

Visuomotor adaptive improvement and aftereffects are impaired differentially following cerebellar lesions in SCA and PICA territory

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Abstract The aim of the present study was to elucidate the contribution of the superior and posterior inferior cerebellum to adaptive improvement and aftereffects in a visuomotor adaptation task. Nine patients with ischemic lesions within the territory of the posterior inferior cerebellar artery (PICA), six patients with ischemic lesions within the territory of the superior cerebellar artery (SCA) and 17 age-matched controls participated. All subjects performed center-out reaching movements under 60° rotation of visual feedback. For the assessment of aftereffects, we tested retention of adaptation and de-adaptation under 0° visual rotation. From this data we also quantified five measures of motor performance. Cerebellar lesion-symptom mapping was performed using magnetic resonance imaging subtraction analysis. Adaptive improvement during 60° rotation was significantly degraded in PICA patients and even more in SCA patients. Subtraction analysis revealed that posterior (Crus I) as well as anterior cerebellar regions (lobule V) showed a common overlap

related to deficits in adaptive improvement. However, for aftereffect measures as well as for motor performance variables only SCA patients, but not PICA patients showed significant differences to control subjects. Subtraction analysis showed that affection of lobules V and VI were more common in patients with impaired retention and de-adaptation, respectively. Data shows that areas both within the superior and posterior inferior cerebellum are involved in adaptive improvement. However, only the superior cerebellum including lobules V and VI appears to be important for aftereffects and therefore true adaptive ability.

Keywords Sensorimotor coordination · Cerebellum · Ataxia · Motor learning · Pointing · SCA · PICA

Introduction

It has been argued in the past that sensorimotor adaptation depends on the integrity of the cerebellum, since patients with cerebellar disease show impaired adaptation to force fields (Maschke et al. 2004; Smith and Shadmehr 2005) and visual distortions while walking (Morton and Bastian 2004), pointing (Gauthier et al. 1979; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008), or performing ballistic elbow flexion and extension movements (Deuschl et al. 1996). Not only adaptive improvement, that is the reduction of errors during adaptation phase, but also aftereffects (Maschke et al. 2004; Morton and Bastian 2004; Smith and Shadmehr 2005; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008) and generalisation (Morton and Bastian 2004) were found to be degraded. Aftereffect tests such as de-adaptation, retention or catch trials (that is single trials without perturbation during the adaptation phase) are

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Table 1 Basic characteristics of patients in the present study

| | Patient | Age | Sex | Cerebellar disorder | Duration of disease | Side | Volume | Ataxia rating scale | | |
|---|---------|-----|-----|---------------------|---------------------|------|--------|---------------------|------------|------|
| | | | | | | | | Total | Upper-limb | |
| | | | | | | | | | Right | Left |
| | CZ | 41 | F | PICA | 19 | L | 0.4 | 0 | 0 | 0 |
| Age, sex (F-female; M-male), cerebellar disorder (PICA, infarct of posterior inferior cerebellar artery; SCA, infarct of superior cerebellar artery), duration of disease (time since lesion in months), side (R-right, L-left), volume of the lesion (in cubiccentimeters), and total as well as upper-limb ataxia scores from SARA (Scale for the assessment and rating of ataxia; Schmitz-Hubsch et al. 2006). Note that subscores of upper-limb ataxia of the right and left arm were summed up, and no means were taken as in the original publication | FL | 59 | M | PICA | 8 | L | 1.7 | 0 | 0 | 0 |
| | GE | 59 | M | PICA | 13 | R | 9.9 | 0 | 0 | 0 |
| | MT | 42 | M | PICA | 20 | R | 22.8 | 0 | 0 | 0 |
| | RK | 46 | M | PICA | 19 | L | 11.9 | 0 | 0 | 0 |
| | SC | 69 | M | PICA | 18 | R | 10.3 | 6 | 1 | 1 |
| | WS | 57 | M | PICA | 15 | R | 31.4 | 2 | 0 | 0 |
| | JM | 64 | M | PICA | 7 | L | 22.7 | 1 | 0 | 0 |
| | KM | 65 | M | PICA | 16 | L | 30.5 | 6 | 0 | 3 |
| | HG | 67 | M | SCA | 0 | L | 2.6 | 4 | 1 | 2 |
| | JL | 18 | F | SCA | 12 | L | 1.0 | 0 | 0 | 0 |
| | KW | 75 | M | SCA | 46 | L | 5.3 | 7 | 0 | 2 |
| | LR | 72 | M | SCA | 11 | R | 1.2 | 2 | 1 | 0 |
| | LZ | 69 | F | SCA | 22 | R | 0.3 | 4 | 0 | 1 |
| | MM | 56 | M | SCA | 15 | L | 1.1 | 2 | 0 | 0 |

commonly conducted to distinguish true adaptation or *recalibration* of sensory-to-motor transformation rules from adaptive improvement. The latter is thought to be achieved by recalibration on the one hand and strategic control such as cognitive updating of perceived feedback positions on the other hand. Since strategic control is thought to be short-lived and task-specific, it exclusively effects adaptation phase and has no impact on post adaptation phases or catch trials (Bock 2005; McNay and Willingham 1998; Redding et al. 2005; Redding and Wallace 1996; Werner and Bock 2007). In accordance with this reasoning sensorimotor recalibration and not just strategic planning is impaired in cerebellar patients.

