J Neurol (2007) 254:1193–1203
DOI 10.1007/s00415-006-0500-9

ORIGINAL COMMUNICATION

Cognitive functions in patients with MR-defined chronic focal cerebellar lesions

Stefanie Richter
Marcus Gerwig
Bakiye Aslan
Hans Wilhelm
Beate Schoch
Albena Dimitrova
Elke R. Gizewski
Wolfram Ziegler
Hans-Otto Karnath
Dagmar Timmann

Received: 8 August 2006
Received in revised form: 27 November 2006
Accepted: 28 November 2006
Published online: 22 March 2007

S. Richter, PhD · M. Gerwig · B. Aslan
H. Wilhelm · A. Dimitrova · D. Timmann
Dept. of Neurology
University of Duisburg-Essen
Hufelandstr. 55
45122 Essen, Germany

B. Schoch
Dept. Neurosurgery
University of Duisburg-Essen
Essen, Germany

E. R. Gizewski
Dept. Neuroradiology
University of Duisburg-Essen
Essen, Germany

W. Ziegler
EKN – Clinical Neuropsychology Research Group,
Dept. of Neuropsychology
City Hospital Bogenhausen
Munich, Germany

H.-O. Karnath · S. Richter, PhD (✉)
Center of Neurology
Neuropsychology Section
Hertie-Institute for Clinical Brain Research
University of Tuebingen
Hoppe-Seyler-Strasse 3
72076 Tübingen, Germany
Tel.: +49-7071/29-84080
Fax: +49-7071/29-5957
E-Mail: stefanie.richter@uni-tuebingen.de

Abstract The aim of the present study was to examine cognitive functions in a group of chronic patients with focal cerebellar lesions. Both effects of localization (anterior vs. posterior lobe) and side (left vs. right cerebellar hemisphere) were of interest. Fourteen patients with infarctions within the territory of the posterior inferior cerebellar artery (PICA) and seven patients with infarctions within the territory of the superior cerebellar artery (SCA) participated. The affected lobules and nuclei were assessed based on 3D MR imaging. The right cerebellar hemisphere was affected in eight PICA and two SCA patients, the left hemisphere in six PICA and four SCA patients. One SCA patient revealed a bilateral lesion. In order to study possible lateralization of functions, subjects performed a language task as well as standard neglect and extinction tests. Moreover, two tests of executive functions were applied. There were no significant group differences apart from a verbal fluency task, in which all cerebellar patients – but especially those with right-sided lesions – were impaired. Voxel-based lesion-symptom mapping (VLSM) revealed that a lesion of the right hemispheric lobule Crus II was associated with impaired performance in the verbal fluency task. In sum, the results showed preserved cognitive abilities in chronic cerebellar patients apart from impairments of verbal fluency in patients with right-cerebellar lesions. The latter findings are in line with the assumption that the right posterolateral cerebellar hemisphere supports functions associated with verbal fluency.

Key words cerebellum · language · visuo-spatial neglect · localization · lateralization

Introduction

A still growing number of brain-imaging and human lesion studies suggests an involvement of the cerebellum in various cognitive functions [7, 44]. Many studies supply evidence for a role of the cerebellum in language functions such as verb generation [13, 17, 35], verbal working memory [46], and verbal fluency [31, 50]. Likewise cerebellar involvement has been

described in visuospatial tasks. Cerebellar activation was found in brain-imaging studies examining line bisection [14, 15]. Patient studies revealed deficits in mental imagery [32], block design [26, 33], and figure drawing/copying [44]. Furthermore, deficits in tests of executive functions, such as the stroop test, Wisconsin card sorting test or reverse digit span (working memory) have been described in cerebellar patients [21, 26, 33, 44, 50]. The verbal fluency task is also often considered a test of executive functions and has been found to be impaired in cerebellar patients [44, 50].

There are, however, contradictory findings. Four studies searched for, but did not observe deficits in verb generation in cerebellar patients [16, 22, 37, 38]. Other studies failed to find effects of cerebellar lesions on visuospatial functions [9, 19, 20, 38]. Executive functions were preserved in cerebellar patients in the study of Globas and co-workers [19].

Differences in cerebellar lesion localization and extent may explain at least in part these contradictory findings in human lesion studies. Anatomical data suggest that the posterolateral parts of the cerebellar hemispheres and dentate nuclei, but not the anterior lobe and the more anterior parts of the dentate, may be involved in cognitive functions [30]. Studies in patients with focal cerebellar lesions, e.g., in patients with ischemic lesions of the superior and posterior inferior cerebellar artery (SCA and PICA), appear to be of particular interest.

Exner and co-workers [11] administered a set of standard neuropsychological tests to six patients with PICA infarctions, five patients with SCA infarctions and eleven matched control subjects. While SCA patients were virtually unimpaired, PICA patients revealed impairments mainly in the area of visuospatial working memory and episodic memory. In a study of Neau and others [33], however, no obvious differences in cognitive functions between patients with an infarction of the posterior inferior or superior cerebellar artery were found. Because the common SCA territory includes the anterior lobe (that is vermal and hemispheric lobules I–V) and lobules VI and Crus I of the posterior lobe as well as most parts of the cerebellar nuclei [5], cognitive dysfunctions in SCA patients with extended lesions may not be unexpected.

Because of the known cerebral lateralization of language and visuospatial functions and cerebellar projections to the contralateral cerebral hemispheres, it has been suggested that the right cerebellar hemisphere is involved in language functions whereas the left cerebellar hemisphere may be involved in visuospatial functions [15, 27, 43, 45]. According to this hypothesis both hemispheres may take part in executive functions, which may involve both verbal or visuospatial stimuli.

The aim of the present study was to examine language, visuospatial and executive functions in patients with SCA and PICA infarctions involving the posterior lobe to a differing degree. The affected lobules and nuclei were assessed based on 3D MR imaging. Behavioral data and individual MRI findings were analyzed using voxel-based lesion-symptom mapping (VLSM) [6, 10]. Both effects of cerebellar lesion localization and side were of interest.

Methods

Subjects

Twenty-one adults with a history of cerebellar stroke participated in the study (five female, 16 male; mean age 55.1 years ± 11.1 years, range 34–71 years). Two patients were left-handed, two ambidextrous, and all other patients right-handed based on the Edinburgh handedness inventory [34]. Educational level was distributed as follows: elementary school n = 13, junior high school n = 5, university entrance diploma n = 3.

