Protocol for a prospective, longitudinal study of cognitive impairment in young patients with cancer: a multidisciplinary neuroscience approach (MyBrain)

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ABSTRACT
Introduction The aim of this research is to investigate young cancer patients’ cognitive functioning and the underlying neurobiological mechanisms when cognitive functions are impaired. The MyBrain protocol is a multidisciplinary study that investigates cancer-related cognitive impairment in children, adolescents and young adults, combining neuropsychology, cognitive neuroscience and cellular neuroscience. The study is exploratory with a wide focus on trajectories of cognitive functions from diagnosis to the end of treatment and into survivorship.

Methods and analysis Prospective longitudinal study including patients diagnosed with non-brain cancers at age 7–29 years. Each patient is paired with a control matched on age and social circle.

Primary objective Evaluation of neurocognitive function over time.

Secondary objectives Evaluation of self-perceived quality of life and fatigue, P300 in an electroencephalography (EEG) oddball paradigm, power spectrum in resting state EEG, serum and cerebrospinal fluid levels of biomarkers of neuronal damage, neuroplasticity, proinflammatory and anti-inflammatory markers and their association with cognitive function.

Ethics and dissemination The study is approved by the Regional Ethics Committee for the Capital Region of Denmark (no. H-21028495), and the Danish Data Protection Agency (no. P-2021-473). Results are expected to guide future interventions to prevent brain damage and support patients with cognitive difficulties.

Trial registration number The article is registered at clinicaltrials.gov NCT05840575 (https://clinicaltrials.gov/ct2/show/NCT05840575)

INTRODUCTION
The past decades of research have indicated that many patients with cancer, regardless of cancer type, develop cancer-related cognitive impairment (CRCI), which may persist for many years after the treatment has ended.1-8 CRCI is characterized by a decline in several cognitive domains, including memory, attention, processing speed and executive functions.9 In daily life, this may manifest as difficulties in learning new material, concentrating, multitasking, mentally organise tasks and cognitive fatigue.10 Research from a wide range of disciplines, including neuropsychology, neuroimaging, biomarkers and animal studies, has provided evidence of the cognitive impact of cancer and its treatments on non-central nervous system (CNS) patients.11

Cognitive impairment affects children, adolescents and young adults (CAYA) with cancer and their families. CAYA are in a formative phase of their lives regarding school, education, work and social bonds.12 Accordingly, young survivors of cancer report difficulties returning to their education or job and in everyday life.13-16 However, for CAYA, there is a lack of knowledge about when a decrease in cognitive capacity may occur, how long it will persist and which cognitive domains are affected.4-8 CAYA may be particularly vulnerable to cognitive impairment as the brain undergoes development in childhood and continues into the 20s.17

Aim
The overarching aim of this study is to take a multidisciplinary neuroscience approach in
The association between evoked brain activity and cognitive function and inflammation.

**Objectives**

The specific objectives are to investigate trajectories of:

- Cognitive functioning, measured with standard as well as automated neurocognitive tests.
- QoL and fatigue.
- Resting state and evoked brain activity with EEG.
- Blood and cerebrospinal fluid (CSF) biomarkers of inflammation and neural damage.
- The association between cognitive function and biomarkers of inflammation and neuronal damage.
- The association between evoked brain activity and cognitive tests of attention.

**METHODS**

**Participants**

**Inclusion and exclusion criteria**

Inclusion criteria: Patients aged 7–29 years who are newly diagnosed with a non-CNS cancer and will undergo chemotherapy are eligible to participate. Each patient is matched (1:1) with a control participant within 24 months of age. The controls are recruited from the patient’s own social circle and can be a friend, partner or close family (sibling or cousin).

Exclusion criteria: Patients as well as controls will be excluded from enrolment in the study if they are unable to speak and understand Danish, have severe intellectual disability or mental health disorder that hinders participation, have brain metastases, terminal illness, are pregnant or have had a previous chemotherapy or radiotherapy treatment.

**Recruitment and screening**

Identification of new patients is done by screening of the electronic medical journals and by weekly contact with the treatment teams at the paediatric, oncological and haematological departments. When a new patient is identified, the inclusion and exclusion criteria are reviewed together with the treating physician.

