ICCTF
International Cognition and Cancer Task Force
March 14-16, 2016, Amsterdam, The Netherlands

Keynote Speakers

Cobi Heijnen
Ysbrand van der Werf
Paul Lucassen
Martin Klein
Saskia Duijts
Venue and date
Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital
Piet Borst Auditorium
Plesmanlaan 121
1066 CX Amsterdam
14-16 March, 2016

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City Map

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Jaap-Willem Mink
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Editorial

International Cognition and Cancer Task Force
We are very pleased to welcome you to the 5th biennial ICCTF meeting in Amsterdam, the Netherlands. The mission of the International Cognition and Cancer Task Force is to advance the understanding of the impact of cancer and cancer-related treatment on cognitive and behavioural functioning in cancer patients, originally with special attention for adults with non-central nervous system cancers. We have recently welcomed work in pediatrics and CNS disease as well. Members of the ICCTF conduct local, national and international research to help elucidate the nature of the cognitive and neurobehavioral sequelae associated with cancer and cancer therapies, the mechanisms that underlie these changes in function, and interventions to prevent or manage these undesired symptoms. Several ICCTF working groups have been formed to identify research needs and opportunities, to help facilitate inter-institutional and multi-national collaboration, and to identify sources of funding to sponsor this research.

Steering Committee members of the International Cognition and Cancer Task Force
Tim Ahles, Ph.D.  Psychologist  Memorial Sloan Kettering Cancer Center, New York
Sanne Schagen, Ph.D.  Neuropsychologist  Netherlands Cancer Institute, Amsterdam
Janette Vardy, Ph.D.  Medical Oncologist  Concord Cancer Centre, Sydney
Jeffrey Wefel, Ph.D.  Neuropsychologist  MD Anderson Cancer Center, Houston

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Florence Joly  Jeff Wefel
Shelli Kesler

Acknowledgements
We would like to thank Jaap-Willem Mink, Puck van Tulder and Emmie Koevoets for their help with the organization of the meeting.
Main program & selected symposia
08.00 - 09.00  
Registration

09.00 - 09.10  
Introduction and Welcome  
Sanne Schagen, Ph.D.,  
The Netherlands Cancer Institute

09.10 - 10.10  
Plenary. Mechanisms underlying cognitive decline in cancer patients  
Cobi Heijnen, Ph.D.,  
The University of Texas M.D. Anderson Cancer Center

10.10 - 10.30  
The protective role of anti-depressant and anti-inflammatory agents against the effects of chemotherapy on cell proliferation in white matter tracts of the CNS  
Ayoub Al-bayti, Ph.D.,  
The University of Nottingham

10.30 - 10.50  
Levetiracetam mitigates doxorubicin-induced synaptic and DNA damage in neurons  
Andrey Tsvetkov, Ph.D.,  
The University of Texas Health Sciences Center at Houston

10.50 - 11.15  
Refreshment break

11.15 - 11.35  
Prospective evaluation of the impact of antiangiogenic treatment on cognitive functions in metastatic renal cancer  
Florence Joly, MD Ph.D.,  
Centre Francois Baclesse

11.35 - 11.55  
Neurocognitive decline in head and neck cancer survivors treated with radiotherapy or chemo-radiotherapy - a prospective longitudinal study  
Lori Bernstein, Ph.D.,  
University Health Network

11.55 - 12.15  
Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with early breast cancer. Updated results from the TEAM trial neuropsychological side study  
Jacobiern Kieffer, Ph.D.,  
The Netherlands Cancer Institute

12.15 - 13.30  
Lunch

13.30 - 14.30  
Plenary. Sleep and cognition  
Ysbrand van der Werf,  
Ph.D., Netherlands Institute for Neuroscience, VU University Medical Center

14.30 - 14.50  
Memory function and symptoms of sleep apnea in long-term survivors of childhood hodgkin lymphoma  
Pia Banerjee, Ph.D.,  
St. Jude Children’s Research Hospital

14.50 - 15.10  
Cardiovascular and metabolic risk factors for neurocognitive impairment in adult survivors of childhood cancer  
Kevin Krull, Ph.D.,  
St. Jude Children’s Research Hospital

15.10 - 15.30  
Changes in cognitive functions and cerebral grey matter and associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment  
Ali Amidi, Ph.D., Aarhus University Hospital & Aarhus University

15.30 - 17.00  
Poster session with wine and cheese reception

18.00 - 22.30  
Guided tour and dinner reception at the hortus botanicus
PROGRAM 5TH BIENNIAL ICCTF MEETING
Tuesday March 15th 2016

09.00 - 10.00
Plenary. Ins and outs of neurogenesis
Paul Lucassen, Ph.D.,
University of Amsterdam

10.00 - 10.20
Chronic exposure to chemotherapy impairs neurogenesis in Sox1-GFP transgenic mice
Valeria Lasio, Ph.D.,
University Of Nottingham

10.20 - 10.40
Regulation of glutamate receptors and transporter by radiation. Possible role in radiation-induced cognitive impairment
Linda Metheny-Barlow, Ph.D.,
Wake Forest School of Medicine

10.40 - 11.05
Refreshment break

11.05 - 12.05
Plenary. Cancer, cognition and ability to work
Saskia Duijts, Ph.D.,
The Netherlands Cancer Institute,
VU University Medical Center

12.25 - 13.40
Lunch

12.40 - 14.40
Plenary. Cancer, cognition and ability to work
Saskia Duijts, Ph.D.,
The Netherlands Cancer Institute,
VU University Medical Center

13.40 - 14.40
Short-term cognitive declines in older breast cancer patients. Possible interactions of treatment exposure and APOE genotype
Jeanne Mandelblatt, Ph.D.,
Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine

14.00 - 15.00
Chemotherapy-related cognitive impairment (CRCI), and neurotransmitter signaling, longevity, and inflammation pathways in 366 breast cancer (BC) patients and 366 age-matched cancer-free controls. A prospective, nationwide, longitudinal URCC NCORP study
Michelle Janelsins, Ph.D.,
University of Rochester Medical Center

15.00 - 15.20
A randomised controlled trial evaluating a web based cognitive rehabilitation programme (CRP) in cancer survivors reporting cognitive symptoms following chemotherapy
Janette Vardy, MD Ph.D.,
Concord Cancer Centre, University of Sydney

15.45 - 16.05
Web-based cognitive training for breast cancer survivors with cognitive complaints – a randomized controlled trial
Gitte Westphael, MSc,
Aarhus University Hospital & Aarhus University

16.05 - 16.25
Round-up

16.35 - 18.00
Poster session with wine and cheese reception
SYMPOSIA 5TH BIENNIAL ICCTF MEETING

Wednesday March 16th 2016

08.00 - 09.30
SYMPOSIUM 1

Overview of non-pharmacologic treatment approaches of cognitive dysfunction among cancer survivors and future directions.

Robert Ferguson, Ph.D. (Chair)

- Introduction.
  Robert Ferguson, Ph.D.

  Robert Ferguson, Ph.D.

- Cognitive training for cancer-related cognitive impairment.
  Shelli Kesler, Ph.D.

- Exercise interventions to alleviate cognitive dysfunction among cancer patients and survivors.
  Michelle Janelins, Ph.D., MPH

- Mindfulness-based stress reduction to alleviate cognitive dysfunction in cancer survivors.
  Diane Von Ah, Ph.D., RN, FAAN

09.45 - 11.15
SYMPOSIUM 2

Chemotherapy-induced cognitive impairment. An animal model approach.

Gordon Winocur, Ph.D. (Chair)

- Introduction
  Gordon Winocur, Ph.D.

- Chemotherapy-induced cognitive impairment in normal and cancerous rodents.
  Gordon Winocur, Ph.D.

- Pre-clinical animal models and targeted therapies on cognition. Direct impact of the PI3K inhibitor buparlisib.
  Helene Castel, Ph.D.

- Protecting hippocampal neurogenesis from chemotherapy.
  Peter Wigmore, Ph.D.

- Preclinical development of novel pharmacotherapies using animal models of chemotherapy-induced cognitive impairment.
  Ian Johnston, Ph.D.

11.30 - 13.00
SYMPOSIUM 3

Brain connectivity changes and cognitive impairment after cancer treatment.

Sabine Deprez, Ph.D. (Chair)

- Introduction.
  Sabine Deprez, Ph.D. and Shelli Kesler, Ph.D.

- Functional hyperconnectivity in resting state networks of testicular cancer survivors 14 years after exposure to BEP chemotherapy.
  Michiel de Ruiter, Ph.D.

- Longitudinal changes in DMN Connectivity following chemotherapy in Breast Cancer.
  Dorothée Vercruysse, MSc

- Structural Connectome Organization and Cognitive Impairment in Pediatric Acute Lymphoblastic Leukemia.
  Shelli Kesler, Ph.D.

- Multimodal neuroimaging examination of brain structure and function after chemotherapy for childhood leukemia.
  Brenna McDonald, Ph.D.
Social event
Monday 14th 6.00 pm - 10.30 pm. Guided tour and dinner at the Hortus Botanicus. Regular Attendee AND Student Rate - €65 Euro.

After the last session on Monday, a bus will pick you up at the Netherlands Cancer Institute and go directly to the social event location. The Hortus Botanicus is located in the center of Amsterdam.

After the event, you can use the public transport system to go to your hotel. Several hotels will be within walking distance.

Address
Hortus Botanicus Amsterdam
Plantage Middenlaan 2a
1018DD Amsterdam

Dutch public transport planner (in English): http://9292.nl/en
Plenary sessions
Chemobrain: Mechanisms and Treatment strategies

Cobi J. Heijnen, Ph.D., Department of Symptom research, Division of Internal Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.

Progress has been made in the treatment of cancer leading to a sharp increase in the number of survivors. However, cancer treatment poses severe side effects like pain, fatigue and cognitive deficits which become apparent during treatment but can remain long into survivorship.

Currently, there are no pharmacologic treatments that have proven value in the management of these neurotoxicities. Platinum-based drugs are widely used for treatment of many solid tumors. Apart from killing tumor cells, these drugs also affect healthy tissue leading to neurotoxic side effects such as damage to the peripheral and central nervous system and cognitive impairments.

We propose that neuronal mitochondrial dysfunction is the central mechanism of cisplatin-induced cognitive dysfunction. Preventing the mitochondrial dysfunction by mitochondrial protectants preserved the functional and morphological integrity of the brain.

BIO - Cobi J. Heijnen is a professor of Neuroimmunology at the M.D. Anderson Cancer Center where she is leading a group of researchers on defining the mechanism and developing novel therapeutic strategies for the treatment of cancer treatment-induced peripheral neuropathy and cognitive dysfunction. Cobi Heijnen was trained as a cellular immunologist and got her Ph.D. at the Sorbonne in Paris, France. She worked for many years in the University Medical Center Utrecht, The Netherlands, where she became the first professor of Psychoneuroimmunology in Europe. Her research in the Netherlands focused on neuroregeneration by mesenchymal stem cells as a treatment for neonatal brain damage as a result of hypoxia-ischemia.
Sleep and Cognition

Ysbrand D. van der Werf, Ph.D., Department Anatomy and Neurosciences; Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Sleep is instrumental in maintaining cognitive capacity in several ways: on the one hand, sleep processes information that has been encountered in the previous day or days. This information may concern things to be memorized but also emotional information that needs to be dealt with.

On the other hand, sleep prepares the individual for processing and dealing with novel information. Recent research has shown various, possibly parallel, ways in which sleep may aid in this dual process of digesting previous and dealing with subsequent information. I will highlight studies investigating which aspects of sleep are important for these functions and suggest ways in which we can use sleep to boost them.

BIO - Ysbrand D. van der Werf, Ph.D. graduated in Biology and Psychology at the University of Groningen. He obtained his Ph.D. from the Graduate School for Neurosciences in Amsterdam and has worked at McGill University in Montreal, Canada and the Netherlands Institute for Neurosciences. He is currently Associate Professor and team leader the VU University medical center in Amsterdam, and supervises a team of postdocs, PhD students and research assistants. His work is primarily concerned with understanding cognitive functions of the brain, in relation to sleep and neurological and psychiatric disease. He served as a member of ‘De Jonge Akademie’, a platform for young scientists in the Royal Netherlands Academy of Arts and Sciences and his work is sponsored by grants from the Dutch Research council NWO (a.o. VIDI, Brain and Cognition), patient foundations and. His work uses neuropsychological investigations, transcranial magnetic stimulation, neural imaging techniques such as functional magnetic resonance imaging, electroencephalography, electromyography and positron emission tomography.
Ins and outs of neurogenesis

Paul J. Lucassen, Ph.D., University of Amsterdam, The Netherlands

Adult neurogenesis, a once unorthodox concept, has by now become a widely accepted form of structural plasticity in the brain, where stem cells continue to form new, functional neurons in adult individuals. This occurs in the subventricular zone and hippocampus, where the addition of new neurons contributes to olfactory discrimination and cognition, respectively.

Neurogenesis is well regulated, e.g. by antidepressive drugs, and by factors like stress, exercise, enriched environmental housing and inflammation. Interestingly, often parallel changes in brain function are observed. Neurogenesis has further been implicated in (cognitive aspects of) brain disorders like epilepsy, depression and dementia e.g..

While its functional impact for cognition remains poorly understood, reductions in neurogenesis following severe stress, either in adult or early life, can lastingly impair hippocampal plasticity and contribute to cognitive deficits common to many brain disorders, including depression and dementia. Normalization of reductions in neurogenesis appears partly implicated in antidepressant action.

BIO - Prof.Dr. Paul J. Lucassen, Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam) obtained his PhD (cum laude) in 1996 at the Netherlands Institute for Brain Research (Promotor: Prof.Dr. D.F. Swaab). After a postdoc at the LACDR in Leiden with Prof.Dr. E.R. De Kloet, he became assistant Professor at SILS CNS UvA with Prof.Dr. M. Joels, where he started his own group and became full professor of 'Brain Plasticity' in 2011.

His research topics include: brain plasticity, neurogenesis, stem cells in the brain, (early life) stress, early nutrition, cognition, depression, epilepsy and Alzheimer's disease. He (co-)authored >140 peer-reviewed publications, >25 book chapters, has an H-factor of 42 (WoS) and is recipient of the Organon Prize for Endocrinology, SILS Award 2014, and visiting professor at Tongji Medical College, Wuhan, China.

He is on various editorial and evaluation boards and grant review panels, and chairman of the SAB of the International Society Alzheimer Research ISAO. His research is supported by the EU, NWO, JPI, VW stiftung, TNO US Army, KNAW and the HersenStichting, ISAO, IPF, Alzheimer Nederland, Corcept Inc, Amsterdam Brain & Cognition, Amsterdam Brain & Mind Project.

He coordinates a popular master track "Psychopharmaca and Pathophysiology' at Uva and has delivered > 200 invited lectures at various (inter)national scientific and laymen meetings.
Brain tumor and neuroplasticity

Martin Klein, Ph.D., VU University Medical Center, The Netherlands

Brain plasticity is the potential of the CNS to reshape itself during ontogeny, learning, or following injuries. The first part of this talk will review the mechanisms underlying plasticity at different functional levels in patients with primary brain tumors, mainly in those harboring low-grade gliomas. While the physiological and pathological anatomofunctional organization of the brain has flexibility, the patterns of reorganization may differ according to the time-course of cerebral damage due to tumor and/or treatment, with better functional compensation in more slowly growing tumors. The second part of this talk will discuss the interactions between brain tumor growth and brain reshaping, using neuroimaging and electro-physiological methods of functional mapping.

Finally, the therapeutic implications provided by a greater understanding of these mechanisms of cerebral redistribution are explored shortly from a surgical point of view. Improved preoperative prediction of an individual’s potential for reorganization ideally is integrated into preoperative surgical planning and preserving neurocognitive functioning through tailored rehabilitation programs to optimize functional recovery following brain tumor resection.

BIO - Martin Klein is professor in medical neuropsychology at VU University Medical Center, Amsterdam, the Netherlands. His research, in close cooperation with the departments of neurology, neurosurgery, and radiation oncology, initially focused on determining neurocognitive functioning and health-related quality of life of patients with brain tumors. This resulted in influential papers on neurocognitive functioning and health-related quality of life of high-grade glioma patients at the time of diagnosis, at follow-up, at the time of recurrence, and on the prognostic value of neurocognitive functioning. Regarding low-grade glioma patients, and other neurological patients, studies on the impact of surgery, radiotherapy, and on epilepsy and antiepileptic drugs on neurocognitive functioning and health-related quality of life are ongoing. The effectiveness of cognitive rehabilitation in patients with focal seizures has been addressed in a number of studies. Currently research aims at determining the brain mechanisms underlying frequent symptoms (e.g., neurocognitive deficits, epilepsy, fatigue, depression), the prevention of treatment effects on neurocognitive functioning, and on behavioral or pharmaceutical symptom treatment in primary and metastatic brain tumor patients and in oncological patients undergoing neurotoxic treatments affecting brain functioning. Within the European Organization for the Research and Treatment of Cancer (EORTC) Martin Klein is responsible for neurocognitive testing as part of the clinical trials initiated by the EORTC Brain Tumor Group.

Martin received the Tim & Tom Gullikson Foundation and Society for Neuro-Oncology Award for Excellence in Quality of Life Research in 2001 and the National Brain Tumor Foundation/Tug McGraw Foundation Caregiver Research Award in 2008.
Cancer, cognition and ability to work

Saskia F.A. Duijts, Ph.D., Department of Public and Occupational Health, VU University Medical Center, and Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam.

An increasing part of cancer survivors is able to return to work or (partly) stay at work during treatment, because of continuing developments in treatment. Specifically, about two third of the cancer patients re-enters the workplace within one to two years after diagnosis. Many survivors are doing well in general terms. However, a significant proportion of those occupationally active experiences work-related physical and/or psychosocial problems. That is, fatigue, depressive or anxious mood, pain, menopausal complaints, and changes in cognitive function can persist for years after primary treatment ends, and do not only affect cancer survivors not at work, but also those at work.

Consequently, impairments may develop that influence cancer survivors’ ability to return to work, but also their work performance, in terms of productivity loss or diminished work ability. As a result, long-term sickness absence or even work disability may occur. In this plenary presentation, a history of cancer and work research will be presented, the role of cognitive functioning related to return to work and the continuation of work will be discussed and the impact of cognitive limitations on work ability will be illustrated.

BIO - Dr. Saskia Duijts is a senior researcher at the VU University Medical Center and the Netherlands Cancer Institute, the Netherlands, and a visiting researcher at the Danish Cancer Society, Denmark. Her main research interest concerns ‘Cancer and Work’, for which she also received a fellowship from the Dutch Cancer Society. Her interest is not only related to the return to work process of cancer patients, but also to the period beyond their return to work, since a high percentage of patients is able to return to work, but experiences physical/psychosocial problems or inadequate support at work. Her current research involves looking at new ways to support patients to return to work and continue working, exploring for example the role of behavioral determinants. Dr. Saskia Duijts is supervising PhD students and Master students on cancer and work-related projects; she is the Associate Editor of the European Journal of Cancer Care and was the editor-in-chief of the Dutch Journal of Psychosocial Oncology for the past six years. She is a board member of the Dutch Association for Psychosocial Oncology, a member of several working committees within this Association and a member of the Research Committee of the International Psycho-Oncology Society.
Oral presentations
Monday & Tuesday
The protective role of anti-depressant and anti-inflammatory agents against the effects of chemotherapy on cell proliferation in white matter tracts of the CNS

Authors: A. Al-bayti, V. Lasio, E. Rabiaa, A. Maqbool, M. Fowler and P. Wigmore

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Background and purpose: Cognitive impairment which has been associated with systemic chemotherapy treatment is likely to have several causes. However patient and animal studies have shown that white matter integrity is affected after exposure to chemotherapy. This may be brought about by an inflammatory response to the chemotherapy treatment which causes a reduction in the proliferation of oligodendrocyte precursors (OPCs) and subsequent demyelination. This study evaluates the impact of acute and chronic systemic 5-FU treatment given to rats, on myelin integrity and oligodendrocyte precursor cell proliferation in the optic nerve (ON) and corpus callosum (CC). We also evaluated the ability of an antidepressant and anti-inflammatory drug to protect myelin and OPCs proliferation when co-administrated with 5-FU.

Material and methods: Adult male rats were either acutely (single dose) or chronically (six doses over 2 weeks) administrated 5Fluorouracil (5-FU). Some groups were co-administered with either Fluoxetine or Indomethacin administered via their drinking water prior to and during chemotherapy. Cell proliferation was quantified in both ON and CC. Transmission electron microscopy (TEM) was used to determine the density of myelinated axons and myelin thickness seven days after treatment.

Results: Acute 5-FU treatment did not influence cell proliferation while chronic treatment caused a significant decrease in cell proliferation in both ON and CC. Co-treatment with either fluoxetine or indomethacin prevented this decline. TEM showed no change in the density of myelinated axons but a decrease in myelin thickness in the ON and CC after chronic 5-FU treatment, whereas there was no significant difference in Fluoxetine or Indomethacin groups co- treated with 5-FU.

Conclusion: Chronic chemotherapy caused a decrease in cell proliferation in ON and CC, which was associated with a reduction in myelin thickness. These changes were prevented by prior Fluoxetine or Indomethacin treatment. This could provide a novel therapeutic approach to reduce cognitive impairment after chemotherapy.
Levetiracetam mitigates fluorouracil-induced synaptic and DNA damage in neurons

Authors: J. F. M. Manchon¹, Y. Dabaghian², S. R. Kesler⁴, J. S. Wefel⁴ and A. S. Tsvetkov¹,⁵

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Purpose: Neurotoxicity may occur in cancer patients and survivors during or after chemotherapy. Cognitive deficits associated with neurotoxicity can be subtle or disabling and frequently include disturbances in memory, attention, executive function and processing speed, but despite their high frequency, there is a paucity of effective treatments. Therefore, safe and effective neuroprotective drugs that relieve or mitigate cognitive dysfunction are urgently needed.

Methods: An automated microscopy system enables the monitoring of large cohorts of individual neurons over their lifetimes. With automated analysis, multiple endpoints in neurons can be measured, including neurotoxicity and survival. Statistical approaches, typically reserved for clinical medicine, can be applied to these data in an unbiased fashion to discover whether factors contribute positively or negatively to neuronal health and survival, and to quantify the importance of their contribution.

Results: Searching for pathways altered by anti-cancer treatments in cultured primary neurons, we discovered that fluorouracil, a commonly used anti-neoplastic drug, reduced synaptic and neurite density and promoted the formation of DNA double-strand breaks (DSB). Pretreatment of neurons with levetiracetam, an FDA-approved anti-epileptic drug, prevented fluorouracil-associated synaptic and neurite loss and reduced the formation of DNA DSBs.

Conclusion: Thus, levetiracetam might be part of a valuable new approach for mitigating synaptic damage and, perhaps, for treating cognitive disturbances in cancer patients and survivors.
Prospective evaluation of the impact of antiangiogenic treatment on cognitive functions in metastatic renal cancer

Authors: F. Joly1,3, N. Heutte3, B. Duclos4, S. Noal1,2, I. Léger-Hardy5, S. Dauchy5, N. Longato4, L. Desruess6, N. Houede7, M. Lange1,3, E. Sevin2, C. Rieux1, B. Clarisse1, H. Castel6 and B. Escudier8

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Background: The mechanisms underlying the specific toxicities associated with new targeted therapies used in metastatic renal cell carcinoma (mRCC) remain poorly documented. While early fatigue induced by antiangiogenic therapies (AATs) is acknowledged as the most frequent adverse event reported by the patients, AATs might also induce neurotoxic effects on patient’s cognitive functions. The aim of this study was to evaluate the impact of AATs on cognition and its connection with fatigue and quality of life (QoL) in patients with mRCC.

Patients and methods: This prospective study enrolled 75 patients starting AAT as first or second line for mRCC. Cognitive functions were assessed with a neuropsychological battery of tests, and fatigue, anxiety/depression and quality of life (QoL) were assessed with validated self-reported questionnaires, over a 6-month period. Biomarker evaluation included cytokine and VEGF levels.

Results: A decline of cognitive functions (executive functions, information processing speed and working memory) was observed in 31% of the patients, the majority of them (71%) exhibiting no cognitive impairment at baseline. Fatigue was reported by 90% of the patients over the study period. Relationship between cognitive complaints and fatigue was observed (p<0.05), although not found statistically significant when objective cognitive decline was considered. Both cognitive complaints and fatigue had a significant impact on most of the domains of QoL. A positive correlation was found between fatigue and inflammatory markers (CRP, orosomucoid and IL-6), but not with cognition.

Conclusion: This pilot study shows that AAT induces cognitive decline in patients with mRCC independently of fatigue. These brain-related side effects impacting QoL should be better assessed in clinical trials and taken into account in routine practice.
Neurocognitive decline in head and neck cancer survivors treated with radiotherapy or chemo-radiotherapy - a prospective longitudinal study

Authors: L. J. Bernstein¹, A. Zer², G. R. Pond³, A. R. A. Razak², K. Tirona¹, H. K. Gan², E. X. Chen², A. J. Hope⁴, J. J. Kim⁴, K. K.W. Chan², A. K. Chan⁴ and L. L. Siu²

Institutional affiliations: ¹Department of Supportive Care, Princess Margaret Cancer Centre, University of Toronto, Canada; ²Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada; ³Department of Biostatistics, McMaster University, Hamilton, Canada; ⁴Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Canada.

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Purpose: Neurocognitive deficits during cancer are distressing to patients, but posttreatment neurocognitive effects (NCE) have the most significant impact. Despite the increasing role of (chemo)radiation treatment in head and neck cancers (HNC), and involvement of central nervous system structures in the radiation field, data are lacking regarding short and long term NCE in HNC.

