



Published in final edited form as:

*Pediatr Blood Cancer*. 2016 March ; 63(3): 527–534. doi:10.1002/pbc.25804.

## Effect of Sensorineural Hearing Loss on Neurocognitive Functioning in Pediatric Brain Tumor Survivors

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### Abstract

**Background**—Intensified therapy with platinum-based regimens for pediatric brain tumors has dramatically increased the number of pediatric brain tumor survivors (PBTS) but frequently causes permanent sensorineural hearing loss (SNHL). Although neurocognitive decline in PBTS is known to be associated with radiation therapy (RT), SNHL represents a potential additional contributor whose long-term impact has yet to be fully determined.

**Methods**—The neurocognitive impact of significant SNHL (Chang Scale 2b) in PBTS was assessed through a retrospective cohort study of audiograms and neurocognitive testing. Scores for neurocognitive domains and subtest task performance were analyzed to identify specific strengths and weakness for PBTS with SNHL.

**Results**—In a cohort of PBTS (n=58) treated with platinum therapy, significant SNHL was identified in over half (55%, n=32/58), of which the majority required hearing aids (72%, 23/32). RT exposure was approximately evenly divided between those with and without SNHL. PBTS were 6.7±0.6 and 11.3±0.7 years old at diagnosis and neurocognitive testing, respectively. In multivariate analyses adjusted for RT dose, SNHL was independently associated with deficits in intelligence, executive function, and verbal reasoning skills. Subtests revealed PBTS with SNHL to have poor learning efficiency but intact memory and information acquisition.

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#### Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

**Conclusion**—SNHL in PBTS increases the risk for severe therapy-related intellectual and neurocognitive deficits. Additional prospective investigation in malignant brain tumors is necessary to validate these findings through integration of audiology and neurocognitive assessments and to identify appropriate strategies for neurocognitive screening and rehabilitation specific to PBTS with and without SNHL.

### Keywords

Late Effects; Brain Tumors; Neuro-oncology; Psychosocial; Chemotherapy neurotoxicity

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### Introduction

Intensified multi-modal therapy for pediatric malignant brain tumors inclusive of chemotherapy and irradiation has substantially improved survival rates over the past decades.[1] The use of irradiation, however, has also resulted in a dose-dependent adverse impact on neurocognitive development, particularly in younger children, with longer term survivors experiencing broad declines in intelligence, executive function, and memory.[2–5] As these hidden costs became evident, strategies to protect neurocognition successfully incorporated dose-intensive chemotherapy followed by myeloablative stem cell transplant to delay or eliminate the need for radiation exposure.[6–10] These regimens rely on platinum-based therapies which effectively cross the blood-brain barrier and are cytotoxic for brain tumors, but also penetrate the blood-labyrinth barrier of the inner ear and cause functional damage to the cochlea.[11] Permanent sensorineural hearing loss (SNHL) has since become one of the principal late effects of irradiation-sparing regimens, affecting over half of those exposed to the chemotherapy agent cisplatin.[12–14]

In the general pediatric and non-brain tumor populations, even mild or unilateral hearing loss is associated with poorer academic performance, language acquisition, and quality of life.[15–19] Schreiber et al. recently reported on SNHL-associated declines in intelligence and achievement in a pediatric brain tumor population. Although performance remained within population norms, the study was conducted with short follow-up and relied only on composite neurocognitive testing scores.[20] Thus, the specific neurocognitive deficits through which SNHL impact intelligence and/or measures of executive function in survivors remain unclear. Insight into how SNHL integrates with other treatment-related sequelae to affect neurocognitive outcomes is essential for designing preventative strategies and appropriate interventions in survivors. We hypothesized that longer follow-up and more in-depth assessments of pediatric brain tumor survivors (PBTS) would demonstrate cognitive declines associated with platinum-associated SNHL across all domains, not only with respect to intelligence but also key aspects of executive function and memory. We therefore undertook this study to better understand how SNHL caused by pediatric brain tumor regimens impacts neurocognitive abilities in survivors. This knowledge will improve both surveillance and neurocognitive rehabilitation for children treated with modern platinum-based regimens.

