Neuro-Oncology Advances
4(1), 1–8, 2022 | https://doi.org/10.1093/noajnl/vdac050 | Advance Access date 13 April 2022

Impact of childhood cerebellar tumor surgery on cognition revealed by precuneus hyperconnectivity

Christian Dorfer, Thomas Pletschko, Rene Seiger, Monika Chocholous, Gregor Kasprian, Jacqueline Krajnik, Karl Roessler, Kathrin Kollndorfer, Veronika Schöpf, Ulrike Leiss, Irene Slavc, Daniela Prayer, Rupert Lanzenberger, and Thomas Czech

Department of Neurosurgery, Medical University of Vienna, Vienna, Austria (C.D., J.K., K.R., T.C.); Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria (G.K., J.K., K.K., V.S., D.P.); Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria (T.P., M.C., U.L., I.S.); Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria (R.S., R.L.)

Corresponding Author: Thomas Czech, MD, Department of Neurosurgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria (thomas.czech@meduniwien.ac.at).

Abstract

Background. Childhood cerebellar pilocytic astrocytomas harbor excellent overall survival rates after surgical resection, but the patients may exhibit specific cognitive and behavioral problems. Functional MRI has catalyzed insights into brain functional systems and has already been linked with the neuropsychological performance. We aimed to exploit the question of whether resting-state functional MRI can be used as a biomarker for the cognitive outcome assessment of these patients.

Methods. We investigated 13 patients (median age 22.0 years; range 14.9-31.3) after a median interval between surgery and examination of 15.0 years (range 4.2-20.5) and 16 matched controls. All subjects underwent functional 3-Tesla MRI scans in a resting-state condition and battery neuropsychological tests.

Results. Patients showed a significantly increased functional connectivity in the precuneus compared with controls ($P < .05$) and at the same time impairments in various domains of neuropsychological functioning such as a lower mean *Wechsler Intelligenztest für Erwachsene* (WIE) IQ percentile (mean [M] = 48.62, SD = 29.14), lower scores in the Trail Making Test (TMT) letter sequencing (M = 49.54, SD = 30.66), worse performance on the WIE subtest Digit Symbol Coding (M = 38.92, SD = 35.29), subtest Symbol Search (M = 40.75, SD = 35.28), and test battery for attentional performance (TAP) divided attention task (M = 783.92, SD = 73.20).

Conclusion. Childhood cerebellar tumor treated by resection only strongly impacts the development of precuneus/posterior cingulate cortex functional connectivity. Functional MRI has the potential to help deciphering the pathophysiology of cerebellar-related cognitive impairments in these patients and could be an additional tool in their individual assessment and follow-up.

Key Points

- The precuneus is heavily involved in the cerebral oversight of cerebellar function.
- Resting-state functional MRI can be used as an additional outcome measure in neuro-oncology.

Cerebellar pilocytic astrocytoma (CPA) constitutes the second most common pediatric brain tumor accounting for approximately 30% of all pediatric central nervous system tumors. Surgical resection without any adjuvant treatment leads to excellent overall survival rates of 80%-95%.[1,2] Despite this good survival prognosis, current evidence emphasizes the cognitive and behavioral problems of these patients in the long run.[3–7] The range of difficulties follows similar patterns as described for the cerebellar cognitive affective syndrome (CCAS), which includes deficits in executive functioning,

© The Author(s) 2022. Published by Oxford University Press, the Society for Neuro-Oncology and the European Association of Neuro-Oncology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Importance of the Study

Our understanding of the role of the cerebellum in cognition has seen a tremendous advance in recent years. The mechanisms of the cerebro-cerebellar interplay at a network level are still poorly understood. In this manuscript, we show that the precuneus brain region is heavily involved in the cerebral associative oversight of cerebellar cognitive function. Furthermore, resting-state functional MRI (rsfMRI) is increasingly used as an imaging biomarker for the neuropsychological outcome of a given disease. We were able to show that rsfMRI has the potential to serve as a valuable measure for the outcome assessment in neuro-oncology patients in the future.

language difficulties, and problems with spatial cognition and affect regulation. The role of the cerebellum in cognition is widely accepted nowadays and conceptualized as the dysmetria of thought and the universal cerebellar transform theories.[8,9] Postoperative cerebellar mutism seems to be triggered by similar mechanisms, which also cause CCAS, but is not a prerequisite to develop intellectual and emotional deficits.[8] The aforementioned deficits in turn impair functional outcomes such as academic achievement.

