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Impaired working-memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit

B. Ziemus[1,5] O.Baumann[3] R.Luerding[1] R.Schlosser[4] G.Schuierer[2] U.Bogdahn[1] M.W.Greenlee[3]

1 Department of Neurology, University of Regensburg, Germany

2 Department of Neuroradiology BKR, Regensburg, Germany

3 Institute for Experimental Psychology, University of Regensburg, Germany

4 Department of Psychiatry, University of Jena, Germany

5 Clinical Neurophysiology, University of Maastricht, Germany

Correspondence to Mark W. Greenlee.

Abstract

A considerable body of evidence supports the notion that cerebellar lesions lead to neuropsychological deficits, including impairments in working-memory, executive tasks and verbal fluency. Studies employing functional magnetic resonance imaging (fMRI) and anatomical tracing in primates provide evidence for a cortico-cerebellar circuitry as the functional substrate of working-memory. The present fMRI study explores the activation pattern during an *n*-back working-memory task in patients with an isolated cerebellar infarct. To determine each patient's cognitive impairment, neuropsychological tests of working-memory and attention were carried out. We conducted fMRI in nine patients and nine healthy age-matched controls while they performed a 2-back task in a blocked-design. In both groups we found bilateral activations in a widespread cortico-cerebellar network, consisting of the ventrolateral prefrontal cortex (BA 44, 45), dorsolateral prefrontal cortex (BA 9, 46), parietal cortex (BA 7, 40), pre-supplementary motor area (BA 6) anterior cingulate (BA 32). Relative to healthy controls, patients with isolated cerebellar infarcts demonstrated significantly more pronounced BOLD-activations in the precuneus and the angular gyrus during the 2-back task. The significant increase in activation in the posterior parietal areas of the cerebellar patients could be attributed to a compensatory recruitment to maintain task performance. We conclude that cerebellar lesions affect remote cortical regions that are part of a putative cortico-cerebellar network.

Introduction

There is mounting evidence that the cerebellum participates in higher-order cognitive tasks such as executive processing, working-memory, verbal fluency and planning. Schmahmann and Sherman (1998) described for the first time a cognitive-affective syndrome following cerebellar lesions with executive, spatial, linguistic and affective symptoms. They postulate a disruption in a widespread cortico-cerebellar circuitry as a cause of impaired cognitive functions denoted as a fronto-cerebellar disconnection syndrome. An anatomical substrate for these functions is a cerebellar feedback loop through the thalamus to the prefrontal and parietal cortex (inferior parietal lobule) as it already has been reported for primates (Clower, West, Lynch, & Strick, 2001; Middleton and Strick, 1994, Middleton and Strick, 2000, Middleton and Strick, 2001; Schmahmann, 1991; Schmahman & Pandya, 1995; Schmahmann & Sherman, 1998). Several neuropsychological reports indicate the presence of working-memory impairments due to an isolated cerebellar lesion (Botez-Marquard, Bard, Leveille, & Botez, 2001; Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Malm et al., 1998; Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000).

In a recent publication, Ravizza et al. (2006) investigated 15 patients with cerebellar damage and found selective impairments in verbal working-memory. Articulatory rehearsal strategies were unaffected thereby supporting non-motor causes for the impaired verbal working-

memory. These clinical observations and above-mentioned anatomical findings in primates are compatible with the results of functional neuroimaging studies: Desmond, Gabrieli, Wagner, Ginier, & Glover (1997) and Chen and Desmond (2005) identified two cerebellar regions activated in verbal working-memory (a bilateral superior region and an inferior region on the right side) in addition to activations in the inferior parietal lobule (BA 40), Broca area (BA 6, 44) and anterior cingulum (BA 32). They propose two cortico-cerebellar networks for verbal working-memory: an articulatory control system with involvement of Broca's area (BA 6, 44) and the superior cerebellum (simplex lobule and crus I) and a phonological storage system connecting parietal areas (inferior parietal lobule) with the inferior cerebellum. Although the inferior parietal lobule is frequently mentioned as the likely locus of verbal short-term memory storage (Fiez et al., 1996; Smith & Jonides, 1998) this view has been recently challenged by Ravizza, Delgado, Chein, Becker, and Fiez (2004), who identified two regions of the intraparietal sulcus, one ventral and the other more dorsal, with the dorsal region responding to short-term memory load and the ventral region being involved in phonological encoding procedures. Neither of these two regions fulfilled, however, the requirements for proper phonological short-term storage. Majerus et al. (2006) deny this specific role of the parietal cortex in working-memory processes and describe its function as a more general superior attentional modulator, shifting focal attention to underlying subordinate networks, according to the cognitive process in question.

