Adaptation to visuomotor rotation and force field perturbation is correlated to different brain areas in patients with cerebellar degeneration

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Abstract

Although it is widely agreed that the cerebellum is necessary for learning and consolidation of new motor tasks, it is not known whether adaptation to kinematic and dynamic errors is processed by the same cerebellar areas or if different parts play a decisive role. We investigated arm movements in a visuomotor rotation and a force field perturbation task in 14 participants with cerebellar degeneration and 14 age- and gender-matched controls. MRI images were used to calculate the volume of cerebellar areas (medial, intermediate and lateral zones of the anterior and posterior lobe) and to identify cerebellar structure important for the two tasks. Corroborating previous studies, cerebellar participants showed deficits in adaptation to both tasks compared to controls ($P < 0.001$). However, it was not possible to draw conclusions from the performance in one task on the performance in the other task, because an individual participant could show severe impairment in one task, and perform relatively well in the other ($\rho = 0.1; P = 0.73$). We found that atrophy of distinct cerebellar areas correlated to impairment in different tasks. While atrophy of the intermediate and lateral zone of the anterior lobe correlated to impairment in the force field task ($\rho = 0.72, 0.70, P = 0.003, 0.005$, respectively), atrophy of the intermediate zone of the posterior lobe correlated to adaptation deficits in the VM task ($\rho = 0.64; P = 0.015$). Our results suggest that adaptation to the different tasks is processed independently and relies on different cerebellar structures.
Introduction

It is widely believed that cerebellar disorders are associated with the failure of cerebellar patients to successfully adapt in a changing environment. For this reason, a clear understanding of the cerebellar regions involved and the specific relationship between ataxia and failure to adapt is of key clinical and theoretical importance. Two types of adaptation of arm movements that have been widely studied are force field adaptation (perturbing forces applied to the hand that cause dynamic errors) and visuomotor adaptation (distortion of the relationship between hand movement and visual feedback that cause kinematic errors).

The literature is equivocal about whether adaptation to visuomotor rotation and to force field perturbation is processed independently in the cerebellum or by the same underlying cerebellar tissue. Previous work by Krakauer et al. (1999) seemed to demonstrate that learning of force fields did not interfere with learning of visuomotor perturbations, suggesting that different mechanisms may underlie the two tasks. They suggested that dynamic and kinematic perturbations might be processed differently. Likewise, other authors found that the tasks differed in how they generalize (Pine et al. 1996; Baizer et al. 1999; Donchin et al. 2003; Criscimagna-Hemminger et al. 2003) and in the underlying coordinate system which seems to be used in processing (Flanagan and Rao 1995; Wolpert et al. 1995; Shadmehr and Moussavi 2000). However, imaging studies specifically focused on uncovering differences in the neural substrate of kinematic and dynamic learning have either failed to find differences between the tasks (Diedrichsen et al. 2005) or else found contradictory localizations (Graydon et al. 2005; Krakauer et al. 2004; Nezafat et al. 2001; Imamizu et al. 2000). This raises the possibility that while the underlying mechanisms may somehow be different, the neural substrates of adaptation may be located in completely overlapping areas of the cerebellum. The same neural structures might perform different computations in different circumstances.
The strongest evidence for involvement of the cerebellum in these two types of adaptation comes from clinical studies. While healthy participants adapt movements within a few trials and learn to reach targets in the new environment after experiencing errors induced by either paradigm, participants with cerebellar disorders show impaired adaptation to visuomotor rotation (Tseng et al. 2007; Martin et al. 1996; Weiner et al. 1983) and to force field perturbation (Smith and Shadmehr 2005; Maschke et al. 2004). The deficit in adaptation correlates with the severity of cerebellar degenerative ataxia for both the visuomotor (Tseng et al. 2007) and force field (Maschke et al. 2004) tasks. Despite these findings, there has only been one study to date that demonstrated a relationship between performance deficits in an arm adaptation task and lesions of specific cerebellar areas (Martin et al. 1996). Thus, the power of clinical studies to address the possibility of a difference in the neural substrate underlying different forms of arm adaptation has not yet been harnessed.

We examined adaptation to errors caused by force fields or visuomotor rotation in participants with neural degeneration specifically limited to the cerebellum. We compared the performance of each participant in both conditions to explore the relationship between the two tasks. Finally, we identified cerebellar regions associated with the two tasks by quantifying the atrophy in different cerebellar compartments from volumetric MRI data.
Materials and methods

Participants

Fourteen participants with isolated cerebellar degeneration [9 male, 5 female; mean age 54 (SD 11.8) years; table 1] and 14 age–and gender-matched controls [9 male, 5 female; mean age 54 (SD 13.3) years] without any known neurological diseases and without deficits in neurological examination participated in this study. All participants were right handed. Three cerebellar participants had a genetically defined spinocerebellar ataxia (SCA) type 6. Two presented with autosomal dominant cerebellar ataxia (ADCA) type III which is a genetic disorder with inconclusive genetic testing and symptoms limited to the cerebellum. Eight cerebellar participants had sporadic adult onset ataxia (SAOA) and one suffered from cerebellitis. These disorders are known to primarily affect the cerebellar cortex (Gomez et al. 1997).

The severity of cerebellar symptoms was assessed by an experienced neurologist (DT) based on the International Cooperative Ataxia Rating Scale (ICARS; Trouillas et al. 1997). In the group of the cerebellar participants the mean ICARS score was 30 (SD 11; range 19.5 to 51; maximum ICARS score = 100).

All participants gave informed oral and written consent approved by the ethics committee of the medical faculty of the University of Duisburg-Essen. The experiment was conducted in accordance with the Declaration of Helsinki.