Recent advances in the acquisition and analysis of functional MRI have catalyzed the understanding of the overall organization of the brain networks and this cerebro-cerebellar interplay.[9–12] Resting-state functional MRI (rsfMRI) measures correlations in spontaneous low-frequency (<0.1 Hz) blood-oxygenation level dependent (BOLD) signal fluctuations generated in the absence of salient stimuli or cognitive goal-driven behavior, ie, a cognitive task. Correlated patterns of BOLD signal fluctuations between spatially remote brain regions generally indicate coherent neuronal activity underlying interregional communication. These resting-state networks reflect physiological networks and have been increasingly used to map multiple brain functional systems linked to cognitive functions.[13]

Moreover, the functional connectivity, ie, the level of functional communication between anatomically remote brain regions, has been shown to correlate well with cognitive functions and emotional measures. For instance, in an increasing number of psychiatric disturbances such as Alzheimer's disease or schizophrenia, rsfMRI is already used as a surrogate marker to monitor the disease.[14,15]

In patients after cerebellar tumor surgery, efforts to identify imaging substrates have mainly used structural imaging methods such as diffusion tensor imaging and voxel-based morphometry analysis. These analyses revealed white matter microstructural changes and gray matter density differences in the supratentorial brain compared with controls even in the absence of any treatment in addition to surgery.[5,16,17]

In an attempt to understand the functional connectivity underlying these structural changes, we aimed to link the neuropsychological performance of young adults after childhood cerebellar tumor lesions with the global functional connectivity of the brain. This link would provide the basis to use functional imaging as an additive measure for the cognitive outcome assessment of these patients.

Patients and Methods

The study protocol was evaluated and approved by the local ethics committee of the Medical University of Vienna, Austria (http://www.meduniwien.ac.at/ethik) according to the Declaration of Helsinki. All children with brain tumors managed at the Departments of Pediatrics and Neurosurgery since 1992 are prospectively registered in a dedicated database. This database was screened for children operated on a pilocytic astrocytoma of the cerebellum.

To create a cohort that had tumor resection within a comparable developmental period and at the same time had a similar interval between surgery and investigation, the following criteria were set.

Inclusion criteria were (1) surgery between 1 year and 13 years of age, (2) age at test older than 15 years, and (3) German as a native language. Exclusion criteria were (1) neurofibromatosis type I, (2) severe visual or auditory impairment, (3) cerebral fluid shunt device, (4) previous radiotherapy or chemotherapy, and (5) major metabolic disorders such as diabetes type I.

From the 88 patients identified in the database, 28 patients met the inclusion/exclusion criteria. In 5 out of these 28 patients, no contact information was available. Of the 23 contacted patients, 9 refused to participate for various reasons such as no interest or being too busy with profession/school. In one patient, the fMRI could not be performed because of claustrophobia resulting in a final sample of 13 patients (6 females and 7 males). The median age at the time of surgery was 7.4 years (range, 3.7-13.7 years). The median interval between surgery and examination was 15.0 years (range 4.2-20.5 years). The median age at the time of testing was 22.0 years (range 14.9-31.3 years). No patient had evidence of cerebellar mutism after surgery. Details on the location of the cerebellar lesion and the perioperative clinical information have been reported previously[18,19] and are summarized in Table 1.

Both friends and relatives of the patients and medical students volunteered as an age- and sex-matched control group, and we were able to obtain a complete neuropsychological and resting-state dataset from 16 healthy subjects (6 females and 10 males; median age 22.2 years; range 15.7-30.1). There was no significant difference in age between the two groups. ($P = .606$).

All fMRI measurements were performed at approximately the same time of the day, between 2:30 and

Table 1. Patients' Characteristics

ID	Gender	Age at Surgery (years)	Age at Exam (years)	Lesion Site	Tumor Size (cm)	EVD Preop	VP Shunt	Postop Cerebellar Mutism
1	M	3.7	24.2	Vermis	4	No	No	No
2	F	3.7	23.9	R hemisphere	3.5	No	No	No
3	M	9.4	23.4	R hemisphere	4	No	No	No
4	M	7.1	21.3	Vermis	3	No	No	No
5	M	13.7	31.3	R hemisphere	3.5	No	No	No
6	F	4..3	16.1	L hemisphere	5	No	No	No
7	M	7.2	14.9	R hemisphere	3.5	No	No	No
8	F	3.4	18.9	Vermis	3.5	No	No	No
9	M	5.4	21.7	R hemisphere	5	No	No	No
10	M	5.0	22.9	Vermis	4	Yes	No	No
11	F	9.9	30.0	L hemisphere	4.5	No	No	No
12	F	9.6	21.3	R hemisphere	1	No	No	No
13	F	12.1	16.2	L hemisphere	3	No	No	No

Abbreviations: EVD, external ventricular drain; VP, ventriculoperitoneal.