The VLPFC (BA 10, 47, 44 and 45) has been especially found to be activated in short-term maintenance (Owen, 2000) and in tasks that require selection, comparison and judgement of stimuli held in short-term and long-term memory (Petrides, 1994). On the other hand, the manipulation of information, reorganization and control of working-memory requires mid-DLPFC (BA 9, 46) (Bor, Duncan, Wiseman, & Owen, 2003; D'Esposito, Ballard, Aguirre, & Zarahn, 1998; Petrides, 1998). Neuropsychological studies support the view that the role of DLPFC activations in working-memory tasks is to increase task performance and facilitate memory, reducing the overall cognitive load with the help of structuring and categorizing information (Bor, Cumming, Scott, & Owen, 2004; Bor et al., 2003).In our study, we test the hypothesis that impairments in working-memory can result from damage to this putative cortico-cerebellar network. Altered BOLD-activation in remote supratentorial brain regions underlying working-memory would point to a role of the cerebellum in human cognition.

Methods

The study was approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Subjects

Nine patients with isolated cerebellar infarctions (five men, four women: mean age 46.2 years, S.D. = 8.1 years; range 38–63 years) were recruited from the Neurology Department of the University Hospital of Regensburg. All patients fulfilled the inclusion criteria of isolated stroke in cerebellum detected by MRI. Infarct size and location (specified on the basis of affiliation to arterial blood supply) were determined on the basis of T2-weighted and in cases

of territorial infarcts as well on T1-weighted images by a neuroradiologist (Fig. 1). We included patients in an acute phase of stroke (2–8 days past infarction), as well as patients in a post-acute phase (2 month past infarction) or in a chronic phase (up to 6 years after cerebellar infarction).

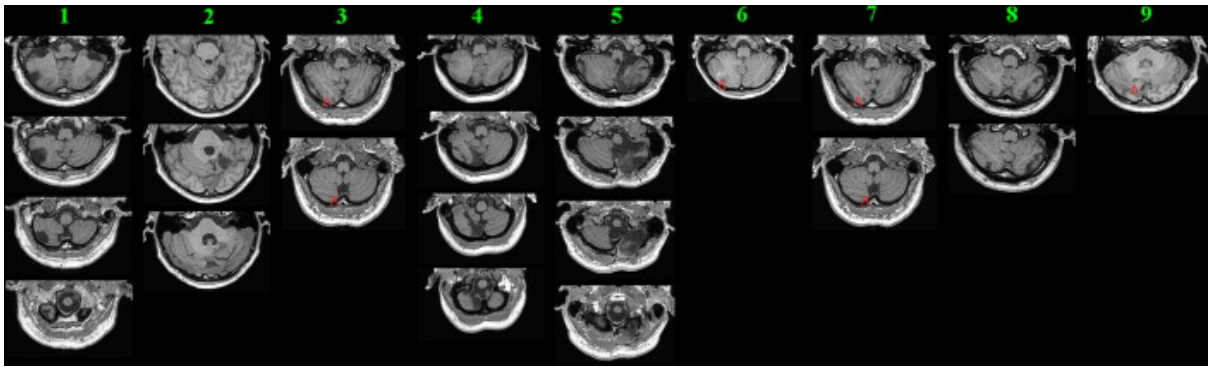

Fig. 1. Representative transversal slices of cerebellar infarcts. T1-weighted MRI at the level of maximal infarct volume for each patient, acquisition at time of the fMRI. Arrows denote location of lesions.

A control group consisted of nine healthy controls matched for age and gender for each patient (mean age 44.2, S.D. = 9.6; range 35–63 years) (Table 1).

Table 1. Overview of patient characteristics

Patient	Age	Sex	Infarct age	Infarct localization	Size (cm)	Neuropsychological function	*z*-Score
1	63	M	5 yrs	Left PICA	3 × 3 × 3	Verbal working-memory	−1
						Non-verbal working-memory	−0.4
						Attention	2.2
						Word fluency	−2.5
2	39	M	4 yrs	Right SCA	1.5 × 2 × 1.5	Verbal working-memory	0.2
						Non-verbal working-memory	−1.3
						Attention	−0.3
3	38	F	18 m	Right SCA	0.3 × 0.3 × 0.5	Verbal working-memory	−1.1

Patient	Age	Sex	Infarct age	Infarct localization	Size (cm)	Neuropsychological function	*z*-Score
						Non-verbal working-memory	1.2
						Attention	2.3
4	43	F	6 yrs	Left PICA	3 × 2 × 0.5	Verbal working-memory	−1
						Non-verbal working-memory	−1.1
						Attention	−1.3
5	48	M	3 yrs	Right PICA	4 × 2 × 5	Verbal working-memory	−1.3
						Non-verbal working-memory	0.7
						Attention	−2
6	54	F	8 d	Left PICA	3.5 × 2 × 0.5	Verbal working-memory	−1.9
						Non-verbal working-memory	−1.1
						Attention	−1.9
7	48	M	2 d	Left PICA	0.5 × 0.3 × 0.5, 0.5 × 0.5 × 0.4	Verbal working-memory	0.6
						Non-verbal working-memory	−1.9
						Attention	−1.3
						Word fluency	−1.8
8	42	M	14 m	Right PICA, left SCA	2 × 2 × 2, 0.5 × 0.4 × 0.5	Verbal working-memory	−1.1
						Non-verbal working-memory	3.3
						Attention	1.3

