Cerebellar regions involved in adaptation to force field and visuomotor perturbation

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Running head: Cerebellar regions involved in adaptation

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Abstract

Studies with patients and functional magnetic resonance imaging investigations have demonstrated that the cerebellum plays an essential role in adaptation to visuomotor rotation and force field perturbation. To identify cerebellar structures involved in the two tasks, we studied 19 patients with focal lesions after cerebellar infarction. Focal lesions were manually traced on magnetic resonance images and normalized using a new spatially unbiased template of the cerebellum. Additionally, we reanalyzed data from 14 patients with cerebellar degeneration using voxel-based morphometry. We found that adjacent regions with only little overlap in the anterior arm area (lobules IV to VI) are important for adaptation in both tasks. While adaptation to the force field task lay more anteriorly (lobules IV and V), lobule VI was more important for the visuomotor task. In addition regions in the posterolateral cerebellum (Crus I, II) contributed to both tasks. No consistent involvement of the posterior arm region (lobe VIII) was found. Independence of the two kinds of adaptation is further supported by findings that performance in one task did not correlate to performance in the other task. Our results show that the ‘anterior arm area’ of the cerebellum is functionally divided into a more posterior part of lobule VI, extending into lobule V related to visuomotor adaption and a more anterior part including lobules IV and V related to force field adaption. The posterolateral cerebellum may process common aspects of both tasks.

Keywords: motor learning, adaptation, cerebellar structures, visuomotor, force field
Introduction

Current knowledge about localization of motor function within the human cerebellum is limited. The cerebellar cortex is subdivided mediolaterally in parasagittal zones (Apps and Hawkes 2009). The medial cerebellar zone (vermis) contributes to posture, gait and oculomotor control, whereas the intermediate and lateral zones are involved in limb coordination (Konczak and Timmann 2007). In addition to the mediolateral distinction, the cerebellar cortex is subdivided anteroposteriorly. Both animal and human studies show two body representations within the cerebellum, one in the anterior cerebellum and a second in the posterior cerebellum (Manni and Petrosini 2004). The anterior body representation is found in lobules III-VI with the anterior hand representation mainly in lobules V and VI, and the posterior body representation is localized in lobule VIII. The functional contributions of the two sensorimotor representations to limb control, however, are currently unknown. One area of motor control, which may be helpful to elucidate the contributions of the anterior and posterior lobe to motor control, is reach adaptation to different kinds of perturbations. Both studies with cerebellar patients and functional brain imaging demonstrate that the cerebellum plays an important role in adaptation to visuomotor (VM) and force field (FF) perturbations (Weiner et al. 1983; Martin et al. 1996; Maschke et al. 2004; Diedrichsen et al. 2005; Smith and Shadmehr 2005; Tseng et al. 2007; Rabe et al. 2009; Criscimagna-Hemminger et al. 2010). In the VM task, visual feedback is rotated from actual arm movement, and, in the FF task, a force is exerted on the hand during a reaching movement. Participants learn to adapt to these deviations by changing the angle of their movement (VM) or by applying a force opposite to the perturbation (FF). While it has been proposed that VM and FF adaptation are processed differently in the cortex (Krakauer et al. 1999; Shadmehr et al. 2005), the existing literature is equivocal about which cerebellar structures are involved and whether they differ between the two tasks. VM adaptation depends on visual input (Krakauer et al. 2000) and FF adaptation on proprioceptive information (Hwang and Shadmehr 2005). Because the anterior...
lobe receives primarily somatosensory information, whereas visual afferents project mainly to the posterior lobe (Bloedel and Courville 1981), the anterior and posterior lobe may contribute differentially to FF and VM adaptation. However, studies report contradictory findings regarding the relative contributions of anterior and posterior parts of the cerebellum. In the VM task, some studies stress the importance of the anterior arm area, which includes lobules IV and V in the anterior lobe plus lobule VI of the rostral posterior lobe (Pisella et al. 2005; Luaute et al. 2009; Werner et al. 2010), others point to the importance of the caudal posterior lobe (Martin et al. 1996; Imamizu et al. 2000; Graydon et al. 2005). For the FF task, one study observed that the anterior arm area is important (Shadmehr and Holcomb 1997). Other brain imaging studies show activation of both anterior and posterior cerebellar arm areas in the FF and VM task (Nezafat et al. 2001; Diedrichsen et al. 2005).

Brain imaging and human lesion studies, however, may lead to different results. Based on functional magnetic resonance imaging (fMRI) it cannot be decided whether activated areas are directly involved in a given task or not. In contrast, only those areas, which are critically involved, will lead to behavioral disorders and will therefore show in lesion studies (Rorden and Karnath 2004). For a long time human lesion studies were hampered by lack of spatial resolution. Newly developed normalization and statistical analysis tools allow for much improved localization of function based on high-resolution structural MR images (Rorden et al. 2009; Timmann et al. 2009).

As yet, four human cerebellar lesion studies addressed the question of localization of cerebellar areas related to reach adaptation (Martin et al. 1996; Pisella et al. 2005; Rabe et al. 2009; Werner et al. 2010) with two studies taking advantage of the newly developed methods of lesion-symptom mapping (Werner et al. 2010; Rabe et al. 2009). In our recent study we have examined the relationship between the location of pathology and impairment of FF and VM adaptation in degenerative patients (Rabe et al. 2009). We reported that the intermediate and lateral parts of the anterior lobe (lobules I-V) contribute to FF adaptation, whereas the
intermediate parts of the posterior lobe (lobules VI-X) are important in VM adaptation. We suggested the possibility that the anterior arm area was key for adaptation in the FF task while the posterior arm area played a role in VM adaptation. As yet no other human cerebellar lesion studies had tried to localize areas in the cerebellum related to FF adaptation. Our VM data agreed with findings of Martin et al. (1996) who associated VM adaptation with the posterior lobe, but are at variance with Pisella’s (2005) and Werner’s (2010) findings who found an association to the anterior cerebellum. However, one confounding factor may be the position of lobule VI, which is part of the anterior hand representation but is also the most anterior lobule of the posterior lobe. In our previous study the primary fissure was used to subdivide the anterior and posterior lobe based on the macroscopic anatomy of the cerebellum. Accordingly lobule VI was assigned to the posterior lobe. This artificially split the superior hand region. This artificial split can lead to significant confusion in the literature.

