Long-term cognitive deficits in pediatric low-grade glioma (LGG) survivors reflect pre-treatment conditions – report from the German LGG-studies

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Conflict of interest

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Contribution of authors

Conception and design: Traunwieser, Gnekow, Kandels
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Abstract

Background: Disease and treatment contribute to cognitive late-effects following pediatric low-grade glioma (LGG). We analyzed prospectively collected neuropsychological data of German pediatric LGG-survivors and focused on the impact of hydrocephalus at diagnosis, neurofibromatosis type 1 (NF1) status and extent of surgery.

Patients and Methods: We used the neuropsychological basic diagnostic screening tool based on the Cattell-Horn-Carroll model for intelligence and the concept of cross-battery assessment at 2 and 5 years from diagnosis for 316 patients from the German pediatric LGG-study and LGG-registry (7.1 years median age; 45 NF1; cerebral hemispheres 16%, supratentorial midline 39%, infratentorial 45%). Hydrocephalus was classified radiologically in 137 non-NF1 patients with infratentorial tumors (95/137 complete/subtotal resection).

Results: Patients with NF1 vs. non-NF1 exhibited inferior verbal short-term memory and visual processing (p<.001-.021). In non-NF1 patients infratentorial tumor-site and complete/subtotal resection were associated with sequelae in visual processing, psychomotor speed and processing speed (p<.001-.008). Non-NF1 patients without surgical tumor reduction and/or non-surgical treatment experienced similar deficits. Degree of hydrocephalus at diagnosis had no further impact. Psychomotor and processing speed were impaired comparably following chemo-/radiotherapy (p<.001-.021). Pre-treatment factors as NF1 or tumor-site were relevant at multivariate analysis.

Conclusion: All pediatric LGG-survivors are at risk to experience long-term cognitive impairments in various domains. Even surgical only management of cerebellar LGG or no treatment at all, i.e. biopsy only/radiological diagnosis did not protect cognitive function. Since pattern and extent of deficits are crucial to tailor rehabilitation, neuropsychological and quality of survival assessments should be mandatory in future LGG-trials.
**Key words**

Pediatric low-grade glioma, neuropsychology, hydrocephalus, neurofibromatosis, resection

**Key points**

1. Pediatric LGG compromises visual processing, motor function, and processing speed

2. Deficits occur independently of tumorsite, major surgery, and degree of hydrocephalus

3. Survivors with NF1 fare worse. The tumor impacts more than adjuvant treatment.

**Importance of the Study**

Reports on cognitive sequelae following pediatric low-grade glioma (LGG) indicate a role for tumor --site, treatment and complications. We analyzed prospectively collected neuropsychological data of 316 German pediatric LGG-patients applying the neuropsychological basic diagnostic screening tool. At 2 and 5 years from diagnosis we identified significant cognitive impairments for the majority of patients with LGG at any site independent of neurofibromatosis type 1 status. Deficits mainly affected visual processing, motor function and processing speed. They occurred i) even following complete/subtotal resection of cerebellar LGG, ii) without non-surgical treatment after biopsy/radiological diagnosis, and iii) were independent of the degree of hydrocephalus at diagnosis. In small subgroups, they did not decline over time or differ between non-surgical treatment modalities. Since type and extent of deficits are crucial to tailor adequate rehabilitation programs, neuropsychological and quality of survival assessments should be mandatory in future LGG trials.
Introduction

Low-grade glioma (LGG) constitute the largest group of pediatric brain tumors with high overall survival rates at 10 to 20 years\textsuperscript{1-4}. Patients may suffer from a multitude of late effects, specifically cognitive impairments generally attributed to tumor site, surgical intervention and complications as well as to non-surgical treatment\textsuperscript{5-9}.

Neuropsychological assessments of pediatric brain tumor survivors disclosed a wide range of late deficits including reduced overall cognitive functioning and intelligence, minor academic achievement and lower income as well as inferior specific neuropsychological skills\textsuperscript{10-12}. Cognitive late effects were found in survivors of high-grade tumors and of LGG\textsuperscript{13}, i.e. lower IQ-score beside long-term health issues\textsuperscript{5}. Survivors were found to be at risk for deficits in neuropsychological dimensions such as attention, processing speed, executive functioning, visual-spatial memory, language and verbal short-term memory over time\textsuperscript{14}. Although some studies proved good functional outcomes without severe quality of life (QoL) issues and few neurocognitive differences when comparing patients after treatment of cerebellar pilocytic astrocytoma to the healthy norm\textsuperscript{15-17}, impairments were detected when comparing LGG-patients to high-achieving peers\textsuperscript{17} or their siblings\textsuperscript{13}.

A large number of risk factors for the development of sequelae and possible predictors for cognitive decline in LGG-patients has been identified\textsuperscript{5,14,18,19} including hydrocephalus\textsuperscript{14,20}, specific tumor sites\textsuperscript{21,22}, extent of surgery and non-surgical treatment\textsuperscript{13,14,23,24}.

Neurofibromatosis type 1 (NF1) positive LGG-patients are often already compromised by pre-existing cognitive difficulties such as lower visual-motor integration and memory function. Nearly one out of two patients meets criteria for attention deficit hyperactivity disease (ADHD)\textsuperscript{25}. Interpretation of results from cognitive testing of LGG-patients is often hampered by small patient series, widespread diagnostic time-points\textsuperscript{17,24,26} or variable
outcome parameters, including overreliance on full-scale IQ scores or adaptive behavior scales, which do not capture the full range of cognitive skills that may be affected by disease and treatment. Specifically, full-scale IQ does not cover all essential outcome parameters.

We analyzed cognitive assessments of German and Swiss LGG-patients from the multicenter SIOP-LGG 2004-study and LGG-registry. Data were prospectively collected in the neuropsychological accompanying study applying the German “Neuropsychological Basic Diagnostic” (NBD) screening tool with age-appropriate tests. We asked whether we were able to corroborate tumor location, surgery, and pre-treatment factors like NF1 status and hydrocephalus as risk factors for cognitive late-effects in a multicenter setting. We added results of longitudinal observation and following non-surgical treatment.

Patients and methods

Eligibility

The prospective, multinational and multicenter SIOP-LGG 2004-study registered patients with LGG of all sites from 2004 to 2012, and was continued in Germany as LGG-registry until 2018. Inclusion criteria comprised age <18 years, histologic diagnosis of LGG according to the effective WHO classification, and no prior non-surgical therapy. Radiologic diagnosis was accepted as an exception. Central review for pathology and radiology was recommended.

Informed consent was obtained from patients, parents and/or guardians. The Institutional Review Board approved SIOP-LGG 2004-study and LGG-registry observed the Declaration of Helsinki in its revised version (Edinburgh, Scotland, 2000), and the WHO and European Community rules of “Good Clinical Practice” (effective 17.01.1997).
Treatment strategy

Following the SIOP-LGG 2004-study strategy (supplementary Figure 1), best safe resection of the primary tumor was recommended at diagnosis. Patients with complete resection were to be observed, as well as patients following incomplete resection, biopsy or radiological diagnosis if no threatening neurological symptoms were present. Severe initial symptoms or clinical/radiological progression during observation indicated the start of non-surgical treatment, if resection remained infeasible. Children <8 years and all children with NF1 were to receive primary chemotherapy. Older children ≥8 years without NF1 were allowed to receive either primary radiotherapy or chemotherapy upon individual decision at the local treatment center. Primary chemotherapy with vincristine and carboplatin for 18 months, without or with additional etoposide for randomized patients, was given as reported elsewhere. Radiotherapy was scheduled with a total dose of 54 Gray using either photons or protons. Brachytherapy/interstitial radiosurgery for suitable tumors was applied with 125-Iodine seeds. Treatment for further clinical and radiologic progression was not standardized, but included all modalities following discussion in local and reference tumor boards.

