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MRI research into changes in the brain and cognitive functioning after treatment for pediatric brain tumor

Submission date 20/12/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 21/04/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 30/09/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Treatment advances have increased survival rates for children with brain tumors. However, many survivors experience neurocognitive problems after treatment that significantly impact their quality of life and unfortunately, there are few evidence-based interventions to improve cognitive deficits after they occur. These impairments are most prominent for children who were treated at a younger age or with cranial radiation therapy (RT)4, and thus, methods to prevent RT-related damage are an ongoing field of research.

There is increasing evidence that the early neurobiological changes that occur after brain tumor treatment are predictive of cognitive functioning in the long term. In this manner, assessment of changes in the brain may provide a marker of vulnerability for future cognitive dysfunction, although knowledge of early and sensitive biomarkers of cognitive decline is limited in children with brain tumors. Therefore, these results indicate that there is a critical need to identify early (bio)markers of neurocognitive decline, so that potential preventative strategies can be implemented prior to the onset of impairments.

This study addresses this knowledge gap by using newly developed, high field 7Tesla (T) Magnetic Resonance Imaging (MRI) techniques measuring vascular health, metabolism, and diffusion in the brain. Previous research has shown that 7T MRI can visualize brain structure and function in an unprecedented manner, including vascular lesions with resolutions of <1mm13-15 and brain pulsatility and metabolism in patients across the age range. Also, small vessel degeneration and low glutamate levels assessed with 7T MRI have previously been associated with worse cognitive performance in adult and pediatric populations. Furthermore, 7T MRI methods have been developed to assess microinfarcts in neurodegenerative diseases, which were then subsequently applied to 3T MRI scanners used in the clinic. These results suggest that 7T MRI techniques can detect brain structural or functional changes in a highly sensitive manner, which can then be applied to clinical settings. These techniques could be developed as an early predictive tool for cognitive deficits, although this has not yet been established for children with brain tumors. Results from the current study will inform future longitudinal research examining whether changes in brain vasculature, metabolism, and diffusion precede or accelerate cognitive

decline over time. Ultimately, knowledge from this research can be used to direct treatment and prevent cognitive decline in pediatric brain tumor.

Who can participate?
Patients (n = 30) aged 6 - 23 years old, who are at least 6 months and up to 5 years after diagnosis and who have completed treatment for a posterior fossa brain tumor. There will be patients who received:
• surgery/chemotherapy only (no RT)
• focal proton radiotherapy
• cranial-spinal proton radiotherapy

What does the study involve?
Participants will come to the research facility at University Medical Center Utrecht (UMCU) to complete MR imaging at 7T (1 hr) and to the Princess Máxima Center to complete neuropsychological testing (2 hr). These appointments will be completed on the same day when possible. Parents/caregivers will also be asked to complete questionnaires.
The primary objective is to examine relationships between neurocognitive performance and MRI parameters of brain vasculature, metabolism, and white matter diffusion in children who have been treated for a posterior fossa tumor. Secondary objectives are to examine relationships between RT dose distribution and neurocognitive outcomes and to evaluate whether the combination of multiple imaging modalities can distinguish between survivors who had relatively better versus poorer neurocognitive functioning.

What are the possible benefits and risks of participating?
MRI is a non-invasive imaging modality, involving high magnetic fields, which in general is not associated with adverse events other than possible claustrophobia due to lying in the small MR bore. All participants will already have an MRI during normal clinical routine; therefore, we can exclude patients with severe claustrophobia. Regarding the neuropsychological testing and questionnaires, some patients and their parents/caregivers will complete these as part of standard care, which therefore minimizes time burden. There are no anticipated risks for participation. One potential benefit is that parents will receive a summary of results from the assessment (and will be referred for services when needed). Otherwise, there are no direct benefits for participation and results will be used to optimize care for future patients.

Where is the study run from?
The Princess Máxima Center Utrecht (the Netherlands)

When is the study starting and how long is it expected to run for?
From May 2022 to December 2025

Who is funding the study?
The Princess Máxima Center/KiKa (the Netherlands)

Who is the main contact?
Marita Partanen, M.H.Partanen@prinsesmaximacentrum.nl

Contact information

Type(s)
Scientific

Contact name
Dr Marita Partanen

ORCID ID
https://orcid.org/0000-0003-1018-9778

Contact details
Heidelberglaan 25
Utrecht
Netherlands
3584CS
+31 889727272
M.H.Partanen@prinsesmaximacentrum.nl

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PNM21SIM

Study information

Scientific Title
Seven tesla imaging biomarkers of cognitive outcome after treatment for pediatric brain tumor

