Predictive control of muscle responses to arm perturbations in cerebellar patients

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Abstract

Objectives—To examine changes in predictive control of early antagonist responses to limb perturbations in patients with defined lesions of the cerebellum.

Methods—Eight cerebellar patients and eight sex and age matched control subjects participated. Subjects held a handle that was rotated around the elbow joint. They were instructed to hold the forearm at 90° flexion against a mechanical perturbation. Extensor torque (5 Nm) was applied for 140 ms (pulse), or for 1400 ms (step through an external motor. Motor responses were tested under two different conditions of anticipatory information. In the expected condition, subjects anticipated and received a pulse. Under the unexpected condition, subjects expected steps, but received unexpected pulses. Biceps and triceps EMG as well as angular kinematics were compared between expected and unexpected pulse perturbations to quantify possible effects of prediction.

Results—In all healthy subjects, the degree of overshoot in the return flexion movement was significantly less in expected pulse perturbations compared with unexpected trials. The degree of amplitude reduction was significantly smaller in the patient group than in the control group (22.8% v 40.0%). During the expected trials, latency of peak triceps activity was on average 20% shorter in the control group, but 4% larger in the cerebellar patients.

Conclusions—In the expected condition, controls achieved a significant reduction in angular amplitude by generating triceps activity earlier, whereas the ability to use prediction for adjusting early antagonist responses after limb perturbation was impaired in cerebellar patients.

Keywords: cerebellum; motor control; limb perturbation

The generation of appropriate muscle responses to a mechanical limb perturbation requires correct prediction of the nature and the physical consequences of that perturbation. Although initial muscle responses to stretch are driven by afferent feedback, their magnitude can be influenced by the instruction or expectation of the subject. The results of animal experiments suggest that this predictive ability is mediated by the cerebellum, most likely via the dentate nucleus.

The mechanisms involved in compensating for sudden changes in load or unexpected displacements of the upper limb have been extensively studied in animals and humans. One critical experiment to explore the role of the cerebellum during perturbed motion was performed by Hore and Vilis. They examined the ability of monkeys to predict the duration of an arm perturbation based on a previous series of perturbations. To investigate the preprogrammed nature of the early antagonist response, the monkey was trained either to expect a long torque perturbation (step=2000 ms) or to expect short pulses (<150 ms). In a subsequent block of trials with step perturbations, unexpected short pulses were applied in pseudorandom order. During those trials, the monkeys were expecting a long duration perturbation, but received a short pulse. A main result of this study was that during the unexpected pulse perturbations the antagonist response was delayed compared with its onset latencies during the expected pulse condition. A similar delay in antagonist activity was obtained after cooling the dentate nucleus, indicating that the integrity of the cerebellum was crucial for this response. Their results suggested that the EMG responses during cerebellar dysfunction lacked a predictive component and were largely driven by spinal stretch reflexes.

Hore and Vilis related set dependent changes in the muscle responses to perturbation to the ability of the system to use predictive information about the nature of the forthcoming disturbance to sequence preprogrammed responses by means of an efference copy. More recently, motor control theorists proposed the use of internal models in different aspects of predictive motor control, which may involve cerebellar circuits. So far, the findings of Hore and Vilis of impaired set dependent control of muscle responses after arm perturbations in monkeys with cerebellar lesions have not been confirmed in humans. In the present study we examined how information about an impending external perturbation affects the kinematics and underlying muscle responses in humans with cerebellar lesions during a holding task.

Material and methods

Subjects

Experiments were performed on eight right handed cerebellar patients (mean age 37.8 years, range 11–64) and on eight control subjects (mean age 37.3 years, range 11–64).
Control subjects and cerebellar patients were matched for age, sex, and handedness. In all patients, the right cerebellar hemisphere was affected and all cerebellar patients showed mild to moderate signs of upper limb ataxia (table 1). None of the patients showed extracerebellar signs on neurological examination or brain MRI.

Three patients had right sided surgical lesions that affected the region of the cerebellar nuclei; one had a right sided cerebellar infarction (superior cerebellar artery) and one had a right sided cerebellar haemorrhage. Three patients had diffuse cerebellar cortical atrophy, with one patient having idiopathic cerebellar ataxia (IDCA) and two being diagnosed as having spinocerebellar ataxia type 6 (SCA 6). All patients had a full neurological examination at the time of the experiments. Cerebellar symptoms were scaled according to the international cooperative ataxia rating scale (ICARS).16 The experiments were approved by the local ethics committee and all subjects and patients gave informed consent.