The initial contact with the patients and parents will occur through the treating physician or nurse when the patients are seen at the clinical ward. If patients or their parents wish to learn more about the study, we will offer a designated time for a study nurse to provide both oral and written information. Written information is given to the parents if the patient is <15 years, to the patient and parents if the patient is 15–17.9 years and to patients if they are ≥18 years of age. Written informed consent is given and can be withdrawn at any time. The recruitment period is anticipated from March 2022 to February 2025.

The matched control participant is nominated by the patient. Patients and/or their parents are encouraged to give a page with short written information to the potential control participant or their parents. Subsequently, the research team will provide more detailed written and oral information before possible consent and enrolment. Inclusion and exclusion criteria are reviewed when the oral information is given. Controls may be recruited several months into the patients’ treatment to avoid any pressure and it is possible for a patient to participate without a control, if nominating a control is considered burdensome. Control participants are reimbursed for their travel costs.

**Design**

**Study design**

MyBrain is a single-centre, prospective, longitudinal study of CAYA with cancer outside the CNS (figure 1).

**Study setting**

The MyBrain study is conducted at Rigshospitalet in Copenhagen, Denmark. Patient recruitment is performed at the Department of Paediatrics and Adolescent Medicine, the Department of Oncology and the Department of Haematology. The initial assessments take place at the hospital department where the patient is treated, either at bedside or in one of the meeting rooms close by. Follow-up assessments and assessments of controls are conducted at testing or meeting rooms at the hospital.

**Time points**

Patients are assessed as close as possible to the day they receive their diagnosis and within 30 days from diagnosis (T0); at up to three time points during treatment (T1abc) for all patients and up to three additional time points for patients treated with high-dose methotrexate (HDM1-3); at end of treatment (T2) and at follow-up 6 months after end of treatment (T3) (figure 2). End of treatment is 2 weeks after the final antineoplastic treatment. For acute lymphoblastic leukaemia patients, end of treatment is considered as the end of consolidation treatment. Long-term follow-up is anticipated 3 years after end of treatment (T4).

All outcome measures are collected at T0, T2 and T3. Neurocognitive tests and EEG are preferably measured on the same date, or two consecutive days, but may be collected on separate dates to make data collection flexible during treatment (with no more than 60 days between test days). Each control participant will be assessed at similar time intervals as T0, T2 and T3 for the corresponding patient with cancer.

Blood samples will be taken immediately before and 10–14 days after chemo treatment for up to three specific chemo cycles (T1abc). The blood samples will be collected at evenly-spaced time points throughout the treatment plan. For example, a rhabdomyosarcoma patient receiving nine cycles of IVA (ifosfamide, vincristine, and actinomycin-D) will have blood samples taken prior to and 10-14
Figure 1 Flow chart of recruitment and participation. EEG, electroencephalography; HDM, high-dose methotrexate.
days after cycles 2, 5, and 8 (corresponding to T1a, T1b, and T1c, respectively). Additionally, patients receiving HDM at any point during their treatment will have up to three extra blood samples taken before HDM treatment begins and 10–14 days after (HDM1-3).

Expected population
We anticipate including 30–40 new patients every year (in total 100 patients during the 3-year recruitment period). The distribution of diagnoses will follow the distribution of non-CNS diagnoses among patients receiving chemotherapy in the age group. The most common diagnoses are expected to be Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, testicular cancer, sarcoma and leukaemia.

We expect to collect CSF from 15 leukaemia and non-Hodgkin’s lymphoma patients per year since they have CSF drawn as part of their treatment.

Data for analysis
A summary of data collection at each time point is shown in table 1.

Participant characteristics
Clinical and sociodemographic information
Medical charts will be accessed to obtain information regarding cancer diagnosis, treatment protocol, duration of treatment and adverse events. Sociodemographic information will be collected using a brief questionnaire.

### Table 1 Overview of data collected

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Diagnosis</th>
<th>During treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0: within 30 days of diagnosis</td>
<td>T1abc: in conjunction with major chemo treatments</td>
<td>HDM1-3: in conjunction with HDM treatments</td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical data</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life and fatigue</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive tests</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample*</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>CSF sample†</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

* T1 blood samples are collected just prior to treatment-start and again after 10–14 days. For leukaemia and non-Hodgkin’s lymphoma patients who are treated with HDM, we will also collect one additional blood sample before and after these treatments.
† Only collected from patients where CSF is drawn as part of their regular treatment.