3:00 p.m. The neuropsychological assessment was conducted between 9:30 and 12:00 a.m. on a separate day.

Imaging Methods

Three-dimensional structural MRI scans were acquired on a 3 Tesla Scanner (Philips Medical System, Best, The Netherlands) using a 3D MPRAGE sequence with repetion time/time to echo (TR/TE) = 2300/4.21 ms, flip angle 90° degrees, inversion time 900 ms, a voxel size of 1 × 1 × 1.1 mm^3, and a field of view (FOV) of 240 × 256 × 176 mm. Functional data were collected by using single-shot-gradient-recall echo-planar imaging. Thirty-five axial slices (4 mm thickness, matrix size of 96 × 96, FOV of 230 mm, and TE/TR of 35/3000 ms) were acquired. Slices were adjusted parallel to the connection between the anterior and the posterior commissure. Functional imaging included the acquisition of a resting-state condition lasting for 5 minutes, in which subjects were visually presented with a black crosshair on a white background image using an MR-compatible visual stimulation system (NordicNeuroLab). Subjects were instructed to focus on the crosshair at all times, not to think of anything in particular, and not to fall asleep.[20]

Preprocessing was conducted with SPM12 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm) within MATLAB v7.12 (R2011a) using default parameters, unless otherwise specified. Initially, slice timing correction was performed using the middle slice as a reference, followed by a realignment step to account for the subject's movement. Spatial normalization to Montreal Neurological Institute (MNI) space was performed, and the data were spatially smoothed using an 8-mm full width at half maximum Gaussian kernel. Furthermore, the data were simultaneously corrected for nuisance signals (white matter, ventricles, and movement parameters) and bandpass filtered with 0.01-0.1 Hz using in-house MATLAB scripts."

After preprocessing, global functional connectivity was conducted. Before the analysis, data were *z*-scored, Pearson correlations were calculated, and Fisher's *R*-to-*Z* transformation was applied to guarantee a normal distribution of the data. Global functional connectivity was calculated by correlating each voxel with the mean of all other voxels of the entire brain. Two-sample *t*-tests between the patients and the healthy controls were calculated including the covariates age and gender to assess differences in global functional connectivity (FC).

Neuropsychological Measures

A battery of neuropsychological tests was administered for each subject. The following neuropsychological parameters and corresponding measures were analyzed.

Overall cognitive functioning—A German version of the *Wechsler Adult Intelligence Scales* (*WAIS-III*),[21] the *Wechsler Intelligenztest für Erwachsene* (*WIE*) was used to evaluate overall cognitive functioning (for a more detailed review, see Jacobs and Petermann).[22,23]

Attentional performance—The computer-based test battery for attentional performance (*Testbatterie zur Aufmerksamkeitsprüfung, TAP 2.0*) was applied to test the attentional performance.[24] It comprises several subtests, which measure statistically independent aspects of attention. In this study, 4 subtests were administered: (1) *Alertness*, (2) *Working Memory*, (3) *Divided Attention*, and (4) *Incompatibility*.

Information processing speed–The *D-KEFS* Trail Making Test (TMT) from the Delis-Kaplan Executive Function System is a widely used neuropsychological test that

provides information on a range of neurocognitive parameters such as visual scanning, processing speed, cognitive flexibility (see later), and executive functions.[24] The task in *Form 2* is to connect numbers (1-2-3, etc.) as fast as possible, whereas *Form 3* asks subjects to connect letters (A-B-C, etc.), and *Form 4* requires subjects to switch between numbers and letters (1-A-2-B-3-C, etc.). In this study, *forms 2* and *3* were used to evaluate information processing speed. Additionally, 2 subtests from the *WIE* were used to obtain additional indicators for visual information processing speed: (1) visuomotor processing speed (*Digit Symbol Coding*) and (2) information processing speed and visual perception (*Symbol Search*).