In this study, we revisit our previous findings by testing focal lesion patients in the same VM and FF tasks. A large sample study in patients with focal lesions can provide a ‘cleaner’ test of the importance of specific areas, because lesions are better defined than in cerebellar degeneration, which affects the whole cerebellum to various degrees. Focal patients also represent a more subtle tool because they are, generally, far less ataxic than patients with cerebellar degeneration, and thus tend to have more specific deficits. In addition, since publication of the results on cerebellar degeneration, we have developed the technology to assess the degree of cerebellar degeneration with a precision approaching that of individual voxels. This is possible because of the development of a technique to accurately map the cerebella of individual subjects onto a standard template, even in cases of severe degeneration. With the new accurate map it is possible to do voxel-based morphometry (VBM) and determine the relative concentration of gray matter for different subjects in different parts of the cerebellum. Thus, we re-analyzed the data from the earlier study using VBM, allowing a more meaningful comparison of our earlier data to the new results. Thus,
this study should provide spatial resolution at least at the level of individual lobules in both
the focal and degenerative cerebellar patient populations (Timmann et al. 2009).

Our initial hypothesis, based on the earlier findings, was that the anterior hand
representation contributes to FF adaptation and the posterior hand representation contributes
to VM adaptation. Our results in both patient groups provide converging evidence that the
‘anterior arm area’ of the cerebellum is actually functionally divided into a more posterior
part that includes lobule VI and extends into lobule V that is more strongly related to VM and
an anterior part that includes lobules IV and V that is related to FF. Our results support the
view that the cerebellum can be divided into many small and distinct functional modules
(Apps and Hawkes 2009). In addition we found areas in the posterolateral lobe (but not the
posterior hand representation) which contributed to function in both tasks and may process
common, perhaps cognitive, aspects of the tasks.
Materials and Methods

Participants

19 patients with chronic ischemic cerebellar lesions (16 male, 3 female; mean age 56.5 years (SD 10.7); Table 1) and 19 age-, gender- and handedness matched controls (16 male, 3 female; mean age 56.4 years (SD 11.0); Table 2) were included in the study. Handedness was assessed based on the Edinburgh Handedness Inventory (Oldfield 1971). 8 patients had an infarction within the territory of the superior cerebellar artery and 12 patients had an infarction within the territory of the posterior inferior cerebellar artery. Lesions were unilateral, except in one patient (# 12 in Table 1) who had a superior cerebellar artery infarction on the left and a posterior inferior cerebellar artery infarction on the right side. Brainstem or extracerebellar involvement was excluded based on neurological examination and magnetic resonance imaging (MRI) of the brain. Mean time between cerebellar infarction and participation in the study was 5.5 years [2 to 11.3 years (SD 2.6)]. All patients except one (see Table 1) and one control (see Table 2), were right-handed. Additionally, 14 patients with cerebellar degeneration [9 male, 5 female; mean age 54 years (SD 11.8)] were included in the study. The data from these patients was also used in an earlier study (Rabe et al. 2009). All patients with cerebellar degeneration were right-handed. Of these, 3 patients had genetically defined spinocerebellar ataxia type 6. 2 presented with autosomal dominant cerebellar ataxia type III, 8 patients had sporadic adult onset ataxia and one suffered from cerebellitis.

The severity of cerebellar symptoms was assessed by an experienced neurologist (DT) based on the scale for the assessment and rating of ataxia scale (SARA; Schmitz-Hubsch et al. 2006). Mean SARA score was 1.5 (SD 2.0; range 0 to 7) in the group with infarctions of the posterior inferior cerebellar artery, 2.0 (SD 1.5; range 0 to 5) in the group with infarctions of the superior cerebellar artery (for individual data see Table 1) and 11.3 (SD 3.7; range 6 to 18) in the degenerative group. All control subjects were examined by an experienced neurologist.
None of the controls had a history of neurological diseases or presented with neurological signs on examination.

Patients with cerebellar infarctions were tested with the hand ipsilateral to their cerebellar lesion. Thus, 7 patients were tested with the left hand and 11 patients were tested with the right hand. Five out of 11 patients with infarction of the posterior inferior cerebellar artery and 5 out of 8 patients with infarction of the superior cerebellar artery were tested with their non-dominant hand. The patient with bilateral infarction was tested on the more severely affected left side. Accordingly, 8 right-handed controls (age matched to the specific patients) were tested with their (non-dominant) left hand. The left-handed cerebellar and control participants were tested with their non-dominant right hand. Patients with cerebellar degeneration were all tested with their right (dominant) hand.

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

**Task**

Details of this task have been described previously (Rabe et al. 2009). Participants were seated in front of a monitor screen and held the handle of a horizontal planar two-joint manipulandum that controlled a small cursor (radius 3 mm). Set-up was the same independently to the performing hand (left or right). Vision of the handle was blocked with a cloth (Fig. 1A). The task consisted of a fast, but precise movement from a constant start position (radius 7 mm) through one of 3 targets (radius 10 mm), which were positioned pseudo-randomly at a distance of 10 cm from the start location. The three targets were located directly away from the subject or at an angle of 24° clockwise or counter clockwise relative to
the middle target (Fig. 1B). The subject’s movement was stopped gently using a simulated soft wall behind the target, and the cursor was extinguished if it reached a distance of 15 cm from the origin. Once the movement came to an end, the subject passively allowed the handle to be returned to the starting location. This method eliminated the necessity for online correction of movements (Tseng et al. 2007) and allowed patients with ataxia to perform the task with close to normal movement speeds. The cursor reappeared when the handle was within 10 mm of the origin. After the cursor disappeared, but before the return movement, the target changed color to give feedback about movement duration (red, too fast; blue, too slow; yellow accompanied with a pleasant sound, correct duration) and accuracy (target disappears without color feedback entirely if the subject misses by more than 6 mm).

