Influences of Load Characteristics on Impaired Control of Grip Forces in Patients With Cerebellar Damage

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INTRODUCTION

Grasping, lifting, and manipulating objects are part of our daily repertoire of skilled motor behavior. Healthy subjects precisely scale grip force to match the load defined by physical object properties, such as weight, shape, and surface friction as well as dynamic properties such as inertia (Flanagan and Johansson 2002; Johansson and Westling 1988). The ability to scale grip force to changes of load force is well documented (Johansson 1996). For self-produced load perturbations, as they appear while moving handheld objects, grip forces are modulated in parallel and synchronous to load-force changes. Anticipatory feedforward control of grip forces is a necessary prerequisite to these abilities (Flanagan and Johansson 2002; Jaric et al. 2005; Johansson et al. 1992a,b; Wing 1996). Based on these and other findings, the theoretical concept of internal forward models has been postulated, which accounts for the causal relationship between actions and their consequences (Kawato et al. 2003; Miall and Wolpert 1996; Wolpert et al. 1998). Internal models of the dynamic properties of the object and the body predict the necessary grip force on the basis of an efference copy of the arm movement command.

It has been proposed that the cerebellum may be one important site where internal models are formed and stored (Kawato et al. 2003; Miall et al. 1993). Several studies have assessed grip-force scaling to self-produced load changes in patients with cerebellar diseases. These studies revealed inaccurate coupling between grip-force and load-force profiles during lifting (Brandauer et al. 2008; Fellows et al. 2001; Müller and Dichgans 1994; Serrien and Wiesendanger 1999a) and free movements of handheld objects (Babin-Ratte et al. 1999; Nowak et al. 2002; for review see Nowak and Hermsdörfer 2005; Rost et al. 2005). This failure is typically attributed to impaired feedforward control.

Cerebellar patients exhibit impaired coordination of multi-joint movements. It has been suggested that this is due to an impaired control of movement dynamics. In particular, interaction torques inherent to multisegmental movements may not be adequately compensated (Bastian et al. 1996; Massaquoi and Hallett 1996; Timmann et al. 2000; Topka et al. 1998). During movements of handheld objects, deficient consideration of torques in arm-movement planning may affect the prediction of the load, for example, by an inaccurate efference copy entering the internal model. Consequently, deficits in feedforward control of the grip force may be influenced by the biomechanical complexity of arm movements.

Therefore the first aim of the present study was to investigate grip-force scaling to self-generated loads with varying demands on upper limb coordination in a relatively large group of patients with cerebellar degeneration. Two conditions were introduced, requiring grip-force scaling to comparable self-generated sinusoidal loads, which were produced either isometrically against a fixed resistance or were movement-induced through free arm movements. Multijoint coordination is more complex and implies a higher level of difficulty in the latter condition and may induce a greater deterioration of grip-force anticipation in cerebellar patients.

Recently, it has been suggested that cerebellar patients may be more impaired in predictive than in reactive motor control (Bastian 2006). Accordingly, anticipatory grip-force scaling to predictable self-generated loads was impaired in cerebellar patients, whereas several studies showed comparable grip-force adjustment to healthy control subjects in tasks with unpredictable externally generated loads (Fellows et al. 2001;
Hermsdörfer et al. 1994; Nowak et al. 2004; Serrien and Wiesendanger 1999b). However, the load characteristics were typically not comparable. To further test the possibility that cerebellar patients have fewer problems to adjust grip forces to externally generated load changes, experimental conditions were included with external load changes being nearly identical to internal load changes.

Therefore sinusoidal load changes were 1) produced externally by a motor or 2) produced by a subject’s own motor activity. Because sinusoidal externally generated load changes may be predictable to some degree in healthy subjects (Hermsdörfer and Blankenfeld 2008), a first control experiment with complex sinusoidal-like external load was included. We considered this load as less predictable, relying on more reactive mechanisms. The performance in the externally generated condition was compared with a self-generated feedforward isometrical condition with a similar load profile. In a second control experiment, externally produced unpredictable load steps were investigated because this condition was typically applied to reveal pure reactive grip-force modulation (Johansson and Westling 1988; Johansson et al. 1992a,b). If cerebellar deficits are more related to the compensation of self-generated predictable than of unpredictable loads, grip-force scaling should be less affected in the externally generated conditions of the main experiment and of the two control experiments.

In sum, the ability to adjust grip forces to internally and externally generated load changes was investigated in a relatively large group of patients with cerebellar degeneration. The load was 1) externally generated by a motor or it was self-generated by the subjects either 2) isometrically by pulling against the fixed sensor device or 3) movement-induced by free arm movements with the device held in the hand in front of the body. All tasks with sinusoidal loads were designed in a way that the load profile was nearly identical and performances of the grip forces could be directly compared.

METHODS

Subjects

Twenty-three adult patients (10 female, 13 male; mean age: 53.9 ± 13.9 yr; range: 27–75 yr) with degenerative cerebellar disease participated in the experiment. Ten patients suffered from sporocerebellar ataxia type 6 (SCA6), 10 from sporadic adult onset ataxia (SAOA), and 3 from autosomal dominant ataxia type III (ADCA III, which is a pure cerebellar disorder with autosomal dominant inheritance and inconclusive genetic testing).