CSF: cerebrospinal fluid; EEG, electroencephalography; HDM, high-dose methotrexate.
We will gather information on level of education, occupation, economic status and the parents’ level of education and occupation.

Outcomes
Cognitive functioning assessed with standard neurocognitive tests
The standard neurocognitive battery is composed of tests that are frequently used in clinical neuropsychology and have versions available for children, adolescents and adults. It includes several subtests from the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) or the Wechsler Adult Intelligence Scale–Fifth Edition (WAIS-V): Digit Span, Matrix Reasoning, Vocabulary, Coding and Symbol Search. Additionally, the Verbal Fluency Test from A Developmental NEuroPSychological Assessment-Second Edition (NEPSY-II), the Wordlist Memory, Recall and Recognition tests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Conners’ Continuous Performance Test-Third Edition (Conners’ CPT-III) and the Grooved Pegboard Test (Lafayette Instrument) are also included.

The test battery was specifically assembled for this study with the aim of evaluating a wide range of cognitive functions within a relatively short assessment duration. The neurocognitive evaluation is intended to take approximately 70 min. The cognitive domains and the tests are shown in table 2.

Cognitive functioning assessed with automated testing
The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computerised method for cognitive testing that can be administered via tablet or PC. The CANTAB tests take approximately 30 min to complete. The tests include simple tasks, typically based on recognising patterns and solving puzzles, and will assess cognitive functions such as working memory, concentration, reaction and processing time and planning (table 2).

Self-reported QoL and fatigue
Health-related QoL will be evaluated using the Paediatric Quality of Life Inventory (PedsQL) Generic Core Scales 4.0 in a validated Danish version. It includes measures of physical, emotional, social and school/education/work functioning. Fatigue will be evaluated with the PedsQL Multidimensional Fatigue Scales 3.0 which measures fatigue, cognitive fatigue and sleep-related fatigue. The questionnaires are filled in as proxy-report (parent) for children <13 years, as self- and proxy-report for adolescents aged 13–17 years and as self-report for participants ≥18. The questionnaires are given as hard copies or on a tablet. Responses to the questionnaires will be scored according to the test guidelines.

Brain functioning measured with EEG
A portable EEG set is used so EEG can be recorded at the bedside or ward when the patients are hospitalised. EEG is recorded using BioSemi EEG with 32 electrodes placed according to the 10–20 system. Electro-oculography (EOG) is recorded from flat-type electrodes placed above and below the right eye (vertical EOG) and at the outer canthi of each eye (horizontal EOG). Reference-electrodes are placed on the mastoids. The EEG session takes approximately 1 hour including electrode placement and removal (see figure 3 for an overview of the EEG recordings).

Resting state EEG is recorded with four alternating eyes-open (EO) and eyes-closed (EC) blocks of 3 min each. The participants are instructed to sit still and relax without thinking about anything in particular. In the EO condition, they are instructed to look straight ahead and keep their gaze still. Measures of absolute power (the total amount of power in a given frequency band) and relative power (the percentage of power in a given frequency band relative to the total power across frequencies) will be calculated for each channel in the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (≥13 Hz). For each block, mean vigilance levels above and below the right eye (vertical EOG) and at the outer canthi of each eye (horizontal EOG). Reference-electrodes are placed on the mastoids. The EEG session takes approximately 1 hour including electrode placement and removal (see figure 3 for an overview of the EEG recordings).

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Cognitive domain assessed and the neuropsychological test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain</strong></td>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>Executive function</td>
<td>Verbal Fluency (NEPSY-II)</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Coding (WISC-V or WAIS-IV)</td>
</tr>
<tr>
<td></td>
<td>Symbol Search (WISC-V or WAIS-IV)</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Word List Memory (RBANS)</td>
</tr>
<tr>
<td></td>
<td>Word List Memory Recall (RBANS)</td>
</tr>
<tr>
<td></td>
<td>Word List Memory Recognition (RBANS)</td>
</tr>
<tr>
<td>Verbal reasoning</td>
<td>Vocabulary (WISC-V or WAIS-IV)</td>
</tr>
<tr>
<td>Non-verbal reasoning/fluid intelligence</td>
<td>Matrix Reasoning (WISC-V or WAIS-IV)</td>
</tr>
<tr>
<td>Working memory</td>
<td>Digit Span (WISC-V or WAIS-IV)</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>Conners’ CPT-III</td>
</tr>
<tr>
<td>Fine motor skills</td>
<td>Grooved Pegboard</td>
</tr>
<tr>
<td>CANTAB tests</td>
<td></td>
</tr>
<tr>
<td>Working memory, strategy use</td>
<td>Spatial Working Memory Test</td>
</tr>
<tr>
<td>Memory</td>
<td>Pattern Recognition Memory</td>
</tr>
<tr>
<td>Working memory</td>
<td>Spatial Span</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Paired Associates Learning</td>
</tr>
<tr>
<td>Memory</td>
<td>Pattern Recognition Memory, Delayed</td>
</tr>
<tr>
<td>Attention, recognition</td>
<td>Delayed Matching to Sample</td>
</tr>
</tbody>
</table>