Participants performed 7 sets which consisted of 63 trials each. Each target appeared pseudo-randomly 3 times every 9 movements. There were 3 baseline sets without external perturbations. After that, the 4th and 6th sets were perturbed (adaptation) sets and the 5th and last sets were unperturbed (washout) sets (Fig. 1C). Perturbations were either VM or FF. Half the participants performed the VM task and the other half the FF task in the fourth set. This was switched for each participant for the 6th set. The order did not have an influence on results, and all analyses were averaged across all subjects. In the VM task, movement of the manipulandum was shown on the monitor rotated 20° counter clockwise relative to the actual movement. In the FF task, a velocity dependent force field (a standard clockwise curl field with strength of 13 N/m/s) was applied by the motors.

Nine pseudo-randomized unperturbed catch trials without visuomotor rotation or force field perturbation were included in each adaptation set. These catch trials produce, in healthy participants, a displacement of the movement opposite to the direction of the perturbation.

Data analysis
The 3rd baseline set for each subject was averaged across the movements to each target, with each movement aligned on movement onset. This produced a baseline trajectory for each subject for each target. Movement onset was defined as the first time that hand velocity exceeded 0.03 m/s for more than 180 ms. Movements that went in the wrong direction more than 1 cm (from the origin towards the subject) 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.

The aiming error (AE) was defined as in Rabe et al. (2009). Briefly, it is the angle between the point of first maximal error – the first time after 160 ms that the hand path curves back towards the target – and a straight line movement to the target. All movements were bias-corrected by subtracting the aiming error in the baseline trajectory for the appropriate movement direction.

To assess the final amount of learning we used a modified version of the learning index (LI; Criscimagna-Hemminger et al. 2003; Maschke et al. 2004). The LI computation takes into account aiming errors in both perturbed trials and catch trials. Our standard bin size for calculating the LI was 7 consecutive trials (this included 6 field trials and 1 catch trial); however, to assess final performance values, we used a bin of the last 35 trials.

The LI lies between -1 and 1, with 1 indicating maximal learning and 0 to -1 indicating no learning at all. To assess after-effects during the washout phase, mean aiming errors of the first three washout-trials were calculated.

Additionally, we assessed the adaptation index (AI) which represents trial-by-trial learning and is a measure for the subject’s ability to change their behavior in response to error. The AI was calculated by fitting the data to a state-space model and extracting the rate
of learning from one trial to the next (Donchin et al. 2003). We describe the process at an
intuitive level here and full details are provided in Supplemental Material. In the state-space
model, error is caused by a difference between the expected perturbation on each movement
and the perturbation actually applied. The perturbation expected is then updated after each
movement by an amount proportional to the error. Our AI is an estimate of that constant of
proportionality: the degree to which error in one movement affects subsequent movements.
To calculate this index, we used a procedure similar to that used by Tseng et al. (2007). One
complication in this calculation, as in Tseng et al. (2007) and Donchin et al. (2003), arises
because errors made towards one target also affect movements towards other targets. This is
called generalization. The degree of generalization is often approximated as a function of the
difference between the two targets. We first estimated the generalization function for each
control subject, and then determined the shape of the generalization function by averaging
across all of the control subjects. Then, we fit the model to all subjects, controls and patients,
assuming that the shape of the generalization function is the same for all of them, and only the
constant of proportionality changes from one subject to the next. By taking the generalization
function from the control subjects for the patients as well, may lead to underestimation in the
amount of adaptation in patients. However, it would be very difficult to derive a
generalization function for patients precisely because adaptation rates are lower in this group
and the group is more heterogeneous. This allowed us to represent the learning with this
single parameter which we called AI. We produced parameter estimates by sampling from the
likelihood function for the parameters given the data using the Metropolis-Hastings algorithm
(Andrieu 2003) and used the sample with the greatest likelihood as an estimate of the
maximum likelihood value for the parameters. AI was assessed both in adaptation phase and
during washout. Because AI in the washout phase was very similar to AI in the adaptation
phase, only the latter is presented in the manuscript. Washout data is shown in the
Supplementary Material.
Statistical analysis of behavioral data

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, III., USA). Paired $t$-tests and analysis of variance (ANOVA) were used to compare performance between groups. Greenhouse-Geisser adjustments were performed where appropriate. Bivariate correlations were performed and the Spearman's rank correlation coefficient was assessed to compare different adaptation parameters and ataxia scores.

MR imaging

MR images of all patients were acquired with a 1.5 T Siemens scanner (focal lesions, Espree, using a 12 channel head coil; degenerative lesions, Sonata, using a standard head coil; Siemens, Erlangen, Germany). A 3D-sagittal volume of the entire brain was made using a T1-weighted, magnetization prepared, rapid acquisition gradient echo sequence (MPRAGE; TR = 2400 ms, TE = 3.63 ms, FOV = 256 mm, 160 slices, voxel size 1.0 x 1.0 x 1.0 mm$^3$). MR images of patients with cerebellar degeneration were taken from our earlier study (Rabe et al. 2009). Images were examined by an experienced neuroradiologist (ERG) and extracerebellar pathology was excluded.

Focal lesions

Cerebellar lesions of focal patients were manually traced on axial, sagittal and coronal slices of the non-normalized 3D MRI data set and saved as regions of brain injury (RBI) using the free MRICro software (http://www.sph.sc.edu/comd/rorden/mricro.html). Because all patients had chronic lesions, RBIs were easy to define as they present as dark regions in MRI.
RBIs were normalized using a spatially unbiased infra-tentorial template of the cerebellum (SUIT; Diedrichsen 2006) using the SUIT toolbox in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Coordinates in the SUIT template “can be treated as being equivalent to MNI coordinates (Montreal Neurological Institute), only with less variance or uncertainty across individuals.” (www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm). At first the program isolates the cerebellum and creates a mask. These masks were manually corrected with the help of CARET software (http://brainvis.wustl.edu/wiki/index.php/Caret:About). This was necessary because parts of the occipital cortex are frequently included when the automated segmentation algorithm is used. The non-linear deformation was then applied to RBIs from the individual participants.

We used the probabilistic atlas of the human cerebellum (http://www.icn.ucl.ac.uk/motorcontrol/imaging/propatlas.htm; Diedrichsen et al. 2009) in MRIcroN to define the affected lobules. The atlas is based on the cerebellum of 20 healthy subjects in which individual lobules are outlined. Affected cerebellar nuclei were defined with a newly developed probabilistic atlas of cerebellar nuclei (Diedrichsen et al. 2011). Superposition of individual lesions is illustrated in Figure 2.