Only subjects with lesions restricted to the cerebellum were included. Fourteen patients presented infarctions within the territory of the PICA, and seven infarctions within the territory of the SCA. The stroke dated back on average 46.7 ± 17.9 months, ranging from 17–96 months. Subjects underwent a standard neurological examination including the International Cooperative Ataxia Rating Scale (ICARS) [49]. One patient (Cb11) was taking antidepressants at the time of testing. None of the remaining patients was taking centrally acting medication when tested. Basic characteristics of patients with cerebellar lesions are summarized in Table 1.

Extent of surgical lesions was defined based on individual 3D MRI data sets. The procedure is described in detail in Gerwig and co-workers [18] and will not be reported here. The cerebellar lesion sites according to MRI analysis are summarized in Table 2 and illustrated in Fig. 1.

Twenty-five healthy subjects, seven women and 18 men, served as controls. Mean age was 54.4 ± 10.8 years (range 34–71 years). Two controls were left-handed, all others right-handed. Educational level was distributed as follows: elementary school n = 9, junior high school n = 5, vocational baccalaureat diploma n = 2, university entrance diploma n = 9. Healthy controls revealed no neurological or psychiatric diseases according to clinical history and neurological examination.

Written informed consent was obtained from all participants, who were recompensed for their travel expenses. The local committee of research ethics approved the study.

Experimental procedure

Language

The language testing involved a verb generation task with a naming and verb generation condition. The design was separated in two naming (1st and 6th block) and four verb generation blocks (2nd to 5th block) presenting always the same photographs of objects in random order.

In the naming condition, subjects were asked to name the pictured object (e.g., "car"). In the verb generation condition, subjects were instructed to say what one can do with the object, i.e.,

Table 1 Patient data

ID	Side of lesion	Age (years)	Sex	EHI-score	Edu	Onset of disease (m)	ICARS-score					
							Posture Gait	Upper limbs	Lower limbs	Speech	Oculo-motor	Total
PICA group												
Cb1	Right	60	M	100	ued	48	0	0	0	0	0	0
Cb2	Right	40	F	100	es	33	2	0	1	0	0	3
Cb3	Right	64	M	30	es	58	1	0	0	0	0	1
Cb4	Right	67	M	100	jhs	54	1	0	0	0	0	1
Cb5	Right	70	M	90	es	50	2	0	0	0	0	2
Cb6	Right	48	M	−10	jhs	53	0	0	0	0	0	0
Cb7	Right	42	M	100	es	23	0	0	0	0	0	0
Cb8	Right	71	M	100	es	96	1	0	2	0	1	4
Cb9	Left	42	F	100	jhs	54	0	0	0	0	0	0
Cb10	Left	55	F	100	es	48	2	0	1	0	0	3
Cb11	Left	54	M	100	es	47	1	0	0	0	0	1
Cb12	Left	65	M	100	jhs	74	1	0	1	0	0	2
Cb13	Left	51	M	100	ued	50	0	0	0	0	0	0
Cb14	Left	45	M	100	es	24	0	0	0	0	0	0
SCA group												
Cb15	Right	70	M	100	es	52	5	1	4	0	1	11
Cb16	Right	59	M	100	es	43	5	1	3	0	0	9
Cb17	Left	54	F	100	jhs	48	0	0	1	0	0	1
Cb18	Left	34	M	100	es	17	0	0	0	0	0	0
Cb19	Left	49	M	100	ued	54	0	0	0	0	0	0
Cb20	Left	50	M	100	es	27	11	3	7	3	3	24
Cb21	Both	68	M	100	es	28	3	3	3	0	0	9

M = male; F = female; EHI = Edinburgh Handedness Inventory, a score of 100 represents complete right-handedness, a score of 0 indicates an ambidextrous person and a score of −100 stands for complete left-handedness [34]; Edu = education; es = elementary school; jhs = junior high school; ued = university entrance diploma; ICARS-score = International cooperative ataxia rating scale [49], total score: maximum = 100, subscores: posture and gait (maximum = 34), upper limb (maximum = 36), lower limb (maximum = 16), speech (maximum = 8), oculomotor (maximum = 6)

to produce the corresponding verb ("drive"). There was a training block of five trials before the first naming block and a training block of nine trials before the first verb generation block using different objects than in the actual experiment.

The onsets of verbal responses (i.e., vocal reaction times) were measured. To this end, the responses were segmented with the help of a MATLAB-routine based on loudness functions [28, 37]. Moreover, we analyzed for each presented object the answers given by the subjects based on a thesaurus of the German language (http://www.wortschatz.uni-leipzig.de) [see also 37].

Visuospatial functions

Two standard neglect tests (letter cancellation, line bisection), a test of visual extinction, and subtest 9 (counting of surfaces) of the LPS ("Leistungsprüfserie"), were performed.

In the letter cancellation test by Weintraub and Mesulam [51], 30 target letters 'A' are distributed amid distractors on each side of a sheet of paper. Subjects were asked to cancel all of the targets. The test was finished when subjects approved twice that they had cancelled all target stimuli.

In the line bisection task, six sheets of paper with one line each were presented one after the other and the subject was asked to mark with a pen the middle of each line. For each trial the signed difference between the subject's estimation and the actual central point was calculated. Deviations to the right had a positive, those to the left a negative sign. Differences were averaged across the six trials and expressed as percentage of half the length of the line.

The extinction test was performed with the help of a custom-made computer program based on Flash-MX (FlashMXPro, Germany, Berlin). Geometrical figures were presented in random order either unilaterally in one half field (10 trials left, 10 trials right) or bilaterally in both half fields (10 trials). Stimuli were about 0.7° in size and presented for 180 ms about 4° left and/or right of a central fixation point. Subjects had to indicate if one stimulus or two stimuli were present.

In subtest 9 of the LPS (counting of surfaces), drawings of geometrical figures were shown from the side and above. Subjects were asked to mark the correct number of surfaces out of a multiple-choice list of answers within a presentation time of 3 minutes. Correct performance of this task necessitates correct mental imagery and mental processing of spatial structures and objects.

Executive functions

In subtest 6 of the LPS (verbal fluency) subjects were asked to write down as many terms with the same initial letter as possible over a time span of 60 seconds for each of three letters.

The identification of rules subtest (LPS 3) involved configurations of geometrical objects constructed according to a certain rule. The subject was asked to find out the rule by identifying the object that did not fit into the pattern given by the rest of the configuration. The presentation time was 5 minutes. In all three LPS subtests, number of correct answers during the presentation time was transformed into t-values on the basis of normative data given in the test manual [23].

Table 2 Cerebellar lesion site

Subject	Vermis	Hemisphere		Nuclei
		Paravermal x = ± 10–24 mm	Lateral Hemispheres x > +24 mm, x < −24 mm	
PICA group				
Right				
Cb1	r: VIIB, VIIIA/B	r: Crus II, VIIB, VIIIA/B	r: Crus II, VIIB	n.a.
Cb2	r: IX, VIIIA/B, VIIB, VIIAt	r: Crus II, VIIB, VIIIA/B		n.a.
Cb3		r: Crus II, VIIB, VIIIA/B, IX	r: Crus II, VIIB, VIIIA/B	n.a.
Cb4	r: VIIB, VIIIA/B, IX	r: VIIB, VIIIA/B, IX	r: VIIIA	n.a.
Cb5	l: IX r: VIIAt, VIIAf, VIIB, VIIIA/B, IX	r: Crus I/II, VIIB, VIIIA/B, IX	r: Crus I/II, VIIB, VIIIA/B	r: dentate
Cb6	l: VIIIA/B, IX r: VIIAt, VIIB, VIIIA/B,IX	r: Crus II, VIIB, VIIIA/B		r: dentate
Cb7	l: VIIB, VIIIA/B, IX r: VIIAt, VIIAf, VIIB, VIIIA/B, IX	r: Crus I/II, VIIB, VIIIA/B, IX	r: Crus I/II, VIIB,VIIIA/B	r: dentate
Cb8	l: VIIIA/B, IX r: VIIIA/B, IX	r: Crus II, VIIB, VIIIA/B, IX	r: Crus II, VIIB, VIIIA/B	r: dentate
Left				
Cb9	r: VIIAt, VIIB l: VIIAt, VIIB	l: Crus II, VIIB, VIIIA	l: Crus II, VIIB, VIIIA	n.a.
Cb10		l: Crus I/II		n.a.
Cb11	l: VIIAt , VIIB, VIIIA/B, IX	l: Crus I/II, VIIB, VIIIA/B	l: Crus I/II, VIIB, VIIIA	n.a.
Cb12	r: VIIAt, VIIB, VIIIA/B, IX l: VIIAt, VIIAf, VIIB, VIIIA/B, IX	l: Crus II, VIIB, VIIIA/B, IX	l: VIIB, VIIIA/B	l: dentate
Cb13	l: VIIAt, VIIB, VIIIA/B	l: Crus II, VIIB, VIIIA/B		l: dentate
Cb14	r: VIIIB, IX l: VIIB, VIIIA/B, IX	l: Crus II, VIIB, VIIIA/B, IX	l: Crus II, VIIB, VIIIA/B	l: dentate
SCA group				
Right				
Cb15		r: V, VI	r: V, VI	n.a.
Cb16	r: IV, V, VI Crus I	r: III, IV, V, VI, Crus I	r: IV, V, VI, Crus I	r: interposed r: dentate
Left				
Cb17		l: IV, V, VI, Crus I	l: VI, Crus I	n.a.
Cb18		l: IV, V, VI	l: V, VI	n.a.
Cb19	l: III	l: IV, V, VI	l: VI	l: interposed
Cb20	l: IV, V	l: V, VI	l: VI	l: interposed l: dentate
Bilateral				
Cb21		r: V, VI	r: VI, Crus I l: Crus I	r: interposed r: dentate

r = right side, l = left side; interposed = interposed nucleus, dentate = dentate nucleus; n.a. = not affeced

Results

Language

Reaction time in the verb generation blocks

Figure 2A shows the means and standard deviations of the reaction times of each of the 16 trials in the six subsequent blocks for the PICA and SCA patients as well as the controls. The first and the last block are naming blocks, the second to fifth block are verb generation blocks.

In all groups reaction times decreased with a similar gradient over the four blocks of the verb generation task. Analysis of variance with Localization (PICA vs. SCA vs. controls) as between-subjects factor and Block as within-subject factor revealed a significant effect of Block ($F_{2,100}$ with Greenhouse Geisser correction of degrees of freedom; $p < 0.0001$), but no significant Localization effect ($F_{2,43}$; $p = 0.348$) or Block by Localization interaction ($F_{5,100}$; $p = 0.770$).

Figure 2B shows the reaction times of the patients with right-sided lesions, left-sided lesions and controls. In all groups, reaction time was reduced across blocks. Analysis of variance with Side (right vs. left vs. controls) as between-subjects factor and Block as within-subject factor revealed a significant effect of Block ($F_{2,96}$; $p < 0.0001$), but no significant side effect ($F_{2,42}$; $p = 0.312$) or Block by Side interaction ($F_{5,96}$; $p = 0.440$).

Visuospatial functions

Cancellation and extinction tasks

None of the subjects showed spatial neglect, i.e., had more than five omissions on the left side in the letter