## Methods

### Study Population

PBTS treated for a malignant brain tumor prior to 21 years of age and who underwent comprehensive neurocognitive testing and audiology evaluations were identified through clinical records from two participating institutions that have collaborative neuro-oncology programs (see CONSORT Diagram, Supplemental Figure 1). All patients received platinum-based chemotherapy and were treated with a broad variety of regimens (Supplemental Table I), including those with and without radiation therapy (RT) or stem cell transplant (SCT). As ordinary care at the participating institutions, PBTS treated on these intensive regimens are routinely referred for comprehensive late-effects screening that includes neurocognitive and audiology testing. Host, diagnosis, and therapy information were extracted including age at diagnosis, age at audiology assessment, age at neurocognitive testing, sex, self-reported ethnicity, tumor diagnosis (medulloblastoma versus other, based on composition of cohort), cumulative cisplatin dose ( $\text{mg}/\text{m}^2$ ), use of SCT (with or without myeloablative carboplatin), cranial RT (dose to whole cranium, posterior fossa), attempted tumor resection, and the presence or absence of post-operative posterior fossa syndrome. The study was approved by each institution's Institutional Review Board.

### Audiology Assessments

Audiology assessments using pure tone audiometry were performed in the study cohort as considered routine care for late effects screening in PBTS (one subject required testing with frequency-specific auditory brainstem response testing).[21] Audiograms were independently reviewed for this study by two authors (EO, BS) who were blinded to neurocognitive outcomes at the time of grading of ototoxicity with consensus obtained for any discrepancies. Where significant air-bone gaps were identified, bone conduction thresholds were utilized to determine hearing thresholds.[22] Hearing loss (HL) was graded according to the validated system established by Chang et. al.[23] For purposes of the study, the presence of significant SNHL was defined as those warranting recommendations for use of a hearing aid ( Chang Grade 2b). The presence of isolated high frequency HL (threshold of 40dB at 4kHz), unilateral HL ( Grade 2b in one ear only), recommendations for hearing aids, and reported tinnitus were collected as well.

### Neurocognitive Assessments

Developmentally appropriate neuropsychological testing was routinely performed following completion of therapy to evaluate intelligence, executive functioning, memory, visual-motor integration and achievement. As per ordinary care, all testing was performed with hearing aids in place if prescribed and/or adequate functional hearing confirmed, and understanding of all instructions ensured for each individual task and test. Age-appropriate Wechsler Intelligence Scales were used to assess verbal and visual-spatial intellectual functioning, working memory, and processing speed. Standard scores compared to population norms (mean 100, standard deviation [SD] 15) were calculated for the Wechsler Full-Scale Intelligence Quotient (FSIQ), Verbal Comprehension Index (VCI, verbal reasoning), Perceptual Reasoning Index (PRI, visual-spatial reasoning), Working Memory Index (WMI, holding and manipulating auditory information in mind), and Processing Speed Index (PSI,

speed of visual scanning and processing). Individual subtests contributing to each composite score were reported as age-adjusted scaled scores (mean 10, SD 3) except for the Wechsler Abbreviated Scale of Intelligence (WASI), for which the T-scores were converted to a scaled score. For measures of memory, achievement, and visual-motor integration, standard or scaled scores were reported as appropriate for the individual test. The wide age range included in the study necessitated combining scores from the same areas of neurocognitive function across age-appropriate tests as per precedent [10,13,24] and current recommendations.[25,26] Due to heterogeneity in memory assessment tools, combined scores for immediate and delayed verbal and visual memory were created for this study by author consensus (SON, KK, TS) from individual subtests based on aspect of memory tested. All tests contributing to each neurocognitive measure are enumerated in full in Supplemental Tables II–III.