Neuro-imaging at diagnosis and follow-up

Neuro-imaging at diagnosis (including the grading of hydrocephalus, supplementary Figure 2), following surgical interventions, assessing response of non-surgical treatment and during the further course of disease followed recommendations of the German pediatric brain tumor network and published consensus and is detailed in the supplementary materials.

Neuropsychological Basic Diagnostic (NBD)

The neuropsychological accompanying study included patients from the SIOP-LGG 2004-study and the LGG-registry for screening of basic neuropsychological functions with the German NBD. Assessments were scheduled at diagnosis (T0), approximately 2 years after
diagnosis (T1), i.e. following end of first-line treatment for those receiving adjuvant therapy, and during follow-up about 5 years after diagnosis (T2). The assessment periods for T1 were 1.6-3.6 years and for T2 3.7-6.6 years, respectively. Anonymized data were forwarded to the study center.

The NBD screening tool is based on the Cattell-Horn-Carroll (CHC) model for intelligence\textsuperscript{30} and the concept of cross-battery assessment (XBA)\textsuperscript{31}. The CHC model represents intelligence in several major domains (supplementary Figure 3), most of which can be tested by age-appropriate tests. Cognitive domains represented in the NBD include fluid intelligence (Gf), visual processing (Gv), verbal short-term memory (Gsm), crystallized intelligence (Gc), psychomotor speed (Gps) and cognitive processing speed or selective attention (Gs) (Table 1). The NBD is a modified version of the “Wuerzburger psychologische Kurzdiagnostik (WUEP-KD)” developed by Ottensmeier et al.\textsuperscript{32} using the XBA by combining different tests and subtests to feasibly measure primary cognitive abilities.

Assessments from non-NF1 and NF1 patients included in this report had to meet the following criteria: (1) patient age of at least 4 years at neuropsychological assessment, (2) adequate visual acuity to be able to participate, (3) intracerebral primary LGG, (4) no concurrent chemotherapy treatment, (5) no record of premorbid neurological or psychiatric diseases (i.e. psychiatric disorders like obsessive compulsive disorder, depression or psychotic symptoms interfering with completion of the tests), and (6) no compromising neurologic symptoms at the time-point of assessment (i.e. the Beery-VMI cannot be completed in the case of severe ataxia, hemiparesis or visual impairment), no tumor progression or oncologic long-term complications.

Younger or visually impaired patients not eligible for the test material were excluded. As well, patients who had had impairing immediate post-operative neurological complications
such as unresolved post-operative pediatric cerebellar mutism syndrome, and those under chemotherapy were excluded in order not to distort the results.

Statistics

For continuous variables median and range are given. Categorical variables are indicated in absolute or relative frequencies.

Results from the NBD were compared with normative data for each test with correction for age. The results are reported as standard scores (SS, mean μ=100 and standard deviation SD=15). We performed one-sample t-test or Wilcoxon-test to compare the data with expected population scores. We computed t-test for patient subgroups or Mann-Whitney-U test, if the data did not meet the necessary criteria for a t-test (normal distribution of data; n>20).

Longitudinal data were analyzed using paired t-test or Wilcoxon signed-rank test. For multiple comparisons, we adjusted the p-value using the Bonferroni-Holm method to control for family-wise error rate at level alpha. Analysis of variance (ANOVA) was performed for group differences. Welch’s F was computed if data did not meet homogeneity criteria for an ANOVA. Multivariate analysis of covariance (MANCOVA) was also computed for group differences and to control for the variables sex and age at diagnosis. Pillai’s Trace criterion was used instead of Wilk’s λ, if unequal covariance matrices were detected. Effect sizes were performed using η²; η²≥0.06 was considered a medium relevant effect. EM algorithm was computed to account for the problem of missing data.

Analyses were exploratory, and p-values were considered as descriptive measures to detect and study meaningful effects. In particular, no significance level was fixed. P-values p<0.05 were considered as statistically noticeable. Analysis was performed using SPSS version 24.
Results

Patient cohort

Thirty-eight participating pediatric oncology centers in Germany and Switzerland used the NBD in the course of standard follow-up care and reported results from cognitive assessments for 339 patients from the SIOP-LGG 2004-study and LGG-registry in the period between 12.03.2009-16.02.2017; patients had their tumor diagnosis before 31.12.2014.

Reports for 316 LGG-patients met the criteria for further analysis. Twenty-three reports were excluded for tumor location in the spinal cord (n=9), presence of neurofibromatosis type 2 (n=1), radiologic diagnosis of LGG not confirmed by central review (n=2), and concurrent treatment while tested (n=5), no data forwarded (n=4), not tested within the fixed T1/T2 intervals (n=2).

Epidemiologic data are given in table 2 and compared to all other study patients diagnosed within that period in supplementary table 1. The group of patients tested with the NBD screening tool has a comparable median age, sex distribution and portion of NF1 patients, but contains more patients in the higher age group, with cerebellar tumors, and PA histology. Epidemiologic details for further subgroups are compiled in supplementary tables 2-5.

Median age at diagnosis was 7.1 years. NF1 was diagnosed clinically in 45 patients. Primary dissemination was present in 7 patients. In 12 patients tumors later progressed with dissemination.

Tumor location was in the cerebral hemispheres for 49/316 (16%) and the supratentorial midline for 123/316 patients (39%), including 60/123 tumors in the visual pathways and 11/123 in the thalamus. Infratentorial tumors (144/316, 45%) comprised cerebellar (121/144) and brainstem tumors (23/144) analyzed together in order to avoid undersized groups. The subgroup of patients with completely or subtotally resected infratentorial tumors contained 6
with brainstem tumors. The cohort of survivors of cerebellar tumors was divided for tumor location in the vermis (56/118), and the left and right hemisphere (29/118 and 30/118, respectively; 3/118 no information).

Histologic review confirmed pilocytic astrocytoma in the majority of all patients (191/316, 60%). Neuroradiological criteria justified the diagnosis of a LGG in 61 patients, (NF1: 30/61; non-NF1 31/61 with 16 visual pathways, 4 diencephalon, 5 hemispheres, 6 cerebellum and caudal brainstem).

For half of the non-NF1 cohort extent of initial resection was complete or subtotal (136/271). A slight majority (137/271, 51%) had infratentorial tumors. Prior to cognitive testing 44/271 patients (16%) had 2 or more resections.

Non-surgical treatment had been given to 96 patients prior NBD-testing (30%). Sixty-five patients received chemotherapy (27/65 NF1), while 31 (1/31 NF1) had radiotherapy. Thirty-eight/271 non-NF1 patients were treated with chemotherapy without (12/38) or with (26/38) prior tumor volume reduction, and 10/38 had also salvage treatments including radiotherapy in 7/10 patients. Primary radiotherapy was applied in 30/271 non-NF1 patients (18 photons, 2 protons, 10 brachytherapy), 27/30 had surgical tumor volume reduction before radiotherapy, 1/30 had additional salvage treatments for subsequent progression.

Radiologic grading classified hydrocephalus at diagnosis in non-NF1 patients with posterior fossa (PF) tumors as minor in 13/137, moderate in 48/137 and severe in 10/137 patients (40/137 without hydrocephalus; 26/137 no information). A permanent shunting procedure (ventriculo-peritoneal) and/or 3rd-ventriculostomy was documented for 21/137 patients with infratentorial and for 41/134 with supratentorial tumors at diagnosis or follow-up (1/134 no information).
Results of NBD

Analysis of neuropsychological impairments included separate T1- and T2-results. Both time-points were combined for two subgroup comparisons to avoid undersized groups. Results of the NBD-testing are compiled in table 3 (compared to the expected population score) and 4 (group comparisons), raw data in supplementary table 6 and 7 (mean with standard deviation, median with interquartile range). Results of multivariate analysis are summarized in table 5a-c.