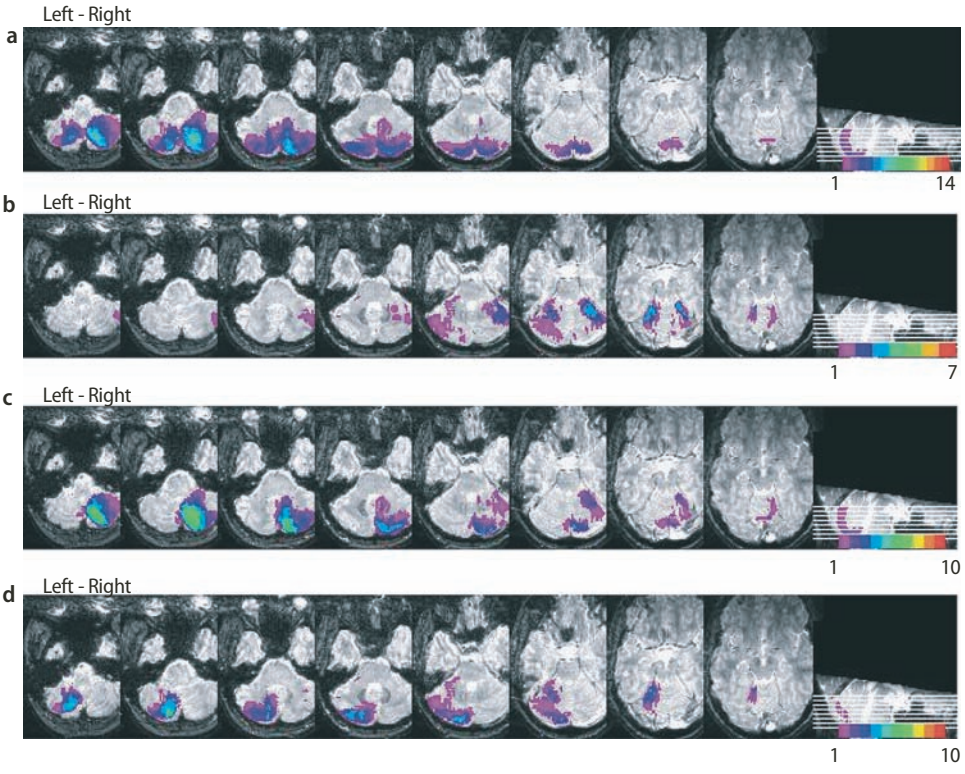

Fig. 1 Individual lesions in patients with PICA infarction (**A**), SCA infarction (**B**), right-sided (**C**) and left-sided lesions (**D**) superimposed on horizontal MR sections of a healthy adult brain. The color scale indicates number of overlaying ROIs from purple (n = 1) to red (n = 14 in PICA infarction, n = 7 in SCA infarction, and n = 10 in left- and right-sided lesions). Ri = right, Le = left

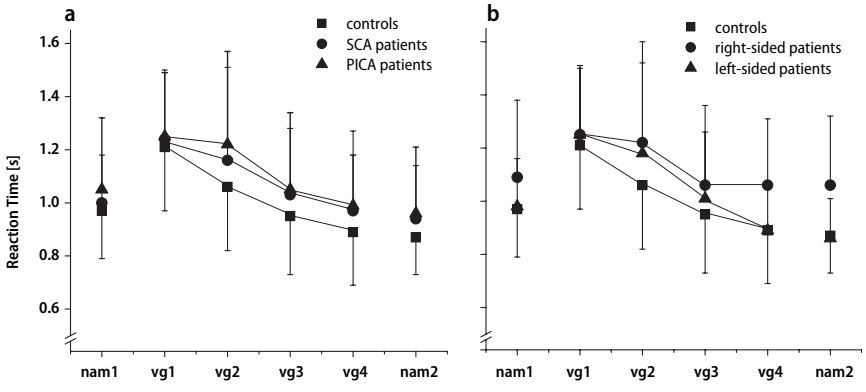

Fig. 2 (**A**) Means and standard deviations of the reaction times [s] across the 16 trials in the six subsequent blocks for the cerebellar subgroups with PICA infarctions, SCA infarctions and controls. (**B**) Means and standard deviations of the reaction times [s] for the cerebellar subgroups with right- and left-sided infarctions and controls. The first and the last block are naming blocks (nam1, nam2), the second to fifth block are verb generation blocks (vg1–vg4)

cancellation task [51]. Two patients with a right-sided (Cb4) and a left-sided PICA-infarction (Cb10) made one error on the critical left side as did one control (Cb20). The left-sided PICA patient (Cb10) made two more errors on the right.

Visual extinction is diagnosed if a subject fails to perceive the left stimulus during bilateral stimulation in more than 50% of the trials while the same stimuli are reported at least 90% correctly with unilateral stimulus presentation [25]. In the present study, each subject perceived 90% or more of the stimuli correctly in unilateral trials. Moreover, no relevant detection errors were made in bilateral trials in patients and controls (percentage correct ≥80%) except from one patient with a right-sided SCA infarction (Cb15), who made five errors on the right and two on the left.

Results of the cancellation and extinction tasks are presented in Table 3. No statistics were computed for these tests because performance was nearly constant in all groups.

Line bisection

All patients and controls tended to define the middle of the line rightward from the actual middle [PICA patients (n = 14): 1.7 ± 3.3%, SCA patients (n = 7): 1.1 ± 5.3%, controls (n = 25): 0.9 ± 3.1%]. Non-

Table 3 Means ± standard deviations in visuospatial tasks in patients' subgroups and controls

		PICA patients	SCA patients	Right-sided patient	Left-sided patients	Controls
Letter cancellation	Percentage targets found on the left side	99.5 ± 1.2	100 ± 0	99.7 ± 1.1	99.7 ± 1.1	100 ± 0
	Percentage targets found on the right side	99.5 ± 1.8	100 ± 0	100 ± 0	99.3 ± 2.1	99.9 ± 0.7
Extinction	Percentage detected on the left – unilateral	99.3 ± 2.7	97.1 ± 4.9	99.0 ± 3.2	99.0 ± 3.2	100 ± 0
	Percentage detected on the left – bilateral	98.6 ± 5.3	94.3 ± 9.8	96.0 ± 8.4	100 ± 0	100 ± 0
	Percentage detected on the right – unilateral	99.3 ± 2.7	100 ± 0	99.0 ± 3.2	100 ± 0	99.2 ± 2.8
	Percentage detected on the right – bilateral	98.6 ± 3.6	92.9 ± 18.9	94.0 ± 15.8	99.0 ± 3.2	99.2 ± 2.8

parametric statistical analysis (Kruskal–Wallis test, df = 2) comparing PICA and SCA patients with controls was not significant (p = 0.750). The same was true for the comparison of right-sided patients (n = 10; 0.5 ± 4.1%), left-sided patients (n = 10;1.9 ± 3.6%) and controls (n = 25; 0.9 ± 3.1%; p = 0.664) with a Kruskal–Wallis test (df = 2). Please note that the bilateral SCA patient was generally excluded from the right-left comparison.

Counting of surfaces

In subtest 9 of the LPS, mean t-value ranged between 50 and 60 in all groups. Accordingly, a Kruskal–Wallis test revealed no statistically significant localization effect (p = 0.578; PICA patients: 53.9 ± 11.2 vs. SCA patients: 52.3 ± 12.1 vs. controls: 56.4 ± 10.0). The same was true for the side comparison (p = 0.111; right-sided patients: 49.2 ± 9.8 vs. left-sided patients: 58.4 ± 11.5 vs. controls: 56.4 ± 10.0).