Methods: In a prospective, longitudinal cohort study, neurocognitive function and quality of life were assessed in HNC patients requiring definitive (chemo-)radiation. Validated and standardized objective and self-reported instruments were administered at 4 time points to patients and healthy controls (baseline, 6, 12, and 24 months after baseline). Objective cognitive test scores were converted to age-corrected scaled scores and transformed to z-scores (mean 0, standard deviation 1) and reported as mean scores, standardized regression-based scores, and frequencies of significant impairments in intellectual capacity, concentration, memory, executive function, speed of processing, motor dexterity, and global cognitive function (an average of the cognitive domain scores). A multivariable analysis was used to identify factors impacting NCE across the two years.

Results: Eighty patients and 40 healthy controls enrolled. Analyses revealed significant deficits in patient’s cognitive performance, compared to controls, in intellectual capacity (p-values 0.007, <0.001, <0.001 for time points 6, 12, and 24 months respectively), concentration (p-values 0.82, 0.15, 0.012), verbal memory (p-values 0.040, 0.014, 0.008), executive function (p-values 0.44, 0.12, 0.025) and motor dexterity (p-values 0.043, 0.029, 0.066). Risk for delayed impairment over time was also higher for patients, with impaired global cognitive function in 38% of patients at 24 months compared to none of controls (p<0.001).

Conclusion: Definitive (chemo-)radiation for HNC is associated with significant delayed neurocognitive sequelae. Patients, family members, and health care teams should be knowledgeable about such risks. Further research is warranted in search of strategies to avoid, reduce and compensate for declines.
Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with early breast cancer: updated results from the TEAM trial neuropsychological side study

Authors: J. M. Kieffer¹, B. J. Small³, C. Seynaeve⁴, W. Boogerd², E. Meershoek-Klein Kranenbarg⁵, C. J. H. van de Velde² and S. B. Schagen¹

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Purpose: Endocrine therapy (ET), prescribed to ER-positive breast cancer patients, either lowers estrogen levels or stops estrogen from acting on breast cancer cells. Since estrogens play an important role in certain cognitive functions it is plausible that ET can affect cognition. Therefore, the aim of this study was to evaluate the effects of tamoxifen and exemestane on cognitive functioning.

Methods: Patients participating in the Dutch part of a randomized trial (TEAM-trial) were randomly allocated to 5 years of adjuvant exemestane (EXE; n=114), or to 2.5 years of tamoxifen followed by 2.5 years of exemestane (TAM/EXE; n=92). Cognitive performance was tested using 15 cognitive subtests subsumed under 7 domains before start of ET (T0), at one year (short-term) and at 5 years of ET use (long-term). A healthy control group (n=120) was also assessed. We used mixed effect models to model baseline to follow-up changes in cognitive performance between groups, adjusting for age, IQ, and drop-out patterns.

Results: Compared to controls, TAM/EXE pts had significantly greater short-term (using tamoxifen) and long-term (using exemestane) decline in performance on Verbal memory (p=0.017, p=0.002, respectively) and Executive functioning (p=0.041, p=0.002, respectively). For the EXE pts, we only found a long-term decrease on Trailmaking B (Executive functioning subtest; p=0.001), compared to controls. Additionally, we found that TAM/EXE pts had a significantly greater short-term decline in performance on Trailmaking A (Information processing speed subtest; p=0.008), compared to EXE pts. The above results were stronger for TAM/EXE pts aged>65yr compared to TAM/EXE pts <65 yr.

Conclusion: Results show that TAM/EXE pts perform worse on several cognitive functions compared to controls, suggesting long-term effects of tamoxifen even though patients switched to exemestane halfway through the treatment. This is less so for EXE pts. Since current guidelines permit the use of both regimens, we argue the necessity of including neuropsychological examinations in prospective safety studies examining the effect of ET.
Memory function and symptoms of sleep apnea in long-term survivors of childhood Hodgkin lymphoma

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Purpose: To examine associations between memory and symptoms of sleep apnea in long-term survivors of childhood Hodgkin lymphoma treated with thoracic radiation.

Methods: 101 Hodgkin lymphoma survivors (mean[SD] age 38.5[7.6] years, 23.5[7.6] years post-diagnosis) and 116 age- and sex-matched controls completed neurocognitive testing (i.e. California Verbal Learning Test-2nd Ed.) and self/informant-report of sleep/sleepiness/fatigue. Sleep apnea symptoms were defined as “long pauses between breaths while sleeping” based on report from a sleep partner (Pittsburgh Sleep Quality Index), combined with clinically elevated daytime sleepiness or fatigue from self-report (Epworth Sleepiness Scale, FACIT Fatigue). Group differences between those with sleep apnea symptoms and those with neither symptom were examined using chi-square and Wilcoxon rank-sum tests.

Results: A higher frequency of survivors (n=25, 25%) compared to controls (n=16, 14%) reported sleep apnea symptoms (X2=4.36, p=0.04). 54% of survivors (n=55) and 65% of controls (n=75) reported no sleep apnea symptoms. No group difference in body mass index was identified between survivors and controls (p=0.14). Overall, survivors performed worse than controls on free recall following short delay (p=0.03) and long delay (p=0.02). A main effect of sleep apnea symptoms across groups was identified for short (p=0.042) and long (p=0.046) delayed recall. While survivors with sleep apnea symptoms performed significantly below population norms on short (mean z-score= -0.50, p=0.05) and long (-0.59, p=0.04) delayed recall, survivors without sleep apnea symptoms demonstrated no difference (short delay -0.15, p=0.26, long delay -0.20, p=0.18). For controls, neither those with symptoms (short delay -0.16, p=0.39; long delay -0.16, p=0.45) nor without symptoms (short delay 0.14, p=0.30; long delay 0.16, p=0.18) differed from population norms.

Conclusion: Survivors of Hodgkin lymphoma treated with thoracic radiation may be at higher risk for sleep apnea compared to community controls. Symptoms of sleep apnea appear to increase risk for memory problems in survivors, but not controls.
Cardiovascular and metabolic risk factors for neurocognitive impairment in adult survivors of childhood cancer

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Purpose: To examine the contribution from cardiovascular risk factors and metabolic syndrome to neurocognitive impairment in long-term adult survivors of childhood cancer.

Methods: Adult survivors of childhood cancer (n=1,479; 47% female; median [range] age 31.0 [18-61] years; median time since diagnosis 24.6 [11-49] years) were recruited from the St. Jude Lifetime Cohort Study. Survivors completed comprehensive medical assessments and neurocognitive testing for attention, memory, processing speed and executive function. Survivors with history of neurologic/neurodevelopmental conditions unrelated to cancer diagnosis or treatment were excluded. Multivariable logistic regression was used to examine relative risk (RR, 95% confidence interval [CI]) for neurocognitive impairment, defined as age-adjusted standard score <10th percentile of population norms. Predictors included current smoking status, abdominal obesity, and the presence of or treatment for hypertension, elevated fasting cholesterol, and elevated fasting glucose. The prevalence and impact of metabolic syndrome was also examined. All models included adjustment for demographic and neurotoxic treatment variables.

Results: Survivors demonstrated high frequency of hypertension (49%), dyslipidemia (64%), abdominal obesity (65%), elevated fasting glucose (33%), current smoking (24%), and metabolic syndrome (33%). High frequency of neurocognitive impairment was identified in attention (28%), memory (29%), processing speed (32%) and executive function (43%) domains. In multivariable models controlling for treatment exposures (CRT dose, cumulative doses of specific chemotherapies), gender, race, and current age, abdominal obesity was associated with risk of attention problems (RR=1.24, CI 1.05-1.47) and slow processing speed (RR=1.19, CI 1.03-1.39). Current smoking was associated with impaired attention (RR=1.47, CI 1.23-1.75), memory (RR=1.52, CI 1.27-1.81), processing speed (RR=1.33, CI 1.13-1.56) and executive function (RR=1.30, CI 1.15-1.48). Slow processing speed was also associated with hypertension (RR=1.26, CI 1.08-1.46) and metabolic syndrome (RR=1.18, CI 1.02-1.37).

Conclusion: Long-term survivors of childhood cancer are at increased risk for neurocognitive impairment, a risk that is increased by factors typically associated with poor cardiovascular health.
Changes in cognitive functions and cerebral grey matter and associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment

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Purpose: Evidence suggests that testicular cancer (TC) and its treatment is associated with cognitive impairment. However, the underlying neural substrate and biological mechanisms are yet to be investigated. This study aimed to investigate changes in cognition and brain grey matter (GM) morphology in TC patients undergoing treatment, and to explore associations between cognition and immune (IL-6, TNF-α) markers, endocrine (cortisol) markers, and genotype (APOE ε4).

Methods: Sixty-five patients with stage I-III TC underwent assessments after surgery but prior to further treatment and six months later. Twenty-two patients (mean age=32.8, SD=11.1) received chemotherapy (+CT), while 43 (mean age=39.6, SD=10.7) did not (-CT). Assessments included neuropsychological testing, whole-brain magnetic resonance imaging, and blood work. Twenty-five matched healthy controls (HC) (mean age=31.9, SD=10.4) underwent neuropsychological testing with a matching time interval. A regression-based approach including age and premorbid intellectual functioning as covariates was used to determine cognitive changes in all groups and longitudinal voxelbased morphometry (VBM) was used to compare changes in GM density between the TC.

Results: Compared with HCs, both TC groups showed higher rates of domain-specific and overall cognitive decline (all p<0.05). A trend towards greater overall cognitive decline was found in the +CT group (63.6%) compared with the -CT group (39.5%) (p=0.07). VBM revealed widespread GM reductions in both TC groups; however, a group-by-time interaction analysis revealed prefrontal reductions specific to the +CT group (p=0.02) that were associated with poorer cognitive performance. Increased TNF-α in the +CT group was also associated with poorer cognitive performance. Furthermore, an interaction effect was found between the APOE ε4 genotype and chemotherapy on cognitive performance with ε4 carriers performing significantly worse.

Conclusion: These findings provide further evidence of cognitive decline related to TC and its treatment, as well as novel insights regarding the underlying neurobiological and biological mechanisms.
Chronic exposure to chemotherapy impairs neurogenesis in Sox1-GFP transgenic mice

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Purpose: Recent patient studies have demonstrated an association between chemotherapy treatment and cognitive impairment. We have previously shown that 5-fluorouracil, a chemotherapy agent widely used for breast, prostate and bowel cancer, induces cognitive impairments and a reduction in hippocampal neurogenesis in a rodent model. In the present study we quantified the impact of chronic 5-FU treatment on cell proliferation (Ki67), differentiation (DCX) and stem cell subpopulations (GFP and GFAP) in the subgranular zone (SGZ) of SOX1-GFP transgenic mice. >90% of SOX1+ cells are neural stem cells and are restricted to SGZ. In SOX1-GFP mice it is possible to distinguish between early radial and later horizontal orientated SOX1+ cells and to distinguish quiescent (GFAP+) and activated (GFAP-) SOX1+ cells.

Methods: Male SOX1-GFP mice were injected with 5-FU or saline twice a day, every second day for two weeks. Animals were killed 24h after the last injection and their brains were processed for immunohistochemistry. Confocal images were acquired and analysed using ImageJ software.

Results: Two weeks of 5FU treatment caused a significant reduction in the number of proliferating (Ki67+) cells but did not affect the number of differentiating (DCX+) cells. A different picture emerged from the examination of neural stem cell subpopulations where chemotherapy reduced the number of quiescent (SOX1+/GFAP+) and activated (SOX1+/GFAP-), radial neural stem cells but had no effect on the numbers of horizontally orientated SOX1+ cells present in later stages of neurogenesis.

Conclusion: Results presented here demonstrate that chronic 5FU has a severe effect on hippocampal neurogenesis by inducing depletion of early neural stem cells, an effect which explains the prolonged reduction in hippocampal neurogenesis and cognitive impairments found in patients and animal models. Further experiments will look at the potential protective effect of fluoxetine and indomethacin on neurogenesis.
Regulation of glutamate receptors and transporter by radiation: possible role in radiation-induced cognitive impairment

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Background: Partial or whole brain irradiation is often administered to treat primary or metastatic brain tumors. Unfortunately, radiation-induced brain injury, including cognitive impairment, can significantly affect the quality of life of cancer patients receiving radiation therapy. The mechanisms regulating radiation-induced cognitive decline are not fully understood, but may involve alterations in neuronal signaling and plasticity.

Purpose: To evaluate glutamate transporter and receptor expression in the brain following fractionated whole brain radiation (fWBI).

Methods: Archived samples from the cortex or hippocampus of rats isolated 48 hours, 2 months or 6 months after administration of a clinically-relevant scheme of fWBI (5Gy x 8 fractions), with or without ramipril, were analyzed for components of the glutamatergic system using real-time PCR and immunohistochemistry.

Results: While AMPA2 or AMPA3 glutamate receptor subunit mRNA was not altered in the cortex 2 months post-fWBI, we found marked impairment of mRNA expression of the AMPA4 subunit (65.75% reduction); at six months post-fWBI both cortical AMPA2 and AMPA4 were observed to be decreased (53.3% and 63.5%, respectively). Similarly, both AMPA2 and AMPA4 subunits were reduced in the hippocampus 6 months post-fWBI. Although administration of the cognition-sparing drug ramipril reverses cortical AMPA4 decrease at 2 months, it has no effect on AMPA4 loss at 6 months. Expression of the GLT-1 glutamate transporter was only modestly altered in the hippocampus at 48 hours and 2 months, but was significantly reduced 6 months post-fWBI (40%). In contrast, in the cortex fWBI decreased expression of GLT-1 glutamate transporter mRNA at both 48 hours (51%) and 2 months (75%), which was reversed by ramipril.

Conclusion: fWBI causes sustained dysregulation of AMPA glutamate receptor subunits and the GLT-1 glutamate transporter, which is partially reversed by the cognition-sparing drug ramipril. Together these data suggest that alteration of glutamatergic signaling may contribute to fWBI-induced cognitive impairment.
Discovering neurocognitive contributors to patient-reported symptoms of attention and memory dysfunction: a Bayesian latent regression Rasch model approach

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Purpose: A subset of cancer survivors report cognitive decline following treatment, yet cognitive performance assessed by standard neurocognitive measures correlates poorly with self-reported cognition. A Bayesian latent regression Rasch model was applied to better elucidate the association between neurocognitive performance and patient-reported cognitive problems.

Methods: In a longitudinal neurocognitive outcomes study that included self-report and objective performance measures, 132 breast cancer survivors and 45 healthy controls (mean age 54) were given a battery of 28 objective neurocognitive tests, including Memory (Verbal, Visual) and Executive Functioning (Attention, Processing Speed). Patient-reported cognitive deficits were assessed by the Multiple Ability Self-Report Questionnaire (MASQ). Associations between the patient-report and objective assessments were made in two separate sets of analyses: 1) conventional correlations between the summary scores; and 2) a more sophisticated Bayesian latent regression Rasch model.

Results: Consistent with previous research, conventional correlation-based analysis between neurocognitive decline and self-reported problems were generally near zero. In contrast, the Bayesian latent regression Rasch model enhanced correlation analysis by identifying additional covariates: 1) subjective memory performance was associated with changes in delayed recall performance, with changes in attention and encoding, and in processing speed; and 2) subjective attention performance was associated with changes in attention and encoding, and with changes in processing speed. The statistical modeling approach also permitted predictions of specific complaints, primarily in Verbal Memory (e.g., “I forget to mention important issues during conversations”) rather than Attention (e.g., “I can keep my mind on more than one thing at a time”).

Conclusion: Sophisticated statistical modeling suggests the roles of attention, initial learning, and sustained attention, rather than overall memory deficit, in patient-reported cognitive problems. We encourage researchers to replace the conventional analytics by correlation with sophisticated statistical modeling to help clarify the relationship of self-report with objective neurocognitive performance measures.
Short-term cognitive declines in older breast cancer patients: possible interactions of treatment exposure and APoE genotype


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Purpose: Older individuals constitute the majority of cancer survivors, but there is limited information about their cognitive outcomes.

Methods: This longitudinal cohort study enrolled newly diagnosed patients ages 60+ with stages 0-3 breast cancer (n=344) and frequency-matched controls (n=380) from 5 US sites from September 2010-present. Baseline data collection occurred prior to systemic therapy (or control enrollment), including neuropsychological testing, surveys, and biospecimens. Participants repeated assessments 12 and 24 months post-baseline. Follow-up is ongoing; we report data from the 96% and 53% of controls and 73% and 50% of cases that have completed 12- and 24-month assessments, respectively. Neuropsychological tests were grouped into three domains: attention, processing speed, and executive function (APE); learning and memory (LM); and visual-spatial (VS). The scores for each domain and time-point were standardized to baseline control scores.

Results: Cases and controls were comparable at baseline (overall mean sample age 68.0, range 60-98). Twenty-eight percent of cases received chemotherapy (+/- hormonal), 74% with anthracyclines; 72% received hormonal therapy alone (91% with aromatase inhibitors). Mixed effects model analyses suggested that most participants improved over time, considering age, WRAT scores, race, and recruitment site, but chemotherapy patients who were APoE e4+ had moderate declines for the APE and LM domains (mean 24-month z-scores -.56 and -.37, p=.18 and .02 respectively); a similar trend was seen for VS, but was not significant (-1.2, p=.5).

Conclusion: The majority of older breast cancer patients have good short-term cognitive outcomes relative to matched non-cancer controls. However, the subset of patients exposed to chemotherapy that have a genetic predisposition for neurodegenerative disease may experience moderate-size cognitive decline over 24 months. If confirmed, genetic testing might be useful to inform treatment decision-making and survivorship care.
Chemotherapy-related cognitive impairment (CRCI), and neurotransmitter signaling, longevity, and inflammation pathways in 366 breast cancer (BC) patients and 366 age-matched cancer-free controls: a prospective, nationwide, longitudinal URCC NCORP study


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Background: CRCI is a burdensome clinical problem for many BC patients. Large studies are needed to definitively assess CRCI and elucidate its’ biological underpinnings. We conducted the largest longitudinal, observational study to date assessing CRCI in BC patients and controls, and assessed whether neurotransmitter signaling, longevity, and inflammation pathways are involved in CRCI.

Methods: NCORPs recruited non-metastatic BC patients (n=366) without previous chemotherapy (CT) and age-matched controls (n=366). Cognitive function was assessed within 1 wk pre-CT and within 4 wks post-CT using the FACT-Cog to assess self-reported function and neuropsychological assessment (computerized CANTAB Verbal Memory (VM), paper-based Controlled Oral Word Association (COWA), and phone-based word recall (RAVLT), backward counting) to assess executive function. Controls were assessed at the same time intervals as patients. SNPs involved in neurotransmitter signaling (COMT) and longevity (FOXO3), and pre- and post-CT cytokines (IL-1β, MCP-1, sTNFR1) were measured.

Results: BC patients (89% white, mean age=53) reported more CRCI on the FACT-Cog (total score and all 4 domains) from pre- to post-CT and performed worse on all 4 executive function tests over time via T-tests (all p<0.05). Using ANCOVA, adjusting for age, education, WRAT-4 reading, anxiety (STAI), and pre-CT cognitive score, BC patients performed worse on all measures post-CT compared to controls: FACT-Cog Effect Size (ES)=0.74, VM ES=0.27, Backward Count ES=0.19, RAVLT ES=0.27, COWA ES=0.33; all p<0.05. FOXO3 and COMT SNPs predicted level of CRCI on the FACT-Cog (both p=0.07). Decreases in executive function were associated with increases in IL-1β, MCP-1 (both p<0.05) and sTNFR1 (p=0.08).

Conclusion: This is the largest longitudinal study to date showing significant CRCI among BC patients receiving CT compared to cancer-free controls. CRCI in BC patients is influenced by neurotransmitter signaling and longevity genes and leads to increased inflammation.
Evaluation of a web based cognitive rehabilitation programme (CRP) in cancer survivors reporting cognitive symptoms following chemotherapy

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Purpose: Self reported cognitive impairment is frequently seen in cancer survivors. We evaluated a CRP in cancer patients with cognitive symptoms.

Methods: Cancer patients who had completed adjuvant chemotherapy within 6-60 months and reported changes in memory and/or concentration on EORTC-QLQ-CF, received a 30-minute telephone consultation and were randomised to a 15-week, home-based CRP (Insight\textsuperscript{™}) or standard care. Primary endpoint was self reported cognitive function (FACT-COG Perceived Cognitive Impairment [PCI] subscale). Secondary endpoints included: neuropsychological (NP) testing, quality of life (QOL), fatigue, anxiety/depression and stress. Primary analysis used linear mixed models comparing the difference in FACT-COG PCI between the groups at post intervention (T2); 6 months later (T3).

Results: 242 patients were randomised: median age 53 (range 23-74); 95% female; 89% breast cancer; 5% colorectal cancer. There were no significant differences between the groups at baseline. There was a significant improvement in all FACT-COG subscales in the CRP group at T2. FACT-COG PCI was statistically different with lower PCI in the CRP group at T2 (p<0.0001), sustained at T3 (p<0.0001). NP results were not significantly different between the groups at T2 or T3. There were significantly lower levels of anxiety/depression and fatigue in the CRP group at T2, with a trend towards benefit at T3. There were significant improvements in stress in the CRP group at both time points. There was no significant difference in global QOL between the groups at T2, but the CRP group had better global QOL at T3. Of those randomised to the CRP, 86% utilised the intervention.

Conclusion: The web-based CRP Insight\textsuperscript{™} led to improvements in cognitive symptoms that were sustained at 6 months. This is the first large RCT showing an improvement in cognitive function in cancer survivors. It is a feasible treatment option that could be recommended to cancer survivors reporting cognitive symptoms.
Web-based cognitive training for breast cancer survivors with cognitive complaints - a randomized controlled trial

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Purpose: Cognitive complaints are common amongst breast cancer survivors, and no standard treatment exists. The present study evaluates whether web-based cognitive training can alleviate subjectively reported and objectively assessed cognitive complaints in a sample of breast cancer survivors. Primary and secondary outcomes were an objective measure of working memory and a measure of perceived cognitive functioning, respectively. Additional outcomes were neuropsychological tests of memory, executive function, verbal learning, and working memory and questionnaire-based assessment of anxiety, depression, and somatization.

Methods: A total of 157 female breast cancer survivors were recruited from an existing cohort and through announcements in open access cancer-related Internet fora. Participants were randomly allocated to either web-based cognitive training (eCogT) with telephone support (n=94) or a waitlist control condition (WLC) (n=63). eCogT encompassed 30 training sessions over 6 weeks. Neuropsychological assessments were undertaken by telephone and questionnaire data were collected online. Data were collected at baseline, post-intervention and at five months follow-up.

Results: Mixed Linear Models revealed no statistically significant change in primary or secondary outcomes through follow-up in either group. Statistically significant improvements (range; p: 0.040-0.043) were found at five months follow-up in the eCogT group for the neuropsychological tests of verbal learning and working memory.

Conclusion: Web-based cognitive training did not result in improvements of the primary or secondary outcome. However, improved performance was observed for verbal learning and working memory, both additional outcomes. These effects were observed at five months follow-up, indicating long-term effects of training. The intervention may be applied in clinical settings at low cost and without risk of adverse effects.
Poster presentations
Monday
Altered brain connectivity networks in testicular cancer patients undergoing chemotherapy: A prospective controlled study

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Purpose: Platinum-based chemotherapy may have neurotoxic effects within the central nervous system. The aims of this study were 1) to prospectively compare changes in brain connectivity networks in newly orchiectomized testicular cancer patients undergoing chemotherapy or in active surveillance; 2) to examine the association between changes in brain network properties and cognitive performance.

Methods: Sixty-four newly orchiectomized TC patients underwent structural magnetic resonance imaging (T1-weighted and diffusion-weighted imaging) and cognitive testing at baseline prior to further treatment and again at a six-month follow-up. At follow-up, 22 participants had received chemotherapy (CT) while 42 were in active surveillance (S). At each time point, weighted brain connectivity networks between 90 cortical and subcortical regions were constructed for each participant. Brain network properties were measured using graph analyses and longitudinally compared across groups adjusting for age, education, and total intracranial volume. Using neuropsychological test scores, domain-specific and global composite scores of cognitive performance over time were calculated for each participant using a standardized regression-based approach.

Results: Compared with the surveillance group, the CT group demonstrated altered global and local brain network properties from baseline to follow-up as evidenced by decreases in small worldness \( p = 0.04 \), network clustering \( p = 0.04 \), and local efficiency \( p = 0.02 \). In the CT-group, poorer overall cognitive performance was associated with decreased small-worldness \( r = -0.46, p = 0.04 \) and local efficiency \( r = -0.51, p = 0.02 \), and verbal fluency was associated with decreased local efficiency \( r = -0.55, p = 0.008 \).

Conclusion: Both local and global brain network properties may be disrupted following treatment with platinum-based chemotherapy. Impaired network properties may underlie poorer performance over time on both specific and non-specific cognitive functioning in patients undergoing chemotherapy. Our results provide novel insights regarding the neurobiological mechanisms of cancer-related cognitive impairment in testicular cancer patients.
Hippocampal TrkB Expression and Cell Proliferation in Chemotherapy-related Cognitive Decline

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Purpose: Chemotherapy is associated with long-term cognitive impairment in a subset of breast cancer survivors. Our lab has previously investigated the effect of hormonal status and systemic chemotherapy treatment on cognitive function in a rodent animal model (Salas-Ramirez et. al. 2015). Cognitive impairment following drug treatment correlated with increased activation of the Akt and ERK 1/2 signaling pathways in the hippocampus of ovariectomized (OVX) Sprague Dawley rats. Furthermore, the levels of brain-derived neurotrophic factor (BDNF), a protein implicated in neurogenesis, survival and memory, were unaffected by drug treatment although OVX rats had an overall increase in the levels of the neurotrophin compared to intact animals.

Methods: To better understand the functional relevance of these chemotherapy associated changes in signal transduction, the protein expression of the BDNF receptor trkB was examined by Western analysis and cell proliferation in the dentate gyrus (DG) of the hippocampus was assessed by immunohistochemistry.

Results: We observed that rats injected once per week for 3 weeks with a combination of doxorubicin and cyclophosphamide show altered expression of the full-length and truncated trkB isoforms. Furthermore both hormonal status and chemotherapy treatment affected cell proliferation in the DG, as assessed by an increase in Ki-67- immunopositive cells in brain sections.