Separate analysis was performed for the small and heterogeneous group of 36 patients, who were tested at both time-points; results for 31 non-NF1 patients are summarized in supplementary table 8.

NBD T0 data were incomplete and difficult to assess in most hospitals and are listed for information, only (supplementary table 9).

Influence of NF1 status on cognitive performance

Analysis disclosed statistically significant impairments for 45 patients with NF1 with respect to Gsm at T1 (p<.001; d=0.89) and Gsm and Gv at T2 (p<.001-.021; d=0.66-1.03) when compared to 271 patients without NF1 (Figure 1a-b). When compared to the expected population score, 271 non-NF1 patients showed statistically noticeable lower results for Gv, Gps and Gs at T1 (p<.001; d=0.37-1.80) and for Gf, Gv, Gps and Gs at T2 (p<.001; d=0.36-1.91).

Additional multivariate analysis confirmed a significant effect for NF1 status vs. non-NF1 (Wilk’s λ=.87, F (8, 305) = 5.67, p<.001), with a medium effect size ($\eta^2_{par}=.13$) controlling for age at diagnosis and sex. Univariate test statistics indicated a significant effect of NF1 on Gf (F (1, 312) = 7.45, p=.038) with a small effect size ($\eta^2_{par}=.02$), on Gc (F (1, 312) = 5.54, p=.019) with a small effect size ($\eta^2_{par}=.02$), on Gsm (F (1, 312) = 20.59, p<.001) with a
medium effect size ($\eta^2_{par}=.06$), and on Gv ($F (1, 312) = 26.02, p<.001$) with a medium effect size ($\eta^2_{par}=.08$). Pairwise comparisons confirmed that NF1 patients achieved significantly lower scores in these domains than non-NF1 patients (Gf: $\Delta M_{adj.}=7.10$, SE=2.60, p=.007; Gc: $\Delta M_{adj.}=6.20$, SE=2.63, p=.019; Gsm: $\Delta M_{adj.}=10.49$, SE=2.31, p<.001; Gv: $\Delta M_{adj.}=10.12$, SE=1.98, p<.001).

**Influence of length of observation time (longitudinal cognitive performance)**

Results from both assessments (T1 and T2) were available for 31 non-NF1 patients. Their median age at diagnosis was 6.13 years. Most tumors were located infratentorially (n=17), 11 were in the supratentorial midline, only 3 were hemispheric. While 23 patients had been observed only (4 without histologic confirmation), 5 patients had received chemotherapy and 3 radiotherapy prior to testing. Test results of this heterogeneous subgroup showed no differences from T1 to T2.

**Influence of site in non-NF1 patients on cognitive performance**

Upon comparison of neuropsychological performance of non-NF1 patients with supratentorial hemispheric (n=48), supratentorial midline (n=86) and infratentorial tumor sites (n=137), group differences were statistically noticeable regarding Gps of the non-dominant hand (p=.027; $d=0.36$) and coordination of both hands (p=.014; $d=0.49$), as survivors with infratentorial locations showed the lowest mean score when compared to survivors of the other tumor sites. Further differences were detected for Gc (p=.032; $d=0.75$) with survivors of supratentorial hemispheric tumors displaying the lowest mean score when rivalled to infratentorial and supratentorial midline sites. Additional comparison of left-sided supratentorial hemispheric tumors (n=19), supratentorial midline (n=86) and infratentorial tumors (n=137) regarding Gc showed statistically noticeable differences (p=.011; $d=0.75$) with lowest mean score for survivors of left-sided supratentorial hemispheric tumors.
Analysis of survivors of right-sided supratentorial hemispheric tumors (n=27), supratentorial midline and infratentorial tumors regarding Gc displayed no statistically noticeable differences between groups.

Multivariate analysis validated no significant effect of localization on cognitive performance, but indicated an interaction between therapy prior to NBD screening and localization (Pillai’s Trace=.27, $F (48, 1416) = 1.40$, $p=.039$), with a small effect size ($\eta^2_{\text{par}}=.05$).

Univariate test statistics had shown a significant main effect of localization on Gf ($F (2, 238) = 4.09$, $p=.018$) with a small effect size ($\eta^2_{\text{par}}=.03$) and on Gv ($F (2, 238) = 4.37$, $p=.014$) with a small effect size ($\eta^2_{\text{par}}=.04$). As indicated by pairwise comparisons, these main effects resulted from significantly lower scores for Gf in patients with supratentorial hemispheric tumors compared to patients with infratentorial tumors ($\Delta M_{\text{adj}}=14.48$, SE=5.59, $p=0.31$).

Further, regarding Gv, patients with supratentorial hemispheric tumors achieved significantly lower scores than patients with infratentorial tumors ($\Delta M_{\text{adj}}=11.95$, SE=4.16, $p=0.13$), as well as lower scores compared to patients with supratentorial midline tumors ($\Delta M_{\text{adj}}=9.80$, SE=3.71, $p=0.27$).

Univariate test statistics for the interaction of therapy before NBD screening and localization indicated a significant effect on Gv ($F (6, 238) = 2.19$, $p=.045$), with a small effect size ($\eta^2_{\text{par}}=.05$). The interaction effect was due to the fact that, on average, radiotherapy patients with supratentorial hemispheric tumors achieved lower scores on Gv ($M_{\text{adj}}=70.35$, SD=8.46) than radiotherapy patients with supratentorial midline ($M_{\text{adj}}=97.01$, SD=3.24) or with infratentorial tumors ($M_{\text{adj}}=95.84$, SD=5.14 ).
Influence of infratentorial tumor site and extent of resection in non-NF1 patients on cognitive performance

NBD results for non-NF1 patients with infratentorial tumor site (137/271) revealed no significant univariate or multivariate effect of tumor site within the posterior fossa. Yet, univariate test statistics indicated a significant main effect of extent of resection on Gps of the non-dominant hand ($F(3, 88) = 3.30$, $p=0.24$), with a medium effect size ($\eta^2_{par}=.10$) and on Gps of coordination of both hands ($F(3, 88) = 3.22$, $p=.027$), with a medium effect size ($\eta^2_{par}=.10$). Pairwise comparisons indicated that these effects resulted from significantly lower scores for Gps of the non-dominant hand ($\Delta M_{adj.}=19.39$, $SE=6.55$, $p=.024$) and for Gps of both hands ($\Delta M_{adj.}=19.52$, $SE=5.82$, $p=.007$) of patients with partial vs. patients with complete or subtotal tumor resection.

Still, patients with infratentorial LGG and complete or subtotal resection prior to NBD testing (95/137; 69%) showed statistically noticeable impairments compared to the expected population score in Gv, Gps and Gs at T1 ($p<.001$; $d=0.58$-$2.38$) and of the same dimensions and effect size at T2 ($p<.001$-$0.08$; $d=0.45$-$1.73$) (Figure 1c).

In addition, 43/95 patients with cerebellar vermil tumors showed larger statistically noticeable impairments at T1 in Gps for coordination of both hands ($p=.048$; $d=0.92$) as compared to 43/95 patients with tumors of cerebellar hemispheric location. When comparing right and left cerebellar hemispheres no differences were detected. However, for combined time-points the comparison of vermil versus right versus left cerebellar site revealed significant differences for Gps of the non-dominant hand and coordination ($p=.012$-$0.035$; $d=0.70$-$0.79$).