Executive functions

Identification of rules

Average t-values in subtest 3 of the LPS were in the normal range, i.e., about 50, for PICA patients (50.7 ± 8.8), as well as SCA patients (52.0 ± 6.4) and controls (54.4 ± 6.7). Thus, a Kruskal–Wallis test resulted in a non-significant localization effect (p = 0.531). Differences between average t-values were also not statistically significant (p = 0.266) between right-sided patients (49.6 ± 6.9), left-sided patients (54.1 ± 7.0), and controls (54.4 ± 6.7).

Verbal fluency

In the verbal fluency task, average t-values were smaller in PICA (35.4 ± 7.5) and SCA patients (36.0 ± 6.6) than in controls (44.0 ± 6.6) (see Fig. 3). Accordingly, a Kruskal–Wallis test revealed a significant localization effect (p = 0.002). Post-hoc tests (Mann–Whitney tests) further showed that both SCA patients (p = 0.018) and PICA patients (p = 0.002) significantly differed from controls. The side of the lesion also had a significant effect on performance (p < 0.0001). Post-hoc analyses (Mann–Whitney tests) showed that while right-sided patients (32.8 ± 5.2) significantly differed from controls (44.0 ± 6.6; p < 0.0001), left-sided patients (39.3 ± 7.1) did not (p = 0.133).

To control for possible age effects, we performed separate Mann–Whitney tests between PICA- SCA-, right-sided, and left-sided patients and controls. For each patient in the four subgroups, just one control was selected whose age corresponded with that of the patient as exactly as possible. The results were the

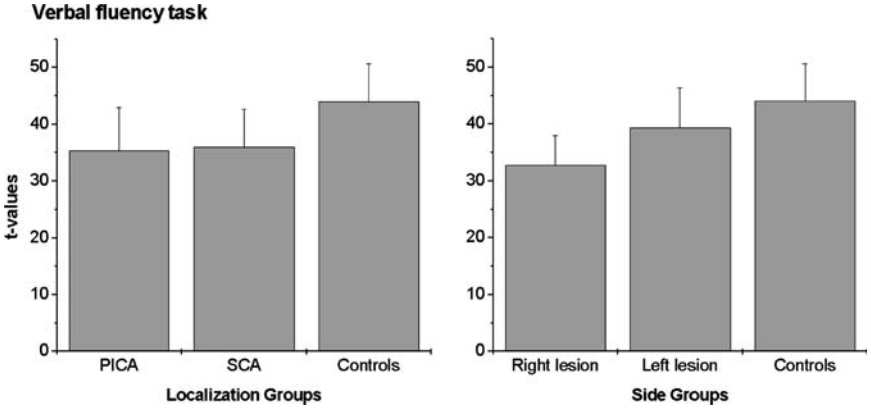

Fig. 3 Means and standard deviations of t-values in the verbal fluency task. Average t-values were smaller in PICA and SCA patients than in controls (p = 0.002; Kruskal–Wallis test). Both SCA patients (p = 0.018) and PICA patients (p = 0.002) significantly differed from controls (Mann–Whitney tests). The side of the lesion also had a significant effect on performance (p < 0.0001). Right-sided patients significantly differed from controls (p < 0.0001), left-sided patients did not (p = 0.133)

same as in the main analysis, i.e., the differences found there are not age-based.

Speech rate analysis

To account for the effects of speech motor deficits on performance in the verbal fluency task, non-parametric (Spearman-Rho) correlations were computed with syllable durations (i.e., speech rate) in a speech motor task.

To assess speech rate, subjects were asked to repeat six consonant–vowel syllables as fast and as regularly as possible. Measurement of syllable durations was based on a syllable-segmentation algorithm operating on loudness contours of the speech signal. For more detailed information see [29, 39].

Syllable durations were only slightly prolonged in patients compared to controls (PICA-patients: 186.3 ± 37.7, SCA-patients: 185.9 ± 46.4, controls: 178.6 ± 32.4). Accordingly, a Kruskal–Wallis test revealed no significant localization effect ($p = 0.910$). Similarly, the side effect was not significant ($p = 0.368$; right-sided patients: 201.5 ± 44.7, left-sided patients: 171.1 ± 31.1, controls: 178.6 ± 32.4).

In the patient group there was no significant correlation between speech rate and t-value in the verbal fluency task ($r = -0.236$, $p = 0.302$). In contrast, in controls, speech rate and t-values in the verbal fluency task correlated significantly ($r = -0.411$, $p = 0.041$).

Voxel-based lesion-symptom mapping

Voxel-based lesion-symptom mapping [6] is valuable to analyze the relationship between brain lesion and behavioral performance on a voxel-by-voxel basis without the need to group patients by behavioral cutoffs.

However, this can only be done if the patients' performance is obtained in the same stage of recovery [42]. In fact, this was the case for the present sample. Patients were tested on the average 46.7 ± 17.9 month after the lesion, i.e., all patients were in a chronic stage. ROIs were reconstructed onto templates and entered the analysis along with the results of the behavioral data. Each voxel was $2 \times 2 \times 2$ mm^2 in size and contained a lesion or was lesion-free. A *t*-test ($p = 0.05$, one-tailed) was conducted at each voxel comparing behavioral data in subjects with and without a lesion of that voxel. Statistical maps with Bonferroni-corrected p-values, calculated according to the formula −log(p), were plotted on a standardized template (see Fig. 4).

Most importantly, VLSM mapping of t-values in the verbal fluency task revealed a statistically significant area ($p \leq 0.05$) within posterolateral parts of the cerebellum, i.e., the right paravermal and hemispheric lobule Crus II (green area in Fig. 4A, x = 16–36 mm, y = −76 to −90 mm, z = −36 to −48 mm). There was a second right-sided statistically significant area ($p \leq 0.05$) consisting of vermal and paravermal white matter including right interposed and dentate nucleus and lobule IX and X (x = 4 to 20 mm, y = −42 to −60 mm, z = −34 to −70 mm).

