

# "Chemo Brain"

Understanding it in Light of Current Research

Jennifer Brunet (PhD) & Sitara Sharma (PhD Candidate)

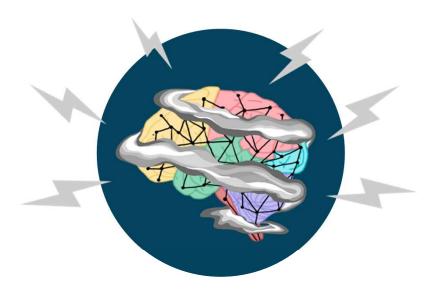
School of Human Kinetics, University of Ottawa April 1, 2025





## Introduction

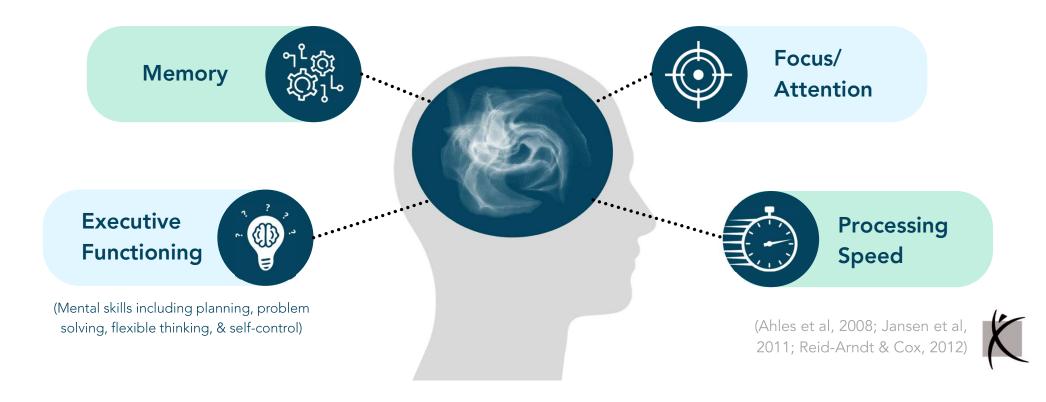
Cognitive problems are among the most frequently reported symptoms/side effects during and after treatment for cancer — especially (but not always!) chemotherapy





# What Do We Mean By Cognitive Problems?

Changes or "fogginess" in domains of:



## Prevalence



Up to 30% of patients experience cognitive problems prior to cancer treatment

Up to 75% experience cognitive problems during treatment

Up to 35% experience cognitive problems months or years following completion of treatment





# Variable Experiences

## Cognitive issues can vary in terms of:

- Cognitive domains affected
- Onset: Earlier → Delayed
- **Severity:** Subtle → Dramatic
- **Duration:** Temporary  $\rightarrow$  Permanent
- **Stability:** Stable → Progressive



# **Association With Chemotherapy**



- Systematic research to understand this phenomena was first reported in the mid 1990s-early 2000s
- Initially established to be associated with anticancer chemotherapy treatments — "chemo brain"
- To date, 35+ longitudinal studies have been done
  - Largely in breast cancer patients
  - 12-82% demonstrated problems in key cognitive domains



(Collin et al, 2009; Jansen et al, 2011; Wefel et al, 2010)

## Other Treatments Can Also Contribute



Radiation Therapy

Associated with **deficits in** similar cognitive domains as chemotherapy



Hormonal Therapies

Linked to **subtle cognitive deficits**, particularly in verbal memory & executive function