METHODS
Subjects performed flexion-extension movements of their right forearm around the elbow joint at the height of the shoulder joint after a perturbation in the extension direction. Their right forearm was inserted into an orthosis, allowing only movements in the horizontal plane. The upper lever was rigidly connected to a lower lever by two flat irons. Mechanical perturbations to the arm-lever system were generated by a torque motor with a shaft attached to the lower lever of the manipulandum. The torque motor received its input from an ELTEC 84/68 K computer. Motor acceleration was 50 revolutions/second within 50 ms from neutral. Angular position (resolution 0.08°) and velocity were measured by a potentiometer and tachometer at the motor shaft. Electromyographic activity (EMG) was recorded from extensor arm muscles (m triceps brachii, caput lateralis) and flexor arm muscles (m biceps brachii) using Hellige Ag/AgCl electrodes. Before the experiment the maximum voluntary contraction (MVC) of both flexor and extensor muscles was recorded while subjects extended and flexed their arm against resistance (isometric contraction). Kinematic data and EMG were sampled at 520 Hz.

Subjects viewed two illuminated arrows on a convex screen about 1.5 m in front of them. One arrow corresponded to the required goal position (here 90° flexion, the other to the actual position of the forearm. In the initial position, the forearm and upper arm formed a 90° angle and this corresponded to 0° position of the manipulandum. Positive values referred to flexion movements and negative values to extension movements (fig 1). Participants were instructed to match the position of the goal arrow with the end point arrow on the convex screen despite possible perturbations through externally generated torques.

Table 1 Patient information

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Disorder</th>
<th>Left cerebellar lesion</th>
<th>Right cerebellar lesion</th>
<th>Duration of disorder (y)</th>
<th>Symptoms</th>
<th>ICARS</th>
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<td>p-3</td>
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<td>Hemorrhage of the right</td>
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To facilitate early antagonist responses, the handle was held against a constant force that loaded triceps and assisted the return movement. At trial onset, a tonic flexor torque of 3 Nm was applied, which effectively led to a tonic activation of the elbow extensors, while subjects assumed their initial 90° elbow position. After two seconds, a torque perturbation of 5 Nm with a duration of 140 ms (pulse) or 1400 ms (step) was generated. Instructions were given to correct any deviations from the goal position as fast as possible. Intertrial intervals were pseudorandomised and ranged between 4 and 10 seconds. Trial duration was 5.4 seconds.

Motor responses were tested under two different conditions of anticipatory information. In the expected condition, subjects expected a brief pulse (blocked presentation). Under the unexpected condition, subjects expected 1400 ms step perturbations and received intermittently unexpected 140 ms pulses. In the expected condition a block of 12 trials of 140 ms pulses was applied. The first two trials were practice trials and were not analyzed. In the unexpected condition, 50 pulses of 1400 ms were applied with 10 pulses of 140 ms randomly interspersed.

Kinematic analyses and EMG were performed on individual traces. Angular position data were filtered offline using a fourth order low pass Butterworth filter with a cut off frequency of 12 Hz. EMG data of each collected channel were rectified and smoothed using a digital moving average filter with a width of 11 data points (22 ms). To control for possible effects of individual differences in muscle strength, electrode position, and connective tissue, EMG parameters were expressed as the percentage of the subject’s maximal voluntary contraction (MVC).

We derived measures of overall flexor and extensor activity by integrating EMG activity over a fixed interval of 200 ms. Due to tonic activation and cocontraction patterns the determination of extensor and flexor onsets turned out to be difficult. To integrate extensor activity, we determined the position of maximum elbow extension after perturbation and selected these points as the initial boundary of the extensor integrals. For calculating integrals of flexor muscles, the initial interval boundary was set at 15 ms past perturbation.

Peak amplitude of the return flexion movement, peak amplitude, and the peak latencies of
each EMG channel were determined individually using an interactive program based on SAS software. The peak biceps and triceps responses were defined in a time window of 300 ms and 1000 ms respectively after perturbation onset. Figure 2 illustrates which parameters were determined.

