky et al. 1997). In the other, patients with cerebellar degeneration showed a significant impairment in processing information regarding duration and velocity of kinesthetic stimuli (Grill et al. 1994). These findings provide strong evidence that the processing of kinesthetic input is impaired as a consequence of cerebellar pathology. Consequently, the deficits in the present experiments may reflect an abnormality in the on-line processing of this specific type of sensory input. This type of impairment could contribute directly to the cerebellum's role in the acquisition of normal compensatory responses to this type of locomotor perturbations.

There is also a possibility that cerebellar patients failed to process temporal information properly, such as the time between the onset of the treadmill speed decrease and the subsequent onset of the speed increase. It has been reported that cerebellar patients have deficits in perceiving the duration of auditory tones (Ivry and Keele 1990; Ivry 1993). Other findings in the literature suggest that cerebellar lesions also can result in impaired temporal properties of executed movements, a factor which also could contribute to the inconsistent EMG responses of the patients. For example, some cerebellar patients have exhibited deficits in timing a finger-tapping movement (Ivry et al. 1988). Neural activities in the monkey's dentate nucleus and peri-dentate regions tightly related to the precise duration of saccadic eye movements, including visually guided, memory guided, and spontaneous saccades made with various amplitudes and directions (Kawagoe et al. 1996). Even though movements tested in the present study were very different from those in tapping and saccade-related paradigms, deficits in the processing of temporal information in these behaviors could be related to those required for normal responses to locomotor perturbations.

In summary, the present results support two conclusions: (1) that cerebellar patients with lesions comparable to those investigated here can adapt their behavior in response to a locomotor perturbation, and (2) that the adaptation implements a different, more variable motor pattern than observed in control subjects. These findings suggest, but do not prove, that these same cerebellar regions are not substrates essential for storing the plastic changes established during this type of adaptation since, if they were, this new behavior could not be acquired during the experiment. This finding is consistent with other observations in our laboratory related to the learning of complex, volitional arm movements (Shimansky et al. 1994; Timmann et al. 1996; Wang et al. 1997). These previous studies demonstrated that cats were capable of acquiring complex forelimb movements during the inactivation of the dentate and interposed nuclei (Shimansky et al. 1994; Bloedel et al. 1996; Wang et al. 1997) and that patients with cerebellar lesions could improve their performance in a tracing task involving the recall of memorized shapes, the mental rotation of the shape, and the execution of a drawing movement (Timmann et al. 1996). Nevertheless, it is also possible that plastic changes in the cerebellum could contribute to the acquisition of this task in the absence of cerebellar pathology.

The fact that the motor patterns employed by cerebellar patients were variable and different from those observed in normal subjects is also consistent with these previous studies. These experiments demonstrated that, although cats with inactivated cerebellar nuclei can learn complex movements, they employ variable, somewhat inefficient motor patterns for their execution (Shimansky et al. 1994; Bloedel et al. 1996; Wang et al. 1997). Similarly, in the study reported here, cerebellar patients clearly underwent adaptive changes in response to the perturbation. However, they could not acquire the same consistent, adaptive strategy observed in the normal subjects. It should be emphasized that the capacity to acquire the postural adjustments observed in these patients could be dependent upon the fact that the midline regions of their cerebella were reasonably intact. Together, these observations support our general hypothesis that the cerebellum is required during task acquisition for the specification of optimal strategies employed in compensatory or learned movements (Bloedel et al. 1996).

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