Task

Participants were seated in front of a monitor screen and held the handle of a two-joint manipulandum (Fig. 1A). Sensors on the manipulandum recorded the position of the handle sampled at 500 Hz. The distance to the manipulandum and the chair height were individually adjusted to ensure a comfortable position and good vision of the monitor screen. Vision of the
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handle was blocked with a cloth stretched from the monitor screen to the neck of the participant. The task consisted of a shooting movement that took the handle from a constant starting position, the origin, towards one of three targets (Fig. 1B). The position of the handle was represented by a cursor (black filled circle of a diameter of 6 mm). The origin was indicated by a green circle of 1.4 cm diameter located in the middle of the lower part of the workspace. With the handle in the origin, the participant’s hand was located directly in front of the body’s sagittal midline. Participants were instructed to initially move the cursor into the origin. After an origin hold of 1 sec, a grey circular target (2 cm diameter) appeared in one of three locations 10 cm from the starting location. The target was located either directly above or 24° to the left or right. Target locations were presented in a pseudo-random order.

Participants were instructed to move the manipulandum quickly through the target. They did not need to stop in the target; the handle was gently brought to stop by a simulated soft wall (implemented by the manipulandum motors, damper constant -3.5 Ns/m, spring constant 35 N/m) directly behind the target. Participants were instructed to move through the target and not try to stop the movement themselves. Thereafter, the robot motors were used to move the handle of the manipulandum back to the starting location. The target was eliminated immediately after the participants arm passed out of the 10 cm radius from origin to target; the cursor was eliminated after it passed the 15 cm radius point. Thus, subjects could see by how much they missed the target. During the braking phase and the return phase, the cursor was not visible to the participant and it reappeared when it came within 2 cm of the origin. If the participant’s movement caused the cursor to pass through the target circle, the target changed color in a way that gave feedback about the movement duration. Red indicated that the movement was too fast and blue indicated that the movement was too slow. If the cursor missed the target, the target turned off as soon as the participant’s movement reached beyond the target with no further feedback. Successful movements passed through the target and were
Perturbed arm movements are processed independently neither too fast nor too slow. In this case, the target became yellow and gave an audible pleasing sound as a reward. Participants with cerebellar degeneration, who tended to have slower movements, were instructed that yellow and red indicated a correct velocity while controls were told that yellow indicated a correct movement and that red meant that they were moving too fast. Participants whose movements were consistently very slow were encouraged to move faster if they could do so and still feel comfortable. After the first set, the researcher checked movement times and told the participant whether their movements were at the correct speed.

The thresholds for a movement being ‘too fast’ or ‘too slow’ was determined by the distribution of movement durations over the last twelve movements. First, any movement duration of less than 200 ms was considered too fast. Other than that, thresholds were changed adaptively such that 50% of the previous 12 trials would be considered successful, 25% too slow and 25% too fast. This threshold titration allowed for a similar success-rate and prevented motivational differences that might be driven by differences in performance.

Participants performed seven sets (Fig. 1C). Each set consisted of 63 trials. Movements were randomized within small blocks so that each target appeared three times approximately every nine movements. The first three sets were performed with no external force or visual rotation to allow participants to familiarize themselves with the task (baseline phase). Each participant performed one set of trials with visuomotor rotation (VM) and one set of trials with force field perturbation (FF) (adaptation sets). In the VM task, movement of the manipulandum was shown on the monitor rotated 20° counter clockwise relative to the actual movement (that is to the left). In the FF task, a velocity dependent force (13 N/m/s times velocity) was applied perpendicular to the hand velocity by the motors, which pushed the manipulandum to the right. The fourth and the sixth sets were both adaptation sets, each followed by a post-adaptation set with no perturbation (5th and 7th sets). The order in which the two perturbations
were used in the adaptation sets was counter-balanced, so that half the participants performed the VM task in the fourth set and the FF task in the sixth set, whereas the other half performed the FF task in the fourth set and the VM task in the sixth set. Participants were informed before beginning the experiment that they should expect the manipulandum to interfere with their performance, and that they should continue to perform as before and to maintain a consistent velocity of movement. They were not provided with any further description of the perturbation. Short breaks during which participants released the handle were given after the first, third and fifth set. Participants were also informed that they could ask for more frequent breaks if they felt tired, but none of the participants did.

During each adaptation set, nine pseudo-randomized unperturbed catch trials were included in which there was no visuomotor rotation and no force field perturbation. A catch trial was made in each direction once every 21 movements. During adaptation, catch trials produce a displacement of the movement opposite to the direction of the perturbation. In FF, catch trials should produce shifts to the left, and, in VM, catch trials should produce shifts to the right.

**MRI volumetry**

MR images of cerebellar participants were acquired with a 1.5 T Siemens Sonata Scanner (Siemens, Erlangen, Germany) using a standard quadratic head coil. A 3D sagittal volume of the entire brain was made using a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE; TR = 2400 ms, TE = 4.38 ms, FOV = 256 mm, 160 slices, voxel size 1.0 x 1.0 x 1.0 mm³) sequence. Images were used to calculate the volumes of the cerebellum, cerebrum and total intracranial volume (TICV). The cerebellum was further divided into medial (vermal), intermediate and lateral zones of the anterior and posterior lobe. Volumetric analysis of MPRAGE images was performed semi-automatically
Perturbed arm movements are processed independently with the help of ECCET-software (http://www.eccet.de), developed for visualization and segmentation of MRI and CT data. Details of this methodology have been reported previously (Brandauer et al. 2008; Dimitrova et al. 2006). In brief, the brainstem was semi-automatically segmented and separated from the cerebellar peduncles, which were included in the cerebellar volume. Next the cerebellum was semi-automatically marked and then segmented with a 3D filling algorithm that is able to differentiate between brain tissue and surrounding cerebrospinal fluid. Segmentation of cerebellar cortex and white matter was performed automatically using intensity contours (Makris et al. 2005). The cerebellar cortex was further subdivided. To separate the anterior and posterior lobes the primary fissure was first identified and then manually traced on each sagittal slice. The cortex of the cerebellum was further subdivided into medial, intermediate and lateral zones. A standardized method that has been shown to provide high interrater reliability (Brandauer et al. 2008) was used. The medial zone was defined as the medial 12 slices of the 160 sagittal slices of the MPRAGE images. Midline was defined by the examiner on coronal images. The intermediate zone was defined automatically as the medial one-quarter of the maximal width of each hemisphere; the lateral zone comprised the lateral three-quarters (Luft et al. 1998). Because movements were performed with the right arm, data of the right intermediate and lateral zones were entered into statistical analysis. The TICV included brain and cerebrospinal fluid volumes extending caudally to the foramen magnum. For measurement of the whole brain volume all grey and white matter voxels belonging to the cerebellum, cortex and brainstem were first automatically marked on the initially filtered MR-volumes and then segmented with the same 3D filling algorithm used to segment the cerebellum. The 3D volume produced was manually adjusted where appropriate. Cerebral volume was calculated by subtracting the volume of the cerebellum from the whole brain volume. To estimate cerebellar atrophy independently of
Perturbed arm movements are processed independently of head size, we used the quotient of the whole cerebellum or cerebellar subareas to TICV for all analyses (Table 2: volumetric data).