Results
In both groups, applied external force resulted in a stretch response of the biceps muscle, the function of which was to resist the perturbation and initiate the return movement. This response was followed by a burst in the antagonist triceps muscle, the function of which was to decelerate the return movement and to terminate it within the target region.

Figure 3 shows characteristic traces of mean angular position and mean triceps EMG responses in a control subject and two cerebellar patients for the 10 expected (hatched line) and the 10 unexpected (solid line) pulse perturbations. In the control subject (fig 3 A), the degree of overshoot in the return flexion movement (upward in fig 3) was reduced when the subject expected the pulse perturbation. Associated with the amplitude reduction were a shorter onset and a shorter time to peak of the antagonist triceps compared with the unexpected condition, where a step perturbation was expected, but a short pulse was received. As a consequence, braking of arm flexion occurred earlier in the expected condition. When compared with the control, patients p-2 and p-1 (fig 3 B and C; clinical description in table 1) showed similar amplitudes in their return movements in the expected and unexpected condition. By contrast with the control subject, onset and time to peak of the triceps response were not significantly different in expected and unexpected pulse perturbations in both cerebellar patients. Rather, time to peak occurred later compared with the control subject in both conditions.

Differences in amplitude of passive elbow extension (downward in fig 3) after the external perturbation mainly reflected differences in arm inertia between subjects, with amplitudes being smaller in subjects with larger inertia. Likewise, amplitude of elbow extension was smallest in the control subject, whose arm inertia was larger compared with both patients (0.17 kg×m² (c-2) vs 0.1 kg×m² (p-2) and 0.13 kg×m² (p-1)). Rotational arm inertia was calculated using an anthropometric model, based on each subject’s limb length, segment circumference, and total body weight.17 18

Differences in amplitudes of the return movement, however, reflected both differences in inertia between subjects and impaired reactive movements in cerebellar patients. As expected in cerebellar hypermetria, the amplitude of the return movement was increased in patient p-2. In patient p-1 the amplitude of the return movement (and the overall magnitude of the triceps EMG size (related to the maximum voluntary contraction)) was smaller as in the control subject (and cerebellar patient p-2) and might well reflect hypometria in this cerebellar patient.

Figure 3 Characteristic traces of angular position (top; 90° elbow flexion corresponds to 0° position of the manipulandum) and triceps EMG responses (bottom) in a control subject (left) and two cerebellar patients (middle, right) are superimposed for the expected (hatched line) and unexpected (solid line) pulse condition. Averages of the 10 expected and 10 unexpected trials are shown. Differences based on expectation are indicated by arrow (top) and hatched area (bottom). The dotted line indicates the time to peak triceps EMG response in the unexpected condition.
Figure 4 Comparison of mean angular positions (SD) in the expected (black columns) and unexpected (open columns) pulse conditions in (A) control subjects and (B) cerebellar patients. 90° Elbow flexion corresponded to 0° position of the manipulandum.

Table 2 Mean (SD) of time to peak angular position, triceps and biceps muscle response in expected (Exp), and unexpected (Unexp) pulse conditions in cerebellar patients (Cer) and age and sex matched control subjects (Con).

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<th>Exp</th>
<th>Unexp</th>
<th>Con</th>
<th>Exp</th>
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(°) Time to peak m biceps brachii response (ms):

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PEAK ANGULAR POSITION DURING THE RETURN MOVEMENT

In all control subjects the amplitude of peak angular position of the compensatory return movement was smaller in expected pulse perturbations compared with unexpected perturbations (mean (SD)° (range): expected condition 5.96 (3.2) (1.2–15.8), unexpected condition 9.54 (3.68) (3.9–20.5); fig 4 A). Although all but one cerebellar patient showed an decrease in amplitude in the expected pulse condition, the percentage decrease was significantly less in cerebellar patients than in control subjects (mean (SD)° (range): expected condition 10.03 (6.79) (2.52–37.82); unexpected condition 12.26 (8.58) (2.66–45.32); fig 4 B). The percentage decrease (100–(expected/unexpected condition×100)) of mean peak amplitude in the expected condition was twice as large in the control as in the cerebellar group (40.07 (SD 9.5)% vs 22.85 (SD 19.9)%).

