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## Comparison of neuropsychological and brain imaging data in pediatric brain tumor patients surviving more than 10 years

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## Abstracts

### NEUROPSYCHOLOGY

#### NP-001. INTRUSION INTO SELF-PERCEPTION BY CNS TUMOR AND TREATMENT IN CHILDHOOD OR ADOLESCENCE: POPULATION-BASED OUTCOMES FROM ADULT SURVIVORS COMPARED WITH THE GENERAL POPULATION

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**BACKGROUND:** Survivors of pediatric central nervous system (CNS) tumors are at risk for persistent tumor/treatment-related morbidity, physical disability and social consequences which may intrude into self-perception, vital for mental health and quality of life. Within the longitudinal Swedish CNS tumor LIFE-study, we studied the long-term impact of the childhood CNS tumor and its' treatment on self-perception in significant domains in adult survivors, by comparing outcomes with those of the general population. **METHODS:** The cohort included 697 Swedish survivors diagnosed between 1982 and 2001 with a primary CNS tumor. Comparison data were collected from a stratified general population random sample. Survivors and general population individuals were compared as regards self-perception in five domains: body image, sports/physical activities, peers, work, and family, and as regards a global self-esteem index. Within the survivor group, determinants of impact on self-perception were identified. **RESULTS:** The final sample included 528 survivors, 75.6% of the entire national study cohort. The control sample consisted of 995 individuals, 41% of 2,500 those addressed. Survivors had significantly poorer self-perception outcomes in domains of peers, work, body image, sports/physical activities, and in the global self-perception index, compared with those from the general population (all  $P < 0.001$ ). Within the survivor group, female gender and persistent visible physical appearance sequelae predicted poorer outcomes in several of studied domains. **CONCLUSION:** Intrusion into self-perception appears as a potential long-term psychological late effect in adult survivors after pediatric CNS tumors and the brain tumor treatment. Because of this risk, patient care and psychosocial follow-up should include measures similar to what was used in this study. Paying attention to self-perception in follow-up care enables identifying, preventing, and managing of here identified adverse psychological impact of the illness on self-identity, crucially related to mental health and quality of survival.

#### NP-002. DO SCHOLASTIC DIFFICULTIES IN CHILDREN WITH EARLY CEREBELLAR INJURY ARISE FROM SPECIFIC OR GENERAL IMPAIRMENTS?

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**OBJECTIVE:** Poor scholastic performance has been reported following early cerebellar injury, but it is currently not known if these difficulties arise from a general cognitive impairment. Hence, it is difficult to target interventions effectively. Using a case series approach, we investigated the extent of scholastic difficulties, above and beyond general cognitive processing, following cerebellar injury sustained through tumour during the pre-school years (<5 years), and the impact of tumour histology/treatment on outcome. **METHOD:** Eleven children (aged 5-15 years) with varying tumour histology/treatment were given comprehensive standardised tests of academic achievement (WIAT- II) and cognitive functioning (WISC-IV). This enabled individual performance on academic subtests of the WIAT-II to be predicted from IQ scores on the WISC-IV. **RESULTS:** Cognitive processing was below average (100) in all of the children and significant impairments (> -2sd) in FSIQ was shown on 7/11 children. However, IQ-achievement test discrepancy analyses revealed significantly poorer performance than expected on the basis of FSIQ in 6/11 children for Reading and Mathematics, 7/11 children for Written Language, and 3/11 children for Oral Language. Most of these children had malignant tumours treated with chemotherapy and/or radiotherapy. For the remaining children, academic performance was either in line with, or was significantly above, that

expected on the basis of FSIQ. Most of these children had benign tumours treated with surgical resection only. **CONCLUSIONS:** These results suggest that early injury to the cerebellum has a generic effect on cognitive processing that underpins development of scholastic skills. Additional academic difficulties are likely to occur in children with invasive tumours requiring more aggressive treatment probably because chemotherapy and radiotherapy are known to affect attentional processing which is critical for scholastic progression.

#### NP-003. CHILDREN WITH CEREBELLAR MEDULLOBLASTOMA AND WORKING MEMORY DISORDERS: A FUNCTIONAL MRI STUDY

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**BACKGROUND AND PURPOSE:** Medulloblastomas are the most common malignant brain tumors in childhood. Children treated for a cerebellar medulloblastoma demonstrated cognitive disorders in working memory (WM), especially visuospatial WM, leading to an impairment of school performance. The purpose of this study is to describe the cerebellar involvement in specific cognitive deficits observed in children treated for cerebellar medulloblastoma. **MATERIALS AND METHODS:** Groups: Nine healthy volunteers children ( $11.1 \pm 2.2$  yo), were compared to 5 patients treated for cerebellar medulloblastoma ( $12.1 \pm 0.6$  yo). All subjects were native French speakers, right-handed, with a global IQ of 70-130. Using 4 block-design 1-back tasks in the sensorial modality (visual/auditory) and the nature of information (verbal/nonverbal) during fMRI acquisitions (T2\* weighted gradient-echo - EPI) and completing with an anatomic acquisitions (3D T1-weighted). **Data Analysis:** Using the Statistical Parametric Mapping (SPM8) and the Spatially Unbiased Infra-tentorial Template (SUIT) for viewing cerebellar topography with BOLD activations. **RESULTS:** In patients group: 4/5 patients had a WM deficit following a resection of the left posterior cerebellar lobe (lobule HVI, HVIIB, HVIII, HIX, Crus I and II) and inferior part of vermis; the only patient without WM deficit was the only one without cerebellar hemispheric resection (figure 1), even though this patient was also treated with radiotherapy and chemotherapy dosages like those in other patients. Greater BOLD activations were found in the left posterior cerebellar lobe for nonverbal vs. verbal contrast and they were presented in this region for visual vs. auditory contrast (figure 2). In healthy subject, greater BOLD activations were found in brain and cerebellar locations which are similar with those in the literature for all four tasks. **CONCLUSION:** The cerebellum plays the same role in WM in children as that has been previously described in adults. The left posterior cerebellar lobe may involve the visuospatial WM.