### Statistical Analysis

To test the hypothesis that SNHL is associated with worse neurocognitive outcomes, the primary analysis assessed the impact of Grade 2b SNHL on neurocognitive testing scores. Host, diagnosis, and treatment factors were compared in those with and without SNHL using the Fisher exact test or Wilcoxon signed-rank test or unpaired two-tailed t-tests, as appropriate. For t-tests, equality of variances were formally tested and Satterthwaite approximation applied to those comparisons with significant inequality of variances ( $p < 0.05$ ). Differences in neurocognitive composite standard scores and subtest scaled scores were assessed in those with versus those without SNHL using Wilcoxon signed-rank test and unpaired one-tailed t-tests (as hearing loss would not be considered to improve neurocognition). Individual multivariate linear regression models were built analyzing all neurocognitive test scores of intelligence and function with  $p < 0.1$  on univariate analysis. As not all subtests were able to be completed due to age and/or comorbidities, to maintain adequate power for each regression model, analyses were limited to tests/scores associated with 35 patients. A base model was constructed using published predictors of neurocognitive decline in PBTS: (1) age at diagnosis, (2) stem cell transplant, radiation dose to (3) whole cranium (RT-C) and (4) posterior fossa (RT-PF), and (5) presence/absence of posterior fossa syndrome (PFS). Additional candidate predictors (Table I) were then individually tested and retained if  $p < 0.15$ . Once the final model was determined, eliminated predictors were reintroduced and retained if they were significant  $p < 0.15$  or improved the fit of the logistic model ( $R^2$ ) [no eliminated predictors met this criteria]. Once the multivariate model for each test was finalized, presence or absence of SNHL was introduced to determine the influence of SNHL on each outcome. To further examine any relative contributions of treatment modality, we also tested for an interaction between RT exposure and presence/absence of SNHL within each model and conducted identical multivariate analyses in two distinct subsets: (1) those treated with RT and (2) those treated for medulloblastoma. To depict the influence of age on use of treatment modality (SCT versus RT), a locally weighted scatter smooth plot (Lowess plot, bandwidth 0.9) was used to show the relative proportions using either treatment across the age range. All analyses were conducted with SAS, Version 9.2 (SAS Institute, Inc. Cary, NC) or STATA Release 10.0 (StataCorp, College Station, TX) with significance set to  $\alpha < 0.05$ .

## Results

Host, diagnosis, and treatment characteristics for the cohort (n=58) are presented in Table I. Mean time from diagnosis to audiology testing was  $2.6 \pm 0.4$  years and from diagnosis to neuropsychological testing  $4.6 \pm 0.5$  years. The time interval from diagnosis to neurocognitive testing was in excess of five years for over a third of the cohort (35%, 20/58). The time between audiology and neurocognitive testing was less than one year for 40% of the cohort (mean interval 1.7 years). There was no significant difference in completion of neurocognitive testing for subjects with or without SNHL (missing subtests, median 6 versus 5.5 subtests respectively,  $p=0.594$ ). The majority of the cohort were male, treated for medulloblastoma and, consistent with our institutional demographics, were of self-reported Hispanic ethnicity. Of specific relevance to the primary aim, exposure to radiation therapy was balanced between those with and without SNHL (23/32 versus 23/26,  $p=0.397$ ). Patients who received irradiation-sparing regimens incorporating stem cell transplant were substantially younger than those treated with conventional chemotherapy and irradiation (Supplemental Figure 2).

### Description of Sensorineural Hearing Loss

Over half of the cohort suffered from Grade 2b SNHL (55%, 32/58) and received speech therapy (57%, 33/58), with 45% (26/58) prescribed hearing aids. The group with SNHL was significantly younger at diagnosis ( $p=0.003$ ) and nine patients in the cohort (16%, 9/58) were younger than three years of age at time of diagnosis, seven of whom (78%, 7/9) experienced SNHL. Relevant to language-specific neuropsychological assessment tools, no significant differences were noted in ethnicity between those with and without SNHL. No significant differences in prevalence of SNHL were found based on diagnosis, RT-C, or RT-PF, use of SCT, and presence of PFS. Consistent with the literature, a trend toward increased SNHL was present in those who were exposed to the additional platinum agent carboplatinum at myeloablative doses ( $p=0.056$ ).<sup>[27]</sup> Too few survivors experienced isolated HFHL (10%, 6/58), unilateral SNHL (12%, 7/58), or tinnitus (9%, 5/58) to analyze impact on neurocognitive outcomes.

### Measures of Intelligence

Despite balanced exposure to RT, assessment of overall intelligence (FSIQ) revealed significant differences on multiple measures between PBTS with and without SNHL (Table II). Those with SNHL demonstrated significantly lower mean FSIQ scores ( $p=0.038$ ) and a nearly three-fold greater risk for below average intellectual ability or worse (FSIQ <85, relative risk 2.8, 95% Confidence Interval [95% CI] 2.7–2.9). Similarly lower mean scores were present for Perceptual Reasoning Index (i.e. visual-spatial reasoning,  $p=0.003$ ), and Working Memory Index (i.e. auditory working memory,  $p=0.003$ ). Although no differences were noted for Verbal Comprehension Index, Processing Speed Index, and Visual Motor Integration, significant differences not evident in the overall score were found for subtests within each domain, such as verbal reasoning and symbol search.