Although there is general agreement that the cerebellum is involved in true sensorimotor adaptation, it is still under debate which specific parts of the cerebellum contribute. Several functional brain imaging studies in healthy human subjects have reported cerebellar activation both in visuomotor and force field adaptation tasks. The majority of studies report activations of the superior parts of the cerebellum (in particular in lobules IV, V and VI) (Della-Maggiore and McIntosh 2005; Diedrichsen et al. 2005; Imamizu et al. 2003, 2000; Seidler and Noll 2008; Seidler et al. 2006; Shadmehr and Holcomb 1997). One of these studies did not cover the more inferior parts of the cerebellum and, therefore, cannot exclude additional contributions of these parts of the cerebellum (Shadmehr and Holcomb 1997). The studies, which covered the entire cerebellum, are partly contradictory. Some studies report adaptation-related activity in the superior cerebellum only (Della-Maggiore and McIntosh 2005;

Seidler and Noll 2008; Seidler et al. 2006), whereas others found activation both in the superior and the posterior inferior cerebellum (lobules VIIB and VIII; Diedrichsen et al. 2005; Nezafat et al. 2001). It has to be noted, however, that not all studies carefully controlled for cerebellar activation related to motor performance such as hand acceleration or on-line motor corrections, which also have been shown to activate the superior (Diedrichsen et al. 2005; Grafton et al. 2008; Seidler et al. 2004), but also inferior parts of the cerebellum (lobule VIII; Diedrichsen et al. 2005).

The comparison of patients with ischemic stroke within the territory of the superior cerebellar artery (SCA) and the posterior inferior cerebellar artery (PICA) is a useful human cerebellar lesion condition to further elucidate the contribution of the superior and inferior cerebellum to sensorimotor adaptation. The SCA commonly supplies the anterior lobe (lobules I–V) and the more superior parts of the posterior lobe (lobules VI and Crus I), whereas the PICA commonly supplies the more inferior parts of the posterior lobe (lobules Crus II–X). Vascular territories, however, are variable and PICA strokes can involve Crus I (Timmann et al. 2009 for recent review).

As yet, two human vascular cerebellar lesion studies have assessed visuomotor adaptation. These studies have revealed contradictory results. One single-case study found a marked adaptation deficit following an SCA lesion (Pisella et al. 2005); however the other, well-cited study claimed that PICA lesions result in adaptation deficits but intact motor performance (Martin et al. 1996). To clarify this issue, we decided to compare motor performance and

Table 2 Cerebellar lesion site

| Patient | Vermis | Hemisphere | | Nuclei |
|---------|----------------------------------|--|--|---------------|
| | | Paravermal | Lateral | |
| CZ | n.a. | n.a. | l: CRI, CRII | n.a. |
| FL | VIIAt, VIIB, VIIIA | l: CRII, VIIB, VIIIA, VIIIB, IX | n.a. | n.a. |
| GE | CRII, VIIAt, VIIB, VIIIB | r: CRI, CRII, VIIB, VIIIA, VIIIB | r: CRI, CRII, VIIB, VIIIA | (r: NI) r: ND |
| MT | n.a. | r: CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX | r: CRI, CRII, VIIB, VIIIA, VIIIB | n.a. |
| RK | VIIAt, VIIB, VIIIA, VIIIB, IX, X | l: (CRI), CRII, VIIA, VIIB, VIIIA, VIIIB, IX | l: CRI, CRII, VIIB, VIIIA, VIIIB | l: ND p |
| SC | VIIAt, VIIB, VIIIA, VIIIB, IX | r: CRII, VIIB, VIIIA, VIIIB, IX | r: CRII, VIIB, VIIIA, VIIIB | n.a. |
| WS | n.a. | r: CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX | r: VI, CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX | r: ND p |
| JM | n.a. | l: (CRI), CRII, VIIB, VIIIA, VIIIB | l: CRI, CRII, VIIB, VIIIA, VIIIB | (l: ND) |
| KM | VIIAt, VIIB, VIIIA, VIIIB, IX, X | l: CRI, CRII, VIIB, VIIIA, VIIIB, IX | l: CRI, CRII, VIIB, VIIIA, VIIIB | (l: ND) |
| HG | n.a. | l: IV, V , VI | l: VI, CRI, CRII | n.a. |
| JL | n.a. | l: IV, V , VI | (l: VI) | (l: ND) |
| KW | III, IV, V, VI | l: V , VI | n.a. | (l: NI) |
| LR | n.a. | r: V , VI | n.a. | (r: ND) |
| LZ | n.a. | r: (V), VI | (r: VI, CRI) | n.a. |
| MM | n.a. | l: V , VI | l: VI | n.a. |

Cerebellar lobules are named according to Schmahmann et al. (2000). *R* right side, *l* left side, *NI* interposed nucleus, *ND* dentate nucleus, *n.a.* not affected, *p* posterior part of dentate, brackets indicate partial lesions. Common lesions sites in SCA patients are marked in bold letters

visuomotor adaptation in a larger sample of patients with either PICA or SCA territory involvement.