SCA6, SAOA, and ADCAIII are considered “pure” cerebellar disorders, which affect predominantly the cerebellar cortex (Klockgether 2007). Twenty-three sex- and age-matched (±2 yr patient’s age) healthy subjects (10 female, 13 male; mean age: 53.8 ± 13.3 yr; range: 28–73 yr), without evidence of neurological or orthopedic deficits, served as controls. All participants were right-handed, determined by the preference for writing and using utensils.

Patients and controls underwent a neurological examination by an experienced neurologist (DT). The Scale for the Assessment and Rating of Ataxia (SARA; Schmitz-Hübsch et al. 2006) was used to score the severity of ataxia symptoms. None of the patients had signs of extracerebellar involvement except mild signs of hyperreflexia in the lower limbs in 7 patients and mild signs of pallenhypaesia in the lower limbs in another 6 patients. All subjects gave written informed consent prior to participation. The study was approved by the local Ethics Committee of the University Duisburg-Essen.

Structural magnetic resonance imaging (MRI)

High-resolution three-dimensional (3D) T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE; repetition time = 2,400 ms, echo time = 4.38 ms, field of view = 256 mm, 160 slices, voxel size 1.0 × 1.0 × 1.0 mm³) scans were obtained for each subject using a 1.5-Tesla MRI scanner (Siemens Sonata). The volumetric analysis of the MR images was realized with ECCET-software (http://ecct.eacs.uni-duesseldorf.de/) as previously described ( Dimitrova et al. 2006; Richter et al. 2005).

The cerebellum was semiautomatically marked and then segmented with a 3D fitting algorithm. Segmentation of cerebellar cortex and white matter was performed automatically using intensity contours (Makris et al. 2005). The cerebellar cortex was further subdivided into the medial (vermis), intermediate, and lateral cerebellum (for details see Brandauer et al. 2008). The total intracranial volume (TICV) included brain and cerebrospinal fluid (CSF) volumes extending caudally to the foramen magnum. Cerebral volume was calculated by subtracting the volume of the cerebellum from the whole brain volume (Dimitrova et al. 2006; Richter et al. 2005). All volumes were expressed as percentage TICV.

Volumes of the entire cerebellum, the cerebellar gray and white matter, and the volume of the medial (vermis), intermediate, and lateral cerebellum were reduced in cerebellar patients compared with control subjects (unpaired t-tests: all comparisons P < 0.01; also see Table 1). Cerebral volume and the total intracranial volume were not significantly different between groups.

General procedure and data acquisition

The main task was characterized by sinusoidal load changes, which were presented in three conditions. In the external-generated condition the load changes were generated by a motor. In the two self-generated conditions the load changes had to be generated 1) either isometrically by the subject’s following a target on a screen or 2) the load changes resulted from free arm movements with a handheld object in front of the subject’s body (the movement-induced condition).

Two tasks served as control tasks. In the first control task, the load profile was characterized by complex sinusoidal-like load changes either externally generated by the motor or isometrically generated by the subject. In the second control task sudden unpredictable load steps were generated externally by the motor.

A more detailed description of the tasks is given in the following text. All tasks were explained to the subjects and a practice trial of 11 s was performed prior to each condition. Each condition consisted of four trials with a duration of 22 s. The whole experiment lasted about 45 min.

In all tasks a custom-made instrumented object was used. The object had a rectangular form with two grasping surfaces (60 × 60 mm) and a width of 26 mm. The grasping surfaces were covered with medium grain sandpaper (No. 240). The object incorporated sensors to record the grip force on each side (0–100 N, accuracy ±0.1 N), the linear vertical and horizontal accelerations tangential to the grasping surfaces (∆50 m/s², accuracy ±0.2 m/s²), and the load force (0–60 N, accuracy ±0.1 N). Grip-force and load-force sensors were mechanically independent, avoiding any cross talk between signals. In all tasks subjects were required to grasp the center of the object with the thumb on the one side and the index and middle fingers on the opposite side. The three-finger grip was used to minimize rotational torques that arise when the object is grasped away from the axis of loading. The grip force of both sensors for each side was averaged. For movement-induced sinusoidal load changes a weight of 300 g was fixed to the object to increase the total weight of the object to 500 g. Vertical acceleration (AccZ) was defined as pure kinematic acceleration due to movement. For this condition the net load force was calculated as the vectorial sum of weight (m × g), acting vertically, and the acceleration-dependent inertial loads in the vertical and sagittal directions.
Patients are sorted according to age (27–75 years). Severity of ataxia was rated with the Scale for the Assessment and Rating of Ataxia (SARA; Schmitz-Hubsch et al., 2006), with higher scores indicating more severe ataxia. Total scores are given; maximum scores are indicated in brackets. Volumes of the cerebellum and cortex are expressed as a percentage of the total intracranial volume (%TICV). SAOA, sporadic adult onset ataxia; ADCA III, autosomal dominant ataxia type III (pure cerebellar); SCA6, spinocerebellar ataxia type 6.