Conclusion: Our results suggest that despite similar hippocampal BDNF levels, the differential expression of trkB isoforms may be linked to the cognitive impairment following treatment. Furthermore, the increase in cell proliferation in the DG could indicate a compensatory response to CNS toxicity after chemotherapy. Ongoing studies will help clarify the potential involvement of the BDNF/trkB signaling pathway and regulation of neurogenesis in the effects of chemotherapy on cognition.
Comparing shape reproducibilities and regional volume differences of automatic and manual hippocampi segmentations

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Purpose: Precise and reproducible hippocampus outlining is important to quantify hippocampal atrophy caused by neurodegenerative diseases and to avoid hippocampal radiation in radiotherapy. We compare outline reproducibilities and regional volumes of manual, FSL-FIRST and FreeSurfer hippocampus segmentations in patients with MCI and AD.

Methods: We use a dataset from ADNI including 80 subjects, 20 controls, 40 MCI’s and 20 AD’s. 3D T1 weighted MPRAGE same session rescans have been obtained at 1.5T using different MRI scanner vendors. Hippocampi have been segmented manually, with FSL-FIRST and with FreeSurfer. Jaccard indices have been computed using same session rescan segmented hippocampi to obtain reproducibilities. Furthermore, regional volumes have been extracted and compared. Results have been statistically analyzed using linear mixed models with repeated measures.

Results: Comparisons of Jaccard indices have shown that FSL-FIRST segmented hippocampi have higher reproducibilities than manual segmented hippocampi, which have a higher reproducibility than FreeSurfer. Furthermore, for all methods the medial region is most and the posterior region least reproducible. This finding is independent of disease. Volume comparisons have illustrated that for both automatic methods the medial region have highest and the posterior region lowest volumes, while for manual segmentation the anterior region is the largest and the posterior region the smallest part. Moreover, the anterior volume of manual segmentations is systematically bigger than the anterior volume of the automatic segmentations. The other two regions of manual segmentations are smaller than the ones from automatic segmentations. For all methods all regional volumes decreased with the severity of disease.

Conclusion: Regional outline reproducibilities have shown that FSL-FIRST replicates hippocampi outlines better than manual and FreeSurfer. The high reproducibility of the medial part for all methods indicates that this part has clearer boundaries from adjacent structures and therefore is easier to outline. Systematic differences of volume distributions for automatic compared to manual segmentations show that hippocampi boundaries are differently defined.
Investigating possible recovery of chemotherapy-induced white matter changes in breast cancer

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Purpose: In a previous longitudinal diffusion tensor imaging (DTI) study, we reported cerebral white matter (WM) microstructural changes 3-5 months after chemotherapy-treatment (t2) when compared with baseline (t1). The current study investigates if the observed changes in fractional anisotropy (FA) are still present 3-4 years after ending chemotherapy (t3).

Methods: Twenty-five young women with early-stage breast cancer who received chemotherapy (C+), 14 who did not receive chemotherapy (C-) and 15 healthy controls (HC) previously studied, underwent reassessment at t3, including neuropsychological testing and DTI. Whole brain DTI SE-EPI images with 45 non-collinear directions and a b-value of 800 s/mm², were acquired on a 3T scanner. DTI pre-processing was performed using ExploreDTI consisting of motion and distortion correction with reorientation of the b-matrix and an iterative nonlinear tensor estimation process. The individual DTI datasets were non-rigidly registered to a population-based atlas. SPM8 was used to build a whole-brain voxel-based repeated-measures ANOVA model and FA values were extracted in 4 regions previously associated with chemotherapy-related changes from t1 to t2. Neuropsychological tests previously showing a significant group x time interaction were selected for further analysis at t3.

Results: Mixed effects modeling with time (t1, t2, t3), group and group x time as fixed effects, revealed significant group x time interactions for verbal memory and processing speed (p<0.05) reflecting regained performance in the C+ group at t3. Furthermore, in chemotherapy-treated patients, FA returned to baseline levels at t3 in all ROIs (p<0.002), whereas no FA changes were seen in healthy controls. Additionally, FA increase from t2 to t3 correlated with time since treatment in two of the four regions (r=0.4, p<0.05).

Conclusion: Initial WM alterations and reduced cognitive performance following chemotherapy-treatment were found to recover in a group of young breast cancer survivors three to four years after treatment.
Lithium prevents irradiation-induced brain injury and long term cognitive dysfunction in the young rat

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Background: There is growing evidence that lithium (Li) is protective in a variety of brain injury paradigms. Cranial radiotherapy in children usually results in cognitive as well as hypothalamic/pituitary dysfunction.

Objective: Our aim was to investigate the effects of lithium treatment on cognitive and endocrine function in the juvenile brain after irradiation.

Design/Methods: Male Wistar rats were injected with 2 mmol/kg LiCl i.p. on postnatal day 7 (P7) and additional lithium injections, 1 mmol/kg, were administered at 24 h intervals for up to 14 days (until P20). On P11 the whole brain received a single IR dose of 6 Gy. Blood samples were collected from the tail vein 1, 3, and 5 weeks after IR.

Results: Irradiation-induced progenitor cell death in the subgranular zone of the hippocampus was reduced by lithium treatment. Neurogenesis was reduced by irradiation but was partly rescued by lithium. Inflammation in the hippocampus at 6 h after irradiation was reduced by lithium. Body growth was reduced by irradiation, but not by lithium treatment. Thyroid-stimulating hormone and growth hormone levels were decreased in irradiated rats but not in rats treated with lithium. Motor hyperactivity and anxiety-like behavior, as well as cognitive impairment after irradiation were normalized by lithium.

Conclusion: Lithium can be safely administered to prevent both short-term and long-term damage to the immature brain caused by ionizing radiation.
Uric Acid, Chronic Morbidities and Neurocognitive Impairment in Long-term Survivors of Childhood Acute Lymphoblastic Leukemia (ALL)

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Purpose: Hyperuricemia is implicated in cardiovascular and cerebrovascular diseases. This study evaluates the association between mild elevations in uric acid (UA) during adolescence, and cardiovascular health and neurocognitive function in long-term survivors of childhood ALL treated with chemotherapy only.

Methods: 226 ALL survivors (48% male, mean[SD] age 25.4[4.2] years, 18.1[4.4] years post-diagnosis) completed comprehensive neurocognitive testing and systematic clinical assessment of cardiovascular health (hypertension, dyslipidemia, abdominal obesity, hyperglycemia, overall metabolic syndrome). UA measurements during adolescence, conducted 12.3[4.0] years before neurocognitive testing, were abstracted through chart review. Survivors were categorized into a “high UA group” if their prior levels fell within the highest quartile of age- and gender-based ranking within the cohort. Chi-square and Mann-Whitney U tests were used to evaluate associations among UA, cardiovascular risk factors and age-adjusted neurocognitive standardized Z-scores.

Results: Compared to population norms, survivors demonstrated lower performance on focused attention (mean[SD] Z-score -0.22[1.22], p=0.007), motor (-1.03[1.36], p<0.0001) and visual processing speed (-0.15[0.97], p=0.021) and executive functions (p's<0.001). Cardiovascular problems were prevalent among survivors (17% to 46%). Survivors with high UA during adolescence were more likely than those with low UA, to have hypertension (45% vs 26.5%, p=0.0063), abdominal obesity (40% vs 21.5%, p=0.0095) and dyslipidemia (58% vs 41%, p=0.025) as adults. Motor processing speed was slower in survivors with dyslipidemia (p=0.041) and abdominal obesity (p=0.03), compared to those without. Visual-motor processing speed was slower for those with abdominal obesity (p=0.06). Poorer attention was marginally associated with hypertension (p=0.056). Cognitive performance was not related to hyperglycemia or metabolic syndrome.

Conclusion: In adult survivors of ALL, relative elevation of UA during adolescence was predictive of future cardiovascular health, which was associated with slower processing speed and poorer attention. Future studies should prospectively evaluate the mediating role of chronic cardiovascular health conditions between elevated UA and subsequent neurocognitive impairment.
Alterations in Brain Structure and Function in Patients with Ovarian Cancer treated with First-Line Chemotherapy

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Purpose: Women diagnosed with ovarian cancer often undergo chemotherapy involving multiple agents. However, little is known about the possible neurotoxicity associated with chemotherapy in survivors of this rare disease. The goal of this study was to assess brain structure and function and neurocognitive abilities in patients with ovarian cancer following first-line chemotherapy.

Methods: Eighteen patients with ovarian, peritoneal and fallopian tube cancer and eighteen healthy controls (HC) matched for age and education participated in the study. The patients were evaluated 1-4 months following completion of first-line taxane and platinum-based chemotherapy. All study participants underwent structural and functional magnetic resonance imaging (MRI), and completed a neurocognitive test battery including measures of attention, executive functions and memory. Neuroimaging assessments included voxel-based morphometry (VBM) for measuring gray matter volume, and functional MRI (fMRI) during the N-back working memory task.

Results: The results of VBM showed that patients had significantly reduced gray matter volume compared to HC in the left supramarginal gyrus and left inferior parietal lobule, and in the right middle and superior frontal gyrus (p<0.005, uncorrected, cluster extent=300). fMRI results indicated significantly decreased activation in patients relative to HC in the left middle frontal gyrus and left inferior parietal lobule during the N-back task (1/2/3-back > 0-back; p<0.005, uncorrected, cluster extent ≥15). There were no statistically significant differences between patients and HC on the neurocognitive tests.

Conclusion: This is the first study to show structural and functional alterations in patients with ovarian cancer treated with first-line taxane and platinum-based chemotherapy. These findings are congruent with prior studies involving women with breast cancer, and provide additional evidence of morphological and functional changes involving frontal and parietal regions following chemotherapy. Prospective studies are needed to further characterize the mechanisms underlying the contribution of disease and chemotherapy to cognitive functions in this clinical population.
Chemotherapy-induced Structural Brain Changes in Patients Undergoing Autologous Stem Cell Transplantation for Lymphoma

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Background: Autologous stem cell transplantation (ASCT) involving the use of high-dose chemotherapy is used as consolidative therapy in patients with central nervous system (CNS) lymphoma. Chemotherapy can be associated with significant neurotoxicity, however, the underlying mechanisms of neurotoxicity remain unclear.

Methods: We reviewed imaging and clinical records of 25 patients who underwent ASCT between 2010 and 2013 for lymphoma with recurrence within the CNS. All patients underwent magnetic resonance imaging (MRI) prior to and after ASCT. We used T1-post contrast weighted and/or MEMPRAGE images to measure ventricular volume, and diffusion tensor imaging (DTI) to measure fractional anisotropy (FA) over time.

Results: Longitudinal imaging revealed significant mean enlargement in the size of the ventricular volume at 3 and 12 months post-transplant, with a mean expansion of 10% and 18%, respectively. This change was significantly greater than the expected 3% percent change over the course of one year reported to occur with normal aging (n = 19, p < 0.01). FA of the temporal lobe decreased by a mean of 9% (n= 23) from baseline to 3 months post-transplant, though this result did not achieve statistical significance (p = 0.057). There was no significant difference at the 12-month time point for this measure. The FA of the body of the corpus callosum decreased by a mean of 16% and 13% at 3 and 12 months post-transplant, respectively (n =6; p= 0.03).

Conclusion: Our findings suggest that patients undergoing high-dose chemotherapy in combination with ASCT are at significant risk for structural brain changes, including brain atrophy and white matter loss. This data contributes to our understanding of the mechanisms underlying neurotoxicity associated with high-dose chemotherapy and ASCT.
Neurocognitive performance and variability in young adults newly diagnosed with cancer: comparisons with population norms and healthy controls

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Purpose: Cancer is associated with neurocognitive sequelae and changes in brain imaging prior to systemic treatment in older adults. In younger adults (YA; age 18-39 years), cancer disrupts acquisition of developmental milestones including education and occupational attainment, but effects on cognition are unknown. In this study, we characterize neurocognitive functions and psychological distress in YA prior to chemotherapy.

Methods: YA with cancers (YAC, n=86; lymphoma, breast, gynecology, gastrointestinal, genitourinary, sarcoma) and healthy YA (HYA, n=54) completed a 2-hr battery of standardized neurocognitive tests and validated questionnaires. YAC were assessed within 3 months of diagnosis, prior to chemotherapy. Test scores were converted to z-scores based on published norms, and grouped into memory, attention, processing speed, and executive function domains.

Results: There were no group differences in neurocognitive domains (all p-values > .1) or number of impaired test scores (defined as z < -1). However, both groups had poorer memory compared to published norms (1-sample t-tests: YAC p=.001; HYA p=.023). Intra-individual test score variability (i.e., dispersion) was also evident, and did not differ, between groups (mean individual difference between lowest and highest z-score: YAC: M=3.24, SD=.84, HYA: M=3.45, SD=1.48). There was no evidence of poor motivation on embedded performance validity tests. YAC were more distressed than HYA (Somatization, p=.004; Anxiety, p=.003). Somatization was correlated with processing speed (ρ =-.26, p=.02) in YAC only.

Conclusions: Prior to treatment, neurocognitive functions of YAC were not different from HYA, suggesting that cancer itself is not a neurocognitive risk factor in YA. Variability in test performance evident in both groups is consistent with previous reports of “abnormal” neuropsychological scores in healthy adults. Whether dispersion changes during chemotherapy remains to be explored. We continue to follow this cohort to document the relation between cognition, distress, and psychosocial development over the course of cancer treatment.
In Vivo Brain Amyloid and Tau in Breast Cancer Survivors

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Purpose: Because cancer treatment may result in accelerated cognitive decline, an aging model may be a useful tool for understanding cognitive decline in cancer patients (Ahles et al., 2012). Beta-amyloid protein deposition in the brain correlates with age and, along with tau protein, is abnormally elevated in Alzheimer’s disease (AD). Positron emission tomography (PET) imaging using 2-{1-{6-[2-[F-18]fluoroethyl](methyl)amino}-2-naphthyl}ethylidene)malononitrile (FDDNP) measures brain amyloid and tau protein in vivo. Higher FDDNP-binding is associated with poorer memory and is higher in AD patients compared with healthy controls (Small et al., 2006). This is the first study to examine brain amyloid and tau deposition using FDDNP-PET in breast cancer survivors (BCS).

Methods: We compared 10 female long-term BCS (X age=61.0, SD=5.9) (Ganz et al., 2012) who underwent FDDNP-PET imaging and memory testing to 10 age-and-sex-matched cancer-free normal controls (NCs; X age=62.3, SD=8.7). Temporal, frontal, and parietal regions of interest were drawn on scans; nonparametric Wilcoxon tests were used to compare groups on FDDNP-binding and learning and delayed recall scores. Spearman rank correlations were used to explore relationships between regional FDDNP-binding and memory scores within each group.

Results: BCS had lower learning scores (p<.03), and higher FDDNP-binding in medial temporal (p<.05) and frontal (p<.005) regions compared to NCs. For NCs, higher medial temporal FDDNP-binding was correlated with poorer learning and delayed recall (r range= -.68 - -.70, p<.03). For BCS, higher FDDNP-binding in frontal, parietal, and medial temporal regions was correlated with better delayed recall (r range=.63 - .70; p value range=.03 - .05).

Conclusions: FDDNP-binding was elevated regionally, and learning was worse in BCS compared to NCs. The positive correlation between FDDNP-binding and delayed recall in BCS could be due to the effects of moderating variables related to neuronal plasticity. These intriguing findings warrant further study with a larger sample.
Online assessment of cognitive problems associated with cancer and cancer treatment: Validation of a new self-administered online neuropsychological test battery

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Objective: Online tests often allow for more efficient cognitive data collection compared to traditional neuropsychological assessments, but thus far their psychometric properties have been poorly studied. The primary focus of the current study was to assess the usability and validity of a new self-administered online neuropsychological test battery.

Methods: We developed an online test battery based on seven traditional neuropsychological tests. Usability was assessed through participant feedback from questionnaires and technical reports. Convergent validity was assessed using Spearman correlations to compare online scores to scores from equivalent traditional face-to-face and computer-assisted tests. A total of 201 (112 female) cancer patients (mean age 53.02 years) completed both an unsupervised online assessment and a supervised traditional assessment.

Results: Technical problems occurred in 3.5% of the online assessments. The larger part of the participants (67.8%) favored an online home assessment. Comparing online and traditional test scores, we observed moderate to strong convergent validity (r= .37 to .70). Correlations were influenced – as expected – by the similarity between the traditional test and its online counterpart.

Conclusion: Cancer patients were able to successfully complete our online neuropsychological test battery in an unmonitored setting. Validity results indicate that most of the tests validly measured cognition. Data on test-retest reliability and criterion validity are currently analyzed to comprehensively identify psychometric properties. Furthermore, norms scores are generated to interpret individual test scores. If adequately reliable, the online test battery would allow us to gather large-scale research data on cancer patients’ cognitive functioning in the near future.
Vasculature and white matter follow-up after brain radiotherapy: preclinical study using multiparametric imaging and immunohistochemistry


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Introduction: Patients treated with brain radiotherapy often develop cognitive deficits that are presumed to result from cerebral vascular alterations leading potentially to white matter (WM) disturbances.

Objectives: Since the underlying neurobiological mechanisms in patients treated with radiotherapy remain unclear, experimental studies in animal models and validation of advanced imaging technics enabling to follow the vasculature and WM changes in response to radiotherapy remain primordial.

Materials & Methods: Rat brains were irradiated with 3 fractions of 10Gy, a protocol known to induce cognitive deficits. Before and 3 days after radiation, MRI was performed to characterize the cerebrovascular permeability, perfusion (blood flow and volume) as well as vasoreactivity after gaseous stimulations (CO2 5%). Analyses of WM fibers were performed with DTI-MRI and subsequent tractography reconstruction, weekly until 2 months post-radiation. Data were treated on ImageJ, DSIStudio (WM reconstruction) and statistical analyses with JMP Software. Moreover, immunohistochemical analyses were performed before, 3 and 10 days after radiotherapy.

Results: In response to fractionated radiotherapy, MRI analyses showed a decrease in cerebral blood volume and perfusion, in accordance with immunohistology data showing a vascular rarefaction associated with hypertrophic large vessels. Paradoxically, these damaged vessels were more reactive than those present in non-irradiated brains. Since the enlarged vessels were particularly covered with astrocytic processes, we speculated that astrocytes could contribute to maintain the vascular tonus as well as to preserve the blood brain barrier integrity. Indeed, any perturbation of vessel permeability was detected by MRI following this radiotherapy protocol. The vascular changes were also accompanied by a radio-induced demyelination as shown by the immunohistochemical study.

Conclusion: Our results support that brain vessels might be the main cellular basis of the relationship between cognitive deficits and radiotherapy but also suggest that astrocytes, which participate to the neuro-glia-vascular unit, could be a crucial interface to compensate radio-induced damage.
Grey matter volume prior and after chemotherapy for breast cancer and correlations with cognitive scores

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Purpose: Reductions in grey matter density, particularly in temporal and prefrontal regions, have been demonstrated just after chemotherapy for breast cancer and more slightly one year later at least. Even prior the start of adjuvant treatment, studies have shown lower than expected cognitive scores, however the few baseline MRI studies have generally not shown significant grey matter decreases between patients and controls. The aim of our prospective, longitudinal study was to measure, in breast cancer patients before and after adjuvant chemotherapy, cognitive performances and structural brain volume, using correlations to take into account the potential effects of confounding variables.

Methods: Twenty-five women with breast cancer and 29 matched healthy controls completed MRI scans (VBM), neuropsychological tests and questionnaires (episodic memory, executive functions, self-representation, anxiety-depression…) before adjuvant chemotherapy (baseline), one month after chemotherapy completion, and one year after (or similar intervals for controls). Data presented concern the two first assessments.

Results: Before chemotherapy, patients showed lower scores in episodic memory and executive functions compared to controls (p<.03). When anxiety was introduced as a covariate, decreases of grey matter in middle frontal and temporal gyri, and temporal pole were observed in patients (punc<.001, k>80), but no significant correlations were found between cognitive and volumetric measurements. One month after chemotherapy, a cognitive decline was not shown in patients, but an extension of the lower grey matter density observed before chemotherapy and the emergence of decreases in new areas (cuneus, lingual gyrus, cerebellum) were revealed.

Conclusion: These preliminary results suggest that, before the start of chemotherapy and independently of anxiety level, mechanisms related to the cancer disease process and/or to the surgery impact on brain structure and cognitive functioning. The chemotherapy appears to increase grey matter volume reductions.
Rethinking attentional deficits in cancer related cognitive impairment

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Purpose: Many chemotherapy patients report cognitive deficits persisting long after the end of treatment (“chemobrain”), but neuropsychological testing has yielded conflicting results. These inconclusive results can be attributed to a number of obstacles, including the sensitivity of neuropsychological tests, inconsistent definitions of “impairment”, and lack of pre-diagnosis assessments. A previously unidentified problem is poor assignment of measures to domains. I illustrate this problem using the domain of attention. Many purported measures of attention, such as memory span or arithmetic tests, have little to do with attention as cognitive scientists understand it. Conversely, tests with some validity as attention measures (e.g., letter cancellation, Stroop, Trails B) are sometimes excluded from the domain. Furthermore, functionally and neurally distinct aspects of attention, such as selective and sustained attention, are averaged together.

Methods: A meta-analysis using data from 17 studies (comprising 682 patients and 689 controls). I identified 10 tests with face validity as measures of selective attention, further subdivided into visual search (e.g., Letter Cancellation) and response selection (i.e., Stroop).

Results: Both visual search ($g = -0.08$, 95% CI $(-0.139, -0.0159)$) and response selection ($g = -0.09$, 95% CI $(-0.218, 0.0429)$) measures showed impairment, though the effect sizes were small and only the search results were statistically significant.

Conclusion: While the results suggest that chemotherapy may be associated with impairments in visual search and response selection, this should only be taken as a starting point for future research. We need measures designed to be sensitive to specific aspects of attention. More broadly, we need a strategic shift in the way we measure cognition in cancer patients. Much progress has been made recently in fields such as schizophrenia by testing patients in way that makes direct connections to contemporary theories from cognitive neuroscience. Cancer and cognition research should follow suit.
Neurocognitive impairment, behavioral problems, and family strain in long-term survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy only

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Purpose: Although modern anticancer therapies have improved survival for childhood ALL, neurocognitive, behavioral, and family problems are often observed in long-term survivors. This study aimed to examine the impact of neurocognitive and behavioral problems on family strain in childhood ALL survivors.

Methods: 213 survivors (mean age: 14.8 years; mean time since diagnosis: 7.7 years) treated with a chemotherapy-only protocol were evaluated at >5 years post-diagnosis. Neurocognitive testing assessed executive function (Delis-Kaplan Executive Function System), working memory (Wechsler Intelligence Scale for Children-IV [WISC-IV]), processing speed (WISC-IV), visual-spatial abilities (Wechsler Abbreviated Scale of Intelligence), and sustained attention (Conners CPT-II). Behavioral problems (Behavioral Assessment System for Children-2: externalizing, internalizing, attention, adaptabilities) and family strain (Impact on Family scale) were reported by parents. Associations of neurocognitive impairment (1SD below age-adjusted norm) with behavioral problems were tested using t-tests. The extent to which neurocognitive impairment and behavioral problems affected family strain was tested using multivariable regression models adjusting for age at diagnosis, sex, and treatment risk status.

Results: Neurocognitive impairment was identified in 18-41% of the survivors (18% working memory; 41% processing speed). Survivors with impaired executive function, processing speed, and visual-spatial abilities had greater externalizing, internalizing, attention, and adaptive behavioral problems (p’s<0.05). Individual behavioral problems did not differ among survivors with or without impaired working memory and sustained attention. In multivariable regression analyses, impairment in any neurocognitive domain independently contributed to increased family strain (p’s<0.05). In contrast, externalizing, internalizing, and adaptive behavioral problems were only associated with increased family strain (p<0.05) in the models that included impaired executive function and visual-spatial abilities.

Conclusion: Impaired executive function, processing speed, and visual-spatial abilities are associated with behavioral problems in childhood ALL survivors. The effects of neurocognitive impairment, especially executive function and visual-spatial abilities, on family strain seem stronger than that of behavioral problems.
Ibudilast prevents and reverses oxaliplatin-induced cognitive impairments in laboratory rats

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Background: Oxaliplatin, a platinum compound used to treat solid tumours, produces temporary memory and learning deficits in laboratory rats if treated once, and permanent impairments if treated chronically. Oxaliplatin treatment is accompanied by abnormal microglia in the central nervous system. Ibudilast, phosphodiesterase inhibitor with a long history of clinical use for asthma in Japan, which has recently been shown to reduce microglial activation. Given the role of abnormal microglia activity in a range of cognitive disorders, we hypothesised that ibudilast would reduce oxaliplatin-induced cognitive impairments.

Method: Rats were treated with either a single dose of oxaliplatin (10 mg/kg i.p.) or saline (Acute treatment model: Experiments 1 & 2), or three doses of oxaliplatin (6 mg/kg/week i.p.) or saline (Chronic treatment model: Experiment 3), and tested for memory in the novel object and novel location tests 9 days after the last injection. Rats were treated with ibudilast (7.5 mg/kg i.p.) or vehicle either 30-min prior to oxaliplatin (Experiment 1), or 2 hours prior to memory testing (Experiments 2 & 3).

Results: Ibudilast injected prior to oxaliplatin treatment prevented the development of impairments in the object and location recognition tests (Experiment 1). Ibudilast injected prior to object recognition testing reduced impairments that persisted for at least 3 days in the acute oxaliplatin treatment model (Experiment 2), and for at least 2 weeks in the chronic model (Experiment 3).

Conclusion: Ibudilast appears to have a long-acting ability to prevent and reverse cognitive impairments caused by oxaliplatin treatment. Importantly, ibudilast has proven clinical safety, and has the potential to be moved into clinical trials quickly. However, it remains to be assessed if ibudilast might have important interactions with tumours.
Determining level, direction, and rate of change of attentional function in women with breast cancer receiving chemotherapy, a pilot study

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Purpose: To describe how levels of attentional function (AF), fatigue, and depression change over time and whether levels and trajectories of fatigue and depression predict levels and trajectories of AF in women with early stage breast cancer being treated with chemotherapy.