Materials and methods

Subjects

We acquired data from fifteen patients with unilateral focal cerebellar lesions (mean age 57.3 ± 15.1 years; 3 female, 12 male). Nine patients had ischemic infarction within the PICA territory. Mean age in this patient group was 55.8 ± 10.3 years, mean time since lesion was 15.0 months, and their mean score on the Scale for the Assessment and Rating of Ataxia (Schmitz-Hubsch et al. 2006) was 1.7. Six patients presented with ischemic infarction within the SCA territory. Their mean age was 59.5 ± 21.3 years, mean time since lesion was 17.7 months, and their mean ataxia score was 3.2. Thus, the magnitude of ataxia was mild in both patient groups. A general survey of patients' clinical and lesion data is given in Table 1. The location and extent of cerebellar lesions was defined from magnetic resonance imaging (MRI) data sets, as summarized in Table 2. MRI revealed no extra-cerebellar lesions in any patient.

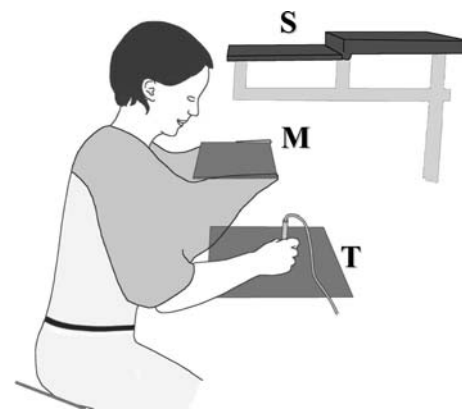


Fig. 1 Scheme of experimental apparatus with display screen (*S*), mirror (*M*), and digitizing tablet (*T*)

A group of 17 healthy, adult volunteers (mean age 54.6 ± 8.6 years; 8 females, 9 males) with no history of neurological disease served as controls. Their data have already been presented in our preceding study (Werner et al. 2008). All patients and controls were right-handed, and did not use any drugs affecting the nervous system. None of the subjects had prior experience in visuomotor research. The authors' local Ethics Committee had

approved the procedure of the experiment, and all subjects gave written informed consent.

Visuomotor adaptation task

As in our previous study (Werner et al. 2008), subjects sat in front of a digitising tablet holding a pen as shown in Fig. 1. They watched a computer screen through a horizontally mounted mirror that projected the image of the screen onto the tablet. The mirror and surrounding shrouds prevented the sight of the arm. A central starting dot and one of eight possible target dots appeared alternately on the screen. The starting dot remained on for 0.3–0.5 s, and was then replaced by one of the target dots, according to a random sequence. The targets were equally distributed on an imaginary circle of 10 cm radius about the centre, and each lit up for 2.0 s. All subjects were instructed to move the pen as accurately and quickly as possible from the starting dot to the target and back. The position of the digitising pen was registered (resolution 0.3 mm, 60 Hz), and displayed on the screen as a cursor to provide visual feedback about momentary hand position.

The experiment was subdivided into episodes of 30 s duration, separated by rest breaks of about 5 s. Within one episode, 6–12 targets were presented. If not stated otherwise, subjects pointed with their dominant, right hand. All were familiarized with the experimental set-up by performing one episode under veridical visual feedback, i.e., pen and cursor position coincided. Data registration began with a *baseline* phase of four episodes, again under veridical feedback, with the left hand used during the first of those episodes. The subsequent *adaptation* phase consisted of 20 episodes, in which visual feedback was rotated by -60° about the starting dot. After a 1-day to 1-week break¹ subjects returned and performed five episodes in a *retention* phase, once again under -60° rotated feedback. This was followed by two episodes of an *intermanual transfer* phase using the left hand, and one *refresh* episode using the right hand, again under rotated visual feedback. Finally came a *de-adaptation* phase of five episodes under veridical visual feedback. The whole experiment including instructions lasted about 20 min on the first, and about 10 min on the second day.

Even though all patients presented with unilateral lesions either in the right or left cerebellum, they all conducted the greatest part of the experiment with their dominant right hand. This is justified by the fact, that even for healthy subjects visuomotor adaptation with the right

hand is faster, independent of the subjects' handedness (Chase and Seidler 2008). Since we still had the possibility to analyse the effect of lesion laterality (see below), we chose to keep the task as practicable as possible for the cerebellar patients.

Data analysis

Subjects' responses were quantified as in our previous study (Werner et al. 2008). We determined the *initial error* of each movement as the angular difference between cursor and target direction 150 ms after movement onset, i.e., before feedback-based corrections could become effective. The median value of this error for each episode and subject was used for subsequent analyses. For further data reduction, we calculated the adaptation indicators

$$\text{adaptive improvement: } AI (^{\circ}) = 60 - B + A, \quad (1)$$

$$\text{adaptive retention: } AR (^{\circ}) = 60 - B + R, \quad (2)$$

$$\text{adaptive transfer: } AT (^{\circ}) = 60 - B + T, \quad (3)$$

$$\text{de-adaptation: } DA (^{\circ}) = D - B, \quad (4)$$

where B and A represent the mean initial error of the last three baseline and adaptation episodes, whereas R , T , and D represent the initial error of the first retention, transfer and de-adaptation episode. No attempt was made to quantify the amount of savings by comparing the adaptation and retention phases.

As in our previous study (Werner et al. 2008), we quantified subjects' motor performance as the standard deviation of initial errors during the baseline phase (response variability, RV), the coefficient of determination between initial errors and the difference between initial and final errors during the adaptation phase (online correction ability, CA), as well as the mean movement time (MT), reaction time (RT), and peak velocity (PV) across the adaptation phase.