### Table 1. Characteristics of cerebellar patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Gender</th>
<th>Disease</th>
<th>Duration, years</th>
<th>Cerebellar Volume, % TICV</th>
<th>Cortical Volume, % TICV</th>
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<tr>
<td>Cer1</td>
<td>27</td>
<td>F</td>
<td>SAOA</td>
<td>2</td>
<td>11.0 (40)</td>
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<tr>
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<td>2</td>
<td>12.0 (9)</td>
<td>6.5 (83.3)</td>
</tr>
<tr>
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<td>F</td>
<td>SAOA</td>
<td>18</td>
<td>15.5 (10)</td>
<td>4.8 (84.6)</td>
</tr>
<tr>
<td>Cer4</td>
<td>40</td>
<td>M</td>
<td>SAOA</td>
<td>3</td>
<td>5.0 (2)</td>
<td>7.9 (82.1)</td>
</tr>
<tr>
<td>Cer5</td>
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<td>ADCA III</td>
<td>23</td>
<td>9.0 (4)</td>
<td>7.3 (83.1)</td>
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<tr>
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<td>SAOA</td>
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<td>11.5 (9)</td>
<td>7.2 (80.7)</td>
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<tr>
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<td>ADCA III</td>
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<td>5.6 (82.7)</td>
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<td>SAOA</td>
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<td>SAOA</td>
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<td>7.9 (82.8)</td>
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<td>6.7 (79.3)</td>
</tr>
<tr>
<td>Cer20</td>
<td>69</td>
<td>M</td>
<td>SCA6</td>
<td>16</td>
<td>13.5 (8)</td>
<td>8.8 (81.4)</td>
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<tr>
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<td>72</td>
<td>M</td>
<td>SCA6</td>
<td>4</td>
<td>12.0 (6)</td>
<td>6.9 (82.4)</td>
</tr>
<tr>
<td>Cer22</td>
<td>72</td>
<td>F</td>
<td>SCA6</td>
<td>9</td>
<td>16.0 (9)</td>
<td>5.7 (82.8)</td>
</tr>
<tr>
<td>Cer23</td>
<td>75</td>
<td>M</td>
<td>SCA6</td>
<td>&gt;35</td>
<td>17.5 (9)</td>
<td>8.4 (80.9)</td>
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</table>

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
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<td>11.8 (5.5)</td>
<td>7.0 (3.5)</td>
<td>7.0 (1.3)</td>
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<td>53.8 (13.3)</td>
<td>11.7 (0.9)</td>
<td>8.0 (0.9)</td>
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<td>Controls</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>9.0 (0.7)</td>
<td>3.0 (0.7)</td>
<td>8.1 (1.9)</td>
<td>8.1 (1.9)</td>
</tr>
</tbody>
</table>

(m × AccZ, m × AccY), acting tangential to the grip surfaces \( LF = m × ((AccZ + g)^2 + AccY^2)^{1/2} \).

**Externally generated load changes**

Participants were comfortably seated on the side of a table. The dominant hand rested on a piece of foam (height 7.5 cm) laterally of the trunk (Fig. 1, *top, left picture*). The object was connected to the shaft of a linear motor (Copley ServoTube Actuator and Xenus Servocontroller). When the load was set to zero, the shaft of the motor floated nearly frictionlessly due to the magnetic drive and the vertical mounting (Fig. 1). A maximum constant load of 42 N could be produced, with an accuracy of approximately ±5% (limited mainly due to movement-induced inertia of the shaft). Connection with a cardan joint prevented blockage during small hand movements or off-axis positions of the sensor. The subjects were instructed to hold the object stationary with the lowest grip force needed.

**Externally generated sinusoidal load changes**

The motor generated downward-pulling sinusoidal load changes with a frequency of 0.9 Hz and an amplitude of 6 N (range: 1–7 N).

**Externally generated complex sinusoidal-like load changes**

The motor generated downward-pulling load changes with a sinusoidal-like profile, according to a function that was the sum of three nonharmonic sinusoids, with a maximum frequency component of 0.8 Hz, a maximum total amplitude of 7 N, and a random phase shift.

**Externally generated load steps**

The motor generated downward-pulling load steps. The baseline load was 3 N with a step of 4 N magnitude and a maximum force rate of 50 N/s. The load steps had a randomized duration of 2 to 3 s and the pauses between load steps were 2 to 4 s.

**Isometrically generated load changes**

As before, participants were comfortably seated on the side of a table. The shaft of the motor was mechanically blocked in a fixed position and the participants were instructed to pull the object in an upward direction against the fixed resistance while following a moving target on a computer screen (Fig. 1, *top, middle picture*). The target consisted of a horizontal line, which was moving continuously upward and downward. The applied pulling load force was displayed as feedback in the form of a vertical bar on the screen. The subjects were instructed to adjust the load force, so that the top of the vertical bar matched the target line, by increasing and decreasing the pulling load.

**Isometrically generated sinusoidal load changes**

The subjects generated sinusoidal load changes by following the target that oscillated with a frequency of 0.9 Hz and an amplitude of ±3 N (min-max load: 1–7 N).

**Isometrically generated complex sinusoidal-like load changes**

The subjects were instructed to follow the moving target on the screen, which moved according to the same function like in the complex sinusoidal-like externally generated load condition (max. amplitude: 7 N; max. frequency: 0.8 Hz).

**Movement-induced load changes**

Participants moved their dominant arm free in front of their trunk (Fig. 1, *top, right picture*). The screen provided an indicator of movement speed but no feedback.
MOVEMENT-INDUCED SINUSOIDAL LOAD CHANGES. Subjects were asked to grasp the object and to hold it in front of their trunk with the grip surfaces vertical and parallel to their front. This orientation was kept constant during the movement. After a verbal command subjects had to move the object in a vertical line up and down with an amplitude of about 30 cm at a frequency of 0.9 Hz, which was provided by the same visual target as that in the isometrically generated sinusoidal load condition. The accurate movement execution was monitored by the examiner. In rare cases corrective instructions were provided between trials.