Multivariate analyses were conducted to determine significant predictors for intelligence and neurocognitive function. As summarized in Table III, after adjusting for radiation dose and

other potential confounding causes of neurocognitive decline, the presence of SNHL was associated with significantly lower scores in intellectual functioning across all domains. We found no evidence for confounding of treatment modality with hearing loss on neurocognitive outcome, in that (1) no interaction was found between exposure to RT and SNHL in any of the multivariate models (all  $p > 0.05$ ), and (2) analyses restricted to the RT ( $n=46$ ) and medulloblastoma ( $n=38$ ) subsets found similarly significant differences associated with SNHL across all neurocognitive domains (data not shown).

As compared to population norms (mean standard score of 100), working memory was found to be affected even in those without SNHL (Table III, intercept 83.81); however, even lower scores were identified in those with SNHL, thereby reflecting severe impairment in working memory. Two archetypal patient scenarios with SNHL predicted by the multivariate models further illustrate this pattern of deficits across all domains (Supplemental Figure 3) and demonstrate an effect of SNHL added to that of RT even in older children. Of the tested predictors other than SNHL, only SCT was associated with significantly better scores (Table III), wherein children who underwent SCT with delayed RT scored higher on FSIQ ( $p=0.051$ ), PSI ( $p=0.014$ ) and WMI ( $p=0.038$ ) despite being younger at time of treatment (Supplemental Figure 2). In order to understand the precise impact of SNHL on task-specific areas of neurocognitive function, multivariate analyses were conducted to determine predictors of poor performance on individual subtests as well. These results are reported in Table IV and reflect the significant influence of SNHL on performance of every subtest except Matrix Reasoning.

### Measures of Memory and Achievement

As shown in Table V, comprehensive testing was carried out to evaluate potential differences in achievement and memory function. Specific memory and achievement tests were targeted to developmental level according to conventional use (list of tests, Supplemental Table II–III). The majority of the cohort was able to complete tests of achievement (59%, 34/58) and/or memory (85%, 49/58). No clear pattern of effect of SNHL was found on memory and achievement with only significant differences found on reading and passage comprehension ( $p=0.004$ ) and immediate/delayed story recall ( $p=0.021$ / $p=0.057$ ). Caution must be exercised in interpretation of these findings, as limited power precluded adjustment for known confounding variables (e.g. age, treatment, radiation). It remains notable that irrespective of hearing status, scores of memory and achievement were overall lower than population norms (standard score of 100, scaled score of 10).

## DISCUSSION

In this report, we have provided a detailed characterization of neurocognitive deficits associated with SNHL in survivors of pediatric brain tumors treated with platinum-based chemotherapy. Consistent with our hypothesis, children with SNHL exhibit discrete neurocognitive deficits in executive function and associated measures of intelligence that cannot be directly attributed to radiation therapy or other treatment factors alone. To our knowledge, this study is the first to pair hearing status with detailed neurocognitive data to show that PBTS receiving platinum-based chemotherapy are at disproportionately greater

risk for clinically significant neurocognitive functional deficits if they develop SNHL. This observation forms the basis for pursuing strategies involving early detection, hearing augmentation, neurocognitive rehabilitation, and primary otoprotection to prevent or ameliorate the functional impact of SNHL.

Although previous studies of cancer survivors with SNHL have primarily attributed poor academic performance to learning skills compromised by hearing- and language-mediated barriers,[18,20] our data suggest SNHL results in a pattern of both verbal and non-verbal neurocognitive deficits that extend beyond knowledge acquisition alone. These include significant impairment of abstract verbal reasoning (but not fund of vocabulary), some elements of visuo-constructional abilities, auditory working memory, and processing speed. By examining both overall neurocognitive domain scores as well as task-specific performance, in PBTS with SNHL we detected a clear pattern of far broader neurocognitive deficits than those attributable to delayed language acquisition and/or knowledge base. These findings are consistent with research from non-oncology populations where hearing loss results in a pervasive neurodevelopmental effect extending beyond language-mediated skills. A study of children with isolated congenital SNHL found that fine motor and visual perception skills decline with age.[28] Studies of children with hearing loss have also shown persistent deficits in fine motor, working memory, and executive function even in those with adequate hearing correction for language acquisition.[29–31] Non-language mediated neurocognitive deficits are theorized to be due to permanent reorganization of neural pathways connecting the auditory and prefrontal cortices resulting from periods of decreased auditory stimulus.[32] Deficits due to SNHL in those studies remained present to a large degree even in those with aided hearing. Thus, while aided hearing should not be considered “normal” hearing, early intervention may still mitigate the consequences of hearing loss. [33,34] The cumulative neurodevelopmental impact of SNHL is of particular concern for PBTS through its exacerbation of existing disease- and treatment-related cognitive dysfunction, especially in younger children who are more likely to be treated with intensive, irradiation-sparing regimens that frequently cause hearing loss.[9,12,35,36] In our cohort of PBTS, SNHL was prevalent, and despite similarly prescribed aided hearing, a clear impact of SNHL on neurocognitive functioning was evident.