Methods: In a secondary analysis of data from two prospective longitudinal studies (N=24; N=44), AF was measured with the Attentional Function Index, depression with Center for Epidemiologic Studies-Depression and fatigue with Patient-Reported Outcomes Measurement Information System-Fatigue and Schwartz Cancer Fatigue Scale, at clinically significant times. Longitudinal multilevel modeling (MLM) was used to accommodate exploration of time-varying covariates in a model with a time-varying primary outcome variable (AF).

Results: In an MLM for AF a fixed quadratic model fit Sample 1 data better than a linear fixed model and adding a random component did not improve the fit ($X^2(2, N=24)=5.15, p=.0754$). In Sample 2 likelihood ratio model testing results were not significant but a fixed quadratic model provided the best fit to the data ($X^2(2, N=44)=3.24, p=.1983$), confirmed with information criteria. Depression and fatigue were fit to fixed quadratic models. Adding depression as a time-varying covariate to a model with AF resulted in a significant coefficient for depression (Sample 1, $\beta=-.76, SE=.19, z=-3.87, p<.001$ and Sample 2, $\beta=-.91, SE=.13, z=-6.96, p<.001$).

Conclusions: These results suggest that the trajectories of AF, depression, and fatigue in a population of women with breast cancer receiving chemotherapy each exhibit a quadratic curve such that after start of chemotherapy each symptom worsens until mid-treatment and starts to improve before the end of treatment, returning to pre-treatment levels by 3-6 months after the end of treatment. In models with AF, trajectories of fatigue and depression predict the trajectory of AF such that a worsening of fatigue or depression predicts a worsening of AF.
Longitudinal Changes in Brain Network Local Efficiency and Verbal Memory Performance Following Breast Cancer Chemotherapy

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Purpose: We previously demonstrated altered structural and functional connectomes in chemotherapy treated, long-term breast cancer survivors compared to healthy controls. Here we extend our research by examining longitudinal changes in connectome organization in chemotherapy treated (C+) compared to non-chemotherapy treated (C-) newly diagnosed, primary breast cancer patients.

Methods: We obtained volumetric MRI and cognitive testing data prior to and 1 month following chemotherapy from 10 C+ patients (mean age = 67 SD = 7 years). Thirteen matched, C- patients were assessed at yoked intervals. We constructed a gray matter structural correlation network for each group and measured group differences in the slopes of global and local network efficiencies using permutation analysis. Group differences in the slopes of cognitive test results were evaluated using general linear models and reliable change index (RCI).

Results: There were no significant group differences in connectome efficiencies at baseline. Change in global efficiency over time was not different between the groups (p = 0.25). However, the C+ group demonstrated diffusely altered local efficiency after chemotherapy compared to C-, including frontal, parietal, temporal, occipital, thalamic and hippocampal regions (p < 0.05). A profile of both increased and decreased local efficiencies was observed. There were no significant group differences on any cognitive test at baseline. The mean slope for each cognitive test did not differ significantly between groups. However, RCI analysis indicated a higher proportion of patients in the C+ group who declined on HVLT-R Total Recall compared to C- (p = 0.05).

Conclusion: These findings provide confirmatory evidence of our previous cross-sectional studies demonstrating that breast cancer chemotherapy results in significant connectome alterations. Diffuse changes in local processing efficiency were noted in the context of reduced verbal learning and memory performance. Replication with individual level connectomes is required to determine associations between local efficiency and cognitive decline.
Mouse connectome for preclinical translational research in cognition and cancer

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Purpose: The connectome is a mathematical model of brain network connectivity that represents one of the most advanced methods of evaluating information processing efficiency. We aimed to establish a protocol for constructing and measuring structural and functional connectomes in mice.

Methods: Diffusion tensor imaging (DTI) and resting state fMRI (rsfMRI) were acquired from four C57BL/6 mice at 7T. RsfMRI was obtained during general anesthesia and DTI was obtained after extracting and fixing the brain. Regions of interest (ROIs) were defined from a standardized mouse brain atlas and warped into native space. The number of DTI fiber tracts connecting each pair of ROIs was determined and fMRI time series data were cross-correlated for all ROIs. This resulted in a structural as well as a functional connectivity matrix for each mouse. Graph theory was applied to the connectivity matrices to model the structural and functional connectome separately for each subject as a system of nodes and edges representing regions and their connections, respectively. Connectome properties including small-worldness index were quantified and compared against benchmark networks using permutation testing.

Results: We determined that both functional and structural connectomes consistently demonstrated expected small-world organization (small-world index > 1) across network densities. Small-worldness was also significant in comparison to benchmark networks (p < 0.0001).

Conclusion: We successfully measured structural and functional connectomes in mice. Our results specify further evidence that connectome properties are preserved across species. This work will provide a translational model of brain network topology for evaluation of mechanisms of and interventions for cancer-related cognitive impairment.
A case-control investigation of cardiorespiratory fitness on executive control in a task switching paradigm

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Purpose: Breast cancer treatment is associated with declines in cognitive health. Higher cardiorespiratory fitness (CRF) has been associated with better performance during cognitive tasks involving greater executive control. This study examined associations between CRF and executive control in a task switching paradigm in breast cancer survivors (BCS) and age-matched controls.

Methods: 28 BCS and 29 age-matched women with no previous cancer diagnoses completed a task switching paradigm assessing aspects of executive control. Global and local switch costs for reaction time (ms) and accuracy (%) were computed. Global switch costs reflect selection of the task to be performed next and efficiency of maintaining multiple task sets in working memory. Local switch costs reflect the effectiveness of executive control processes responsible for activation of the currently relevant task set and deactivation of the relevant task set on the previous trial. CRF was measured via a submaximal exercise test, from which an estimated V02peak was derived. BCS and age-matched controls were stratified by fitness level (higher and lower fit) and associations between CRF and executive control were investigated by group.

Results: Lower fit BCS had poorer CRF (23.5 ml.kg.min) than higher fit controls (33.9 ml.kg.min; p<.001, d=1.93). CRF was not related to global switch cost reaction time (p=.253) or response accuracy (p=.173). However, lower fit BCS had greater local switch costs (156.1 ms) reflected by longer reaction times from non-switch to switch trials versus higher fit controls (81.6 ms; p=.001, d=1.22). Lower fit BCS were also less accurate in this switch condition (-12.9%) than higher fit controls (-4.1%; p=.003, d=0.92).

Conclusion: Findings suggest CRF may moderate differences in executive control between BCS and age-matched women. These differences were associated with local but not global switch costs, suggesting CRF-related differences in cognitive performance emerged during task conditions requiring facilitation and inhibition.
Ambient Temperature Influences the Neural Benefits of Exercise

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Purpose: Many of the neural benefits of exercise require weeks to manifest. It would be useful to accelerate onset of exercise-driven plastic changes, such as increased hippocampal neurogenesis. Exercise represents a significant challenge to the brain because it produces heat, but brain temperature does not rise during exercise in the cold. This study tested the hypothesis that exercise in cold ambient temperature would stimulate hippocampal neurogenesis more than exercise in room or hot conditions.

Methods: Adult female rats had exercise access 2 hours per day for 5 days at either room (20°C), cold (4.5°C) or hot (37.5°C) temperature. To label dividing hippocampal precursor cells, animals received daily injections of BrdU. Brains were immunohistochemically processed for dividing cells (Ki67+), surviving cells (BrdU+) and new neurons (doublecortin, DCX) in the hippocampal dentate gyrus.

Results: Animals exercising at room temperature ran significantly farther than animals exercising in cold or hot conditions (room 1490 ± 400 meters; cold 440 ± 102 meters; hot 291 ± 56 meters). We therefore analyzed the number of Ki67+, BrdU+ and DCX+ cells normalized for shortest distance run. Contrary to our hypothesis, exercise in either cold or hot conditions generated significantly more Ki67+, BrdU+ and DCX+ cells compared to exercise at room temperature.

Conclusion: A limited amount of running in either cold or hot ambient conditions generates more new cells than a much greater distance run at room temperature. Taken together, our results suggest a simple means by which to augment exercise effects, yet minimize exercise time.
Brain activity changes in breast cancer patients depend on treatment type and cognitive domain

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Purpose: Adjuvant chemotherapy for breast cancer (BC) is associated with alterations in brain activation during cognitive task performance. Previous prospective fMRI studies administered a single cognitive task. Here, we employed two fMRI tasks assessing executive function and memory to allow a direct comparison of changes per cognitive domain. Three groups were compared according to ICCTF recommendations.

Methods: The Tower of London (executive functioning) and the paired associates task (episodic memory) were administered in between breast surgery and further treatment (T0) and 6 months after completion of adjuvant chemotherapy (T1) or matched intervals. fMRI analyses were performed within SPM8 using a flexible factorial design for longitudinal data

Results: We collected data at T0 and T1 for 28 BC patients exposed to antracycline-based chemotherapy (ChT+) plus or minus endocrine therapy, 24 unexposed patients (ChT-) and 32 no cancer controls (NC). Few effects were found for the memory task. In contrast, during the executive functioning task, ChT+ showed an increase in activation in parietal brain regions compared to T0 (p<.05 corrected). This hyperactivation was accompanied by worse physical functioning, greater fatigue, and more cognitive complaints compared to the baseline measurement. In the ChT- group, a different pattern of results emerged with aberrant levels of brain activity and quality of life at T0 that generally normalized at T1. For the NC, activation levels remained stable over time.

Conclusion: Hyperactivation after adjuvant chemotherapy plus or minus endocrine therapy possibly reflects compensatory processes to maintain adequate levels of task performance. This over-recruitment of brain regions depends on the probed cognitive domain and might be a response to decreased neural integrity after systemic treatment including chemotherapy. It cannot be excluded that antiestrogen therapy contributes to these effects. Overall these results suggest different neurobehavioral trajectories in breast cancer patients depending on treatment type.
Verbal Memory Deficits Associated with Chemotherapy for Breast Cancer

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Purpose: To review evidence of, and measurements for, verbal memory deficits associated with chemotherapy for breast cancer in women.

Methods: Data Sources: Searches of 5 databases (PubMed, Embase, Cochrane CENTRAL, PsycINFO, CINAHL) with no date or language restrictions identified 1,701 unique results. Search terms included breast cancer, chemotherapy, chemobrain, chemofog, and terms on cognition, memory, and language deficits.

Study Selection: Included studies: (1) described verbal memory deficits in women undergoing (or who had undergone) chemotherapy for breast cancer (2) provided objective measurements of cognition or language, and (3) were published in peer-reviewed journals.

Data Extraction: Data were extracted according to Cochrane recommendations. Quality assessment of all 68 eligible studies was performed using adapted PEDro & JADAD criteria. Screening, data extraction, and quality assessment reliability was performed.

Results: Across studies, comparisons of varying breast cancer treatment groups at varying time points (and group by time interactions) revealed that verbal memory deficits are indeed a pervasive problem for this population of women who have undergone chemotherapy. Further, a review of all of the objective neuropsychological measures that were used to test verbal memory revealed that the RAVLT seems most sensitive to this disorder.

Conclusions: This study confirmed that a subset of women who undergo chemotherapy treatment for breast cancer experience persistent verbal memory deficits. Dysfunctional word retrieval critically affects the ability to establish collaborative clinical relationships, and to maintain usual communicative participation in occupational, familial, and social spheres. In order to address this problem, verbal memory deficits must be officially recognized as a possible after-effect of cancer treatment, and, must be properly diagnosed using appropriate test instruments. Future research should focus on identifying and confirming the sensitivity of verbal memory test instruments for this population, and on developing treatments for this disorder.
Comparison of the sensitivity of a traditional neuropsychological battery and a brief computerized battery (CNS-VS) in detecting chemotherapy-related cognitive decline in breast cancer patients

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Purpose: Cognitive complaints are common among cancer patients but the time and resources required for traditional neuropsychological testing is a barrier to accessing assessment and treatment. We sought to determine if a brief computerized battery with potential for self-administration and automatic scoring would be sufficiently sensitive to detect subtle treatment-related cognitive changes in breast cancer patients.

Methods: Data for the current analyses were collected as part of a prospective, longitudinal study in which 60 breast cancer patients were assessed prior to chemotherapy and following each chemotherapy cycle (up to 7 times). Sixty healthy matched controls were assessed at equivalent intervals. A battery of traditional neuropsychological tests, as well as CNS-Vital Signs, a 30-minute computerized cognitive test battery, were administered at each test session. A cognitive summary score was derived from each battery by standardizing scores on the constituent tests to the control group at each time point and then averaging the standardized scores. Multi-level modeling was used to evaluate changes in the computerized and traditional cognitive summary scores over the course of chemotherapy in the breast cancer patients.

Results: Both the traditional and computerized cognitive summary scores declined significantly over test sessions (p < .001 in both cases). The traditional battery was more sensitive to cognitive decline (test session accounted for 29% of the variance in cognitive performance when using the traditional tests versus 14% when using the computerized measures). Combining the computerized and traditional measures did not increase sensitivity beyond the traditional measures alone.

Conclusions: CNS-VS, a brief, self-administered computerized cognitive test battery, is sensitive to subtle cancer-related cognitive impairment and may be a practical alternative to traditional neuropsychological testing for routine clinical screening and for clinical drug trials.
Assessment of neurocognitive impairments in adjuvant and neo-adjuvant chemotherapy: the role of chemobrain in patients with early stage breast cancer

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Purpose: Neurocognitive decline in oncologic patients treated with chemotherapy (Chemobrain) is a known issue in medical practice. Our aim is to assess the effects of chemotherapy on neurocognitive functions, in patients with early stage breast cancer, before and after the neo-adjuvant or adjuvant treatment, and in a control group with no chemotherapy treatment. If the hypothesis that the patients suffer from neurocognitive impairments related to chemotherapy will be confirmed, this would imply the possibility of an early neuropsychological rehabilitation since the first diagnosis, to prevent the worsening of the quality of life and to avoid the use of additional medications to regulate for example the severity of fatigue and the mood.

Methods: In our on-going study the aim is to enroll 80 patients with early stage breast cancer. For each patient we administer MMSE, part of the Cogstate neurocognitive battery, TMT-A, TMT-B and COWA test. Patients are also asked to complete EORTC QLQ-C30 and QLQ-BR23, MDASI questionnaire and the HAD scale. Each administration is performed during the week before the first chemotherapy treatment in the experimental group or during the first oncological visit in the control group, at months 6, and finally one year after.

Results: We expect our patients to show a variable degree of worsening in neurocognitive functions during the chemotherapy, and a consequent improving months after the treatment’s withdrawal. We suspect that at the first tests’ administration, some variables such as reactive low mood and maybe the lack of experience with this kind of tests could reduce the patients’ performance. We will present our preliminary results at the 5th Biennial ICCTF Meeting.

Conclusion: The assessment of neurocognitive functions in oncology patients is important to establish possible impairments related to the chemotherapy treatments making feasible early rehabilitation strategies. Imaging techniques might be useful in improving impairment detection to be developed in further studies.
Lateral prefrontal cortex resting-state connectivity in breast cancer survivors and healthy controls

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Chemotherapy-induced cognitive change has been shown to be associated with structural and functional alterations in wide-ranging cortical and subcortical areas in survivors of breast cancer. Previous work has identified structural and functional changes in dorsolateral prefrontal cortex specifically. Given these alterations, functional connectivity of the prefrontal cortex with other brain regions may be expected to be disrupted. The present cross-sectional study used resting-state functional MRI (rs-fMRI) to examine differences in functional connectivity between 13 breast cancer survivors, approximately one-month post chemotherapy treatment, and 11 healthy age-matched controls. Participants underwent a resting state scan of 5 minutes duration while instructed to lie in the scanner with eyes closed, while remaining unfocused on any particular mental content. Functional connectivity analyses were performed using the CONN toolbox. To define lateral prefrontal connectivity, bilateral middle frontal gyrus (MFG) was identified as the seed region of interest. Within groups, a correlation map was generated for each participant between the MFG seed and the whole brain in a voxel-wise manner. Connectivity maps of the MFG were compared to identify regions with differential connectivity between groups. We report differences in connectivity of the lateral prefrontal cortex as a marker of cognitive alteration among chemotherapy-treated breast cancer survivors. Because rs-fMRI is task-independent, alterations of neural network activity suggest disruptions to the communication of interconnected regions that would be expected to disrupt cognitive tasks that rely on these regions during recruitment. Results from this study will contribute a better understanding of the pervasive neural changes that underlie chemotherapy-induced cognitive change.
Functional near-infrared spectroscopy (fNIRS)-based correlates of prefrontal cortical dynamics during a working memory task in adult breast cancer patients

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Introduction: Cancer patients/survivors (>80%) often experienced memory difficulties that can deleteriously effect their psychosocial functioning. We examined changes in brain hemodynamics using fNIRS during a working memory task in breast cancer patients.

Methods: We recorded optical brain imaging using a 16-channel continuous-wave fNIRS system at a rate of 2Hz. The international 10-20 electrode placement system was used to ensure accurate/repeatable positioning of a flexible headpiece sensor pad containing 16 optodes of light sources and detectors. The 16-channel fNIRS sensor had 4 light emitting diodes (730nm-850nm wavelengths) and 10 photo detectors, with a temporal resolution of 500 milliseconds per scan with 2.5 cm source-detector separation allowing for approximately 1.25 cm penetration. Cognitive Optical Brain Imaging Studio software was used for data acquisition/visualization. We used HomER software for channel-wise waveform analysis (CWA). We applied General-Linear-Modeling on 567-to-1098 temporal data points from two 56-year-old right-handed (RH) breast cancer patients (with Repeatable Battery for the Assessment of Neuropsychological Status, RBANS<50%ile) and a 48-year-old RH healthy control (HC) female (RBANS=58%ile) to define t-maps of task-stimuli-related hemodynamic changes in dorsolateral prefrontal (DLPFC) and frontopolar (FPC) cortices using NIRS-SPM8.

Results: CWA revealed maximum oxygenated hemoglobin (HbO) in left inferior-FPC (LI-FPC) for the cancer patients, and increased activation (0-Back=low activation to 2-Back=positive activation) in the LI-FPC for the HC. Cancer patients showed sustained/increased activation in left FPC with increased working memory load. Brain activities did not return to baseline for the cancer patients during the 2-Back task, which may be due to possible sustained brain activation between blocks during resting states. We observed an overall ceiling effect with a short period of activation for the 3-Back task.

Discussion: These findings confirmed previous outcomes of fNIRS studies with non-cancer populations, and suggested that optical brain imaging can be used to provide hemodynamic based-biomarkers of memory performance for cancer patients.
Feasibility of Neurocognitive Baseline Assessment using Cogstate During the First Month of Therapy for Childhood Leukemia

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Purpose: Neurocognitive impairment is frequently observed among Acute Lymphoblastic Leukemia (ALL) survivors within the domains of intelligence, attention, processing speed, working memory, and learning. Research implicates central nervous system (CNS)-directed treatments, including intrathecal or high-dose intravenous methotrexate, glucocorticoids and whole brain irradiation. Furthermore, host genetic variation may contribute to differences in susceptibility to chemotherapy. Although neurocognitive functioning among survivors is well described, few have investigated treatment-induced changes in neurocognitive function during the first months of treatment. Additionally, dysfunction during treatment may be preceded by changes in biomarkers measured within cerebrospinal fluid (CSF). Identification of acute declines in cognitive function, as well as predictive genotypes or biomarkers, could guide therapeutic trials of protective interventions. Our primary objective is to document changes in cognitive functioning early in therapy, when an intervention might prevent further decline.

Methods: This study collects CSF while prospectively assessing neurocognitive functioning (working memory, executive function, memory, processing speed, and attention) of ALL patients using the Cogstate computerized battery at five time points during the 2 years of leukemia treatment through the Dana-Farber Cancer Institute/ALL Consortium.

Results: Baseline data collected during the first 3 weeks of induction chemotherapy indicate reliable data as all subjects (N=29) completed Cogstate testing, while performance checks indicate that subjects complied with test requirements. An analysis of subject performance across all 5 tests reveals scores within normal limits (±1sd) at baseline compared with age peers. Preliminary analysis of CSF biomarkers (folate, homocysteine, 8-isoprostane and myelin basic protein) similarly reveals values at baseline within expected normal ranges.

Conclusion: Given the feasibility of assessing cognition during CNS-directed therapy using a brief computerized battery, it might be possible to identify subgroups of ALL patients at increased risk for neurocognitive decline, warranting proactive interventions and targeted support to improve their level of functioning both during treatment and well into survivorship.
Insomnia and subjective cognitive impairments in cancer patients: A prospective analysis

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Purpose: Cognitive functioning complaints are frequent in cancer patients during and after treatment. While cancer treatment (e.g., chemotherapy) appears to have an impact on cognitive functioning, other variables may contribute to these difficulties. Cross-sectional findings suggest a relationship between insomnia and cognitive impairments (Caplette-Gingras et al., 2013). However, to our knowledge, this relationship has never been investigated prospectively.

Methods: 953 patients with mixed cancer sites were recruited at their pre-operative visit. Participants completed a battery of self-report scales, including the Insomnia Severity Scale, the Cognitive Failures Questionnaire (CFQ) and the two cognitive functioning items of the EORTC-QLQ-C30 questionnaire, at baseline, 2, 6, 10, 14 and 18 months later. At each time point, they were also administered a clinical interview to categorize them into insomnia syndrome, insomnia symptoms and good sleepers subgroups.

Results: Patients with an insomnia syndrome at all time points on the interview consistently had significantly more cognitive impairments than those who remained good sleepers. Partial correlations between ISI and cognitive impairment scores, controlling for age, education and menopausal status, were all positive and significant. Cross-lagged correlations of ISI scores with subjective cognitive functioning indices revealed bidirectional significant relationships, with no clear directionality (e.g., previous CFQ -> current ISI: $r = .31$, $p < .001$; previous ISI -> current CFQ: $r = .32$, $p < .001$). Moreover, cross-panel analyses using EQS indicated that, after controlling for autocorrelation, cognitive functioning at each time was slightly more strongly related with insomnia scores at the subsequent time (CFQ $\rightarrow$ ISI: $\beta = .13$; EORTC-concentration $\rightarrow$ ISI: $\beta = .13$; EORTC-memory $\rightarrow$ ISI: $\beta = .15$, all $ps < .001$) than the reverse (ISI $\rightarrow$ CFQ: $\beta = .05$; ISI $\rightarrow$ EORTC-concentration: $\beta = .10$; ISI $\rightarrow$ EORTC-memory: $\beta = .10$, all $ps < .001$).

Conclusion: These results indicate a strong relationship between insomnia and cognitive functioning assessed subjectively. However, the direction of relationships does not support the hypothesis that insomnia is a risk factor for subjectively-assessed cognitive disturbances. Additional prospective studies using objective measures of cognitive functioning and investigating possible mediators of the insomnia-cognitive functioning relationships are needed.
Feasibility of ecological assessments of breast cancer survivors’ cognitive performance and subjective cognitive complaints

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Purpose: Cognitive complaints are common quality of life issues among breast cancer survivors; however there is a discrepancy between the percentage of survivors retrospectively reporting subjective complaints and those meeting criteria for impairment on lab-based neuropsychological tests. One solution is to enhance ecological validity by assessing objective and subjective cognitive performance in daily life. The purpose of this study was to establish feasibility of ecological assessments of cognitive performance among breast cancer survivors. This approach can identify both individual differences (i.e., which survivors experience the most objective and subjective problems) but also identify particular daily contexts (i.e., work/home) and precursors (i.e., fatigue, cancer-related thought) during which performance deficits and subjective complaints are likely.

Methods: Breast cancer survivors who completed chemotherapy treatment 6-12 months prior are recruited from a comprehensive cancer center. Survivors complete standard tests of neuropsychological functioning and retrospective subjective reports, and 14 days of ecological momentary assessment (EMA). Daily cognitive functioning is assessed 5 quasi-random times each day via cognitive tasks administered as ‘brain games’ on smartphones tapping domains of attention, non-verbal memory and processing speed; they also report on current symptoms, emotions, and contexts. Subjective cognitive complaints are reported each evening.

Results: Data collection is currently in progress. To date, two individuals have completed the study. Compliance with the protocol was excellent: survivors completed 96% of mobile brain games (134 observations, with 3 games per observation) and 97% of daily surveys of subjective cognitive complaints (28 evening surveys). EMA and evening assessments were completed in 5 to 6 minutes on average. Participants described the surveys and brain games as interesting.

Conclusion: This innovative approach leverages objective and subjective cognitive assessments in daily life in order to answer important questions in survivorship research: which survivors experience cognitive deficits and when are these deficits most likely to occur.
Brain functional connectivity and lung cancer

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Purpose: Chemotherapy and cancer-related cognitive deficits have been associated with structural and functional neural changes. We explored Resting State Networks (RSN) in a group of Lung Cancer Patients.

Methods: Three matched groups of 15 Lung Cancer Patients following platinum-based Chemotherapy (C+), 15 Lung Cancer Patients before Chemotherapy (C-) and 15 Healthy Controls (HC) were included. Analysis was performed using an Independent Component Analysis. After the identification of RSN, differences between groups were computed. Additionally, multivariate pattern analysis (MPVA) was used to classify groups based on profiles of functional connectivity.

Results: Both cancer groups exhibited a significant higher rate of cognitive impairment (40\% of C+ and 40\% of C) compared to healthy controls (7\%). We found significant differences between groups in four of the RSN identified: Default Mode Network (DMN), Predominantly Left Anterior Temporal network (LAT), Predominantly Right Anterior Temporal network (RAT) and Cerebellum network (Cb). Whereas the DMN showed a lower activation in both lung cancer groups compared to HC (precuneus and middle occipital gyrus bilaterally) and in C+ in comparison of C- (left cuneus), the other three RSN exhibited higher activation in both lung cancer groups compared to HC as well of C+ in comparison of C-.
Specifically, significant differences between lung cancer groups and HC were found in left Inferior Temporal Gyrus, right midbrain and parahippocampal gyrus; and between C+ and C- in right inferior temporal gyrus and middle temporal pole. In addition, there was a higher activation of the C+ group compared to HC in right and left midbrain and of the C- group compared to HC in cerebellum bilaterally. MPVA discriminated significantly and accurately between all groups.