Data analysis

All movements from the third baseline set were averaged time step by time step to calculate baseline trajectories. Movements were truncated to the shortest movement duration to prevent discontinuity in the average trajectory. Movement onset was defined as the time that hand velocity exceeded 0.03 m/s for more than 180 ms. Movements that crossed a line perpendicular to the vertical 1 cm below the origin were disregarded. Movements were considered terminated when the cursor passed out of a 10 cm circle around the origin. Movement time was defined as the time between movement onset and termination.

Error in the movement was defined as the perpendicular distance to a line connecting cursor position at movement onset and target position. First maximal error (FME) was the first local maximum of this function after 160 ms: the point in time where the movement path first curved back towards the target. The aiming error (AE) is the angle between a line segment connecting start of the movement to the cursor position at FME and a straight line movement to the target (Fig. 2).

The AE was our chief measure of the degree of perturbation in a movement. Restricting the FME to be after 160 ms excluded noise caused by early oscillations in the movements of some cerebellar participants. Because participants were instructed to move through the target without stopping, intention tremor probably did not influence our results. We also did not see any evidence of intention tremor in the participants’ movements. All movements were bias-corrected by subtracting the AE in the baseline trajectory for the appropriate movement direction. Because AE is influenced by stiffness of the arm (Smith and
Shadmehr 2005), we used a modified learning index (LI; Criscimagna-Hemminger et al. 2003; Maschke et al. 2004) to assess the amount of adaptation.

\[ LI = \frac{AE_{\text{Catch trials}}}{|AE_{\text{Catch trials}}| + |AE_{\text{Perturbed trials}}|} \]

The LI computation took into account AE in both perturbed trials and catch trials. If a participant stiffens his arm, his performance in field trials would improve, but AE in catch trials would not be affected (Smith and Shadmehr 2005). This would result in a learning index of 0. In contrast, learning to anticipate the AE leads to errors in the catch trials that grow as errors in the field trials are reduced. With complete learning, the LI should reach 1.

We used a modified version of the LI calculation used by Criscimagna-Hemminger et al. (2003) and Maschke et al. (2004) that corrects for the higher variability in movements of the cerebellar participants. Since most cerebellar patients show poor adaptation, their catch trial movements are quite similar to baseline and AE in catch trials is around zero. The relatively high variability of their movements leads to errors on both sides of the target. However, only catch trial AE which is opposite to perturbation AE indicates learning. For this reason, we removed the absolute value from the numerator so a catch trial in the direction of perturbation resulted in a negative LI. In our formulation, the LI will be between -1 and 1, with 1 indicating maximal learning and 0 to -1 indicating no learning. Our standard bin size for calculating the LI was seven consecutive trials (this included six field trials and one catch trial); however, to assess final performance values, we used a bin of 35 trials.

**Statistical analysis**

Statistical analysis of the data was performed using the Matlab 7.0 with the Statistics Toolbox (Mathworks, Inc., Natick, MA, USA) and SPSS 15.0 (SPSS Inc., Chicago, Ill., USA). Paired \( t \)-tests were used to compare baseline movement bias and variability between groups. An ANOVA with repeated measures was used to compare interaction and group
Perturbed arm movements are processed independently 12 effects. The Spearman rank correlation coefficient was used to assess bivariate correlations. Significance levels were set to 0.05. We tested for correlation of the LI with MRI volumetry and with clinical ataxia measures. We used a modified version of the Holm test (Holm 1979) to adjust for multiple testing against the different cerebellar areas, and separately for multiple testing against different ataxia sub-scores. Because of covariation in the tests (atrophy and ataxia are correlated across brain areas and ataxia measures), the Holm test can be quite conservative. We used a resampling method (described in the appendix) to correct for this problem. In addition, we calculated confidence intervals for the Spearman's correlation. Here, we made no effort to account for the multiple tests. We transformed the correlations to the range $+/-\infty$ using Fisher's z transform, then, using a Jacknifed estimate of the standard deviation, we calculated a 95% confidence interval for the transformed correlation. This was then transformed back to get confidence intervals for the untransformed correlations. Finally, we did a power analysis to assess the probability of false negatives (Supplementary Figure 1).
Results

Cerebellar deficits in performance

Participants initially performed three baseline sets, followed by two perturbed sets and two post-adaptation sets. Figure 3A shows movement trajectories during the last baseline set to each target for a representative control and cerebellar participant. While the control participant makes straight movements to the target, the movements of the cerebellar participant have a consistent curvature ($t = 2.05; P = 0.025$; Fig. 3B).

The majority of cerebellar participants demonstrate a leftward bias at the beginning of their movements followed by a correction towards the target at the end of their movement to all three targets. Cerebellar participants showed a higher variability in path direction than controls in all sets ($t = 4.44; P < 0.001$). Both the bias and the higher variability in cerebellar participants might be the result of failure to compensate for interaction torques (Bastian et al. 1996) or for the passive dynamics of the robot (Smith and Shadmehr 2005). However, any correlation there might be between baseline variance and severity of ataxia in cerebellar participants did not reach statistical significance, even when we excluded one outlier cerebellar participant (subject number 10 in Table 1) with extremely high variance and low ataxia (ICARS: $\rho = 0.51, P = 0.075$). In addition to the higher within-participant variance, between-subject variability was also greater in the cerebellar group ($F = 11.1, P = 0.0026$).

