2018 International Cognition and Cancer Task Force Conference

April 9th-11th, Sydney, Australia

PROGRAM BOOK

KEYNOTE SPEAKERS

Dr Florence Joly (Centre François Baclesse, France)

Dr Donald Mabbott (The Hospital for Sick Children, Canada)

Dr Paul Maruff (University of Melbourne, Australia)

Dr Adam Walker (Monash University, Australia)

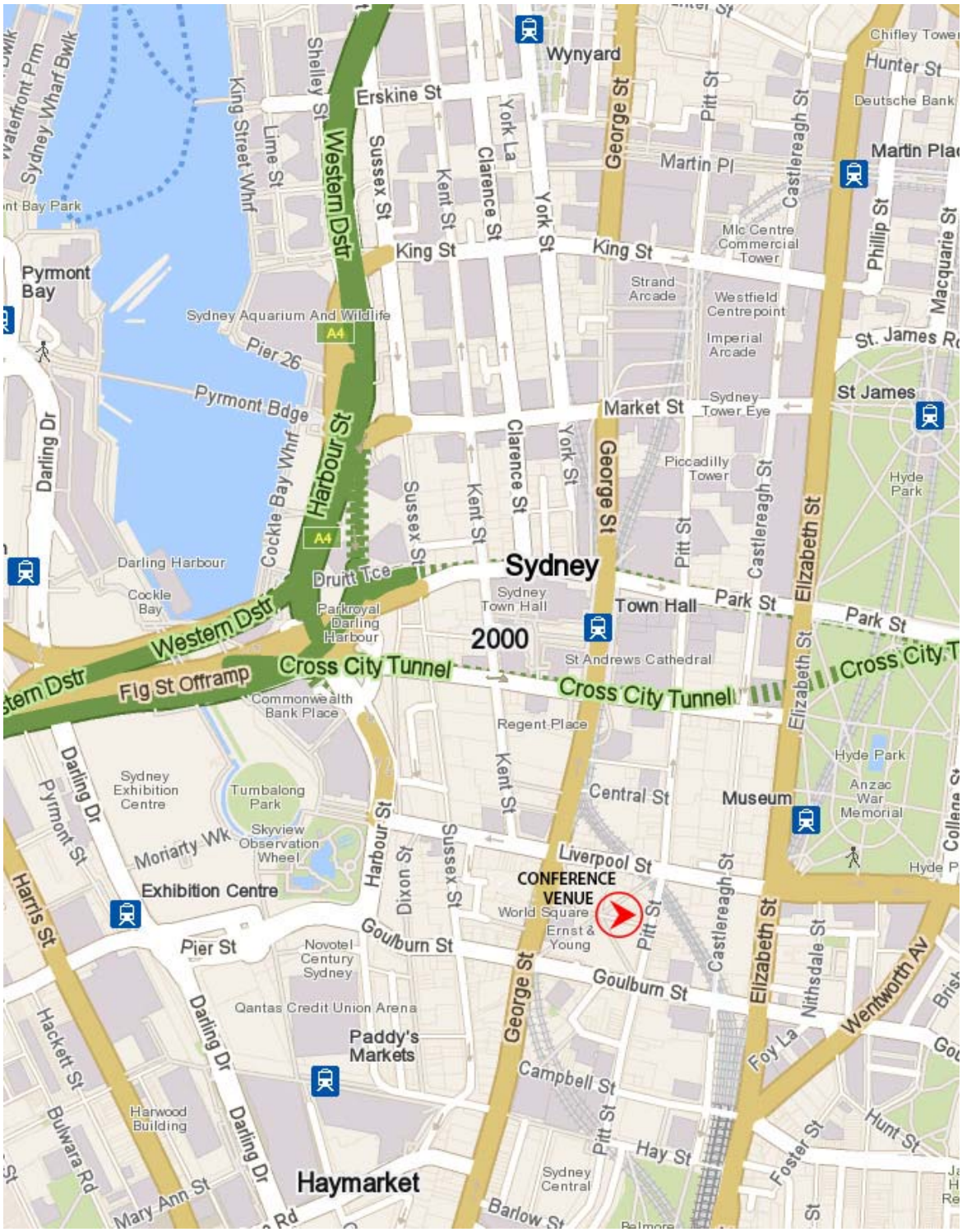
VENUES AND DATES

Main conference: Monday / Tuesday April 9th – 10th

Rydges World Square Hotel

389 Pitt St, Sydney NSW 2000 | Ph: 02-8268 1888

(https://www.rydges.com/accommodation/sydney-nsw/world-square-sydney-cbd/)



Imaging and Preclinical Workshops (optional)

Wednesday April 11th

Imaging workshop: 8.00 – 11.00am

Preclinical workshop: 8.30 – 11.00am,

Charles Perkins Centre, The University of Sydney (www.sydney.edu.au)

Camperdown NSW 2006 | Ph: 02-9351 2222

For full details on the workshops please go to page 10 of the program book.