#### NP-004. THE EFFICACY OF COMPUTERIZED COGNITIVE REHABILITATION TRAINING IN THE CHILD TREATED FOR MEDULLOBLASTOMA

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**OBJECTIVES:** Neurocognitive deficits are common after brain tumor treatments. Our study suggests that computer-based means of rehabilitation lead to better cognitive functioning. Thus there is a need to include cognitive rehabilitation in a standard protocol. The present single case study evaluates the improvement of general cognitive functioning of pediatric patient who underwent rehabilitation program targeting memory, alertness and attention. **METHODS:** The pediatric patient (age 7;5) diagnosed with medulloblastoma underwent surgery, craniospinal irradiation (23.4 Gy, with additional boost to the tumor bed up to 54 Gy) and 8 courses of maintenance treatment (CCNU, Vincristin, Cisplatin) in 6 weeks intervals. Postoperative MRI did not reveal any tumor remnant. Neuropsychological tests (WISC III, CCT, CCTT) showed below average performance in all areas of cognitive functioning. He started CogniPlus computer training targeting alertness (ALERT), mental rotation (ROTATE), working memory (VISP, NBACK, DATEUP), and attention (SELECT, FOCUS, SPACE). He participated in 35 rehabilitation sessions (11 hours). After a year, the neuropsychological battery was repeated. **RESULTS:** Regression analysis revealed significant improvements in alertness, mental rotation, visuospatial working memory,

spatial working memory, visuospatial attention (at  $p < 0.001$ ) and selective attention ( $p < 0.05$ ). Reliable change index (RC) confirmed improvements on neuropsychological tests. **CONCLUSIONS:** Computer-based cognitive rehabilitation program shows positive improvements in cognitive functioning a year after brain surgery. Following up the patient will reveal long-term effects of the rehabilitation program. Our goal is to extend these findings to a larger population and develop a cognitive rehabilitation program that will by protocol include and rehabilitate our brain cancer patients in the future.

#### NP-005. COMPARISON OF NEUROPSYCHOLOGICAL AND BRAIN IMAGING DATA IN PEDIATRIC BRAIN TUMOR PATIENTS SURVIVING MORE THAN 10 YEARS

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**AIM:** To explore the relationship between neuropsychological outcome and magnetic resonance imaging (MRI) findings in paediatric brain tumour patients surviving more than 10 years. **BACKGROUND:** Cognitive late sequelae after paediatric brain tumour have a multifactorial origin. Low age at diagnosis, cranial radiation therapy, intrathecal methotrexate treatment and increased intracranial pressure are known to predict cognitive sequelae. Cognitive sequelae have been related to MRI findings, but the relation between neuroimaging findings and neuropsychological impairment needs to be explored further. **METHOD:** Sixteen paediatric brain tumour survivors completed an extensive neuropsychological test battery and MRI 10 to 13 years after diagnosis. Patients were first separately classified as positive or negative regarding neuropsychological impairment and MRI findings and then coded as congruent or incongruent, depending on whether neuropsychological outcome was in agreement with MRI also considering clinical data such as type and location of the brain tumour, post-operative status, treatments or premorbidity. **RESULTS:** Ten patients were classified as either positive or negative for both MRI and cognitive impairment if blinded for the second parameter and clinical data, and were also congruent for these two parameters when not blinded for clinical data and the second parameter. In five out of six initially incongruent patients the neuropsychological profile was in accordance with MRI findings when evaluating all data with the multidisciplinary holistic approach. **CONCLUSIONS:** Cognitive outcome in survivors of paediatric brain tumours depends on many different detrimental processes and shows high individual variation. Congruity between neuropsychological impairment and MRI findings might at first seem low. However, in the perspective of a clinical holistic evaluation of MRI findings and neuropsychological outcome considering the knowledge of clinical data such as type and location of the brain tumour, type of MRI findings (atrophy, gliosis, post-operative lesion), undergone treatments and radiation field as well as premorbid cognitive impairment congruity increases.

#### NP-006. NEW APPROACH TO ASSESSMENT OF NEUROPSYCHOLOGICAL LATE EFFECTS IN CHILDHOOD BRAIN TUMOR SURVIVORS. CHALLENGES AND BENEFITS OF THE NEW METHODOLOGY

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**PURPOSE:** The purpose of the study was to analyze the usefulness of standard psychological and neuropsychological assessment tools used in evaluating neuropsychological consequences of childhood brain tumors. The hypothesis was that in this specific group of patients standard tests are not sufficient to evaluate long term effects of childhood brain tumor. **METHOD:** The base of the study was psychological repeated testing performed in 350 childhood brain tumor survivors (various tumors types and localizations). Age at psychological diagnosis: 6 to 26 years. Full psychological outcome included assessment of problems with: memory, visual-motor skills, attention, flexibility, problem solving, semantic memory and fluency, motor skills, processing speed. The patients were examined by using standardized psychological and neuropsychological methods, mainly: Wechsler Intelligence Scales; Benton Visual Retention Test; L. Bender - E. Koppitz Visual Motor Test; Rey - Osterrieth Complex Figure Test; Auditory Verbal Learning Test. Meta-analysis of results to verify the accuracy, relevance and reliability of the standard tests used to assess cognitive status of these patients was performed. **RESULTS:** Our results showed that assessment of brain tumor survivors based on common psychological tests

is insufficient. Their specific cognitive and emotional functioning is the cause of non-standard results. For example some scales based on sense of humor and understanding of the absurdities are difficult to understand for patients with cerebellar cognitive-affective syndrome; subtest Information of WISC-R contains items of structural thinking, disordered in patients with brain damage; most tests are time limited, which reduces patients outcomes. **CONCLUSIONS:** Reliable assessment of neuropsychological functioning in brain tumors survivors requires a specific methodology and special tests. This new tool is designed for screening, diagnosis, prognosis of neuropsychological consequences, planning and evaluation of rehabilitation process. Proposal of this tool specific for brain tumor survivors and draft recommendations for diagnosis of specific neuropsychological consequences will be presented and discussed.