Patient	Age	Sex	Infarct age	Infarct localization	Size (cm)	Neuropsychological function	*z*-Score
9	41	M	2 m	Left PICA, left PICA	1 × 1 × 1, 0.5 × 0.4 × 0.5	Verbal working-memory	−1.4
						Non-verbal working-memory	−2.3
						Attention	−1
						Word fluency	−1.3

d, days; F, female; M, male; m, month; PICA, posterior cerebellar artery; SICA, superior cerebellar artery; yrs, years.

The average difference in age between matching pairs was 2.4 years (S.D. = 2.7; range 0–7 years). All study subjects were right handed according to the Edinburgh Handedness Inventory. Exclusion criteria were the use of psychotropic medication, vascular damage in other brain regions or a history of former strokes, cognitive impairment due to dementia, history of neurological and/or psychiatric illness, claustrophobia, pregnancy and the presence of ferromagnetic surgical pins.

Neuropsychological assessment

All patients were tested with a neuropsychological assessment battery. Verbal and non-verbal cognition was measured using a short form of the German version of the Wechsler Intelligence Scale for Adults Revised (WAIS-R; Tewes, 1994). Verbal long-term-memory was measured with the Logical Memory delayed free recall (LM II; Wechsler, 1987). Non-verbal long-term-memory was assessed with the Rey Complex Figure delayed free recall (Lezak, 1995). Verbal working-memory was measured with the digit span forward and backward (Tewes, 1994). Non-verbal working-memory was tested with the Corsi block span (Milner, 1971). The results of part B of the Trail Making Test (TMT-B) is reported as an attention measure (Lezak, 1995). The Ruff 2&7 Test (Ruff, Niemann, Allen, Farrow, & Wylie, 1992) was employed to measure attention. The Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989) provided a measure of lexical verbal fluency. Semantic verbal fluency was measured by asking participant to produce animal names in 60 s (Aschenbrenner, Tucha, & Lange, 2000). Test values are described as z-scores with respect to age-matched norms.The group was not uniform regarding education and general IQ, so neuropsychological test results of intact and impaired abilities were also very heterogeneous. Because of these interindividual differences we assessed cognitive deficits relative to the stable measure of the full-scale IQ for the individual patient.

Although following cerebellar infarction the full-scale IQ can be diminished, it is one of the most stable of all neuropsychological measures. The full-scale IQ consists of verbal, non-verbal, education-related and non-education-related items.

Working-memory paradigm

All participants performed a 2-back working-memory task (Braver, Cohen, Nystrom, Jonides, Smith, & Noll, 1997; Cohen et al., 1994; Gevins and Cutillo, 1993; Mellers et al., 1995) during fMRI acquisition. With the help of the PC-controlled stimulation software Presentation (Version 9.2, Neurobehavioral Systems, Inc.) a pseudorandom sequence of uppercase characters of the alphabet was presented on a back-projection screen. During the 2-back condition participants had to press a button with the right index finger whenever the presented letter was the same as the one before the last (2-back). In the control condition (0-back) they just had to press a button each time the letter "X" appeared. A fibre optic response box (Lumitouch, Photon Inc.) was used. Stimulus presentation time for one letter was 1300 ms with an interstimulus interval of 700 ms with 21.4% targets. Subjects were scanned through four alternating blocks of the 2-back and 0-back conditions over a total of eight epochs. Each experimental epoch lasted 57 s. At the beginning of each epoch the subject was informed which task to perform via written instructions (3 s per epoch), resulting in a total epoch length of 60 s and an experimental length of 8 min. To score the precision of hits and false positives, we used a discrimination score DS based upon the ability to distinguish targets from distractor items: $\{1 - [(\text{false positives} + \text{misses})/(\text{targets} + \text{distractors})]\} \times 100$. The DS varies from 100% (all responses are hits or correct rejections) to 0% (all responses are false positives or misses).