**Lesion-symptom mapping in focal lesions; Subtraction analysis**

For statistical analysis of focal lesions and adaptation rates, the effects of lesions were evaluated using the lesion map subtraction analysis performed by the MRIcroN software (http://www.sph.sc.edu/comd/rorden/mricron). The logic and power of subtraction analysis of focal lesions is described in Karnath et al. (2002).

The lesion maps for all left-sided lesions were flipped along the midline. Patients were divided in subgroups depending on their behavioral performance. In order to create a group of
'unimpaired' and 'impaired' patients, we found a threshold which optimally separated the control group from the patients. That is, we found the threshold such that

$$#(\text{controls} > T) - #(\text{controls} < T) = #(\text{patients} < T) - #(\text{patients} > T)$$

was maximized. We did this separately for the VM task and the FF task and for the AI and LI measures of adaptation. For each behavioral measure and each voxel, we can say that a patient’s lesion is ‘consistent’ for that voxel if the patient is impaired and has a lesion in that voxel or if the patient is unimpaired and has no lesion in that voxel. MRIcroN calculates the ‘consistency’ for each voxel by taking the percentage of ‘consistent’ patients and subtracting the percentage of ‘inconsistent’ patients. This yields a value between 100 % (all patients consistent) and -100 % (all patients inconsistent). The ‘consistency measure’ is illustrated in Figure 3 for one example voxel in lobule VI with a “consistency” of +57 % (MNI coordinates $x = 17$ mm, $y = -65$ mm, $z = -21$ mm) (data is based on LI measure in the VM task; see also Fig. 9b). Participants who have a lesion of this voxel are presented in red and participants with sparing of this voxel lesion are presented in blue. Inconsistent participants (sparing and LI below threshold or lesion and LI above threshold) are indicated by a triangle. For this voxel 14/19 patients (73.7 %) were consistent and 5/19 patients were inconsistent (26.3 %). Therefore, subtraction analysis revealed a consistency of 57.4 % (73.7 % consistent -26.3 % inconsistent). The lobules where voxels were at least 25% consistent, were determined based on MNI coordinates and the probabilistic atlases described above.

Cerebellar degeneration: Voxel-based morphometry

We implemented a version of the standard VBM method (Ashburner and Friston 2000) using SUIT normalization to morph the individual’s cerebellum into the SUIT atlas space (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm). For each patient, we calculated the quantity of gray matter that mapped from that patient’s MRI scan onto each
voxel in the SUIT atlas. This was done by multiplying the size of the region mapped on to that voxel by the density of gray matter in the region mapped. The density of gray matter was determined by the brightness of the MRI scan, using a probabilistic segmentation algorithm (Ashburner and Friston 2005, unified segmentation). This map built the basis of the VBM. The sum of the gray matter mapped onto each voxel over the voxels in a specific lobule could be interpreted as the absolute amount of gray matter in that lobule. This was done by multiplying the size of the region mapped onto that voxel by the density of gray matter in the region mapped.

To validate the method, VBM values for individual lobules have been correlated with manual volumetric data that were assessed semi-automatically with the help of ECCET-software (http://www.eccet.de). Details of this methodology have been reported previously (Dimitrova et al. 2006; Brandauer et al. 2008). Correlation of the VBM values for each lobule with the manual volumetry of the lobules averaged 0.80 (range 0.72-0.89). This high correlation of VBM values and manual volumetry values validates the use of VBM to get voxel-level maps of the relationship of cerebellar cortex to our behavioral tasks. Correlation between LI and VBM values with a p-value below 0.05 was considered statistically significant.
Results

Patients with focal cerebellar lesions

Behavioral data

Motor performance

Participants initially performed 3 sets without perturbation. The 3rd set was used to assess baseline performance. Patients had a higher between-subject variability of baseline aiming error than controls (Levene’s test, \( p = 0.034; F = 4.877 \)) and a higher within-subject variability although the difference was not statistically significant (\( p = 0.175, t(22.7) = 1.4 \)).

Because the force field in the perturbed set was velocity-dependent, patients and controls were encouraged to move at similar speeds. In fact, patients and controls had comparable movement times during all sets (ANOVA, set x group, group effect: \( p = 0.532, F(1) = 0.397 \); Fig. 4). However, 3 patients did move slower than the other participants during parts of the sets [# 13 (set 1 to 4), # 18 (set 4, 5 and 7) and # 3 (set 5) in Table 1]. Patients were not excluded from further analysis.

Analysis of adaptation in the FF and the VM task

Figure 5 shows individual movement trajectories for a representative control (A) and three patients (B and C, superior cerebellar artery infarctions; D, posterior inferior cerebellar artery infarction). For the control participant (A, # 17 in Table 2) good adaptation is indicated with perturbed trials (solid line) that approach the target during the end of the perturbed set, and unperturbed (“catch”) trials (dotted lines) that deviate to the opposite direction of field trials. In the FF task (first row), perturbed trials deviate to the right, whereas in the VM task (second row), perturbed trials deviate to the left. Figure 5B and C show two patients with superior cerebellar artery infarctions (# 15 and 17 in Table 1). The 1st patient has impaired
adaptation to the VM task, which is indicated by perturbed trials that do not reach the target.

The 2nd patient has poor adaptation to the FF task – catch trials do not deviate from the target.

Figure 5D shows a patient with a posterior inferior cerebellar artery infarction (# 10 in Table 1). This patient has normal adaptation to both tasks.

AE is plotted as a function of time for these 4 subjects in the first 2 columns of Figure 6 (Fig. 6A, FF and then VM), and LI for the 2 tasks are shown in the 3rd column (Fig. 6B). This figure supports the impression given by Figure 5: the control and the patient with posterior inferior cerebellar artery infarction adapt successfully in both tasks while the 1st patient with superior cerebellar artery infarction is impaired in the VM task (red) and the 2nd is impaired in the FF task (blue). This can be seen both in the field trials (small dots), which do not converge to zero error when the patient is impaired, and in the catch trials (large dots), which continue to be relatively straight. This is reflected in larger LIs when subjects successfully adapt and smaller ones when they do not.