Previous studies showed that cerebellar participants move slower than controls (Bastian et al. 1996; Maschke et al. 2004). As described in the methods, the structure of rewards in our tasks encouraged all participants to move at the same speed. Participants who tended to move slower were also verbally encouraged to move faster, if possible. Nevertheless, two cerebellar participants moved much slower than controls. Controls tended to move faster than cerebellar participants (Fig. 4). A set by group mixed model ANOVA on the movement speeds showed that the difference in movement times between the two groups
Perturbed arm movements are processed independently was not statistically significant \((F = 2.34, P = 0.14)\). Movement time also did not significantly change during the experiment \((F = 1.95, P = 0.075)\).

**Cerebellar deficits in adaptation to perturbations**

In this study, we tested adaptation to the VM task and FF task; we compared the performance of cerebellar participants in the two tasks and also compared their performance to healthy controls.

Figure 5 shows representative movement trajectories and speed profiles to the middle target during the VM (Fig. 5A,B) and FF (Fig. 5C,D) task. As can be seen for the VM task (Fig. 5A), the control participant adapted to visuomotor rotation. Initial exposure caused the participant’s movement trajectories to deviate to the left by approximately 20°. Over the course of the set, the participant’s error decreased. Correspondingly, trajectories of catch trials (dashed lines) deviated further to the right during later movement trials, as the participant adapted to rotation. During post-adaptation, the control participant showed after-effects in which movements deviated to the right (not shown). The cerebellar participant showed limited reduction of error during perturbed trials (Fig. 5B). Catch trials deviated to the right during later movements, but deviation was less than in the control participant.

The story for the force field perturbation is quite similar. The control participant’s movements initially deviated to the right and adapted over the course of the set to near-zero error (Fig. 5C). Trajectories of catch trials deviated to the left during later movement in the set. Imposed catch trials prevented complete adaptation. The cerebellar participant showed less adaptation (Fig. 5D). There was no systematic decrease of aiming error, and error in catch trials remained close to zero. This participant did not show after-effects during post-adaptation.
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Figure 6A shows the mean aiming error (corrected for baseline errors) for both groups during perturbation and post-adaptation sets. Although both groups showed some adaptation to visuomotor rotation and force field perturbation, adaptation was more complete and catch trials had larger errors in the control group. Performance is similar in both tasks. During later movements, cerebellar participants had significantly larger errors than controls in field trials. Here, we also see incomplete adaptation probably due to the interposed catch trials. In each set, the graph shows the first movement, followed by a bin of 6 movements, and then the rest of the set is divided into bins of 7 movements. This is to show that AE of the first trial did not differ between groups (VM; $t = 0.86; P = 0.40$; FF; $t = 0.57; P = 0.57$). The aiming errors of the first trials were 17.0 (cerebellar) and 19.1 (control) for the VM perturbation and 27.2 (cerebellar) and 24.4 (control) for the FF perturbation.

The LI for both tasks is presented in Figure 6B. The first LI was -0.16 (cerebellar) and 0.11 (control) for the VM task and -0.06 (cerebellar) and 0.09 (control) for the FF task. A $t$-test revealed a significant difference between both groups for the visuomotor task ($t = -2.2; P = 0.04$) but not for the force field task ($t = -1.3; P = 0.19$). This indicates that within the first 7 trials, controls showed significant higher learning than cerebellar participants during the VM task. In both groups the learning index reaches a plateau around the 20th trial for both tasks, and this plateau is higher in the control group. The slope of the LI during the first movement trials (adaptation rate, first three bins) was comparable in both groups for both tasks (ANOVA: group x task; bin x task x group interaction: $F = 1.25, P = 0.589$; bin x task effect: $F = 0.77, P = 0.467$). Control participants had significantly higher LI than cerebellar participants in the FF task (mixed model ANOVA on set x group; group effect: $F = 17.06; P = 0.0004$) and VM task ($F = 18.63; P = 0.0002$) considering all bins.

Adaptation deficits in both tasks do not correlate
In both groups, participants reach a comparable maximal adaptation in the FF task and the VM task (ANOVA of mean LI on group x task; task effect: $P = 0.794$; task x group interaction effect: $P = 0.718$; Fig. 6B). While adaptation to VM stays on a plateau, adaptation to FF is more variable (ANOVA on all LI; LI x task interaction effect: $P = 0.051$). Looking at all participants, it seems that cerebellar participants learn both tasks to a similar extent. However, individual participants seem to have different success in the two tasks. Figure 7 plots the mean LI of the VM task against the mean LI of the FF task. Most control participants are gathered at the upper right corner, indicating normal performance in both tasks, while the cerebellar participants were more variable. Both groups showed no correlation between their ability in the two tasks (cerebellar participants, $\rho = 0.29; P = 0.32$; control participants, $\rho = -0.09; P = 0.77$). Disassociation of success in the two tasks suggests that performance in the two tasks may reflect details of cerebellar degeneration in each patient.

*Adaptation deficits in both tasks correlate to different cerebellar subareas*

We correlated the mean LI of both tasks to the volume of cerebellar subareas, with each subarea normalized to TICV. Table 3 summarizes the results. The sizes of different subareas correlated to success in the VM task and the FF task. We found a statistically significant correlation between the FF task and the intermediate and lateral zones of the anterior lobe ($\rho = 0.72, 0.70, P = 0.003, 0.005$, respectively; Fig. 8A) and between the VM task and the intermediate zone of the posterior lobe ($\rho = 0.64; P = 0.015$; Fig. 8B).