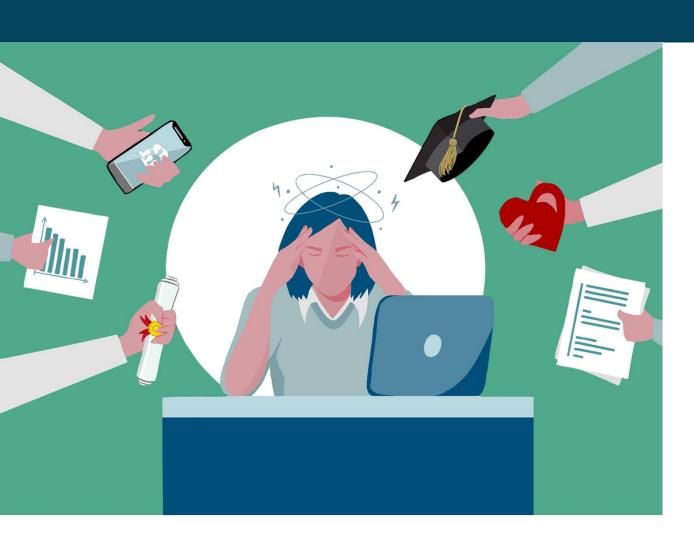
Immunotherapy & Targeted Therapies

Emerging evidence suggests they may contribute to cognitive problems

"Cancer-related cognitive impairment" (CRCI) may be a more appropriate term



# **Consequences of Cognitive Problems**



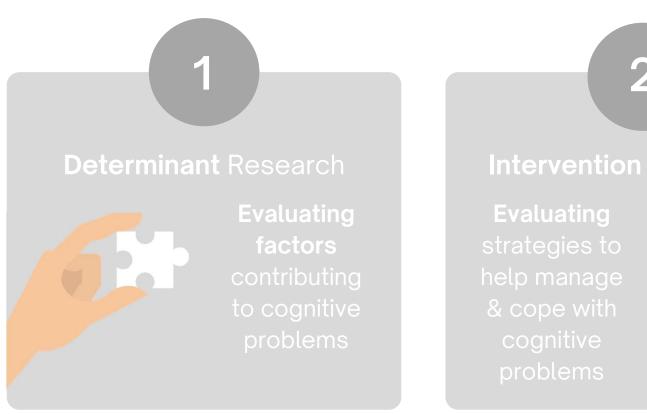
## Cognitive problems ↓:

- Quality of life
- Ability to function at/in:
  - Home
  - Work/school
  - Life (e.g., relationships)
  - Self-evaluations
- Functional independence
- Treatment compliance
- Clinical follow-up

(Bradley et al, 2005; Myers, 2012; Reid-Arndt et al, 2009; Wefel et al, 2004)



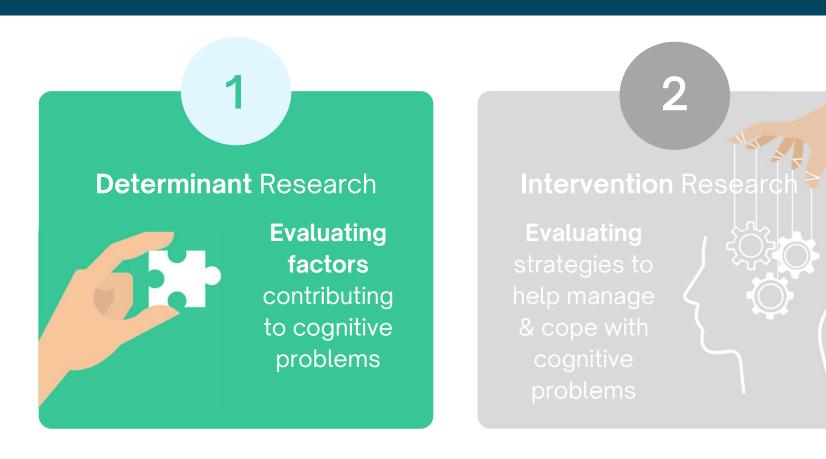
## **Current Research Areas**







## **Current Research Areas**





## Socioemographic & Medical



- Several sociodemographic & medical factors may contribute to cognitive problems, but none are firmly established
  - Age is the most cited, yet both young & older patients experience cognitive problems
  - Other factors: Race, ethnicity, socio-economic status, stage of disease, menopausal status, diet, body mass index
- Unclear how other symptoms (e.g., fatigue, anxiety, depression, sleep dysfunction, nausea) may influence effects on cognitive function