MRI-imaging

The functional studies were performed on a 1.5 T Siemens Magnetom (Sonata, Siemens, Erlangen, Germany) equipped with a fast gradient system for echo-planar (EPI) imaging and a eight-channel phase array full-head radio-frequency (RF) receive-transmit headcoil (MR-Devices). Functional imaging was performed using a $T2^*$-weighted gradient echo planar imaging (EPI) covering the whole brain. We acquired volumes with 39 axial slices with a gap of 0.3 mm and could thus image the entire brain. The field of view (FOV) measured 192 mm with a voxel matrix size 64 × 64, resulting in a voxel size of 3 mm × 3 mm × 3 mm. The TR was 3500 ms. The time to echo corresponded to TE = 50 ms, the flip angle corresponded to 90°. The first two EPI images were discarded as "dummy" images before the start of the experimental paradigm in order to obtain steady-state. After the functional runs, anatomical high-resolution sagittal T1-weighted images were acquired with the MP-Rage sequence (magnetization prepared, rapid acquisition gradient echo).

fMRI data analysis

Data were processed and analyzed on a single-subject level using Statistical Parametric Mapping SPM 2 (SPM2, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion./ucl.ac.uk/spm/) implemented in MATLAB (The MathWorks Inc.). Echo planar images were unwarped and realigned to the first acquired volume to correct for head movement.

The images were then transformed into a standard stereotaxic anatomical space (Friston, Frith, Liddle, & Frackowiak, 1991; Friston et al., 1995a; Talairach & Tournoux, 1998). We used the following procedure to normalize the scans: a T2*-weighted mean image of the

unsmoothed images was co-registered with the corresponding anatomical T1 weighted image of the same individual. The individual T1-image was used to derive the transformation parameters for the stereotaxic fit using the MNI-Template (Friston et al., 1995a), which were then applied to the individual single co-registered EPI images. The normalized images were smoothed with a Gaussian filter of 12 mm.Analysis using the General Linear Model (GLM) (Friston et al., 1995b) was done after applying high-pass filtering (cut-off: 180 s). The periods in which subjects performed the task were modeled separately for the 2-back and the 0-back condition by using a boxcar convolved with the hemodynamic response function. The specified contrast on single subject level was "2Back > 0Back".

On random-effects group level, we used the "2Back > 0Back" contrast image for every subject representing the difference between the two conditions on an individual level. These images were analyzed on the group level with the non-parametric SnPM-Toolbox (Holmes, 1994, Holmes et al., 1996), with the test for "2 groups, 1 scan per subject", the non-parametric equivalent of a t-test. This method uses the assumption that the contrast values of non-activated voxels distribute evenly around zero. We chose a non-parametric approach, since the sample size was quite small.

A 3D variance smoothing using a FWHM of 8 mm was performed. Variance smoothing can enhance the power of the group analysis even above the parametric methods of Gaussian random fields if the assumption of sufficient smoothness of the parametric maps is violated. For small group sizes this is often the case. Voxels surpassing a statistical threshold of $p = 0.05$ (Tmax-contrast analysis, corrected for multiple comparisons) were identified as activated. MNI coordinates were transformed to Talairach coordinates by using the WFU-Pickatlas (Wake Forest University Pickatlas, Version 1.02; Maldijan, Laurienti, Kraft, & Burdette, 2003). The anatomical locations were identified by using the program MSU by S. Pakhomov. This tool relies on the mni2tal program combined with data of the Talairach demon (Lancaster, Summerln, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000). Apparent cerebellar activations of the cerebellum are not reported for the patient group, since even with an optimized normalization method the activations could be artificial due to the lesions and would therefore not be interpretable.

Results

Neuropsychological test results

Table 1 shows the results of the neuropsychological tests performed on the patient group. Differences between *z*-scores on digit span and full-scale IQ indicate that the patients were impaired in verbal working-memory functions. *z*-Score differences between non-verbal working-memory (Corsi block span) scores and full-scale IQ served as an indicator of impairment in non-verbal memory functions after infarction. All patients exhibited a deficit in either verbal or non-verbal working-memory with a *z*-score difference greater than −1. Impairments in attention were observed in six, in verbal fluency in three patients (Table 1).

Task performance in fMRI study

There was no significant difference in performance of the 2-back task during scanning between patients and controls (*U*-Test, $p = 0.24$). Patients achieved a mean discrimination score (DS) of 91.9%, whereas the controls had a DS of 89.1% in the 2-back task. In the 0-back condition, no differences (U-Test, $p = 0.572$) were evident between the patients (mean DS = 99.6%) and the controls (mean DS = 99.3%). Reaction times showed a significant delay for the 2-back-task compared to the 0-back-task. (Wilcoxon-test, $p = 0.008$). No significant differences were found for the reaction times between patients and controls (*U*-Test, $p = 0.76$ for the 0-back-task and $p = 0.97$ for the 2-back-task).