Multivariate analysis showed no significant multivariate effect for the interaction between infratentorial sub sites and extent of resection, while univariate tests indicated a significant
interaction between infratentorial sub sites and extent of resection on Gps of the non-dominant hand ($F (6, 88) = 2.37$, $p=.036$), with a medium effect size ($\eta^2_{pa}=.14$). The interaction effect resulted from lower score in patients with left hemispheric tumors and partial resection ($M_{adj.}=33.34$, $SD=11.60$) as compared to patients with left hemispheric tumors and biopsy ($M_{adj.}=57.73$, $SD=20.98$) and to patients with complete or subtotal tumor resection ($M_{adj.}=82.96$, $SD=5.73$). Likewise, patients with right hemispheric tumors and partial resection ($M_{adj.}=64.83$, $SD=10.61$) showed lower scores than patients with right hemispheric tumors and complete or subtotal resection ($M_{adj.}=82.75$, $SD=5.98$) and patients receiving biopsy only ($M_{adj.}=103.73$, $SD=21.27$). Patients showed significant impairments at T1 in Gv ($p=.041$; $d=1.53$) if the tumor was located left-sided (14/29) as compared to right-sided (15/29). No differences were detected between the cerebellar sub-sites at T2.

For 11/31 non-NF1 patients with completely or subtotally resected infratentorial tumors and paired assessments at T1 and T2, no differences were noted between results of the 2 time points.

**Influence of hydrocephalus at diagnosis in posterior fossa tumor survivors on cognitive performance**

Patients with PF-tumors that had moderate/severe hydrocephalus (n=58) displayed significant worse Gf at T1 ($p=.032$; $d=0.78$) when compared with 53 patients with no/minor hydrocephalus (information available for 111/137 patients). No differences were detectable at T2. Seventeen/111 patients received shunting procedures.

Univariate tests indicated a significant effect of hydrocephalus on Gc ($F (1, 88) = 5.80$, $p=.018$), with a medium effect size ($\eta^2_{pa}=.06$). Multivariate analysis displayed no multivariate effect for hydrocephalus at diagnosis and pairwise comparisons revealed subgroup mean scores within the norm.
Yet, multivariate test statistics indicated a significant effect for the interaction between infratentorial subsites and degree of hydrocephalus (Wilk’s λ=.65, $F_{(24, 236)}=1.60$, p=.039), with a medium effect size ($\eta^2_{par}=.14$). For these parameters, univariate tests indicated a significant effect on Gc ($F_{(3, 88)}=3.35$, p=.023) with a medium effect size ($\eta^2_{par}=.10$) and Gsm ($F_{(3, 88)}=3.01$, p=.035) with a medium effect size ($\eta^2_{par}=.09$); however, pairwise comparisons revealed subgroup mean scores within the norm.

**Influence of management on cognitive performance**

**Observation group:** Thirty-one non-NF1 survivors with tumors in supratentorial hemispheric (5/31), supratentorial midline (20/31) and infratentorial locations (6/31) without surgical tumor volume reduction (radiological diagnosis n=20, biopsy n=11) and no adjuvant chemo- or radiotherapy had statistically noticeable lower results in Gps and Gs at T1 (p<.001-.030; d=0.65-0.85) and at T2 (p=.008; d=0.88) compared to the expected population score (Figure 1d). Fourteen/31 had moderate/severe hydrocephalus and 12/31 had permanent shunting procedures.

**Chemo- and radiotherapy groups:** The relevant discrepancy of patient age between the two non-NF1 treatment groups (supplementary table 4) precluded direct group comparison. Compared to the expected population score the chemotherapy group demonstrated lower scores for Gps and Gs at T1 and T2 (p<.001-.020; d=1.99-3.50) and for Gv at T2 (p=.032; d=1.42). The radiotherapy group scored lower for Gps of the non-dominant hand and Gs at T1 and T2 (p=.008-.030; d=1.87-3.74), for Gps of the dominant hand at T2 (p=.021; d=2.06), and for coordination of both hands at T1 (p=.014; d=3.14) (supplementary table 10, Figure 1e-f).

Multivariate analysis of non-NF1 patients showed no significant multivariate influence of the respective treatment arms before NBD screening, though univariate test statistics indicated a
significant main effect of therapy on Gv ($F(2, 238) = 2.85, p=.038$), with a small effect size ($\eta^2_{par}=.04$). Again, pairwise comparisons revealed subgroup mean scores within the norm.

The significant multivariate effect for the interaction between treatment arms, localization and extent of resection (Pillai’s Trace=.23, $F(32, 936) = 1.74, p=.007$) has a medium effect size ($\eta^2_{par}=.06$), while univariate test statistics indicated a significant effect for this interaction on Gsm ($F(4, 238) = 3.01, p=.019$), with only a small effect size ($\eta^2_{par}=.05$). However, there were no or too few cases in various combinations of factor levels.

**Discussion**

Results of cognitive testing within our prospectively registered cohort that followed the comprehensive treatment algorithm of the SIOP-LGG 2004 protocol point to significant reductions in nearly all domains of cognitive performance (if compared to the normative population). They stress the negative impact of NF1, as well as of hydrocephalus at diagnosis for infratentorial tumors in non-NF1 patients and the impact of tumor site in its relation to extent of surgery.

**Cohort and assessment comparison**

Our cohort is well comparable to other LGG-cohorts with respect to age, sex distribution, NF1 status, tumor location and histology$^{2-4}$, but excluded very young patients due to the premises of the NBD test battery. Corresponding to the defined time-points of cognitive assessment 2 and 5 years after diagnosis the cohort grew older. Yet, only few (n=36, 31/36 non-NF1) patients were examined at both occasions limiting statements about individual longitudinal development.
In view of the heterogeneous spectrum of pediatric LGG with respect to age, NF1 status, tumor site and treatment, results of limited patient numbers have to be interpreted with caution for significance\textsuperscript{15,17,26}. Analysis of neuropsychological sequelae has to implement distinct cognitive outcome variables apart from full-scale IQ-score, which are essential for quality of survival (QoS) and neuropsychological functioning, while remaining brief in execution\textsuperscript{28}. Otherwise, smaller centers may have problems to implement full neuropsychological assessment due to restricted resources\textsuperscript{35}. Still, brief assessments as the NBD meet satisfying psychometric criteria for valid analysis of cognitive functioning\textsuperscript{32}. Specific time-points of assessments are important because of time-related effects of cognitive decline such as “growing into deficit”\textsuperscript{36}. Current recommendations from the Children’s Oncology Group and the SIOP-E Brain Tumor Group for analysis of neuropsychological late effects include a broad but brief assessment of cognitive functions\textsuperscript{37-39}. Our results are based upon a representative sample size, an assessment approach for specific aspects of the CHC model and distinct diagnostic time-points.