(Conroy et al, 2013; Loef & Walach, 2012, 2013; Sherwin, 2012; Morrow et al, 2005; Mustian et al, 2012; Palesh et al, 2012; Ryan et al, 2007; Vearncombe et al, 2009)



# **Biological & Molecular**

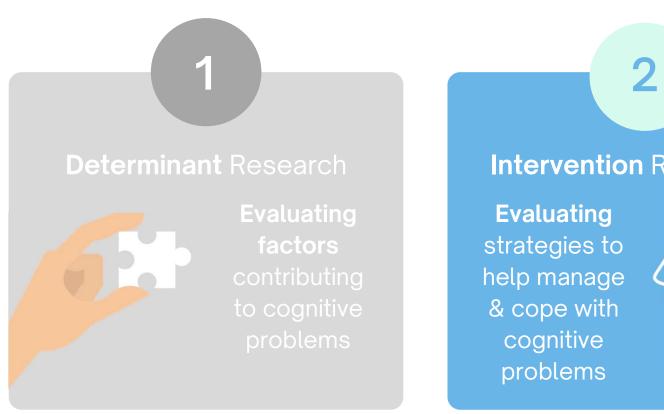


- Inflammation in the brain
- Oxidative stress
- DNA damage to brain cells
- Low energy in brain cells (mitochondrial dysfunction)
- Changes in gene activity
- Problems with brain connections (white matter)
- "Leaky" blood-brain barrier

Understanding these processes can help researchers find ways to prevent or treat cognitive problems in the future

(Janelsins et al, 2014; Fleming et al, 2023

## **Current Research Areas**







# Ongoing Research: How Can Cognitive Problems Be Managed?



Cognitive Behavioural Therapy



Cognitive Training & Rehabilitation



Physical Activity



# Cognitive Behavioural Therapy (CBT) to Manage & Cope



#### **Definition & Research**

- Structured, goal-oriented approach that **can help support cognitive function** by changing unhelpful thoughts/behaviours, building coping skills, & improving confidence
  - $\circ$  "I always forget things"  $\rightarrow$  "I sometimes forget, but I can use strategies to help me remember"
- Improved perceived cognition & quality of life in cancer survivors

### Some Ways to Access CBT:

Cancer survivorship programs & organizations

Healthcare Services

E.g., MindShift CBT, CBT Thought Diary, MindDoc

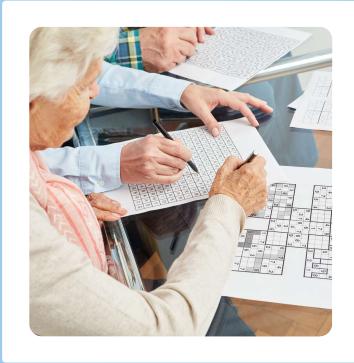
Apps/Websites

E.g., This Way Up, MoodGYM, BounceBack

Online Programs



# Cognitive Training & Rehabilitation to Manage & Cope



#### **Definition & Research**

- Structured activities to improve/restore different mental abilities
- Improved perceived & objective cognition in cancer survivors across the lifespan & of different tumour types/stages
- Some variability in effectiveness across cognitive domains (e.g., processing speed) & perceived cognition

### **Everyday Brain Boosters to Try:**















**NYT Games** 

Sudoku Duolingo



## Physical Activity to Manage & Cope — Our Research!



#### **Definition & Research**

- Any bodily movement produced by skeletal muscles that results in energy expenditure
- Considerable variability in findings & effect sizes are small-to-medium, but it is a promising approach to managing cognitive problems

Journal of Cancer Survivorship https://doi.org/10.1007/s11764-023-01441-x

REVIEW



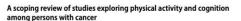
A scoping review of studies exploring physical activity and cognition among persons with cancer

Jennifer Brunet 1,2,3 · Sitara Sharma1





## Lab Research: Scoping Review



Jennifer Brunet 1.2.3 - Sitara Sharma

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Purpose This scoping review aimed to identify and synthesize published studies on physical activity (PA) and cognition manage persons with cancer and elucidate knowledge gaps.