For statistical analysis, we submitted the initial errors of the adaptation phase to analyses of variance (ANOVAs) with the within-factor Episode and the between-factor Group (levels: control/PICA/SCA). To compensate for heterogeneity of variances, we applied Huynh–Feldt-corrections when necessary. In addition we submitted each adaptation indicator and motor performance parameter to a one-factor ANOVA with the between-factor Group. Significant effects of Group were explored with Fisher LSD post hoc tests.

Again as in our previous study (Werner et al. 2008), we examined the relationship between cerebellar disease, motor performance, and adaptive success by partitioning the variance of each adaptation indicator. To this end we first calculated several multiple linear correlations. R_p^2 is

¹ The patients were also participating in a different study where mixed pause lengths were necessary. The results of our previous study show no effect of break length on retention, transfer and de-adaptation (Werner et al. 2008).

the multiple coefficient of determination between adaptation indicator and motor performance measures, R_G^2 is the simple coefficient of determination between adaptation indicator and Group (PICA/controls in a first step and SCA/controls in a second step), and R_{PG}^2 is the multiple coefficient of determination between adaptation indicator and Group *as well as* motor performance measures. With the help of those coefficients it is possible to calculate the variance that each adaptation indicator shares with motor performance measures (Var_P), with Group (Var_G), and with performance measures *and* Group jointly (Var_J). These shared variances are given by

$$\begin{aligned}\text{Var}_G &= R_{PG}^2 - R_P^2, \quad \text{Var}_J = R_G^2 + R_P^2 - R_{PG}^2, \\ \text{Var}_P &= R_{PG}^2 - R_G^2,\end{aligned}\quad (5)$$

For a more detailed explanation of this method, see, e.g., Bock and Girgenrath (2006).

Imaging data analysis

In the cerebellar patients, a 3D sagittal volume of the entire brain was acquired using a T1-weighted MPRAGE sequence (FOV = 256 mm, number of partitions = 160, voxel size = $1.00 \times 1.00 \times 1.00 \text{ mm}^3$, TR/TE = 2,400/4.38 ms, flip angle = 8°) on a Siemens Sonata 1.5 T MR scanner. Ischemic lesions were manually traced on axial, sagittal and coronal slices of the non-normalized 3D-MRI data set and saved as region of interest (ROI) using MRIcro software (<http://www.sph.sc.edu/comd/rorden/mricro.html>). Spatial normalization into standard proportional stereotaxic Montreal Neurological Institute (MNI) space was performed according to the masking technique described by Brett et al. (2001) using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>; Wellcome Department of Cognitive Neurology, London, UK). Based on the MNI spatial coordinates of cerebellar lesions the corresponding cerebellar lobules were defined with the help of 3D-MRI atlases of the cerebellum (Schmahmann et al. 2000) and the cerebellar

nuclei (Dimitrova et al. 2002). Lesions of vermis, paravermis and lateral hemispheres were considered separately (Schoch et al. 2004).

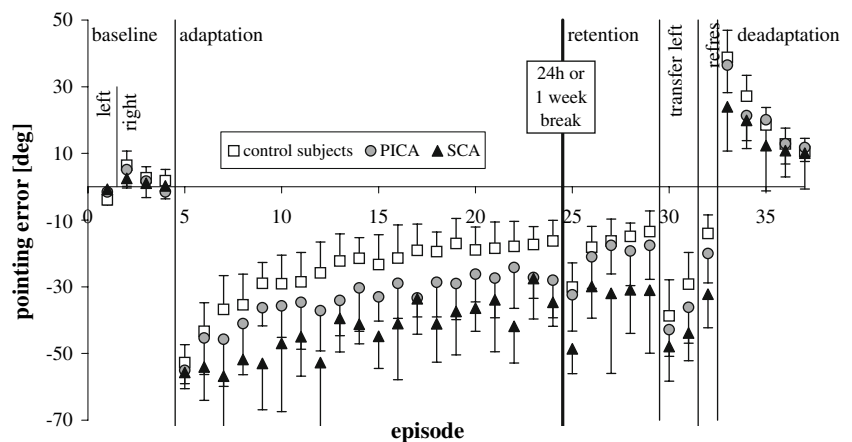
By performing a subtraction analysis (Karnath et al. 2002; Rorden et al. 2007) with the ROIs in MRICroN (<http://www.sph.sc.edu/comd/rorden/mricron/>), we were able to identify those cerebellar regions related to adaptation data (AI, AR, AT and DA). In a first step right-sided lesions were flipped to the left. Secondly, we assorted all patients into one subgroup with impaired AI, AR, AT or DA and one without impairment in AI, AR, AT or DA, respectively. The cut-off value for this classification was the mean value of all control subjects minus one standard deviation. The lesions for the impaired and unimpaired patients were added together, creating traditional overlap images showing the regions of mutual involvement. Thirdly we subtracted the overlap image of the unaffected patients from the impaired groups' overlap image. This was done for each adaptation variable separately. Our resulting images show regions which are commonly damaged in patients with affected AI, AR, AT or DA.