Moreover, cerebellar lesion sites were related to speech motor variables. VLSM of speech rate revealed the smallest p-value (≤0.05) in the left superior cerebellum (green area in Fig. 4B). This region included vermal and paravermal lobule VI and vermal lobule VIIAf (x = −6 to −16 mm, y = −70 to −86 mm,

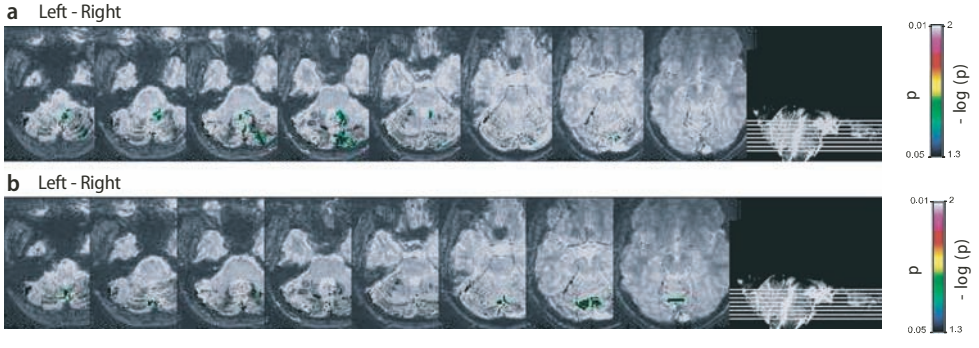

Fig. 4 (**A**) VLSM mapping for t-values in the verbal fluency task. Statistically significant areas were found within right paravermal and hemispheric lobule CRII (x = 16–36 mm, y = −76 to −90 mm, z = −36 to −48 mm) (green, $p \leq 0.05$), right vermal and paravermal white matter including interposed nucleus, vermal lobule IX/X, parts of right dentate nucleus and lobule IX (green, $p \leq 0.05$) (x = 4–20 mm, y = −42 to −60 mm, z = −34 to −70 mm). (**B**) VLSM mapping for syllable durations in the syllable repetition task. Significant areas ($p \leq 0.05$, green) were found in the left vermal lobules VI/VIIAf and paravermal lobule VI (x = −6 to −16 mm, y = −70 to −86 mm, z = −14 to −28 mm), vermal lobules VIIB/VIIIA (x = 0 to −8 mm, y = −56 to −68 mm, z = −48 to −54 mm), right vermal and paravermal lobule V/VI (x = 0–14 mm, y = −66 to −78 mm, z = −16 to −26 mm), and hemispheric lobule CR I (x = 36–46 mm, y = −74 to −84 mm, z = −32 to −40 mm). Ri = right, Le = left

z = −14 to −28 mm). A small statistically significant area in the posterior cerebellum enclosing vermal lobules VIIB and VIIIA (x = 0 to −8 mm, y = −56 to −68 mm, z = −48 to −54 mm) was found as well as a statistically significant ($p \leq 0.05$) region in right vermal and paravermal lobule V and VI (x = 0 to 14 mm, y = −66 to −78 mm, z = −16 to −26 mm). Finally, there was a small critical hemispheric region in right lobule Crus I (x = 36 to 46 mm, y = −74 to −84 mm, z = −32 to −40 mm).

Discussion

In all but one of the cognitive tasks applied here no significant differences between PICA patients, SCA patients, and controls were found. Similarly, the side of the lesion had no significant effect on performance. The only exception was the verbal fluency task, in which a significant difference between both patient groups and controls was observed. Patients with right-sided cerebellar lesions performed worse than patients with left-sided lesions, who did not significantly differ from controls. Moreover, VLSM revealed a correlation between lesions including parts of the right posterolateral cerebellar hemisphere (that is Crus II) and impaired verbal fluency. These findings support the hypothesis of an involvement of the right posterolateral cerebellar hemisphere in verbal fluency.

Verbal functions

In accordance with previous results, no significant group differences were found in the verb generation task. In the study of Helmuth and others [22], a group of adult chronic patients were unimpaired in the verb generation task. Our group found preserved verb generation in patients with cerebellar atrophy [37] and in children and adolescents with acute and chronic focal cerebellar lesion after tumor resection [16, 38]. It has to be noted, however, that there is also evidence for impaired learning and/or quality of answers in adult cerebellar subjects [12, 13].

In the present study cerebellar patients – especially those with right-sided lesions – were impaired in a verbal fluency task. Right cerebellar involvement in verbal fluency has been implicated both in lesion [31] and functional brain imaging studies [24] and could be interpreted to result from a deficit in verbal working memory. This is because after having retrieved words from memory, the subject has to keep in mind which words have already been produced. Verbal working memory may be impaired in cerebellar patients for different reasons. First, disturbances of motor function affecting articulation may reduce subvocal rehearsal [2, 3]. Functional magnetic resonance imaging studies using overt and covert speech production tasks showed that the hemodynamic response associated with internal speech was found in the superior paravermal right cerebellum, i.e., lobule HVI and Crus I [4, 40]. In the present study, speech rate was indeed related to lesions of the superior cerebellum, i.e., vermal and paravermal lobule VI and hemispheric lobule Crus I. However, there was no significant correlation between speech rate and performance in the verbal fluency task in cerebellar patients. Though the missing correlation may be due to small sample size, results of a lesion study by Ravizza and others [36] suggested that the cerebellum might contribute to verbal working memory during the initial phonological encoding and/or by strengthening memory traces rather than by fundamentally subserving covert articulatory rehearsal.

Results of a study by Chen and Desmond [8] show that the cerebellum may also be part of a phonological storage system. In their fMRI-study, two cerebellar-cerebral networks were identified. The "articulatory control system" involved the superior cerebellar hemispheres (VI/Crus I) bilaterally and the frontal cerebral cortex. It was active both in a working memory and a motoric rehearsal task. Activations of the "phonological storage system" were unique to verbal working memory and involved the right inferior cerebellar hemisphere (VIIB) and the parietal cerebral cortex.

In the present study, VLSM showed a significant correlation between performance in the verbal fluency task and lesions of the right posterolateral hemisphere within Crus II. These findings are in accordance with the notion that posterolateral parts of the cerebellar hemispheres and dentate nuclei may be involved in tasks accessing verbal working memory independent of impairment in covert articulation [11, 30].