To control for possible effects of the subject’s inertia, peak amplitudes of individual trials were normalised and expressed as a percentage of the individual mean of all trials under the expected pulse condition in each subject. A 2x2 (group by condition) analysis of variance (ANOVA) with normalised peak angular position as dependent variable disclosed a significant condition effect (expected vs unexpected; p=0.0001). A significant group effect (p=0.0327) and group by condition interaction (p=0.025) reflected the different degree of amplitude change between conditions in both groups, which was significantly less in the cerebellar group.

Statistical analysis in individual subjects showed a significant decrease of peak amplitudes in expected trials in all controls (all p values<0.01; paired t test, Bonferroni correction). Although effects of prediction were less in the cerebellar group than in the controls, three of eight cerebellar patients showed a significant reduction of peak amplitudes in the expected condition compared with unexpected trials (p-3, p-4, p-5 in fig 4 B).

Individual data in control subjects showed a tendency for time to peak angular position to be earlier in the expected condition (table 2). However, there were no significant differences comparing groups or conditions (all p values>0.05; ANOVA).

EARLY ANTAGONIST TRICEPS RESPONSE

Between conditions, mean peak latency of the early triceps response was 17.7% (SD 9.36) shorter in the expected condition in the control group (mean (SD) (ms): expected: 360 (73); unexpected: 437 (95), but remained almost the same in the cerebellar group (+3.52% (17.9); same in the cerebellar group as in the controls, three of eight cerebellar patients showed a signifi-

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cerebellar patients, likely obscured possible effects of condition (see SDs in fig 5 and table 2). Therefore, separate paired t tests were calculated to examine differences between conditions for each group. In the control group, the mean peak latency of the triceps EMG was significantly shorter in expected pulse perturbations (p=0.0042), whereas no significant difference between conditions was found in the cerebellar group (p=0.62).

We found no significant difference comparing the normalised (percentage of MVC) peak amplitude and the 200 ms fixed EMG integral of the triceps lateralis response between groups and conditions (200 ms fixed EMG integral: Mean (SD) %MVC×ms: expected condition 85.1 (43) (controls), 68.8 (36) (cerebellar); unexpected condition 77.2 (36) (controls), 61.7 (35) (cerebellar); all p values>0.05, ANOVA). Likewise, the percentage difference between conditions of peak amplitude and integrated EMG (200 ms interval) of the early antagonist triceps response was not significantly different between groups (p values >0.05; unpaired t test).

Finally we tested if the lack of significant differences of the early antagonist response between the expected and unexpected pulse perturbation in the cerebellar group was related to the severity of clinical signs. The ICARS score of upper limb ataxia and the total ICARS score were correlated with the difference in time to peak amplitude and fixed 200 ms EMG integral of triceps in the expected and unexpected condition. No significant correlation was found (Pearson’s correlation coefficient).

**AGONIST BICEPS RESPONSE**

In most control subjects and cerebellar patients individual reflex components in the agonist (M1, M2, and M3) could not clearly be separated. A likely explanation was that individual EMG traces were analyzed rather than average responses as in most previous studies on stretch evoked response. Therefore, parameters (200 ms fixed EMG integral, time to peak and peak amplitude) were quantified for the entire early agonist burst.

A 2×2 (group by condition) ANOVA for peak latency of biceps yielded no significant effect for group and condition, and no significant interaction (all p values>0.05; individual data in table 2). There was no significant difference comparing the normalized (percentage of MVC) peak amplitude and fixed 200 ms integral of the biceps response between groups and conditions (200 ms fixed EMG integral: mean (SD) %MVC×ms: expected condition 204 (240) (controls), 134 (145) (cerebellar); unexpected condition 158 (142) (controls), 126 (165) (cerebellar); all p values>0.05, ANOVA).

**Discussion**

The aim of the present study was to investigate the role of the cerebellum in predictive control of reactive muscle responses after arm perturbations in humans. Although the underlying muscle response pattern was preserved in cerebellar patients, a significant difference was found in the ability to use prediction of the upcoming perturbation to adjust the amplitude of the return movement compared with controls. On average, control subjects reduced the overshoot of the arm during the return movement by 40% when correctly expecting a pulse perturbation. Control subjects, therefore, were able to effectively use predictive information about the duration of the perturbation (short pulse = prolonged step) to reduce the amplitude of the return movement. The degree of amplitude reduction in expected pulse perturbations was significantly less in cerebellar patients (only about 22%). This result indicates that cerebellar patients were less able to use advance information about upcoming perturbations based on prior experience to adjust the amplitude of reactive movements.