**Impact of NF1 status**

Deficits in memory, attention, visual-spatial functions and lower IQ-score were reported in NF1 patients without brain tumors\textsuperscript{25}, but had been apparent for IQ-scores upon comparison of patients with LGG with and without NF1, as well\textsuperscript{5}. Our cohort showed noticeably different results from the expected population scores in various domains across both time points. Nevertheless, the majority of non-NF1 LGG-survivors displays scores within normal limits of one standard deviation from the population mean for most dimensions except for fine motor skills and processing speed. Comparison of results of LGG-patients affected by NF1 and without NF1 corroborates statistically noticeable differences of cognitive function for verbal short-term memory and visual-motor integration with lower scores in the NF1 cohort\textsuperscript{36,40}. Additionally, lower scores for NF1 versus non-NF1 patients were confirmed for fluid and
crystallized intelligence, verbal short-term memory, and visual processing by multivariate analysis. For crystallized intelligence however, there is only a small effect and mean scores for both NF1 and non-NF1 patients are within the norm. As in other series, the majority of NF1 patients had visual pathway glioma (28/45) and no primary surgery (32/45), but 60% (27/45) received standard-chemotherapy for progression. Results for visual-motor integration were noticeably lower for the small subgroup of NF1 patients with visual pathway glioma following chemotherapy as compared to the population norm41. Chemotherapy-associated changes in fractional anisotropy are increased in NF1, and these white matter changes may contribute to the differences in cognitive results42. Within our older cohort we could not replicate reports on language difficulties in young children with NF1 as stressed by Brei et al.43. This may be due to specific support for dyslectic children in the German school system44.

**Impact of tumor site, resection and hydrocephalus in non-NF1 patients**

Reports on the role of location stressed that patients with tumors of the cerebral hemispheres experience the greatest impairment in cognitive functioning18. Comparing patients with hemispheric, midline and brainstem LGG within the first year after surgery, Ris et al. reported no differences in cognitive functions, though – consistent with the functional organization of the brain – patients with left hemispheric tumors were at significantly greater risk for lower scores of language functions (verbal IQ and communication) than patients with right hemispheric tumors45. Upon long-term surveillance, significantly more impairment of verbal functions was revealed in survivors of supratentorial tumors, whereas an interaction with age and treatment had been ruled out13. Comparison of results from our subgroups with either supratentorial hemispheric, supratentorial midline or infratentorial tumors did show significant results concerning impairments in language functions for our patients with supratentorial hemispheric sites, more pronounced for survivors with left-sided tumors, thus
supporting the fact of relevant language impairment in supratentorial tumor sites. Multivariate analysis additionally revealed impairments for survivors of supratentorial hemispheric tumors in fluid intelligence and visual processing, further underlining the more pronounced deficits in patients with tumors of the cerebral hemispheres\textsuperscript{18}. For this subgroup, the portion of patients with chemo- (n=2) and/or radiotherapy (n=2) was too small to permit separate analysis.

On the other hand, results of psychomotor functioning were lower for our patients with infratentorial tumors as compared to other locations, reflecting the specific functional key position of this area of the brain. Deficits in patients with completely or subtotally resected cerebellar LGGs without adjuvant treatment were compiled in several reports and included problems regarding sustained attention, processing speed, language, visual-spatial functions, executive functioning, memory, as well as behavioral problems, motor dysfunction and increased proportion of reduced full-scale IQ\textsuperscript{13,23,24}. Motor deficits were already apparent within the first year after cerebellar tumor surgery in the series of Beebe et al.\textsuperscript{27} with largest effect sizes in those cognitive exams that required motor responses. Their results could not relate deficits to tumor location within the cerebellum or pre-, peri- and postsurgical factors\textsuperscript{27}. Within our patient series, complete or subtotal resection of cerebellar LGG without adjuvant treatment was followed by impairments in visual processing, psychomotor speed and processing speed/selective attention. The pattern of neuropsychological and cognitive late effects of cerebellar LGG have been described as cerebellar cognitive affective syndrome (CCAS)\textsuperscript{46}. The CCAS includes sequelae in visual-spatial functions, language, memory and regulation of affect, which are also apparent in children\textsuperscript{47} and associated with tumor location in the vermis\textsuperscript{21} and in the left cerebellar hemisphere\textsuperscript{22}. More pronounced deficits in cognitive function and fine motor skills were correlated with tumors of the cerebellar vermis\textsuperscript{21} and in visuospatial functions with LGG of the left cerebellar hemisphere\textsuperscript{22}, as well.
In our cohort of non-NF1 patients with completely or subtotally resected infratentorial tumors, those with tumors in the vermis experienced greater deficits in psychomotor speed than those with tumors in the cerebellar hemispheres two years after diagnosis, while these differences were no longer detectable at five years. Comparison of results between patients with tumors of the left or right cerebellar hemispheres did not reveal differences, though results were still inferior to the population norm. Thus, we did not observe recovery or further decline of neurocognitive function beyond T1 for survivors of all PF-sites. At this time-point median scores for vermic and hemispheric locations align, mostly displaying a downward trend (supplementary table 7), whereas within the small subgroup with consecutive assessments no differences between the results at two and five years were detected. This argues against profound recovery, while improved performance within the first year after diagnosis was reported20.

The results of the multivariate analysis indicated no differences in cognitive function between patients with vermic and both cerebellar hemispheric tumors. Nevertheless, the extent of resection impacted upon fine motor skills with lowest scores for survivors with partially resected LGG of the left cerebellar hemisphere. Yet, patients with completely/subtotally resected tumors achieved results below normal, as well. Our results support previous findings of cognitive sequelae in LGG-patients following complete and subtotal resection of cerebellar LGG5,13,14. They correspond to the concept of “growing into deficit”36, which should be borne in mind for all LGG-patients, especially those with few apparent cognitive difficulties after complete or subtotal surgery.

Patients with infratentorial tumors and moderate or severe hydrocephalus at diagnosis experienced no significant additional constraints except for fluid intelligence two years after diagnosis compared to those without or with minor signs of increased intracranial pressure at
diagnosis. Yet, both results are still within the norm, while psychomotor and processing speed are significantly lower than the expected population score at both time points.

Reports on cognitive sequelae following biopsy or radiological diagnosis in LGG are scant. Compromise of supratentorial white matter and intellectual outcome was reported by Lui et al. for a smaller patient subgroup\(^48\). These effects occurred in the wake of hydrocephalus, shunting procedures and no or just minimal surgery with tumor infiltration into healthy tissue or compression and subsequent damage of healthy tissue by mass effect\(^48\). Reduction of normal appearing white matter was linked to reduced cognitive functioning\(^19,49\) and was observed in survivors of high-grade tumors following intensive treatment\(^19\), but even in LGG-patients treated without radiotherapy\(^48\) or chemotherapy\(^50\). In our patients, when compared to the expected population score, cognitive sequelae concerning psychomotor and processing speed/selective attention were detected in patients without relevant tumor reductive surgery besides biopsy and in those with radiological diagnosis only.

Neuropsychological late effects in cerebellar LGG-patients and patients without adjuvant treatment are often “overlooked” due to conflicting results from studies and seemingly uneventful oncological treatment. We would underline that they deserve scrutinious neuropsychological surveillance for long-term cognitive outcomes and adequate rehabilitation to the same degree as patients receiving more intensive treatments to optimize their outcomes\(^45,51\).

**Impact of first-line non-surgical treatment on cognitive performance**

The use of chemotherapy for LGG instead of radiotherapy was encouraged by reports about declining IQ-scores during long-term observation, especially in younger patients and patients with NF1, despite conformal radiation therapy\(^6,52\). As a consequence, younger patients and all NF1 patients are currently rather allocated to chemotherapy\(^53\), as in our study, and NBD
results of the two treatment modalities cannot be compared directly. For both non-surgical treatment groups, psychomotor and processing speed are significantly impaired at 2 and 5 years following treatment. These results align with other reports. Weaknesses in verbal working memory, psychomotor speed, visual perception, attention and processing speed as well as overall cognition were reported for pediatric LGG-patients treated without radiotherapy. Among causative predictors of cognitive deficits, multiple surgical interventions, hydrocephalus, shunting procedures, NF1 status, and supratentorial tumor location were identified besides chemotherapy. Lower 5-years scores for the younger non-NF1 chemotherapy cohort in our report should be commented cautiously as non-surgical treatment started at individual time-points following diagnosis. Thus, the interval between non-surgical treatment and NBD-testing varies, and lower scores do not invariably indicate declining abilities over time. Almost a quarter of our chemotherapy patients had more than one treatment line, including radiotherapy for some. Our study cannot answer the question, if the preferred use of chemotherapy instead of early radiation in younger patients will be beneficial for cognitive outcome; however, the current mode of treatment allocation results in a comparable pattern of deficits and supports the demand to focus on more parameters besides radiation induced injury.