Cognitive flexibility—The *TMT Form 4* (number-letter switching) served as an indicator of cognitive flexibility/cognitive shifting.[25]

Neuropsychological Analysis

Group differences regarding neuropsychological parameters were analyzed using SPSS version 20 (SPSS, Inc.). Independent sample *t*-tests (Welch correction) were carried out to test for differences between patients and healthy controls. Whenever assumptions for parametric data were violated, Mann-Whitney *U*-tests were computed. A significance threshold of $P < .05$ was used for the interpretation of the results. Effect sizes for group differences are denoted by Cohen's *d* (Cohen) as well as *r* (*U* tests). The following categorization is used to interpret effect sizes: small effect: $d = .2$ and $r = .1$; medium effect: $d = .5$ and $r = .3$; and large effect: $d = .8$ and $r = .5$.

Results

Neuropsychological Testing

The detailed results of the neuropsychological testing are given in Table 2.

The results show significant group differences in overall cognitive functioning (IQ) as denoted by the norm-corrected percentile ($U = 176.00$, $z = 3.162$, $P < .01$, $r = .587$), with a higher mean WIE IQ percentile in controls (M = 85.25, SD = 15.45) than in patients (M = 48.62, SD = 29.14). Similarly, controls (M = 75.69, SD = 15.35) scored higher in the TMT letter sequencing than their patient counterparts (M = 49.54, SD = 30.66, $U = 155.00$, $z = 2.278$, $P < .05$, $r = .423$). Also, healthy subjects (M = 70.00, SD = 24.20) showed a significantly better performance on the WIE subtest *Digit Symbol Coding* than tumor patients (M = 38.92, SD = 35.29, $U = 154.50$, $z = 2.224$, $P < .05$, $r = .412$). Mann-Whitney *U*-tests for the WIE subtest *Symbol Search* revealed a similar advantage of healthy controls (M = 77.38, SD = 25.08) over patients (M = 40.75, SD = 35.28, $U = 147.00$, $z = 2.380$, $P < .05$, $r = .442$). Finally, there were significant differences with regard to the TAP divided attention task ($t(1, 25.450) = 10.651$, $P < .01$, $d = .511$); again, the control group had a lower median reaction time to the visual stimulus (M = 695.94, SD = 70.96) than the patient group (M = 783.92, SD = 73.20). Regarding the other indices of neuropsychological functioning, no significant group differences were found, although the observed effects for alertness and working memory ranged from small to medium ($d = .205$ – $d = .397$).

Global Functional Connectivity Results

The results of global FC showed increased connectivity in the patient cohort in contrast to the controls in the area of the precuneus (MNI: 2/–74/46; *t*-value = 5.67) and the posterior cingulate cortex (PCC) (–10/–44/36; $t = 4.25$). Furthermore, reduced connectivity in the cerebellum was detected bilaterally (2/–70/–18, $t = 5.89$; –4/–54/–40, $t = 4.24$). Results reported survive Family-Wise-Error (FWE)-cluster correction ($P < .05$) (Figure 1).

Discussion

In this 15 years follow-up study of low-grade childhood cerebellar tumor patients treated by surgery only, we were able to relate the neuropsychological outcome of the patients to the global functional connectivity of the brain. Compared with controls, the patients showed an increased functional connectivity in the precuneus and PCC and impairments in various domains of overall intellectual functioning, executive functioning, information processing speed, and attentional performance. The differences in the neuropsychological functioning of the patients were subtle compared with the expected average percentile and reached significance in a small set of subdomains only and only when compared with high-achieving controls.[19] Nevertheless, an increase in the functional connectivity of the precuneus/PCC could be detected which could qualify rsfMRI as a new additive method. As such, the cumulative effect of many subtle impairments in subdomains of cognitive functioning, which were hardly detectable with detailed neuropsychological testing, could be directed to the precuneus/PCC area with rsfMRI.

The difficulty to measure the impact of cerebellar tumor resection on neuropsychological functioning may partly reflect the contradictory results available in the literature. In a study by Levisohn et al, for instance, abnormal deficits in domains of working memory were encountered in 5 out of 15 tested (33%) patients with only 2 of these 5 patients treated with surgery alone.[3] Steinlin and Imfeld investigated a group of 24 children and found an impairment in visual sequential memory in 6 out of 13 patients.[6] Moberget et al reported on a series of 20 patients in comparison to age- and sex-matched controls.[5] In this series, patients performed significantly worse in working memory and information processing speed. In contrast, Konczak et al were unable to replicate these findings and found normal values for visual sequential memory and other aspects of working memory.[26] Corroborating these latter observations, Law et al found no impairment in working memory assessed by the Working Memory Index in a group of 12 children with pilocytic astrocytomas.[16] In our series when comparing the patients with a norm population on