Results

Time course of adaptation

Figure 2 shows the mean initial error for each group and episode. During the baseline phase, initial errors were low for control subjects as well as for patients. At the beginning of adaptation phase, initial errors abruptly increased by a similar amount in all groups, and then gradually decrease again throughout the adaptation phase. This decrease was most pronounced and consistent in control subjects, less so in PICA patients, and least in SCA patients. These group differences persisted throughout the remaining experimental phases, except for the convergence of groups at the end of the de-adaptation phase. Initial de-adaptation errors

Fig. 2 Initial pointing error for all experimental episodes in SCA patients (*black*), PICA patients (*grey*), and controls (*white*). “Left” or “right” indicate episodes in which subjects used their left or right arm for pointing. *Symbols* represent across-subject means, and *bars* the pertinent standard deviations



abruptly increase without returning to baseline level within five episodes, thus showing that at least some learning has taken place in all groups.

In accordance with these observations, ANOVA of the adaptation phase yielded significant effects of Group ($F(2,29) = 18.38$; $p < 0.001$), Episode ($F(19,551) = 9.50$; $p < 0.001$) and their interaction ($F(19,551) = 18.99$; $p < 0.05$), and post hoc decomposition revealed significant differences between control subjects and PICA ($p < 0.01$), control subjects and SCA ($p < 0.001$), as well as PICA and SCA ($p < 0.05$). For the retention and transfer phase, ANOVA yielded significant effects of Group ($F(2,29) = 8.58$; $p < 0.01$, and $F(2,29) = 4.55$; $p < 0.05$, respectively), and Episode ($F(4,116) = 3.47$; $p < 0.001$, and $F(1,29) = 12.73$; $p < 0.01$, respectively). Post hoc analysis showed significant differences between controls and SCA ($p < 0.001$), as well as PICA and SCA ($p < 0.01$) during the retention phase, but only between controls and SCA ($p < 0.01$) during the transfer phase. ANOVA for the de-adaptation phase yielded significant effects of Episode ($F(4,116) = 3.37$; $p < 0.001$) and Group \times Episode ($F(4,116) = 6.74$; $p < 0.001$), with significant difference between controls and SCA ($p < 0.001$), and PICA and SCA ($p < 0.01$) in the first episode. Furthermore, comparing the last baseline with the first de-adaptation episode reveals significant differences for all groups (controls $t(16) = 15.009$; $p = 0.000$, PICA $t(8) = 10.573$; $p = 0.000$ and SCA $t(5) = -4.149$, $p = 0.009$), thus showing some aftereffect in all subjects.

To explore the role of lesion laterality, we submitted the initial errors of all experimental phases to an ANOVA with the within-factor Episode, and the between-factors Group (PICA/SCA) and Lesion Side (right/left). No significant effects including Lesion Side were yielded. Because all

patients were tested with the right hand, one may expect that adaptation was less impaired in patients with left-sided cerebellar lesions compared to right-sided lesions. Ataxia score of the right upper limb, however, was not significantly different from the left upper limb in SCA ($t(5) = -1.168$; $p = 0.296$) and PICA patients ($t(8) = -1.000$; $p = 0.347$).

Comparison of each adaptation indicator and motor performance parameter for PICA and SCA patients with either right or left sided lesions showed neither significant differences nor any trends. Note that our number of patients is small and a larger sample might lead to different results.

Overall adaptation and performance scores

One-way ANOVAs yielded significant effects of Group for the adaptation indicators AI ($F(2,29) = 12.12$; $p < 0.001$), AR ($F(2,29) = 9.73$; $p < 0.001$), and DA ($F(2,29) = 4.23$; $p < 0.05$), as well as for the performance parameters RT ($F(2,29) = 3.85$; $p < 0.05$), and MT ($F(2,29) = 7.14$; $p < 0.001$). The corresponding means are shown in Fig. 3, along with the outcome of post hoc analyses. For AT ($F(2,29) = 0.95$; $p = 0.40$), CA ($F(2,29) = 1.07$; $p = 0.36$), RV ($F(2,29) = 2.45$; $p = 0.10$), and PV ($F(2,29) = 1.66$; $p = 0.21$), the effect of Group did not reach statistical significance. For the performance measure RV we found an exceptionally large standard error in SCA patients as also shown in Fig. 3. The poorer adaptation as well as motor performance of the SCA group cannot be explained by a larger lesion size, since lesions were actually smaller in that group (SCA: 1.92 ± 1.82 cc; PICA: 14.40 ± 10.28 cc; $t(13) = -2.91$, $p < 0.05$). Nor can it be explained by a larger ataxia, since ataxia scores did not differ between groups ($t(13) = -1.14$, $p > 0.5$).