**Limitations of our report**

This report comprises a significant patient cohort, following a comprehensive treatment strategy, but allows cautious interpretation of results only.

- The NBD program was added to the SIOP-LGG 2004 brain tumor trial in 2009 and continued with the LGG-registry without a predefined research question.
- It was performed in a large number of German and Swiss institutions, where the professional experience of the involved psychologists and neuropsychologists was comparable. Yet, inclusion of patients remained a local decision.
• Although the brief NBD assessment battery meets satisfying psychometric criteria\textsuperscript{32}, it cannot be considered a full neuropsychological assessment and thus may have failed detecting other possible cognitive sequelae. Also, the distinct time-points may have failed to detect neuropsychological late effects, which may evolve at later points of time.

• Though comparison of cognitive outcome of patients receiving chemotherapy or radiotherapy was of prime interest, disparity for basic characteristics like age or tumor site rendered statistical calculation impossible.

• Further, the Beery-VMI is dependent on motor abilities and Gv score may therefore be influenced by these skills.

• The study also did not implement indirect assessment of QoL, socioeconomic status or comparable questionnaires, while current recommendations agree on combining a brief assessment of direct and indirect measurements to analyze late effects in brain tumor trials\textsuperscript{37-39}, implemented as Core-Plus approach in QoS assessments in the European Ependymoma II trial\textsuperscript{55}.

Conclusions

Patients with LGG of all intracranial sites without and with neurofibromatosis experience long-term cognitive impairments in various domains. This even concerns patients following complete/subtotal resection of a cerebellar LGG and LGG-patients without adjuvant treatment after biopsy or radiological diagnosis; their deficits relate to visual processing, motor function and processing speed. The degree of hydrocephalus at diagnosis does not seem to augment the extent of these deficits. Treatment allocation to either chemo- or radiotherapy results in a comparable pattern of deficits.

Though impairment of cognitive abilities translates differently in each patient, most patients show functional deficits in everyday life. Since adequate rehabilitation programs should be
tailored to ameliorate these deficits, timely assessment of QoS status is crucial in clinical practice and mandatory as an endpoint in future LGG-trials. Previous mono-institutional data were confirmed within our multi-institutional brain tumor network. Based on current recommendations direct neuropsychological and indirect QoL assessments should be combined and evaluated at distinct time-points.
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Legends to the figures

Figure 1 Bar graphs for main results of the NBD screening

a: T1 bar graphs for statistically noticeable results for NF1 patients vs. non-NF1 patients; b: T2 bar graphs for statistically noticeable results for NF1 patients vs. non-NF1 patients; c: T1 and T2 bar graphs for statistically noticeable results for non-NF1 patients with infratentorial tumors and complete or subtotal tumor resection; d: T1 and T2 bar graphs for statistically noticeable results for non-NF1 patients without surgical tumor volume reduction and no adjuvant chemo- or radiotherapy; e: T1 and T2 bar graphs for statistically noticeable results for non-NF1 patients following chemotherapy; f: T1 and T2 bar graphs for statistically noticeable results for non-NF1 patients following radiotherapy.
| CHC-Domain                          | Test                                                                 | Age range of test (years; months) |
|------------------------------------|----------------------------------------------------------------------|-----------------------------------|
| Fluid intelligence (Gf)            | Raven’s Coloured Progressive Matrices (CPM)                          | 6;0-10;11                         |
|                                    | Raven’s Standard Progressive Matrices (SPM)                          | from 11;0                          |
| Crystallized intelligence (Gc)     | Picture Naming subtest Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) | 4;0-5;11                          |
|                                    | Vocabulary subtest Wechsler Intelligence Scale for Children IV (WISC-IV) | 6;0-16;11                         |
|                                    | Vocabulary subtest Wechsler Intelligence Scale for Adults (WAIS-III)  | from 17;0                          |
| Verbal short-term memory (Gsm)     | Subtest Number Recall Kaufman Assessment Battery for Children II (K-ABC II) | 4;0 – 18;11                       |
| Visual processing (Gv)             | The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) | from 4;0                           |
| Psychomotor speed (Gps)            | Purdue Pegboard test (Pegboard)                                     | from 5;0                           |
| Cognitive processing speed or selective attention (Gs) | Cognitive Performance Test – short version (CPT-k) | 6;6 – 14;6                         |
Table 2 Epidemiologic data

|                                    | All (n=316) | Non-NF1 all sites (n=271) | Non-NF1 posterior fossa (n=137) |
|------------------------------------|-------------|---------------------------|---------------------------------|
| Median age at diagnosis            | 7.1         | 7.5                       | 6.0                             |
| (years, range)                     | 0.2-17.5    | 0.2-17.5                  | 0.4-16.8                        |
| Median age at assessment T1        | 9.9         | 10.0                      | 8.3                             |
| (years, range)                     | 4.0-20.6    | 4.0-20.6                  | 4.0-19.8                        |
| Median age at assessment T2        | 11.9        | 12.5                      | 11.6                            |
| (years, range)                     | 4.0-21.8    | 4.0-21.8                  | 4.0-21.7                        |
| Age group at diagnosis             |             |                           |                                 |
| <1 year                            | 7           | 7                         | 2                               |
| 1-8 years                          | 167         | 135                       | 82                              |
| >8 years                           | 142         | 129                       | 53                              |
| Sex                                |             |                           |                                 |
| Male                               | 166         | 145                       | 74                              |
| Female                             | 150         | 126                       | 63                              |
| Tumor localization                 |             |                           |                                 |
| Supratentorial                     | 172         | 134                       | --                              |
| Cerebral hemispheres               | 49          | 48                        | --                              |
| (right/left/both/)                 | (28/19/2)   | (27/19/2)                 | --                              |
| Supratentorial midline             | 123         | 86                        | --                              |
| Visual pathways                    | 60          | 32                        |                                 |
| Thalamus                           | 11          | 11                        |                                 |
| Other SML                          | 52          | 43                        |                                 |
| Infratentorial                     | 144         | 137                       | 137                             |
| Cerebellum                         | 121         | 118                       | 118                             |
| (right/left/vermis/nn)             | (30/31/57*/3)| (30/29/56*/3)         | (30/29/56*/3)                    |
| Caudal brainstem                   | 23          | 19                        | 19                              |
| Hydrocephalus at diagnosis         |             |                           |                                 |
| None                               | 133         | 100                       | 40                              |
| Minor                              | 38          | 35                        | 13                              |
| Moderate                           | 82          | 77                        | 48                              |
| Severe                             | 21          | 20                        | 10                              |
| No information                     | 42          | 39                        | 26                              |
| Shunt implantation                 |             |                           |                                 |
| 3rd ventriculostomy                | 21          | 20                        | 2                               |
| VP-Shunt                           | 50a         | 42a                       | 19a                             |
| Other                              | 1           | 1                         | 0                               |
| No shunt                           | 243         | 208                       | 116                             |
| No information                     | 1           | 0                         | 0                               |
| Histology                          |             |                           |                                 |
| PA                                 | 191         | 178                       | 117                             |
| PA WHO-grade I                     | 187         | 174                       | 116                             |
| PMA                                | 4           | 4                         | 1                               |
| SEGA                               | 1           | 1                         | 0                               |
| Glioneuronal tumors WHO-grade I    | 36          | 36                        | 10                              |
| GG                                 | 27          | 27                        | 9                               |
| Abbreviations: | 2 | 2 | 0 |
|---------------|---|---|---|
| Diffuse glioma WHO-grade II | 15 | 14 | 4 |
| PXA | 4 | 4 | 0 |
| LGG nos | 8 | 7 | 3 |
| Non-diagnostic biopsy | 4 | 3 | 0 |
| No histology | 57 | 28 | 3* |