Conclusions: Lung cancer patients prior and following platinum-based chemotherapy treatment exhibit cognitive deficits together with a functional connectivity disruption in DMN in conjunction with bilateral temporal and cerebellar regions.
Functional connectivity changes in attention-related networks of childhood leukemia survivors

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Purpose: High dose methotrexate (MTX) is associated with neurocognitive sequelae in childhood leukemia survivors. Still, the underlying mechanisms remain enigmatic. Altered functional brain connectivity might offer an explanation. Previous research indicated that the default mode network (DMN) and fronto-parietal network (FPN) are involved in cognitive flexibility. The goal of this study was to compare resting state functional connectivity (RSFC) between childhood leukemia survivors and control participants, within and between these networks.

Methods: We acquired Rs-fMRI in survivors (n=35) (x̅=12years [1.5:16yrs] since treatment, no cranial irradiation), and healthy age-matched controls (n=35). RSFC was examined using two analyses. (1) For each network, connectivity (i.e. temporal correlation) matrices were constructed between spherical regions of interest (ROIs), based on earlier MNI coordinates. Unpaired T-tests were used to compare RSFC between patients and controls. (2) Secondly, independent component analysis (ICA) yielded sample-specific DMN and FPN masks. Through dual regression analysis, we assessed RSFC between each network and the rest of the brain. Both analyses were Bonferroni-corrected. Finally, with a regression analysis we linked survivor’s RSFC to subjective cognitive complaints (Cognitive Failure Questionnaire), and objectively measured cognitive flexibility (subtask of the Amsterdam Neuropsychological Tasks) in. Socio-economic status (SES), age and relative MTX-dose were included as covariates.

Results: ROI-based analyses showed differences within the FPN, at uncorrected level. However, these effects disappeared after Bonferroni-correction (p<.05). By contrast, dual regression analysis resulted in a significant lower connectivity in survivors between DMN and the inferior temporal gyrus (ITG), located in the FPN (p<.05). This connectivity correlated significantly with impaired cognitive flexibility (p=.019), but not with subjective complaints (p=.253).

Conclusion: The DMN and ITG, was less functionally connected in childhood leukemia survivors compared to controls, suggesting a modified coherence between the DMN and FPN. Furthermore, this connectivity was related to reduced patient’s cognitive flexibility.
Mouse Cranial Irradiation Employing Conformal Hippocampal Avoidance: A Model for Studying Mitigation Strategies for Cognitive Impairment

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Purpose: To present a cranial irradiation mouse model as a tool to better understand the mechanisms of hippocampal-dependent cognitive decline. This mouse model replicates the results of RTOG 0933, a clinical phase II trial on hippocampal sparing whole-brain radiation therapy (WBRT) in patients with brain metastases.

Methods: Single dose 10 Gy cranial irradiation was administered to 16-week-old female C57BL/6J mice using either WBRT or conformal hippocampal-sparing irradiation (HSI). These animals, and sham-irradiated controls, were then subjected to behavioral cognitive assessment tests. General behavior was assessed using open field, olfactory and elevated plus maze tests. The highly hippocampal-dependent object placement (OP) test (a.k.a. novel object location test) was used to assess spatial memory. An object recognition (OR) test was used to test hippocampal-independent cognitive function. The results were determined based on previously validated pass/fail criteria and treatment groups were analyzed using a likelihood ratio test for $\chi^2$ distributions and pairwise $\chi^2$ comparisons for pairwise differences.

Results: General behavior was not different between groups. Animals exposed to WBRT showed significant deficits compared to sham-irradiated controls in the OP task ($p = 0.039$). In contrast, HSI mice did not perform differently from control mice ($p = 0.956$) and performed significantly better than WBRT mice in the OP task ($p = 0.032$). These results were further supported by immunohistochemical analysis showing less inflammation and more proliferating cells in the HSI group, compared to the WBRT group. No difference between groups was found in the hippocampal-independent OR task ($p = 0.699$).

Conclusion: These results show that hippocampal-dependent spatial memory is impaired after WBRT, but preserved in animals receiving HSI, consistent with the result of RTOG 0933 in humans. This animal model could prove a valuable tool for researchers exploring mechanisms and novel strategies for mitigating cognitive impairment following high dose cranial irradiation.
Patterns of Resting-State EEG associated with Memory Impairment and Depression in Breast Cancer Survivors (BCS)

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Purpose: Self-reported cancer-related cognitive decline (CRCD) in BCS has been found to be variably associated with objective decline and also mood. Resting-state quantitative EEG (qEEG) may be an informative biomarker for studies of mood and cognitive performance in BCS, as well as exploring the “accelerated aging” hypothesis of CRCD.

Methods: We assessed depression severity (Beck Depression Inventory, BDI-II), neuropsychological test performance (Memory domain), and neurophysiologic function (qEEG) in a cross-sectional analysis of 62 BCS (x̄ age = 57.40 ±8.39, x̄ years post-treatment = 4.42 ±0.61). Analyses included: 1) partial correlations controlling for age between qEEG measures (i.e., qEEG cordance, relative anteroposterior (AP) gradient) and memory and depression scores; and 2) ANOVA and Bonferroni-corrected post-hoc tests of qEEG measures among 3 groups: Memory Impaired (M; z < -.50; n=10); Depressed (D; BDI-II ≥14; n=12); or Neither (N; n=40).

Results: Memory domain scores correlated with qEEG relative theta AP gradient (r=.26, p<.05), and with a trend towards prefrontal theta cordance (r=.24, p=.06). BDI-II score correlated with relative theta AP gradient (r=-.30, p=.02), relative delta AP gradient (p=-.251, p=.05), and prefrontal (.45, p<.01) and global (.323, p=.01) alpha cordance. The D group had greater prefrontal alpha cordance and lower anterior delta and theta power vs. N, and greater posterior beta power vs. M and N (p’s<.05). A group difference trend for prefrontal theta cordance showed lower power in the M vs. N group (p=.9).

Conclusions: qEEG measures appear to be differentially sensitive to memory performance and depression symptoms in BCS, and may be useful biomarkers of these factors in CRCD. Our findings are consistent with emerging evidence that higher resting-state theta power may indicate successful cognitive aging (Vlahou et al., 2014), relevant to the “accelerated aging” model of CRCD.
**Longitudinal Changes in Cognitive Function in Patients with Colorectal Carcinoma**

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**Purpose:** Two prior longitudinal studies reached differing conclusions concerning the development of cognitive dysfunction in patients with colorectal carcinoma (CRC) treated with chemotherapy. We examined longitudinal changes in cognitive function and explored potential component processes underlying memory impairment.

**Methods:** Thirty-five patients (M age = 54.3, SD = 10.3; M education = 12.9, SD = 3.0; 71% male; stage IV = 43%) completed a battery of six cognitive tests at baseline and following chemotherapy (M cycles = 6, SD = 3.0; M re-test interval = 2.5 months, SD = 2.9). Changes in cognitive function from baseline were categorized based on the reliable change index (RCI).

**Results:** Decline on at least one test was observed in 63% of patients with 40% showing decline on 2 or more. Decline was most frequent on HVLT-R [Total Recall, 20%; Delayed Recall, 11%; Recognition, 14%] and Grooved Pegboard [Dominant, 29%; Nondominant, 35%]. Patients demonstrating HVLT-R decline had better baseline HVLT-R performances than those that improved. Single trial learning (STL) performance was significantly lower in patients that declined compared to patients that improved (p < .001). Change in STL was associated with change in HVLT-R for the entire sample (r = 0.45 to 0.79, all p < .006). However, STL was not associated with attention (i.e., Digit Span).

**Conclusion:** Many patients with CRC experience some cognitive decline during chemotherapy. No specific pattern was evident, though worsened manual dexterity and increased learning/memory difficulties following treatment were most common. Learning/memory dysfunction appears driven by reduced initial encoding. While this aspect of learning is considered related to attention, we did not observe an association with a measure of attention. Accordingly, it is possible that reduced encoding may be related to deficits in higher level executive processing required to actively encode information, though further study is needed.
Cognitive and neurobehavioral symptoms following localized prostate cancer treatment with androgen deprivation therapy or without - A mixed methods study

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Purpose: Few studies have investigated prostate cancer patients’ experiences of cognitive impairment or neurobehavioral symptoms (i.e., behavioral changes associated with neurological dysfunction) following androgen deprivation therapy (ADT). The purpose of this study was to explore and characterize the: 1) experience of cognitive and neurobehavioral functioning in non-metastatic prostate cancer patients undergoing ADT compared with patients who had not undergone ADT; 2) perceived causes of cognitive and neurobehavioral symptoms; 3) impact of these symptoms on quality of life; and 4) strategies used to cope with or compensate for these symptoms.

Methods: Semi-structured interviews were undertaken in 19 non-metastatic prostate cancer patients undergoing ADT and 20 who had not undergone ADT. Neuropsychological performance was also assessed via an online cognitive assessment battery.

Results: Overall, ADT patients experienced marginally more cognitive problems than non-ADT (nADT) patients even though there were no significant differences between groups in neuropsychological performance. ADT patients experienced more declines in prospective memory and multi-tasking than nADT patients. Significant proportions of participants in both groups experienced retrospective memory, attention/concentration, and information processing declines. With respect to neurobehavioral symptoms, more ADT patients experienced emotional lability and impulsivity (both aspects of disinhibition) than nADT patients. Both groups attributed declines primarily to aging, but a majority of ADT patients also attributed declines to ADT. For both groups, increased cognitive and neurobehavioral symptoms negatively impacted quality of life, and most participants developed strategies to ameliorate these problems.

Conclusion: ADT patients experience more specific cognitive and neurobehavioral symptoms than non-ADT patients. This study highlights the importance of capturing: a) cognitive symptoms not easily detected using neuropsychological tests; b) neurobehavioral symptoms that can be confused with psychological symptoms, and c) attributed causes that may affect how patients cope with these symptoms.
Cancer Treatment and Cognitive Decline in the Health and Retirement Study

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Purpose: Cancer treatment is associated with declines in cognitive health, but few studies have examined the effects of cancer treatment in the growing population of older adults diagnosed with and surviving cancer. This study examined whether recent cancer and its treatment accelerated cognitive decline in older adults.

Methods: Observations were drawn from the Health and Retirement Study (HRS), a population-based sample of older adults in the United States. Total cognitive summary score (TCSS) was assessed as a sum of measures including Telephone Interview of Cognitive Status, immediate word recall, delayed word recall, and the Serial 7 subtraction test. Participants were observed biennially over 12 years, with 2002 serving as the baseline. Cognitive trajectories of individuals who had been diagnosed with cancer between 2000 and 2002 (n=291) and those who had never had cancer (n=7,540) were estimated using latent growth modeling adjusted for age, gender, race/ethnicity, and education.

Results: On average, participants were 73.9 years old at baseline with a TCSS of 21.8. TCSS decreased an average of 3.9 points over the 10 year follow-up. Cancer status or treatment type was not associated with TCSS at baseline or with increasing age. Latent slope estimates in participants with cancer who opted for no treatment (b = -1.44, SE = .88), radiation and/or surgery (b = 0.32, SE = .33), only chemotherapy (b = 0.54, SE = .93), or chemotherapy in addition to other treatment (b = -0.14, SE = .79) did not significantly differ from individuals reporting never having cancer.

Conclusion: The cognitive trajectories of older cancer survivors were comparable to persons who never had cancer. Recent cancer treatment may have minimal impact on cognitive function of older adults, or the cognitive measures used in HRS may not be sensitive enough to detect cognitive changes due to cancer and cancer treatment.
Poster presentations
Tuesday
Effect of cognitive impairment before the start of adjuvant therapy for breast cancer, and changes in cognitive functioning after adjuvant therapy on employment status 2 years later

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Purpose: Systematic treatment for breast cancer (BC) is associated with a decline in cognitive functioning. In some cases BC patients already show lower than expected cognitive performance before systematic treatment. The aim of current initiative is to study the association between cognitive impairment before and after adjuvant therapy and employment status 2 years later.

Methods: Data were collected before and after adjuvant treatment in 59 BC patients with employment; 30 received chemotherapy plus or minus endocrine therapy (ChT+), and 29 received no chemotherapy (ChT-). We also collected data of a convenience sample of 28 no cancer controls (NC). The assessments consisted of a battery of questionnaires (assessing functioning, anxiety, depression, emotions, stress, personality, perceived cognitive functioning) and neuropsychological assessments on six cognitive domains (executive functioning, attention, visual memory, verbal memory, processing speed and motor speed). Cognitively impaired patients were identified by Multiple Normative Comparisons (MNC), a method that compares the scores of each participant against the distribution of the scores of controls, taking the covariance between scores into account. We assessed employment situation two years later for this same sample.

Results: Results will be available for a poster presentation.

Conclusion: Maintaining employment status is important for BC patients, therefore insight in the cognitive changes after cancer and cancer therapy and its influence on employment situation is needed.
Cytokine gene polymorphism, plasma concentration and cognitive impairment: intricate relationships in chemotherapy-receiving breast cancer patients

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Purpose: Expression of plasma cytokines is tightly controlled by cytokine genes, and cytokines are implicated in the development of post-chemotherapy cognitive impairment. Hence, this study was designed to examine the intricate relationships among cytokine gene polymorphisms of IL-6 (rs1800795 C>G) and TNF-α (rs1800629 G>A), plasma concentrations of cytokines (IL-6 and TNF-α) and cognitive function in early-stage breast cancer patients.

Methods: Early-stage chemotherapy-receiving breast cancer patients (Stage I to III) were prospectively recruited from two cancer centers. Patients' cognitive function was longitudinally assessed using the validated FACT-Cog (ver. 3) and an objective computerized battery, Headminder® at three time points: prior to chemotherapy (T1), at midpoint (T2), and end of chemotherapy (T3). Plasma IL-6 and TNF-α levels were analyzed using the multiplex immunoassay, and genotyping was performed using Sanger sequencing. Regression analyses and generalized estimating equation were utilized to evaluate the associations among cytokine gene polymorphisms, plasma concentration and cognitive function.

Results: A total of 125 patients were recruited (mean age: 50.3; Chinese: 80.8%; post-menopausal: 48.0%). Higher plasma IL-6 level was associated with higher severity of self-perceived cognitive impairment (estimate=-0.036, p=0.001), particularly the functional interference (estimate=-0.004, p=0.028) and mental acuity domains (estimate=-0.003, p=0.025). Variation of IL-6 and TNF-α levels was not associated with cognitive domains of Headminder. Polymorphisms of cytokine genes were not associated with development of cognitive impairment and expression of plasma cytokines.

Conclusion: This is the first study to evaluate the intricate relationships of cytokine gene polymorphisms, plasma cytokine levels and cognitive function. Our results suggest that patients with higher IL-6 levels experienced more severe self-perceived cognitive impairment. Interestingly, cytokine gene polymorphisms do not influence cytokine levels and cognition, which implies that cytokine gene polymorphisms do not play a major role on plasma cytokines dysregulation.
Brain-derived neurotrophic factor genetic polymorphism (rs6265) and self-perceived chemotherapy-associated cognitive impairment: A detailed analysis of cognitive domains

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Purpose: Brain-derived neurotrophic factor (BDNF), a neurotrophin that regulates neuronal function and development, is implicated in several neurodegenerative conditions. We hypothesized that a single nucleotide polymorphism (rs6265) of the BDNF gene may predispose cancer patients to cognitive impairment post-chemotherapy. This study aimed to evaluate the effect of BDNF gene polymorphism on impairment of cognitive function post-chemotherapy.

Methods: Overall, 145 patients receiving chemotherapy for early-stage breast cancer (mean age: 50.8±8.8 y; 82.1% Chinese) were recruited. Patients’ cognitive functions were assessed longitudinally using the validated Functional Assessment of Cancer Therapy–Cognitive Function (v.3). Genotyping was performed using Sanger sequencing. Logistic regression was used to evaluate the association between BDNF Val66Met polymorphism and cognition after adjusting for ethnicity and clinically important covariates.

Results: Of the 145 patients, 54 (37%) reported cognitive impairment post-chemotherapy. The Met/Met genotype was associated with statistically significant lower odds of developing overall cognitive impairment (odds ratio [OR]: 0.26; 95% CI: 0.08–0.92; p=0.036). In a subgroup analysis involving patients aged ≥ 55 years (n =54), carriers of the Met allele (OR: 0.07; 95% CI: 0.01–0.83; P=0.035) were associated with decreased odds of overall cognitive impairment compared with the Val/Val homozygous group. In particular, expression of the Val/Met heterozygous genotype conferred a protective effect against cognitive decline (OR: 0.06; 95% CI: 0.01–0.77; P=0.031). In addition, the Val/Met heterozygous genotype was associated with lower odds of impairment for multitasking ability (OR: 0.09; 95% CI: 0.01–0.90; P=0.040).

Conclusion: Breast cancer patients who are carriers of the BDNF Met allele are protected against cognitive impairment, and this benefit remains within the older subgroup. Further studies are required to validate the findings.
Chemotherapy-associated impairment in Adult and Young Adolescent (AYA) patients with breast cancer: A pilot evaluation

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Purpose: A plethora of evidence has shown that chemotherapy-associated cognitive impairment is a common concern among cancer patients. This sequela may pose great difficulty for Adolescent and Young Adult (AYA) patients who resume their normal lives after chemotherapy. This study aims to determine the onset and trajectory of self-perceived cognitive impairment among AYA patients.

Methods: Twenty-six AYA patients diagnosed with breast cancer were prospectively recruited from two cancer centers in Singapore during 2011 to 2015. Perceived cognitive impairment was assessed using the Functional Assessment of Cancer Therapy–Cognitive (FACT-Cog v.3.0) which evaluates the concentration, functional interference, mental acuity, memory, multi-tasking and verbal fluency domains. Patients were assessed before chemotherapy (T1), midpoint of chemotherapy (T2) and end of chemotherapy (T3). Patients’ fatigue, anxiety and insomnia statuses were also assessed. The repeated measure ANOVA was used to assess the change over time in FACT-cog scores.

Results: Majority of patients were Chinese (76.9%), diagnosed with Stage II (53.8%) receiving anthracycline-based regimen (65.4%) and at least college educated (84.6%). Changes of fatigue, anxiety and insomnia severity were not statistically significant. A consistent decrease in the global FACT-Cog score (T1: 129.3±14.8, T2: 124.6±25.6, T3: 119.5±27.9) was observed. This uniform decline in FACT-Cog score was seen in all of the domains, and was statistically significant in the concentration domain (p=0.04). Compared to baseline, a higher proportion of patients were presented with a clinically meaningful self-perceived cognitive impairment at T3 (38.5%) than T2 (23.1%)

Conclusion: Data from this pilot evaluation suggests that AYA patients with breast cancer experience chemotherapy-associated cognitive impairment and the greatest cognitive impairment occurred at the end of chemotherapy. Further studies with a larger population are required to validate the findings.
Agreement between Cognitive Impairment Defined Using Study-specific Standardization Methods and Population-Based Norms for the Neuropsychological Assessment Battery (NAB) Measures

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Purpose: Considerable variability exists across methods to define cognitive impairment associated with cancer. In this study, agreement between impairment defined using population-based norms and study-specific methods was evaluated.

Methods: Data collection occurred prior to systemic therapy for newly diagnosed patients ages 60+ with stages 0-3 breast cancer (n=344) and frequency-matched controls (n=380) from 5 US sites were included. The neuropsychological testing included 7 measures from the Neuropsychological Assessment Battery (NAB) for which population-based age and education adjusted normative results are available. Linear regression models, with and without age and education as independent variables, were used to obtain raw and studentized residuals for each of the neuropsychological measures. Cognitive impairment was defined as having a score of 1.5 standard deviations below the mean for each measure. The agreement between impairment defined using the residuals and impairment defined using the normative scores provided by the NAB was evaluated using kappa statistics.

Results: Adjusting for age and education, impairment defined using the raw residuals only had fair to moderate agreement ($\kappa$=0.56) with impairment defined using the population-based norms. Using the studentized residuals generated better agreement. Even without adjustment for age and education, agreement using the studentized residuals was substantial ($\kappa$=0.69) for 4 measures and moderate ($\kappa$=0.60) for 3 measures. Adjusting for age and education, the agreement was very good ($\kappa$=0.83-0.87) for 2 measures, substantial ($\kappa$=0.71) for 4 measures, and moderate ($\kappa$=0.52) for only one measure.

Conclusion: The results suggest that cognitive impairment based upon age and education normative values and those derived by statistical control of these confounds produce similar results. This may facilitate the use of the statistical adjustment procedures for neuropsychological tests that do not have existing normative values.
Estrogen Receptor Alpha (ESR1) Genetic Polymorphisms And Chemotherapy-Associated Cognitive Impairment In Early-Stage Breast Cancer (ESBC) Patients

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Purpose: The ESR1 single-nucleotide polymorphisms (SNPs) namely, PvuII (rs2234693, -397T>C) and XbaI (rs9340799, -351A>G) have been reported to increase the risk of Alzheimer’s disease. However, there is a lack of studies investigating the associations between ESR1 genetic variants and chemotherapy-associated cognitive impairment in ESBC patients. This study was designed to elucidate the associations between the ESR1 polymorphisms and chemotherapy-associated cognitive impairment.

Methods: This was a prospective cohort study conducted between 2011 and 2015. Patients’ cognitive function was assessed longitudinally over three time points, using the validated FACT-Cog and an objective computerized battery, Headminder™. Genotyping was performed using Sanger sequencing. Logistic regression was used to evaluate the associations between the SNPs and cognition, adjusting for ethnicity and confounders.

Results: A total of 145 chemotherapy receiving ESBC patients (mean age: 50.8 ± 8.8 years; 82.1% Chinese) were analyzed. The genotype distributions for the PvuII (T/T: 0.31; T/C: 0.56; CC: 0.13) and XbaI (A/A: 0.57; A/G: 0.37; G/G: 0.06) SNPs were in Hardy-Weinberg equilibrium (p>0.05). The heterozygous genotypes of the PvuII (adjusted OR = 8.25, 95% CI: 1.54–44.19, p = 0.01) and XbaI (adjusted OR = 4.40, 95% CI: 1.33–14.59, p = 0.02) polymorphisms were associated with an increased likelihood of developing impairment in the attention domain. No associations were established between the ESR1 polymorphisms and the FACT-Cog global and individual domain scores. Among the pre-menopausal women, carriers of the PvuII TC heterozygous genotype were more likely to experience self-perceived mental acuity impairment (adjusted OR = 8.63, 95% CI:1.73 to 43.03, p = 0.01) compared to carriers of the TT homozygote.

Conclusion: This is the first study to provide evidence that carriers of the ESR1 polymorphisms (PvuII and XbaI) are associated with increased susceptibility to chemotherapy-associated cognitive impairment in ESBC patients. Further validation studies are required to confirm the findings.
Confidence Intervals for Adjusted Relative Effects for Ordinal Outcome Data

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Purpose: The comparison of groups (e.g. chemotherapy: yes, no) with respect to an ordinal outcome (e.g. self-reported cognitive function score ranging from “No at all” to “Very much”) is usually performed using Wilcoxon-Mann-Whitney tests or ordinal logistic regression models. These methods have practical limitations, including the lack of effect estimates for the tests, and the proportional odds assumption for the models. We present alternative statistical methods that provide confidence intervals for adjusted relative effects for ordinal data.

Methods: The nonparametric methods estimate the relative effect (e.g. the probability that a participant who received chemotherapy has a higher ordinal score than a participant who did not receive chemotherapy) controlling for potential confounders. We present two methods, a rank-based method (Schacht et al. 2008) and a new method based on jackknife empirical likelihood, and compare them with respect to the empirical coverage of the confidence intervals by using a simulation study. We illustrate the use of the methods using data from a cross-sectional sample of 264 Latina breast cancer survivors from US.

Results: The results of the simulation study provide evidence that the two nonparametric methods perform similarly with respect to the empirical coverage of the confidence intervals. As an example of the application of the new jackknife empirical likelihood method, the unadjusted relative effect of chemotherapy on memory was 0.64, 95% CI: (0.56, 0.71), p<0.0001, while the adjusted relative effect was 0.51, 95% CI: (0.43, 0.62), p=0.781. We notice that after adjustment the relative effect is not statistically significantly different from the null value of 0.50.

Conclusion: Given that the jackknife empirical likelihood method has several advantages over the rank-based method, including flexibility on how the adjustment can be performed, we recommend the use of this new method to construct confidence intervals for adjusted relative effects for ordinal outcome data.
Does regular physical activity predict cognitive function in breast cancer survivors?

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Purpose: Previous research has provided evidence of physical activity’s role in improving cognitive function in older adults. The trajectory of cognitive decline after cancer is thought to parallel that of aging, but may occur earlier and at an accelerated rate. This study examined the effects of moderate-to-vigorous physical activity (MVPA) on cognitive function (executive function, processing speed, working memory) in breast cancer survivors.

Methods: This study represents baseline data from a subsample of breast cancer survivors (Mage=58.8; N=169) enrolled in an ongoing study. Participants completed questionnaires and cognitive tests using an iPad application. The questionnaires assessed demographics, breast cancer history, and lifestyle and psychological factors. Developed using the BrainBaseline platform, the cognitive tests included the Flanker, Task-Switch, and N-Back tasks. Participants wore an accelerometer for one week to assess MVPA (average daily minutes). Linear regression was used to test the effects of MVPA on accuracy, reaction time, and cost as measured by the cognitive tasks. Hypothesized covariates were also tested.