Data analysis

To quantify the performance in the main task conditions (sinusoidal load changes) of load force and grip forces, a computer algorithm first searched for peaks (local maxima and minima) in the load-force profiles. To quantify the magnitude of the produced grip forces, the maxima and the minima of grip force (GFmax and GFmin) were determined in a window around each load peak. The load-force amplitude (LFampl) and the mean load force (LFmean) as well as the mean grip force (GFmean) and the force ratio (GF/LF ratio) between grip-force and load-force maxima were calculated. The force ratio represents a measure of the efficiency of the grip-force output in relation to the load. The coupling between the modulation of grip force and load force was evaluated by calculating the cross-correlation function between both time series. From the cross-correlation function two measures were extracted. The maximum cross-correlation coefficient (Rx) was taken as the indicator of the precision of the coupling, independent of possible phase shifts. Phase shifts indicative of the temporal control mode (feedforward vs. feedback grip-force control) were measured by the time lag (Tlag) of the maximum cross-correlation. Trials with maximum cross-correlation coefficients <0.3 were excluded from the time lag analysis since the relationship between grip-force and load-force profiles was considered random in those trials. As a consequence, data from five patients and four control subjects (three patients and three control subjects for the external generated load condition, two patients and one control subject for the movement-induced load condition) were excluded from the analysis of time lags. Grip-force modulation lagged behind load changes if the value was positive. Measurements of grip force, load force, GF/LF ratio, maximum cross-correlation coefficient, and time lag of cross-correlation were determined for each trial.

The analysis was performed for intervals containing seven full cycles (seven up and down load-force oscillations). From each trial the first two cycles were excluded to avoid start effects and the two consecutive intervals were selected. For statistical analyses data were averaged across the eight intervals of the four trials performed. To analyze within-subject variability the SD of the eight intervals was calculated for the GF/LF ratio, the maximum cross-correlation coefficient, and the time lag.

For the first control task, which was characterized by complex sinusoidal-like load changes, the same principal analyses as those for
the main task were used. Instead of amplitudes, the mean load force (LFmean) and the SD of the mean load force (SD-LFmean) were calculated due to the variable load profiles and also the mean grip force (GFmean) and the SD of the mean grip force (SD-GFmean) were determined. Again, the coupling between the modulation of grip force and load force was evaluated by calculating the cross-correlation function between both time series (Rx and Tlag).

For the second control task consisting of load steps, four time points were determined during the phase of increasing load steps: 1) load-force onset (LFonset), 2) grip-force onset (GFonset), 3) load-force maximum (LFmax), and 4) grip-force maximum (GFmax). The temporal coupling between grip force and load force was assessed by calculating the time lag between grip-force onset and load-force onset (TLFonset – TGFonset) and the time lag between the time of maximum grip force and the time of maximum load force (TGFmax – TLFmax). As a measure of the precision of the modulation of the grip-force profile with the load-force profile, a linear regression analysis was performed between grip force and load force during load increase phases of the load steps. Linear regressions were calculated and the $r^2$ regression coefficient was used to characterize the linearity and precision of the grip-force modulation with the load-force change.

Statistical analyses

To assess the differences between the single-task conditions, repeated-measures ANOVAs were calculated with the between-subject factor “group” (controls, patients) and the within-subject factor “condition” (externally generated, isometrically generated, and movement-induced load conditions). A similar ANOVA was calculated for the first control experiment (sinusoidal-like load changes) with the adequate within-subject factor “condition” (externally generated and isometrically generated). Paired t-tests were used for post hoc analyses with Bonferroni correction when necessary. For all other group comparisons (e.g., in the second control experiment with sudden load jumps) unpaired t-tests were used. A $P$ value $<0.05$ was considered significant. In addition, correlations were performed with the results from the clinical rating scales and volumetric MRI measures. Spearman’s correlation tests were used.

RESULTS

Main experiment: sinusoidal load changes

PERFORMANCE OF SINGLE PATIENTS. Grip-force and load-force profiles of one trial in the three conditions are shown in Fig. 1 for one control subject and three patients (bottom part). The control subject showed sinusoidal grip-force profiles according to the produced loads for all three conditions. The first patient (Cer17 in Table 1) exhibited a strong increase of grip-force scaling. Despite this high force level the patient showed reasonably good modulation of the grip force with the load forces in the externally and isometrically generated load conditions. The second patient (Cer6) was able to adjust the grip-force profile only in the externally generated load condition. In both self-generated conditions this patient was severely impaired to modulate the grip force synchronously with the occurring load changes. The patient compensated externally produced loads with small grip-force amplitudes, although a clear coupling between grip force and load was present. Precise compensation of external load, however, was not the typical finding in cerebellar patients (see following text). In addition, this patient showed in the movement-induced condition a modulation of the grip force that was nearly antiphase to the load force. This behavior was not found in any other patient but in one of the control subjects (see following text). In contrast the third patient (Cer9) was able to modulate the grip forces for the movement-induced condition, although with an exaggerated grip-force level; modulation was also preserved for the isometrically generated condition, but with normal grip forces. In the externally generated condition the third patient was more impaired to adjust the grip force to the load forces, especially compared with the second patient (Cer6). Overall, these three patients demonstrated the wide range of variability within the patient group in the performance across the three different load conditions.