During trials with expected pulse perturbations, the peak amplitude of the triceps muscle response occurred earlier compared with unexpected pulse perturbations in controls. Thus, based on prior experience, control subjects used advance knowledge of the upcoming perturbation to control timing of the peak antagonist response. In cerebellar patients, however, the ability to use prediction to adjust timing of the peak antagonist response was impaired. Braking of the return movement was delayed in both expected and unexpected pulse perturbations compared with the control group.

These results corroborate earlier primate data that showed delayed antagonist responses in monkeys after cooling of their cerebellar nuclei in expected pulse perturbations. Our study expands on this known finding by documenting that this necessary antagonist response is equally delayed during unexpected pulse perturbations in cerebellar patients. Knowing, in addition, that delayed onsets of antagonist responses have also been found in goal directed single and multi-joint voluntary movements that require braking, the conclusion seems warranted that the integrity of the cerebellum is essential for the precise timing of the antagonist response, and therefore for accurate braking of movement, in both active and reactive fast and goal directed movements.
Although effects of prediction were significantly less in the cerebellar group than in the controls, individual cerebellar patients showed significant effects of prediction (see p-3, p-4, p-5 in fig 4 B). It is likely that the ability to perform this motor adaptation task depends on the localisation and extent of the cerebellar lesion. The patients with preserved predictive ability had circumscribed lesions of the right cerebellar hemisphere (table 1), whereas the ability to use prediction was most markedly disturbed in patients with diffuse, degenerative disorders (p-1, p-6, p-8). However, the number of cerebellar patients was too small to lay down the parts of the cerebellum which are critically involved in the present task. Moreover, although MRI was available in all patients, the precision of diagnostic brain scans was not good enough to define the degree of cortical and deep cerebellar nuclei involvement (that is, of the dentate nuclei).

Our main finding was an impaired ability of cerebellar patients to use prediction of the upcoming perturbation to accurately time the antagonist response and to effectively reduce the overshoot of the return movement. Hore and Vilis proposed that an impaired efference copy mechanism leads to this inadequate antagonist response. 5 6 In their thinking, the correct antagonist command could be computed on the basis of the reafference from the agonist command. Although Hore and Vilis did not explicitly model how a correct antagonist command could be computed based on the agonist reafference, recent models have proposed that reafferent information could be used to update upcoming motor plans and to adjust the parameters of an internal motor model. 14 15 27 28 Particularly, it has been suggested that internal forward models of the musculoskeletal plant help to predict the sensory consequences of movements. 29 This way, the inherent time delays associated with feedback control could be overcome and a neural controller could issue efferent commands for achieving a desired movement trajectory. 14 15 27 28 Based on prior experience, an adaptable forward model of the arm could then compensate upcoming perturbations and would provide a correct prediction of the expected arm kinematics. In turn, these “updated” kinematics could be used for correct sequencing (for example, timing of the early antagonist) of arm movements. Following this conceptual framework, a main function of the cerebellum would be to predict the expected arm kinematics that would arise from a specific motor plan (including external forces). Thus, our finding that cerebellar patients fail to compensate for external forces during movement compensation is in line with the notion of a flawed forward model that involves cerebellar circuits.

Additional support for this interpretation comes from studies of anticipatory grip force adjustments. The study of Flanagan and Wing of grip force adjustments during arm movements with hand held loads indicated that the CNS is able to predict the load force and the kinematics of hand movement on which the load depends. 29 Support for the suggestion that the cerebellum contributes to anticipatory grip force adjustments comes from a study by Miall et al. 30 31 Cerebellar patients did not adapt their grip force rise rates to match different loads. 30 Flanagan and Wing suggested that this prediction is based on an internal model comprising the dynamics of the motor apparatus and all present external loads. 27 It is used to determine the grip forces required to stabilise the load.

In summary, cerebellar patients were less able to use advance knowledge of an upcoming perturbation based on prior experience to reduce the amplitude of the return movement. More specifically, predictive control of timing of the antagonist response after arm perturbations was impaired in cerebellar dysfunction. In conjunction with the results of previous research discussed above, our findings support a role of the cerebellum in feedback control—for example, by updating or utilising internal, forward models of the motor system.

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