Thresholds for significance were determined using a bootstrapped version of the Holm post hoc correction (described in the appendix). The correlation of the anterior vermis to the VM task is on the threshold of significance, but does not reach statistical significance. Our
interpretation is that the FF task depends on the integrity of the anterior lobe (intermediate and lateral zone) while the VM task depends on the posterior lobe (intermediate zone). However, this interpretation must be seen in light of the large variance in subject scores and small sample sizes. As can be seen in the confidence intervals for the correlation coefficients (Table 3), there is almost always a large overlap in the confidence region for the FF and the VM task, meaning that our results do not succeed in showing a true double dissociation. The only exception to this is the lateral anterior lobe, where the 95% confidence for the FF task does not overlap with the 95% confidence region for the VM task, indicating that subjects with sparing in lateral anterior lobe performed better in the FF task than in the VM task.

To assess whether learning deficits are related to clinical ataxia scores, we correlated the mean LI of both tasks to the total score and to the kinetic function sub-score of the ICARS. We did not find a statistically significant correlation between the mean learning index of VM and the total ICARS score or the kinetic function sub-score ($\rho = 0.47, 0.41, P = 0.091, 0.146$, respectively). Similarly, there was no correlation between the FF task and the total ICARS and kinetic function score ($\rho = 0.05, 0.09, P = 0.863, 0.748$, respectively). Thresholds for all tests were corrected using the bootstrap Holm correction. We did the same analysis with other sub-scores of the ICARS and the total score and sub-scores of the Scale of the Assessment and Rating of Ataxia (SARA; Schmitz-Hubsch et al. 2006) with consistent results.

We found no correlation between cerebellar subareas and the total scores or kinetic function (right arm) sub-score of the ICARS.
Discussion

Our results corroborate earlier findings that adaptation to perturbation of reaching movements depends on the cerebellum for both force field and visuomotor perturbations. We also corroborate and significantly extend previous findings that these tasks are supported by different neural substrates by showing (1) that the success of cerebellar participants in the two tasks is independent, and (2) that the success in each task is associated with different brain areas. Impairment in the visuomotor task is correlated with degeneration of the intermediate cerebellar zone of the posterior lobe. In contrast, impairment in the force field task correlates with degeneration in the intermediate and lateral zone of the anterior cortex. While these results are consistent with the literature on how the cerebellum is related to these tasks, they are nevertheless surprising because they are not easily interpreted in the context of our current understandings of the roles of these different cerebellar areas. The specific deficits associated with degeneration that we show will require us to reassess our understanding of the roles of the different cerebellar zones, at least in these tasks. Finally, we also found differences in the degree of correlation of success in the two tasks and clinical impairment: while cerebellar participants who were more impaired clinically tended to show decreased performance in the visuomotor task, they did not show a similarly decreased performance in the force field task.

Previous studies have shown a failure to adapt to perturbation of reaching movements in force field (Smith and Shadmehr 2005; Maschke et al. 2004) and visuomotor perturbations (Tseng et al. 2007; Martin et al. 1996). However, these studies, with the exception of Martin (1996; described below), have not investigated more precise localization in much depth. These findings are consistent with our results of impaired adaptation in both tasks and show that the cerebellum is required for processing of error during reaching movements, but leave room for further study of the precise cerebellar areas required for these forms of adaptation.
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This study was the first to address performance in the two tasks in the same cerebellar participants, and our results show that performance in these tasks corroborates the belief that they have different neural substrates. Although cerebellar participants presented with deficits in both tasks, their performance in the two was quite variable. A participant could perform relatively well in the force field task and show severe deficits in the visuomotor task and vice versa (Fig. 7).

This is consistent with previous studies suggesting that learning and consolidation of VM and FF perturbation are processed differently by the brain. First, the generalization properties of the two tasks are quite different. VM generalizes very narrowly (Pine et al. 1996) and does not generalize across limbs (Baizer et al. 1999) while FF generalizes more broadly (Donchin et al. 2003) and partially generalizes across limbs (Criscimagna-Hemminger et al. 2003). Also, VM distortions seem to be adapted to maintain planning in extrinsic coordinates (Flanagan and Rao 1995; Wolpert et al. 1995) while FF generalization suggests adaptation in joint coordinates (Shadmehr and Moussavi 2000). Second, the two tasks are independent in the sense that learning of one does not interfere with learning of the other (Krakauer et al. 1999). Finally, deafferented patients do not show impairment on the VM task (Bernier et al. 2006) although proprioception has been shown to be dominant in force field adaptation (Hwang and Shadmehr 2005). There has been some dispute in the literature about what it is about these two tasks that causes them to be processed differently (Tong et al. 2002), but there is no disagreement that the two tasks, while both cerebellum dependent, reflect different neural mechanisms. Thus, the finding that the success of cerebellar participants on the two tasks is uncorrelated is consistent with previous findings on their psychophysics.

Impairment in the VM and FF tasks correlated with the degree of degeneration in distinct cerebellar structures. Cerebellar participants with greater atrophy in the anterior
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cerebellum performed worse in the force field task and cerebellar participants with major
atrophy in the posterior cerebellum are impaired in the visuomotor task (Fig. 9).

It is tempting to theorize that the anterior lobe and posterior lobe seem to be related
preferentially to FF and VM, respectively. The small numbers of imaging studies that have
addressed localization of these two tasks produce results that are consistent with ours. Only
one imaging study investigated localization of the force field task (Nezafat et al. 2001). While
their method of data presentation makes it difficult to draw clear conclusions from their
results, a careful examination of the figures shows activation of the lateral zone during force
field learning. Also, activation of the anterior cerebellum was higher during initial learning
than during long-term recall, supporting our claim that the anterior cerebellum is associated
with FF adaptation.

