



Engaging carers in neuropsychological rehabilitation for brain cancer survivors: The “I’m aware: Patients And Carers Together” (ImPACT) program

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ABSTRACT

Background: Cognitive impairment is a common late effect in child and adult brain cancer survivors (BCS). Still, there is a dearth of research aimed at therapeutic interventions and no standard treatment options for most BCS. **Objective:** To describe 1) a novel neuropsychological rehabilitation program for BCS – the “I’m aware: Patients And Carers Together” (ImPACT) program, and 2) two studies that aim to assess the feasibility of the ImPACT program in child and adult BCS, respectively. The program adapts the holistic neuropsychological approach pioneered by Leonard Diller and Yehuda Ben-Yishay to an outpatient setting.

Methods: Two feasibility studies are described: 1) A single-armed study with 15 child BCS (10–17 years) (ImPACT Child); and 2) a randomized waitlist-controlled trial with 26 adult BCS (>17 years) (ImPACT Adult). In both studies, patients will undergo an 8-week program together with a cohabiting carer. Primary outcomes (i.e., cognitive and neurobehavioral symptoms), and secondary outcomes (i.e., behavioral and psychological symptoms, e.g., quality of life, fatigue) will be assessed at four time points: pre-, mid-, and post intervention, and 8 weeks follow-up. Adult waitlist controls will be assessed at equivalent time points and will be included in the intervention group after all study assessments. Semi-structured interviews will be conducted at follow-up.

Expected outcomes: Results will provide feasibility data in support of future larger scale trials.

Discussion: The findings could potentially improve the management of cognitive impairment in BCS and transform available services. The program can be delivered in-person or remotely and harnesses existing resources in patients’ lives.

1. Rationale and background

Cognitive impairment is one of the most common late effects in child and adult brain cancer survivors (BCS), with up to 80% and 69% respectively, experiencing cognitive impairment even years after treatment [1–4]. The etiology of cognitive impairment is multifactorial and likely determined by several interacting factors such as tumor type, treatment modality, and age [5–7]. Regardless of the specific etiology,

observed impairments are likely to affect several cognitive domains simultaneously, e.g., processing speed, attention, memory, and executive functions [4,5]. Concomitant neurobehavioral impairments are often observed in BCS (e.g., adynamia and emotional lability) and may contribute to and/or exacerbate cognitive impairment [6–9]. For example, neurofatigue may contribute to impaired memory. These symptoms often have negative effects on quality of life [10,11] and adaptive outcomes such as socioeconomic status [12]. For example,

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cognitive impairment in long-term survivors of childhood brain cancer has been associated with lower educational attainment, lower household income, and never having been married [12], and cognitive impairment in adult BCS has been associated with impaired social well-being (e.g., not feeling close to family and friends) and functional well-being (e.g., not being able to work or enjoy life) [11]. However, despite the negative impact of cognitive impairment on daily life functions in BCS, there is a scarcity of research on interventions to ameliorate them.

Neuropsychological rehabilitation-based interventions have proven effective in other populations experiencing cognitive impairment, e.g., traumatic brain injury (TBI) and stroke [13]. However, few studies have examined neuropsychological rehabilitation approaches in BCS. Neuropsychological rehabilitation approaches can generally be divided into those aimed at restoration of lost functions (bottom-up), and those focusing on compensation for lost functions (top-down) [14]. Multi-component approaches that combine restoration and compensation seem most suitable for BCS, but their investigation have been limited to few studies [15,16]. These limitations in the available evidence prevent firm conclusions about the effects of neuropsychological rehabilitation approaches in BCS, and thus, there continues to be no gold standard approach to treating cognitive impairment in BCS [17,18].

Four key elements are missing from most studies of neuropsychological rehabilitation in BCS:

I. Transfer of learning from training tasks to real-world functional outcomes:

Several retraining studies with BCS have used massed practice approaches (i.e., repeated training of skills), showing improvements on tasks similar to the training tasks (“near transfer” [19]), but with limited transfer to other domains or real-world functional outcomes (“far transfer” [15,20–23]). Evidence from the broader neuropsychological rehabilitation field suggests that approaches that train patients on tasks closely aligned with daily life activities may be more effective than decontextualized and mass practice approaches [13,23].

II. Awareness training to enhance utilization of compensatory strategies

Patients with brain lesions often suffer from unawareness of their impairments in general (i.e., anosognosia), but also metacognitive unawareness of impairments as they unfold in real-time [24,25]. Research supports that this also applies to BCS [26,27]. If a person is unaware that he/she has cognitive difficulties, this will likely undermine rehabilitation participation and use of strategies [24]. Indeed, when patients have awareness problems, approaches that engage awareness through self-monitoring of behaviors are more likely to improve performance on those behaviors [28,29].

III. Inclusion of carers

Carers can support transfer of learning by helping the BCS to apply strategies outside of sessions and provide “coaching” at times when the BCS is unaware that a problem is happening. Indeed, evidence supports that carer involvement can improve outcomes more than direct clinician-delivered interventions [30] and the mere act of having carers monitor patients’ behaviors can lead to improvements in those behaviors [31,32]. Yet few neuropsychological rehabilitation studies in BCS have included carers. For example, a systematic review of cognitive training programs for children with leukemia or brain cancer identified only two studies that involved parents [23], and in adult BCS, to the best of our knowledge, only one available study, a feasibility study, included carers [33].

IV. Recognition of the interrelated hierarchical nature of cognitive and neurobehavioral functions

Most existing neuropsychological rehabilitation studies in BCS focus on discrete cognitive functions [17,23], and thereby ignore the hierarchical and interrelated nature of cognitive functions. Memory functions, for example, are dependent on lower-level cognitive functions such as attention, and neurobehavioral functions such as behavioral control [9,34,35]. Approaches that integrate the interrelated nature of these functions are likely to be more efficacious than those that focus on discrete functions.

2. Study goals and objectives

A context-sensitive neuropsychological rehabilitation intervention has been developed and adapted for BCS – the “I’m aware: Patients And Carers Together” (ImPACT) program. It adapts the holistic approach pioneered by Leonard Diller and Yehuda Ben-Yishay at the Brain Injury Day Treatment Program at the Rusk Institute of Rehabilitation Medicine of New York University Medical Center [36] to a clinic setting, thereby targeting the elements missing in previous neuropsychological rehabilitation studies with BCS. Holistic programs usually involve carers/loved ones and are often concerned with: (i) increasing an individual’s awareness of what has happened; (ii) fostering acceptance and understanding of the situation; (iii) offering strategies or exercises to ameliorate cognitive challenges; (iv) developing compensatory skills; and (v) providing vocational counseling [14,36]. Based on a solid body of evidence, holistic neuropsychological rehabilitation is recommended as the practice standard for adults with acquired neurocognitive impairments and disability [13]. However, the absence of studies focused on cognitive rehabilitation in brain tumor patients, as well as in children, makes the investigation of a program like ImPACT timely.

The overall goal here is to describe two planned studies aiming to assess the feasibility and acceptability of the ImPACT Program in child (study 1) and adult (study 2) BCS.

2.1. Specific aims

- I. To determine the feasibility of the ImPACT program in child and adult BCS.
- II. To evaluate the preliminary efficacy of the ImPACT program on primary outcomes (i.e., self and carer-reported cognitive and neurobehavioral functions) in adult BCS.
- III. To evaluate the preliminary efficacy of the ImPACT program on secondary outcomes (i.e., objective cognitive outcomes and relevant behavioral and psychological symptoms, e.g., fatigue and depression) in adult BCS.

2.2. Study designs

Fig. 1 illustrates the study designs. Given the lack of evidence concerned with the applicability of the holistic approach in child populations, we will conduct a single-armed feasibility study with 15 dyads (i.e., child patient and carer). For adults, in order to assess the feasibility and preliminary efficacy of the holistic approach in BCS, 26 dyads will be randomized to an intervention or a waitlist control (WLC) group. WLCs will be included in the ImPACT program after participation in the follow-up (T4) assessment. The WLC group will then be assessed at 3 additional time points in order to match the assessments that the intervention group received during their participation in the ImPACT program.

The sample sizes have been determined based on estimates deemed sufficient for gauging the feasibility of the program, taking into account

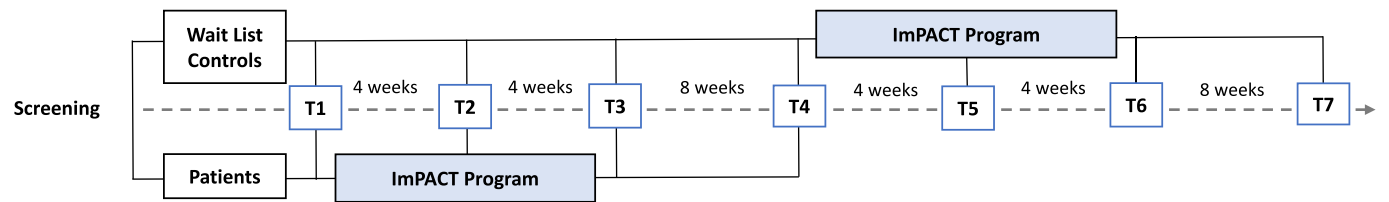


Fig. 1. Study timeline. Note that the ImPACT Adult study will include wait list controls, but the single-armed ImPACT Child study will not.

the expected number of patients available for screening. In the adult study, the total pool of patients followed at Aarhus University Hospital is approximately 150 patients. Based on earlier research with cancer survivors involved in a cognitive rehabilitation study that also involved 8 sessions, we expect 35% to express interest and be eligible [29], corresponding to around 50 patients. If approximately 50% of these patients are likely to have a cohabiting carer willing to participate, then we anticipate including a total of 26 dyads in the adult study. For the child study, with a total pool of around 60 patients at Aarhus University Hospital and referencing a prior study with children in which approximately 25% were interested and eligible [15], we anticipate being able to include 15 dyads.

3. Methodology

3.1. Participants and recruitment

Child and adult participants are recruited through the Department of Pediatrics and Adolescent Medicine and the Department of Oncology at Aarhus University Hospital, respectively, at a regular clinical visit or through an invitation letter in a public, secure digital mailbox (‘e-Boks’) inviting them to participate in the study. Potential participants who show an interest in the study are then contacted by telephone by a research team member who will screen them for eligibility using the criteria listed in Table 1. With respect to cognitive and/or neurobehavioral impairments, eligibility to participate in the ImPACT Child study will be based on parent reports of child cognitive and/or neurobehavioral impairment. Specifically, eligibility is determined as a score corresponding to 1 standard deviation below the normative mean (T score = 40) on the Pediatric Perceived Cognitive Function short form (PedsPCF) [37,38], and/or a score corresponding to the category of “potentially clinically significant” on the Behavior Rating Inventory of Executive Function® Second Edition (BRIEF®2) Screening – Parent Form [39]. In choosing proxy measures through which carers could report on adult BCS symptoms, we were challenged by the lack of

available brief proxy measures, most having been developed for child and dementia populations. Consequently, for the ImPACT Adult study, we developed a custom screening tool comprising 8 items addressing cognitive impairment and 6 items addressing neurobehavioral impairments (See Supplementary Table S1). These items were carefully selected to represent key symptoms covered by the Patient Assessment of Own Functioning Inventory (PAOFI) [40], and the Frontal Systems Behavior scale (FrSBe) [41] in order to screen for cognitive and neurobehavioral impairments, respectively. Response options include “No”, “To some extent”, and “Yes”. Eligibility is then confirmed in cases where the patient and/or carer respond with “Yes” or “To some extent” to one or more of these questions, and “Yes” to each of two subsequent questions asking 1) whether these issues have a negative impact on the patient’s life and 2) whether they wish to receive help for these issues.

Following screening, eligible and interested participants are guided through the informed consent process, and consenting participants are scheduled for the T1 assessment (after randomization for the ImPACT Adult study participants: see below). At T1, patients and carers undergo a brief, open-ended clinical interview in which they are asked questions in layperson’s terms about the nature of the cognitive and neurobehavioral changes that have occurred since the patient’s brain tumor diagnosis, the impact of those changes on daily life, any strategies they have tried to implement to compensate for such problems, and their thoughts about such changes. Patients are then taken through a neuropsychological assessment battery, before both patients and carers complete self-report questionnaires as outlined in Fig. 1. After the T1 assessment, participants assigned to the intervention group are scheduled for the first session in the program.

3.2. Randomization procedures

In the ImPACT Adult study, participants are randomized using a computerized block randomization module in REDCap [42]. The allocation sequence is generated by an independent biostatistician and set up to randomize a total of 26 dyads to two conditions.

Table 1
Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Both studies	- Received a diagnosis of central nervous system tumor. - Completed primary treatment at least 6 months ago. - Medically stable.	- Confounding psychiatric and/or medical condition that might contribute to cognitive and/or neurobehavioral impairment. - Unable to understand and/or speak Danish. - One or more legal carers do not consent to the child’s participation in the study.
ImPACT Child	- Living with a parent/guardian (age > 17 years) who understands Danish and consents to participate in the study alongside the patient. - Age 10–17 years. - Screened as having carer reported cognitive and/or neurobehavioral impairment, defined as: 1 standard deviation below the normative mean (T score = 40) on PedsPCF, and/or - a score corresponding to the category of “Potentially clinically significant” on the BRIEF®2 Screening – Parent Form.	
ImPACT Adult	- Age > 17 years. - Living with a family carer (age > 17 years) who understands Danish and consents to participate in the study alongside the patient. - Screened as having self and/or carer reported cognitive and/or neurobehavioral impairment on custom screening scale (See Supplementary Table S1).	

Abbreviations: BRIEF®2 Screening = Behavior Rating Inventory of Executive Function® Second Edition Screening; PedsPCF = The Pediatric Perceived Cognitive Function Short Form.

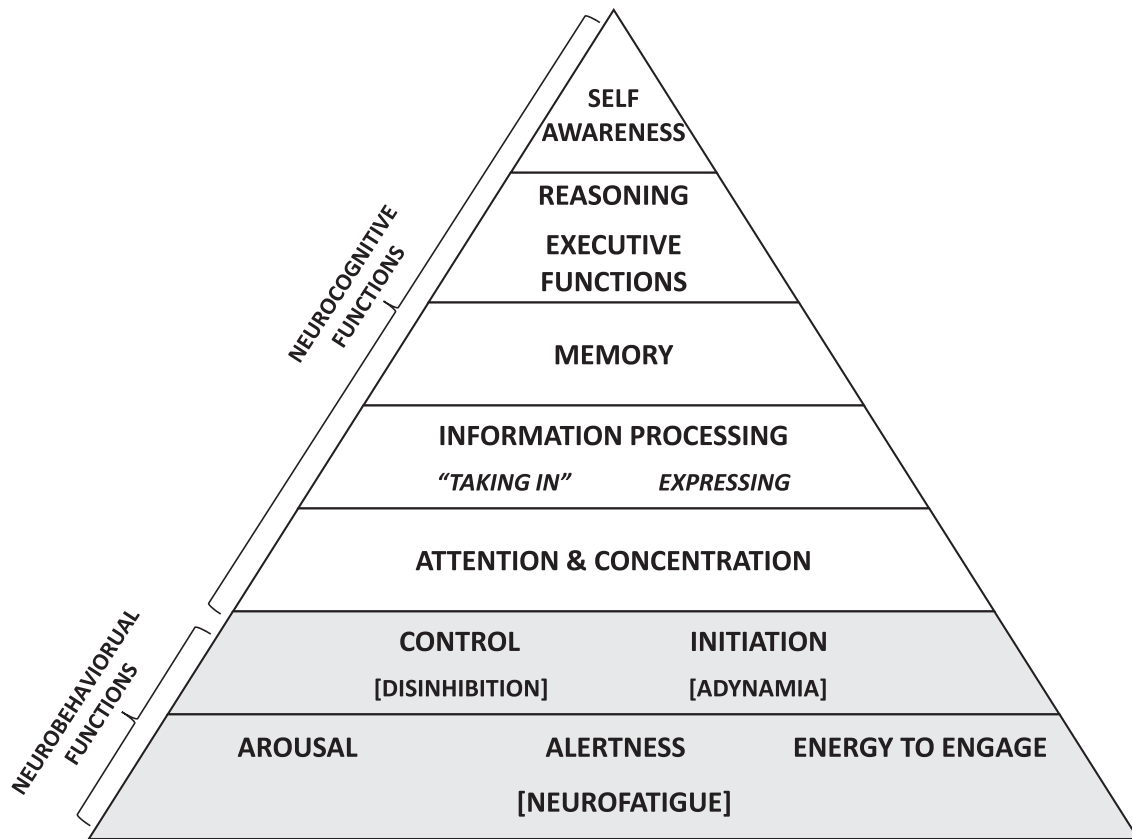


Fig. 2. Neuropsychological pyramid (adapted from the original pyramid by Yehuda Ben-Yishay, PhD at New York University School of Medicine [43]). Functions are interrelated such that lower-level problems are theorized to underlie and therefore contribute to and/or exacerbate higher-level problems.

3.3. ImPACT program

The ImPACT program is built upon the premise that cognition, emotion, and behavior are interlinked and should be addressed together [25]. The neuropsychological pyramid developed by Yehuda Ben-Yishay [43] (Fig. 2), is a key conceptual reference for the program. This pyramid provides a simplified illustration of how cognitive functions are hierarchically ordered with basic neurobehavioral functions on the bottom, and increasingly complex cognitive functions towards the top. This conceptualization of cognitive functions highlights the interrelationship between lower-level impairments and higher-level impairments, and also illustrates how lower-level functions may support higher level functions [25]. The model is consistent with Luria's early notion of cognitive processes as complex, hierarchically embedded functional systems [44], and also more recent conceptualizations of the brain as a complex network [45]. In accordance with this conceptualization, ImPACT is structured around the "lynchpin problem", i.e., the essential element that holds everything together, typically the most prominent, hierarchically lowest level function that is impaired. Upon program entry, each patient's lynchpin problem is identified through a neuropsychological evaluation from the T1 assessment. Program components are then tailored to promote participant's awareness about this problem, how it manifests in everyday life, and the building of compensatory strategies. In practice, ImPACT consists of 8×1 -h sessions with a clinical psychologist (patient and carer together) hosted weekly at either Aarhus University or online, if more feasible. A detailed description of the ImPACT program is provided in Table 2.

A compelling example of a lynchpin problem within the context of ImPACT is in the following illustration of neurofatigue, corresponding to the lowest level in the neuropsychological pyramid (Fig. 2). Neurofatigue has the potential to exert widespread impact on various aspects of daily life [46]. For instance, an individual may struggle with family

visits due to neurofatigue, preventing him/her from actively engaging in conversation. Furthermore, the neurofatigue may also impede the individual's ability to sustain attention and effectively encode and remember information in the context of such a visit. The result is that the neurofatigue may impair the individual's family relationships due to appearing disinterested and disconnected when with family. By addressing neurofatigue as a lynchpin problem, the person would then be supported in identifying specific instances in which the problem occurs, which in this case could include family visits, in order to facilitate the learning and application of tailored compensatory strategies specifically for such situations. Engaging the carer in the sessions would facilitate shared review of the content of the sessions at home, promote the implementation of the strategies, and optimize review of progress after the fact. Finally, progress could be discussed in sessions with the psychologist in order to facilitate the fine-tuning of strategies or creation of new ones for new situations.

3.4. Assessments and outcome measures

Fig. 1 illustrates all patient assessments, including i) study enrollment (baseline [T1]), ii) between session 4 and 5 (mid-point [T2]), iii) one week after the last session (post-intervention [T3]), and v) 8 weeks follow-up [T4]. The ImPACT Adult study will also include WLCs who will participate in assessments at corresponding time points upon starting the ImPACT program, i.e., i) between sessions 4 and 5 (mid-point [T5], corresponding to [T2]), ii) one week after the last session (post-intervention [T6], corresponding to [T3]), and iii) an 8 week follow-up [T7], (corresponding to [T4]).

Table 3 provides an overview of all outcomes and measures. Primary outcomes include patient and carer-reported cognitive and neurobehavioral functioning. Secondary outcomes include objective cognitive impairment measured with a brief neuropsychological test battery

Table 2
ImPACT program content.

Key components:			
1. Building malleability 2. Building awareness 3. The lynchpin problem 4. Compensation			
Key techniques used by the interventionist coach (i.e., psychologist) and taught to trainees (i.e., patients) and home coaches (i.e., carers) throughout sessions: Socratic questioning: Used to probe thinking with the aim of building awareness. Externalization: Supports a tone of collaboration, i.e., “<i>putting the issues on the table to explore, understand, and work on them together</i>”. Verification: Restating what was said in one's own words: Used extensively to ensure understanding and promote awareness, and to model a key compensatory strategy. Saturation cuing: Used as a principle for training tasks, i.e., starting with maximum cues, then gradually removing cues as mastery is achieved. Behavioral ratings: In order to build awareness, when trainees and home coaches rate trainees' behaviors, the trainee reports their rating first, before the home coach and/or the interventionist coach. Discrepancies are then discussed in a collaborative and supportive manner. Sandwich approach: Home coaches are encouraged to ask for trainee permission before delivering any coaching suggestions. Then the coaching suggestion is ideally sandwiched between encouraging and supportive comments regarding the trainee's progress.			
Session	Objective of the session	Session content	Homework
1. Building malleability	Support the trainee to become optimally responsive to the intervention in general and the guidance of the coaches (i.e., the psychologist and the carer, in particular). Malleability is fostered through the promotion of respectful, collaborative relationships between all parties.	Introduction to the ImPACT philosophy, i.e., discussions about: - How brain tumors and their treatment may be related to cognitive and neurobehavioral problems. - The ultimate program goal, i.e., to achieve “optimal function” through successful compensation. - The cognitive hierarchy, cognitive domains, and the concept of the “lynchpin problem”, i.e., the most prominent, lowest level ability that is impaired. - Awareness problems that often occur in brain tumor patients, i.e., organic problems in one's ability to fully and accurately observe one's own behavior and see how the brain tumor has changed it. - The importance of: - Coaches (i.e., psychologist and carers), e.g., to point out problems “in-the-moment” and support the trainee in using compensatory strategies. <i>At this point, the terminology of trainee and coach is introduced.</i> - Working with real-world manifestations of the lynchpin problem through homework to promote transfer of learning. - Becoming aware of own strengths and challenges, e.g., through self-monitoring of behavior and daily reviews with home coach, so that strategies can be tailored. - Noting key points to promote awareness, i.e., that both the trainee and home coach will be asked to take notes, both in session and as part of homework. Establishing “collaboration contracts”: - Both between participants (i.e., trainee and home coach), and between participants and the interventionist coach.	Pay attention to challenging activities/ behaviors in everyday life. <i>It will be emphasized that while the trainee and home coach are encouraged to discuss noted activities/ behaviors at least one time daily, they should take notes separately and may disagree.</i>
2. Building awareness & understanding	Formulating the lynchpin problem. While the formulation of the problem happens in session together with participants with reference to their completed homework, the psychologist brings a preliminary formulation of the lynchpin problem made through evaluation of the T1 assessment.	Lynchpin problem: - Recap from Session 1 and further psychoeducational introduction to/discussion about the cognitive hierarchy, cognitive domains, and the concept of the lynchpin problem. Establishing challenges: With reference to the completed homework and through an active psychoeducation process, participants will be supported to become aware of and understand: - The nature of the trainee's core strengths and challenges. - How challenges interfere with various aspects of everyday life (cf., homework). - That the goal of the program is to attain successful compensation for those challenges to promote “optimal function”, i.e., best possible level of functioning given the trainee's circumstances. The lynchpin problem:	Identify real-world manifestations of the lynchpin problem, i.e., how the lynchpin problem concretely affects aspects of everyday life.

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Table 2 (continued)

Session	Objective of the session	Session content	Homework
		At the end of the session and based on the discussion, the lynchpin problem will be formulated, and participants will be introduced to the concept of the lynchpin poster, i.e., a poster illustrating the lynchpin problem, a solution to the problem, and key compensatory strategies that support the solution. The lynchpin poster will be formulated in the following session (i.e., Session 3).	
3. The Lynchpin poster	Introduction to compensation work and formulation of the lynchpin poster. While the formulation of the lynchpin poster happens in session together with participants, the interventionist brings a preliminary formulation of the lynchpin poster.	Recap of the lynchpin problem and how it affects everyday life: - With reference to the completed homework and through an active psychoeducation process, participants will be supported to become aware of and understand how the lynchpin problem manifests in everyday life. Introduction to compensation work: - Based on the discussion about how the lynchpin problem manifests, there will be an introduction to the compensation phase of treatment (i.e., sessions 4–7), including a psychoeducational discussion about what it means to “compensate”. The lynchpin poster: - At the end of the session and based on the discussion, the lynchpin poster will be formulated.	Tailored to participants, e.g., further monitoring of real-world manifestations of the lynchpin problem, or identification/monitoring of current compensatory strategies.
4–7. Compensation	During Sessions 4 to 7, focus is on identifying target manifestations of the lynchpin problem, creating, and practicing compensatory strategies, and evaluating those strategies continuously. The lynchpin poster is used as a reference and present in each session (e.g., placed on the table).	COMPENSATION – GENERAL STRUCTURE Identification of target real world activities/behaviors: This is a collaborative effort between the trainee, home coach, and interventionist coach, respectively. The target activities/behaviors should be concrete real-world manifestations of the lynchpin problem that participants are dedicated to working on. Creating compensatory strategies: The target activity/behavior is broken down into small, discrete steps, and the trainee is taught <i>in-session</i> how to accomplish the activity/behavior following the steps. When possible, examples are created and practiced in session. Assigning homework: One or two target activities/behaviors are assigned as homework. Through dialogue, it is established to what extent the supporting elements listed below are implemented as part of homework. Identification of new target activities/behaviors: When participants have achieved mastery of the target activity/behavior, and it has become well integrated into their behavioral repertoire, the steps are repeated with new targets. SUPPORTING ELEMENTS Strategy reminders: Reminders about a given strategy are important to promote optimal learning. Reminders should ideally be given verbally from the home coach but may alternatively be entered to appear on a smart phone at key moments of the day or written on note cards. The latter formats may be introduced later in treatment as an add-on to coaching reminders. Daily reviews: At relevant times of the day, the trainee and home coach should check-in with each other to review target activities/behaviors and progress. Optimally, this would be two times a day as outlined below, but should be tailored as appropriate: Morning strategy review: Target activities/behaviors and associated strategies for the day are reviewed –	One or two target activities/behaviors are assigned as homework between sessions. <i>For trainees with low levels of awareness, homework will often continue to center on different forms of structured self-monitoring.</i>

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Table 2 (continued)

Session	Objective of the session	Session content	Homework
		ideally by the home coach asking the trainee using Socratic questioning what they will be working on today. This may be very brief (1–2 min), and may be through the phone/messaging, depending on what is most feasible. End of day review: In the afternoon or evening, the trainee and home coach should review the day's work using a behavioral rating sheet.	
8. Wrap-up	Focus of the final session is to evaluate participants' experiences with the program and support them to continue to use the ImPACT principles in the future.	Evaluation: - Through dialogue about participants' experiences with the program in general and the compensation work in particular, intervention steps that were particularly helpful versus less helpful are identified. Developing strategies for using ImPACT principles in the future, i.e.: - Exploring the extent to which participants are motivated to use ImPACT principles in the future. - Discussion about challenges/obstacles of continuing to use these principles. - Creation of gestalt strategies for continuing to use the principles.	Participants will be encouraged to continue to work with target activities in the future.

consisting of tests with high sensitivity for measuring cognitive domains that are commonly impaired in cancer patients, including processing speed, attention, verbal learning and memory, and executive functioning. Other secondary outcomes that may be affected in BCS include fatigue, anxiety and depression, quality of life, as well as process measures, i.e., participant satisfaction and enjoyment. Finally, both studies include a semi-structured interview at the last assessment where patients and their carers both have an opportunity to talk about their experience of the program in an open-ended manner with respect to the elements they found most helpful and least helpful.

For most outcomes, both patients and carers are respondents. Given a lack of available carer-report measures for adult BCS, carer-reports of patient cognitive functioning, fatigue and quality of life, respectively, are measured with adapted versions of the corresponding patient-report measure, i.e., the PAOFI [40], the Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F) [60], and the Functional Assessment of Cancer Therapy - Brain scale (FACT-Br) [61], with the original items modified to ask carers how they perceive the patient's assessment of his/her symptoms.

4. Discussion

A particular strength of the proposed “ImPACT” program is that while it has a clearly defined conceptual foundation, it is not a classically manualized treatment with strict content structure, but rather, a set of evidence-based key principles tailored to each participant dyad. Consequently, the program may be adapted for any given patient population presenting with cognitive and/or neurobehavioral impairments. In the planned studies, ImPACT is designed to treat both child and adult BCS, and thus, demands different forms of tailoring. In particular, the relationship dynamics between patients and carers tend to differ between these two populations, e.g., the asymmetrical relationship between children and parents versus the often more symmetrical relationship between romantic partners. However, given that a key

ImPACT principle is that patients and carers are collaborating as trainees and coaches (see Table 2), relationship dynamics are always actively addressed. Indeed, since BCS are likely to present with a lack of awareness of their own impairments, including the impact of those impairments on daily life functioning (including functioning at work/school and in interpersonal relationships), carer involvement is essential not only to support the patient in building awareness and understanding, but also to report on a patient's symptoms and symptom changes across treatment. Carers are also important for helping BCS build awareness and understanding regarding any discrepancies in their appraisal of situations, e.g., possible misperceptions in their interactions with others. Finally, carers are essential for helping BCS build awareness of impairments as they happen ‘in-the-moment’.

By having carers report on the patient's symptoms, we were challenged by the lack of available proxy measures, most having been developed for child and dementia populations. Consequently, for the ImPACT Adult study, we have modified the wording of three patient-report scales to make them suitable for proxy report, namely the PAOFI [40], FACIT-F [57], and FACT-Br [59]. This is similar to the process undertaken in a previous study with hepatocellular carcinoma patients, which ultimately found that family carers were adequate proxies for measuring patients' quality of life using the FACT-Hep measure [73]. However, given that the measures have not been validated for proxy use, results will be interpreted with caution. Additionally, carers of BCS may undergo a significant degree of carer burden, accompanied by associated psychosocial symptoms [74,75]. In the present studies, we do not include direct measures of caregiver symptoms beyond the semi-structured interview in the last assessment due to carer participation burden. However, this is an important area for future investigation due to the potential significance of the caregiver experience on patient and caregiver outcomes.

To be eligible for inclusion in the present studies, patients must have completed primary treatment for brain tumor at least 6 months ago. This time frame was selected based on consultation with clinicians with the

Table 3
Measures and assessment time points.

Study	Outcome variable	Scale	Subscale	Respondent	Number of items	Answer format	Total score range	Direction indicating impairment	Screening	T1	T2/ T5	T3/ T6	T4/ T7
<i>ImPACT Child</i>	<i>Primary outcomes</i>												
	Cognitive functioning	PedsPCF ¹	–	Child/parent	7	1–5	7–35	Lower	x	x	x	x	x
	Neurobehavioral functioning	BRIEF®2	–	Child/parent	55/63	1–3	55–165/ 63–189	Higher	x ²	x	x	x	x
	<i>Secondary outcomes</i>												
	Objective cognitive functioning	WISC-V subtests, D-KEFS subtests, TOMAL-2	–	Child	7 different tests	Various	–	Various		x		x	x
	Fatigue	PedsQL	MFS	Child/parent	18	0–4	0–100	Lower		x	x	x	x
	Anxiety and depression	CADS	SAD	Child/parent	47	0–3	0–141	Higher		x	x	x	x
	Quality of life	PedsQL	Core	Child/parent	23	0–4	0–100	Lower		x	x	x	x
			Cancer	Child/parent	27	0–4	0–100	Lower		x	x	x	x
	Parent sense of competence	PSC ¹	Satisfaction	Parent	9	1–6	9–54	Lower		x	x	x	x
			Efficacy	Parent	8	1–6	8–48	Lower		x	x	x	x
	<i>Process measures</i>												
	Participant satisfaction	CSQ-8	–	Child/parent	8	1–4	8–32	Lower			x	x	x
	Participant motivation	IMI	Interest/ enjoyment	Child/parent	7	1–7	1–7 (Average)	Lower			x	x	x
	Semi-structured interview	–	–	Child/parent	–	Open-ended	–	–					x
<i>ImPACT Adult</i>	<i>Primary outcomes</i>												
	Cognitive functioning	PAOFI	–	Patient/carer	33	1–6	0–33	Higher		x	x	x	x
	Neurobehavioral functioning	FrSBe	Apathy	Patient/carer	14	1–5	14–70	Higher		x	x	x	x
			Disinhibition	Patient/carer	15	1–5	15–75	Higher		x	x	x	x
			Executive dysfunction	Patient/carer	17	1–5	17–85	Higher		x	x	x	x
	<i>Secondary outcomes</i>												
	Objective cognitive functioning	WAIS-IV subtests, HVLT-R, TMT A/B, CCPT, COWAT	–	Patient	8 different tests	Various	–	Various		x		x	x
	Fatigue	FACIT-F	–	Patient/carer	13	0–4	0–52	Lower		x	x	x	x
	Mental fatigue	MFS	–	Patient/carer	15	0–3	0–42	Higher		x	x	x	x
	Depression	CESD	–	Patient	20	0–3	0–60	Higher		x	x	x	x
	Quality of life	FACT-Br	–	Patient/carer	50	0–4	0–200	Lower		x	x	x	x
	Community integration	CIQ-R ¹	–	Patient/carer	18	0–2	0–35	Lower		x	x	x	x
	Sleep	ISI	–	Patient	7	0–4	0–28	Higher		x	x	x	x
	<i>Process measures</i>												
	Participant satisfaction	CSQ-8	–	Patient/carer	8	1–4	8–32	Lower				x	x
	Participant motivation	IMI	Interest/ enjoyment	Patient/carer	7	1–7	1–7 (Average)	Lower				x	x
	Semi-structured interview	–	–	Patient/carer	–	Open-ended	–	–					x

Abbreviations: BRIEF®2 = Behavior Rating Inventory of Executive Function 2nd Edition [47,48,]; CADS = Revised Children's Anxiety and Depression Scale short form [49]; CESD = Center for Epidemiologic Studies Depression Scale [50]; CIQ-R = Community Integration Questionnaire Revised [51]; COWAT = Controlled Oral Word Association Test [52]; CSQ-8 = Client Satisfaction Questionnaire [53,54]; Conner's Continues Performance Test [55]; D-KEFS = Delis Kaplan Executive Function System [56]; FACIT-F = Chronic Illness Therapy–Fatigue scale [57,58]; FACT-Br = Functional Assessment of Cancer Therapy–Brain [59]; FACT-Cog = Functional Assessment of Cancer Therapy–Cognitive [60]; FrSBe = Frontal Systems Behavior Scale [41,61,]; HVLT-R = Hopkins' Verbal Learning Test Revised [62]; IMI = Intrinsic Motivation Inventory [63]; ISI = Insomnia Severity Index [64]; MFS = Mental Fatigue Scale [65]; PAOFI = Patient Assessment of Own Cognitive Functioning Inventory [40]; PedsPCF = The Pediatric Perceived Cognitive Function short forms [37,38,]; PedsQL = Pediatric Quality of Life – Multidimensional Fatigue Scale [66]; PSC = The Parenting Sense of Competence Scale [67]; TMT A/B = Trail Making Test A and B [68]; TOMAL-2 = Test of Memory and Learning 2nd Edition [69]; T1 = Time 1: Baseline assessment; T2 = Time 2: Mid-point assessment; T3 = Time 3: Post intervention assessment; T4 = Time 4: Follow-up assessment; WAIS-IV = Wechsler Intelligence Scale for Adult 4th Edition [70]; WISC-V = Wechsler Intelligence Scale for Children 5th Edition [71].

¹ Danish versions were created for the present study following a procedure of two independent forward translations, reconciliation, and then back translation.

² The 12-item screening version of the BRIEF-2 Parent form is used for screening.

goal of limiting the presence of treatment-related side effects, while also intervening as early after treatment as possible. Indeed, one may speculate that interventions should be initiated as early as possible to prevent impairments from developing and/or manifesting in patients' daily life behaviors. On the other hand, some impairments may either be temporary and resolve shortly after treatment or may take months to develop. Knowing when patients are most likely to benefit from intervention participation is important, not only to maximize the ratio of benefits to patient-burden, but also to make the most out of limited personnel resources [23]. This, however, remains to be established.

In conclusion, the ImPACT program may help to ameliorate cognitive and neurobehavioral symptoms in child and adult BCS, and results of the present studies will provide important feasibility, acceptability, and preliminary efficacy data needed to prepare for future larger scale evaluations of the program.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cct.2023.107419>.

Trial status

At the time of submission of the present manuscript, both studies (i. e., ImPACT Child and ImPACT Adult) were open for recruitment.

Safety considerations

Participants may experience mild distress when discussing the problems, they are facing in daily life because of the cancer and its treatment. However, any issues will be addressed promptly with appropriate empathy and care, and clinical referral if deemed necessary. There are no likely long-term risks, side-effects, or disadvantages.

Data management and statistical analysis

Data are handled confidentially and only accessible for the primary research team. Electronic data are collected and managed in REDCap [42], which complies with the European General Data Protection Regulation (GDPR).

Statistical analyses are planned according to the study aims:

Aim 1: To determine the feasibility of the ImPACT program, we will examine the: a) percentage of eligible persons who agree to participate; b) retention rates; c) completion rates; d) completed sessions; and e) participant satisfaction and motivation. Statistics will primarily be descriptive.

Aims 2 and 3: To evaluate the preliminary efficacy of the ImPACT program in adult BCS, repeated measures mixed linear models (MLMs) will be used to examine differences between the groups over time.

Quality assurance

All program sessions will be video recorded with the purpose of 1) retaining information for the participants, and 2) for research quality assurance, supervision, and program optimization.

Expected outcomes of the study

While there is an urgent need for effective rehabilitation programs for BCS, the current evidence-base is insufficient to support recommendations. As an important step towards this endeavor, results of the present studies will provide feasibility and acceptability data in preparation for future larger scale trials, which are necessary to inform evidence-based implementation decisions [72]. As such, the outcomes may have significant clinical implications that could transform the nature of services provided to both child and adult BCS.

Duration of the project

Data collection is expected to run from September 2022 to May 2025 (ImPACT Child) and May 2023 to May 2025 (ImPACT Adult).

Ethics

The study protocols have been approved by the regional ethics committee and pre-registered with clinicaltrials.gov (ImPACT Child study: #NCT05483166; ImPACT Adult study: #NCT05858359). The study adheres to the Danish Cancer Society Ethical and Danish Data Protection Agency guidelines. In the ImPACT Child study, all children receive oral information about the study in terms consistent with their age, and children aged 15–17 also receive written information.

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CRediT authorship contribution statement

C.R. Buskbjerg: Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **A. Amidi:** Methodology, Supervision, Writing – review & editing. **A. Munk:** Methodology, Writing – review & editing. **J.T. Danielsen:** Methodology, Writing – review & editing. **L.T. Henriksen:** Resources, Writing – review & editing. **S. Lukacova:** Resources, Writing – review & editing. **L. Haldbo-Classen:** Resources. **J. Evald:** Resources, Writing – review & editing. **L. Evald:** Resources, Writing – review & editing. **Y. Lassen-Ramshad:** Writing – review & editing. **R. Zachariae:** Resources, Writing – review & editing. **M. Høyer:** Resources, Writing – review & editing. **H. Hasle:** Resources, Writing – review & editing. **L.M. Wu:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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