Sydney public transport planner

Sydney has an extensive public transport network incorporating trains, light rail, buses and ferries. Public transport in Sydney utilises a pre-paid smartcard ticketing system to pay for travel called an Opal card. Opal cards can be purchased through a number of channels, see website link below.

Website: https://transportnsw.info/#/ (includes a trip planner)

https://transportnsw.info/tickets-opal/opal (smartcard ticketing system)

App: https://transportnsw.info/apps

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EDITORIAL

International Cognition and Cancer Taskforce

We are very pleased to welcome you to the 6th biennial ICCTF Cognition and Cancer Conference in Sydney, Australia. The mission of the ICCTF is to advance our understanding of the impact of cancer and cancer-related treatment on cognitive and behavioural functioning in patients with central nervous system cancer and non-central nervous system cancer. 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, and to develop and test interventions to prevent or manage these undesired symptoms and/or toxicities.

The potentially detrimental effects of cancer and related treatments on cognitive functioning are emerging as a key focus of cancer survivorship research. Many patients with central nervous system (CNS) or non-CNS tumours develop cognitive problems associated with their disease and during the course of their treatment that can result in diminished functional independence.

The research conducted by the ICCTF members and others around the world is devoted to increasing our understanding of the incidence, severity, individual risk factors, and causes of cognitive and behavioural dysfunction, as well as investigations into ways to prevent and intervene against these adverse symptoms.

Over the next three days we will hear and have the chance to discuss state-of-the-art research. You will also have the opportunity to network with other researchers working in this field.

We look forward to meeting you as we cruise on Sydney Harbour and admire the sights from Sydney Tower. We hope you are able to spend extra time exploring our beautiful city!

Local conference convenors

Dr Janette Vardy MD PhD, Medical Oncologist, Concord Cancer Centre / The University of Sydney, Sydney

Dr Haryana Dhillon PhD, Behavioural Scientist, The University of Sydney, Sydney

ICCTF Steering Committee members

Dr Tim Ahles PhD, Psychologist, Memorial Sloan Kettering Cancer Centre, New York

Dr Sanne Schagen PhD, Neuropsychologist, Netherlands Cancer Institute, Amsterdam

Dr Janette Vardy MD PhD, Medical Oncologist, Concord Cancer Centre / The University of Sydney, Sydney

Dr Jeffrey Wefel PhD, Neuropsychologist, MD Anderson Cancer Centre, Houston

2018 ICCTF conference abstract review committee

Tim Ahles
Catherine Bender
Lori Bernstein
Hélène Castel
Monique Cherrier
Peter Cole
Denise Correa
Michiel de Ruiter
Haryana Dhillon
Jorg Dietrich
Kim Edelstein
Patti Ganz
Karin Gehring
Bénédicte Giffard
Heather Green
Michelle Janelsins
Heather Jim
Ian Johnston
Florence Joly
Shelli Kesler
Kevin Krull
Jeannie Mandelblatt
Brenna McDonald
John Merriman
James Root
Stephen Sands
Andrew Saykin
Sanne Schagen
Dan Silverman
Brent Small
Ian Tannock
Janette Vardy
Adam Walker
Jeffrey Wefel
Gordon Winocur

Acknowledgements

We would like to thank Anne Warby for assistance with organising the conference, and Ann Dixon and Cathy Barnett for their support during the conference.

MAIN PROGRAM & WORKSHOPS

PROGRAM: MAIN CONFERENCE

Monday April 9th

08.00 – 09.00
Conference Registration

09.00 – 09.10
Introduction and Welcome:
Dr Janette Vardy
Acknowledgement to the traditional owners: Kathryn Dodd Farrawell

09.10 – 10.10
Highlights and future directions in cognition and cancer
(15 mins each)
Chair: Dr Sanne Schagen

Neuropsychology: Dr Janette Vardy, The University of Sydney

Preclinical models: Dr Hélène Castel, Normandie University

Neuroimaging: Dr Daniel Silverman, University of California, Los Angeles

Rehabilitation: Dr Haryana Dhillon, The University of Sydney

10.10 – 10.30
REFRESHMENT BREAK

10.30 – 11.30
Chair: Dr Tim Ahles

Plenary: Dr Paul Maruff, University of Melbourne
The use of new technologies to assess cognition in oncology: Opportunities and challenges

11.30 – 12.30
Oral presentations
Chair: Dr Kevin Krull

11.30 – 11.50
Dr Shelli Kesler, University of Texas MD Anderson Cancer Center
Accelerated brain aging in patients with breast cancer post chemotherapy

11.50 – 12.10
Dr Tim Ahles, Memorial Sloan Kettering Cancer Center
Association of frailty and cognitive function in older breast cancer survivors

12.10 – 12.30
Dr Kathleen Van Dyk, UCLA Jonsson Comprehensive Cancer Center
The effect of endocrine therapy (ET) on neuropsychological functioning in breast cancer survivors (BCS) over time

12.30 – 14.00
LUNCH & POSTER SESSION

14.00 – 15.00
Chair: Dr Janette Vardy
Plenary: Dr Florence Joly, Centre François Baclesse
Immunotherapy agents and cognition

15.00 – 15.40
Oral presentations
Chair: Dr Andrew Saykin

15.00 – 15.20
Ms Danielle Tometich, Indiana University-Purdue University Indianapolis
Sleep disturbances and cognitive decline in older cancer patients: Interaction with APOE e4 and BDNF genotype

15.20 – 15.40
Dr Lisa Wu, Northwestern University Feinberg School of Medicine
Systematic light exposure and cognition in hematopoietic cell transplant survivors: A pilot study

15.40 – 16.00
REFRESHMENT BREAK

16.00 – 17.00
Oral presentations
Chair: Dr Andrew Saykin

16.00 – 16.20
Dr Ashley Henneghan, University of Texas MD Anderson Cancer Center
Predicting chemotherapy-related brain injury using connectomics and machine learning

16.20 – 16.40
Dr Michiel de Ruiter, Netherlands Cancer Institute
Changes in the executive functioning network in breast cancer patients: Preliminary results from a prospective fMRI study with 6 month and 3 year follow up

16.40 – 17.00
Dr Kimberly van der Willik, Netherlands Cancer Institute
High levels of inflammatory markers in breast cancer survivors 20 years after cessation of chemotherapy are associated with impaired cognitive performance

18.30 – 22.30
CONFERENCE DINNER

PROGRAM: MAIN CONFERENCE

Tuesday April 10th

09.00 – 10.00
Chair: Dr Haryana Dhillon

Plenary: Dr Adam Walker, Monash University
The influence of cancer on cognition in preclinical models

10.00 – 10.20
REFRESHMENT BREAK

10.20 - 12.00
Oral presentations
Chair: Dr Linda Ercoli

10.20 – 10.40
Ms Antigone Matsos, The University of Sydney
Nicotinamide mononucleotide prevents and reverses doxorubicin and oxaliplatin-induced fatigue and memory impairments in the laboratory rodent.

10.40 – 11.00
Dr Jorg Dietrich, Massachusetts General Hospital
Bone marrow is critical for brain repair after radiation injury

11.00 – 11.20
Dr Ian Johnston, The University of Sydney
Cannabidiol as an effective treatment against oxaliplatin-induced memory impairments and peripheral neuropathies

11.20 – 11.40
Dr Denise Correa, Memorial Sloan Kettering Cancer Center
Cognitive functions and dopaminergic polymorphisms in brain tumor patients

11.40 – 12.00
Dr Sabine Deprez, University Hospitals Leuven, KU Leuven
Impact of a mindfulness-based intervention on chemotherapy-induced cognitive dysfunction and brain alterations: A pilot study

12.00 – 13.00
LUNCH

13.00 – 14.00
Chair: Dr Jeff Wefel

Plenary: Dr Donald Mabbott, The Hospital for Sick Children
Cognitive and neuroimaging outcomes in cognitive/brain rehabilitation approaches

14.00 – 15.00
Oral presentations
Chair: Dr Michelle Janelsins

14.00 – 14.20
Dr Ingrid Tonning Olsson, St. Jude Children's Research Hospital
Neurocognitive and neuroimaging outcomes of anesthesia exposure in long-term survivors of childhood acute lymphoblastic leukemia