Correlation of VM impairment with atrophy of the intermediate zone of the posterior
cerebellum is in accordance with findings of Graydon (2005) who found increased activation
related to learning in the medial posterior lobe of the left cerebellum. Further, a positive
correlation between degeneration of the posterior lobe and visuomotor learning is supported
by previous findings suggesting that the posterior lobe plays a major role in acquisition of
visuomotor mappings (Graydon et al. 2005; Krakauer et al. 2004; Imamizu et al. 2000). Two
studies of prism adaptation also support this hypothesis. In these studies, participants look
through prisms while performing a throwing task, and adaptation to the prisms is widely held
to be similar to the VM task. Martin et al. (1996) investigated cerebellar participants with
lesions in the distribution of the posterior inferior cerebellar artery (PICA) and the superior
cerebellar artery (SCA) in the prism task. Only cerebellar participants with infarction in the
PICA area showed impairment. Similarly, monkeys with lesions in the posterior cerebellum
were impaired in adapting to prism distortions (Baizer et al. 1999).
While our results imply that different cerebellar structures play important roles in the two tasks, a carefully done study by Diedrichsen (2005) failed to find significant differences in activation between VM and FF. Errors in both tasks activated cerebellar right lobule V and bilateral lobule VIII. This makes our findings especially important because Diedrichsen’s study carefully controlled error across tasks and included a third task (target jump) with the same size of error but which is not cerebellar dependent. This allowed Diedrichsen to make a more meaningful comparison between tasks and suggested that earlier findings may have been artifacts of differences in the movements across the tasks being compared in imaging studies or somehow a result of different tasks being tested in different laboratories in the patient studies. However, activation in an fMRI study does not necessarily mean that this area is essentially involved in a given task. This is why human cerebellar lesion studies are an important addendum to functional brain imaging studies (Rorden and Karnath 2004). Notably cerebellar areas shown by Diedrichsen and coworkers overlap with the areas found to be important in the present study. Results of our study suggest that the areas shown by Diedrichsen (2005) may contribute differentially to VM and FF adaptation on a behavioral level. However, our study cannot exclude that cerebellar regions showing no significant correlation may also contribute to the adaptation tasks. Given the relatively small group of cerebellar subjects, the power of statistical analysis was not strong enough to fully exclude possible relationships with parts of the cerebellum showing a non-significant correlation.

Although our findings are consistent with previous reports, they highlight the lack of clarity on the precise roles associated with different areas of the cerebellum. For instance, one classical view is that the lateral cerebellum, receiving input from cerebral cortex, is more involved in movement planning and that the intermediate cerebellum, receiving somatosensory input, plays a role in control of ongoing movements (Allen and Tsukahara 1974; Evarts and Thach 1969). Adaptation in our tasks is essentially predictive because the
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task allows no feedback correction. Thus, our results indicate that the intermediate zone probably has predictive functions. Indeed, recent reviews by Bastian (2006) and Shadmehr (2008) have suggested that the intermediate cerebellum may well be involved in predictive control, a perspective reinforced also by recent clinical studies (Ilg et al. 2008).

A reason to expect that adaptation to force field and to visuomotor perturbation is located in different anatomical regions is the different kind of feedback received. While adaptation to the visuomotor task depends on visual input (Krakauer et al. 2000), adaptation to the force field task relies on proprioceptive information (Hwang and Shadmehr 2005). We found that adaptation to the force field task is correlated with atrophy of the intermediate (and possibly also lateral) anterior lobe. This is consistent with the assumption that the intermediate and lateral hemispheres of lobules IV-VI play an important role in integrating somatosensory information and motor control. This region receives proprioceptive input and has an important function in voluntary limb movements (see Bastian 2002). Although there is evidence for visual input to all functional zones (Cerminara et al. 2005; Glickstein et al. 1994), the inferior intermediate cerebellum receives particularly powerful visual input.

Various anatomical considerations suggest that the anterior and posterior lobes are involved in different functions. First, not all sub-zones are represented in both the anterior and posterior lobe. Zones X and B of the vermis are only to be found in the anterior cerebellum, and zones C1 and C3 of the intermediate cerebellum run not continuously from the anterior to the posterior parts (Voogd 2003). Second, the anterior and posterior lobes have separate somatotopic maps of the body. Finally, sub-zones of the intermediate cerebellum receive different projections in the anterior lobe than in the posterior lobe (Apps and Garwicz 2005).

From clinical observations it is known, that patients with infarctions in the supply area of the PICA recover faster from symptoms than patients with infarctions due to the SCA. Therefore, the anterior cerebellum seems to be more involved in chronic lesions. In line with
Perturbed arm movements are processed independently

this observation, we found stronger correlations between the anterior lobe and the FF task, than between the posterior lobe and the VM task in a group with chronic degenerative disorders. It is expected that the anterior and posterior lobe process different aspects of movement control (Apps and Garwicz 2005). Our findings suggest that the force field task is located in the anterior lobe and the visuomotor task mainly in the posterior lobe.

Differences between VM and FF adaptation may reflect the type of error processed in each case: kinematic errors in VM and dynamic errors in FF (Krakauer et al. 1999). However, other explanations are possible. For instance, uncontrolled eye, head and neck movements may be quite different in the two tasks. Perhaps gaze is more coordinated with shoulder and elbow movements in the VM task. Since the posterior lobe of the cerebellum has been shown to be important for eye movements (Ron and Robinson 1973) and coordination of eyes and arm movements (Glickstein et al. 1994), this might well explain our results. Therefore, differences in correlation analysis may at least in part be explained by differences in motor requirements of the tasks.

The lesion-symptom mapping approach in degenerative cerebellar disorders has limitations. Volumetric measures likely reflect cerebellar physiological dysfunction only in part, and our approach does not assess the degree of function (or malfunction) of the remaining cerebellar cortex and cells. Likewise, as degeneration is a chronic disease, the cerebellum (and the rest of the CNS) has adapted, at least partly, to the damage. Nevertheless, correlations between cerebellar sparing and behavioural success appear meaningful. Significant negative correlations between total cerebellum volume (Guerrini et al. 2004; Richter et al. 2005) or cerebellar grey matter (Brenneis et al. 2003; Lasek et al. 2006) and total ataxia scores have been shown. In our own study, we found significant correlations between ataxia sub-scores and functionally meaningful cerebellar subvolumes (Brandauer et al. 2008).
Contrary to findings of Tseng et al. (2007) and Maschke et al. (2004) we did not find a statistically significant correlation between the VM task or the FF task and the severity of ataxia measured with the ICARS score. It is possible that cerebellar participants in our study were less severely affected. Another possibility is that the distribution of cerebellar atrophy in patients with SCA type 6 and 8 (the majority of the patients in the earlier studies) might be different than the distribution in patients with SAOA (the majority of the cerebellar participants in our study). It certainly seems from our results that cerebellar areas important for the development of internal models (as in these adaptation tasks) may not be sufficiently represented by commonly used ataxia scores.