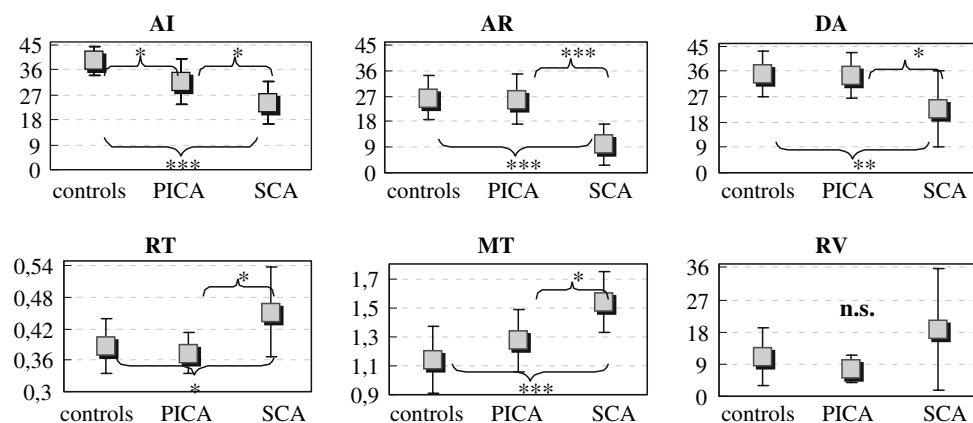


Fig. 3 Mean values and standard deviations for all three groups for AI, AR, DA, RT, MT, and RV. The adaptation indicators were calculated by $AI (^{\circ}) = 60 - B + A$, $AR (^{\circ}) = 60 - B + R$, $AT (^{\circ}) = 60 - B + T$ and $DA (^{\circ}) = D - B$, where B and A represent the mean initial error of the last three baseline and adaptation episodes,

whereas R , T , and D represent the initial error of the first retention, transfer and de-adaptation episode. ***, **, *, and n.s. indicate $p < 0.001$, $p < 0.01$, $p < 0.05$, and $p > 0.05$, respectively. Note that the values of the y-axis stand for pointing errors in ($^{\circ}$) (AI, AR, DA, RV) or for time in s (RT, MT)

Table 3 Results of multiple linear regression analyses for PICA/controls and SCA/controls

| (a) PICA | Var _G | Var _J | Var _P |
|----------|------------------|------------------|------------------|
| AI | 0.096 | 0.146 | 0.366*** |
| AR | 0.001 | 0.000 | 0.150 |
| AT | 0.073 | -0.062 | 0.197* |
| DA | 0.000 | 0.001 | 0.232* |
| (b) SCA | Var _G | Var _J | Var _P |
| AI | 0.049 | 0.523*** | 0.171* |
| AR | 0.021 | 0.467*** | 0.197* |
| AT | 0.015 | 0.059 | 0.137 |
| DA | 0.003 | 0.254* | 0.283** |

The total variance of each adaptation indicator was partitioned into a component Var_G shared with subject group, but not with motor performance, a component Var_J shared jointly with group and motor performance, and a component Var_P shared with motor performance alone. Symbols ***, **, and * indicate $p < 0.001$, $p < 0.01$, and $p < 0.05$, respectively, and the absence of a symbol indicates $p > 0.05$

Finding an impairment in AI and DA for SCA patients and in AI but not DA for the PICA patients does not necessarily show, that the pattern is statistically significant for AI and DA measures. Therefore, we performed a further ANOVA with the within-factor Adaptation measure (AI, DA), and the between-factor Group. This analysis yielded a significant effect of Group ($F(2,29) = 7.42$; $p < 0.01$) and a significant interaction Group \times Adaptation measure ($F(2,29) = 3.86$; $p < 0.05$). Post hoc analysis showed significant differences between PICA and controls ($p < 0.05$) as well as between SCA and controls ($p < 0.001$) for AI, and between SCA and controls ($p < 0.001$) and between SCA and PICA ($p < 0.01$) but not between PICA and controls ($p > 0.05$) for DA.

One might argue that our results might be confounded by the fact that some of the patients show involvement of interposed (IN) and/or dentate nucleus (DN). However, replicating the one-way ANOVAs with the factor Group (controls/nucleus involvement/no nucleus involvement) or Group (control/DN involvement/no DN involvement) yielded no significant differences between those two patient groups.

Partitioning of variances

When control subjects and PICA patients are considered, the variance of our four adaptation indicators can be partitioned into the components shown in Table 3a. Thus, no indicator shares significant variance with Group only, nor with Group and motor parameters jointly, but three indicators share significant variance with motor parameters only. The corresponding analysis for control subjects and

SCA patients is found in Table 3b. Again, no indicator shares significant variance with Group only, but three share significant variance with Group and motor parameters jointly, as well as with motor parameters only.

To determine whether some motor parameters are more important than others, we replicated the analyses in Fig. 3, leaving out one motor parameter at a time. It was impossible to exclude any parameter without reducing the number of significant effects, which suggests that all parameters contribute to our results.

Localisation of adaptation and motor performance

Figure 4 shows the results of the ROI subtraction analyses for all adaptation variables. The percentage subtraction plots show areas that are more commonly damaged in patients with abnormal AI, AR, AT and DA compared to patients with those variables within the normal range based on control data. The lightest red represents 70% affected group and darkest blue designates regions where there is an identical percent of affected and unaffected groups (0%). Cerebellar regions with the highest relative percentages of the number of ROIs in the impaired group were analysed based on MRI coordinates as outlined above.

Subtraction of the sum of the lesions of the subgroup with unimpaired AI from the patients with impaired AI revealed that affection of Crus I (green colour; MNI coordinates: $x = -18$ mm, $y = -82$ mm, $z = -36$ mm and $x = -18$ mm, $y = -80$ mm, $z = -38$ mm) was 36% and lobule V (green colour; coordinates: $x = -20$ mm, $y = -46$ mm, $z = -20$ mm) was 27% more common in the AI-impaired subgroup (Schmahmann et al. 1999). For AR only affection of lobule V (green colour; coordinates: $x = -20$ mm, $y = -46$ mm, $z = -20$ mm) was 38% more common in impaired patients. Furthermore, for the transfer to the other hand Crus II bordering Crus I (yellow colour; coordinates: $x = -10$ to -20 mm, $y = -82$ to -90 mm, $z = -32$ to -36 mm) was 50% more commonly affected in the impaired subgroup and for DA lobule VI (yellow colour; coordinates: $x = -20$ mm, $y = -56$ mm, $z = -24$ mm) was 50% more commonly affected in DA-impaired patients.