Methods Articles were identified through electronic and manual searches (02/21 and 03/22) using the following inclus

criteria: (1) empirical, peer-reviewed publication in English, (2) sample comprised persons with cancer, and (3) reported at least one statistical association between Ph and cognition. Multiple reviewers independently performed study selection and data extraction, and results were mapped in tabular and narrative form.

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Implications for cancer survivors. Concervelated cognitive impairment (CRCI) thwarts quality of life. This review summittee of the configuration o

marizes what is known about the association between PA and cognition among persons with cancer and concludes that the evidence is currently equivocal. Hence, it remains uncertain if PA interventions can reduce CRCI, and large-scale PA intervention trials explicitly designed to promote cognition are greatly needed.

Keywords Oncology · Cognitive function · Exercise · Review

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- <sup>2</sup> Institut du savoir Montfort, l'Hôpital Montfort, Ottawa, ON, Canada
- Cancer Therapeutic Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Introduction appetite loss, insomnia, distress, dyspeea, constipation, numberes/fingling) that impair their quality of life (Odd.) and increase healthcare demands [2, 3]. Critically, many to 2000 [1], the Word and Sustained 193 (inflow) for survival Is improving, persons with cancer docking a many inflower and a concerved the co tion, language, learning, memory, motor coordination, and information processing speed; if not identified and treated in a timely manner, this can cause considerable burden years into survivorship [6-8]. While estimates of the prevalence and incidence of CRCI are influenced by methodological differences (e.g., assessment methods, diagnostic criteria) and/or other factors (e.g., eligibility criteria), data suggest CRCI affects between 21 and 90% of persons with cancer [9]. Consequently, CRCI is now recognized as an ongoing, pervasive, and disabling symptom, and thus, optimizing

2 Springer

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#### What Did We Do?

• Synthesized results from **97 articles** reporting ≥1 statistical association between physical activity & cognition in persons with cancer

#### What Did We Find?



32% — Positive Associations or Effects

Physical activity promoted cognition (or vice versa)



### 2.1% — Negative Associations or Effects

Physical activity was associated with declines in cognition (or vice versa)



#### 66% — Inconclusive Associations or Effects

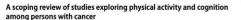
No significant associations between physical activity and cognition



(Brunet & Sharma, 2023



# Lab Research: Scoping Review



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#### What Do These Results Mean?

Results are currently equivocal, but physical activity may play a role in preserving or improving cognition in adults diagnosed with cancer

• Several methodological factors (i.e., gaps found in the research) may help explain null/negative findings

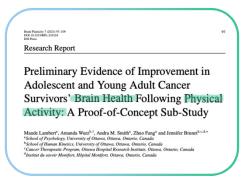
### Cognition may also predict physical activity participation

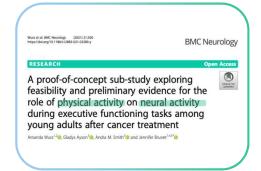
Suggests this relationship may be bidirectional

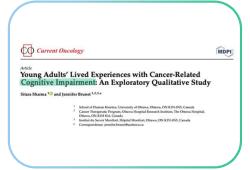


## Hot Off the Press: More Relevant Research from the Lab



















## Lab Research: Proof-of-Concept



Brain Plasticity 7 (2021) 97-10 DOI 10.3233/BPL-210124 IOS Per--

Research Report

Preliminary Evidence of Improvement in Adolescent and Young Adult Cancer Survivors' Brain Health Following Physical Activity: A Proof-of-Concept Sub-Study

Maude Lambert<sup>a</sup>, Amanda Wurz<sup>b,†</sup>, Andra M. Smith<sup>a</sup>, Zhuo Fang<sup>a</sup> and Jennifer Brunet<sup>b,c,d,\*</sup>
<sup>a</sup>School of Psychology, University of Ottawa, Ottawa, Ontario, Canada

- b School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada Cancer Therapeutic Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
- d Institut du savoir Montfort, Hôpital Montfort, Ottawa, Ontario, Canada

Background: Cognitive impairment is common among adolescent and young adult (AYA) cancer survivors. Physical activity (PA) may help mitigate cognitive impairment post-treatment by positively impacting two indicators of general brin health: fractional anisotropy (PA) and functional connectivity (PC). As part of a two-arm, mixed-methods pilot randomized controlled

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PC among AYA cancer survivors post-treatment to help inform decisions about proceeding to larger trials.