Functional MRI data

2-back-task in controls

For the contrast 2-back > 0-back in the control group significant clusters were found bihemispherically in ventrolateral prefrontal cortex (VLPFC) (BA 44, 45, 47, 10), dorsolateral prefrontal cortex (DLPFC) (BA 9, 46), pre-supplementary motor cortex (BA 6), the cerebellum and the parietal cortex. The parietal activation comprised clusters in the precuneus and the superior parietal lobule (BA 7), the supramarginal gyrus and inferior parietal lobule (BA 40). Further there were clear bilateral activations in the thalamus and a left hemispheric activation of the cingulate gyrus (Table 2; Fig. 2).

Table 2. (Pseudo)-*t*-values and Talairach coordinates of activation maxima for the contrast 2-back > the 0-back in healthy controls ($p < 0.05$, corrected for multiple comparisons)

Region	Hemisphere	Brodmann area	Talairach coordinates			(Pseudo)-*t*-values of maxima (clustersize in number of voxels)
			x	*y*	*z*	
2-back > 0-back, controls						
Cerebellum	R		34	−63	−19	10.45 (436)
IPL/SPL	R	7/40	36	−56	45	9.22 (1135)
IPL/SPL/PrCu	L	7/40	−28	−58	45	9.40 (1332)
IFG/MFG	R	9	44	32	26	8.40 (900)
MFG/PCG	L	6	−30	−5	50	8.36 (270)
MFG/PCG	R	6	34	−8	52	9.12 (396)
IFG/Insula	L	13/45/47	−32	23	1	7.66 (216)
IFG/MFG	L	9	−48	13	27	7.65 (295)
Cerebellum	L		−36	−59	−19	6.92 (102)
MFG	R	10	42	50	−4	6.83 (72)
MFG/SFG	L/R	6/8	2	12	49	6.47 (140)
MFG	L	10	−34	5	9	6.31 (27)
MTG	R	21	59	−43	−5	6.27 (51)
IPL	R	40	48	−38	54	6.22 (54)
IFG	R	13/47	34	21	−1	6.13 (30)

For each cluster the hemisphere, Brodmann areas and anatomical structures are specified, in which the respective cluster is located. *Abbreviations*: AG, angular gyrus; CG, cingulate gyrus; FFG, fusiform gyrus; SMG, supramarginal gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SPL, superior parietal lobule; PCG, precentral gyrus; PrCu, precuneus.

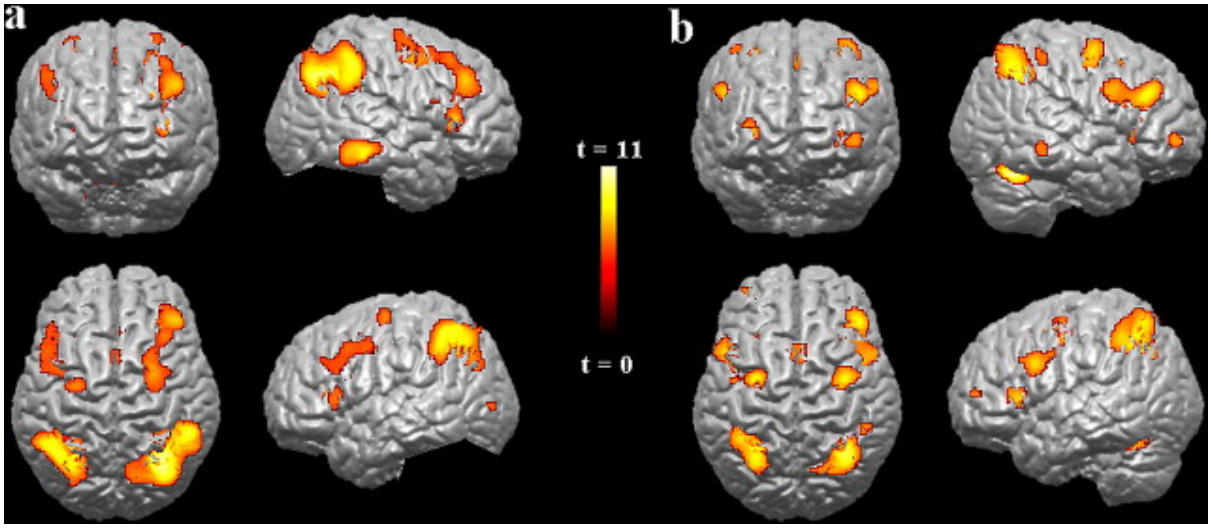

Fig. 2. Group activation maps for the contrast 2-back > *x*-back. Pseudo-*t*-values are overlaid onto a rendered MNI-normalized template (activated voxels deep in sulci are projected onto the surface). Significant voxels surpassing a threshold of $p = 0.05$ (corrected for multiple comparisons) are presented. (a) Results for the patient group ($n = 9$). (b) Results for the control group ($n = 9$).

2-back-task in patients

For the contrast 2-back > 0-back we found an activation pattern in the patient group similar to that found in the control group, with an extended cluster in the right parietal association cortex including precuneus, supramarginal gyrus, inferior parietal lobule and the superior parietal lobule (BA 7, 19, 40) and in homologue regions in the left hemisphere. The second largest cluster lies in the DLPFC (BA 9, 46) and VLPFC (BA 10, 44, 45, 47) and the pre-supplementary motor cortex (BA 6) (Table 3). As mentioned in Section 2, cerebellar activations are not reported, since apparent activations are likely to be artifacts due to cerebellar lesions. Since our aim is to investigate the effect of a cerebellar lesion on the remote neocortical activations associated with working-memory, this potential artifact does not pose a problem in our context.

Table 3. (Pseudo)-*t*-values and Talairach coordinates of activation maxima for the contrast 2-back > the 0-back in patients ($p < 0.05$, corrected for multiple comparisons)

Region	Hemisphere	Brodmann area	Talairach coordinates			(Pseudo)-*t*-values of maxima (cluster size in number of voxels)
			x	*y*	*z*	
2-back > 0-back patients						
AG/IPL/PrCu/SMG/SPL	**R**	**7/19/39/40**	**30**	**−62**	**38**	**10.21 (3778)**
AG/IPL/PrCu/SMG/SPL	**L**	**7/19/39/40**	**−40**	**−56**	**53**	**8.78 (2145)**
ITG/MTG	**R**	**20/21/37**	**59**	**−37**	**−10**	**9.20 (573)**
IFG/Insula/MFG/PCG/SFG	**R**	**6/8/9/13/45/47**	**−36**	**20**	**5**	**7.55 (1634)**
MFG/PCG/SFG	**L**	**6**	**−28**	**−9**	**60**	**6.48 (144)**
IFG/Insula	**L**	**13/45/47**	**−36**	**22**	**6**	**6.20 (116)**
MFG/PCG	**L**	**6/8/9**	**−48**	**14**	**40**	**5.94 (436)**
SFG	**L/R**	**6**	**2**	**10**	**51**	**5.81 (69)**

For each cluster the hemisphere, Brodmann areas and anatomical structures are specified, in which the respective cluster is located. For abbreviations see Table 2.

Evidence for a significant activation in the thalamus was only present for the right side. Smaller activation clusters were located in the middle temporal gyrus on both sides (Table 3; Fig. 2).

Differential group analysis of 2-back results

The results of the differential random-effects contrast between the patients and controls with respect to the 2-back > 0-back contrast are shown in Fig. 3 and Table 4 (height threshold: p = 0.05, cluster-defining threshold: t = 3). During the 2-back task the patient group exhibited two BOLD clusters that were significantly more activated in comparison to the healthy control

group. The clusters were located bilaterally in the parietal cortex including angular gyrus, the inferior parietal lobule, the supramarginal gyrus and the precuneus (BA 7, 19, 39, 40; see Table 4 and Fig. 3).