However, tests of executive functions may not only be impaired due to deficits in verbal working memory. In their review of frontal lobe functions, Smith and Jonides [47] make a distinction between storage functions (phonological buffer, subvocal rehearsal) and five executive processes ("attention and inhibition", "task management", "planning", "monitoring" and "coding"). Successful performance in the verbal fluency task may not only require a functioning verbal working memory, but also preserved attention and inhibition (not naming words twice) or task management (switching of the initial letters of the words to be produced). In previous studies, in which cerebellar patients were impaired, executive functions were assessed by means of the stroop test (attention and inhibition), the Wisconsin card sorting test (task management) or reverse digit span (coding, moni-

toring) [21, 26, 33, 44, 50]. Our second test of executive function, which measured the ability to detect rules, i.e., cogitation and logical reasoning, revealed no significant group differences.

Finally, an alternative explanation has to be considered. The verbal fluency task used in the present study required a timed written response. Below-average performance in the verbal fluency task was not correlated with upper limb ataxia score or performance in the Archimedes spiral drawing task. Furthermore, none of the PICA patients showed any signs of upper limb ataxia. However, it is likely that the ICARS score is not sensitive enough to assess disorders in writing. Therefore influence of upper limb ataxia on results in the verbal fluency task cannot be excluded.

Visuospatial functions

Two previous group studies could associate visuospatial deficits with left-sided cerebellar lesions [41, 45]. The assumption of more pronounced deficits in left-sided patients was not supported by the results of the present study. In addition, there was no indication that patients with PICA infarctions were more severely impaired than patients with SCA infarctions. Visuospatial functions as measured by the letter cancellation, line bisection, extinction and LPS task were generally preserved in the present patients.

In the letter cancellation task number of missed targets was small both in patients and controls and not a single subject missed more than one left-sided target. Moreover, cerebellar patients perceived almost all stimuli in the extinction task apart from one patient with a right-sided SCA infarction (Cb15). There was no effect of lesion localization (PICA vs. SCA) or lesion side on performance in the LPS subtest "counting of surfaces". Finally, there was a tendency of left-sided patients to define the middle of the line more to the right of the veridical center compared to right-sided patients and controls. However, deviations were very small in all groups and analyses revealed no statistically significant differences.

The present results are in accordance with a previous study of our group in children and adolescents with chronic cerebellar lesions [38] using neglect and extinction tasks. In contrast to the present findings, in the study by Aarsen and co-workers [1] deficits in line bisection were found in children after surgery for cerebellar astrozytoma. Significant correlations between severity of preoperative hydrocephalus and visual-spatial skills were found. That is, raised intracranial pressure, which was absent in our patient group, may be an important factor. Differences in age and lesion location may also play a role.

Other studies showing visuospatial deficits used more complex tasks, i.e., block design [21, 26] or copying and recall of the Rey-Osterrieth complex figure [21, 44, 45, 48]. Comparison with the present tasks is therefore restricted, except for the "counting of surfaces" test, given that it requires mental imagery and mental processing of spatial structures and objects.

Conclusion

All but one of the verbal, visuospatial and executive functions examined here were preserved in cerebellar patients with chronic lesions. Because the number of subjects in each subgroup was limited it cannot be excluded that small differences become significant in larger patient populations. Significant impairment was found in a verbal fluency task only for patients with right-sided cerebellar lesions. Findings agree with the hypothesis that the right posterolateral cerebellar hemisphere is involved in tasks related to verbal fluency.

Acknowledgements We like to thank the participating patients and controls for their time and effort. The study was supported by a grant of the Deutsche Forschungsgemeinschaft (DFG Ti 239/5-2).

References

1. Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE (2004) Long-term sequelae in children after cerebellar astrocytoma surgery. Neurology 62(8):1311–1316
2. Ackermann H, Hertrich I, Hehr T (1995) Oral diadochokinesis in neurological dysarthrias. Folia Phoniatr Logop 47(1):15–23
3. Ackermann H, Mathiak K, Ivry RB (2004) Temporal organization of "internal speech" as a basis for cerebellar modulation of cognitive functions. Behav Cogn Neurosci Rev 3(1):14–22
4. Ackermann H, Wildgruber D, Daum I, Grodd W (1998) Does the cerebellum contribute to cognitive aspects of speech production? A functional magnetic resonance imaging (fMRI) study in humans. Neurosci Lett 247:187–190
5. Amarenco P (1991) The spectrum of cerebellar infarctions. Neurology 41(7):973–979

6. Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, Dronkers NF (2003) Voxel-based lesion-symptom mapping. Nat Neurosci 6(5):448–450
7. Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12(1):1–47
8. Chen SH, Desmond JE (2005) Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. Neuroimage 24(2):332–338
9. Dimitrov M, Grafman J, Kosseff P, Wachs J, Always D, Higgins J, Litvan I, Lou JS, Hallett M (1996) Preserved cognitive processes in cerebellar degeneration. Behav Brain Res 79(1–2):131–135
10. Dronkers NF, Wilkins DP, Van Valin RD, Jr Redfern BB, Jaeger JJ (2004) Lesion analysis of the brain areas involved in language comprehension. Cognition 92(1–2):145–177
11. Exner C, Weniger G, Irle E (2004) Cerebellar lesions in the PICA but not SCA territory impair cognition. Neurology 63:2132–2135
12. Fabbro F, Tavano A, Corti S, Bresolin N, De Fabritiis P, Borgatti R (2004) Long-term neuropsychological deficits after cerebellar infarctions in two young adult twins. Neuropsychologia 42(4):536–545
13. Fiez JA, Petersen SE, Cheney MK, Raichle ME (1992) Impaired non-motor learning and error detection associated with cerebellar damage A single case study. Brain 115(Pt1):155–178
14. Fink GR, Marshall JC, Shah NJ, Weiss PH, Halligan PW, Grosse-Ruyken M, Ziemons K, Zilles K, Freund HJ (2000) Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. Neurology 54(6):1324–1331
15. Fink GR, Marshall JC, Weiss PH, Zilles K (2001) The neural basis of vertical and horizontal line bisection judgements: an fMRI study of normal volunteers. Neuroimage 14(12):59–67
16. Frank B, Schoch B, Hein-Kropp C, Dimitrova A, Hovel M, Ziegler W, Gizewski ER, Timmann D (2006) Verb generation in children and adolescents with acute cerebellar lesions. Neuropsychologia [Epub ahead of print]
17. Gebhart A, Petersen S, Thach WT (2000) Evidence for functional lateralization of language operations to the right posterior cerebellum. Soc Neurosci Abstr 26:1246
18. Gerwig M, Dimitrova A, Kolb FP, Maschke M, Brol B, Kunnel A, Boring D, Thilmann AF, Forsting M, Diener HC, Timmann D (2003) Comparison of eyeblink conditioning in patients with superior and posterior inferior cerebellar lesions. Brain 126(Pt 1):71–94
19. Globas C, Bosch S, Zuhlke Ch, Daum I, Dichgans J, Burk K (2003) The cerebellum and cognition. Intellectual function in spinocerebellar ataxia type 6 (SCA6). J Neurol 250(12):1482–1487
20. Gomez Beldarrain M, Garcia-Monco JC, Quintana JM, Llorens V, Rodeno E (1997) Diaschisis and neuropsychological performance after cerebellar stroke. Eur Neurol 37(2):82–89
21. Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM (2004) Evidence for distinct cognitive deficits after focal cerebellar lesions. J Neurol Neurosurg Psychiatry 75(11):1524–1531
22. Helmuth LL, Ivry RB, Shimizu N (1997) Preserved performance by cerebellar patients on tests of word generation discrimination learning and attention. Learn Mem 3(6):456–474
23. Horn W (1983) Leistungsprüfsystem (LPS) Handanweisung (2 erweiterte und verbesserte Auflage). Hogrefe, Göttingen
24. Hubrich-Ungureanu P, Kaemmerer N, Henn FA, Braus DF (2005) Lateralized organization of the cerebellum in a silent verbal fluency task: a functional magnetic resonance imaging study in healthy volunteers. Neurosci Lett 319(2):91–94
25. Karnath H-O, Himmelbach M, Küker W (2003) The cortical substrate of visual extinction. Neuroreport 14(3):437–442
26. Malm J, Kristensen B, Karlsson T, Carlberg B, Fagerlund M, Olsson T (1998) Cognitive impairment in young adults with infratentorial infarcts. Neurology 51:433–440
27. Marien P, Engelborghs S, Fabbro F, De Deyn PP (2001) The lateralized linguistic cerebellum: a review and a new hypothesis. Brain Lang 79(3):580–600
28. Merk M (2002) Entwicklung und Implementierung PC-gestützter akustischer Analyseverfahren für die klinische Diagnostik neurogener Sprechstörungen. Dissertation Universität der Bundeswehr, München
29. Merk M, Ziegler W (1999) MoDiaS – A PC-based system for routine acoustic speech analysis of neurogenic speech disorders. In: Maasen B, Groenen P (eds) Pathologies of speech and language. Advances in clinical phonetics and linguistics. Whurr, London, pp 315–321
30. Middleton FA, Strick PL (2001) Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 21(2):700–712
31. Molinari M, Leggio MG, Silveri MC (1997) Verbal fluency and agrammatism. Int Rev Neurobiol 41:325–339
32. Molinari M, Petrosini L, Misciagna S, Leggio MG (2004) Visuospatial abilities in cerebellar disorders. J Neurol Neurosurg Psychiatry 75(2):235–240
33. Neau JP, Arroyo-Anllo E, Bonnaud V, Ingrand P, Gil R (2000) Neuropsychological disturbances in cerebellar infarcts. Acta Neurol Scand 102:363–370
34. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1:97–113
35. Petersen SE, Fox PT, Posner ML, Mintun M, Raichle ME (1989) Positron emission tomographic studies of the processing of single words. J Cogn Neurosci 1:153–170
36. Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA (2006) Cerebellar damage produces selective deficits in verbal working memory. Brain 129(Pt 2):306–320
37. Richter S, Kaiser O, Hein-Kropp C, Dimitrova A, Gizewski E, Beck A, Aurich V, Ziegler W, Timmann D (2004) Preserved verb generation in patients with cerebellar atrophy. Neuropsychologia 42(9):1235–1246
38. Richter S, Schoch B, Kaiser O, Groetschel H, Hein-Kropp C, Maschke M, Dimitrova A, Gizewski E, Ziegler W, Karnath HO, Timmann D (2005) Children and adolescents with chronic cerebellar lesions show no clinically relevant signs of aphasia or neglect. J Neurophysiol 94(6):4108–4120
39. Richter S, Schoch B, Ozimek A, Gorissen B, Hein-Kropp C, Kaiser O, Hövel M, Wieland R, Gizewski E, Ziegler W, Timmann D (2005) Dysarthria is a rare sign in children with cerebellar tumors. Brain Lang 92(2):153–167
40. Riecker A, Ackermann H, Wildgruber D, Dogil G, Grodd W (2000) Opposite hemispheric lateralization effects during speaking and singing at motor cortex insula and cerebellum. Neuroreport 11(9):1997–2000
41. Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development – Evidence from a series of children surgically treated for posterior fossa tumours. Brain 123:1051–1061
42. Rorden C, Karnath HO (2004) Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nat Rev Neurosci 5(10):813–819

43. Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE (2001) Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. J Cogn Neurosci 13(6):829–843
44. Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579
45. Scott RB, Stoodley CJ, Anslow P, Paul C, Stein JF, Sugden EM, Mitchell CD (2001) Lateralized cognitive deficits in children following cerebellar lesions. Dev Med Child Neurol 43:685–691
46. Silveri MC, Di Betta AM, Filippini V, Leggio MG, Molinari M (1998) Verbal short-term store-rehearsal system and the cerebellum. Evidence from a patient with a right cerebellar lesion. Brain 121:2175–2187
47. Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. Science 283(5408):1657–1661
48. Steinlin M, Imfeld S, Zulauf P, Boltshauser E, Lövblad K-O, Ridolfi Lüthy A, Perrig W, Kaufmann F (2003) Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain 126:1998–2008
49. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, Bryer A, Diener HC, Massaquoi S, Gomez CM, Coutinho P, Ben Hamida M, Campanella G, Filla A, Schut L, Timmann D, Honnorat J, Nighoghossian N, Manyam B (1997) International cooperative ataxia rating score for pharmacological assessment of the cerebellar syndrome. J Neurol Sci 45:205–211
50. Vokaer M, Bier JC, Elincx S, Claes T, Paquier P, Goldman S, Bartholome EJ, Pandolfo M (2002) The cerebellum may be directly involved in cognitive functions. Neurology 58(6):967–970
51. Weintraub S, Mesulam M-M (1985) Mental state assessment of young and elderly adults in behavioral neurology. In: Mesulam M-M (ed) Principles of behavioral neurology. FA Davis, Philadelphia, pp 71–123