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Retains a provided and post-intervention. Data were analyzed with descriptive statistics, independent component analysis, and paired sample

Results: Post-intervention, participants showed increases in FA of the bilateral hippocampal cingulum, left anterior corona radiata, middle cingulum, left anterior thalamic radiation, and left cerebellum. A decrease in overall FC of the default mode network and increases in the cerebellar and visual networks were also noted post-intervention (p < .05).

Conclusion: Results provide preliminary evidence for the possible positive effects of PA on FA and FC among AYA cancer

survivors post-treatment. On the basis of these results, larger trials assessing the effects of PA on specific brain health indicators, as captured by FA and FC, among AYA cancer survivors are appropriate and warranted.

Keywords: Exercise, neuroimaging, cancer survivors, fractional anisotropy, functional connectivity

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Wurz et al. BMC Neurology (2021) 21:300 https://doi.org/10.1186/s12883-021-02280-y

**BMC** Neurology

A proof-of-concept sub-study exploring feasibility and preliminary evidence for the role of physical activity on neural activity during executive functioning tasks among young adults after cancer treatment

Amanda Wurz<sup>1,2</sup>, Gladys Ayson<sup>3</sup>, Andra M. Smith<sup>3</sup> and Jennifer Brunet<sup>1,4,5</sup>

treatment. Physical activity (PA) may enhance neural activity underlying EF among older adults affected by cancer. Establishing whether PA enhances neural activity among AYAs is warranted. As part of a two-amm, mixed-methods pilot randomized controlled trial (RCT), this proof-of-concept sub-study sought to answer the following questions: is it feasible to use neuroimaging with EF tasks to assess neural activity changes following a 12-week PA intervention? And (2) is there preliminary evidence that a 12-week PA intervention enhances neural activity among AYAs after cancer treatment?

Methods: AYAs in the pilot RCT were approached for enrollment into this sub-study. Those who were eligible and enrolled, completed functional magnetic resonance imaging (MMRI) with EF tasks (letter n-back, Go/No Go) pre- and post-PA intervention. Sub-study enrollment, adherence to scheduled fMRI scans, outliers, missing data, and EF task performance data were collected. Data were analyzed with descriptive statistics, blood oxygen level dependent (BOLD) analyses, and paired sample t-tests.

Results: Nine eligible participants enrolled into this sub-study; six attended scheduled fMRI scans. One outlier was dentified and was subsequently removed from the analytical sample. Participants showed no differences in EF task performance from pre- to post-PA intervention. Increases in neural activity in brain regions responsible for motor ontrol, information encoding and processing, and decision-making were observed post-PA intervention (p < 0.05;



#### What Did We Do?

- Assessed physical activity's effect on executive functioning & two brain health indicators
- 5 AYAs (M=37.7 years) post-cancer treatment were enrolled from a larger pilot exercise trial
- Measures: Neurocognitive tests (i.e., "brain games") & neuroimaging (i.e., "brain scans")

#### What Did We Find?

- No change in test performance
- Signs of **improved brain structure** post-exercise
- Brain activity patterns shifted—some networks became more connected, others less

(Lambert et al, 2021; Wurz et al, 2021





### Lab Research: The ACTIVATE Trial

Received: 22 March 2024 Revised: 21 May 2024 Accepted: 3 June 2024 DOI: 10.1002/cncr.35540