Discussion

The purpose of the present study was to further elucidate the role of the cerebellum in visuomotor adaptation. We quantified several measures of motor performance as well as of visuomotor adaptation, and found that compared to healthy controls, patients with PICA territory lesions had deficits of adaptive improvement while their adaptive aftereffects and motor performance were not reliably

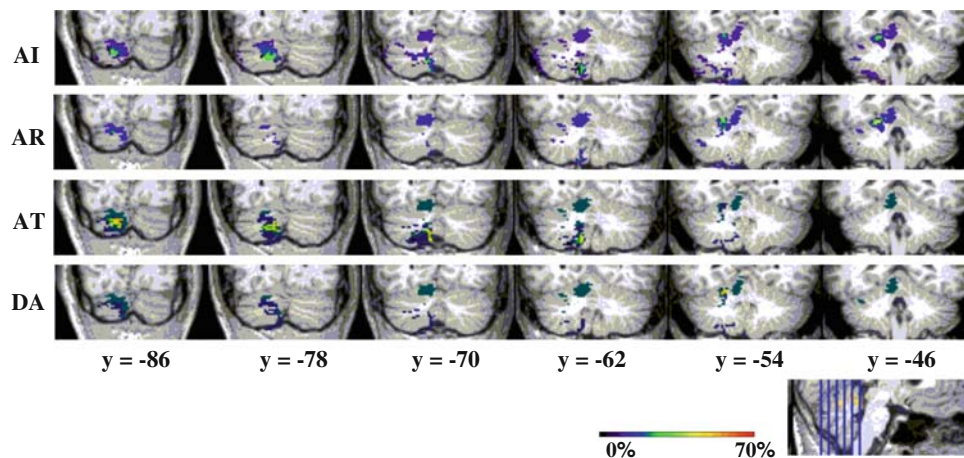


Fig. 4 MRI subtraction analysis comparing lesions in patients with impaired AI, AR, AT, or DA and unimpaired AI, AR, AT, or DA, respectively. The adaptation indicators were calculated by $AI (^{\circ}) = 60 - B + A$, $AR (^{\circ}) = 60 - B + R$, $AT (^{\circ}) = 60 - B + T$ and $DA (^{\circ}) = D - B$, where B and A represent the mean initial error

of the last three baseline and adaptation episodes, whereas R , T , and D represent the initial error of the first retention, transfer and de-adaptation episode. Coronal views are shown ($-y$ = mm behind anterior commissure). The *colour* indicates the level of percentage of a region to be more common lesioned in the impaired group

degraded. Our aftereffect tests, adaptive retention and de-adaptation, require newly developed sensory-to-motor transformation rules and thus indicate existing recalibration. Previous studies have shown a dissociation of adaptive improvement and aftereffect measures, for example dependent on age (Bock 2005) or on feedback source (Clower and Boussaoud 2000). Therefore, different underlying processes have been assumed. One might argue, that the de-adaptation measure must merely be the difference between the error of the last adaptation episode (with adaptation being achieved by strategic control or recalibration) minus the rotation magnitude (60°). This is true for the first de-adaptation movement. But already in the second movement, the subjects are cognitively aware of the change and must dismiss their previous strategy because it now becomes unsuccessful. Therefore, the first de-adaptation episode (about 15 movements) is dominated by recalibration (Clower and Boussaoud 2000; Bock 2005; McNay and Willingham 1998; Redding and Wallace 1996).

The pattern of our findings therefore suggests that adaptive recalibration remained largely intact in the PICA patients, while strategies like anticipations, associative stimulus–response pairings, and cognitive workaround schemes may be impaired. This would fit well with the observation that subjects with PICA territory lesions have problems on complex (Exner et al. 2004; Kalashnikova et al. 2005; Schmahmann and Sherman 1998) albeit not on simpler (Richter et al. 2007) cognitive tasks.

We further found that patients with SCA territory involvement had even more profound deficits of adaptive improvement, and were additionally impaired on adaptive aftereffects and motor performance. Also, we showed a

significant interaction for $AI/DA \times Group$ which confirms the assumption of a differentially impaired pattern for SCA and PICA patients. Following again the above line of reasoning, it appears that the SCA group in contrast to the PICA group indeed had deficits of adaptive recalibration. This finding fits well with a previous single-case study which also observed deficient adaptation effects and aftereffects in an SCA patient (Pisella et al. 2005), and with neuroimaging studies reporting adaptation-dependent neuronal activation in regions commonly supplied by the SCA but not the PICA territory. Furthermore, our findings are consistent with the results of a recent diffusion tensor imaging (DTI) study by Della-Maggiore et al. (2008). Here a positive correlation between the rate of adaptation and cerebellar white matter integrity was found in SCA regions. Also, our results are partly in line with the findings of Martin et al. (1996). Both studies agree that PICA patients show impaired adaptive improvement but intact motor performance. In our study, however, PICA patients were not impaired in measures of aftereffect, therefore, different to Martin et al. our results did not find impairment in true adaptation. Also, for SCA patients Martin et al. found normal adaptive improvement, deadaptation and motor performance in two subjects, and not measurable adaptation with substantial performance deficits in their third subject. At a more general level, the distinction between SCA- and PICA-related deficits in the present work is compatible with earlier research on other forms of motor learning: SCA but not PICA patients were found to be impaired on different types of eyeblink conditioning (Gerwig et al. 2003, 2005, 2006).