#### NP-007. LONG-TERM NEUROCOGNITIVE FUNCTIONING IN A CASE SERIES OF MEDULLOBLASTOMA SURVIVORS: THE IMPACT OF CEREBELLAR MUTISM SYNDROME

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**OBJECTIVE:** About 25% of pediatric patients with medulloblastoma develop Cerebellar Mutism Syndrome (CMS+) post-resection resection and worse neurocognitive outcomes have been reported but not systematically studied beyond Global IQ. We aim to present a matched case series of children with medulloblastoma with and without CMS on a range of neuropsychological functions. We predict that CMS+ children will perform worse than CMS- children and will have a greater prevalence of clinical impairments. **PARTICIPANTS AND METHODS:** We present 5 matched pairs of medulloblastoma patients off-treatment for at least 1 year; half were CMS+. Participants were matched by diagnosis age, age at assessment, and treatment. All participants underwent a full neuropsychological evaluation. Descriptive data was calculated, and variables were dichotomized for clinical significance at one standard deviation below the mean. **RESULTS:** Age range was 9-18 yrs at time of evaluation ( $M = 14.6$ ;  $SD = 2.41$ ), with 50% males. Time off treatment for the CMS+ participants ranged from 1-13 yrs ( $M = 7.0$ ;  $SD = 4.18$ ), and 1-8 yrs ( $M = 4.0$ ;  $SD = 2.34$ ) in the CMS- group. 90% received radiation. CMS+ participants consistently showed scores below CMS- on Performance IQ, particularly Matrix Reasoning. PIQ was impaired in 80% of the CMS+ group and never in the CMS- group. Verbal IQ was impaired in 40% of the CMS+ group, and none of the CMS-. Similar patterns emerged for working memory, flexibility, memory, processing speed, and visual-motor integration. **CONCLUSION:** Based on this matched sample of medulloblastoma survivors, results suggest that CMS is associated with greater impairments across a range of neurocognitive functions (not just language) in the years following treatment. This lends support to the idea that the presence of CMS is an indication of a disruption in cortical pathways associated with higher-order cognitive development and functioning.

#### NP-008. EPISODIC MEMORY IMPAIRMENTS IN PAEDIATRIC TEMPORAL BRAIN TUMORS

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**BACKGROUND:** Memory impairment has been reported in paediatric brain tumors using global neuropsychological assessments, but no study focused on long-term memory consolidation processes have been conducted in these children. Therefore, we tested a long-term memory retrieval paradigm in children treated for temporal brain tumors. **METHODS:** We included 10 patients (6 to 18 yrs.) treated for a malignant ( $N = 6$ ) or benign ( $N = 4$ ) temporal brain tumor in the Paediatric Department of Gustave Roussy Institute (France) and 12 matched controls (6 to 18 yrs.). The protocol involved two parts: 1) 9 recent daily memories were first collected, 2) after a delay of 16 days, a free recall (FR) of memories was requested. When memories were not retrieved in FR, a semantic cues recall (CR) was performed. We first analysed the amount of memories retrieved (QM) in part 2 and then, the qualities of memories using the episodic

score (ES) as a measure of the recall of rich contextual details. RESULTS: For FR, QM and ES were significantly lower in patients than in controls (QM:  $p < 0.01$ ; ES:  $p < 0.001$ ). For CR, QM did not differ significantly between patients and controls ( $p = 0.97$ ), whereas ES was lower ( $p < 0.05$ ). DISCUSSION: Patients showed episodic memory impairments characterized by a lower amount of memories retrieved and poorer details. However, patients were sensitive to semantic cues recall. Episodic memory impairment may be more associated with retrieval strategies than with consolidation impairments. Thus, investigating daily memories is relevant to capture memory deficits and their impact on quality of life of children treated for brain tumors. These findings also suggest new potential rehabilitation perspectives.

#### NP-009. PREOPERATIVE NEUROPSYCHOLOGICAL AND BEHAVIOR EVALUATION OF CHILDREN WITH THALAMIC TUMORS

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INTRODUCTION: Functional involvement of the thalamus in cognitive processing has been only anecdotally reported in the literature and mostly related to thalamic haemorrhages; there is no available information on cognitive development in children with thalamic tumors. CLINICAL MATERIALS AND METHODS: All the children admitted with a diagnosis of thalamic tumor at our Institution between January 2008 and January 2011 were considered for the present study. Exclusion criteria were: age under 18 months and the presence of severe neurological deficits, both preventing a reliable neuropsychological evaluation. A complete preoperative neuropsychological evaluation was performed. RESULTS: Twenty children were selected (mean age 102.4 months). Total IQ was in the normal range in all patients (mean: 90.1; SD: 13.87) with a significant difference between VIQ (mean 97.70 SD 17.77) and PIQ (84.82 SD 17.01). A significant correlation was found between global cognitive impairment and an histological finding of low grade tumors ( $p = 0.001$ ). Children with mesial thalamic tumor had higher working memory deficit and delayed recall disorders ( $p = 0.001$ ). Naming disorders were related to the presence of a bilateral ( $p = 0.0001$ ) or mesial thalamic tumor ( $p = 0.001$ ) without a significant difference between the involvement of the left or right hemisphere. A significant correlation was also found between the presence of neurolinguistic disorders and mesially located tumors ( $p = 0.001$ ). Children with right sided tumors had more frequently constructional praxia and executive function disorders ( $p = 0.0005$ ). CONCLUSION: The present study suggests that differently located thalamic tumors might have specific neuropsychological profiles.