GROUP DATA. Load-force amplitude and the mean load force were calculated to evaluate whether loads were produced with the intended profiles (see METHODS) in the different conditions (Fig. 2). A main effect of condition was found for the mean load force [$F$($2,88$) = 111.04, $P < 0.001$]. Post hoc tests revealed a significantly higher mean load force in the movement-induced load condition than that in the externally and isometrically generated load conditions ($P < 0.001$); the last two did not differ significantly. The higher load level of the movement-induced load condition could be attributed to the object weight and/or the movement acceleration (instructed frequency of 0.9 Hz with a movement amplitude of $\sim 30$ cm), which were obviously higher than required. Patients and control subjects produced similar mean load forces.

The analysis for the load-force amplitude yielded a significant main effect of condition [$F$($2,88$) = 17.75, $P < 0.001$] and of group [$F$($1,44$) = 5.00, $P < 0.05$], as well as a significant interaction effect of group $\times$ condition [$F$($2,88$) = 12.42, $P < 0.001$]. Post hoc analyses showed significantly higher load-force amplitudes for patients in the isometrically generated load condition than in control subjects; in the two other conditions patients showed load forces similar to those in

![Fig. 2. Median, spread, and interquartile range of (A) the mean load force and (B) the load-force amplitude of cerebellar patients (black bars) and control subjects (gray bars) for the externally generated (ext), isometrically generated (isom), and movement-induced (mov) sinusoidal load conditions. The asterisk demonstrates a significant group difference.](https://example.com/fig2.png)
controls. Patients failed to adjust the load-force accuracy to the moving target because they overshot the target maxima.

To quantify the scaling of grip force, two parameters were analyzed: mean grip force and the GF/LF ratio between grip force maximum and load force maximum (see Fig. 3). Patients showed significantly higher mean grip forces than did control subjects \( [F_{(1,44)} = 19.71, P < 0.001] \) in all conditions (Fig. 3A). Additionally, a main effect of condition \( [F_{(2,88)} = 68.06, P < 0.001] \): the highest grip forces were produced in the movement-induced load condition followed by the externally generated and the lowest grip forces were produced in the isometrically generated condition (each post hoc test \( P < 0.01 \)). No significant interaction effect was found.

The ratio between grip force and load force describes the relation of the grip force to the actually occurring load force (Fig. 3B). Patients produced exaggerated grip forces in all conditions compared with controls \( [F_{(1,44)} = 13.74, P < 0.01] \). The three conditions differed significantly \( [F_{(2,88)} = 35.58, P < 0.001] \). Post hoc comparisons revealed the lowest GF/LF ratio in the isometrically generated condition compared with the two other conditions (both \( P < 0.01 \)), which did not differ from each other. Even though patients produced higher load-force amplitudes in the isometrically generated load condition than healthy controls, the grip forces of patients related to the produced loads were similarly increased in all conditions.

Phase shifts indicative of the timing of grip force with respect to the load were measured by the time lag (Tlag) of the force amplitudes in the isometrically generated load condition from each other. Even though patients produced higher load-profile. No significant interaction between the three conditions differed significantly \( [F_{(1,44)} = 23.67, P < 0.001] \). The adjustment of the grip forces to the different load conditions was less precise than that in control subjects, but the patients were not more severely impaired in any of the conditions (no interaction effect was found).

To quantify within-subject variability, the SDs of the GF/LF ratio, the maximum cross-correlation coefficient, and the time lag were analyzed. A significant main effect of group was found for the SD of GF/LF ratio \( [F_{(1,44)} = 10.34, P < 0.01] \) because patients showed a significantly higher variability of the grip-force level. Thus in addition to an increased force level, patients performed more variably across trials, irrespective of the condition. For the SD of time-lag analysis no significant differences were found. Analysis of the SD of maximum cross-correlation coefficient revealed a significant main effect of condition \( [F_{(2,88)} = 3.66, P < 0.05] \) and a significant main effect of group \( [F_{(1,44)} = 22.41, P < 0.001] \) was also found. With respect to the force level, patients showed a slightly higher variability than that of control subjects.

To evaluate whether the modulation differed between conditions in the patient group, correlation analyses between the cross-correlations were performed. In both self-generated (isometrically and movement-induced) conditions there was a moderately significant relationship \( (r = 0.48, P < 0.05; black line in Fig. 5C) \) after exclusion of a single patient (see Fig. 5C: correlation coefficient \( r = 0.29, P > 0.1 \); gray line). For the externally generated load condition there were no significant correlations with either of the two self-generated conditions (see Fig. 5, A and B; \( r < 0.2, P > 0.4 \)).

Correlations between the mean grip force and the maximum cross-correlation coefficient for each condition were calculated to define a possible influence of high grip forces on a decreased precision of modulation between grip force and load force in the patient group. A significant correlation was found for the externally generated condition \( (r = -0.63, P < 0.01) \) and for the movement-induced condition \( (r = -0.55, P < 0.01) \). Patients who produced higher mean grip forces showed lower cross-correlation coefficients.

**Correlations with Ataxia Score and Degree of Cerebellar Atrophy.** The SARA score of the upper limb ataxia items showed a significant correlation with the mean grip force \( (r = 0.56, P < 0.05) \) and the grip force/load force ratio \( (r = 0.60, \)
For the movement-induced load condition. Patients with higher ataxia scores showed a higher grip-force level in self-generated continuous up and down movements.