ORIGINAL ARTICLE

Aerobic exercise and CogniTIVe functioning in women with breAsT cancEr (ACTIVATE): A randomized controlled trial

Jennifer Brunet PhD<sup>1,2,3</sup> | Sitara Sharma MA<sup>1</sup> | Kendra Zadravec PT, MSc<sup>4</sup> | Monica Taljaard PhD<sup>5,6</sup> | Nathalie LeVasseur MD<sup>7</sup> | Amirrtha Srikanthan MD<sup>8</sup> | Kelcey A. Bland MSc<sup>9</sup> | Elham Sabri PhD<sup>5</sup> | Barbara Collins PhD<sup>10</sup> | Sherri Hayden PhD<sup>11</sup> | Christine Simmons MD<sup>7</sup> | Andra M. Smith PhD<sup>10</sup> | Kristin L. Campbell PT, PhD4.9 0

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<sup>1</sup>Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

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Background: As the prevalence of chemotherapy-related cognitive impairment rises, investigation into treatment options is critical. The objectives of this study were to test the effects of an aerobic exercise intervention initiated during chemotherapy compared to usual care (wait list control condition) on (1) objectively measured cognitive function and self-reported cognitive function, as well as on (2) the impact of cognitive impairment on quality of life (QOL) postintervention (commensurate with chemotherapy completion)

Methods: The Aerobic exercise and CogniTIVe functioning in women with breAsT cancEr (ACTIVATE) trial was a two-arm, two-center randomized controlled trial conducted in Ottawa and Vancouver (Canada). Fifty-seven women (Maio, 48.8 ± 10 years) diagnosed with stage I-III breast cancer and awaiting chemotherapy were randomized to aerobic exercise initiated with chemotherapy ( $n_{EX} = 28$ ) or usual care during chemotherapy with aerobic exercise after chemotherapy completion (n<sub>UC</sub> = 29). The intervention lasted 12-24 weeks and consisted of supervised aerobic training and at-home exercise. The primary outcome was objective cognitive function measured via 13 neuropsychological tests (standardized to M  $\pm$  SD, 0  $\pm$  1); secondary outcomes of self-reported cognitive function and its impact on OOL were assessed via questionnaires. Data collected pre- and postintervention (the primary end point) were analyzed.

Results: Although no significant differences between groups were found for objective cognitive function outcomes postintervention after accounting for multiple testing, four of six self-reported cognitive function outcomes showed significant differences favoring the aerobic exercise group.

This trial was registered at ClinicalTrials.gov (NCT03277898)

#### What Did We Do?

- Clinical trial conducted in Ottawa & Vancouver
- 57 women (M=48.8 years) diagnosed with stage I-III breast cancer & awaiting chemotherapy were randomized to either:
  - An aerobic exercise (EX) intervention initiated alongside chemo (n=28)
  - **Usual care during chemo** with EX after chemo completion (n=29)
- Assessed: Objective cognitive function (via 13 neuropsychological tests), selfreported cognitive function & its impact on quality of life (via questionnaires)

#### What Did We Find?

- Similar cognitive performance on neuropsychological testing between groups
- Better self-reported cognition in the intervention group than those who received standard care without exercise

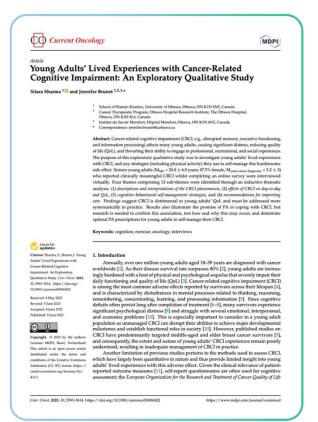




(Brunet et al, 2024

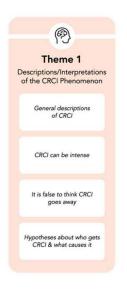


## Lab Research: CRCI Lived Experiences



#### What Did We Do & Find?

- Interviewed **16 young adults** (M=30.8 years) post-cancer treatment to explore their experiences with CRCI & any strategies they use to self-manage it
- Identified 4 key themes:









(Sharma & Brunet, 2023)





# Lab Research: CRCI Lived Experiences (Qualitative)



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Abstract: Cancer-related cognitive impairment (CRCI; e.g., disrupted memory, executive functioning and information processing) affects many young adults, causing significant distress, reducing quality of life (QoL), and thorating their ability to engage in professional, recreational, and social experiences. The purpose of this exploratory qualitative study was to investigate young adults' lived experiences with CRC, and any strategies (including physical activity) they use to self-manage this bundensome side effect. Sixteen young adults ( $M_{agg}$ = 30.8  $\pm$  6.0 years; 87.5% female;  $M_{yeans since diagnosis}$  = 3.2  $\pm$  3) who reported clinically meaningful CRCI whilst completing an online survey were interviewed virtually. Four themes comprising 13 sub-themes were identified through an inductive thematic analysis: (1) descriptions and interpretations of the CRCI phenomenon, (2) effects of CRCI on day-to-day anasysis. (1) accorptions and interpretations of the LRL pineamenton, (2) effects of LRL of magacount and QoL, (3) cognitive-behavioural self-management strategies, and (4) recommondations for improving care. Findings suggest CRCI is detrimental to young adults' QoL and must be addressed more systematically in practice. Results also illuminate the promise of PA in coping with CRCI, but research is needed to confirm this association, test how and why this may occur, and determine optimal PA prescriptions for young adults to self-manage their CRCI.

Keywords: cognition; exercise; oncology; interviews



0,5593-5614. https://doi.org/



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Annually, over one million young adults aged 18-39 years are diagnosed with cancet worldwide [1]. As their disease survival rate surpasses 80% [2], young adults are increasingly burdened with a host of physical and psychological sequelate that severely impair their daily functioning and quality of life (Qol.) [3]. Cancer-related cognitive impairment (CRCI) as mong the most common adverse effects reported by survivors across beint lifespan [3], and is characterized by disturbances in mental processes related to thinking, reasoning, membering, concentrating, learning, and processing information [3]. Since cognitive deficits often persist long after completion of treatment [6-2], many survivors experienced significant psychological distress [9] and struggle with several emotional, interpersonal. and economic problems [10]. This is especially important to consider in a young adult population as unmanaged CRCI can disrupt their abilities to achieve major developmental milestones and establish functional roles in society [10]. However, published studies on CRCI have predominantly targeted middle-aged and older breast cancer survivors [5].

CRL Taw prelominantiny targeted mixed segar and order treast a core survivors [3], and consequently, the actent and result roll young adults' CRC experiences smain poorly understood, resulting in inadequate management of CRL to the methods used to assess CRCI, Antober limited more previous studies pertains to the methods used to assess CRCI, which have largely been quantitative in arturn and thus provide limited insight into young adults' lived experiences with this active effect. CRL description of the control of the control of pertain the provided in the control of th

Curr. Oncol. 2023, 30, 5593-5614. https://doi.org/10.3390/curroncol30060422

"One size may not fit all" when managing CRCI, but young









(Sharma & Brunet, 2023)

# The Verdict? Physical Activity is Promising, But...





# Gaps to Address in Future Research





# Determine the optimal timing & parameters of physical activity (PA) for cognitive benefits

• Investigate different doses/contexts of PA and combine/compare different types (e.g., aerobic, strength, balance, mind-body practices)



# Explore whether combining PA with other CRCI management strategies offers added value

• E.g., PA + cognitive training; PA + meditation



• Co-design & evaluate trainings with stakeholders



## Main Takeaways



Cognitive problems are real, common, and vary in severity, often negatively affecting quality of life even years after cancer treatment ends



The underlying cause of cognitive problems is not well understood; likely a combination of sociodemographic, medical, biological, & molecular factors



There is **no single cure**, but psychological & behavioural **management strategies exist and are continuing to be developed and tested** 





# Thanks for your attention!

Have questions? Feel free to contact us.

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