In addition, these plots show the error predicted by the state-space model that we fit to the data (solid black line: perturbed movements; dashed black line: catch trials). From these lines, we can see that the model captures the lack of adaptation in subjects with superior cerebellar artery infarctions, and successful adaptation in the subject with posterior inferior cerebellar artery infarction and control subject.

Comparison between groups

Patients with superior cerebellar artery infarctions performed worse (mean LIF 0.59; mean LIB 0.61) than patients with posterior inferior cerebellar artery infarctions (LIF 0.69; LIVM 0.64) and worse than controls (LIF 0.79; LIVM 0.71) in both performance measures (Fig. 7A,B). This difference was statistically significant in ANOVA comparing the three groups (group effect: p = 0.042, F(2) = 3.472). Posthoc analysis revealed significant differences
comparing SCA patients and controls (F = 11.770; p = 0.002), but not comparing PICA patients and controls (F = 2.171; p = 0.152).

Correlation between LI and AI

We found a strong correlation between LI and AI for the FF task (Fig. 8A, p = 0.001, R = 0.533) and the VM task (Fig. 8B, p < 0.001, R = 0.675) across participants. In the patient group, we had a correlation for both tasks (FF, p = 0.021, R = 0.525; VM, p = 0.002, R = 0.663). In the control group, we had a correlation for the VM task (p = 0.002, R = 0.661), but no correlation for the FF task (p = 0.130, R = 0.360).

Correlation between FF and VM task

There was no significant correlation between performance in the FF and VM task for focal patients (LI, p = 0.994, R = -0.002, Fig. 8C; AI, p = 0.251, R = -0.277, Fig. 8D) or controls (LI, p = 0.482, R = 0.172; AI, p = 0.972, R = -0.009).

Lesion-symptom mapping: subtraction analysis

Figure 8 shows that performance was quite variable between cerebellar participants. In patients with superior cerebellar artery infarctions and with posterior inferior cerebellar artery infarctions, there were individual patients who performed below the normal and others who were within the normal range. It was assumed that different cerebellar regions were involved in patients performing well than in patients performing more poorly. To determine the areas of the cerebellum that were specifically important for degrading performance MRI subtraction analysis between patients with impaired and unimpaired adaptation was used.
Patients were divided into 2 groups according to thresholds optimized to distinguish them from controls as described in the methods. The optimal thresholds were: \( L_{II}^{FF} \): 0.59, \( AI_{FF} \): 0.18, \( LI_{VM} \): 0.60, \( AI_{VM} \): 0.11. In both tasks, more patients had a decreased LI (\( L_{II}^{FF} \): 9 patients impaired and 9 not impaired; \( LI_{VM} \): 7 and 12) than AI (\( AI_{FF} \) and \( AI_{VM} \): 4 impaired and 15 unimpaired for both tasks).

Figure 9 shows the RBI subtraction analysis for the FF and VM task. Indicated are regions with highest ‘consistency’. ‘Consistency’ of a voxel was determined as the difference between the percentage of patients with a ‘consistent’ lesion (sparing with LI above threshold or lesion with LI below threshold) and with an ‘inconsistent’ lesion (sparing with LI below threshold or lesion with LI above threshold; Fig. 3). Lesion-symptom correlations were quite circumscribed in the FF task (Fig. 9A). In patients with \( L_{II}^{FF} \) impairments, lesions were 33% more common in lobule IV and V, up to 46% more common on the border between Crus I and II, and up to 44% more common in the posterolateral dentate nucleus. Regions involved in \( AI_{FF} \) were comparable to those involved in \( L_{II}^{FF} \). These regions include lobule IV and Crus I (25%), but also lobule IX (up to 38%).

As can be seen in Figure 9B, lobule VI was most commonly involved in \( LI_{VM} \), but lobule V, part of lobule IV and the posterolateral dentate were also implicated. These areas were up to 57% more commonly damaged in \( LI_{VM} \) impaired than in unimpaired patients. Damage in Crus I (anterior part, at the border to lobule VI) was up to 43% more common in patients with reduced \( LI_{VM} \). This picture is reinforced when we compare patients impaired in \( AI_{VM} \) with those not impaired: lobules V and VI (up to 43%) where implicated in impairment in both measures. Additionally lobule VIIb (up to 37%), Crus II (up to 43%) and lobule VIIIb (up to 25%) were affected in patients impaired in \( AI_{VM} \).
The regions that appear involved in the 2 tasks were largely adjacent. We found a small overlap of regions impaired in LI_{VM} and LI_{FF} in the posterolateral dentate nucleus (Fig. 9C). We did not find overlap between regions correlated with AI_{VM} and AI_{FF}.

Adaptation and ataxia scores

We did not find a significant correlation between adaptation in patients and the SARA score or the subscore for upper extremities. Generally, patients were clinically mildly impaired, and had low ataxia scores. The maximal SARA score was 7 out of 40. Ten patients had a SARA score for the upper extremities of 0. In patients with an upper extremities score higher than 0, lobules IV, V, VI and Crus I were up to 44% more often affected than in patients with scores of 0.

Degenerative patients

Behavioral data

In our earlier study of patients with cerebellar degeneration, we found a significantly lower LI for the FF task (t-test; p = 0.027) and the VM task (p = 0.002) in patients than in controls (Rabe et al. 2009). In the current study, we re-analyzed the data of degenerative patients to assess AI. Patients showed a significantly reduced AI for both tasks in comparison to controls (FF, p = 0.015; VM, p < 0.001). Figure 10A and B show that the two performance measures are highly correlated across subjects, just as with the focal lesion results (FF, p < 0.001, R = 0.833; VM, p < 0.001, R = 0.938). Figure 10D demonstrates that performance on the two tasks is not correlated when measured by AI (patient group, p = 0.681, R = 0.121), as previously shown for LI (patient group, p = 0.318, R = 0.288, Fig 10C).
To identify regions important for adaptation in the two tasks for patients with cerebellar degeneration, we performed a VBM analysis. For the FF task (Fig. 11A), LI was mainly associated with a region centered in right lobule V, but additionally involved a region located in the left posterior caudal cerebellum and in the right lateral cerebellum (Crus I and II). The association with the AI performance measure was much weaker, although a region in the white matter next to right lobule V showed a relation to the performance in this index. For the VM tasks (Fig. 11B), a region in the anterior cerebellum (centered in lobule VI, but stretching into lobule IV and V) and in the posterior cerebellum (lobules VIIIb to X) was associated with both LI and AI. Additionally, the right lateral posterior cerebellum (Crus I) was correlated with AI.