Results: MVPA predicted reaction time on congruent Flanker trials (β= -0.26, p=0.004) independently of time since treatment. MVPA and MVPA*months of chemotherapy predicted reaction time on incongruent trials (β= -0.21, p=0.02, β= -0.29, p=0.001) independently of months of chemotherapy and time since treatment. The interaction effect was also significant in the reaction time cost model (β= -0.31, p<0.001). MVPA predicted reaction time on the Task-Switch switch trials (β= -0.16, p=0.03) independently of age. On the N-Back, MVPA predicted 2-Back accuracy (β= 0.17, p=0.065) independently of months of chemotherapy. A significant MVPA*age interaction was observed in relation to 2-Back reaction time (β= -0.18, p=0.01).

Conclusion: Physical activity may represent a promising modality for mitigating cancer-related cognitive impairment (CRCI). Results suggest a particularly protective effect for older women and those with longer chemotherapy treatment. These findings, with the growing health impact of CRCI, support further investigation in this area.
In search of predictors of the long-term cognitive impact of chemotherapeutics in childhood leukemia survivors

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Background: Despite increasing survival rates after childhood leukemia, little is known about moderators of methotrexate (MTX)-induced neurotoxicity and long-term cognition. Cerebrospinal fluid (CSF) markers of neurotoxicity during treatment and polymorphisms in MTX-affected enzyme pathways, such as methyltetrahydrofolate reductase (MTHFR), offer an opportunity to study individual differences in susceptibility in an early stage.

Purposes: (1) Comparing cognitive function between controls and survivors. (2) Linking MTHFR polymorphisms and CSF-Tau during treatment and (3) investigating moderators of cognitive outcome in survivors.

Methods: CSF-Tau was determined during treatment in 35 childhood leukemia patients at defined time points and the genotype on position 677 and 1298 of the MTHFR gene was analyzed. Self-reported cognitive problems (Cognitive Failure Questionnaire), IQ (Wechsler Adult Intelligence Scale) and executive functioning (Amsterdam Neuropsychological Task, ANT) of survivors were compared with sex- and age-matched controls without history of cancer.

Results: (1) Survivors had longer reaction times (RT) on cognitive flexibility in the ANT (p= 0.001) and lower total IQ (p= 0.002). Self-reported cognitive functioning and accuracy on the ANT did not differ significantly. (2) MTHFR1298GC genotypes presented with higher CSF-tau at diagnosis (p= 0.075) and after the first intrathecal MTX administration (p= 0.008) as compared to the wild-types, suggesting higher MTX sensitivity. (3) Age at diagnosis was negatively correlated with RT, possibly indicating higher vulnerability of the young brain to chemotherapeutics. The positive correlation between time since treatment and total IQ might reflect a recovery process after chemotherapy-induced neurotoxicity. Treatment intensity nor CSF-tau predicted long-term neurocognitive outcome.

Conclusions: Our study confirms the long-term cognitive impact of chemotherapeutics and suggests that developmental stage of the brain at diagnosis and recovery after treatment moderate late cognitive outcome. The results provide evidence that MTHFR1298 polymorphisms might help to early identify children at risk for neurotoxicity. These insights allow intervention with learning programs already during treatment in vulnerable children.
Proton Radiation Therapy for Pediatric Brain Tumors: Early Attention and Memory Outcomes

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Purpose: Conventional photon radiation therapy for brain tumors is associated with negative cognitive sequelae (e.g., attention deficits), particularly in children. Minimizing unnecessary exposure to radiation is critical for children. Proton radiation (PRT) provides better targeting of tumors than photon therapy and spares healthy tissues outside the target region. For this reason, it is expected that radiation-related cognitive sequelae would be less after PRT. This study examined attention and memory following PRT given their relevance for learning and academic success.

Methods: 44 patients, ages 6.58-21.67 years (M =13.09, SD =3.59; 50% <12.7years) at PRT initiation (baseline, BL), were administered age-appropriate standardized measures assessing intelligence (IQ), attention, and visual/verbal/working memory at BL and ≥1 year follow-up (M =2.58, SD=1.67).

Results: Patients were 52% male; 93% Caucasian. Mean household income was $78,950. At diagnosis, 41% had hydrocephalus. Histology was medulloblastoma (36%), glial (23%), craniopharyngioma (16%), and other (25%). Median lesion size was 912.50 mm². Most received resection (77%), involved-field (IF) PRT alone (55%), chemotherapy (59%), and had supratentorial tumors (57%). Median IF dose was 52.2 Gy. Median craniospinal irradiation dose was 23.4 Gy and median boost dose was 54.0 Gy. BL/follow-up mean scores were in the average range and unchanged at follow-up (p>0.05). Age at BL, histology, hydrocephalus, radiation dose, chemotherapy, resection, location, and income were not significantly related to change on any measure. Mean scaled scores approached significance for lower delayed verbal memory for females at follow-up (p=0.069).

Conclusion: At follow-up from PRT, intelligence, attention, and memory were intact and largely stable. Younger patients did not fare worse. Females did not make age-appropriate gains in verbal memory, although no decline was observed. These early outcomes are encouraging and compare favorably with the literature. PRT shows promise as a treatment for pediatric brain tumor patients, reducing specific cognitive sequelae and increasing the potential for learning and academic success.
Results of a Randomized Trial of Videoconference CBT for Breast Cancer Survivors with Self-Reported Cognitive Dysfunction

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Purpose: Chemotherapy-related cognitive dysfunction (CRCD) occurs for a large portion of cancer survivors but there is no established treatment for the problem. We report results of a small randomized controlled trial of videoconference-delivered Memory and Attention Adaptation Training (MAAT) vs. videoconference-delivered supportive therapy (ST). Electronic treatment delivery can improve survivor care access through reduced travel and time burden.

Methods: Forty-seven breast cancer survivors reporting CRCD were randomized to MAAT or ST (attention control) and assessed at baseline, post-treatment and 2-month follow-up. Measures included The FACT-Cog Perceived Cognitive Impairments scale (self-report) and brief telephone-based neuropsychological battery. The Meta-Memory in Adulthood-Anxiety scale (MIA-A) was also used to assess anxiety about cognitive failures. Eleven videoconference sites were utilized throughout the state of Maine (USA) which encompasses about 53,108 KM².

Results: Adjusting for baseline scores, MAAT participants made significant gains over ST controls in perceived cognitive impairments at two-month follow-up (p = .02) and processing speed at post-treatment (p = .03). Effect sizes (Cohen’s d) were .52 and .50, respectively. MAAT participants tended to have continued reductions of anxiety about cognitive symptoms (MIA-A) at 2-month follow-up whereas ST controls tended to regress to baseline with marginal significance 2 months after cessation of clinician contact (p = .07; d = .90). Survivors rated MAAT with high satisfaction and indicated videoconference delivery was critical for participation due to distance traveled and concerns of missing work after intensive cancer treatment.

Conclusion: MAAT may be an efficacious psychological treatment of CRCD that is feasibly delivered with communications technology to improve survivor care access. More research is needed with multiple clinicians, sites and a larger sample to enhance efficacy confidence in an electronically delivered CBT that may improve survivor care access.
Efficacy of cognitive and physical trainings in pediatric cancer survivors

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Purpose: Cancer survival comes at a price: pediatric cancer survivors have a high risk for a wide range of cognitive difficulties. The aim of this ongoing, interdisciplinary longitudinal study is to extend empirical knowledge on training and transfer effects in children with a history of cancer. It is hypothesized that cognitive and physical interventions affect the remediation of pediatric cancer survivors in terms of both improved working memory performance as well as transfer to areas of other cognitive functions. These changes are further hypothesized to be associated with structural and functional white matter changes.

Methods: 180 pediatric cancer survivors and 40 matched controls will be included. Initially, all participants will perform an extensive neuropsychological assessment and a physical exam. The cancer survivors will then be randomly assigned to either a computerized memory training, a physical training, or a waiting control group. The pre-intervention tests will be repeated shortly after the 10 weeks of training as well as at 6 months post-training. Neuroimaging will be performed before and after training to study the impact of the interventions on white matter organization.

Results: Analyses of variance will be conducted to examine effects on training as well as on global transfer while controlling for correlations among outcome measures. To test whether inter-individual differences predict training or transfer effects, a multiple linear regression analysis will be performed. Imaging data will be analyzed with a standard general linear model design. Pilot-data and preliminary results will be presented.

Conclusion: With an increasing number of childhood cancer survivors suffering from cognitive problems, proper interventions are needed to improve these deficits. Additionally, insights into training-related plasticity in the developing brain will hopefully help to design tailored rehabilitation programs for these patients.
Self Regulatory Demands Impacting Survivors’ Cognitive Capacities

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Purpose: It is now recognized that factors typically labeled “covariates” or “confounders”, especially psychosocial factors (e.g. stress and distress), may be important to understanding the manifestation and persistence of cognitive dysfunction among breast cancer survivors. A Self Regulatory Theory has been proposed to study cancer related cognitive impairment in cancer survivors, but has not yet been evaluated in breast cancer survivors. This study aims to describe the constructs of Self-regulation Theory (emotional and behavioral self-regulatory demands and cognitive capacity) from the perspective of breast cancer survivors experiencing self-reported cognitive dysfunction.

Methods: 10-15 breast cancer survivors of varying ages (between 21 and 65) will be interviewed. They will have completed adjuvant treatment between 6 months and less than 6 years previously and have a history of Stage 0-III breast cancer. These women will be recruited from a group of women who have already participated in our cognitive rehabilitation intervention study (n=20). After obtaining verbal consent, the first author will arrange a time to meet with participants to conduct semi structured interviews. Data will be audio-recorded, transcribed, and analyzed using qualitative content analysis as described by Sandelowski (2000, 2010). Miles & Huberman’s, (1994) method of deductive interpretation will be used to identify descriptive categories in the data relative to self-regulation theory. The second author will conduct the same analyses on 30% of the participant interviews to enhance trustworthiness of the study.

Results: IRB approval has been received and recruitment has begun.

Conclusion: Findings from this study will facilitate a better understanding of perceived daily demands that may influence survivors’ cognitive abilities. Additionally, findings will aid in validating this theory on a larger scale in the future and could lead to more effective interventions to assist cancer survivors with cognitive limitations.
The efficacy of cognitive interventions for improving academic achievement in children after cancer treatment: A systematic review

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Purpose: Academic decline has been reported in children after cancer treatment, believed to be as a result of cognitive impairment. Cognitive interventions may improve both the present and future outcomes for children after cancer treatment by improving academic performance. Purpose: The aim of this review was to investigate the efficacy of cognitive interventions for improving academic achievement in children after cancer treatment.

Methods: A systematic search based on the PRISMA guidelines for systematic reviews was conducted within the PsycInfo and PubMed databases. Search terms described participants, cancer and its treatment, cognition and interventions. Participants were required to be aged less than 21 years and to have undergone cancer treatment. The primary research studies were required to report cognitive or academic outcomes with pre and post intervention results, be published in English, and peer reviewed.

Results: The search resulted in the identification of 11 relevant intervention studies; three involved specific academic skills training. Improvements in cognitive performance were found in the domains of attention, working memory and executive function. Improvements in academic achievement were associated with early intervention and specific skills training. Computerised and home based cognitive interventions were most successful at improving cognitive skills. However, few cognitive interventions assessed academic achievement specifically. Longer interventions were associated with better outcomes than brief interventions. It should be noted that sample sizes were often small and only half of the studies employed a control group.

Conclusions: This review found support for early intervention and skills based training in maths and for computerised home-based interventions to improve cognitive performance. It remains unclear whether cognitive interventions result in improvements in academic achievement outcomes due partly because few cognitive interventions included outcome measures of academic achievement. Future research regarding the effectiveness of early, home based and computerised intervention is warranted in order to reduce the short and long-term outcomes for those who receive cancer treatment during development.
Perceived Cognition in Older Women with Breast Cancer Prior to Treatment Initiation and Non-Cancer Controls

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Purpose: Cancer treatments such as chemotherapy can have a lasting negative impact on cognitive functioning. However, research suggests cognitive problems may be present even before treatment starts. The degree to which older cancer patients perceive problems with their cognition in the period prior to treatment initiation is poorly understood. The aim of the current analyses was to characterize perceived cognition in older women with breast cancer prior to treatment and non-cancer controls, and to explore sociodemographic and clinical correlates of perceived cognition in the breast cancer group.

Methods: Older women (age > 60 years) with stage 0-3 breast cancer and age-matched female non-cancer controls were invited to participate in a larger study of cognitive function. Participants completed the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) scale following surgery but before initiation of any subsequent therapy.

Results: Data on 315 patients (M=68.1 years) and 353 controls (M=68.0 years) showed no (p<.05) differences for the FACT-Cog summary or Perceived Cognitive Impairment, Comments From Others, and Perceived Cognitive Abilities subscale scores. However, patients scored lower (i.e., greater negative impact) on the Impact on Quality of Life subscale, t=2.55, p= 0.01. Among breast cancer patients, worse FACT-Cog summary scores were related to having more comorbidities (r=-.15, p<.01) or a family history of cognitive decline or dementia (r=-.12, p<.05), and worse Impact on Quality of Life subscale scores were related to a family history of cognitive decline or dementia (r=-.14, p=.02).

Conclusions: There is no difference in perceived cognition between breast cancer patients prior to treatment and non-cancer controls, however, there is a difference in how women with breast cancer feel about these problems and the impact of perceived cognitive impairment on quality of life. Family history of cognitive decline and the presence of more comorbidities may contribute to perceptions of impaired cognition in breast cancer patients starting treatment.
The Impact of Short-term Cognitive Declines on Quality of Life Outcomes in Older Breast Cancer Patients


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Purpose: Older individuals constitute the majority of cancer survivors, but there are limited data on how any cancer-related cognitive declines affect quality of life (QOL).

Methods: Newly diagnosed patients ages 60+ with stages 0-3 breast cancer (n=344) and frequency-matched controls (n=380) were enrolled into a longitudinal cohort study. Baseline data collection occurred prior to systemic therapy, including neuropsychological testing and surveys; assessments are repeated annually. Follow-up is ongoing; in this abstract we report on the first 73% of cases completing 12-month assessments (n=251). Standardized (to the controls) changes in cognitive test scores were calculated for three domains: attention, processing speed, and executive function (APE); learning and memory (LM); and visual-spatial (VS). Linear regression models evaluated bivariate associations between standardized changes in cognition and 12-month QOL outcomes: cancer-specific QOL (FACT physical, emotional, general QOL, and fatigue), general QOL (SF12, instrumental activities of daily living [IADLs], and timed IADLs), depression (CESD), and anxiety (STAI-state).

Results: Associations between changes in standardized cognition scores and QOL outcomes varied by cognitive domain. Declines in APE were associated with significantly greater times on the 12-month timed IADL (p=0.005) and more self-perceived cognitive difficulties (p=.05), while declines in LM and VS were associated with greater fatigue (each p=.03). LM declines were also associated with lower overall cancer-specific QOL (p=.03). Cognitive declines were not related to depression or anxiety for any domain.

Conclusion: These preliminary short-term follow-up data suggest that specific domains of cancer-related cognitive decline may differentially affect aspects of QOL important to daily life for older survivors. If these findings are confirmed with complete follow-up data and persist over time, it may be important to include cognitive testing in survivorship care for older breast cancer patients to identify those in need of assistance and/or intervention.
Long-Term Trajectories of Self-Reported Cognitive Declines in Older Breast Cancer Patients

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Purpose: To determine if chemotherapy is associated with long-term self-reported cognitive function trajectories in older breast cancer survivors.

Methods: This study includes survivors (n=1273) from 78 US-cooperative group sites, who had primary, non-metastatic invasive breast cancer diagnosed between 2004-2011. Patients had normal cognitive function at enrollment based on Blessed Memory Orientation and Concentration scores. Telephone surveys were completed at baseline, 6-months, and annually for up to 7 years. Cognitive and physical function was self-reported using the EORTC-QLC30; scores ranged from 0-100 with higher scores indicating better function. Mixture models trajectory analysis estimated trajectories and we assigned women to a trajectory based on the highest predicted probability of membership. Multinomial regression evaluated the association of chemotherapy with trajectories.

Results: Survivors were aged 65-91 years; 41% received chemotherapy. The analysis identified three cognitive trajectories: “maintained high” (41.7% of survivors; baseline mean self-reported cognitive function 99.2 [SD 4.3]); “phase shift” (50.8%), with scores slightly below but parallel to the maintained high trajectory; and “accelerated decline” (7.5%), with the lowest baseline scores and greatest decline (from 70.8 [SD 20.0] to 58.3 [SD 21.9]). The adjusted odds of being in the accelerated decline group (vs. maintained high) were 2.2 times higher (95% CI 1.3-3.7) for those receiving chemotherapy (+/- hormonal therapy) vs. hormonal therapy alone. Comorbidity or frailty were also significantly associated with accelerated decline, and cognitive trajectories were related to physical function trajectories.

Conclusions: Trajectory analysis showed that the majority of older survivors maintained high levels of self-reported cognitive function or experienced slight decrements in the 7 years after diagnosis and treatment. Chemotherapy receipt increased the odds of having accelerated cognitive decline. If confirmed with more detailed self-report measures and neuropsychological testing, the results suggest that treatment decisions and care planning for older survivors should include discussion of cognitive outcomes.
Impact of exercise training during chemotherapy on cancer related cognitive impairments in patients suffering from acute myeloid leukemia and myelodysplastic syndrome - Preliminary results of a randomized placebo-controlled trial

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Purpose: Besides other positive aspects, it is well described that exercise improves brain health and ameliorates cognitive functioning. First studies suggest that exercise interventions may be used as an efficient method to improve cognitive functions and counteract cancer related cognitive impairments. However, recent research in this field is limited by several methodological limitations (assessments, control groups, measurement time points).

Methods: 54 AML/MDS patients will be stratified by age and ECOG state and subsequently randomized in one of three study groups before receiving high dose chemotherapy. The exercise group will work-out 3x/week at moderate intensity on a cycle ergometer, whereas the placebo control group will receive a supervised stretching program (3x/week) and control group will get usual care. As primary endpoint objective cognitive performance will be assessed using a test battery comprising TMT-A/B, COWA, HVLT-R as recommended by the International Cognition and Cancer Task Force. Additionally, hippocampus associated cognitive functions (spatial memory) will be assessed using a computer-based version of the water maze test and the Rey-Osterrieth Complex Figure test. Secondary endpoints will be self-perceived cognitive functioning (FACT-COG), electroencephalographic recordings as well as neurotrophic and inflammatory serum markers. Confounding factors, such as intelligence, post-traumatic stress due to diagnosis, depressions and fatigue will be assessed as well. All assessments will be conducted immediately after hospitalization (week 1), immediately before discharge of hospital (week 4-5) as well as before continuing medical treatment 2-3 weeks after discharge.

Results: The present study will start in December 2015. First results of approximately ten patients will be presented at the conference.

Conclusion: This is the first trial investigating the impact of aerobic exercise on cancer related cognitive impairments in AML/MDS patients. We hope that the study design and the state-of-the-art assessments will help to increase the knowledge about cancer related cognitive impairments and potential treatment options.
Functional scales Karnofsky Performance Status (KPS) or ECOG Performance Status (PS) to evaluate functionality in Glioblastoma (GBM) patients

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Purpose: Patients themselves, their caregivers and medical professionals could have different perceptions concerning patient’s functional status. Our aim was to explore the concordance of evaluation with different scales by different observers to establish what scale better defines the patient’s functional daily state among the many used in daily clinical practice.

Methods: Glioblastoma (GBM) patients treated at our Neuro-Oncology Unit were evaluated with Mini-Mental State Examination (MMSE), Barthel Index (BI), ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) and Karnofsky Performance Status (KPS). These last 2 scales were performed by the medical staff (MS), an independent investigator (II), the patient and the main caregiver. Demographics and clinical variables were recorded.

Results: Fifty patients were enrolled. Concordance in KPS evaluation among the 4 observers was low (Fleiss’ K = 0.354; p<.001). Even using PS score the agreement was poor (Fleiss’ K = 0.424; p<.001), nevertheless higher. PS concordance between the MS and the II was strong (K = 0.731; p<.001) while poor between the caregiver and the MS (K = 0.350; p=.007) and between the patient and the MS (K = 0.250; p=.005). We found a statistically significant correlation between the different KPS, MMSE and BI (p<.005).

Conclusions: Caregivers’ evaluation is frequently worse than the professionals’. Evaluating patient’s functionality with PS seems to cover better the perception of caregivers and professionals. Both KPS and PS don’t consider some important aspects concerning neurocognitive impairments that can affect for example the capacity to perform a qualified job but not a non-qualified job. Concomitant medication, except corticosteroids, did not influence the performance status’ evaluation. Cognitive impairment is related to patients’ grade of disability and both are linked to patients’ functionality probably due to the influence of these factors on GB patients’ life style.
Evaluating cognitive impairments in Glioblastoma and Sarcoma or Gastrointestinal Stromal tumor patients through Mini-Mental State Examination

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Purpose: Patients suffering from brain tumor usually show cognitive impairments related to their own disease. On the contrary, it might be possible that in no-glioma patients, the decreasing in cognitive domains could be due to other clinical variables. Our aim was to explore the difference in cognitive impairments in a group of patients with brain tumor and in a no-glioma cohort, using the Mini-Mental State Examination (MMSE).

Methods: We evaluated cognitive performances using MMSE in two groups, Glioblastoma (GB) and Sarcoma or Gastrointestinal Stromal (GIST) tumors, treated at our Medical Oncology Service. Age and educational level were recorded to establish the normalized t scores of MMSE. A MMSE < 27 and a t score <29 were suggestive of cognitive impairments. Concomitant medication in Sarcoma and GIST group was analysed. No differences on age and educational level were found among the two study groups.

Results: Fifty-three GB patients and forty-three with GIST or Sarcoma tumors were enrolled. The MMSE’s results in the first group were lower than in the second one (p=.000). In the latter group, the correlation between the test results and anxiolytics (p=.104), opioids (p=.233), antidepressants (p=.344), antiepileptic drugs (AEDs) used for neuropathic pain (p=.603) and the chemotherapy (p=.384), was not statistically significant.

Conclusions: MMSE’s results in GB patients were low in the majority of cases, also when adapted to educational level and age. On the contrary, the most of Sarcoma and GIST patients showed higher scores, and the concomitant medication did not influence the test results.
A behavioural intervention for executive dysfunction in brain tumour survivors: Preliminary evidence for immediate and sustained effects


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Purpose: Brain tumour survivors face unique challenges from chronic cognitive dysfunction, with executive deficits among the most common. Cognitive rehabilitation is a relatively new field, with few well-controlled studies in cancer patients. This pilot study evaluated two behavioural interventions for feasibility and potential immediate and longer-term cognitive and functional effects.

Methods: We adapted Goal Management Training (GMT), which integrates mindfulness and strategy training. As an active control condition, we developed a Brain Health Workshop (BHW) offering supportive psychoeducation about living with a brain tumour. Both programs involved 8 individual sessions and daily homework. Using a prospective randomized design, 6 adult brain tumour survivors (3 months post-radiation or surgery, with cognitive deficits) were enrolled in GMT or BHW and completed a battery of measures at baseline, post-training and 4-month follow-up. Composite z-scores and change scores were calculated by domain, with objective tests of processing speed, memory, and executive functioning, and self-report measures of coping, mood, behavioral regulation and cognitive symptoms. Individualized rehabilitation goals were identified and post-training gains measured using goal attainment scaling. Participant feedback about the programs was obtained in qualitative interviews.

Results: Participants were 1-8 years post-diagnosis, and completed all study activities. The GMT group had greater gains in executive functioning at post-training (GMT M(SD) = 1.8(1.3), BHW = -1.6(1.8), p<.05) and follow-up (GMT M(SD) = 2.2(0.9), BHW = -0.4(1.3), p<.05), and greater post-training goal attainment (Mann-Whitney U=0, p<.05). Participants in both groups reported satisfaction with their program and continued frequent (daily to every other day) use of their new knowledge after training and at follow-up.

Conclusion: This pilot study demonstrated the feasibility of individualized cognitive rehabilitation for brain tumour survivors. Results provide preliminary evidence of training-related cognitive and functional gains with maintenance on follow-up. Effects of each program are being further explored in a larger trial.
Working Memory Rehabilitation is Feasible and Improves Neuropsychological, Cognitive, and Behavioral Functioning in Breast Cancer Survivors Post-Chemotherapy

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Purpose: Investigate the feasibility and efficacy of using a home-based software program targeting improving working memory in breast cancer survivors (BCS) with cognitive impairments.

Methods: We conducted a randomized controlled trial with Stage I-III BCS, 1-10 years post-chemotherapy (54% ACT) who demonstrated cognitive impairments. Participants completed assessments prior to randomization (T1), immediately following Cogmed Working Memory Training (CWMT) (T2), and 3 months later (T3). Assessments included a neuropsychological evaluation, a measure of cognitive abilities and functional complaints. Participants were randomized to an adaptive version of CWMT (N=25) that was calibrated to the participant’s ability or an active placebo version (N=23) that was static in its difficulty throughout training. Participants trained with CWMT 5 days a week, half hour a day, for 5 weeks. A total of 57 participants were recruited and 48 completed CWMT (84% completion rate).

Results: Analyses of change scores from pre to post-training using standardized neuropsychological tests revealed seven times more BCS randomized to adaptive CWMT reliably improved in WM (p<.05) and 3 times more BCS improved in visual WM compared to the active placebo group (p<.05). Using a linear mixed model for the three assessments revealed that adaptive CWMT led to faster reaction time (parameter estimate: -0.76, p<.05) and consistency (parameter estimate: -0.79, p<.05) in sustained attention from T2 to T3 compared to the active placebo group. Significantly improved cognitive and functional abilities were reported at T2 by the adaptive training group (p<.05) and improved cognitive abilities were maintained at T3.