will be classified using the VIGALL algorithm and plotted against time since start of the block.21

Event-related potentials are recorded during a two-tone auditory oddball task to evaluate brain potentials in response to attended tones. The participants are instructed to mentally count the rare stimulus. Standard tones of 500 Hz are presented in 280 trials, rare tones of 1000 Hz are presented in 60 trials with an interstimulus interval of 0.9 s. The task takes 6 min to complete. Stimuli are presented with the built-in speakers of a laptop. The event-related potential, the P300 peak, will be used as a measure of attention. The P300 response in the EEG signal to the oddball stimuli is quantified by its peak amplitude and latency.

Biological markers associated with cognitive functioning

Blood samples will not exceed 3 mL/kg and a maximum of 10 mL per drawing (8 mL serum and 2 mL fullblood). If sufficient CSF is drawn during treatment-related lumbar punctures, an additional up to 2 mL CSF sample will be collected.

Biological samples are brought to the in-house laboratory (Bonkolab, Rigshospitalet) for handling and storage. The biological samples will be processed within 30 min of collection. Serum will be allowed to clot for 30–60 min. Following, it will be centrifuged for 10 min at 2500 × g, distributed into 1.5 mL tubes and stored immediately at −80°C. Fullblood will be stored at −20°C. CSF is stored at −80°C. Time from collection of the samples to processing is registered.

For both serum and CSF samples, levels of brain-derived neurotrophic factor (BDNF), neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), interferon-gamma (IFN-γ), interleukin-10 (IL-10), IL-12p70, IL-17A, IL-6, IL-1β and tumor necrosis factor alpha (TNF-α) levels will be measured blinded to clinical data by single molecule array technology (Simoa, HD-X Analyser (Quanterix)), using the commercially available 2-Plex assay for the quantitative determination of NIL and GFAP and 6-plex assay for IFN-γ, IL-10, IL-12p70, IL-17A, IL-6 and TNF-α (Quanterix).

**ANALYSIS PLAN**

**General approach**

Large inhomogeneity in the data is anticipated due to the inclusion of patients over a wide age-span with different cancer types, varying treatment protocols and varying timelines from diagnosis to end of treatment, and we have no prespecified, specific hypotheses due to the many possible sources of inhomogeneity. Therefore, all analyses are exploratory, and confidence limits rather than nominal p values will be used as the indication of the strength of an association when quantified in statistical analyses.

The initial analyses will be graphical evaluations. The data visualisations of quantitative variables will include trajectories for single variables, bivariate plots with smoothed mean curves added and plots of patient observations against the corresponding observations for the matched control connecting the points in temporal order for each matched pair. The trajectories will be presented for different timescales, for example, age at examination, time since diagnosis or time from T2. Potential risk factors, like cancer type, sex or age will be investigated by applying different symbols and colours to indicate different values of the risk factor in the data visualisations.22

Associations found in the graphical analyses will be quantified in numerical, statistical analyses based on repeated measurements models. The linearity of the association with quantitative covariates will be evaluated using linear splines with knots at appropriate percentiles.23 In case of non-linearity that cannot be solved by transformation of the covariate, the covariate will be modelled using the linear spline.

Quantitative outcome variables may be transformed before analysis if necessary to improve normality. For cognitive scales, raw scores with long tails to the left will be reversed before transformation. When only T2 and T3 are considered, an unstructured covariance matrix will be used to account for the repeated measurements. When additional time points are considered, different covariance structures, including random slope models,
will be evaluated to find a sufficiently flexible covariance structure to address the potential inhomogeneity caused by a large variation in time between measurements for different patients. Comparisons of covariance structures will be based on Akaike’s information criterion.