#### NP-010. NEUROCOGNITIVE DEFICITS IN CHILDREN WITH BRAIN TUMORS AT DIAGNOSIS

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Survivors of brain tumors are faced with a high risk for a wide range of cognitive problems and learning difficulties. These problems are caused by the lesion itself and its surgical removal as well as by the treatments to follow (chemo- and/or radiation therapy). A few recent studies have indicated that children with brain tumors (BT) might exhibit cognitive problems already at diagnosis, i.e. before the start of any medical treatment. The aim of the present study was to investigate the "baseline" neuropsychological profile in children with BT in comparison to children with an oncological diagnosis not involving the central nervous system (CNS). 20 children with BT and 27 children with an oncological disease without involvement of the CNS (age range: 6.1 to 16.9 years) were evaluated with an extensive battery of neuropsychological tests tailored to the patient's age. Furthermore, the child and its parents completed self-report questionnaires about emotional functioning and quality of life. In both groups, tests were administered before any therapeutic intervention such as surgery, chemotherapy or irradiation. Groups were comparable regarding age, gender and social economic status. Compared to the CG, patients with BTs performed significantly worse in tests of working memory, verbal memory and attention. In contrast the areas of perceptual reasoning, processing speed and verbal comprehension were preserved at this time. Younger children with BT were especially disadvantaged. Compared to aged matched children with malignancies not involving the CNS and older BT patients the young BT patients showed deficits in attention, working memory and verbal memory measures. Our results highlight the need for cognitive assessments

and interventions early in the treatment process in order to minimize or even prevent academic difficulties as patients return to school.

#### NP-011. ASSESSMENT OF EXECUTIVE FUNCTIONING IN CHILDREN AND YOUNG ADULTS TREATED FOR FRONTAL LOBE TUMOURS USING ECOLOGICALLY VALID TESTS

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The first aim of the study was to evaluate executive functions in children and adolescents treated for benign and malignant frontal lobe tumours. To measure and to evaluate executive functioning in our population, both ecological valid tests and a classical evaluation of executive functions was performed. For ecological neuropsychological tests, the BADS-C (Behavioral Assessment of the Dysexecutive Syndrome for Children) an ecological battery and the BRIEF questionnaire were performed for parents and teachers' child or adolescent; both for children and matched comparison group. Classical tests of executive functions such as the Wisconsin Card Sorting test and the Tower of London. To our knowledge, no study to date has directly measured ecological measures and classical tests measures in frontal benign or malignant lobe tumours in children and adolescents. The second aim of the study was to assess correlations between the classical tests and ecological tests, such as the BADS-C and the BRIEF questionnaire in our population. The third aim of the study was to identify and to determine specific factors (medical factors, social factors) influencing performances in our population. METHOD: Between September 2010 and June 2012, 21 patients treated for frontal benign/malignant lobe tumour were included aged 8-21 years at time of evaluation. Age at surgery was 8.3 years old. A comparison group of 42 patients were matched on gender, age and level education, on classical tests and on the BADS-C battery. RESULTS: Statistical analysis of our study revealed executive functions disturbances in children and adolescents. Working memory disabilities, planning and organisation difficulties were found, in both classical and ecological tests in our population. Significant and strong correlations were found between IQ measures and EF measures. Medical factors were identified on performances based in our population, such as epilepsy in our population, for medical factors, and socioeconomic status for social factors.

#### NP-012. IQ CHANGE OVER TIME IN PEDIATRIC BRAIN TUMOR PATIENTS TREATED WITH PROTON BEAM RADIATION THERAPY VERSUS PHOTON RADIATION THERAPY

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BACKGROUND: Cranial radiation therapy (RT) is associated with neurocognitive toxicity. Compared to photon radiation (XRT), proton therapy (PT) reduces the volume of normal tissue receiving radiation dose, which may lead to better neurocognitive outcomes. We examined change in IQ over time between patients treated with PT versus XRT. METHODS: We abstracted IQ scores of pediatric brain tumor patients treated with PT or XRT. A general linear mixed model examined change in IQ over time by RT type (PT vs. XRT), controlling for age-at-RT, total-RT-dose, craniospinal irradiation (CSI), shunt, and tumor location. RESULTS: IQ scores were available for 99 patients (55 PT, 44 XRT). Median RT dose was 54.0 Gy. Mean first-last evaluation intervals were: PT = 2.3 years, XRT = 5.3 years. Tumor histologies included: 40.4% medulloblastoma/PNET, 19.2% glioma, 14.1% germ cell, 12.1% ependymoma, and 14.1% other. CSI was administered to 52.7% of PB and 54.5% of XRT patients. Mean IQ declined significantly in both groups ( $p < .001$ ). IQ was significantly lower in the XRT group (by 6.9 points on average) compared to the PT group ( $p < .05$ ); however, the rate of IQ decline did not differ significantly between groups (XRT = 1.4 points/year, PT = 1.1 points/year,  $p = .604$ ). IQ was also significantly lower among patients with shunts ( $p < .01$ ). CSI neared significance ( $p = .057$ ), while age-at-RT ( $p = .495$ ), total-RT-dose ( $p = .568$ ), and tumor location ( $p = .601$ ) were not significantly associated with IQ after controlling for all other variables in the model.



**CONCLUSIONS:** Findings suggest both PT and XRT are associated with cognitive risk. While the rate of IQ decline did not differ significantly between RT types in this sample, IQ scores in the XRT group started and remained lower compared to the PT group. Possible differences in early neurocognitive toxicities between RT types should be considered. Replication with a larger sample and examination of longer-term cognitive outcomes, particularly for non-CSI PT patients, are needed.