Conclusion: Study results indicate that a home-based software program is feasible for use with BCS experiencing cognitive dysfunction. Near and far transfer effects of CWMT were detected leading to improved working memory, sustained attention, cognitive abilities, and behavioral functioning. Our preliminary evidence indicates transfer of CWMT to untrained tasks leading to improved functioning.
Cognition in Allogeneic Stem Cell Transplanted Patients and Sports - design of the CaSpo study

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Purpose: Studies suggest that patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are at risk for cognitive decline and long-term cognitive dysfunction, but cognitive intervention studies are sparse. To address this issue, a randomized controlled intervention trial on the effect of physical exercise on cognition is conducted. In addition, the impact on psychological and physical health outcomes such as depression, fatigue, health-related quality of life and physical fitness is evaluated.

Methods: This is a prospective mono-center randomized controlled trial to compare an exercise intervention with usual care in patients with hematological malignancies and allogeneic HSCT (ClinicalTrials.gov Identifier: NCT02533947). We aim to consecutively enroll 80 patients 3 to 5 months following allogeneic HSCT. Patients will be randomly assigned to either an intervention or a waitlist control condition. The intervention was developed during a pilot phase and consists of a 16-week supervised home-based exercise program. The primary outcome (cognitive functioning) and the secondary outcomes (e.g., self-perceived cognitive impairment, physical fitness, severity of GvHD, symptom burden) are assessed at baseline, at completion of the intervention and at 7 months follow-up. A healthy control group matched to the patients on age, gender, and education will be included to control for practice effects on neuropsychological measures and allow comparisons on self-report measures. Healthy controls will undergo neuropsychological testing and questionnaire survey at baseline and at 4 months. Demographic data will be collected from all study participants at baseline. Medical data will be collected from patients at all time points.

Results: During the conference, the study methodology will be presented.

Conclusions: The CaSpo study evaluates the effectiveness of a supervised home-based exercise program on cognition in patients with allogeneic HSCT. Results may benefit survivors who suffer from disease- or treatment-associated cognitive change.
A Systematic Review on the Cognitive Effects of Stereotactic Radiotherapy in Adult Patients with Brain Metastases

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Purpose: Stereotactic radiotherapy (SRT) is increasingly applied in patients with brain metastases and is expected to have less adverse effects on cognitive functioning than whole brain radiation therapy (WBRT). However, relatively few studies have investigated its cognitive (side) effects.

Methods: This review evaluates published studies (prospective trials only) on the effects of SRT on cognitive functioning in patients with brain metastases. Studies were identified by a systematic search of PubMed, Medscape, Cochrane, and ScienceDirect databases until present using appropriate search terms. In addition, research in progress was identified via ClinicalTrials.gov.

Results: In all, eight studies were found to match the selection criteria: five single-group trials and three randomized trials (with diverse designs including SRT and/or WBRT as treatment under study).

Conclusion: In general, the results indicate that treatment with SRT has little to no (negative) effect on cognitive function (as compared to WBRT). However, most of the trials suffered from serious methodological limitations; hence suggestions for future studies are discussed. By presenting a comprehensive overview, we aim to stimulate researchers to probe deeper into this area.
Hypofrontality in chemotherapy-treated breast cancer patients?

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Background: The PECOG trial is a longitudinal study on the role of perseverative thoughts in the vulnerability for cognitive deterioration and complaints after diagnosis and treatment of breast cancer. Patients were 110 women between 25-65 years of age recruited from the Breast Clinic of the Ghent University Hospital, scheduled to have either chemotherapy treatment, eventually followed by radiotherapy and/or endocrine therapy and patients scheduled to have endocrine and/or postoperative radiotherapy. Neurocognitive measures, besides data on anxiety, depression, repetitive thoughts were obtained before the start of adjuvant therapy, after chemotherapy, 6 months later and 1 year later.

Objective: In the context of a prospective study on the effect of chemotherapy on cognitive functioning, we performed neuropsychological and psychological assessments in recently diagnosed breast cancer patients. This study focuses on the comparison of the two treatment groups in terms of their patterns in cognitive functioning.

Method: A Mixed Model Analysis approach will be applied in order to interpret the longitudinal data. This model is chosen, because of its usefulness in settings with repeated measurements in longitudinal studies, the ability to accommodate missing data points and to prevent false positive associations and the capacity to model non-linear individual characteristics.

Results: In relation to the matched healthy controls, proactive interference increased significantly in both patient groups after treatment. The chemo-group recovered and showed more resistance to proactive interference in the subsequent testing, but the non-chemo group progressed worse. The only difference between the chemo and non-chemo group was in phonological fluency; patterns between chemo and non chemo were opposite.

Conclusion: The present results indicate that a weakened executive ability, but only in proactive interference and phonological fluency. Further analysis should reveal if this weakened ability is associated with the inability to resist interference of task-unrelated thoughts and thus may be involved in more rumination/worrying.
**Longitudinal brain changes associated with prophylactic cranial irradiation in lung cancer**

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**Purpose:** The toxic effects of prophylactic cranial irradiation (PCI) and platinum-based chemotherapy on cognition in lung cancer population have not yet been well-established. In the present study we examined the longitudinal neuropsychological and brain structural changes observed in lung cancer patients under these treatments.

**Methods:** Twenty-two small-cell lung cancer (SCLC) patients that underwent platinum-based chemotherapy and PCI were compared to two control groups: an age and education-matched healthy control group (HC, n=21) and a non-small-cell lung cancer group (NSCLC, n=13) that underwent platinum-based chemotherapy. All groups were evaluated using a neuropsychological battery and multimodal structural magnetic resonance imaging (MRI: T1-weighted and diffusion-tensor imaging, DTI) at baseline (prior to PCI for SCLC and to chemotherapy for NSCLC) and at 3 months following treatment. Voxel-based morphometry (T1-VBM) and Tract-based Spatial Statistics (DTI-TBSS) were used to analyze gray matter (GM) and white matter (WM) integrity.

**Results:** SCLC patients exhibited cognitive deterioration over time in verbal fluency. Structural MRI showed GM decreases at 3 months in SCLC compared to both control groups in right subcortical regions and the bilateral insular cortex and superior temporal gyrus. Additionally, SCLC showed GM decreases over time in the aforementioned regions plus the right parahippocampal gyrus and hippocampus, together with lower WM integrity in the entire corpus callosum.

**Conclusion:** This longitudinal study documents neuropsychological deficits together with brain-specific structural changes (GM and WM) in SCLC following chemotherapy and PCI, suggesting that chemotherapy and specially PCI are associated with the development of cognitive and structural brain toxic effects.
Cognitive impairments in patients with glioblastoma: preliminary results of the postoperative assessments

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Purpose: Assessment of cognitive impairments in primary brain tumors is important because neurological deficits can alter the health-related quality-of-life (HR-QOL) but also be markers of tumor progression and/or treatment-related neurotoxicity. The EpiBrainRad study consists in prospective investigations of clinical, biological and cognitive modifications in patients managed for glioblastoma. We present the preliminary results of the postoperative cognitive assessments.

Methods: We prospectively evaluated global functioning, verbal episodic memory, visual episodic memory, information speed processing, executive functions, oral production, oral comprehension and visuo-spatial abilities in 23 with glioblastoma. Assessments were performed 4 weeks after surgery (complete or partial resection, or biopsy alone) and before initiation of radiochemotherapy.

Results: Our cohort was composed of 23 patients (19 men, 4 women). Mean age was 62 years (22-73). All the tests were achieved in 14 patients (60%). The most frequently tumor localizations were the temporal (52%) and frontal lobes (39 %). Left and right hemispheres were equally represented (47% each) and 1 patient presented a bi-hemispheric involvement. A complete resection was performed in 8 patients (35%), a partial resection in 6 patients (26%) and a biopsy alone in 7 patients (30%). The most affected domains were executive functions (60%), verbal episodic memory (57%) and information speed processing (35%). In patients who experienced all the tests, no deficit was observed in 3 patients (21%). The impairments were reported in 1 domain for 3 patients (21%). The alteration of 2 and 3 domains were described in 4 (28%) and 4 patients (28%), respectively.

Conclusion: After surgery and before radiochemotherapy, about 80% of the patients experienced cognitive deficits, mostly involving executive functions, verbal episodic memory and information speed processing. Furthermore, these functions are known to be sensitive to radiochemotherapy. Thus, an hypothesis could be that neurotoxicity of radio-chemotherapy may increase a pre-existing post-surgical cognitive dysfunction.
Non-pharmacological interventions for cognitive impairment due to systemic cancer treatment: a Cochrane Collaboration review

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Purpose: Cancer-related cognitive impairment (CRCI) affects up to 75% of cancer patients during treatment and may last for up to 10 years for up to 50% of cancer patients following treatment. CRCI involves a breakdown or change in cognitive processes. Chemotherapy is commonly linked to the development of CRCI, often known as, ‘chemo-brain’ or ‘chemo-fog’. Hormonal treatments are also associated with CRCI. CRCI impacts greatly on the lives of cancer survivors and their families. This systematic review aims to assess the effectiveness of non-pharmacological interventions to manage or treat cancer survivors with CRCI.

Method: We searched the Cochrane Centre Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PUBMED, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and PsycINFO databases. We also searched ongoing registered trials, grey literature including theses, dissertations and conference proceedings. Searches were conducted for articles published from 1980 to October 2014. Randomised controlled trials (RCTs) of non-pharmacological interventions to improve cognitive impairment or, maintain cognitive functioning among survivors of adult-onset cancers who have completed systemic cancer therapy (in isolation or combination with other treatments) were eligible. Studies among individuals continuing to receive hormonal therapy were included. We excluded interventions targeted at cancer survivors with Central Nervous System (CNS) tumours or metastases, non-melanoma skin cancer or those who have received cranial radiation or, were from nursing or care home settings. There were no language restrictions applied.

Results: We identified five eligible studies describing six interventions. The interventions included two computerised cognitive skills practice interventions, two cognitive coping skills training interventions, one meditation intervention and one exercise intervention. Each of the studies included women who had been treated for breast cancer. There were some problems with how the studies were carried out and we need to be cautious with our conclusions. The current findings suggest that cognitive skills practice and cognitive coping skills training may be useful in improving patient reports and formal assessments of cognition, as well as, quality of life. However, there is insufficient evidence to know if meditation and exercise interventions had any effect on cognition.

Conclusion: There is not enough evidence yet to make a decision on which intervention is most effective at improving cognitive impairment or maintaining cognitive function among people who have received systemic treatment for cancer.
Measuring Subjective Cognitive Functioning in Breast Cancer Survivors (BCS) with the FACT-Cog: Relationship with Neuropsychological Performance and Mood

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Purpose: Subjective cognitive decline in BCS has significant functional consequences. Subjective decline is variably associated with neuropsychological performance and mood, and questionnaires that discriminate between complaints associated with cognitive dysfunction vs. mood would direct appropriate treatment. The Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog) is a multidimensional self-report instrument measuring cognitive strengths with the Perceived Cognitive Ability (PCA) scale, weaknesses with the Perceived Cognitive Impairment (PCI) scale, Comments from Others (CO), and Cognitive Quality of Life (QoL); few studies have examined its association with cognition and mood.

Methods: 103 BCS (x̄ age = 56.81 ± 7.91, x̄ years since treatment = 4.44 ± .66) were evaluated with a neuropsychological battery; the Beck Depression Inventory, 2nd edition (BDI-II), and FACT-Cog (higher scores = better ratings). Four hierarchical linear regressions were performed with PCA, PCI, CO, or QOL as the dependent variable, BDI-II, and Memory and Attention cognitive domain scores as predictors, controlling for age and IQ. FACT-Cog scores were then compared between groups of those with Depression and intact Memory (D; BDI-II≥14; n=17), Memory Impairment (z<-.5) with or without Depression (M+/D; n=17), or Neither depression nor impairment (N; n=69).

Results: All final models were significant (p<.05); both the BDI-II and the Memory domain were significant predictors of PCA (β =-.46 and β=.24, respectively) and CO (β =-.51 and β=.27, respectively), whereas the BDI-II was the only significant predictor of PCI (β =-.65) and QOL (β =-.71). The D group had the lowest PCI scores (p<.05); M+D and D groups had lower PCA, CO and QOL than the N group, but weren’t different from each other.

Conclusion: The FACT-Cog scales are differentially sensitive to objective cognition and mood, and are a useful tool to screen for further workup and identify appropriate clinical interventions.
Improved cancer-related cognitive dysfunction up to one year after comprehensive psycho-educational intervention “Emerging from the Haze™”

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Purpose: Mounting evidence portrays vulnerability and expression of cognitive decline related to cancer and its treatment as highly variable. Accordingly, cognitive, educational, and behavioral interventions have each shown promise; however, optimum intervention timing is unclear. Emerging from the Haze™ (Haze) is a 6-week multi-disciplinary psycho-educational intervention for cognitive dysfunction related to cancer and its treatment designed to integrate cognitive, educational, and behavioral approaches. Clinically, it is offered at any point along the cancer trajectory, with pilot studies demonstrating positive effects. In this retrospective cohort study, we examined if the benefits of Haze differed by stage of treatment pre- and up to one year post-intervention.

Methods: Patients with any cancer type currently receiving primary cancer treatment (CA Tx), <12 months post-CA Tx, or >12 months post-CA Tx were assessed at baseline, post-intervention (n=80), 3-months (n=39), 6-months (n=29), and 12-months (n=20) follow-up with the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) scales of Perceived Cognitive Impairment (PCI), Comments from Others (CO), and Cognitive Quality of Life (QoL). Four mixed-model repeated-measures ANOVA were conducted with each FACT-Cog scale as the DV, Time as the within-subjects IV, and Time since CA-Tx was the between-subjects IV.

Results: A main effect of time was found for PCI and QoL across analyses (p’s<.01), indicating improvement post-intervention that is maintained at 3, 6, and 12 months, with large effect sizes. PCA scores improved up to 3 months post-intervention (p’s<.01). There was no main effect of group, and only one time x group interaction for QoL at 3 months (p<.05).

Conclusion: As the manifestation of cognitive decline related to cancer and its treatment is likely multifactorial, lasting benefits of a comprehensive psycho-educational intervention such as Haze can be derived whenever intervention is indicated along the cancer trajectory. The next important step is evaluating efficacy against a control group.
Do women who self-report cognitive symptoms after breast cancer treatment have more cognitive impairment than those who do not report symptoms? A mechanistic cohort study with functional MRI

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Purpose: Some women report cognitive impairment after adjuvant chemotherapy for breast cancer. Here we explore underlying mechanisms with blood tests and functional imaging.

Methods: 125 women diagnosed with localized breast cancer within 5 years, and without recurrence, were recruited to three groups based on FACT-COG scores. Group A (n=44) had received chemotherapy and self-reported cognitive symptoms (FACT-COG <85/156); group B (n=51) had received chemotherapy but did not report cognitive problems (FACT-COG, >100); group C (n=30) had not received chemotherapy. Clinical and computer-based CANTAB tests of neuropsychological function were performed. Blood tests included sex hormones, coagulation factors, 10 cytokines, and apolipoprotein-E genotype. Functional MRI scans were obtained on 102 subjects while they performed an n-back (1-,2-,3-) memory task.

Results: Median age 50 (29-60); median 17 months post-diagnosis. On clinical neuropsychological tests 19% had cognitive impairment using Global Deficit Score (GDS), and 13% using ICCTF criteria. There were no significant differences in overall cognitive impairment rates between groups on clinical or CANTAB batteries using GDS: Group A 26% and 14%, Group B 14% and 10%, Group C 18.5% and 20% (p=0.36 and 0.52) respectively. There was no difference in cognitive impairment rates comparing Group (A+B) vs C. Group A had significantly more fatigue, anxiety/depression and poorer QOL.

Across groups, fMRI results showed a significant main task-effect for all contrasts in frontal and parietal areas.
Group C showed hyperactivation compared to chemotherapy groups: Group C vs A more activation in temporal, parietal and frontal regions. Group C vs B more activation in parietal and temporal regions. Group C vs (A+B) showed hyperactivation in right precentral gyrus, left putamen and amygdala and bilateral cerebellum. Group A had more frontal activation than Group B.

Conclusions: There were no significant differences in rates of cognitive impairment between groups. Women who received chemotherapy had hypoactivation on fMRI in various brain regions.
Impact of Attentional Fatigue on Perceived Work Ability in Breast Cancer Survivors

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Background: Breast cancer survivors (BCS) comprise the largest group of cancer survivors with over 2.4 million female BCS estimated to be living in the United States alone. Up to 83% of BCS report some degree of cognitive impairment. Problems with directed or selected attention are commonly reported by BCS and have been shown to impact quality of life. However, little is known regarding the impact of attentional fatigue on work ability in BCS.

Purpose: To examine the impact of attentional fatigue on perceived work ability in BCS.

Methods: A cross sectional, descriptive design was used. BCS who were currently working and at least 1 year post-adjuvant treatment were recruited from a NCI-designated Cancer Center. BCS completed questionnaires regarding attentional fatigue (Attentional Function Index [AFI]) and perceived work ability (Work Ability Index [WAI]). Descriptive statistics and linear regression was used to examine the impact of attentional fatigue on work ability, controlling for known covariates of age, education, household income and time post-treatment.

Results: 68 female BCS who ranged from 29 to 68 years of age (M=52.12; SD=8.603) and were on average 4.97 (SD=3.36) years post-treatment participated. Over one-fourth (26.5%) of BCS reported poor to moderate perceived work ability, indicating substantial concerns regarding work performance. Attentional fatigue was found to significantly predict perceived work ability (p<0.001), explaining 40% of the variance of perceived work ability.

Conclusions: Findings indicate that attentional fatigue is a prevalent symptom post-treatment that negatively impacts perceived work ability in BCS. These findings are important clinically as they lend further support for the need for individual, comprehensive survivorship care plans to effectively address symptoms that impact the quality of life of cancer survivors. Further longitudinal research studies, which also includes objectively measured cognitive performance, is needed to fully understand the impact cognitive impairment on work-related outcomes in BCS.
Preliminary efficacy of a computerized cognitive training program for prostate cancer patients on androgen deprivation therapy

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Purpose: Androgen deprivation therapy (ADT) has been associated with cognitive impairment in prostate cancer (PC) populations. The purpose of this study was to evaluate the preliminary efficacy of a computerized cognitive training program (BrainHQ) vs. usual care (UC) for improving basic level cognitive functions in ADT patients.

Methods: Forty-six PC survivors (mean age=67) who had completed ≥3 months of ADT were randomized to BrainHQ training or UC and assessed at baseline (T1), post-intervention (T2) and 2 months later (T3). Primary outcomes were performance on basic cognitive functions (reaction time, motor speed, simple attention, and processing speed). Secondary outcomes were performance on higher-level functions (verbal/visual memory, executive functioning), and perceived cognitive functioning. The intervention consisted of prescribed BrainHQ training for 1 hour/day 5 days/week for 8 weeks. Participants who completed <10 hours of training were excluded from analyses.

Results: Average total training time was 33 hours. Between-within group effect sizes from T1-T2 and T1-T3 were examined. The BrainHQ group showed marginal to significant improvements in reaction time with medium effect sizes (dT1-T2=0.57, p=.07; dT1-T3=0.64, p=.04). With respect to secondary outcomes, being in the UC group was more favorable on memory tests at Time 2. By T3, neither group allocation was more favorable, except on a delayed verbal memory test where being in the UC group was more favorable (dT1-T3=.64, p=.04). There were no significant differences in change scores on perceived cognitive functioning. Individual-level analyses indicated that 71% and 73% of BrainHQ participants’ improved in reaction time at T1 and T2 respectively, significantly exceeding the frequency in the UC group.

Conclusion: BrainHQ appeared to be efficacious in improving basic level cognitive functions. However, there was a suppression of performance on higher level tasks post-intervention, but less so 2 months later. Due to the small sample size, these findings warrant further investigation.
Ethical challenges in Awake craniotomies for glioma; 
Introducing the learning health care system

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Purpose: Awake craniotomies are increasingly considered a favorable procedure for brain tumor surgery urging for objective standards to decide upon when, who and for whom this procedure should be available and in what ethical framework. This challenges not only the neurosurgeon but also all involved, including the patient and the multidisciplinary team. Here we will assess how the objectives of the learning healthcare system can contribute towards decision making in glioma surgery.

Methods: Recently, the concept of a “learning health care system” (LHCS) was introduced and morally justified. This system is defined by the Institute of Medicine as a system “in which knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the healthcare delivery process and leads to continual improvement in care.” In case of glioma surgery, the best net outcome would be an oncological favorable and a functional optimal outcome strongly dependent on cognitive outcome and personal integrity. We adapted the framework of LHCS to the healthcare system surrounding awake craniotomies and discuss whether this offers handhelds to combine research and clinical practice in the most optimal patient care.

Results and conclusion: Based on literature review and clinical experience we discuss with the following: a). value the patients’ autonomy b) a strong focus on multidisciplinary teamwork and shared decision making based on research and clinical judgments, c). enhance accessibility for all patients to awake craniotomy d). enhance the learning environment for all disciplines involved
Coping strategies as predictors of self-esteem in women with breast cancer

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Purpose: Health is the basis for well-being and participation in many aspects of life. Including social, physical, emotional and mental, it is a fundamental human right. In 1995, The Beijing Declaration, defined health as complete well-being, not just the absence of illness or infirmity. The present study aims to provide empirical evidence to develop psychological interventions to help improve levels of well-being of women with breast cancer. Specifically, we analyze the possible predictive valor of using different coping styles with the disease and levels of self-esteem in a sample of Spanish women diagnosed with breast cancer, controlling the influence of age and stage of their disease.

Methods: To achieve this objective, we used one sample of thirty breast cancer patients with an average age of 47.47 years old, and a standard deviation of 6.35. In the sample 3.3% were in stage 0 of disease; 13.3% in stage 1; 56.7% in stage 2; 23.3% in stage 3; and 3.3% in stage 4. They were measured with the Rosenberg Self Esteem Scale (RSES) and the Stress-Management Evaluation Scale (COPE for its Spanish acronym) in its Spanish adaptation.

Results: Correlation analysis showed significant associations between coping strategies Venting, Acceptance and Personal Growth and higher Self-Esteem. Hierarchical multiple regression analysis confirmed these findings and revealed that Personal Growth predicted part of the variance of Self-Esteem not accounted for age and the illness stages.

Conclusion: These results provide empirical evidence on how to promote the use of Personal Growth an effective coping strategy could help improve Self-Esteem levels of women with breast cancer.
Psychological factors and wellbeing in breast cancer patients compared to healthy women

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Background: Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed every year. This represents about 12% of all new cancer cases and 25% of all cancers in women. Also, it is estimated an increase of between 22.000-25.000 new cases per year. Even more, in spite of being considered a multi-causal disease, we must consider that between the 70% and the 80% breast cancer occurs in women without a likely risk factor.

Purpose: This overview is an attempt to explore the role of some psychological factors in relation to breast cancer, especially to the quality of life in women who have been diagnosed with breast cancer. More concretely the main purpose of the study was to assess the relationship between level of self-esteem, psychological well-being and life satisfaction in breast cancer patients compared to healthy women.

Methods: To achieve this objective, we used two samples: thirty breast cancer patients and thirty healthy women. They were measured with the Rosenberg Self Esteem Scale, the Satisfaction With Life Scale and the Ryff’s Scales of Psychological Well-Being, in its Spanish adaptation.

Results: One way analysis of variance (ANOVA) revealed significant differences (p <0.05) between the study and comparison groups. Specifically, these breast cancer patients reported more self-esteem, more well-being and major life satisfaction, than healthy women. In addition, breast cancer patients who scored higher on self-esteem showed relation to major psychological well-being and life satisfaction.

Conclusion: These results show that women diagnosed with breast cancer develop her ability to overcome this traumatic circumstance. Breast cancer survivors have learned to cope better with their personal situation, and now they are more satisfied with themselves and with life in general.
Meta-analysis of the effects of neuropsychological interventions on cognitive function in non-central nervous system cancer survivors

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Background: Cognitive impairment is a common complaint among cancer survivors, significantly impacting working memory, attention, executive function and information processing speed. This meta-analysis aims to evaluate the effect of neuropsychological interventions on the cognitive function of non-central nervous system (non-CNS) cancer survivors.

Methods: Three databases (PubMed, PsycInfo, and CAJ Full-text Database) were searched from January 2010 to September 2015. Controlled clinical trials of neuropsychological interventions for the treatment of cognitive impairment in cancer survivors were considered for inclusion.

Results: A total of 10 eligible trials were included in this meta-analysis. Three trials assessed the effects of cognitive rehabilitation (CR) interventions, and the weighted mean difference (WMD) for the overall intervention effect was -0.19 (95% confidence interval-CI: -2.98 to 2.61). Two trials examined the effects of cognitive training (CT) interventions on the cognitive function of cancer survivors; the standardized mean difference (SMD) for the overall effect was 0.52 (95% CI: 0.06 to 0.98). The overall effect of CR interventions on neuropsychological status at post-intervention was 5.66 (95% CI: 2.97 to 8.35). The SMD of CR and CT intervention for objective function by verbal learning tests was 0.50 (95% CI: 0.19 to 0.81) at post-intervention, and 0.58 (95% CI: 0.19 to 0.98) at follow-up assessment within six months.

Conclusion: Findings from this meta-analysis indicate that neuropsychological interventions can improve cognitive function in non-CNS cancer survivors, and support the need for future research. However, the conclusion from this meta-analysis was based on trials with small sample sizes. Future research should be conducted using a larger sample size. Relevant clinical implications were discussed accordingly.
Exercise interventions in the context of cancer related cognitive impairments - Levels of evidence and methodological issues for future research

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Purpose: Physical activity and exercise have been described as physiological and psychological mediators of brain health and cognitive functioning. Current data on effects of exercise interventions and physical activity behavior on objective and subjective cancer related cognitive impairments (CRCI) will be discussed.

Methods: PubMed and Medpilot were systematically screened to obtain relevant literature. All selected studies were ranked according to the Oxford levels of evidence system.