However, based on the present study alone, it cannot be directly differentiated between effects of strategic change

and recalibration. The assumption of a differential contribution of the SCA and PICA territory to strategic change and recalibration needs to be confirmed in future experiments in cerebellar patients including clear manipulations (e.g. see Mazzoni and Krakauer 2006).

Unlike both previous studies with patients with focal lesions (Martin et al. 1996; Pisella et al. 2005), we found no lateralization of the adaptation deficit to the lesioned side. That is, in our study both lesions ipsi- and contralateral to the tested hand appeared to result in deficits in adaptive improvement and recalibration. This is in accordance to imaging data showing activation of bilateral anterior cerebellar regions correlated to the transfer between different angles of rotation (Seidler and Noll 2008), to error correction (Imamizu et al. 2000), and to motor execution (Grafton et al. 2008). In our study, however, no comparison of the lesioned and non-lesioned side was made. Also because of the small sample size, we cannot exclude that deficits are more pronounced on the ipsilesional compared to the contralesional side in a larger group of patients with focal lesions.

To further scrutinize the interrelation between adaptation and motor performance, we determined the variance shared between each adaptation indicator and group only (Var_G), motor performance only (Var_P), and group jointly with motor performance (Var_J). Applying this approach to PICA patients and control subjects, we found that only Var_P , but not Var_G , was significant for most adaptation indicators, suggesting that regions outside of PICA territory are involved in motor performance which correlates with adaptive success. However, applying the same approach to SCA patients and controls revealed significant contributions of Var_J in addition to Var_P to the variances of adaptation variables. This can be interpreted as the involvement of SCA territory and extracerebellar brain regions in the monitoring and control of movements which correlates with adaptation. Confirming the outcome of our previous study (Werner et al. 2008), Var_G did not reach statistical significance in either data set, i.e., we found again no evidence for a cerebellar contribution to adaptation but *not* to motor performance. This, however, does not say that adaptation disorders are caused by motor performance deficits. Likewise, similar disorders may lead to both disordered adaptation and motor performance abnormalities, or, adaptation deficits may lead to motor performance deficits.

A subtraction analysis of MRI lesion data revealed that regions of the posterior lobe (Crus I) as well as regions of the anterior lobe (lobule V) show common overlap for disordered adaptive improvement. Crus I is commonly supplied by the SCA. However, variation exists and PICA territory can involve Crus I. In fact, in our study, in 7 of 9 PICA patients Crus I was affected, but only in 2 of 6 SCA patients. For visuomotor recalibration, however, lobules V

(anterior lobe) and VI (most superior part of the posterior lobe) were the most crucial lesion sites. In line with the results of our subtraction analysis only 3 of 9 PICA patients with Crus I involvement were impaired in AR and 2 of 9 patients in DA. This region of the superior cerebellum has been discussed in numerous imaging studies as important for the processing of performance errors (Diedrichsen et al. 2005; Grafton et al. 2008), for the transfer of adaptation (Seidler and Noll 2008), and as a storage site for internal models (Imamizu et al. 2000). A recent lesion study tested visuomotor adaptation in patients with cerebellar degeneration (Rabe et al. 2009) and found a significant negative correlation between the adaptation deficits and the degree of cerebellar atrophy in the intermediate zone of the posterior lobe. Since their adaptation measure includes aiming errors during adaptation phase as well as catch trials, it can be compared to both our AI and DA. For those variables we find an involvement of the more intermediate parts of lobules Crus I and VI (which are parts of the cerebellar posterior lobe) and are in accordance with the results in degenerative patients. For the transfer to the other hand subtraction analysis reveals an involvement of a more posterior region (Crus II bordering Crus I). This result indicates that the intermanual transfer might not indicate a deficit in recalibration in cerebellar patients but does require strategic control. Finally, our results cannot be explained by a difference in lesion size in the two patient groups. On the contrary, mean lesion size of our PICA patients was significantly larger than that of our SCA patients. This shows that the exact location of the lesion is more essential than mere size.

The present study as well as previous human cerebellar lesion studies (Deuschl et al. 1996; Gauthier et al. 1979; Maschke et al. 2004; Morton and Bastian 2004; Smith and Shadmehr 2005; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008) examined adaptation to sudden visuomotor perturbations. Animal cerebellar lesion studies suggest that abnormalities may be more marked following adaptation to gradual perturbations (Robertson and Miall 1999). It would be of interest to compare adaptation to gradual and sudden perturbation in future studies in cerebellar patients.

In conclusion, the present study confirms the importance of the cerebellum for visuomotor adaptation. While adaptive improvement was impaired in both PICA and SCA patient groups visuomotor recalibration seems to be located within the SCA territory especially lobules V and VI being of particular importance.

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