Also a significant correlation resulted between the precision of grip-force/load-force modulation (Rx) and the upper limb ataxia score for the isometrically generated load condition ($t = -0.51$, $P < 0.05$) as well as for the movement-induced load condition ($t = -0.63$, $P < 0.05$). Patients with a higher ataxia score modulated their grip forces less precisely to the self-generated load changes. No significant correlations with the degree of cerebellar atrophy of the total cerebellum and any of the subvolumes were found.

**Control experiments**

For the first control experiment (complex sinusoidal-like load profile) the mean load force and the SD of the mean load force were analyzed. Patients and control subjects did not differ in mean load force. The conditions yielded a significant main effect $[F_{(1,44)} = 4.84$, $P < 0.05]$. The load force was significantly higher in the externally generated load condition. For the SD of the mean load force a significant interaction effect was found $[F_{(1,44)} = 13.03$, $P < 0.05]$. Patients showed more variability in the isometrically generated condition than that in the externally generated load condition, whereas for control subjects no difference was found.

For the grip-force scaling patients produced exaggerated grip forces compared with those of controls [GFmean: $F_{(1,44)} = 7.24$, $P < 0.05]$. Both groups showed higher grip forces in the externally generated condition $[F_{(1,44)} = 15.90$, $P < 0.001]$. No significant interaction was found. Control subjects and patients showed no difference in both load conditions for the grip force variability (SD-GFmean).

The precision of the grip force modulation was determined with the cross-correlation coefficient and the phase shift. Both groups showed a clearly significant time lag in the externally generated load condition compared with that in the isometrically generated load condition $[F_{(1,44)} = 86.02$, $P < 0.001]$, whereas they did not differ between each other (Fig. 6A).

For the cross-correlation coefficient (Rx; see Fig. 6B) control subjects achieved a better adaptation of their grip forces to the load forces compared with that of patients $[F_{(1,44)} = 10.07$, $P < 0.01]$ and the adaptation for patients and control subjects was better in the isometrically generated than that in the externally generated load condition $[F_{(1,44)} = 24.33$, $P < 0.001]$. The intercorrelation of the coefficients of the two tasks was not statistically significant ($r = 0.2$, $P > 0.4$).

No significant correlations with the ataxia score or degree of cerebellar atrophy were found.

For the second control experiment (load steps) the load difference between onset and maximum of load force was calculated. Patients and control subjects did not differ significantly from each other ($P > 0.6$).

Analogously, the grip force difference between onset and maximum of grip force was calculated, which also did not differ between groups ($P > 0.6$). However, patients generated significantly higher values than did the controls for grip force onset ($t = 4.71$, $P < 0.001$) and grip force maximum ($t = 2.75$, $P < 0.01$). The GF/LF ratio between grip force and load force describes the relation of the grip force to the actually occurring load force. Patients achieved a significantly higher ratio due to their exaggerated grip forces ($t = 3.61; P < 0.01$).

The time lag between the grip-force and load-force profiles reflects the temporal control mode of grip-force modulation. At load step onset both groups showed a positive time lag, which indicates a reactive response of the grip force to the occurring load jump. Patients tended to react later than controls ($t = 2.58$; $P = 0.078$, Bonferroni-corrected). For the time lag between grip and load-force maxima no significant group difference

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**Fig. 4.** Median, spread, and interquartile range of (A) the time lag (Tlag) and (B) the maximum cross-correlation coefficient (Rx) of cerebellar patients (black bars) and control subjects (gray bars) for the externally generated (ext), isometrically generated (isom), and movement-induced (mov) sinusoidal load conditions. Significant main effects of group (patients vs. control subjects) are marked by an asterisk.

**Fig. 5.** Relationship between the grip-force load coupling (cross-correlation coefficient [Rx]) in the externally generated load condition (cross-correlation-coeff_ext) and (A) the isometrically generated load condition (cross-correlation-coeff_isom) as well as (B) the movement-induced load condition, and (C) between the two self-generated—isometrically (cross-correlation-coeff_isom) and movement-induced (cross-correlation-coeff_mov)—load conditions in cerebellar patients (exclusion of a single patient, shown as gray dot, resulted in a significant correlation).
was found; patients and controls lagged the load-force maximum with their grip force maximum (see Fig. 7A). The regression coefficient ($r^2$) was used to characterize the linearity and precision of the grip force modulation with the load-force change, which did not differ between patients and control subjects (see Fig. 7B).

No significant correlations with the ataxia score and degree of cerebellar atrophy were found.

DISCUSSION

It has been repetitively demonstrated that patients with cerebellar lesions fail to produce grip forces in precise anticipation of the loads generated by movements of a grasped object. Although this failure was typically attributed to impaired feedforward control, a role of impaired prediction and compensation of movement-induced torques and deficient coordination of multiple-joint movements is also feasible. We directly investigated this possibility by introducing a condition with isometrical load production and lower demands on coordination. Moreover, some studies suggested that cerebellar patients show closer to normal performance when externally generated loads—as opposed to self-generated loads—have to be compensated by the grip force. By introducing a condition with external load production, we also investigated this question. In particular, we designed the tasks in a way that the load profile was nearly identical and grip force performance could be directly compared. The load was (1) externally generated by a motor or it was self-generated by the subjects either (2) isometrically by pulling against the fixed sensor or (3) movement-induced by free arm movements in front of the body.