Results: A total of 19 studies met all inclusion criteria. Besides five animal models, 14 studies (six RCTs, one controlled trial, two prospective non-controlled trials, one case series, one observational study and three cross-sectional studies) investigated the impact of exercise interventions or physical activity behavior on CRCI in cancer patients. The results from animal models revealed positive effects of exercise during and after chemotherapy or radiation on structural alterations of the central nervous system, physiological as well as neuropsychological outcomes. The overall study quality in patient studies was poor. The current data on intervention studies showed preliminary positive effects of Asian-influenced movement programs (e.g. Yoga) with benefits on self-perceived cognitive functions as well as a reduction of chronic inflammation for breast cancer patients in the aftercare.

Conclusion: Exercise potentially contributes to the prevention and rehabilitation of CRCI. Major limitations of all human studies are inadequate or missing control groups, lacking standardized neuropsychological assessments (according to the recommendations of the Cancer and Cognition Task Force) and missing patient information about cognitive side effects. Furthermore, recording of potential confounders, such as post-traumatic stress, depressions, fatigue and age is necessary. Finally, one should always scrutinize if the scheduled exercise intervention is associated with improvements in the assessed cognitive domains when planning an interventional study.
Symposium 1
Overview of Non-Pharmacologic Treatment Approaches of Cognitive Dysfunction Among Cancer Survivors and Future Directions

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Purpose: Long-term cognitive dysfunction associated with systemic cancer treatment among adult cancer survivors with non-central nervous system disease is a growing problem worldwide. To date, there is no single established treatment. However, over the past decade several approaches have emerged. This symposium will summarize research to date on various non-pharmacologic treatment approaches, review the quality of available data and identify areas of methodological improvement to help advance treatment development and dissemination.

Methods: Research investigators will present their research to date from 4 broad treatment categories: 1) cognitive training with computer technology; 2) cognitive-behavioral therapy; 3) mindfulness based stress reduction; and 4) physical activity.

Results: Several studies have found some support for efficacy in improving self-reported, neuropsychological and quality of life outcomes among cancer survivors with persistent post-treatment cognitive dysfunction. However, many of the studies evaluating the various treatment methods have had a number of methodological limitations which include small sample sizes, either no control condition or waitlist control conditions with few active or attention control conditions and limited long-term follow-up. In addition, there are no multi-site, multi-clinician trials specifically designed to assess cognitive outcomes with varying cancer populations. Relative strengths of research include standardization of treatment approaches and heterogeneous outcomes assessments that include self-report, neuropsychological and quality of life outcomes.

Conclusions: A discussion will take place to synthesize ideas and make suggestions for improvements in research methods, possible collaborations to grow sample sizes and generalizability and identify means of translating treatments to survivor services such as using mobile technology.
Cognitive-Behavioral Therapy for Cancer-Related Cognitive Dysfunction: Research to Date and Future Directions

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Purpose: Various treatments for persistent cognitive dysfunction associated with cancer have been developed but no one approach has fully established efficacy. Memory and Attention Adaptation Training (MAAT) is a cognitive-behavioral therapy (CBT) that has been developed and researched over the past decade. This presentation will review MAAT research and development to date and identify future directions of study.

Methods: In brief, MAAT is a CBT designed to assist survivors to improve self-awareness of at-risk situations for memory failure, modify behavior with compensatory memory skills for improved task performance and enhance self-regulation of stress. The theoretical underpinnings of MAAT from a diathesis-stress model will be discussed. Three MAAT studies (a single arm, wait-list control and active treatment control study with videoconference delivery) will also be summarized.

Results: MAAT participants have made significant gains over controls in both self-report and neuropsychological outcomes in past research. For example, in the most recent trial, MAAT participants made gains over supportive therapy controls in perceived cognitive impairments (p = .02) and processing speed (p = .03; Cohen’s d = .52 and .50, respectively). MAAT participants also reported high treatment satisfaction and reported videoconference delivery of MAAT has also enabled participation in treatment through reduced travel and time off work. However, small sample sizes, using only one clinician in each treatment arm and using only samples of breast cancer survivors are limitations and call for future research addressing these.

Conclusion: MAAT may be an effective treatment of cognitive dysfunction among breast cancer survivors and convenience of electronic delivery may broaden dissemination. However, more research is needed with multiple clinicians, sites and a larger sample to establish efficacy. Further study will also help determine which individuals benefit most from CBT versus other approaches such as physical activity, computerized training or mindful-based approaches.
Cognitive Training for Cancer-Related Cognitive Impairment

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Purpose: Along with other groups, we previously demonstrated preliminary evidence that cognitive training (CT) can be effective for managing cognitive impairments in cancer survivors. However, effects on subjective outcomes tend to be lower than those for objective outcomes. We aimed to determine the feasibility and preliminary effects of adding a patient workbook focused on compensatory strategies to a CT program.

Methods: Because the workbook increases participant burden, we conducted a single arm feasibility study with 12 chemotherapy treated breast cancer survivors (mean age = 57 +/- 5 years). Survivors were at least 18 months off-therapy with self-rated cognitive impairment of 3 or higher out of 10. Participants completed 15 hours of computerized CT across 6 weeks and were instructed to implement daily compensatory strategies described in the companion workbook. Cognitive tests, patient self-rating measures and resting state fMRI were administered before and after the intervention.

Results: Targeted enrollment was met within 2 days of opening the study. All 12 participants (100%) completed all CT sessions and demonstrated significant improvement on CT task performance (p < 0.0001) indicating adequate effort. Participants rated their compensatory strategy use as 5.4 +/- 1.3, range 4-7 corresponding to “often” on a scale from 0-8. Participants demonstrated significant improvement on the primary outcome measure, Trails B (p = 0.035). Improvements were also noted on an in-house self-rating measure of cognition (p = 0.032) as well as in functional brain network global efficiency (p < 0.0001). Participants rated the intervention program with respect to improving cognitive problems in everyday life as 6.2 +/- 1.3 (range 4-8) corresponding to “helpful” on a scale of 0-8. There were no adverse effects of the intervention.

Conclusion: The addition of a patient workbook to computerized CT seems feasible and is associated with preliminary improvements in both objective and subjective cognitive status.
Exercise Interventions to Alleviate Cognitive Dysfunction among Cancer Patients and Survivors

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Purpose: Interventions are needed to alleviate cancer-related cognitive dysfunction in cancer patients and survivors. Exercise interventions have been shown to be beneficial for cognitive outcomes in a number of disease settings but there has been limited systematic research of these interventions on cognition in cancer patients and survivors and no large randomized controlled trials (RCTs) specifically designed to assess exercise interventions in patients and survivors have been published.

Methods: We have conducted two Phase III randomized clinical trials assessing exercise interventions (i.e. yoga, walking/resistance training) in a multi-site nationwide setting; these studies were not specifically designed to assess cognitive function as a primary outcome but self-reported cognitive function was assessed as secondary endpoints. In two current studies, we are assessing the effects of exercise interventions in cancer patients currently undergoing chemotherapy with reported cognitive dysfunction.

Results: In a RCT of 328 cancer survivors, Janelsins et al. found that a 4 wk yoga program (YOCAS©; 2x/wk, 75 min sessions) reduced self-reported memory impairments by 19.2% in yoga participants compared to 5.4% in controls receiving standard care. In a RCT of 479 patients receiving chemotherapy, Mustian, Janelsins et al. found a significant improvement in FACT-Cog overall scores and domain scores in those randomized to 6 weeks of EXCAP©, a home-based daily walking and resistance training program.

Conclusions: These studies provide important preliminary data that exercise can improve perceived cognitive function in cancer patients and survivors. In current work, we are focused on assessing the impact of EXCAP© in breast and gastrointestinal cancer patients currently receiving chemotherapy and reporting cognitive dysfunction to assess the impact of walking and resistance training on objective and subjective outcomes, as well as biological mechanisms. Future RCTs are needed to test the best mode, frequency, and duration of exercise in order to assess the biggest impact on CRCD.
Mindfulness-Based Stress Reduction to Alleviate Cognitive Dysfunction in Cancer Survivors

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Background: Cognitive dysfunction is a common, bothersome, and potentially debilitating symptom after cancer and cancer treatment. Despite the high prevalence and severe consequences of cognitive dysfunction, the scientific basis for managing this problem in cancer survivors is extremely limited. Emerging evidence suggest that mindfulness-based stress reduction (MBSR) may be an effective treatment option. Purpose: In this session, we will explore the underlying basis for the use of MBSR and provide an overview of the studies to date including our team’s most recent pilot study.

Methods: Only a few RCTs have examined the impact of MBSR on cognitive dysfunction in cancer survivors. The largest RCT by Hoffman et al. showed significant improvement on a confusion subscale; however, like most studies, results are limited by the lack of a rigorous attention control comparator group. Most recently, Johns, Von Ah et al., conducted a RCT of an 8-week MBSR intervention compared to attention control in 71 fatigued breast and colorectal cancer survivors. The Attentional Function Index (AFI) and the Stroop test were collected at baseline (T1), after the 8-week intervention period (T2), and 6 months later (T3) using intent-to-treat analysis.

Results: MBSR participants reported significantly greater improvement in subjective attention compared to attention control at T2 ($d = 0.83$, $p = 0.001$) and T3 ($d = 0.55$, $p = 0.021$). MBSR also produced greater accuracy rates relative to controls on the Stroop test at T2 ($p = 0.005$) and T3 ($p = 0.030$). No significant differences in Stroop reaction time between groups were noted.

Conclusion: These studies provide preliminary evidence to support that MBSR may be an important treatment option for cognitive dysfunction after cancer; however, more work is needed to establish efficacy.
Chemotherapy-Induced Cognitive Impairment: An Animal Model Approach

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For years, cancer survivors who had received chemotherapy complained of cognitive problems that appeared to be related to the anti-cancer drugs. However, for the most part, the medical community attributed these complaints to the psychological challenges of dealing with a life-threatening disease and a difficult treatment. Neuropsychological investigations involving clinical populations provided some evidence that chemotherapy can adversely affect cognition but methodological issues often undermined those results. Arguably, the demonstration of chemotherapy-induced cognitive impairment (CICI) under rigorously controlled conditions in animal models was a turning point in legitimizing this condition.

Over the last 10 years, research on animals has greatly advanced our understanding of the nature of CICI and its underlying mechanisms. The aim of this symposium is to highlight progress that has been made through this approach and chart future directions.

Gordon Winocur will review his program that has characterized the cognitive profile of rodents following chemotherapy, and report new results that dissociate the effects of cancer and chemotherapy in a transgenic mouse model of breast cancer.

Hélène Castel will report her work with buparlisib, an inhibitor of the PI3K/AKT/mTOR signalling pathway that is being investigated as a possible treatment for various cancers. Her results indicate that buparlisib is not associated with cognitive deficits or other common side effects of chemotherapy, thereby reinforcing its potential value as a treatment.

Peter Wigmore has shown that behavioural deficits resulting from 5-fluorouracil treatment are linked to suppression of hippocampal neurogenesis. He reports that prior treatment with the anti-depressant, Fluoxetine or the anti-inflammatory, Indomethacin, prevents the decline of neurogenesis and loss of cognitive function.

Ian Johnston has been investigating promising pharmacotherapies and reports new studies involving Ibudilast, a phosphodiesterase inhibitor; Cannabidiol, a component of cannabis; Nicotinamide, part of the Vitamin B group. All three compounds were found to prevent and reverse CICI.
Chemotherapy-Induced Cognitive Impairment in Normal and Cancerous Rodents


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Our research program has demonstrated that cognitive impairment frequently seen in cancer survivors treated with chemotherapy occurs in analogous form in animal models. Cross-sectional and longitudinal experiments have shown that a range of cognitive processes, mediated in particular by hippocampal and pre-frontal brain regions, are affected and that, while some recovery can occur, many of the effects are long-lasting. On the positive side, we have also shown that adverse effects of chemotherapy on cognitive function can be substantially reduced by behavioural (physical activity, environmental enrichment) and pharmacological (donepezil) interventions. Our results are in accord with findings of other labs but, significantly, all studies to date have been conducted on normal rodents. We present the first investigation of chemotherapy-induced cognitive and neurobiological changes in the MMTV-neu (ErbB2/HER2) FVB transgenic mouse, a well characterised model of breast cancer with many similarities to the complex tumourigenesis which occurs in humans. The results show that even before chemotherapy treatment, tumour-bearing mice exhibited learning and memory deficits. Following treatment, the deficits were exacerbated, relative to non-cancerous controls. In terms of underlying mechanisms, cognitive performance in the cancerous mice, before and after treatment, was found to be related to (1) increased levels of pro-inflammatory cytokines accompanied by a reduction in anti-inflammatory cytokines (2) suppression of hippocampal neurogenesis; (3) decreased volume in several brain regions, as measured by structural MRI. These results have important implications for understanding how disease-related factors and the effects of chemotherapy interact to alter brain and cognitive function.
Pre-clinical animal models and targeted therapies on cognition: Direct Impact of the PI3K inhibitor buparlisib

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Background: Cancer treatments such as chemotherapy can induce cognitive troubles (memory deficits, psychomotor slowing) referred to as “Chemofog”. Recently, targeted therapies have been introduced in cancer treatment and preliminary investigations suggest direct actions on the central nervous system. In current clinical practice, some targeted therapy-treated patients report fatigue, lethargy and selective cognitive disorders. Our group previously explored the direct impact of targeted therapies on cognition and brain functioning and demonstrated that drugs targeting the mTOR pathway did not induce cognitive deficits but altered cytochrome oxidase activity in selected brain regions related to the sleep/wake cycle, feeding and motivation, and that anti-angiogenics targeting VEGFA, reduced learning processes. The recent promising effects of phosphatidylinositol-3-kinase (PI3K) inhibitors in cancer therapy, and the crucial role of PI3K in cell proliferation, synaptic plasticity and transmission, led us to question whether PIK3 inhibitors, in particular buparlisib (BKM120 - Novartis Pharmaceutical), may alter cognitive functions and emotional reactivity during cancer treatments.

Method: BKM120 was tested on anxious-like (elevated plus maze) and depressive-like behaviours (tail suspension test, TST; forced swimming task, FST) in C57Bl/6J Rj mice. Spontaneous activity, object recognition memory, motor impulsive behaviours in the dark emergence test and compulsive-like behaviours in the marble burying test were also evaluated.

Results: Buparlisib did not affect memory performances but delayed helplessness in the TST and FST, reduced anxiety/increased impulsivity in the emergence test, and decreased exploratory behaviours and compulsive stereotypy.

Conclusion: Our original observations indicate that inhibition of PI3K is responsible for anti-depressive like behaviour, impulsivity and/or reduced anxiety. It could be associated with a dysfunction of interactions between prefrontal cortex, raphe nucleus and hippocampus sustained by abnormal cross talk between serotonergic and GABA-ergic neurotransmission. This study suggests the beneficial opportunity of co-administration of psychiatric preventive therapeutics or selection of PI3K inhibitors unable to cross the brain blood barrier.
Protecting hippocampal neurogenesis from chemotherapy

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Systemic chemotherapy causes cognitive decline in a proportion of patients, an effect which can be replicated in rodent animal models. Many animal studies have found deficits in hippocampus-specific behavioural tasks which are associated with a long term decline in hippocampal neurogenesis. The cause of this remains unclear. The process of neurogenesis starts with the division of large radial stem cells which span the dentate gyrus. These slow dividing cells produce rapidly dividing progenitors lying parallel to the inner edge of the dentate gyrus in the sub granular zone (SGZ). We have used the Sox1-GFP transgenic mouse in which the cytoplasmic expression of GFP driven by the Sox1 promotor enables the morphology of neural stem and progenitor cells to be recognised. Chronic treatment with 5Fluoruracil (5FU) causes a significant decline in cell proliferation in the SGZ and a loss of radial GFP positive cells. Prior treatment of rats or Sox1-GFP mice with either the antidepressant Fluoxetine or the anti-inflammatory Indomethacin before 5FU treatment, prevents the decline in cell proliferation produced by chemotherapy. We are currently looking at chemotherapy-induced inflammation as a possible mechanism behind the decline in neurogenesis.

Not all dividing cells in the SGZ appear to be equally sensitive to chemotherapy. Approximately 40% of dividing cells are on the surface of the microvasculature in the SGZ and these cells remain after chemotherapy while cells some distance from blood vessels are lost or cease to divide. Co-culture involving cell to cell contact between neural stem cells and either endothelial cells or astrocytes but not 3T3 cells protects them from chemotherapy. An understanding of how elements of the neural stem cell niche in the SGZ affect the susceptibility of neural stem cells to chemotherapy and the protective effects of different pharmaceuticals may reduce the impact of cognitive decline in cancer survivors.
Preclinical development of novel pharmacotherapies using animal models of chemotherapy-induced cognitive impairments

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Background: Our lab and others have shown that experimentally administering chemotherapy drugs to laboratory animals induces cognitive impairments with similar characteristics to those reported clinically. Chemotherapy-treated animals display impairments in tasks that require short- and long-term memory, or executive function. In this talk, I will describe how we have used these models to investigate several promising new pharmacotherapies to prevent and reverse these cognitive impairments.

Method: Recent work with three novel pharmacotherapies will be described: Ibudilast, a phosphodiesterase inhibitor with a long history of clinical use for asthma in Japan, which has recently been shown to reduce microglial activation; Cannabidiol, a non-psychoactive component of cannabis, which has been shown to have powerful anti-inflammatory and anti-oxidative stress properties; Nicotinamide mononucleotide, an endogenous precursor to the mitochondrial metabolite NAD+, which has been shown to reverse metabolic ageing.

Results: All three compounds described above not only prevent and reverse chemotherapy-induced cognitive impairments in laboratory rats, but are also effective against other side effects of chemotherapies, such as peripheral neuropathies and decreased voluntary exercise.

Conclusion: The development of valid animal models of chemotherapy-induced cognitive impairments has been a vital component of the preclinical development of novel and safe potential treatments. All three of the treatments described above have proven clinical safety, and have the potential to be moved into clinical trials quickly. However it remains to be assessed if these treatments might have important interactions with tumours.
Symposium 3
Brain connectivity changes and cognitive impairment after cancer treatment

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Cognitive impairment is a common toxicity of cancer treatment. A better understanding of changes in brain structure and function may provide information regarding the neural basis of cancer-related cognitive impairment and facilitate therapeutic development. Cognition is believed to be supported by dynamic functional brain networks that depend heavily on underlying structural connectivity. Therefore, investigations of brain connectivity may contribute novel information regarding the neurobiologic mechanisms of cancer-related cognitive impairment.

In this symposium, researchers will present the advantages and application of brain connectivity approaches to evaluating the chemotherapy-related neurotoxicity that may underlie cancer-related cognitive difficulties. These presentations will encompass multi-modal methods including resting state functional MRI (fMRI), diffusion tensor imaging and connectomics. Alternate but complementary methodological options for measuring functional connectivity from resting state fMRI will be demonstrated. Brain connectivity associated with both adult-onset and pediatric cancers will be discussed in addition to the relationships between altered brain connectivity and cognitive status.

The research that will be presented demonstrates chemotherapy-related alterations in both structural and functional connectivity including both short-and longer-term brain connectivity changes. These studies consistently show correlations between brain connectivity and cognitive outcome, and demonstrate the complexity of interpreting these relationships.

We aim to engage in a discussion that will highlight the significant potential of brain connectivity as a biomarker of chemotherapy-related cognitive impairment. This discussion will include advantages and disadvantages of these approaches as well as ideas for improving the implementation of these methods in future studies.
Functional hyperconnectivity in resting state networks of testicular cancer survivors 14 years after exposure to BEP chemotherapy

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Purpose: Chemotherapy (CT) for testicular cancer is associated with late impairment of cognitive functioning 1-4. Alterations in functional brain networks due to neurotoxicity of chemotherapy might (partly) underlie these effects.

Methods: We acquired resting-state fMRI in 25 TC survivors who had been exposed to BEP chemotherapy (CT group) and in 22 TC survivors not exposed to chemotherapy (S(urgery) group, completion of treatment on average 14.4 y prior). Within the FSL software package, data were temporally concatenated and decomposed with ICA. Components of interest were selected by visual inspection based on previous literature. A voxel-wise comparison was carried out on the selected components using a dual-regression approach5. Nonparametric permutation tests at a corrected cluster level of p<.05) were used to detect statistically significant differences for each component between the CT and S-only group, correcting for age.

Results: The group ICA estimated 27 components, of which 13 components were found to represent functional resting state networks. Significant hyperconnectivity of the CT group relative to the S group was observed in 4 networks: 1) the precuneus, 2) the sensory and motor function, 3) the executive control and 4) the ventral stream network. In the CT group these networks encompassed brain regions not conventionally considered part of the affected network.

Conclusion: Fourteen years after completion of BEP chemotherapy, TC survivors show hyperconnectivity in functional resting state networks relevant for cognitive functioning. Resting state hyperconnectivity might reflect functional and compensatory over-recruitment of brain regions in response to decrements in neural integrity as a result of late neurotoxicity of BEP chemotherapy. Resting state hyperconnectivity might be a sensitive neuromarker for late neurotoxicity of BEP chemotherapy.
Longitudinal changes in DMN Connectivity following chemotherapy in Breast Cancer

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Purpose: Women treated for breast cancer often experience cognitive complaints. We studied whether longitudinal changes in resting state functional connectivity from pre-treatment to shortly after chemotherapy could possibly underlie these cognitive complaints.

Methods: Fifteen women with early-stage breast cancer scheduled to receive adjuvant chemotherapy underwent resting state fMRI (rs-fMRI) before the start of therapy (t1) and 4 to 6 months after treatment (t2). Fourteen women with early-stage breast cancer who did not receive chemotherapy and 17 matched healthy controls underwent rs-fMRI at matched intervals. Images were preprocessed and warped to MNI space using SPM. Regions within the default mode network (DMN) and frontoparietal network (FPN), both linked with cognitive impairment, were defined as spherical regions of interest (ROIs) around literature-based MNI coordinates1. The functional connectivity was assessed calculating the partial correlations between the different regions within each network. We used one-way ANOVA and paired t-test to examine differences between groups at baseline and changes overtime within groups. A correlation analysis was performed to link the functional connectivity results to the subjective cognitive complaints (CFQ). All analyses were Bonferroni-corrected for multiple comparisons.

Results: Paired t-test revealed significantly increased (p<.05) connectivity from t1 to t2 in the chemotherapy-treated group between the right inferior temporal gyrus (ITG) and anterior medio prefrontal cortex (MPFC) of the DMN. This increase, however, did not correlate with the subjective complaints. In the FPN no significant results were found after Bonferroni-correction. At baseline, no differences were found between chemotherapy-treated patients and controls. This result was not influenced by the inclusion of depression scores.

Conclusion: Our findings provide evidence for longitudinal changes in DMN connectivity following chemotherapy-treatment. This might reflect underlying neurotoxic changes in the brain. Future research will add DTI fiber tractography to study possible related white matter microstructural changes.
Structural Connectome Organization and Cognitive Impairment in Pediatric Acute Lymphoblastic Leukemia

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Purpose: Survivors of pediatric acute lymphoblastic leukemia (ALL) are at increased risk for cognitive impairments. Previous studies consistently demonstrate significant white matter pathology underlying these impairments. We aimed to extend this literature by examining the organization of the white matter structural connectome.

Methods: We applied graph theory to diffusion tensor imaging (DTI) obtained from 31 survivors of ALL age 5-19 years and 39 matched healthy controls. Regions of interest (ROIs) were defined from a standardized atlas and warped into native space. The number of DTI fiber tracts connecting each pair of ROIs was determined and graph theory was applied to model the structural connectome separately for each participant. Connectome properties were quantified and compared between groups using permutation testing. We administered a brief battery of cognitive tests that was used to categorize participants as cognitively impaired or not. Boosted decision tree classification was implemented to determine predictors of cognitive impairment from connectome, demographic and medical variables.

Results: The ALL group demonstrated significantly decreased small-worldness index (p = 0.007) and network clustering coefficient (p = 0.019) as well as greater cognitive impairment (p = 0.027) compared to controls. Decision tree analysis revealed a model of connectome and demographic variables that could automatically classify survivors of ALL as having cognitive impairment or not (accuracy = 0.89, 95%CI = 0.81-1.0, p < 0.0001).

Conclusion: These findings provide further evidence of brain injury in young survivors of ALL, even those without a history of cranial radiation. Efficiency of local information processing, reorganization of hub connectivity and cognitive reserve may contribute to cognitive outcome in these children.
Multimodal neuroimaging examination of brain structure and function after chemotherapy for childhood leukemia

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Purpose: Children treated with chemotherapy for acute lymphoblastic leukemia (ALL) can demonstrate cognitive impairment and altered brain structure and function relative to healthy controls (HC). We previously showed increased frontal activation during working memory processing after ALL chemotherapy that correlated with cognitive performance, suggestive of compensatory alterations in brain function. The present analyses examined integrity of brain white matter using diffusion tensor imaging (DTI) and functional connectivity using resting state fMRI (rsfMRI) to investigate factors potentially related to post-chemotherapy alterations in brain function.

Methods: Participants were children aged 10-15 at least three years post ALL chemotherapy (without radiation) and HC. A comprehensive structural and functional MRI scanning session (including DTI and rsfMRI), neuropsychological assessment, and parental behavioral ratings were completed. DTI data were analyzed using a tract-based spatial statistics (TBSS) approach in FSL. rsfMRI were analyzed using independent component analysis in AFNI and group comparisons in SPM.

Results: ALL patients evidenced significantly greater axial diffusivity in left frontal and temporal white matter tracts relative to HC. On rsfMRI the ALL group showed altered left frontal functional connectivity relative to HC with regions within the default mode network. These changes were observed in the same left frontal region where we previously reported increased working memory-related brain activation in the ALL group relative to HC. Furthermore, resting state and task-based performance activation were highly correlated in this region across participants.

Conclusion: These data provide additional evidence for alterations in brain structure and function after chemotherapy treatment for ALL. The finding of reduced white matter integrity in left frontal and temporal regions, together with altered resting connectivity of left frontal regions which correlated strongly with working memory-related activation, offers further support for the hypothesis that previously seen alterations in task-related brain activation reflect a compensatory process related to dysfunction of underlying neural circuitry.
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