If compared to results of the subtraction analysis of focal patients, areas are less localized and additionally involve the left cerebellum. Degeneration usually affects the whole cerebellum to various extents. Therefore, analyses of patients with focal lesions allow a more precise mapping of involved areas. However, peak regions are similar in both analyses. Mainly lobule V and Crus I and II are involved in the FF task. In the VM task, lobule VI is affected. Areas in the posterior cerebellum are less congruent, but Crus I, II and the medial inferior cerebellum seem not consistently affected.
Discussion

The present study was conducted to identify in more detail cerebellar regions involved in adaptation to visuomotor rotation and force field perturbations. We confirmed earlier findings that patients with cerebellar disorders show impaired motor learning in both tasks. Infarctions in the supply area of the superior cerebellar artery were followed by more severe adaptation deficits than infarctions in the supply area of the posterior inferior cerebellar artery. Accordingly, in further analyses we found a more consistent relation between lesions in the anterior arm region and impairment in the two tasks than in the posterior arm region.

Based on our results in focal patients and the improved analysis in degenerative patients we must revise our previous interpretation that the two tasks depend on different arm areas. Instead, we find that both adaptation tasks depend on the anterior arm region and additionally, less consistently, on the posterior cerebellum. Most importantly, our findings suggest that the anterior arm area may be divided into distinct functional pieces. Present results are a very first clinical confirmation of current understanding of localized cerebellar information processing in cerebellar microzones and microcomplexes (Garwicz 2000; Ekerot and Jorntell 2003; Apps and Hawkes 2009).

Anterior arm region

In the previous study in patients with cerebellar degeneration we reported that atrophy of the intermediate zone of the posterior lobe was related to impaired adaptation in the VM task, whereas atrophy of the intermediate and lateral zone of the anterior lobe was related to the FF task (Rabe et al. 2009). In that study we used the primary fissure as the anatomical landmark to separate the anterior (lobules I-V) and posterior lobes (lobules VI-X). Therefore the anterior arm area was artificially split. Lobules IV and V are in the anterior lobe and lobule VI is in the posterior lobe. The present study – investigating focal patients and using
advanced methods to reassess the data from degenerative patients – allowed analysis of individual lobules. Results confirmed our previous findings for the two tasks, but suggested that our interpretation may have been influenced by an artificial division of the anterior arm area. We found that the FF task was principally related to lobules IV and V of the anterior arm area, supporting our previous finding that it is related to the anterior lobe. The VM task was primarily related to lobule VI, supporting our previous finding that it is related to the posterior lobe, but undermining our interpretation that it is related to the posterior arm area. The VM task, however, was not exclusively related to lobule VI, but in addition, although to a lesser extent to lobules V and IV in the anterior lobe. Importantly there was very little overlap with FF adaptation related areas.

Indeed, our findings are consistent with previous reports. Studies of VM adaptation, using patient deficits or functional imaging, regularly find the VM task associated with lobule VI (Imamizu et al. 2000; Graydon et al. 2005; Seidler and Noll 2008; Werner et al. 2010). Involvement of the posterior lobe is supported by a recent study using diffusion tensor imaging (Della-Maggiore et al. 2009). One study of both force field and visuomotor adaptation found overlapping areas of the cerebellum involved in the two tasks (Diedrichsen et al. 2005). However, a careful examination of Figure 8A in that paper shows relatively larger activation associated with the VM task adjacent to the primary fissure separating lobule V and VI in the posterior lobe and activation associated with the FF task adjacent to the primary fissure in the anterior lobe. This is consistent with our expectations although the distinction did not reach significance in that study.

Our findings, however, do seem to contradict a classic human lesion study of prism adaptation. Martin et al. (1996) reported dissociation between motor performance and adaptation deficits in patients with posterior inferior cerebellar artery and superior cerebellar artery lesions. Performance was disordered in patients with superior cerebellar artery
infarctions but not in patients with posterior inferior cerebellar artery infarctions, but adaptation deficits were seen only in patients with posterior inferior cerebellar artery infarctions. Prism adaptation and cursor rotation tasks such as ours have much in common but there are also differences. Therefore, it may well be that prism adaptation relies on different cerebellar areas than cursor rotation. For example, in a prism task the whole environment is shifted. That implies that the system of eye and head movements has to adapt independently to the task. Because oculomotor functions are localized in the territory of the posterior inferior cerebellar artery lesion of that artery might affect performance in this task more strongly. Finally, group size in the Martin study was small, and the data presented in the paper suggest that some posterior inferior cerebellar artery infarcts reach up to lobule VI. Thus, these findings need to be reassessed in a larger group of focal patients with the more advanced methods of lesion-symptom mapping now available.

Our findings suggest that the anterior arm area may be divided into distinct functional pieces. As outlined above findings are a clinical confirmation of the current understanding of localized cerebellar information processing in cerebellar microzones and microcomplexes (Garwicz 2000; Ekerot and Jorntell 2003; Apps and Hawkes 2009). In general, cerebellar microcomplexes are histologically similar (but see Apps and Hawkes 2009), and differences in afferent and efferent connections explain differences in function. In our case, the anterior lobe primarily receives somatosensory information, whereas visual afferents project mainly to the posterior lobe including lobule VI of the anterior arm region (Bloedel and Courville 1981). This is consistent with findings showing that VM adaptation depends on visual input (Krakauer et al. 2000) and FF adaptation on proprioceptive input (Hwang and Shadmehr 2005). Our findings that lobules IV and V are involved to a smaller extent in VM adaptation suggest that additionally proprioceptive information is needed in this task to correct movements according to visual information.
Behaviorally, the lack of correlation in performance on the two tasks, which we now have seen in two different patient groups, supports the involvement of separate cerebellar areas in each task. Previous data suggest that different mechanisms are involved in the two tasks. These include differences in generalization (Pine et al. 1996; Baizer et al. 1999; Donchin et al. 2003; Criscimagna-Hemminger et al. 2003), learning (Krakauer et al. 1999) and in which coordinates (extrinsic, joint) adaptation is planned (Flanagan and Rao 1995; Wolpert et al. 1995; Shadmehr and Moussavi 2000).