**First surgery before NBD screening**
(including ChT & RT patients)

| Procedure | Complete resection | Subtotal resection | Partial resection | Biopsy | No surgery |
|-----------|--------------------|--------------------|------------------|--------|------------|
| Complete resection | 104 | 103 | 71 |
| Subtotal resection | 34 | 33 | 24 |
| Partial resection | 63 | 59 | 29 |
| Biopsy | 52 | 45 | 10 |
| No surgery | 63 | 31 | 3* |

**Number of resections before NBD**

| Number of resections | 1 | 2 | >2 | none |
|----------------------|---|---|----|------|
| Total | 205 | 196 | 111 |
| Surgery only | 189 | 183 | 121 |
| Biopsy only | 12 | 11 | 3 |
| Tumor reduction only | 177 | 172 | 118 |
| Primary chemotherapy | 65 | 38 | 6 |
| >1 (no RT) | 5 | 3 | 0 |
| >1 (including RT) | 7 | 7 | 1 |
| Primary radiotherapy | 31 | 30 | 7 |
| RT only | 30 | 29 | 7 |
| RT and salvage chemotherapy | 1 | 1 | 0 |
| No intervention/intervention after NBD | 31 | 20 | 3* |

**Interventions before NBD**

| Intervention | Surgery only | Biopsy only | Tumor reduction only | Primary chemotherapy | Primary radiotherapy | RT only | RT and salvage chemotherapy | No intervention/intervention after NBD |
|-------------|--------------|-------------|----------------------|----------------------|----------------------|---------|-------------------------------|---------------------------------------|
| Total | 189 | 12 | 177 | 65 | 31 | 30 | 1 | 31 |
| Surgery only | 189 | 11 | 172 | 65 | 30 | 29 | 1 | 20 |
| Biopsy only | 12 | 3 | 172 | 65 | 29 | 29 | 1 | 20 |
| Tumor reduction only | 177 | 11 | 172 | 65 | 29 | 29 | 1 | 20 |
| Primary chemotherapy | 65 | 6 | 172 | 65 | 29 | 29 | 1 | 20 |
| Primary radiotherapy | 31 | 7 | 172 | 65 | 29 | 29 | 1 | 20 |
| RT only | 30 | 7 | 172 | 65 | 29 | 29 | 1 | 20 |
| RT and salvage chemotherapy | 1 | 7 | 172 | 65 | 29 | 29 | 1 | 20 |
| No intervention/intervention after NBD | 31 | 20 | 20 | 29 | 29 | 29 | 1 | 20 |

**N for time-point of assessment**

| Time-point | T1 | T2 |
|------------|----|----|
| Total | 149 | 203 |
| T1 | 128 | 174 |

* including n=2 tumors with bilateral hemispheric involvement and n=5 with "cerebellar midline" designation

▲ VP-shunt after 3rd ventriculostomy: n=4 for all patients; n=3 for non-NF1 patients; n=0 for posterior fossa patients

* cerebellar tumors without histologic confirmation (n=3): junction of cerebellar peduncle and medulla oblongata, right cerebellar peduncle, right cerebellar hemisphere and vermis

Δ including 36 (all)/ 31 (non-NF1 all) / 17 (non-NF1 posterior fossa) patients who were tested at T1 as well

Abbreviations:
SML: supratentorial midline, PA: Pilocytic astrocytoma, PMA: Pilomyxoid variant, SEGA: Subependymal giant cell astrocytoma, GG: Ganglioglioma, DIG: Desmoplastic infantile ganglioglioma, DNT: Desmoplastic neuroepithelial tumor, RGNT: Rosette forming glioneuronal tumor, PXA: Pleomorphic xanthoastrocytoma WHO-grade II, LGG nos: Low-grade glioma not otherwise specified, ChT: chemotherapy, RT: radiotherapy
Table 3 Results of the NBD screening for all patients (n=316), for NF1 (n=45) and for non-NF1 patients (n=271) and non-NF1 subgroups when compared to the expected population score (adjusted p-values, *p<0.05, **p<0.01, ***p<0.001, including number of tests at T1 and T2)

| Domains                      | Time-points | All T1=149 T2=167 | Biopsy/radiological diagnosis T1=128 T2=13 | T1=18 T2=13 | Infratentorial tumor localization following complete or subtotal resection | Infratentorial tumor localization for extent of hydrocephalus at diagnosis | Non-NF1 | NF1 |
|------------------------------|-------------|--------------------|---------------------------------------------|-------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|---------|-----|
|                              |             | All T1=43 T2=52    |                                              |             | T1=21 T2=24                                                                | T1=19 T2=24                                                              |         |     |
| Fluid intelligence (Gi)      | T1          | 0.30*              | 0.291                                       | 0.480       | 0.284                                                                      | 0.057                                                                    | 0.060   |     |
|                              | T2          | <0.001***          | 1.000                                       | 0.582       | 1.000                                                                      | 0.651                                                                    | <0.001***|     |
| Crystallized intelligence (Gc)| T1          | 0.602              | 0.834                                       | 0.872       | 0.284                                                                      | 0.704                                                                    | 0.351   |     |
|                              | T2          | 0.541              | 1.000                                       | 0.768       | 0.900                                                                      | 0.903                                                                    | 0.195   |     |
| Verbal short-term memory (Gsm)| T1          | 0.003**            | 0.766                                       | 0.840       | 0.906                                                                      | 0.704                                                                    | <0.001***|     |
|                              | T2          | 0.018*             | 1.000                                       | 0.768       | 1.000                                                                      | 0.651                                                                    | <0.001***|     |
| Visual processing (Gv)       | T1          | <0.001***          | 0.001***                                    | 0.008*      | 0.662                                                                      | 0.016*                                                                   | <0.001***|     |
|                              | T2          | <0.001***          | 0.112                                       | 0.340       | 0.016*                                                                    | <0.001***                                                                |         |     |
| Psychomotor speed (Gps)      | T1          | <0.001***          | <0.001***                                   | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Dominant hand                | T2          | <0.001***          | 0.012*                                     | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Psychomotor speed (Gps)      | T1          | <0.001***          | <0.001***                                   | 0.030*      | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Non-dominant hand            | T2          | <0.001***          | 0.075                                       | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Psychomotor speed (Gps)      | T1          | <0.001***          | <0.001***                                   | 0.008**     | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Coordination                 | T2          | <0.001***          | <0.001***                                   | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
| Processing speed/attention (Gs)| T1          | <0.001***          | <0.001***                                   | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
|                              | T2          | <0.001***          | 0.008**                                     | <0.001***   | <0.001***                                                                  | <0.001***                                                                | <0.001***|     |
Table 4 Results of group comparisons of the NBD screening for non-NF1 patients (n=271) and NF1-patients (n=45); group comparisons for non-NF1 patients for tumor-location in relation to extent of resection and hydrocephalus (adjusted p-values, *p<0.05, **p<0.01, ***p<0.001)

| Domains                     | Time-points | NF1 vs. non-NF1 | Non-NF1 | Infratentorial tumor localization following complete or subtotal resection | Infratentorial tumor localization for extent of hydrocephalus at diagnosis |
|-----------------------------|-------------|-----------------|---------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|
|                             |             | NF1 vs. non-NF1 |         | Supratentorial hemisphere vs. supratentorial midline vs. infratentorial (combined time-points) (n=48 vs. n=86 vs. n=137) | Vermis vs. cerebellar hemisphere T1=11/8 T2=13/11 | Vermis vs. right vs. left cerebellar hemisphere (combined time points) (n=43 vs. n=24 vs. n=19) |
| Fluid intelligence (Gf)     | T1          | 1.000           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Crystallized intelligence (Gc) | T1          | 1.000           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Verbal short-term memory (Gsm) | T1          | <0.001***       |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              | T2          | 0.208           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              |             | 0.032*          |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              |             | 0.781           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Visual processing (Gv)       | T1          | 0.126           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              | T2          | <0.001***       |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              |             | 0.794           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Psychomotor speed (Gps)     | T1          | 1.000           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              | T2          | 0.363           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Dominant hand               | T1          | 0.0421          |         |                                                                          | 1.000                                      | 0.572                                                   |
| Psychomotor speed (Gps)     | T2          | 0.421           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Non-dominant hand           | T1          | 1.000           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              | T2          | 0.363           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              |             | 0.421           |         |                                                                          | 1.000                                      | 0.572                                                   |
|                              |             | 0.421           |         |                                                                          | 1.000                                      | 0.572                                                   |
| Psychomotor speed (Gps)     | T1          | 0.027*          |         |                                                                          | 0.189                                      | 0.012*                                                   |
| Coordination                | T2          | 0.014*          |         |                                                                          | 0.511                                      | 0.012*                                                   |
|                              |             | 0.014*          |         |                                                                          | 0.511                                      | 0.012*                                                   |
| Processing speed/ selective attention (Gs) | T1        | 1.000           |         |                                                                          | 0.048*                                      | 0.035*                                                   |
|                              | T2          | 0.090           |         |                                                                          | 1.000                                      | 0.035*                                                   |
|                              |             | 0.303           |         |                                                                          | 1.000                                      | 0.035*                                                   |
|                              |             | 0.224           |         |                                                                          | 1.000                                      | 0.035*                                                   |
|                              |             | 0.093           |         |                                                                          | 1.000                                      | 0.035*                                                   |
|                              |             | 0.093           |         |                                                                          | 1.000                                      | 0.035*                                                   |
Table 5a. Multivariate analysis of covariance - main effects of the fixed factor (NF) and the covariates (age at diagnosis and sex) on NBD screening measures

| Variables | Wilk's Λ | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² |
|-----------|---------|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|
| Fixed factors | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NF | 0.87 5.67 *** | 8 305.05 | 0.13 | 7.45 ** | 1 301.02 | 2.00 | 1 301.00 | 0.05 | 1 301.00 | 0.30 | 1 301.00 | 4.44 1 301.00 | 0.01 |
| Covariate | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sex | 0.98 0.76 | 8 305.02 | 0.01 | 0.25 | 1 301.00 | 0.31 | 1 301.00 | 0.04 | 1 301.00 | 0.13 | 1 301.00 | 2.81 1 301.00 | 0.01 |
| Age at diagnosis | 0.95 1.97 | 8 305.05 | 0.05 | 1.64 | 1 301.00 | 0.04 | 1 301.00 | 0.06 | 1 301.00 | 0.21 | 1 301.00 | 1.42 1 301.00 | 0.01 |

Note: For pairwise comparisons, mean scores were adjusted for the interrelations between the covariates and the dependent variables (M_a).

Table 5b. Multivariate analysis of covariance - main and interaction effects of the fixed factors (treatment arms, localization and extent of resection) and the covariates (age at diagnosis and sex) on NBD screening measures for non-NF patients

| Variables | Pillai's Trace | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² |
|-----------|----------------|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|
| Fixed effects | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Therapy | 0.06 0.83 | 24 699.03 | 0.03 | 1.94 | 3 238.02 | 0.48 | 3 238.01 | 2.85 * | 3 238.04 | 1.62 | 3 238.02 | 0.36 | 3 238.00 | 0.34 | 3 238.00 | 0.94 | 3 238.00 | 0.09 | 3 238.00 | 0.01 |
| Localization | 0.09 1.29 | 16 464.04 | 0.04 | 4.09 * | 2 238.03 | 0.12 | 2 238.00 | 4.37 * | 2 238.04 | 0.29 | 2 238.00 | 0.26 | 2 238.00 | 0.01 | 2 238.00 | 0.00 |
| Extent resection | 0.07 0.69 | 24 699.02 | 0.01 | 0.27 | 4 238.05 | 0.05 | 4 238.03 | 1.45 | 4 238.02 | 0.56 | 4 238.01 | 1.65 | 4 238.03 | 1.32 | 4 238.02 | 0.03 | 4 238.00 | 0.06 | 4 238.01 | 0.03 | 4 238.00 | 0.01 |
| Age at diagnosis | 0.06 1.71 | 8 231.00 | 0.03 | 0.55 | 1 238.00 | 0.01 | 1 238.00 | 0.11 | 1 238.00 | 0.05 | 1 238.00 | 0.76 | 1 238.00 | 0.57 | 1 238.00 | 0.50 | 1 238.00 | 0.00 |

Note: Pillai’s Trace criterion was used instead of Wilk’s Lambda due to unequal covariance matrices (Box-Test: p < .05). For pairwise comparisons, mean scores were adjusted for the interrelations between the covariates and the dependent variables (M_a).

Table 5c. Multivariate analysis of covariance - main and interaction effects of the fixed factors (cerebellar localization, extent of resection and grade of hydrocephalus) and the covariates (age at diagnosis and sex) on NBD screening measures for non-NF patients (infratentorial)

| Variables | Wilk's Λ | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² | F | df1 | df2 | η² |
|-----------|---------|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|---|-----|-----|-----|
| Fixed factors | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Localisation cerebellar | 0.74 0.82 | 32 300.07 | 0.07 | 0.17 | 4 88.01 | 1.08 | 4 88.05 | 0.54 | 4 88.02 | 1.28 | 4 88.06 | 0.19 | 4 88.08 | 0.39 | 4 88.02 | 0.13 | 4 88.00 | 0.08 | 4 88.00 | 0.01 |
| Extent resection | 0.69 1.34 | 24 236.12 | 0.12 | 0.20 | 3 88.00 | 1.00 | 3 88.03 | 0.39 | 3 88.01 | 1.15 | 3 88.04 | 1.08 | 3 88.04 | 3.30 * | 3 88.10 | 0.32 * | 3 88.10 | 0.26 | 3 88.02 | 0.00 |
| Hydrocephalus grade | 0.86 1.62 | 8 181.14 | 0.73 | 0.67 | 3 88.04 | 0.59 | 3 88.04 | 0.55 | 3 88.01 | 1.64 | 3 88.10 | 0.72 | 3 88.05 | 2.27 * | 3 88.14 | 0.64 | 3 88.04 | 0.73 | 3 88.05 | 0.05 |
| Age at diagnosis | 0.88 1.41 | 8 181.12 | 0.12 | 0.97 | 1 88.00 | 0.01 | 1 88.00 | 0.06 | 1 88.00 | 0.17 | 1 88.00 | 0.01 | 1 88.00 | 0.36 | 1 88.00 | 0.02 | 1 88.00 | 0.03 | 1 88.00 | 0.00 | 1 88.00 | 0.01 |

Note: For pairwise comparisons, mean scores were adjusted for the interrelations between the covariates and the dependent variables (M_a).