Table 2. Group Differences in Neuropsychological Functions

Neuropsychological Functions	Patients (n = 13) M (SD)	Controls (n = 16) M (SD)	t-Welch (d)	U(r)	P
Overall cognitive functioning (%ile)					
WIE IQ	48.62 (29.14)	85.25 (15.45)		176.00 (*.587*)	.001**
Information processing speed (%ile)					
TMT (numbers)	51.23 (35.29)	75.88 (13.58)		142.00 (*.322*)	.092
TMT (letters)	49.54 (30.66)	75.69 (15.35)		155.00 (*.423*)	.025*
WIE visuom. proc.	38.92 (35.29)	70.00 (24.20)		154.50 (*.412*)	.025*
WIE info. processing	40.75 (35.28)	77.38 (25.08)		147.00 (*.442*)	.017*
Cognitive flexibility (%ile)					
TMT (numbers/letters)	53.00 (29.82)	72.40 (17.08)		134.00 (*.316*)	.098
Attentional performance					
TAP alertness (signal)					
Median	238.15 (47.76)	223.38 (36.90)	0.838 (*.346*)		.370
Variability	35.62 (20.22)	27.81 (10.30)		75.50 (*–.233*)	.215
TAP Alertness (no signal)					
Median	230.38 (32.61)	227.13 (35.55)	0.066 (*.205*)		.799
Variability	32.77 (11.75)	26.19 (10.53)		72.50 (*–.257*)	.170
TAP working memory					
Median	624.08 (146.49)	566.06 (145.85)	1.129 (*.397*)		.298
Completeness	2.08 (2.10)	0.81 (0.98)		65.50 (*–.327*)	.092
Accuracy	12.92 (2.10)	14.19 (0.98)		142.50 (*.327*)	.092
TAP incompatibility					
Median	420.31 (85.93)	380.56 (46.55)		73.00 (*–.252*)	.184
Completeness	0.00 (0.00)	0.00 (0.00)		104.00 (*.000*)	1.000
Accuracy	57.62 (3.64)	58.63 (1.03)		93.50 (*–.089*)	.650
TAP divided attention (cross-modal)					
Median—auditive	530.77 (66.85)	551.13 (75.77)	0.590 (*-.157*)		.449
Completeness—auditive	0.69 (1.03)	0.69 (0.70)		113.00 (*.080*)	.714
Accuracy—auditive	15.31 (1.03)	15.31 (0.70)		95.00 (*–.080*)	.714
Median—visual	783.92 (73.20)	695.94 (70.96)	10.651 (*.511*)		.003**
Completeness—visual	1.00 (1.23)	0.63 (0.62)		95.00 (*–.080*)	.714
Accuracy—visual	16.00 (1.23)	16.38 (0.62)		113.00 (*.080*)	.714

Abbreviations: M, mean; SD, standard deviation; *t,* independent samples *t*-test (Welch correction); *d*, effect size (Cohen's *d*); *U,* Mann-Whitney *U*-test; *r*, effect size; WIE, Wechsler Intelligence Scales; IQ, intelligence quotient; TMT, Trail Making Test; TAP, test battery for attentional performance (*Median* = reaction time in seconds, *Variability* = SD of reaction time in seconds, *Completeness* = number of omissions, *Accuracy* = number of correct answers); *%ile*, computed percentile based on the reference norm population for each subject (expected average = 50, average range = 16-84); *visuom.proc.*, visuomotor processing.
*P < .05, **P < .01 (2-tailed).

measures of cognitive functioning, only a few significant differences could be detected, which were mostly related to aspects of attention.[19]

Resting-state fMRI has already been shown to work as an additive method in the effort to better understand the brain functional correlates of neuropsychological performance.[14,27,28] The precuneus/PCC area is a well-characterized hub in the default mode network, which has a greater activity during rest compared with action and is implicated in various aspects of self-referential processing.[29,30] Likewise, the PCC is implicated as a key structure for arousal and awareness, controlling the balance between internal and external attention and environmental change detection.[31,32] All of these functions interplay to a various and dynamic extent in the neuropsychological performance. The activity of these cortical areas has clearly been correlated with the efficiency of cognitive processing in various contexts.[33]

In this regard, the hyperconnectivity of the precuneus/PCC in our series underlines the central role of these areas in the