Acronym
SIMBA

Study objectives
This is an exploratory study using a 7T MRI techniques that haven't been used in this patient group in research before. Therefore, there are no specific hypotheses. Based on previous research, it is expected that changes in brain vasculature, metabolism and diffusion are related to cognitive performance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/03/2022, Netherlands Medical Ethics Committee (Medisch-Ethische Toetsingcommissie NedMec, Heidelberglaan 100, Utrecht 3584 CX, Netherlands; +31 (0)88 7556376; metc@nedmec.nl), ref: 21/851, NL79739.041.21

Study design
Single-center observational study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Pediatric brain tumor treated with radiation therapy

Interventions
For this observational study, participants will complete one 7 Tesla MRI scan. From this scan, parameters of brain vasculature, metabolism and white matter diffusion will be obtained. Additionally, a neuropsychological assessment will be administered measuring performance on the following cognitive domains: working memory, processing speed, sustained attention, executive function, memory, visual motor (WISC-V/WAIS-IV, KCPT-2/CPT-3, IDS-2, RAVLT, Purdue Pegboard). Questionnaires will be completed by parents/caregivers and/or the patients to obtain information on the child's executive skills (BRIEF-2/BRIEF-A), behavior (SDQ parent/SDQ informant), quality of life (PedsQL Generic), fatigue (PedsQL Fatigue). Information on background (education level and current work situation of parent/caregiver) will be obtained via questionnaires filled out as part of standard care.

Intervention Type
Other

Primary outcome(s)
Measured once:
1. Performance on a sustained attention task (K-CPT-2/CPT-3 measure)
2. 7T MRI metrics measuring vascular health, metabolism, and diffusion in the brain measured using MRI processing

Key secondary outcome(s))
1. Neuropsychological measures:
1.1 Estimated IQ measured using the Vocabulary and Matrix Reasoning subtests from WISC-V /WAIS-IV at 1-5 years after diagnosis
1.2 Working memory measured using the Digit Span, Picture Span and/or Arithmetic subtests from WISC-V/WAIS-IV at 1-5 years after diagnosis
1.3. Processing speed measured using the Coding and Symbol Search subtests from WISC-V /WAIS-IV at 1-5 years after diagnosis
1.4. Executive functioning measured using the subtests Road Walking and Word Naming from IDS-2 at 1-5 years after diagnosis
1.5. Memory measured using RAVLT at 1-5 years after diagnosis
1.6. Visual-motor measured using the Purdue Pegboard at 1-5 years after diagnosis
1.7. Questionnaires filled out by parents and/or patients to measure executive skills (BRIEF-2 /BRIEF-A), behavior (SDQ parent/SDQ informant), quality of life (PedsQL Generic), fatigue (PedsQL Fatigue) and pre-morbid medical, psychosocial and school functioning (PAT2.0).
All neuropsychological measures are administered at one timepoint at 1-5 years after diagnosis. Parents are asked to complete the questionnaires via a safe, online KLIK portal at this same timepoint
2. Clinical, biological, and psychosocial variables will be identified from the medical record and

parent questionnaires. This will include clinical data (e.g., demographic, treatment, RT dose, complications), and premorbid history (e.g., birth, health, school, SES). Scores are either continuous or categorical (yes/no) depending on the metric.

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Age between 6 - 23 years old
2. Have been treated for a posterior fossa brain tumor with surgery/chemotherapy only, focal proton RT, or cranial-spinal proton RT
3. At least 6 months and up to 5 years after diagnosis, and completed treatment
4. Able to complete MRI without anesthesia

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
6 years

Upper age limit
23 years

Sex
All

Total final enrolment
31

Key exclusion criteria
1. No signed informed consent (either by patient and/or parents/legal guardian)
2. Insufficient knowledge of the Dutch language to perform the neuropsychological assessment or complete questionnaires
3. Significant visual, motor, or developmental problems and thus alternative neuropsychological assessments would be needed (e.g., blindness, deafness, profound developmental delay)
4. MRI-specific exclusion criteria, such as metal implants. Screening for MRI specific exclusion criteria will be done using the typical 7-Tesla MRI safety screening.

Date of first enrolment
01/06/2022

Date of final enrolment

31/07/2025

Locations

Countries of recruitment
Netherlands

Study participating centre
Princess Máxima Center
Heidelberglaan 25
Utrecht
Netherlands
3584 CS

Sponsor information

Organisation
Princess Máxima Center

ROR
https://ror.org/02aj7yc53

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes