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Exercise Capacity, Physical Activity, Fatigue, and Neurocognitive Function in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Background: Adult survivors of childhood acute lymphoblastic leukemia (ALL) are at risk of reduced exercise capacity, decreased physical activity levels, persistent fatigue, and neurocognitive deficits. The aim was to investigate exercise capacity and physical activity levels of adult survivors of childhood ALL and their associations with neurocognitive outcomes, including processing speed and functional frontal cortical brain connectivity.

Methods: This cross-sectional study included 47 adult survivors of childhood ALL; 29 (61.7%) were male, with a median age of 29 years (min–max 21–47). Participants completed questionnaires, a graded exercise test on a cycle ergometer, neurocognitive tests, and frontal cortical brain imaging with functional near-infrared spectroscopy. Associations between predicted peak exercise capacity and fatigue (Fatigue Severity Scale [FSS]), processing speed (Processing Speed Composite), and functional frontal cortical network connectivity (global efficiency and modularity) were analyzed using linear regression. Parallel analyses were performed with physical activity level as the independent variable.

Results: Participants achieved a mean peak exercise capacity corresponding to 83.8% (standard deviation [SD] = 13.1) of the age- and sex-predicted value ($p < 0.001$), and 42.2% did not meet WHO-recommended levels of physical activity. Statistically significant associations were identified between higher predicted peak exercise capacity and lower fatigue (FSS total score $\beta = -0.33$, 95% CI [confidence interval] −0.66 to −0.05, $p = 0.02$) and between higher physical activity levels and lower fatigue (FSS total score $\beta = -0.4$, 95% CI −1.8 to −0.2, $p = 0.015$). No other significant associations were found.

Abbreviations: ALL, acute lymphoblastic leukemia; BHW-Q, Swedish National Board of Health and Welfare questions for physical activity; BHW-Q MPA, Swedish National Board of Health and Welfare question for measuring moderate physical activity; BHW-Q VPA, Swedish National Board of Health and Welfare question for measuring vigorous physical activity; CI, confidence interval; fNIRS, functional near-infrared spectroscopy; FSS, Fatigue Severity Scale; LTFU, Long-Term Follow-Up Clinic; MPA, moderate physical activity; PSC, Processing Speed Composite; RPE, The Borg rating of perceived exertion; SD, standard deviation; SED-GIH-Q, Swedish School of Sport and Health Sciences question for assessing sedentary time; VPA, vigorous physical activity.

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Conclusion: Adult survivors of childhood ALL had reduced exercise capacity, and a substantial proportion did not meet recommended physical activity levels. Exercise capacity and physical activity levels were associated with fatigue. No significant associations were observed with functional frontal cortical network connectivity or cognitive measures.

1 | Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent childhood cancer, with a survival rate that has significantly improved in recent decades, reaching >90% today [1]. Although cranial irradiation is less common, many survivors are at an increased risk of late effects, including neurocognitive impairments and fatigue due to the use of high-dose intravenous and intrathecal methotrexate [2–4]. These complications have been shown to impede the ability of adult survivors of childhood ALL to work, pursue education, and participate in social activities [5, 6]. Adult survivors of childhood cancer are recommended to follow WHO's physical activity guidelines, including >150 min of moderate- or >75 min of vigorous-intensity activity per week, while limiting sedentary time [7]. However, these individuals often exhibit poor cardiorespiratory fitness levels and fail to reach physical activity recommendations, possibly due to late effects of treatment [8, 9].

In the general population, regular physical activity and higher cardiorespiratory fitness have been linked to improved cognitive performance, attributed in part to increased cerebral blood flow and oxygen delivery [10]. Physical activity interventions have frequently been shown to reduce cancer-related fatigue in adult cancer survivors [11]. However, among adult survivors of childhood ALL, the association between physical activity and fatigue is not as clear [12]. Additionally, there is limited evidence on the association between cardiorespiratory fitness and neurocognitive outcomes in this population [13, 14], and the existing literature is largely based on younger survivors or diagnostically mixed samples [15]. Theoretical models in adult cancer survivors suggest that cancer-related fatigue may reflect alterations in brain networks involved in motivation and effort processing, leading to increased perceived effort and reduced engagement in physical activity [16]. Such network-level disruptions may also affect cognitive domains that rely on efficient neural communication, particularly processing speed, a foundational cognitive function that supports higher order executive processes, for example, working memory, inhibition, and cognitive flexibility [17–19]. Processing speed is highly sensitive to disruptions in neural function and may serve as an early indicator of neurocognitive difficulties [20, 21].

Cancer-related fatigue has increasingly been conceptualized as a neurobiological phenomenon involving altered large-scale brain network organization rather than a subjective symptom experience [22]. Functional network measures, such as modularity (the degree to which brain networks are organized into distinct functional subnetworks) and global efficiency (a measure of how efficient information transfer across distributed brain regions), may, therefore, provide insight into how neural communication efficiency relates to fatigue and cognitive performance [17]. In particular, frontal network alterations have been associated with reduced processing efficiency and impaired cognitive control in cancer survivors and neurological populations [18, 19]. Such alterations in brain activation can be measured with functional near-infrared spectroscopy (fNIRS), a noninvasive, portable optical imaging technique [23]. Understanding how exercise capacity and physical activity relate to cognition and fatigue in long-term survivors of childhood ALL may help clinicians provide targeted, evidence-based guidance to support informed decision-making about self-care, physical activity, and long-term health management.

This study aimed to describe exercise capacity, physical activity levels, and sedentary time in adult survivors of childhood ALL and to examine associations between exercise capacity and physical activity levels and fatigue, as well as processing speed and functional frontal cortical network connectivity (i.e., changes in modularity and global efficiency). Overall, this was an exploratory study; however, we hypothesized that lower exercise capacity and physical activity levels would be associated with higher fatigue, poor processing speed, and altered functional frontal cortical network connectivity.

2 | Methods

This was a cross-sectional cohort study conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (https://www. strobe- state ment. org/).

2.1 | Participants

Adult survivors of childhood ALL were recruited from the Long-Term Follow-Up Clinic (LTFU) at the Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden. Inclusion criteria were age ≥18 years, diagnosis and treatment for ALL at <18 years of age, and previous attendance at the LTFU. Exclusion criteria were <5 years since end of ALL treatment, history of radiation therapy, recurrence or secondary malignancy at enrollment, mental disability, physical or sensory impairments interfering with performing the required study procedures, and insufficient knowledge of the Swedish language. In addition, survivors who had participated in a previous exploratory study involving the same assessments [24] or who resided outside the study region were not invited to participate. Eligibility was assessed through review of medical records from previous follow-up visits at the LTFU. None of the participants had symptoms of heart failure, and all had normal echocardiograms performed according to the Swedish National Guidelines. All participants received oral and written information and gave written informed consent before participation. The Swedish Ethical Review Authority approved the study protocol (Approval number 2022-04457-01), and the study conformed to the principles outlined in the Declaration of Helsinki [25].

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2.2 | Procedure

Data were collected between March 2023 and December 2024 as part of a larger study with an expanded set of variables (Supporting Information File 1). A physician screened eligible individuals and provided written study information during the clinic visit or by mail. A study coordinator followed up by phone within 1 week to provide verbal information and arrange assessment appointments for those who agreed to participate. On the assessment day, participants completed a questionnaire, underwent neuropsychological and cognitive testing with fNIRS, provided blood samples, and performed a graded exercise test on a cycle ergometer.

2.3 | Measurements

2.3.1 | Demographic Variables

Background data, including sex, age, age at diagnosis, treatment dose, and risk group, were collected from patient records. Sociodemographic data, including educational background and work status, and lifestyle factors, including body mass index (BMI) and nicotine use, alcohol consumption, and history of mental disorders, were collected using a questionnaire.

2.3.2 | Exercise Capacity

Participants completed a graded exercise test on a cycle ergometer until peak exertion was reached. Exercise testing was conducted at the Department of Clinical Physiology, Sahlgrenska University Hospital, except for one assessment performed at the Center for Health and Performance Development, University of Gothenburg, using the same standardized protocol. Perceived exertion was assessed using the Borg rating of perceived exertion (RPE) 6–20 scale. Breathlessness, leg fatigue, and chest discomfort were rated using Borg's Category Ratio 10 (CR10 scale) (0–(10)). Heart rate, blood pressure, and electrocardiography (ECG) were monitored. After cycling, participants were permitted to rest in a supine position, whereas recovery ECG and blood pressure measurements were obtained. Peak exercise capacity was defined as the highest achieved workload during the graded cycle ergometer test, measured in watts (W). Predicted peak exercise capacity was derived from Swedish age- and sex-specific reference values and represents the expected peak exercise capacity for an individual of the same age and sex, expressed in percent (%) [26]. All participants reported a perceived exertion of >15 on the Borg RPE 6–20 scale.

2.3.3 | Questionnaires

2.3.3.1 | Physical Activity and Sedentary Time. Physical activity was assessed using the Swedish National Board of Health and Welfare's physical activity questionnaire (BHW-Q), which includes one question measuring vigorous physical activity (BHW-Q VPA): "During a regular week, how much time do you spend exercising at a level that makes you short of breath, for example running, fitness class, or ball games?" (response options: 0 min (1), <30 (2), 31–60 (3), 61–90 (4), 91–120 (5), and >120 min (6)), and one question measuring moderate physical activity (BHW-Q MPA): "During a regular week, how much time are you physically active in ways that are not exercise, for example, walks, bicycling, or gardening? Add together all activities lasting at least 10 min." (response options: 0 min (1), <30 (2), 31–60 (3), 61–90 (4), 91–150 (5), 151–300 (6), and >300 min (7)). Total moderate physical activity was assessed using a modified question (BHW-Q MPAtot) reflecting physical activity of any duration, as the recommended 10-min bouts were removed in the 2020 updated guidelines [27]: "During a regular week, how much time are you physically active in ways that are not exercise, for example, walks, bicycling, or gardening?", with the same response options as the BHW-Q MPA. To determine adherence to physical activity recommendations, their BHW-Q VPA score was doubled and added to their BHW-Q MPAtot score. A total score of ≥11 indicated that the recommended 150 min per week of physical activity was met.

Sedentary time was reported using the Swedish School of Sport and Health Sciences (GIH) question for assessing sedentary time (SED-GIH-Q): "How much time do you spend sitting during a normal day, not counting sleep?" (response options: "basically all day" (1), 13–15 h (2), 10–12 h (3), 7–9 h (4), 4–6 h (5), 1–3 h (6), and "never" (7)).

The BHW-Q and GIH questionnaires have been validated in adult childhood cancer survivors [28–30].

2.3.3.2 | Fatigue. General fatigue was assessed using the Fatigue Severity Scale (FSS), a 9-item instrument that measures the impact of fatigue on daily functioning and has demonstrated reliability and validity in patients with multiple sclerosis and systemic lupus erythematosus [31, 32]. Items are rated on a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree) and summed to yield an FSS total score ranging from 9 to 63, with higher scores indicating higher fatigue severity. Clinically relevant fatigue was defined as an FSS total score ≥36 [33].

2.3.4 | Neurocognitive Function

From the broader neurocognitive test battery, measures of processing speed were selected for the present analyses, as processing speed has been shown to be commonly affected neurocognitive domain in survivors of childhood ALL [4, 34].

2.3.4.1 | Processing Speed. Attention, mental and psychomotor processing speed, and visual discrimination were assessed using the Symbol Search and Digit Symbol Coding subtests of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [35]. Participants were instructed to correctly identify and code as many symbols as possible within a 2-min time limit, and the measured performance on each subtest was converted to an age-normed score on a scale ranging between 1 and 20 (where 75% of the normal population scores between 8 and 12). The average of the Digit Symbol Coding and Symbol Search scaled scores was used as a Processing Speed Composite (PSC) [24].

2.3.4.2 | Functional Frontal Cortical Network Connectivity. fNIRS was performed to measure brain function during three resting-state blocks. Each block lasted 5 min. The first resting-state block was conducted at the beginning of an experimental session lasting 70–90 min, the second block in the middle, and the third block at the end of the session. During each resting state,

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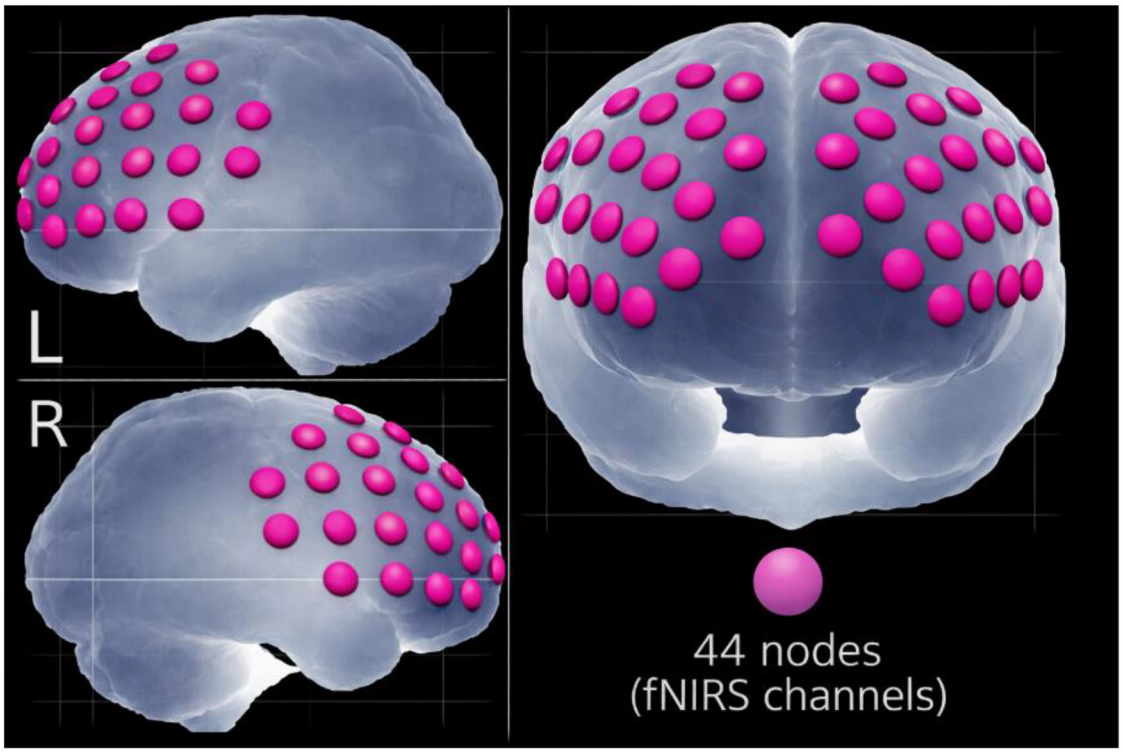

FIGURE 1 | fNIRS channel locations. fNIRS, functional near-infrared spectroscopy.

participants were instructed to close their eyes, relax, and avoid active thinking, returning their focus to relaxation if their minds wandered.

fNIRS data were collected with the NTS Optical Imaging System (Gowerlabs Ltd., UK), a continuous-wave device at 780 and 850 nm to measure oxygenated, deoxygenated, and total hemoglobin [36]. The system included 16 sources and 16 detectors. Forty-four channels had a 30-mm source–detector distance and served as network nodes. Six interhemispheric channels using a 45-mm distance were excluded due to poor signal quality. Pearson correlations between all node pairs yielded a 44 × 44 symmetric weighted connectivity matrix for each participant and session. Short-separation channels (10 mm) were used to isolate scalp hemodynamics, which were regressed out of the regular-separation channels [37, 38]. Optodes were positioned to cover frontal cortical areas linked to executive function and cognitive control (Figure 1).

fNIRS data were preprocessed using the Homer3 toolbox in MATLAB 2018 [39]. All analytical steps are documented in the pipeline (https://github.com/SimonSkau/NAFA_conn_pipeline). Functional connectivity and network metrics were computed following a protocol [40] using the Brain Connectivity Toolbox in MATLAB [41]. Modularity quantified the degree to which nodes formed densely interconnected communities, representing functional subnetworks. Global efficiency measured the ease of information transfer across the entire network, reflecting large-scale integration. Together, these metrics characterize the balance between specialized processing (modularity) and integrative communication (global efficiency) [41]. The change from the first and last values (delta) was used as the outcome.

2.4 | Statistical Analysis

Statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to report demographic data and physical activity levels, sedentary time, and fatigue assessed with the aforementioned questionnaires. Ordinal and interval data were described using median and range (min–max) or median (Q1, Q3). Continuous variables were presented using mean and standard deviation (SD) or median and range (min–max), depending on the data distribution. Nominal data were presented as numbers and percentages. Univariable linear regression analyses were conducted to assess the associations between predicted peak exercise capacity or physical activity levels and fatigue, processing speed, and changes in functional frontal cortical network connectivity. All β coefficients are presented as standardized estimates to allow comparison across variables measured using different scales and assessments. This study was exploratory and aimed to generate hypotheses and preliminary evidence to inform future research. It was not designed with sufficient statistical power for formal inferential analyses. The findings should be interpreted accordingly.

3 | Results

3.1 | Participants

A total of 107 adult survivors of childhood ALL were screened for eligibility; 10 individuals were excluded, as they had participated in a previous exploratory study [24]. Seven individuals were excluded due to physical, psychological, or cognitive impairments, and two were excluded as they resided outside the region.

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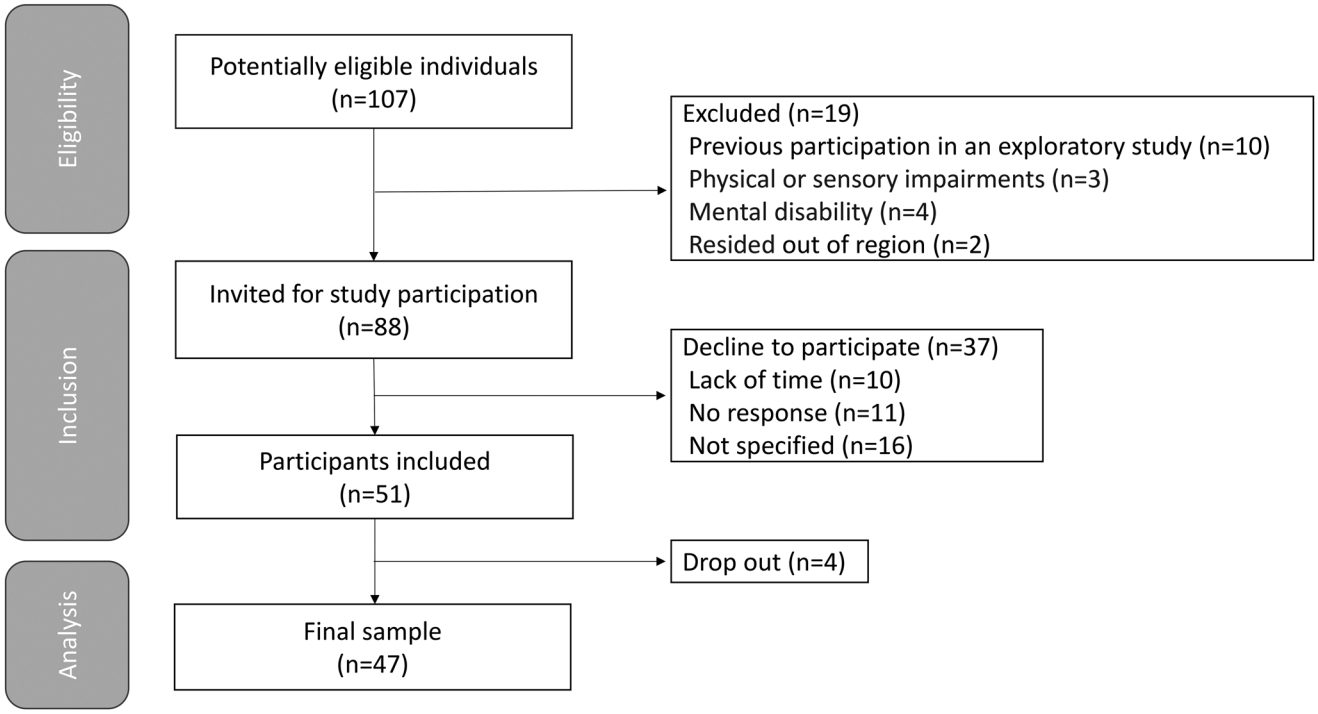

FIGURE 2 | Flowchart of the recruitment procedure.

In total, 88 individuals were invited, and 51 agreed to participate in the study. Reasons for declining were lack of time ($n = 11$), no response ($n = 10$), or not specified ($n = 16$). A flowchart of the recruitment procedure is shown in Figure 2.

Four participants dropped out after inclusion. Therefore, 47 participants (64% men), with a median age of 29 (min–max 21–45) years, were included in the analysis. Median age at diagnosis was 4 (min–max 1–6) years. All participants received chemotherapy. Most participants were treated according to the NOPHO ALL-92 protocol (61.7%), followed by the NOPHO ALL-2000 (25.5%) and NOPHO ALL-2008 (8.5%) protocols. Two participants (4.2%) were treated according to Swedish protocols used in the 1980s. Additional characteristics, such as education level, cancer treatment doses, risk group, and lifestyle factors, are reported in Table 1. Available data indicated that nonparticipants were similar in age, with a median age of 26 years (min–max 18–47), although the proportion of females was lower among nonparticipants (49% vs. 64%).

3.2 | Physical Activity, Sedentary Time, and Exercise Capacity

Of the 47 participants, 19 (42.2%) did not meet WHO-recommended levels of physical activity, and 27 (71%) reported sitting for ≥7 h per day (Table 2 and Supporting Information File 2). Participants achieved a mean peak exercise capacity corresponding to 83.8% (SD 13.1) of the age- and sex-predicted peak exercise capacity based on Swedish reference values, which was 16.2% lower than expected ($p < 0.001$) [26]. There was a significant positive association between physical activity levels and predicted peak exercise capacity ($\beta = 0.57$, 95% confidence interval [CI] [0.84, 2.22], $p < 0.001$). One participant was, after the study, diagnosed with chronotropic insufficiency during the exercise test but achieved a Borg RPE 6–20 scale rating of >15 and was included in the analysis. Participants who met the physical activity recommendations showed higher peak exercise capacity (W) than those who did not (90.4% vs. 74.9%; $p < 0.001$; mean difference −15.54 [95% CI −21.85 to −9.24]).

3.3 | Fatigue

Participants had a median FSS sum score of 25 (Q1, Q3 [16, 42]). Fifteen (32%) had an FSS mean score of >36, consistent with clinically significant physical fatigue.

3.4 | Neurocognitive Function

The mean PSC for participants was 10.3 (SD 2.3). When functional frontal cortical network connectivity during a resting-state recording before and after cognitive testing, the difference in mean modularity was 0.04 (SD 0.07), and global efficiency was −0.09 (SD 0.09) (Table 2).

3.5 | Associations of Exercise Capacity and Physical Activity With Fatigue, Processing Speed, and Functional Frontal Cortical Network Connectivity

Higher predicted peak exercise capacity was associated with significantly lower fatigue ($\beta = -0.3$, 95% CI −0.7 to −0.1, $p = 0.022$). No statistically significant association was observed between peak exercise capacity and processing speed ($\beta = 0.19$, 95% CI −0.02 to 0.09, $p = 0.212$). No significant associations were found between

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TABLE 1 | Demographic and clinical characteristics of the study population ($n = 47$).

Adult survivors of childhood ALL, $n = 47$[a]	
Sex, men, *n* (%)	30 (64)
Age at diagnosis, years, median (min–max)	4 (1–6)
Years since treatment, years, median (min–max)	22 (8–35)
Age at study inclusion, years, median (min–max)	29 (21–45)
Highest level of education, *n* (%)	
Compulsory or lower level	2 (4.3)
Upper secondary school	20 (42.6)
Postsecondary school or higher education	25 (53.2)
Treatment, median (min–max)	
Mtx dose iv (mg/m^2)	40,000 (3000, 45,144)
Mtx dose it (mg)	160 (96, 288)
Doxorubicin (mg/m^2)	120 (80, 210)
Vincristine (mg/m^2)	28 (12, 52)
Risk group at diagnosis, *n* (%)	
Standard risk	18 (38.3)
Intermediate risk	23 (48.9)
High risk	6 (12.8)
Lifestyle factors	
Body mass index (kg/m^2), mean (SD)	25.2 (5.1)
Nicotine use, *n* (%)	11 (23.4)
Alcohol consumption (glasses per week), median (min–max)	1 (0–22)
Previous depression/anxiety/exhaustion disorder, *n* (%)	26 (55.3)

Abbreviations: ALL, acute lymphoblastic leukemia; SD, standard deviation.
[a]Data are presented as median (min–max), mean (SD), or as number (*n*) and percent (%). Cumulative dose expressed as milligram per meter square (mg/m^2) for intravenous (iv) chemotherapeutic agents and milligram (mg) for intrathecal (it) methotrexate (Mtx).

this measure and modularity, or global efficiency (Table 3). A higher physical activity level was associated with significantly lower fatigue ($\beta = -0.4$, 95% CI −1.8 to −0.2, $p = 0.015$). No significant associations were found between physical activity levels and processing speed or changes in modularity or global efficiency (Table 3). Including methotrexate as an additional covariate did not change the observed associations between predicted peak exercise capacity and fatigue, processing speed, and modularity, or global efficiency (Supporting Information File 3).

TABLE 2 | Descriptive statistics for the graded exercise test on a cycle ergometer, self-reported physical activity, sedentary behavior, fatigue, processing speed, and functional frontal cortical brain connectivity ($n = 47$).

Variable[a]	
Exercise test outcomes ($n = 47$), mean (SD)	
Peak exercise capacity (W)	212.7 (59.3)
Predicted peak exercise capacity (%)	83.8 (13.1)
Peak heart rate (HR_{peak})	181 (12.6)
HR_{peak} (%)	95 (6.7)
Self-reported physical activity and sedentary time	
BHW-Q VPA ($n = 45$), median (Q1, Q3)	3 (1, 6)
BHW-Q MPA ($n = 46$), median (Q1, Q3)	5 (3, 6)
BHW-Q MPAtot ($n = 46$), median (Q1, Q3)	5 (3, 6)
Physical activity score ($n = 45$), median (Q1, Q3)	12 (7, 16)
SED-GIH-Q ($n = 41$), median (Q1, Q3)	4 (1, 6)
Not meeting physical activity guidelines ($n = 45$), *n* (%)	19 (41%)
Sedentary ≥7 h a day ($n = 41$), *n* (%)	29 (71%)
Self-reported fatigue ($n = 47$)	
FSS total score, median (Q1, Q3)	25 (16, 42)
Fatigue (FSS >36), *n* (%)	15 (32)
Cognitive measurement	
Processing Speed Composite ($n = 47$), mean (SD)	10.3 (2.3)
Brain connectivity	
Δ Modularity ($n = 46$), mean (SD)	0.04 (0.07)
Δ Global efficiency ($n = 46$), mean (SD)	−0.09 (0.09)

Note: Peak exercise capacity: Highest achieved mechanical power output (W). *Predicted peak exercise capacity*: Peak exercise capacity expressed as a percentage of age- and sex-specific Swedish reference values. HR_{peak}: maximal recorded heart rate (beats per minute). HR_{peak}: proportion of individual maximal heart rate. *BHW-Q VPA*: the Swedish National Board of Health and Welfare question about exercise. *BHW-Q MPA*: the Swedish National Board of Health and Welfare question about everyday physical activity (10-min bouts). *BHW-Q MPAtot*: the Swedish National Board of Health and Welfare question about everyday physical activity (all activity). *SED-GIH-Q*: the Swedish School of Sport and Health Sciences question for assessing sedentary time. *Physical activity minutes*: (BHW-Q VPA × 2) + BHW-Q MPAtot. *FSS total score*: Fatigue measured with the Fatigue Severity Scale (FSS), based on all 9 items (range 9–63). *Processing speed*: Processing speed measured using the Processing Speed Composite. Δ *Modularity*: a network metric describing the degree of segregation between functional brain network modules; the difference between the first and last values (delta) was used as an outcome measure. Δ *Global efficiency*: a network metric indicating how effectively information is transferred across the brain network; the difference between the first and last values (delta) was used as an outcome measure.
Abbreviations: SD, standard deviation.
[a]Data are presented as mean (SD), median (Q1, Q3), or *n* (%).

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TABLE 3 | Linear regression analysis of peak exercise capacity and physical activity levels and their association with fatigue (FSS total score), processing speed (PSC), and functional frontal cortical network connectivity (global efficiency and modularity).

	FSS total score ($n = 46$)		**PSC ($n = 47$)**		**Δ Global efficiency ($n = 46$)**		**Δ Modularity ($n = 46$)**	
Independent variable	β (95% CI) n	p	β (95% CI) n	p	β (95% CI) n	p	β (95% CI) n	p
Peak exercise capacity	−0.33 (−0.66 to −0.05) $n = 46$	0.022	0.19 (−0.02 to 0.09) $n = 47$	0.212	-0.10 (-3×10^{-3} to 1×10^{-3}) $n = 46$	0.500	3×10^{-3} (-2×10^{-3} to 2×10^{-3}) $n = 46$	0.986
Physical activity level	−0.36 (−1.82 to −0.20) $n = 45$	0.015	0.01 (−0.14 to 0.14) $n = 45$	0.964	−0.09 (−0.01 to 0.00) $n = 45$	0.566	0.02 (−0.00 to 0.01) $n = 45$	0.900

Note: Physical activity level: (BHW-Q VPA × 2) + BHW-Q MPAtot. *Predicted peak exercise capacity:* Peak exercise capacity expressed as a percentage of age- and sex-specific Swedish reference values. *FSS total score:* Fatigue measured with the Fatigue Severity Scale (FSS), based on all 9 items (range 9–63). *PSC:* Processing speed measured with the Processing Speed Composite (PSC), a cognitive measure reflecting processing speed and mental efficiency. Δ *Modularity:* a network metric describing the degree of segregation between functional brain network modules; the difference between the first and last values (delta) was used as an outcome measure. Δ *Global efficiency:* A network metric indicating how effectively information is transferred across the brain network; the difference between the first and last values (delta) was used as an outcome measure.
Abbreviation: CI, confidence interval.

4 | Discussion

This study examined 47 adult survivors of childhood ALL and found that lower peak exercise capacity and lower physical activity levels were associated with higher fatigue. No significant associations were observed between the selected measures of processing speed or functional frontal cortical network connectivity. Participants also showed reduced exercise capacity compared to the Swedish reference population, and many did not meet current physical activity recommendations. These findings provide relevant context for the observed associations and support the growing evidence that physical fitness and physical activity are related to fatigue in adult survivors of childhood cancer. However, given the cross-sectional design, the directionality of these associations cannot be determined.

The finding that many adult survivors of childhood ALL have reduced exercise capacity and lower physical activity levels is consistent with previous reports describing similar patterns in childhood cancer survivors [9, 14]. Reduced exercise capacity in adult survivors of childhood ALL is likely multifactorial. Potential contributors include treatment-related cardiopulmonary toxicity, metabolic, endocrine, and musculoskeletal late effects. Noticeable exercise intolerance has been reported in ALL cohorts [9, 14]. Psychological and environmental barriers documented across adult childhood cancer survivors may also contribute to lower physical fitness levels, including fear of symptoms during exertion, low self-efficacy, lack of specific advice from healthcare professionals, and limited social support from peers or family [42].

Higher exercise capacity and physical activity levels were associated with lower fatigue in this cohort, consistent with evidence from adult oncology, where structured exercise interventions are well-established as an effective way to reduce cancer-related fatigue [43]. Existing data in adult survivors of childhood ALL are, however, mixed. Small studies and reviews suggest that higher physical activity levels are associated with reduced fatigue, whereas others report no clear association [12]. These discrepancies may be explained by differences in study design, sample size, treatment exposures, outcome assessments, and population characteristics (e.g., survivor age). This study contributes to the evidence base by examining a homogeneous group and combining self-reported fatigue with an objective assessment of peak exercise capacity. The findings support the hypothesis that decreased physical fitness and lower activity levels are relevant to fatigue in this population. As fatigue may reduce motivation and capacity for physical activity, creating a cycle of inactivity, deconditioning, and worsening fatigue [44], the need for more robust evidence is emphasized to clarify these relationships.

Previous studies have reported associations between higher cardiorespiratory fitness, higher levels of physical activity, and better neurocognitive performance in adult survivors of childhood ALL [13, 14]. However, we did not observe similar significant associations with processing speed or functional frontal cortical network connectivity. This may reflect differences in study design, sample size, cognitive outcomes, assessments (e.g., physical activity measures and neuroimaging methods), or statistical power. Processing speed is a sensitive but relatively nonspecific cognitive measure, and metrics, such as modularity and global efficiency, reflect overall brain network organization; together, these approaches may have limited sensitivity to detect subtle or region-specific alterations, which could partly explain the lack of observed associations [35, 41]. In addition, processing speed was largely within the normal range and did not support our initial hypothesis. Although not statistically significant, the association between predicted peak exercise capacity and processing speed was in the hypothesized direction and should be explored further.

A key study strength is its use of objective measures of exercise capacity, validated questionnaires, and neurocognitive assessments, including functional brain imaging with fNIRS. These measures ensured multidimensional evaluation of fatigue, physical functioning, cognition, and functional frontal cortical network connectivity in a well-characterized cohort of adult survivors of childhood ALL. The inclusion of a relatively homogeneous diagnostic group can be considered a strength as it reduces some of the heterogeneity that complicates interpretation in broader childhood cancer survivor studies.

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Several limitations should be considered. First, the cross-sectional design prevents conclusions about causality or directionality. Second, the relatively small sample size limits statistical power and restricts the ability to adjust for potential confounders; however, we employed the predicted peak exercise capacity, as it is inherently adjusted for age and sex. Third, the absence of a control group limits comparisons with the general population, although the data were compared with applicable population-based reference values. Fourth, physical activity was assessed through self-reporting, which may introduce recall bias or social desirability bias. Fifth, the neuroimaging and cognitive outcomes included in this study may not capture all relevant brain or cognitive processes related to fatigue. Finally, the present analyses were restricted to measures of processing speed, and associations with other neurocognitive domains were not examined.

Larger longitudinal and interventional studies are needed to clarify potential links between physical activity, exercise capacity, fatigue, cognition, and brain function in adult survivors of childhood ALL. Further studies could help determine whether interventions aimed at increasing daily physical activity or improving exercise capacity can lead to clinically meaningful reductions in fatigue, and whether these changes are accompanied by improvements in cognitive function or brain network organization.

From a clinical perspective, the findings suggest that physical activity and exercise capacity are relevant aspects of long-term follow-up care for adult survivors of childhood ALL. Although formal exercise testing is not always available in routine survivorship care, simple questions about physical activity can serve as an easy-to-implement alternative to identify individuals who are physically inactive and potentially at risk of fatigue or reduced physical functioning. Clinicians should consider providing individualized advice and, when appropriate, referring patients to physiotherapy, rehabilitation, or exercise services. Encouraging gradual increases in everyday physical activity may be a feasible strategy to support long-term health and potentially reduce fatigue in this population.

In summary, this cohort of adult survivors of childhood ALL exhibited reduced exercise capacity, and a substantial proportion did not meet recommended physical activity levels. Lower exercise capacity and lower physical activity levels were associated with higher fatigue, suggesting that physical fitness and physical activity are clinically relevant in this population. No significant associations were observed between exercise capacity, physical activity levels, and processing speed or functional frontal cortical network connectivity. Longitudinal and interventional studies are needed to determine whether increasing physical activity or improving exercise capacity may reduce fatigue. Further research is necessary to clarify whether other cognitive domains or measures of frontal brain function are related to fatigue in adult survivors of childhood ALL.

Author Contributions

All authors contributed to the conception and design of the paper. Marianne Jarfelt identified eligible participants, Laura Jess coordinated participant recruitment, and Simon Skau and Gustaf Glavå carried out the data collection. Laura Jess performed the statistical analyses and the first interpretation of the data. Marianne Jarfelt, Maria Bäck, Hans-Georg Kuhn, Simon Skau, and Gustaf Glavå contributed to the interpretation of the results. Laura Jess wrote the first draft of the manuscript, and all authors commented on versions of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary File 1: Overview of the study day. **Supplementary File 1**: Appendix 2 - Distribution of physical activity and sedentary time categories and estimated time equivalents (minutes and hours). **Supplementary File 3**: Adjusted models with peak exercise capacity as independent variable including intravenous and intrathecal methotrexate as covariate.

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