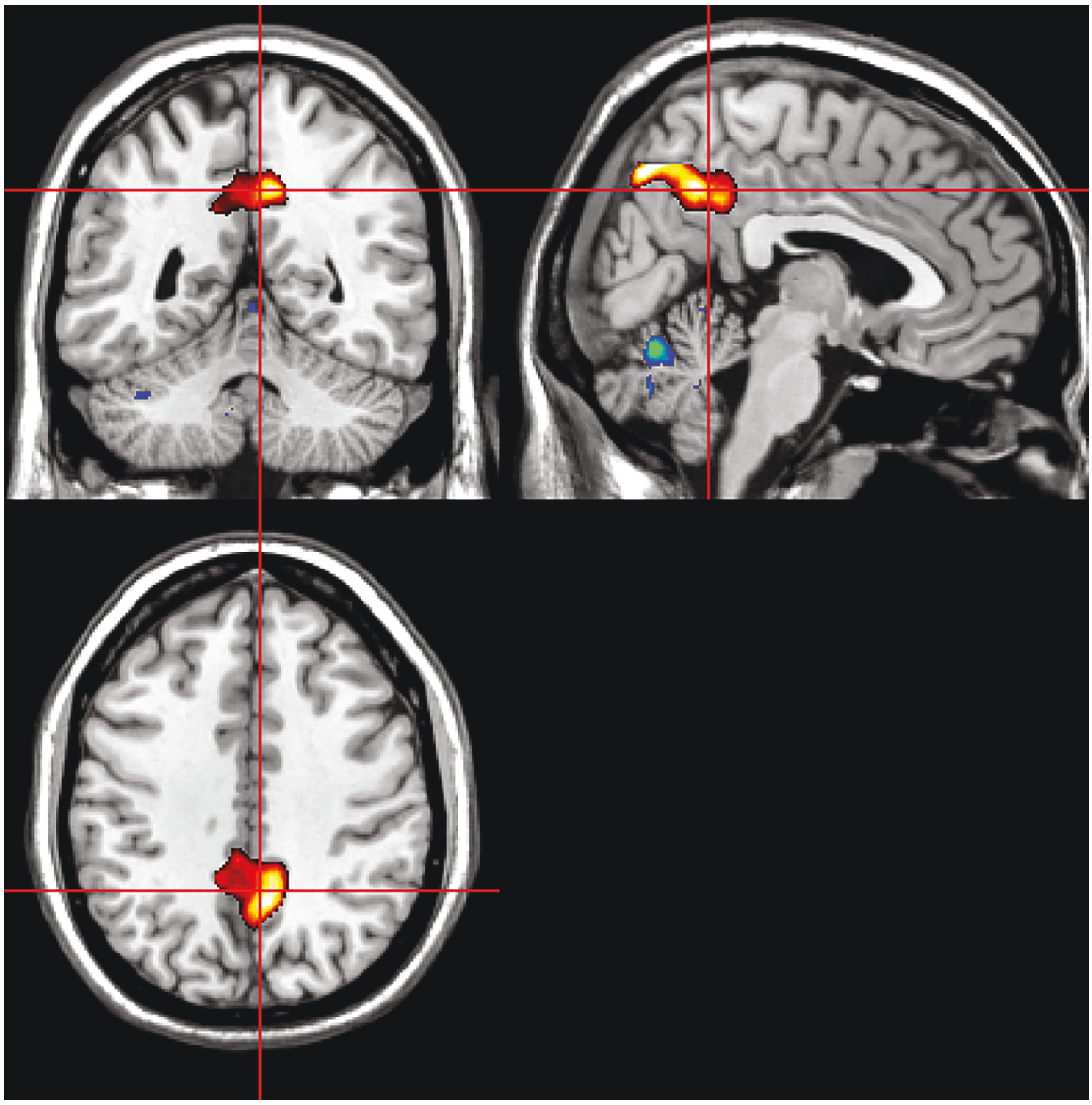

Figure 1. Global functional connectivity. The precuneus/posterior cingulate cortex area shows increased functional connectivity in patients compared with controls.

functional organization of the brain and confirms the cerebellar contribution to it.[29–34] As such, our finding adds a new insight into the cerebellar input to brain functional systems and their behavioral correlates, as a former study linking the functional connectivity of the brain to the cerebellum was confined to healthy subjects.[29,35,36] Information processing uses the aforementioned skills to include attention mechanisms for bringing in information, working memory for actively manipulating information, and long-term memory for passively holding information back for the future.[37]