#### NP-013. NEUROCOGNITIVE SCREENING TOOL FOR PEDIATRIC BRAIN TUMOR: RELIABILITY AND VALIDITY

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**PURPOSE:** Research on pediatric brain tumor (PBT) patients has identified long-term neurocognitive deficits in attention, memory, and executive functioning. There is a need for brief neurocognitive screening measures that can readily detect impairment and be easily administered to guide early intervention. This study examined the reliability and validity of the Leiby-Asbell Neurocognitive Screening Examination (LANSE) for PBT patients in a clinical setting. **METHODS:** Participants were 53 PBTP (M age = 10.90, SD = 3.26; 52.8% White; Med months from diagnosis = 93.00, SD = 46.25) and 30 comparison traumatic brain injury (TBI) patients (M age = 11.89, SD = 4.08; 50% Caucasian; Med months from injury = 133.00, SD = 61.19). The LANSE is a brief (20-25 minutes) measure of patient orientation, attention, executive functioning, language, verbal and visual memory, and visual-spatial functioning normed on children with TBI. BT and TBI patients between the ages of 6 to 17 years were administered the LANSE by trained psychology staff. A subset of children with PBT and TBI (n = 6 to 18) also completed the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), California Verbal Learning Test for Children (CVLT-C), and/or Children's Memory Scale (CMS). **RESULTS:** PBT patients exhibited a similar degree of impairment as TBI patients on the LANSE. Specifically, PBT patients exhibited similar impairments as TBI patients across the domains of attention, language, executive functioning, as well as visual and verbal memory. These domains showed good reliability ( $\alpha$ 's ranged from 0.67 to 0.88) and correlated significantly in the hypothesized direction with similar domains on the WISC-IV, CVLT-C, and CMS ( $r$ 's range from 0.55 to 0.93). **CONCLUSION:** Screening results from the LANSE are consistent with full neurocognitive examination results reported in the literature. The LANSE is a reliable and valid screening measure easily administered in clinic that may be a valuable tool for detecting neurocognitive impairment during and after treatment.

#### NP-014. NEUROPSYCHOLOGICAL FOLLOW-UP OF HEAD START II SURVIVORS: AN UPDATE

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**PURPOSE:** Given the neuropsychological deficits associated with irradiation in young children diagnosed with malignant CNS tumors, the Head Start II protocol employed high-dose myeloablative chemotherapy followed by autologous hematopoietic cell transplantation to avoid or delay craniospinal irradiation. This research examined long-term neuropsychological functioning of patients treated on the Head Start II protocol between 1997 and 2003. **METHODS:** Patients completed baseline testing prior to autologous transplantation and biannually thereafter. Assessments were completed for 49/51 (96%) patients at baseline (T1 mean age = 3.4 years; SD = 2). Twenty patients passed away between T1 and T2. 27/31 (87%) completed assessments at T2, 16/31 (52%) at T3, 6/31 (19%) at T4, and one at T5. Analyses compare neuropsychological functioning at baseline to most recent follow up assessment (T2 to T5; mean length of follow up = 7.39 years, SD = 3.21) and examine outcomes for patients who received intravenous methotrexate (IVMTX) compared to those who did not. **RESULTS:** Dependent samples t-tests comparing performance at baseline and most recent follow-up revealed no significant change over time on FSIQ, PIQ, VIQ, reading, spelling, math, general memory, verbal or visual delayed memory. For the entire group, Full Scale IQ remained stable (mean change score decreased by 0.43 points). Although not significant, PIQ scores declined 3.25 points and VIQ scores increased 3.25 points from baseline. Mean scores at most recent follow-up indicate that survivors performed within the average to low average ranges on all measures. Comparison of most recent treatment group means did not reveal any significant differences, with the exception of lowered visual delayed memory for those who received IVMTX ( $p = 0.03$ ). **CONCLUSIONS:** These analyses include neuropsychological outcome data for children up to 12-years post-diagnosis of a malignant CNS tumor, indicating that children treated with a protocol aimed to

reduce late effects on neurocognitive development continue to display broadly stable neuropsychological functioning over extended follow-up.

#### NP-015. WHITE MATTER DAMAGE DISRUPTS NEURAL PHASE SYNCHRONY AND IMPAIRS COGNITIVE PERFORMANCE IN CHILDREN TREATED WITH CRANIAL RADIATION FOR BRAIN TUMOURS OF THE POSTERIOR FOSSA

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Cognitive impairments are consistently reported in children treated with cranial radiation (CRT) for brain tumours. These deficits are, at least in part, reliably attributed to white matter damage. We investigated how white matter damage and poor task performance related to neural function by comparing functional measures obtained with Magnetoencephalography and structural measures obtained with Diffusion Tensor Imaging to visual-motor task performance in eighteen healthy children (12M/6F: 11.3 yrs  $\pm$  3.5) and 20 pediatric Posterior Fossa (PF) brain tumour patients (13M/7F: 12.07 yrs  $\pm$  2.58) who had been treated with CRT (15 medulloblastoma, 5 ependymoma, all received CRT treatment of either focal (PF only), whole-brain low-dose with PF boost, or whole-brain standard-dose with PF boost). White matter health/injury measures predicted reaction times in both groups. White matter structure predicted faster reaction times on task performance in both healthy children ( $r = -.72$ ,  $p < .001$ ) and patients ( $r = -.52$ ,  $p < .05$ ). Functionally, phase synchrony of the visual cortex in response to the visual cue was the best predictor of performance. Phase synchrony is the temporal consistency of the neural response from trial to trial and reflects the coordination of neural communication arriving at a downstream target. In healthy children, increased phase synchrony was correlated with increased white matter health ( $r = .64$ ,  $p < .01$ ) and faster reaction times ( $r = -.51$ ,  $p < .05$ ). In patients, decreased phase synchrony was correlated with decreased white matter health ( $r = .53$ ,  $p < .05$ ) with no relationship to reaction time. We propose that the condition of white matter influences reaction time on a visual-motor task through the temporal coordination of information arriving at the visual cortex. The phase synchrony of the neural response may be a biomarker of white matter injury and cognitive impairment in children treated for brain tumours.