Load generation

As intended, the three sinusoidal load conditions exhibited similar and comparable load profiles. The movement-induced load profile was somewhat higher than expected (see RESULTS). Patients produced load profiles comparable to those of controls. One exception was the isometrically generated load condition, where the load was produced by following a moving target on the screen. In this condition many patients produced exaggerated load-force amplitudes, particularly in the upper target range. This deficit can be attributed to influences of ataxia, which also results in hypermetric movements (Timmann and Diener 2007). Similarly, patients showed a higher variability of the load in the isometrically generated complex sinusoidal-like load condition, reflecting an overshooting of the upper target range.

Grip-force level

The analysis of measures reflecting the level of the produced grip forces revealed significant differences between the different sinusoidal load conditions and between groups, but no statistically significant interactions. The effect of conditions was mainly explained by the fact that in the isometrically generated condition patients and controls produced lower grip forces relative to load forces (GF/LF ratio) compared with the other two conditions. For the comparison between the isometrically active loading and the externally loading condition this result reflects the findings of Hermsdörfer and Blankenfeld (2008) who showed threefold increased grip forces to externally generated sinusoidal load profiles if compared with self-generated load profiles. Higher grip forces in response to an external load perturbation in comparison with a self-produced perturbation have also been shown in collision and catching studies (Delevoye-Turrell et al. 2003; Nowak et al. 2004). However, this seems not to be generally valid since in the self-produced inertial condition, when the object had to be moved up and down in front of the body, the scaling of the grip force was higher than that in the isometrically generated condition and equal to the external loading condition. One possible explanation may be a higher safety margin, due to a serious damage of the object in case it might slip from the hand.
and drop down. A second reason may be insecurities in load-force generation that have to deal with the complex dynamics of multijoint arm movements. This insecurity to determine the load force may have resulted in a higher safety margin. Studies of aiming movements found a greater deficit in cerebellar patients when multiple joints in contrast to single joints had to be coordinated (Bastian et al. 1996; Massaquoi and Hallett 1996; Timmann et al. 2000; Topka et al. 1998). Brandauer et al. (2008) showed an improvement in grip-force scaling in cerebellar patients when a multijoint reach-to-grasp task was simplified to a single-joint (wrist) grasping movement where the forearm was supported. However, the benefit of the single-joint condition for patients did not exceed the benefit in control subjects (Brandauer et al. 2008), since patients produced similarly increased grip forces in both conditions. This finding is in accordance with the present results, in that patients produced higher grip forces in all tasks and showed no greater impairments in the movement-induced condition, where multiple joints had to be controlled.

Apart from the sinusoidal load conditions that enable a direct comparison of forces, the grip force of cerebellar patients was also increased in all control tasks. The finding of generally increased grip forces is in line with prior studies showing that cerebellar patients produced exaggerated grip forces under various task conditions (e.g., Fellows et al. 2001; Nowak et al. 2004; Rost et al. 2005; Serrien and Wiesendanger 1999a).

Anticipation of self-generated movement-induced versus self-generated isometric loads

The temporal modulation of the grip-force profile with respect to the load-force profile is indicated by the time lag. The time lag was close to zero in the two self-generated sinusoidal load conditions and is comparable for patients and healthy control subjects. Although the cerebellum seems to be considerably involved in predictive mechanisms, the synchronous modulation of grip force and load force therefore seems to be unimpaired in patients with cerebellar degeneration. This finding is in accordance with other studies that demonstrated preserved temporal coupling between grip force and load force (Fellows et al. 2001; Nowak et al. 2002; Rost et al. 2005). For example, Rost et al. (2005) also showed preserved synchrony of grip force and load force during cyclic movements in patients with cerebellar degeneration. Despite a high variability, on average cerebellar patients performed comparably with control subjects.

Apart from timing, the precision of predictive grip-force modulation can be expressed by the maximum coefficient of cross-correlation. For self-generated sinusoidal load changes the precision was, as expected, high in healthy control subjects. That means that for self-generated load changes the load force was precisely anticipated and the grip force was adjusted in a predictive feedforward manner. The coefficient of cross-correlation was higher under isometric than that under movement-induced loading. Since load generation is more complex during movement-induced loading and interaction torques must be compensated only in this condition, less-precise modulation of the grip force with the load force was expected in this condition (see earlier text and INTRODUCTION). Importantly, it is obvious that cerebellar patients were similarly impaired in both self-generated conditions and they did not benefit from a less-complex isometric task, where joint movements were largely absent and the forearm was supported, thus avoiding any movement-induced torques. Therefore impairments in the control of dynamics of multijoint movements due to cerebellar lesions do not specifically affect the anticipatory control of grip forces. Rather, the predictive mechanism per se seems to be affected in the task, irrespective of the exact dynamics. This assumption receives support from the correlation between the coefficients in the isometric and movement-induced conditions within the patient sample (exception may be explained by individual strategies). The present findings further support the interpretation that internal feedforward models are located in the cerebellum and their function generalizes across different tasks (Bastian 2006; Kawato et al. 2003; Miall and Wolpert 1996; Wolpert et al. 1998).