14.20 – 14.40
Dr Nicholas Phillips, St. Jude Children's Research Hospital
Cerebellar volumes and neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy alone

14.40 – 15.00
Dr Tara Brinkman, St. Jude Children's Research Hospital
Genome-wide association study of attention problems and executive dysfunction in adult survivors of childhood leukemia

15.00 – 15.20
Round-up and presentations: Dr Janette Vardy

15.20 – 17.00
POSTER SESSION WITH WINE AND CHEESE RECEPTION

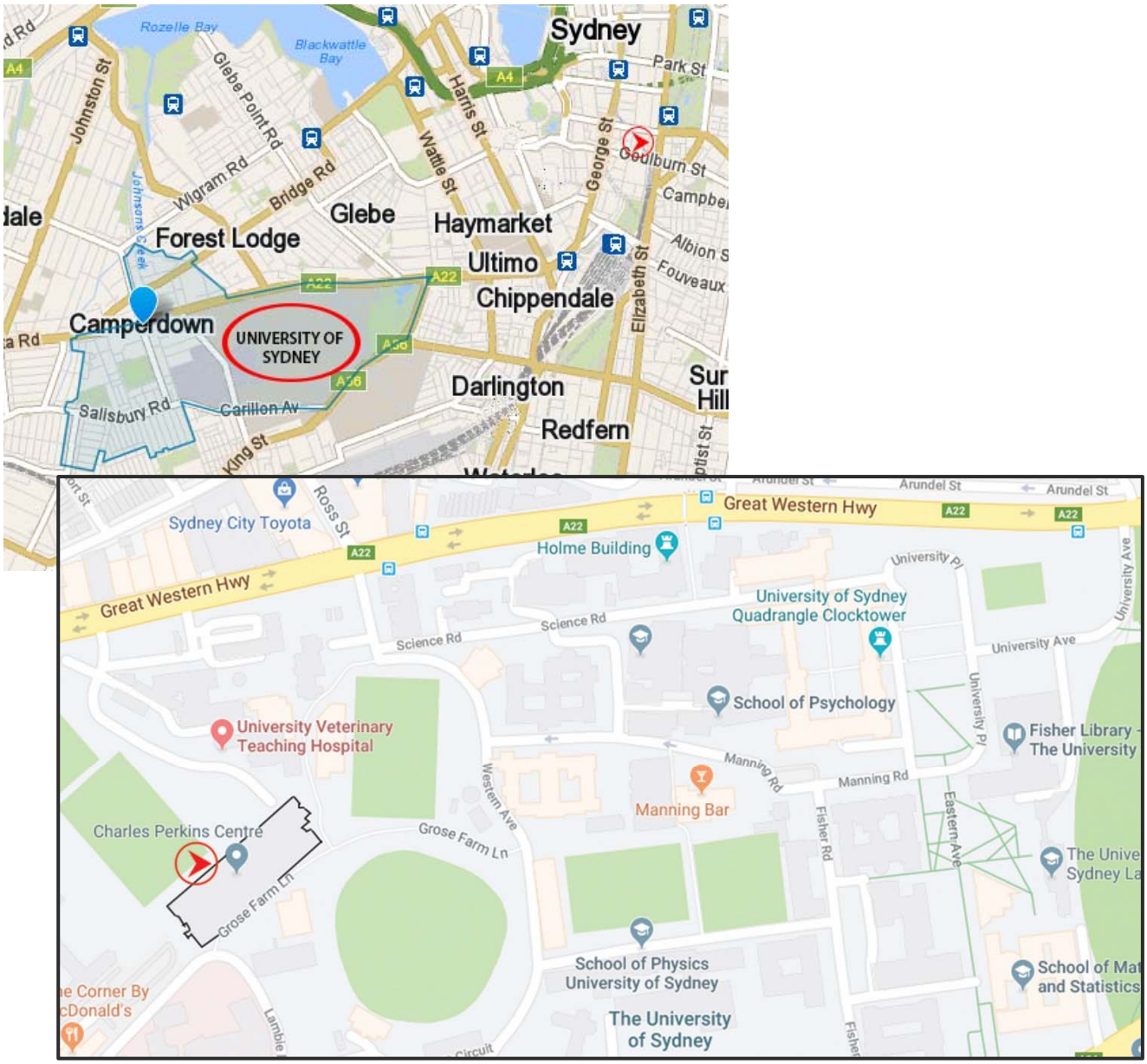
IMAGING AND PRECLINICAL WORKSHOPS

Wednesday, April 11th (Imaging: 8.00 – 11.00am / Preclinical: 8.30 – 11.00am)

Charles Perkins Centre (CPC), The University of Sydney

Seminar Rooms 2.1 and 2.2 (located on level 2 of the CPC)

University maps: http://sydney.edu.au/maps/campuses/?area=CAMDAR



The Charles Perkins Centre is located towards the western end of the Camperdown campus on Grose Farm Lane, which runs off Western Avenue.