The data for the matched controls may be used as a covariate in the analyses of outcomes for the patients with cancer or may be used as outcomes in simultaneous analyses of both patients and matched controls; the former giving flexibility to adapt to non-linear associations, the latter being less sensitive to intermittent missing data for either patient or with cancer matched control. If outcomes for patients with cancer and matched controls are analysed simultaneously, matched-pair ID will be included as a random effect and, if needed, the within-subject covariance matrix may be allowed to depend on the subject group (patients with cancer and matched controls, respectively).

**Comments for specific outcomes**

**Neurocognitive tests**

Neurocognitive test scores will be examined at T0, T2 and T3. To explore patterns in the neurocognitive data, we will calculate the scores for each individual cognitive test. Raw as well as scaled scores, age-adjusted from Danish population norms, will be evaluated. The neurocognitive tests are grouped into cognitive domains and tests from the same domain will be presented together (see table 2). For the visualisations of the raw patient scores, the scores will be plotted as a function of age including reference curves based on back-converted means, ±SD and −2 SD (cognitive domain impairment on a single test is defined as a z-score less than or equal to −2.0 SD below healthy controls on a single test according to International Cognition and Cancer Task Force recommendations).24

**Biological samples**

Time between collection and processing as well as time in storage will be considered since the length of these time intervals may influence assay performance.25

**Data management and availability**

All data will be stored and managed with the Research Electronic Data Capture (REDCap) database hosted at Copenhagen University Hospital.26,27 REDCap is a secure, web-based application designed to facilitate data capture and management for research studies. The biological samples will be stored in a biobank at Rigshospitalet until they are analysed. The individual-subject data collected and analysed during the current study will not be made publicly available due to Danish and EU personal data legislation.

**Patient and public involvement**

The MyBrain project was initiated in response to the request for more research and information about CRCI voiced by the patient youth panel at Rigshospitalet (Kræftværket).28 The project has in its preparation phase been presented several times to the youth panel to identify patient concerns and priorities. Also, feedback was sought by the nurses and physicians at all the departments involved in the study to identify their priorities and concerns about implementing the study. Participants will be informed about the study results in individual letters. Furthermore, the study results will be disseminated to the youth panel and the departments through follow-up presentations and discussions.

**DISCUSSION**

We have designed the MyBrain study to investigate young cancer patients’ cognitive functioning, brain activity and biomarkers of neurotoxicity. Below, the main aspects of the MyBrain protocol are discussed.

**Study design**

We have chosen a prospective and longitudinal design across cancer types to explore the various trajectories of CRCI. For instance, a meta-analysis on patients with breast cancer indicates that CRCI may already start before chemotherapy, and that some patients will decline over time while others improve.29

We have chosen to have the first time point (T0) as close to diagnosis as possible because the patients will be in a similar situation at this time. Later in time, they will have started different treatment protocols, resulting in varying amounts of toxins received and different side effects. We are aware that T0 is a vulnerable time, as the patients and families must come to terms emotionally with having a severe illness. The patients are most likely also burdened by their cancer symptoms and may experience side effects if their treatment has been initiated. Therefore, all testing is planned in a manner that takes the needs of each patient into consideration. Appointments are made in a flexible manner and the tests can be done over several days.

The study requires time and commitment as well as decision-making close to when the diagnosis is given. It is, therefore, possible that some patients and families opt out because they already have a lot to take care of. To remedy this issue, we allow for participation in parts of the study (eg, only participating in neurocognitive tests), and, in addition, there is also an option to be approached again about the study a few weeks after diagnosis.