Anticipation of externally versus self-generated loads

In addition to the two self-generated load conditions, a comparable externally generated sinusoidal load profile was investigated. There was a clear positive time lag in the external sinusoidal load condition, indicating that grip force lagged the load. This suggests a more reactive processing of the load forces as opposed to the predictive processing in the self-generated condition with time lag around zero. However, the time lag (40 ms) in the present experiment is considerably lower than the time lag of 70–140 ms commonly found for unpredictable discrete load steps (Johansson et al. 1992a, b). In healthy subjects, equivalent results were found by Hermsdörfer and Blankenfeld (2008) who argue that continuous sinusoidal load changes are predictable due to their repetitive time course and therefore do not solely rely on reactive mechanisms. These authors hypothesize that during external load changes reactive and predictive mechanisms are combined in a flexible way depending on task conditions (see Hermsdörfer and Blankenfeld 2008; Turrell et al. 1999). In addition, the updating of the ongoing grip-force response may require a shorter time than its initiation in sudden load steps (Johansson et al. 1992a). Patients modulated their grip force according to the externally generated load changes with the same time lag as that in control subjects (although Fig. 3A shows longer average time lags in patients than those in controls, suggesting a strong contribution of reactive mechanisms; a post hoc test did not reveal a statistically significant difference between groups). Therefore the temporal aspects of the mechanisms involved in controlling the externally generated load seem comparable in patients and in control subjects.

For externally generated sinusoidal load changes the precision of predictive grip-force modulation (cross-correlation coefficient) was less precise than that for the self-generated loads, as expected from previous findings in healthy subjects (Hermsdörfer and Blankenfeld 2008). That means that, irrespective of the time lag, grip-force modulation was less precise for externally generated loads compared with anticipatory modulation in the self-generated condition. As obvious from a lower coefficient of cross-correlation, cerebellar patients were impaired in the external load conditions. This finding is unexpected since the cerebellum is thought to be involved in predictive feedforward mechanisms (Bastian 2006), whereas reactive feedback control seems to be less prominent.

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One factor that may have influenced the precise coupling between grip force and load force in cerebellar patients is stiffening of the muscles of hand and arm to avoid excessive movements during load perturbations or active load production. However, the correlation between grip-force level and the measure of coupling is inconsistent between conditions. In addition, clear dissociations between exaggerated forces and preserved coupling are obvious in individual patients (see Fig. 1). Therefore stiffening may affect the precise modulation of the grip force but cannot be a major factor.

As outlined earlier, predictive mechanisms may contribute substantially to the successful compensation of sinusoidal external loads and since the cerebellum is particularly important for this aspect of the tasks, patients deteriorate in overall performance. To resolve this issue, another external task was tested with a nonpredictable time course.

Role of predictability of external loading

To assess the role of the predictability of a continuous external load we introduced a load profile with complex sinusoidal-like but irregular load changes. Comparable to the sinusoidal conditions the complex sinusoidal-like loading was tested under isometrically self-generated conditions, replicating the findings for the sinusoidal load. For the externally generated complex sinusoidal-like load condition there was a clear time lag (70 ms), which indicates a clear feedback processing of the afferent information about load changes. The longer time lag compared with sinusoidal loading suggests an increased contribution of nonpredictable mechanisms in compensating the new load profile. There was no difference between patients and control subjects in their temporal coupling. Importantly, for the precision of the modulation of grip-force to the load-force profile patients revealed a considerably lower coefficient of cross-correlation than that in control subjects, just as was found for the sinusoidal loads. This finding does not support the assumption that the contribution of predictable mechanisms in external loading is specifically responsible for impaired performance in cerebellar patients. It rather suggests that the cerebellum is also involved in reactive mechanisms under external load conditions in addition to feedforward control in self-generated load conditions. These two functions seem independent as suggested by the missing correlation between impaired coefficients of cross-correlation in the self-generated and the external conditions demonstrated for the patients under sinusoidal as well as complex sinusoidal conditions. As the anatomical counterpart of the dissociation, the intermediate zone of the cerebellum receives somatosensory input and may be involved in on-line control of movements while the lateral cerebellum receives input from the cerebral cortex and is more involved in movement planning and prediction (Allen and Tsukahara 1974; Evarts and Thach 1969). Recent evidence suggests, however, that the intermediate zone may also have predictive functions (Bastian 2006; Rabe et al. 2009; Shadmehr and Krakauer 2008). Lesion symptom mapping in degenerative disease is limited due to the generalized nature of the disease. Studies in patients with focal disorders are needed to specify a clear localization.

Rapid external load step

The finding of impaired precision during sinusoidal and sinusoidal-like loads leaves open the possibility that reaction during rapid load changes that occur at arbitrary time points—as for example tested in catching and illusion experiments (Nowak et al. 2004; Turrell et al. 1999)—may be better preserved following cerebellar damage. Therefore in a second control experiment sudden externally generated load jumps were produced. The time lag between load-force onset and grip-force onset was significantly positive, indicating a clear reactive response of the grip force to the load jump (83 ms). Patients tended to react later than controls (88 vs. 79 ms). There was also a clear time lag between grip-force and load-force maxima (66 ms), but no significant group difference. In addition, the strength of the correlation between the increase in grip force and load force did not differ between patients and control subjects. Therefore impairments of grip-force responses to external loading were largely absent when the load changes occurred rapidly and started from a stable baseline at arbitrary times compared with continuous load changes. One reason for this discrepancy may be a dominant role of the pyramidal system with reflectory responses, including long-loop reflexes (Macefield and Johansson 2003) during such rapid load jumps that do not, or only to a smaller extent, request cerebellar contributions.

Conclusions

The various experiments in patients with degenerative cerebellar damage emphasize the important role of the cerebellum in predictive feedforward mechanisms in the control of self-generated loads. The physical characteristics of the load do not critically influence this function. In parallel to feedforward control, the cerebellum is also involved in reactive responses when a continuous externally generated load destabilizes the grip, but less involved when rapid load changes disturb the grip.

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