The hyperconnectivity of the precuneus/PCC area in patients after childhood cerebellar tumor surgery may be interpreted as either a compensation mechanism or a failure to downregulate and supress its activity during development. As a consequence, multiple brain functional systems were influenced in a cumulative manner hindering our patients to develop the same level of cognitive functioning as our high-achieving controls. Likewise, cerebellar dysfunction has already been linked to impairments in information processing speed, and it has been suggested that a lack of the optimization and automation role of the posterior cerebellum may induce information processing speed slowness.[27,38] One explanation could be that in analogy to motor skills, the role of the cerebellum involves a transition from controlled to automatic processing. Cognitive tasks that initially require problem-solving and attention become increasingly efficient, stereotyped, and independent from the

oversight of the precuneus/PCC area.[37] In case of a cerebellar functional disturbance following childhood cerebellar tumor surgery, this oversight may be restored as reflected by the increased functional connectivity of the precuneus/PCC seen in our patients.[34,39,40]

The potential value of rsfMRI with global functional connectivity analysis as an outcome assessment tool could be that (1) it can measure brain functional systems in a global unbiased manner and (2) it can be incorporated into the routine follow-up imaging schedule.

Limitations of the Study

Our group-level analysis of a relatively small sample size may have little informative value for the individual patients. Therefore, a larger patient cohort and a related global FC database consisting of healthy control subjects may be needed to draw definite conclusions for the individual patient in creating cutoff biomarkers.

Conclusion

Resting-state fMRI has the potential to serve as an additive measure for the cognitive outcome assessment in neuro-oncology. The precuneus/PCC brain region is heavily involved in the cerebral associative oversight of cerebellar cognitive function.

Keywords

cerebellar pilocytic astrocytoma | cognitive outcome | precuneus | resting state functional MRI.

Funding

This work was supported by the Austrian Science Fund (FWF), project KLI 252 dedicated to C.D.

Conflict of interest statement. The authors have declared that no competing interests exist.

Authorship statement. Conception and design: C.D. and T.C; provision of study material or patients: C.D., M.C., T.P., T.C., I.S. D.P., U.L., and V.S; collection and assembly of data: J.C., C.D., M.C., T.C., K.K., and G.K; data analysis and interpretation: R.S., R.L., C.D., and T.C; manuscript writing, final approval of the manuscript, and accountable for all aspects of the work: all authors.

Data Availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

References

1. Aarsen FK, Paquier PF, Arts WF, et al. Cognitive deficits and predictors 3 years after diagnosis of a cerebellar pilocytic astrocytoma in childhood. *J Clin Oncol*. 2009;27(21):3526–3532.
2. Beebe DW, Ris DM, Armstrong D, et al. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National collaborative research studies (CCG 9891/POG9130). *J Clin Oncol*. 2005;23(22):5198–5204.
3. Levisohn L, Cronin-Colomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumor resection in children. *Brain*. 2000;123(5):1041–1050.
4. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science*. 1994;266(5184):458–461.
5. Moberget T, Andersson S, Lundar T, et al. Long-term supratentorial brain structure and cognitive function following cerebellar tumour resections in childhood. *Neuropsychologia*. 2015;69:218–231.
6. Steinlin M, Imfeld S. Neuropsychological long-term sequelae after posterior fossa tumor resection during childhood. *Brain*. 2003;126(9):1998–2008.
7. Davis E, Pitchford NJ, Jaspan T, McArthur D, Walker D. Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood. *Cortex*. 2010;46(7):919–932.
8. Schmahmann J, Guell X, Stoodley C, et al. The theory and neuroscience of cerebellar cognition. *Annu Rev Neurosci*. 2019;42:337–364.
9. Guell X, Gabrieli J, Schmahmann J. Embodied cognition and the cerebellum: perspectives from the dysmetria of thought and the universal cerebellar transform theories. *Cortex*. 2018;100:140–148.
10. Biswal B, Yetkin F. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34(4):537–541.
11. Habas C, Kamdas N. Distinct cerebellar contribution to intrinsic connectivity networks. *J Neurosci*. 2009;29(26):8586–8594.
12. Ziemus B, Baumann O, Luerding R, et al. Impaired working memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit. *Neuropsychologia*. 2007;45(9):2016–2024.
13. Raichle ME. Cognitive neuroscience. *Nature*. 2001;12:128–130.
14. Sorg C, Riedl V, Muhlau M, et al. Selektive changes in resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2007;104(47):18760–18765.
15. Wang K, Liang M, Wang L, et al. Altered functional connectivity in early Alzheimer's disease: a resting state fMRI study. *Human Brain Mapp*. 2007;28(10):967–978.
16. Law N, Bouffet E, Laughlin S, et al. Cerebello-thalamo-cerebral connections in pediatric brain tumor patients: impact on working memory. *Neuroimage*. 2011;56(4):2238–2248.
17. Rueckriegel SM, Bruhn H, Thomale UW, et al. Cerebral white matter fractional anisotropy and tract volume as measured by MR imaging are associated with impaired cognitive and motor function in pediatric posterior fossa tumor survivors. *Pediatr Blood Cancer*. 2015;63(7):1252–1258.