#### NP-016. LONG-TERM OUTCOME IN SUBGROUPS OF MEDULLOBLASTOMA

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**BACKGROUND:** Treatment for medulloblastoma is associated with white matter damage and cognitive morbidity. Reducing treatment in subgroups of medulloblastoma with better prognosis could spare certain group(s) from neuro-toxic complications. We examined relations between subgroup (WNT, SHH, Group 3, Group 4) and late effects to identify differences in long-term outcome. **METHODS AND RESULTS:** (i) Quality-of-life data (Health Utilities Index) were collected from 67 patients (6 WNT, 18 SHH, 11 Group 3, 27 Group 4, 4 unclassified) across 8 sites in the Medulloblastoma Advanced Genomic International Consortium. Of 13 attributes assessed, only cognition differed between subgroups; the mean single-attribute utility score was higher for SHH (0.98  $\pm$  0.03) than Groups 3 (0.95  $\pm$  0.04;  $p = 0.007$ ) and 4 (0.96  $\pm$  0.03;  $p < 0.029$ ). We further investigated cognitive outcome by comparing rate of change in (ii) intellectual functioning of 91 patients (41 Group 4; 20 Group 3; 18 SHH; 12 WNT) treated at SickKids. WNT was excluded from the following analyses due to its relatively small sample size. Groups 3 and 4 declined by  $>4.5$  IQ points/year (all  $p < 0.001$ ), whereas SHH declined by 2.2 IQ points/year ( $p = 0.18$ ). A subset of these patients (14 Group 4; 6 Group 3; 8 SHH) and 38 controls underwent diffusion tensor imaging to assess (iii) white matter microstructure and identify potential structural correlates of cognitive morbidity. Relative to controls, Group 4 had reduced FA and increased RD/MD in temporal (mean differences: FA = 0.03  $\pm$  0.009; RD = 0.000041 +

0.000013), occipital ( $FA = 0.037 + 0.009$ ;  $RD = 0.000042 + 0.000013$ ) and posterior fossa ( $FA = 0.024 + 0.008$ ;  $MD = 0.000066 + 0.000018$ ;  $RD = 0.000070 + 0.000016$ ) regions (all  $p < 0.05$ ), Group 3 had reduced FA in the occipital region ( $0.041 + 0.013$ ;  $p = 0.015$ ), and SHH had increased MD and RD ( $MD = 0.000069 + 0.000022$ ;  $RD = 0.000066 + 0.000020$ ; all  $p < 0.05$ ) only in the posterior fossa. **CONCLUSION:** Medulloblastoma subgroups have heterogeneous intellectual and white matter outcomes following treatment. SHH may be least vulnerable to radiation-induced neurotoxicity, whereas Groups 3 and 4 may be more susceptible.

**NP-017. PREDICTORS OF INTELLECTUAL FUNCTIONING IN NEWLY DIAGNOSED CHILDREN WITH A BRAIN TUMOR**  
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Children diagnosed and treated for a brain tumor often experience cognitive problems. Identification of factors associated with the tumor and its treatment having an impact on cognitive functioning is relevant. However, most studies investigating these factors are retrospective, making it difficult to disentangle the effects of the tumor, the acute (e.g. hydrocephalus) and treatment (e.g. radiotherapy) phase. The aim of the present study is to investigate intellectual functioning after a diagnosis of a brain tumor and to identify predictive factors for intellectual functioning in these children. A total of 68 children diagnosed with a brain tumor at the UZLeuven between 1996 and 2013 enrolled in the study and were tested with the age-appropriate Wechsler scale. This test was conducted as soon as possible after diagnosis and before initiation of further treatment with chemo- or radiotherapy. Mean age at testing was 10.21 years. The localization was in 66% of the cases infratentorial, 56% received surgery and 18% received ventricular drainage before testing. Binomial distribution analyses demonstrated that the proportion of children showing 'below average' intellectual performance exceeded normative expectations ( $p = 0.002$ ). Performance IQ was significantly lower than verbal IQ ( $p < 0.001$ ). A linear regression model was used to investigate the impact of potential predictive factors (age at diagnosis, tumor type, localization, grade of tumor, surgery before testing, ventricular drainage). Tumor type ( $p = 0.018$ ) and age at diagnosis ( $p = 0.010$ ) were significant predictors for cognitive outcome. Our results demonstrate a discrepant intelligence profile in newly diagnosed children. Younger age at diagnosis and tumor type (embryonal tumours worse outcome) significantly predict intellectual outcome after diagnosis. More specific neuropsychological testing after diagnosis is recommended to refine the cognitive profile. Longitudinal follow-up of these children is required to investigate the additional effects of treatment. Therefore a systematized protocol with extensive (neuro)psychological testing has been incorporated in the follow-up of these children at UZLeuven.

**NP-018. EXERCISE INCREASES HIPPOCAMPAL VOLUME IN CHILDREN TREATED WITH CRANIAL RADIATION**  
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**OBJECTIVES:** Cranial radiation has been linked to smaller hippocampal volumes, which may underlie the observed memory impairments in children treated for brain tumours. There is evidence from the animal and adult literature suggesting that aerobic exercise can increase hippocampal volume, and improve memory performance. In this study, we conducted a waitlist control cross-over design study to examine the effects of exercise on hippocampal volume in children treated with cranial radiation. **METHOD:** 9 participants (age =  $10.88 \pm 2.58$ ) were assigned to the treatment group (TXT), and 9 participants (age =  $12.22 \pm 3.37$ ) were assigned to the waitlist control group (CTRL). The TXT group participated in group aerobic activities 3 times per week for 3 months. Participants were evaluated at baseline (T1) and post-intervention (T2). Then, the TXT group underwent a follow-up assessment 3 months after intervention (T3). The CTRL group underwent a third assessment (T3) after receiving the exercise intervention. Participants were scanned using a GE 1.5T or Siemens 3T MRI. Hippocampal regions were traced blind to group status and corrected for intra-cranial volume, scanner type and age. **RESULTS:** A repeated measures ANOVA revealed a significant group by time interaction ( $F(1,14) = 25.43$ ,  $p = .0001$ ). At T2, the TXT group exhibited significantly more change in average hippocampal volume ( $+82.48 \text{ mm}^3$ ) as compared to the CTRL group ( $+28.90 \text{ mm}^3$ ;  $F(1,14) = 25.43$ ,  $p = .0001$ ). Strikingly, average hippocampal volume of

the TXT group at T2 ( $1974.08 \text{ mm}^3$ ) resembled those of healthy controls ( $1981.38 \text{ mm}^3$ ) reported in our earlier study (Riggs et al., epub ahead of press). At the 3 months follow-up, hippocampal volumes of the TXT group continued to increase. **CONCLUSIONS:** The current results suggest that aerobic exercise may be an effective intervention in repairing some of the damage following radiation. Future work will examine the relation between hippocampal volume increase and cognitive change, particularly in learning and memory.