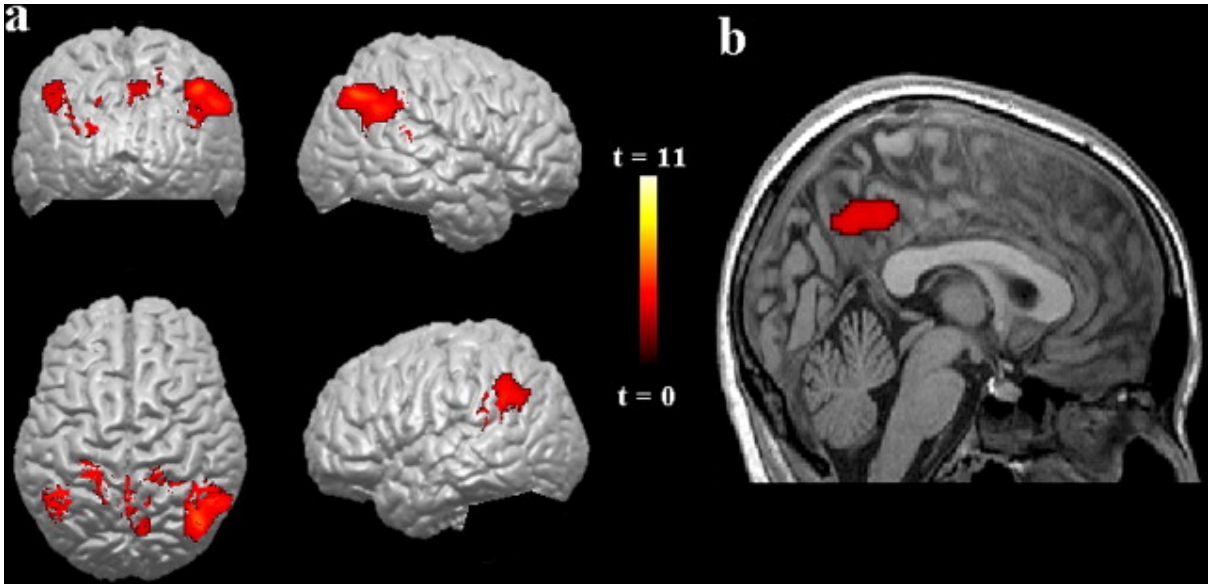

Fig. 3. Group activation maps illustrating the contrasts between patients and controls (2-back vs. 0-back in patients >2-back vs. 0-back in controls). Significant clusters surpassing a threshold of $p = 0.05$ (corrected for multiple comparisons, cluster-defining threshold $t = 2.5$) are presented. (a) Pseudo-*t*-values are overlaid onto a rendered MNI-normalized template (activated voxels deep in sulci are projected onto the surface). (b) Sagittal section showing regions of interest located in the precuneus and in the cingulate cortex.

Table 4. (Pseudo)-*t*-values and Talairach coordinates of activation maxima for the differential contrasts between patients and controls ($p < 0.05$, corrected for multiple comparisons, cluster-defining threshold $t = 2.5$)

Region	Hemisphere	Brodmann area	Talairach coordinates			(Pseudo)-*t*-values of maxima (clustersize in number of voxels)
			x	*y*	*z*	
Patients (2-back > 0-back) > controls (2-back > 0-back)						
AG/SMG/IPL/PrCu	R	7/19/39/40	44	−66	44	5.69 (1630)
AG/CG/SMG/IPL/PrCu	L/R	7/31/39/40	−44	−51	32	4.65 (1903)

For each cluster the hemisphere, Brodmann areas and anatomical structures are specified, in which the respective cluster is located. For abbreviations see Table 2.

The reversed comparison was conducted to determine if any clusters were significantly more activated in the control-group. This comparison did not reveal any significantly activated BOLD-clusters.

Discussion

In this fMRI study, we investigated the pattern of BOLD-activation during a working-memory task in patients with isolated cerebellar infarcts. Although these patients were not severely affected in daily life, the neuropsychological tests revealed that they exhibited cognitive impairments in the domain of working-memory, verbal fluency and attention. These neuropsychological results are consistent with previous findings from other groups (Gottwald et al., 2004; Hokkanen, Kauranen, Roine, Salonen, & Kotila, 2006; Malm et al., 1998, Neau et al., 2000, Ravizza et al., 2006) indicating the presence of cognitive impairments in patients with cerebellar lesions. The impairment in working-memory and attention is suggestive for a cortico-cerebellar disconnection syndrome, as first described by Schmahmann and Sherman (1998). In this syndrome, the cerebellar modulation in a network that links prefrontal, posterior parietal and superior temporal areas with the cerebellum is defective. Hence, we hypothesized an altered BOLD signal within this cortico-cerebellar network as a result of a disruption in cerebellar projections.To investigate working-memory we chose the n-back task in this study. This task requires, in addition to pure maintenance of information, executive functions such as monitoring, updating and manipulation of remembered information and is therefore suitable for investigating working-memory (Owen, McMillan, Laird, & Bullmore, 2005). The task performance during the fMRI measurement showed no significant difference

between patient and control group, which underlines the fact that patients were capable of carrying out the n-back task despite their documented working-memory deficits.

Choosing the n-back paradigm using letters, we realize that this task involves possibly both spatial and verbal processing components and is not, as stated before in many studies, a pure verbal working-memory task (Meegan, Purc-Stephenson, Honsberger, & Topan, 2004). Regarding the cognitive deficits in our patient group they showed both verbal and non-verbal working-memory deficits. Consequently, a pure verbal or non-verbal task was not a prerequisite for our study. It was further not our intention in this study to investigate inherent differences between verbal and non-verbal working- memory pathways. Our concern was to provide evidence for a disrupted cortico-cerebellar circuitry in patients with cerebellar lesions during a working-memory task.

A meta-analysis of functional imaging studies using the n-back working-memory paradigm (Owen et al., 2005) revealed that – in verbal as well as in non-verbal versions – robust activations occur bilaterally in the following brain regions forming the putative cortico-cerebellar network: the medial posterior parietal cortex, including precuneus and the inferior parietal lobule (BA 7, 40), bilateral premotor cortex (BA 6, 8), dorsal cingulate/medial premotor cortex, including SMA (BA 32, 6), bilateral rostral prefrontal cortex (BA 10), bilateral mid-ventrolateral prefrontal cortex including the frontal operculum (BA 45, 47) and bilateral dorsolateral prefrontal cortex (BA 9, 46). In addition to this pattern of activity, activations in the medial cerebellum have been reported. The only reported difference for non-verbal n-back tasks compared to verbal working-memory tasks was a lack of activation in the left ventrolateral prefrontal cortex.