However, we did not succeed in creating an interpretable separation of function using the two different learning indices. The final amount of learning (LI) was highly correlated with trial-by-trial learning (AI) in patients. In fact, although Tseng et al. (2007) suggested that trial-by-trial learning was a more sensitive measure of the cerebellar adaptation deficit, we found that more patients showed impairments in LI than AI. Another way that adaptation has been divided functionally is between processes involved in adaptation and those involved in retention (Hadipour-Niktarash et al. 2007; Werner et al. 2010), possibly reflecting the activity of fast and slow adapting systems (Sing and Smith 2010) Theory suggests that LI should be more influenced by the slow adapting system and more strongly correlated with retention, and that AI should be more influenced by the fast adapting system and more strongly correlated with acquisition of an adaptation (Sing and Smith 2010). However, in our data, where AI and LI are so strongly correlated, it is unlikely that we would see any dissociation between these two measures, and cannot address the question of whether acquisition and retention of adaptation depend on different neural substrates (Werner et al. 2010).

Posterior cerebellum

Lesion-symptom mapping results were most consistent for the anterior arm region. However, both in focal lesion and degenerative patients, there were also symptom correlations
with areas of the posterior cerebellum. We found that lesions in the lateral posterior lobe (in particular Crus I) and the posterolateral dentate nucleus were related to disordered FF and VM adaptation in focal and degenerative patients. In addition, lesions in the caudal posterior lobe (lobules VIII –X) led to impairment in VM in degenerative and to a lesser extent in focal patients.

Functional brain imaging studies also suggest a contribution of the posterior lobe to VM and FF adaptation. Diedrichsen et al. (2005) found activation of lobule VIII in both tasks, whereas others report additional activation in Crus I and II in FF (Nezafat et al. 2001) and VM tasks (Imamizu et al. 2000; Krakauer et al. 2004). Crus I and II are thought to contribute to non-motor tasks, whereas lobule VIII represents the posterior arm area (Grodd et al. 2001; Kelly and Strick 2003; Manni and Petrosini 2004; Stoodley and Schmahmann 2009). Non-motor and motor cerebellar areas may contribute differentially to FF and VM adaptation.

The function of the second body representation in the posterior lobe remains unclear. However, contribution of the representation in the posterior lobe to motor control appears to be less essential. For example, spinocerebellar connections of the posterior arm areas are much smaller than the anterior ones (Brodal 1981). Furthermore, it is known from clinical observations that in patients with posterior inferior cerebellar artery strokes (where the posterior body representation is affected) recovery of cerebellar ataxia is faster than in patients with superior cerebellar artery strokes (Tohgi et al. 1993; Kelly et al. 2001). In fact, in Martin et al.’s study (1996) the one patient with an older posterior inferior cerebellar artery infarction did not show impaired adaptation in the VM task whereas all patients with acute infarctions were impaired. A study in a larger group of patients with acute posterior inferior cerebellar artery and superior cerebellar artery lesions would be of interest, as significant abnormalities in VM and FF adaptation may be present in patients with acute posterior inferior cerebellar artery infarctions.
In focal and degenerative patients we found a small, but consistent region of high correlation with both tasks in Crus I and Crus II. Whereas intermediate parts of Crus II may contribute to reach adaptation because of its reciprocal connections with reach and grasp related areas in the parietal cortex, lateral parts of Crus I and Crus II may support the initial, more strategic part of learning (Werner et al. 2010): reciprocal connections of intermediate Crus II have been shown to the posterior parietal cortex (Prevosto et al. 2010; Glickstein et al. 2011). Lateral parts of Crus I and II, on the other hand, have known reciprocal connections with the prefrontal lobe and may contribute to more cognitive functions (Schmahmann and Sherman 1998; Stoodley and Schmahmann 2009).

Conclusions

We showed that the anterior hand area is of major importance both in visuomotor and force field adaptation. Different regions of the hand area appear to be involved in each task with areas in the anterior lobe being more associated with FF and posterior lobe areas being more associated with VM. Additionally, the posterolateral cerebellum contributes to both tasks. Further studies, with high-resolution imaging or using recordings from individual neurons, are needed to localize the areas involved with more precision. In addition, studies in acute patients will allow us to test the possibility that the contribution of the posterior hand area is masked by compensatory mechanisms in the chronic subjects.
Acknowledgements

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References


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Figure legends

Figure 1:
A. Participants sat in front of a monitor screen and held the handle of a robot in their right or left hand (according to lesion side for patients and the matched side for controls). Vision of the handle was blocked with a cloth. B. Position of the handle was visualized by a small black cursor on the screen. Participants were instructed to move the black cursor into a green circle at the bottom of the screen which indicated the starting position. This induced the appearance of one of 3 targets (pseudo-randomized; gray circles) either 10 cm straight above the starting position or 24° to the left or right. Participants made a shooting movement through the target. C. To get used to the movement, participants performed 3 sets of baseline trials. Then, half the participants performed a FF (force field) task in the 4th set and a VM (visuomotor) task in the 6th set, while the other half first performed the VM task and then the FF task. Each perturbed set was followed by a washout set.

Figure 2:
Regions of brain injury of all patients with focal lesions overlapped in one figure. Up to eight patients had lesions in the posterior arm region and up to seven patients’ lesions in the anterior arm region, whereas parts of the posterolateral cerebellum were intact in all patients.

Figure 3:
The figure shows our consistency measure for lobule VI (voxel with coordinates 17, -65, -21) in the visuomotor task. Participants with a lesion in this voxel are presented in red and participants without a lesion in blue. Participants with a lower learning index (LI) than threshold (dashed line) are considered impaired and with a higher index are considered not
impaired. A patient is ‘consistent’ if the patient has a lesion in that voxel (presented in red) and LI below threshold or if the patient has no lesion (presented in blue) and LI above threshold. Patients with a lesion but no impairment in learning or without a lesion but LI below threshold are ‘inconsistent’ and indicated with a triangle. MRIcroN calculates the ‘consistency’ for each voxel by taking the percentage of ‘consistent’ patients and subtracting the percentage of ‘inconsistent’ patients. This yields a value between 100% (all patients consistent) and -100% (all patients inconsistent).