**NP-019. HIPPOCAMPAL VOLUMES DECREASE OVER TIME IN CHILDREN TREATED FOR MEDULLOBLASTOMA**

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**OBJECTIVES:** The hippocampus is critical for learning and memory. Children treated for medulloblastoma exhibit lower memory performance and smaller hippocampal volumes as compared to healthy controls (Riggs et al., epub ahead of press). However, it is not clear how hippocampal volumes change over time, and how such changes may deviate from normal development. The current study is the first to examine longitudinal changes in hippocampal volume in both a medulloblastoma (MB) and healthy control (HC) group. **PARTICIPANTS AND METHODS:** 16 MB (age =  $9.02 \pm 2.47$ ) and 20 HC participants (age =  $9.70 \pm 2.21$ ) were included. Participants were scanned annually over 4 years using a 1.5T Siemens, 1.5T GE or a 3T GE scanner. For the MB group, the first scan occurred at around the time of diagnosis (i.e. baseline). All participants had at least two scans. The hippocampus was defined using an automated segmentation program (Chakravarty et al., 2013) and volumes were corrected for intra-cranial volume, scanner type and age. **RESULTS:** A mix model regression was used to examine changes in hippocampal volume over time. This revealed a significant decline in hippocampal volume in the MB group ( $t(34) = -2.1$ ,  $p = .04$ ), but not in the HC group ( $p = .49$ ). In the MB group, there was an estimated 2.89% decrease in hippocampal volume each year (baseline =  $3568.14 \text{ mm}^3$ , 3 year follow-up =  $3275.04 \text{ mm}^3$ ). **CONCLUSIONS:** The current results show that treatment for MB is associated with atypical development of the hippocampus in children. Future work will examine the impact of clinical factors such as radiation dose and the occurrence of hydrocephalus on hippocampal volume and its developmental trajectory.

**NP-020. PSYCHOLOGICAL ASSESSMENT IN CHILDREN WITH TUMORS OF POSTERIOR FOSSA: FROM DIAGNOSIS TO FOLLOW UP**

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Lesions of the posterior fossa account for 20 % of all the patients with brain tumors and although tumor related neuropsychological sequelae have been reported, few data describe the psychosocial consequences faced at the end of the treatment. We assessed emotional, behavioral and social impairments from diagnosis to follow-up (6-12 months), in children referred to our institution, using the Achenbach Child Behavior Checklist for ages 1-5 years (group-1) and 6-18 years (group-2). The possible correlation between impairments and tumor's location was also evaluated. We enrolled 23 patients (14 M, 9 F), 11 (48%) in group-1 and 12 (52%) in group-2. Mean age was 89 months at diagnosis and 101 months at follow-up. The location was vermian in 8 patients (35%); emispheric in 2 (9%), vermian-emispheric in 3 (13%) and extending to the fourth ventricle in 3 (13%). Most frequent histology was medulloblastoma (74%), followed by pilocytic astrocytoma (18%) and ependymoma (8%). All the patients underwent surgical resection, 14 patients (61%) received chemotherapy, 8 (35%) chemotherapy and radiotherapy. Mean Internalizing scores were 52 at diagnosis and 53 at first follow up in group-1, 57 and 64 respectively in group-2. Mean Externalizing scores were 47 and 53 for younger children and 46 and 51 for the other group (diagnosis and follow-up, respectively). Changes of emotional, behavioral and social profiles were not found to be significant in both groups. A trend toward increase of attention issues was found in patients with lesions involving the fourth ventricle. Our preliminary data

suggest that emotional, behavioral or social impairments at diagnosis tend to stably persist throughout treatment and must then be target of early intervention. Moreover, specific neuropsychological rehabilitation might be beneficial in case of lesions involving the fourth ventricle. A larger cohort of patients and longer follow-up are required to better characterize our results.

#### NP-021. SOCIAL COGNITIVE DEFICITS AND REDUCED SOCIAL ATTAINMENT IN ADULT SURVIVORS OF CHILDHOOD CENTRAL NERVOUS SYSTEM (CNS) TUMORS

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**BACKGROUND:** Pediatric CNS tumor survivors are at risk for neurocognitive impairment, yet little is known about social cognition in adult survivors. **METHODS:** Participants included 78 adult survivors of childhood CNS tumors [55% infratentorial, 45% supratentorial] enrolled in the St. Jude Lifetime Cohort (mean [SD] current age = 28.1 years [5.8], age at diagnosis = 9.4 years [4.7], and time since diagnosis = 18.8 years [6.0]). Age-adjusted standard scores were calculated for measures of intelligence and social cognition including affect recognition (i.e. facial expression of emotion) and prosody (i.e. emotional tone of voice). Impairment was defined as performance >1SD below the normative mean. Multivariable general linear models were used to examine associations between tumor location and treatment and social cognition. Logistic regression models examined associations between social cognition and attainment (i.e. employment, independent living). **RESULTS:** 30% of CNS tumor survivors were impaired on measures of facial affect labeling ( $p = 0.001$ ), 32% for identifying prosody ( $p < 0.001$ ), and 34% for matching prosody with nonverbal social cues (e.g. body posture, affect;  $p < 0.001$ ). Infratentorial tumor survivors treated with craniospinal radiotherapy (CSI) performed significantly worse than infratentorial tumor survivors treated with focal RT, supratentorial survivors treated with focal RT, and survivors treated with no CRT on facial affect naming ( $p = 0.017$ ), prosody identification ( $p < 0.001$ ) and matching prosody with social cues ( $p = 0.007$ ). These differences persisted after accounting for IQ. In models adjusted for IQ, sex and age, better performance on social cognition tasks increased the likelihood of full time employment by 55% (OR = 1.5, 95% CI 1.2-2.1) and independent living by 20% (OR = 1.2, 95% CI, 1.1-1.4). **CONCLUSIONS:** Adult survivors of pediatric CNS tumors demonstrated considerable impairment on measures of social cognition, with greater impairment observed for survivors of infratentorial tumors treated with CSI. Observed social impairment confers risk for reduced occupational attainment in adulthood and may have implications for the social independence and achievement of survivors.