18. Reichert J, Chocholous M, Leiss U, et al. Neuronal correlates of cognitive function in patients with childhood cerebellar tumor lesions [published online ahead of print March 21, 2017]. *PLoS One.* 12(7):e0180200.
19. Pletschko T, Felnhofer A, Lamplmair D, et al. Cerebellar pilocytic astrocytoma in childhood: investigating the long-term impact of surgery on cognitive performance and functional outcome. *Dev Neurorehabil.* 2018;21(6):415–422.
20. Kollndorfer K, Fischmeister FPS, Kasprian G, et al. A systematic investigation of the invariance of resting-state network patterns: is resting-state fMRI ready for pre-surgical planning? *Front Hum Neurosci.* 2013;7(95):95.
21. Christensen BK, Girard TA, Bagby RM. Wechsler adult intelligence scale-third edition short form for index and IQ scores in a psychiatric population. *Psychological Assessment,* 2007;19(2),236–240.
22. Jacobs C, Petermann F. Wechsler Intelligenztest für Erwachsene (WIE). *Z Psychiatr Psychol Psychothe.* 2007;55(3):205–208.
23. Von Aster M, Neubauer AC, Horn R. *Wechsler Intelligenztest für Erwachsene (WIE). German Version of the WAIS-III by David Wechsler.* Göttingen: Hogrefe; 2006.
24. Zimmermann P, Fimm B. *Testbatterie zur Aufmerksamkeitsprüfung (TAP).* Herzogenrath: Psytest; 2006
25. Fine E.M., Delis D.C. (2011) Delis -Kaplan Executive Functioning System. In: Kreutzer J.S., DeLuca J., Caplan B. (eds) Encyclopedia of Clinical Neuropsychology. New York, NY: Springer.
26. Konczak J, Schoch B, Dimitrova A, et al. Functional recovery of children and adolescents after cerebellar tumour resection. *Brain.* 2005;128(6):1428–1441.
27. Bonnet M, Allard M, Dilharreguy B, et al. Cognitive compensation failure in multiple sclerosis. *Neurology.* 2010;75(14):1241–1248.
28. Bassett DS, Nelson BG, Mueller BA, et al. Altered resting state complexity in schizophrenia. *Neuroimage.* 2012;59(3):2196–2207.
29. Zhang S, Li CS R. Functional connectivity mapping of the human precuneus by resting state fMRI. *Neuroimage.* 2012;59(4):3548–3562.
30. Fox MD, Snyder AZ, Vincent JL, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *PNAS.* 2005;102(27):9673–9678.
31. Laureys S, Faymonville ME, Luxen A, et al. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet* 2000;355(9217):1790–1791.
32. Mesulam MM. From sensation to cognition. *Brain.* 1998;121:1013–1052.
33. Weissman DH, Roberts KC, Visscher KM, et al. The neural bases of momentary lapses in attention. *Nat Neurosci.* 2006;9(7):971–978.
34. Hagmann P, Cammoun L, Gigandet X, et al. Mapping the structural core of the human cerebral cortex. *PLoS Biol.* 2008;6(7):e159.
35. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain.* 2014;137(1):12–32.
36. Cavanna A, Trimble M. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* 2006;129(3):564–583.
37. Koziol LF, Budding D, Andreasen N, et al. Consensus Paper: The cerebellum's role in movement and cognition. *Cerebellum.* 2014;13(1):151–177.
38. Moroso A, Ruet A, Lamargue-Hamel D, et al. Posterior lobules of the cerebellum and information processing speed at various stages of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2017;88(2):146–151.
39. Brodt S, Pöhlchen D, Flanagin V, et al. Rapid and independent memory formation in the parietal cortex. *Proc Natl Acad Sci USA.* 2016;113(46):13251–13256.
40. Levy DA. Towards an understanding of parietal mnemonic processes: Some conceptual guideposts. *Front Integr Neurosci.* 2012;6:41.