Our study provides insights into alleviating the impact of SNHL-associated neurocognitive deficits through developing compensatory strategies for PBTS. While Gurney et al.[18] first showed survivors of pediatric neuroblastoma to face achievement and attention difficulties due to severe platinum-associated SNHL, the specific cognitive deficits contributing to these poor outcomes over time were not defined. More recently, Schreiber et. al.[20] showed in a cohort of PBTS that SNHL adversely affects General Intellectual Ability (GIA), a composite score reflecting intelligence, as well as math and reading achievement. Our cohort confirms and more completely characterizes the adverse effect of SNHL in PBTS on intelligence by contributing a novel description of the pattern of domain-specific strengths and weaknesses in cognitive function underlying these declines. Our cohort of PBTS compared those with and without SNHL and demonstrated inferior specific verbal- and visual skill-based scores, with limitations in abstract verbal and visual-spatial reasoning, auditory working memory, and processing speed.

These findings have significant practical implications for suggesting coping strategies in daily living as well as prescribing academic accommodations. Learning efficiency in these students will be dramatically affected by weaker aspects of executive function including working memory and processing speed. PBTS with SNHL would be expected to have even greater difficulty than other PBTS holding information in their mind, sustaining attention, self-monitoring performance of tasks, executing multiple-step instructions, and they will work at a slower pace needing extra assistance, extended time, and repetition/review of content. A student could therefore have difficulty with such basic classroom tasks as copying information from the board, aural note-taking, and producing written work, especially in timed exercises under pressure. Moreover, unique educational strategies are likely necessary for PBTS with SNHL versus children with other etiologies for SNHL. The use of classic multi-modal classroom instruction as for other hearing impaired children[37] may be counterproductive in hearing impaired PBTS who could instead suffer from information overload as a result of the combined effects of their underlying therapy and SNHL. Even in those patients where a ~1SD decline results only in low-average intellectual ability, SNHL still diminishes health-related quality of life. Students classified as “borderline” (between 1–2 SD beneath the normalized mean on multiple domains) suffer a disproportionate clinical impact and academic failure from the combined effect.[38] In contrast to other cohorts, we did not find significant differences in vocabulary, reading, and math achievement scores. This may be due to the longer follow-up and delayed assessment for a large portion of this cohort, indicating survivors with SNHL may be able to cognitively adapt over time to successfully learn the necessary information.

A major strength of our study is its incorporation of comprehensive and detailed neuropsychological testing results. The range of survivor ages and abilities in our cohort necessitated combining results from an array of measures. Despite the high correlation of many of these measures, prospective research using a specified age-specific battery of tests is needed to delineate further this late effect. Nonetheless, our study represents a “real world” approach that we have shown feasible for future prospective, multicenter studies where a unified battery may not be possible. Our cross-sectional study design was unable to determine the rate of decline in this population, or whether some degree of adaptation and recovery occurs earlier in follow-up for some patients. This design also precluded exploring the effects on neurocognitive outcomes of early audiology intervention, adherence to hearing aids or speech therapy, and the differences in aided versus normal/unaffected hearing. We also acknowledge that while all survivors of therapy for the included diagnoses at our institutions are routinely referred for audiology and neurocognitive evaluation, we cannot completely exclude the potential for some level of selection bias. However, even in the unlikely scenario wherein our cohort represents only those at greatest risk based on clinical concerns, our data still supports the presence of an adverse association between SNHL and neurocognition in such a group of highly-affected survivors. While SCT was associated with better neurocognitive functioning, the study was not designed to further explore this or other secondary findings, such as the influence of PFS on neurocognition. Such an effect of SCT has been reported previously in the literature due to delaying or eliminating irradiation therapy,[13] and further prospective investigation into the complex



interactions of age, platinum-associated hearing loss, stem cell transplant, and radiation therapy, is planned on an upcoming clinical trial for pediatric malignant brain tumors.