Figure 4:
Bar graphs show movement times measured from movement onset to a distance of 10 cm from the start point. Median: black dot; 25th and 75th percentile: upper and lower end of the box; shortest and longest: ends of lines; outliers: plus (+). Data is shown for participants with superior cerebellar artery infarctions, posterior inferior cerebellar artery infarctions and controls for 3 baseline sets, the VM and FF tasks and the washout sets. Movement times did not differ significantly between participants with cerebellar infarctions and control participants during all sets. Three patients moved significantly slower than other participants (outliers; difference to mean larger than two standard deviations).

Figure 5:
Movement trajectories for a representative control (first column) and 3 cerebellar participants [infarction of the superior cerebellar artery: 2nd and 3rd columns; infarction of the posterior inferior cerebellar artery: 4th column] for FF (1st row) and VM task (2nd row). Affected lobules are indicated for each patient. The solid line and shaded area around it represent the mean and standard deviation of the last 18 perturbed trials of the FF or VM set. The three last unperturbed (“catch”) trials in a set are shown with dotted lines. In a participant with intact
adaptation we expect that perturbed movements will pass close to the target while unperturbed movements deviate to the opposite side of perturbation. This was observed in the healthy control (first column) and in the participant with a posterior inferior cerebellar artery infarction (last column). Impaired adaption in the VM task in the first participant with superior cerebellar artery infarction (second column) is represented by perturbed movements that do not approach the target. The second participant with superior cerebellar artery infarction (third column) had impaired adaptation in the FF task. His catch trials deviated only slightly to the side.

Figure 6:

(A) Aiming errors (AEs) for the four patients are shown in this figure. First column shows aiming errors in FF (force field) trials, second column shows aiming errors in VM (visuomotor) trials. Small dots represent AEs in control trials and large dots represent AEs in catch trials. The solid colored line shows AEs in perturbed trials averaged across 6 sequential perturbed movements (2 in each direction). The solid black line shows AEs predicted for perturbed trials (black dashed line: catch trials) by fitting the state space model. Adaptation index (AI) represented by the fit is noted on each graph. The control participant (first row) and the participant with a posterior cerebellar artery infarction (last row) have successful adaptation, a good fit for the model, and a relatively large AI. This contrasts with failed adaptation in VM of one patient (2nd row) with an infarction of the superior cerebellar artery and in FF of the other (3rd row). (B) Learning index (LI) in the two tasks calculated in bins of 7 movements. Participants who succeed in adapting reach higher LI than those who do not.

Figure 7:
Participants with superior cerebellar artery infarctions have less adaptation in both tasks than participants with posterior inferior cerebellar artery infarctions or controls as measured by LI (A) and AI (B). Box plots show median, 25th and 75th percentile (lower and upper end of box) and minimal and maximal values (whiskers).

Figure 8:

Plots show individual LIs and AIs with standard error for participants with superior cerebellar artery (red) and posterior inferior cerebellar artery (blue) infarctions and controls (black). Black lines indicate the threshold between impaired and unimpaired participants. LI and AI are significantly correlated for FF (A) and VM (B) task. Performance in one task does not correlate to performance in the other task as measured by LI (C) or AI (D).

Figure 9:

Lesion-symptom mapping; subtraction analysis: The subtraction analysis shows regions that are at least 25% more often lesioned in cerebellar patients impaired in the task than in cerebellar patients not impaired. Regions which are correlated with impaired learning are indicated in red for the FF task (A) and in green for the VM task (B). Brighter colors indicate higher consistency. Overlap between regions correlated with FF and VM are shown in (C). For LI, overlap was present in the posterolateral dentate. No overlap was found for AI (not shown). Cerebellar nuclei are presented in blue.

Figure 10:

Plots show individual LIs and AIs with standard error for participants with cerebellar degeneration (red) and controls (black). LI and AI are significantly correlated for FF (A) and
Donchin O. Cerebellar regions involved in adaptation

VM (B) task. As in the participants with focal lesions, performance in one task did not correlate with performance in the other task measured either by LI (C) or AI (D).

Figure 11:

Lesion-symptom mapping; VBM, degenerative patients: Figure shows regions that have a significant correlation with task performance (p < 0.05). A t-value of 1.77 corresponds to a p-value of 0.05 and a t-value of 2.65 corresponds to a p-value of 0.01. For the FF task (A), LI is associated with a region centered in lobule V and in the left caudal posterior cerebellum. A much smaller region located in the white matter next to right lobule V is associated to AI. For the VM task (B), a region in the anterior cerebellum (centered in lobule VI) and in the caudal posterior cerebellum is associated with LI and AI.
A  Learning index

Force field

Adaptation index

B  Learning index

Visuomotor

Adaptation index

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</table>

Patients showed only minor clinical impairment. The clinical ataxia scores (SARA) ranged between 0 and 7 (maximal score 40). LI<sub>VM</sub>, AI<sub>VM</sub>, LI<sub>FF</sub>, and AI<sub>FF</sub>: learning (LI) and adaptation (AI) indices in the visuomotor (VM) and force field (FF) tasks. Highlight indicates impaired performance. The last column indicates whether the dentate nuclei were affected. SCA = Infarction of the superior cerebellar artery, PICA = Infarction of the posterior inferior cerebellar artery; HD = Hand dominance; Cr: Crus.
Table 2: Control participants.

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Gender</th>
<th>HD</th>
<th>Hand</th>
<th>LI\textsubscript{VM}</th>
<th>AI\textsubscript{VM}</th>
<th>LI\textsubscript{FF}</th>
<th>AI\textsubscript{FF}</th>
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<td>0.81</td>
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<td>0.16</td>
<td>0.77</td>
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<tr>
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<td>54</td>
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<td>right</td>
<td>right</td>
<td>0.72</td>
<td>0.20</td>
<td>0.91</td>
<td>0.23</td>
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<td>right</td>
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<td>0.31</td>
<td>0.94</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Tested side (Hand) was matched to handedness and lesion side in the cerebellar patients.

Performance scores ($L_{VM}$, $A_{VM}$, $L_{FF}$, and $A_{FF}$) classified as impaired are highlighted. HD = handedness; Cr: Crus.