In conclusion, we demonstrated that dynamic and kinematic transformations are processed independently and that they depend on different cerebellar structures. While greater atrophy of the intermediate and lateral zones of the anterior cerebellum was correlated with impairment in the force field task, atrophy of the intermediate zone of the posterior cerebellum was correlated with impairment in the visuomotor task.
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References


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**Smith MA, Shadmehr R.** Intact ability to learn internal models of arm dynamics in Huntington's disease but not cerebellar degeneration. *J Neurophysiol* 93: 2809-2821, 2005.


Figure legends

FIG. 1. A, The participant sits in front of a monitor and holds the handle of a robot with his right hand. Vision of his hand is blocked. B, The black cursor (6 mm) has to be moved from the origin (1.4 mm) through one of three targets (2 cm). In this figure, only the left target is visible to the participant. C, All participants have to perform 7 sets of 63 trials. The first 3 sets are performed without external force or visual rotation. The 4th and 6th sets were adaptation phases, during which half of the participants performed the visuomotor task (VM) in the 4th set and the force field task (FF) in the 6th set and the other half first the FF task and then the VM task.

FIG. 2. Aiming error (AE) $\alpha$ at maximal error. Blue circle indicates origin; red circle indicates target; green dot is cursor position at first maximal error (FME).

FIG. 3. A, Movements of a characteristic cerebellar (subject number 2 in Table 1) and control participant to all targets during the last baseline set. While the control shows straight movements, the cerebellar participant presents curved movements to the left. B, Baseline errors for all participants. Positive values represent deviation to the right. Most cerebellar participants show a bias to the left.

FIG 4. Dots represent the mean movement time of each individual during each set. The solid lines show the mean movement time over all participants for both groups. Movement times are not significantly different between both groups. The blue dots showing significantly longer movement times represent two cerebellar participants (subject number 3 and 9 in Table 1). Cer, cerebellar; Con, control; N, no perturbation; VM, visuomotor rotation; FF, force field perturbation.
**FIG 5.** Movement trajectories and velocity profiles in the visuomotor task (A, B) and in the force field task (C, D) to the middle target for a representative control (A, C) and cerebellar (B, D) participant (subject number 2 in Table 1). Trajectories and speeds are marked with a color gradient ranging from light blue to dark blue (cerebellar) and light red to dark red (control) indicating initial movements to late movements, respectively. The dashed lines represent catch trials (same color code).

**FIG. 6. A,** Aiming error (AE) averaged over participants of the two groups. In each set, the graph shows the first movement, followed by a bin of 6 movements, and then the rest of the set is divided into bins of 7 movements. Solid lines represent perturbed movements and dashed lines represent catch trials. The shaded area shows ±1 standard error of the mean (S.E.M.). Cerebellar participants show a higher S.E.M. than controls. **B,** Learning indices for both groups and both tasks. Each LI is composed of 6 field trials and 1 catch trial. Error bars show ±1 S.E.M. Controls present significantly higher learning indices during all movements. Cer, cerebellar; Con, control; VM, visuomotor rotation; FF, force field perturbation.

**FIG. 7.** Comparison of mean learning indices (LI) between both tasks. Error bars show ±1 S.E.M. While most controls show comparable performance in both tasks, the mean LI in the two tasks is not correlated in the cerebellar group.

**FIG. 8.** Correlations between mean learning index (LI) of the visuomotor (VM) and force field (FF) task and volumes of cerebellar subareas normalized to total intracranial volume (% TICV). **A:** FF task; **B:** VM task
FIG. 9. This figure (Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience 5: 241-9, copyright (2004)) illustrates significant correlation between distinct cerebellar regions and adaptation deficits in the visuomotor task (VM) and the force field task (FF). While the disorders in FF task correlated with atrophy of the intermediate and lateral zone of the anterior lobe, disorders in VM task correlated with atrophy of the intermediate zone of the posterior lobe. V, vermis; IM, intermediate zone; LAT, lateral zone
Appendix

Most methods of correcting the significance level in the face of multiple tests assume that the tests are independent. They can be quite conservative if the tests are correlated (Westfall et al. 1999). This is specifically true for the Holm test. In our tests for correlation of the LI with MRI volumetry data, the correlation in the volume of different cerebellar areas led to correlation in the significance level of the correlations. A similar problem exists also for correlations of the LI with clinical ataxia scores, and we will describe our solution with reference to the MRI data but it applies equally well in more general settings.

We calculated the covariance matrix for the MRI data with \( k \) different subareas measured for each of \( N \) different participants. We then sampled \( N \) times from a \( k \)-dimensional Gaussian distribution with the same covariance structure as the data. This gave us data with the same covariance structure as our original data, but which obeyed the null hypothesis of being uncorrelated with the LI data. We generated \( B = 5,000 \) Monte Carlo data sets in this manner. For each data set and each subarea, we calculated the correlation with the LI. This gave us \( k \times B \) correlation values. We considered the distribution of the \( B \) largest correlations across the subareas and compared this to the largest correlation value measured in the data. The significance level for the largest correlation in the original data was set to give a false rejection of \( H_0 \) for exactly 5% of the Monte Carlo largest correlations. If the largest correlation was significant, we tested the second largest correlation in the data. We now used only \( k-1 \) variables, and tested the second largest correlation in the data against a threshold which produces exactly 5% false positives for the largest Monte Carlo correlations among \( k-1 \) variables. If this turned out to be significant, we proceeded to test the third largest correlation in the data.