Notwithstanding these limitations, the study's principal finding shows an additive adverse effect of SNHL on neurocognitive outcomes in PBTS even after controlling for radiation therapy and other potential confounding variables through multivariate and subset analyses. Our findings require validation in additional cohorts, but as survival and neurocognitive outcomes improve with the replacement of radiation by platinum-based therapy with SCT, attention must now be given to identification and prevention of the neurocognitive impact resulting from other components of these regimens.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The authors would like to thank Dr. Richard Sposto and Colleen Azen of the Children's Center for Cancer and Blood Diseases Biostatistics Core for their insight and assistance with implementation of the statistical analyses.

**Funding:** Supported in part by the National Institutes of Health/National Center for Advancing Translational Sciences (UL1TR000130) via the Southern California Clinical and Translational Science Institute, and by The Saban Research Institute.

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TABLE I

Demographic, Disease, and Treatment Variables (n=58)

Variable	Entire Cohort N (%)	Hearing Loss <sup>1</sup> N (%)	No Hearing Loss <sup>1</sup> N (%)	p <sup>2</sup>
Cohort	58 (100)	32 (55)	26 (45)	
Age, years (mean±SE)				
At Diagnosis	6.7±0.6	5.1±0.6	8.7±0.9	<b>0.003</b>
At hearing assessment	9.2±0.7	7.8±0.8	10.6±1.0	0.151
At neurocognitive testing*	11.3±0.7	10.7±0.9	12.0±1.1	0.352
Sex				
Male	36 (62.1)	20 (63)	16 (62)	1.000
Female	22 (37.9)	12 (37)	10 (38)	
Ethnicity				
Hispanic	34 (58.6)	19 (59)	15 (58)	1.000
Non-Hispanic	24 (41.4)	13 (41)	11 (42)	
Diagnosis				
Medulloblastoma	39 (67.2)	23 (72)	16 (62)	0.574
Other CNS tumor <sup>3</sup>	19 (32.8)	9 (28)	10 (38)	
Cumulative CDDP, mg/m2 (mean±SE)	333±16	343±22	320±24	0.348
Stem Cell Transplant				
Yes	20 (34.5)	14 (41)	6 (25)	0.164
No	38 (65.5)	20 (59)	18 (75)	
Myeloablative Carboplatinum				
Yes	19 (32.8)	14 (44)	5 (19)	0.056
No	39 (67.2)	18 (56)	21 (81)	
Cranial Radiation				
Yes	46 (79.3)	23 (72)	23 (88)	0.397
No	12 (20.7)	9 (28)	3 (12)	
Radiation Dose, Gy (Mean±SE) <sup>4</sup>				
Whole Brain	29.5±1.8	29.1±2.3	29.9±3.0	0.838
Posterior Fossa	33.7±1.8	32.1±2.3	35.3±2.7	0.372
Tumor Resection Attempted (n,%)				
Yes	54 (93.1)	31 (97)	23 (88)	0.316
No	4 (7.9)	1 (3)	3 (12)	
Posterior Fossa Syndrome <sup>5</sup>				
Present	24 (41.4)	11 (39)	13 (50)	0.584
Absent	30 (51.7)	17 (61)	13 (50)	

<sup>1</sup> Significant hearing loss defined as Chang Grade 2b.<sup>2</sup> Comparison of presence/absence of hearing loss via Fisher exact test, Wilcoxon sign-rank test, or unpaired t-test, all tests 2-tailed, significance set at  $\alpha < 0.05$  (bolded).

<sup>3</sup> Anaplastic Ependymoma (n=9), Supratentorial primitive neuroectodermal tumor (PNET, n=3), CNS Germinoma (n=3), Atypical Teratoid/Rhabdoid Tumor (AT/RT, n=1), unknown (n=3).

<sup>4</sup> Data presented for those who received radiation.

Dose to posterior fossa reported as additional boost dose or target volume <sup>5</sup>Post-operative status unknown (n=4,6.9%).

\* Adjusted to "time to testing" for multivariate analyses.

SIOP=International Society of Pediatric Oncology. CNS=Central Nervous System. CDDP=Cisplatinum.