**Recruitment of control participants**

We have chosen to recruit controls via participating patients or their parents, who nominate a person from their own social circle to participate. This strategy has been chosen to get a closer match in level of school/education and socioeconomic and lifestyle factors to reduce unmeasured confounding of the comparison between patients and controls. We do not require the control to be healthy, instead we use the same exclusion criteria as used for the patients to make the two groups as comparable as possible. The inclusion of case patients’ friends has been debated and comes with several limitations, such as possible. The inclusion of case patients’ friends has been debated and comes with several limitations, such as possible. The inclusion of case patients’ friends has been debated and comes with several limitations, such as possible. The inclusion of case patients’ friends has been debated and comes with several limitations, such as possible.
as the bias to favour the inclusion of controls for extrovert patients with several friends.30,31 Furthermore, full participation in the study requires the time and commitment to attend the hospital on three separate occasions for approximately 2–3 hours per visit. It is, therefore, possible that there will be bias towards controls who live closer to the hospital and are able to dedicate the time to participate. To remedy this, we allow participation after working hours and during weekends with travelling costs reimbursed. If finding time to come to the hospital is an obstacle for participation, the option of having the neurocognitive tests done at home will be offered.

Outcome considerations
We have chosen to include a standard neurocognitive battery that covers multiple cognitive domains, including those that are most frequently affected, namely learning and memory, processing speed and executive function.31 We have also included CANTAB, which allows for automated and computerised testing and has the potential to be applied more widely and for long-term follow-up because it is easy to administer and can be used remotely.

Neuroscientific studies of brain changes have mostly applied static neuroimaging (eg, grey and white matter measured with MRI), while dynamic measures that combine behaviour and brain activity (eg, task functional MRI and EEG) have been applied in relatively fewer studies.32 Compared with other imaging techniques, EEG equipment is affordable and can be used at the bedside, an important quality for this study and a necessity if such testing should be implemented in clinical practice later. In addition, this technique has a high temporal resolution, which enables recordings of dynamic neural activity.33 We include event-related brain potentials during a task and resting state activity recorded with EEG, since these EEG measurements hold the potential to give information about more subtle changes in cognitive processing.34–36 For the event-related potentials, an easy task will lead to relatively larger peak amplitude and a relatively shorter latency, while a task requiring more cognitive resources will lead to smaller P300 amplitude with longer peak latency.37 In resting state EEG, increased power in the slow delta/theta frequency spectrum has been shown in patients with breast cancer with cognitive complaints.38 Slowing of resting state EEG has long been associated with mild cognitive impairment in the ageing literature.39,40 Several biological mechanisms might underlie cognitive and neural impairment. The research is complicated, as patients undergo different treatments that may impact them through different mechanisms. Evidence is mounting that both CNS-directed and non-CNS-directed chemotherapy cross the blood–brain barrier (BBB) and induce direct brain damage.41 Particularly, HDM has been associated with neurotoxicity and later decline in cognitive performance.42 Further, the biology of cancer itself as well as the treatment with chemotherapy may illicit inflammatory responses that trigger neurotoxic cytokines indirectly resulting in brain damage.43 To capture changes in biomarkers associated with neuronal damage, we collect blood samples before and after three major chemotherapy cycles, as well as before and after HDM treatments.

Direct and indirect brain damage are closely interconnected. The direct toxicity is to be regarded as neuronal brain damage due to an increase in apoptosis in addition to a reduction in neurogenesis,43 whereas the indirect toxic effect after treatment with chemotherapeutics involves an increase in proinflammatory cytokines, which can cross and disrupt the BBB, activate microglia or astrocytes, and potentially increase permeability for cytotoxic agents.44 Our investigation of neurotoxicity involves biomarkers that reflect direct brain damage as well as biomarkers that reflect a proinflammatory state within the CNS.

Future perspective
The MyBrain protocol includes data from multiple domains and for several patient groups, which have mostly been studied separately. Therefore, this study has the potential to indicate patterns across patient groups and measured domains. We anticipate that the current protocol will result in multiple follow-up studies that will allow for formal hypothesis testing.

ETHICS
This study has been approved by the Regional Ethics Committee for the Capital Region of Denmark (no. H-21028495), the Danish Data Protection Agency (no. P-2021-473) and is conducted in accordance with the Helsinki Declaration. Signed informed consent is obtained from all participants prior to participation. Participation in the study does not interfere with the care that the patients receive at the hospital, and they can withdraw consent at any time without any further consequences. Research results will be disseminated in international peer-reviewed scientific journals and at relevant conferences. The study will also be communicated to national patient societies and health professionals via meetings and newsletters.

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Contributors BJTN, MT, BLT, MH, TWK, HP and LLH devised the study concept, design and protocol. BJTN drafted the manuscript. All authors contributed to writing and reviewing the manuscript and made the decision to submit the manuscript for publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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