This procedure produces thresholds that are identical to those of the Holm test if the data is uncorrelated. For correlated data, simulations show the procedure accurately generates
Perturbed arm movements are processed independently.

significance levels for the first three significance levels after which the combinatorics make further simulation unwieldy.
<table>
<thead>
<tr>
<th>Baseline</th>
<th>Baseline</th>
<th>Baseline</th>
<th>Adaptation (VM/FF)</th>
<th>Post-adaptation</th>
<th>Adaptation (FF/VM)</th>
<th>Post-adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set 1</td>
<td>Set 2</td>
<td>Set 3</td>
<td>Set 4</td>
<td>Set 5</td>
<td>Set 6</td>
<td>Set 7</td>
</tr>
</tbody>
</table>
Table 1: Characteristics of Cerebellar Subjects

<table>
<thead>
<tr>
<th>Number</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Duration</th>
<th>Total</th>
<th>Kinetic functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>49</td>
<td>ADCA III</td>
<td>6 years</td>
<td>24/100*</td>
<td>3.5/20*</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>44</td>
<td>ADCA III</td>
<td>4 years</td>
<td>11.5/100</td>
<td>1/20</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>Cerebellitis</td>
<td>5 years</td>
<td>51/100</td>
<td>5.5/20</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>50</td>
<td>SAOA</td>
<td>30 years</td>
<td>47/100</td>
<td>4.5/20</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>SAOA</td>
<td>10 years</td>
<td>28/100</td>
<td>5/20</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>58</td>
<td>SAOA</td>
<td>9 years</td>
<td>19.5/100</td>
<td>2.5/20</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>51</td>
<td>SAOA</td>
<td>21 years</td>
<td>28/100</td>
<td>5/20</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>57</td>
<td>SAOA</td>
<td>3 years</td>
<td>22/100</td>
<td>1.5/20</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>30</td>
<td>SAOA</td>
<td>2 years</td>
<td>39/100</td>
<td>5/20</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>66</td>
<td>SAOA</td>
<td>3 years</td>
<td>22/100</td>
<td>1.5/20</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>62</td>
<td>SAOA</td>
<td>5 years</td>
<td>24/100</td>
<td>2/20</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>74</td>
<td>SCA 6</td>
<td>14 years</td>
<td>30/100</td>
<td>5/20</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>64</td>
<td>SCA 6</td>
<td>7 years</td>
<td>30.5/100</td>
<td>3/20</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>69</td>
<td>SCA 6</td>
<td>16 years</td>
<td>43.5/100</td>
<td>5/20</td>
</tr>
</tbody>
</table>

M, male; F, female; ADCA, autosomal dominant cerebellar ataxia; SAOA, sporadic adult onset ataxia; SCA, spinocerebellar ataxia; ICARS, International Cooperative Ataxia Rating Scale; *, maximum score/subscore
Table 2: Volumetric MRI data of cerebellar subjects

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Anterior Lobe in % TICV</th>
<th>Posterior Lobe in % TICV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medial zone</td>
<td>Intermed. zone</td>
</tr>
<tr>
<td>1</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>2</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>4</td>
<td>0.21</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>6</td>
<td>0.28</td>
<td>0.20</td>
</tr>
<tr>
<td>7</td>
<td>0.38</td>
<td>0.36</td>
</tr>
<tr>
<td>8</td>
<td>0.31</td>
<td>0.27</td>
</tr>
<tr>
<td>9</td>
<td>0.28</td>
<td>0.22</td>
</tr>
<tr>
<td>10</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>11</td>
<td>0.32</td>
<td>0.29</td>
</tr>
<tr>
<td>12</td>
<td>0.37</td>
<td>0.31</td>
</tr>
<tr>
<td>13</td>
<td>0.25</td>
<td>0.17</td>
</tr>
<tr>
<td>14</td>
<td>0.23</td>
<td>0.20</td>
</tr>
</tbody>
</table>

TICV, total intracranial volume.
**TABLE 3: Correlation between the mean LI of FF and VM tasks and cerebellar subareas.**

<table>
<thead>
<tr>
<th>Zone</th>
<th>Task</th>
<th>$\rho$</th>
<th>95% Confidence</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior lobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermis</td>
<td>VM</td>
<td>0.61</td>
<td>-0.29 – 0.94</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.50</td>
<td>-0.07 – 0.83</td>
<td>0.067</td>
</tr>
<tr>
<td>Intermediate right</td>
<td>VM</td>
<td>0.25</td>
<td>-0.54 – 0.81</td>
<td>0.392</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.72</td>
<td>0.28 – 0.91</td>
<td>0.003*</td>
</tr>
<tr>
<td>Lateral right</td>
<td>VM</td>
<td>0.17</td>
<td>-0.69 – 0.46</td>
<td>0.563</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.70</td>
<td>0.51 – 0.82</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>Posterior lobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermis</td>
<td>VM</td>
<td>0.57</td>
<td>0.12 – 0.82</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.10</td>
<td>-0.58 – 0.69</td>
<td>0.748</td>
</tr>
<tr>
<td>Intermediate right</td>
<td>VM</td>
<td>0.64</td>
<td>0.26 – 0.84</td>
<td>0.015*</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.17</td>
<td>-0.48 – 0.70</td>
<td>0.553</td>
</tr>
<tr>
<td>Lateral right</td>
<td>VM</td>
<td>0.39</td>
<td>-0.25 – 0.79</td>
<td>0.164</td>
</tr>
<tr>
<td></td>
<td>FF</td>
<td>0.48</td>
<td>-0.02 – 0.79</td>
<td>0.081</td>
</tr>
</tbody>
</table>

* indicates significance at $P < 0.05$ using a bootstrapped Holm post hoc correction
LI, learning index; FF, force field task; VM, visuomotor task.