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TABLE II

Assessment of intelligence and neurocognitive function

Measure (n)	Hearing Loss <sup>1</sup>		No Hearing Loss <sup>1</sup>	p <sup>2</sup>
	N (%)	Mean±SE	Mean±SE	
<b>Full Scale IQ</b>	47 (81)	85±3.2	93±2.7	<b>0.038</b>
<b>Verbal Comprehension Index</b>	47 (81)	88±3.3	95±3.1	0.082
Similarities or Word Reasoning	50 (86)	8.6±0.7	10.0±0.7	<b>0.048</b>
Vocabulary/ Receptive Vocabulary	53 (91)	6.6±0.6	8.2±0.6	<b>0.039</b>
Comprehension/Information Subtest	35 (60)	7.0±0.9	8.9±0.7	0.057
<b>Perceptual Reasoning Index/Performance</b>	50 (86)	88±2.6	100±2.7	<b>0.003</b>
Block Design	53 (91)	7.5±0.5	9.3±0.6	<b>0.011</b>
Picture Concepts, Visual Puzzle, Object assembly	28 (48)	9.1±1.0	10.5±0.5	0.149
Matrix Reasoning	42 (72)	9.0±0.6	10.5±0.7	<b>0.048</b>
<b>Working Memory Index</b>	38 (66)	84±2.8	95±2.7	<b>0.003</b>
Digit Span <sup>3</sup>	42 (72)	6.9±0.5	9.5±0.6	<b>&lt;0.001</b>
L-N Sequence/ Arithmetic	27 (47)	7.4±0.7	8.6±0.5	0.138
<b>Processing Speed Index<sup>4</sup></b>	46 (79)	78±4.3	85±2.8	0.126
Coding	47 (81)	5.8±0.6	7.1±0.6	0.059
Symbol Search	46 (79)	6.5±0.7	7.7±0.6	<b>0.044</b>
<b>Visual Motor Integration</b>	23 (40)	72±4.8	92±5.6	0.102

<sup>1</sup>Significant hearing loss defined as Chang Grade 2b.

<sup>2</sup>Wilcoxon or unpaired 1-tailed t-test, significance set at  $\alpha < 0.05$  (bolded).

<sup>3</sup>Digit span forward and digit span backward compared with no significant differences.

<sup>4</sup>One subject recorded a “0,” analysis run above as lowest reportable value (40), repeated as “0” with no significant change in results.

L-N Sequence = Letter-Number Sequencing.

TABLE III

Effect of sensorineural hearing loss on intelligence and neurocognitive function

Predictor	Neurocognitive Measure <sup>1</sup>				
	FSIQ Coeff [95%CI]	VCI <sup>2</sup> Coeff [95%CI]	PRI Coeff [95%CI]	PSI Coeff [95%CI]	WMI Coeff [95%CI]
Age at diagnosis (yrs)	-0.84 [-2.03,0.35]	-0.25 [-1.43,0.94]	-0.67 [-1.91,0.58]	-0.28 [-1.88,1.32]	-0.36 [-1.46,0.75]
Underwent SCT	12.85 [-0.03,25.73]	6.63 [-6.41,19.68]	5.62 [-6.62,17.85]	<b>24.19 [7.03, 41.36]**</b>	<b>13.71 [0.80, 26.61]*</b>
Presence of PFS Radiation Therapy	5.09 [-3.48,13.66]	2.65 [-7.22,12.52]	2.42 [-6.27,11.11]	-0.78 [-12.93,11.37]	-7.80 [-15.75,0.15]
Dose to WB (cGy)	-0.02 [-0.31,0.27]	-0.02 [-0.31,0.27]	0.03 [-0.27,0.32]	0.26 [-0.18,0.71]	<b>0.42 [0.10, 0.74]*</b>
Dose to PF (cGy)	-0.06 [-0.34,0.21]	-0.22 [-0.50,0.05]	-0.08 [-0.35,0.18]	-0.09 [-0.28,0.47]	0.27 [-0.02,0.56]
Presence of Hearing Loss <sup>3</sup>	<b>-16.14 [-25.66,-6.63]<sup>†</sup></b>	<b>-13.19 [-23.04,-3.34]**</b>	<b>-16.09 [-25.93,-6.26]**</b>	<b>-15.41 [-29.02,-1.81]*</b>	<b>-17.10 [-25.76,-8.43]<sup>†</sup></b>
Intercept	99.61 [80.94,118.28]	98.31 [78.86,117.75]	105.57 [86.85,124.30]	77.73 [70.39,112.87]	83.81 [63.59,104.02]

<sup>1</sup> Individual hierarchical linear regression models constructed for each neurocognitive measure, significance set at  $\alpha < 0.05$  (bolded). See statistical methods for additional details.