In line with the results in the literature (Chen & Desmond, 2005; Desmond & Fiez, 1998; Hautzel, Mottaghy, Schmidt, Mueller, & Krause, 2003; Krause et al., 2000, Schlosser et al., 2003; Schlosser, Wagner, & Sauer, 2006) we found in both groups activations of a cortico-cerebellar network during performance of the working-memory task, namely in the frontal cortex (DLPFC and VLPFC) and the superior and inferior lobules during 2-back, compared to 0-back, task performance (Fig. 2). We also found cerebellar activations in both groups, but the explanatory power of cerebellar activation is very limited for the patients, as the lesions are likely to cause artefacts.

For the contrast '2-back versus 0-back in patients > 2-back versus 0-back in controls' we found more pronounced activations in the parietal cortex (i.e., angular gyrus (BA 39), supramarginal gyrus (BA 40), precuneus (BA 7), and posterior cingulate gyrus (BA 31) (Fig. 3; Table 4). These areas were also identified as activated in the separate group analysis for controls and patients as reported above (Fig. 2; Table 2, Table 3). As anticipated the pattern of activation during the 2-back task is similar in patients and controls, whereas the contribution of posterior parietal regions to this network appears to be augmented in the patients. In light of the relatively high performance exhibited by the patients in the 2-back task, the results shown in Fig. 3 could be interpreted as a compensatory up-regulation to offset a lack in cerebellar input into this complex cerebello-cortical-subcortical network (Mottaghy et al., 2003).

Regarding the role of the parietal cortex in WM tasks, the precuneus (BA 7) has been shown to be involved in all types of executive function (Wager & Smith, 2003). In verbal working-memory tasks the inferior parietal lobule (namely the angular gyrus and the supramarginal gyrus) is the likely locus of the phonological store (Fiez et al., 1996; Smith & Jonides, 1998). In contrast to this, a recent study by Ravizza et al. (2004) places in question whether the supramarginal gyrus is a dedicated site for phonological short-term storage. They could demonstrate that the ventral part of the supramarginal gyrus supports phonological encoding whereas the dorsal part responds to short-term memory load, for visual and as well verbal stimulus material. The precise function of the parietal cortex in working-memory tasks is still a matter of debate.

It should be noted that the differences in brain activation observed between patients and controls during the working-memory task could reflect, at least in part, altered attentional processes, which are recruited by the working-memory task. The working-memory task places more demands on attentional resources compared to the control task. In addition, several of the patients showed mild impairments in attention. In the light of our results we favour the view that the PPC takes on the role of a superordinate attentional modulator for different neural networks during a working-memory task as proposed by Majerus et al. (2006). Depending on the type of information (item, order, verbal, non-verbal) that has to be processed, different underlying neuronal networks will be recruited. The intraparietal sulcus may play a role in coordinating and synchronizing these neuronal substrates, which accordingly would up-regulate parietal cortex in patients with deficits in the underlying task-specific regions. Ravizza et al. (2004) also reported domain-independent activations in the dorsal part of intraparietal sulcus in tasks where the working-memory demands on attention are high.

According to a meta-analysis of 60 imaging studies on working-memory conducted by Wager and Smith (2003), BA 6, 8, 9 in the superior frontal cortex respond most when working-memory must be continuously updated, as required in an n-back paradigm. We did not find significant enhancement of frontal working-memory specific areas in the patients. One explanation for this might be the impaired integrity of the cerebello-thalamo-frontal network leading to downstream activation alterations in parietal cortex. According to a combined ERP- and fMRI study by Brass, Ullsperger, Knoesche, von Cramon, Phillips (2005) there is strong evidence that in a system of hierarchical cognitive control, activations in the prefrontal cortex precede activations in the parietal cortex. They interpret this sequential order with the notion that the prefrontal cortex defines task goals in very abstract terms, while the parietal lobe focuses on the specific concrete action. Accordingly, this network compensates for the cerebellar dysfunction by means of up-regulated parietal activation following commands from the prefrontal cortex. In addition to these considerations, the parietal cortex is, due to its widespread connections and its heteromodality, a likely locus for functional plastic changes.

Conclusion

We conclude that the cerebellum is involved in higher cognitive processes such as working-memory. Our findings point to the cerebellum as part of a widespread cortico-cerebellar

network involving the frontal lobe, parietal cortex and subcortical brain areas. Patients with isolated cerebellar infarcts show cognitive impairments on neuropsychological tests of working-memory. These deficits can be attributed to a disruption of afferent or efferent fibres to cortical connections as part of a cortico-cerebellar circuitry. Increased BOLD responses in the angular gyri and the inferior parietal lobule may be an expression of the compensation process evoked after lesion to the cerebellum.

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