#### NP-022. COMPUTERIZED ASSESSMENT OF NEUROCOGNITIVE FUNCTIONING IN PRESCHOOL- AND SCHOOL-AGED CHILDREN WITH BRAIN TUMORS

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**OBJECTIVE:** Psychometrically-valid and reliable neurocognitive assessment tools for young children are lacking, particularly for domains affected by brain tumors and their treatment. We examined the utility and construct validity of a brief, computerized assessment in a sample of preschoolers (aged 4-6) and school-aged children (aged 7-16) diagnosed with brain tumors (BT). **METHODS:** Five computerized tasks using touch-screen technology were developed using the CogState assessment platform. Two versions of the tasks were used: one tailored for children 4-6 and one developed for older children and adolescents. Tasks included measures of processing speed, visual attention, working memory, visual learning, and executive functioning. Children completed these tasks as well as traditional measures of intellectual, memory, visual-motor, and executive functioning. **RESULTS:** To date, 37 children with BT (M age = 10.4, 60% male, 84% White) have completed computerized testing. Participants ranged from 0-14 years since diagnosis (M = 4.5 years), 50% had received cranial radiation therapy. Mean intellectual functioning and parent-rated working memory were in the average range (FSIQ = 99.4, SD = 18.93; BRIEF Working Memory T = 57.9, SD = 12.99; CBCL/BASC Attention T = 52.4, SD = 8.30). Data supported the convergent validity of many computerized tasks for both the preschoolers and school-aged groups. For example, worse performance on a computerized visual attention task was associated with parent ratings of executive dysfunction ( $r = 0.41$ ,  $p < .05$ ), longer time since diagnosis ( $r = 0.35$ ,  $p < .05$ ), and younger age at diagnosis ( $r = -0.43$ ,  $p < .05$ ). **CONCLUSIONS:** Computerized cognitive testing has potential advantages

over traditional paper-and-pencil measures for children with BT at risk for neurocognitive sequelae, including brevity, multiple alternate forms, and reduced motor demands. If reliable and valid, these tasks could serve as rapid, low-cost cognitive monitoring tools that can be administered without an on-site neuropsychologist.

#### NP-023. NEUROINFO FOR KIDS – DEVELOPMENT OF A MANUAL TO HELP CHILDREN WITH A BRAIN TUMOR TO MAKE THE BEST OUT OF THEIR NEUROPSYCHOLOGICAL TEST RESULTS

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As survival rates in pediatric neuro-oncology have risen over the past decades, tumor- and treatment related neurocognitive late effects remain problematic for survivors. Various guidelines emphasize the importance of neuropsychological evaluation at different time points and give recommendations concerning the way assessment is carried out. However, the test situation itself as well as the report of the test results can be very challenging for the survivors, possibly facing their own deficits and therefore feeling degraded. For this reason we developed a standardized, resource-oriented manual facilitating the reporting of test results, NeuroInfo for Kids (NIK). NIK is based on the concept of salutogenesis and focuses on empowering the child, inter alia, through helping the child to get realistic knowledge of his own strengths and weaknesses and to get ideas of how to best deal with potential deficits. **PARTICIPANTS:** 23 patients with different types of brain tumors at the Department of Pediatrics, Medical University of Vienna; 12 girls, 11 boys; mean age 10.7 [7-13 years]; mean age at onset 5, 61; mean time since onset 5,39; treatment with surgery, chemotherapy and/or radiotherapy. **METHODS:** The first draft of NIK was evaluated in a pilot study, with respect to the study questions whether NIK has an influence on comprehensibility, manageability and the feeling of meaningfulness. The young patients had to fill out standardized questionnaires before and after the intervention with NIK, which was carried out by a trained neuropsychologist. SPSS was used for statistical analysis. **RESULTS:** We found that NIK significantly increased knowledge about personal strengths and weaknesses. Moreover knowledge about possible interventions was significantly improved. However, general knowledge about neuropsychological assessment could not be increased. Besides, NIK had no impact on self-esteem of the participants. As a result of the pilot study the improved version NIK<sup>2</sup> was defined.

#### NP-024. COGNITIVE OUTCOMES IN MEDULLOBLASTOMA PATIENTS WITH CEREBELLAR MUTISM AND SHUNTED HYDROCEPHALUS

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**PURPOSE:** Medulloblastoma survivors have lower cognitive scores than healthy peers, attributed to radiation therapy. We sought to assess the impact of cerebellar mutism and shunted hydrocephalus. **METHODS:** A retrospective chart review was completed of all 95 medulloblastoma patients treated at our institution between 1/2001 and 12/2013. Patients were excluded for age older than 21 years (4), incomplete data (8), no surgical resection (2), and rapid death (1). 80 charts were reviewed for age at diagnosis, sex, treatment, diagnosis of cerebellar mutism, presence of cerebral spinal fluid (CSF) shunt, and results and timing of cognitive testing. **RESULTS:** 38/80 had documented post-treatment neuropsychological evaluations, 26 males and 12 females, with a mean age of 8.2 years at diagnosis. 37/38 received radiation. 10 had cerebellar mutism, 8 a CSF shunt, and 4 had both. All patients received the age appropriate Wechsler exam providing measures of full scale IQ (FSIQ), Verbal Comprehension, Perceptual Reasoning, Memory, and Processing Speed. The mean FSIQ in patients without cerebellar mutism or a shunt was 92.1, as compared to the normative mean of 100. In those with a CSF shunt it was 87, and 71.7 in those with cerebellar mutism. Performance was weakest in patients with cerebellar mutism and a CSF shunt, 67. Verbal scores were better than Perceptual and Working Memory measures in all groups. Processing speed was low to below average in all. **CONCLUSIONS:** After treatment for medulloblastoma, patients demonstrate lower than average cognitive scores. Cerebellar mutism worsens the outcome further, particularly in patients requiring a shunt.