<sup>2</sup> Model additionally includes ethnicity and diagnosis <sup>3</sup> Significant hearing loss defined as Chang Grade 2b.

95%CI=95% Confidence Interval, SCT=hematopoietic stem cell transplant, PFS=posterior fossa syndrome, WB=Whole Brain, PF=Additive dose to posterior fossa, IQ = Intelligence Quotient, VCI = Verbal Comprehension Index, PRI = Perceptual Reasoning Index/Performance IQ, WMI = Working Memory Index, PSI = Processing Speed Index, VMI = Visual-Motor Integration score.

\* p<0.05,

\*\* p 0.010,

<sup>†</sup> p 0.001.

Effect of sensorineural hearing loss on task-specific subtests of intelligence and neurocognitive function

TABLE IV

Neurocognitive Test	N (%)	Coeff <sup>1</sup>	[95% CI]	P	Additional Significant Covariates included in model <sup>2</sup>
<b>Verbal Comprehension Index</b>					
Similarities or Word Reasoning	46 (79)	-2.20	[-4.39, -0.01]	<b>0.049</b>	<i>ethnicity, diagnosis</i>
Vocabulary/ Receptive Vocabulary	49 (85)	-2.44	[-4.19, -0.70]	<b>0.007</b>	<i>ethnicity, diagnosis</i>
<b>Perceptual Reasoning Index/Performance</b>					
Block Design	49 (85)	-3.45	[-5.23, -1.66]	<b>0.001</b>	<i>duration to neurocognitive testing</i>
Matrix Reasoning	40 (69)	-1.90	[-4.16, 0.35]	0.095	<i>None</i>
<b>Working Memory Index</b>					
Digit Span	38 (66)	-3.54	[-5.23, -1.86]	< <b>0.001</b>	<i>ethnicity</i>
<b>Processing Speed Index</b>					
Coding	43 (74)	-3.11	[-5.09, -1.13]	<b>0.003</b>	<i>none</i>
Symbol Search	42 (72)	-2.82	[-5.09, -0.56]	<b>0.016</b>	<i>none</i>

<sup>1</sup> Coefficient represents Stepwise linear regression models constructed for above neurocognitive tests, significance set at  $\alpha < 0.05$  (bolded). See statistical methods for additional details.

<sup>2</sup> Base model includes age at diagnosis, history of hematopoietic stem cell transplant, history of posterior fossa syndrome, radiation dose [Gy] to whole brain, and additional radiation dose [Gy] to posterior fossa. Additional included covariates indicated.

Cddp = cisplatinum



TABLE V

Assessment of achievement and memory testing

Measure (n)	Hearing Loss <sup>1</sup>		No Hearing Loss <sup>1</sup>		p <sup>2</sup>
	N (%)	Mean±SE	Mean±SE		
<b>Tests of Achievement</b>					
Single Word Reading	34 (59)	84±3.8	88±3.7		0.212
Math Calculation	32 (55)	91±5.0	97±3.5		0.203
Spelling	30 (52)	85±3.9	84±8.2		0.370
Reading/Passage Comprehension	21 (36)	76±4.3	94±2.2		<b>0.004</b>
<b>Tests of Memory</b>					
Verbal Memory (Combined)					
Immediate	47 (81)	88±2.8	93±2.9		0.082
Delayed	41 (71)	89±3.7	91±4.0		0.315
Visual Memory (Combined)					
Immediate	46 (79)	93±2.9	96±2.7		0.203
Delayed	39 (67)	96±3.5	94±3.8		0.307
Story Recall					
Immediate	27 (47)	7.9±0.8	10.5±1.0		<b>0.021</b>
Delayed	27 (47)	7.7±0.8	9.7±0.8		0.057
CVLT Free Recall					
Short Delay	27 (47)	-0.6±0.3	-0.4±0.2		0.283
Long delay	26 (45)	-0.3±0.3	-0.6±0.3		0.247
Spatial Memory					
Immediate	25 (43)	9.1±0.9	8.9±0.9		0.429
Delayed	25 (43)	10.6±0.7	9.7±1.0		0.213
Faces					
Immediate	26 (45)	10.3±0.6	9.1±1.0		0.137
Delayed	25 (43)	10.6±0.8	9.4±1.5		0.213

<sup>1</sup> Significant Hearing loss defined as Chang Grade 2b.

<sup>2</sup> Wilcoxon or unpaired 1-tailed t-test, significance set at  $\alpha < 0.05$  (bolded).

CVLT = California Verbal and Learning Test.