Travelling to the University

There are a number of ways to travel to the University, with both bus and rail public transport options. Alternatively the University is only a short taxi or Uber trip from the city centre (approximately 15-20 minutes).

By bus

The University is situated on several major bus routes which depart from the city and there are convenient stops on Parramatta Rd and City Rd at the University's main entrances.

For stops on Parramatta Road (closest to the Charles Perkins Centre) catch routes 412, 413, 436, 438, 439, 440, 461, 480, 483 or Metrobus M10 and alight at the 'Ross Street Gate' stop (TransportNSW Stop ID 205021).

For stops on City Road (which borders the eastern side of the Camperdown campus and requires a slightly longer walk to reach the Charles Perkins Centre) catch routes 422, 423, 426, 428, 370, 352 or Metrobus M30 and alight at the 'City Rd before Butlin Ave' stop (TransportNSW Stop ID 200817).

By train

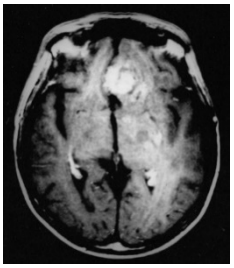
The Charles Perkins Centre is around 20 minutes' walk from Redfern train station, and Redfern station is only a limited number of stops from the main city stations (one stop from Central station, two stops from Town Hall and three stops from Wynyard). When you exit Redfern station turn left down Lawson Street, left along Abercrombie Street, right into Codrington Street, and then cross City Road to the main Camperdown Campus.

Alternatively from Central station it is about a 15 minute walk down Parramatta Rd to the main entrance of the University, just behind Victoria Park.

Imaging Workshop (8.00–11.00am)

Organising Committee Members

Michiel de Ruiter
Sabine Deprez
Brenna McDonald
Andrew Saykin
Daniel Silverman



Part I

Overview of studies since last meeting (for experts)

Data pooling project

ICCTF Neuroimaging Group Guidelines paper

Cutting-edge subjects ripe for multi-centre collaboration?

- Big data issues, multi-omics, genetics, and informatics
- Prediction and diagnosis of cognitive decline assisted by neuroimaging
- Image-guided selection and monitoring of therapy

Refreshment break *

Part II

How to move the field forward? Brain-storming sessions in small groups

Summaries by each group

The imminent future – where do we go from here? Concrete ideas for grant proposals

Preclinical Workshop (8.30–11.00am)

Organising Committee Members

Hélène Castel
Ian Johnston
Adam Walker

Part I

Overview of studies since last meeting

Review of the recommendations proposed since the 2016 ICCTF Amsterdam Animal Research Working Group (Guidelines paper). Issues to discuss:

- Better animal models of chemotherapy or cancer-induced cognitive impairment.
- Reducing duplication and redundancies
- Increasing replicability and comparison by standardising methods, doses, dosing schedules; cognitive and emotional tests
- Experience sharing and reporting of unsuccessful studies
- Translational studies from clinic to pre-clinic and *vice versa*

Refreshment break *

Part II

Presentation of the different future directions:

- How to move the field forward?
- Developing complex and better animal models
- Improving knowledge between cognitive domains and neurobiological mechanisms
- Testing of strategies of intervention (pharmacology and/or behavioural)
- Finding international grants, from bench to bed and bed to bench

* Please note: refreshments are not provided but Taste Café is situated just outside the Charles Perkins Centre and serves premium Campos coffee and snacks.

NETWORKING / SOCIAL EVENTS

CONFERENCE DINNER

Monday, April 9th from 6.30 – 10.30pm @ STUDIO, Sydney Tower

Level 4, Sydney Westfield Centre (between Pitt and Castlereagh Streets), Sydney NSW 2000

Ph: 02-8001 6760

Access: Enter Westfield Sydney at the corner of Market & Castlereagh Streets. Take the escalator up one level to Level 4. The Sydney Tower Dining lifts and reception desk will be on the left. Check in at reception to be directed to the venue.

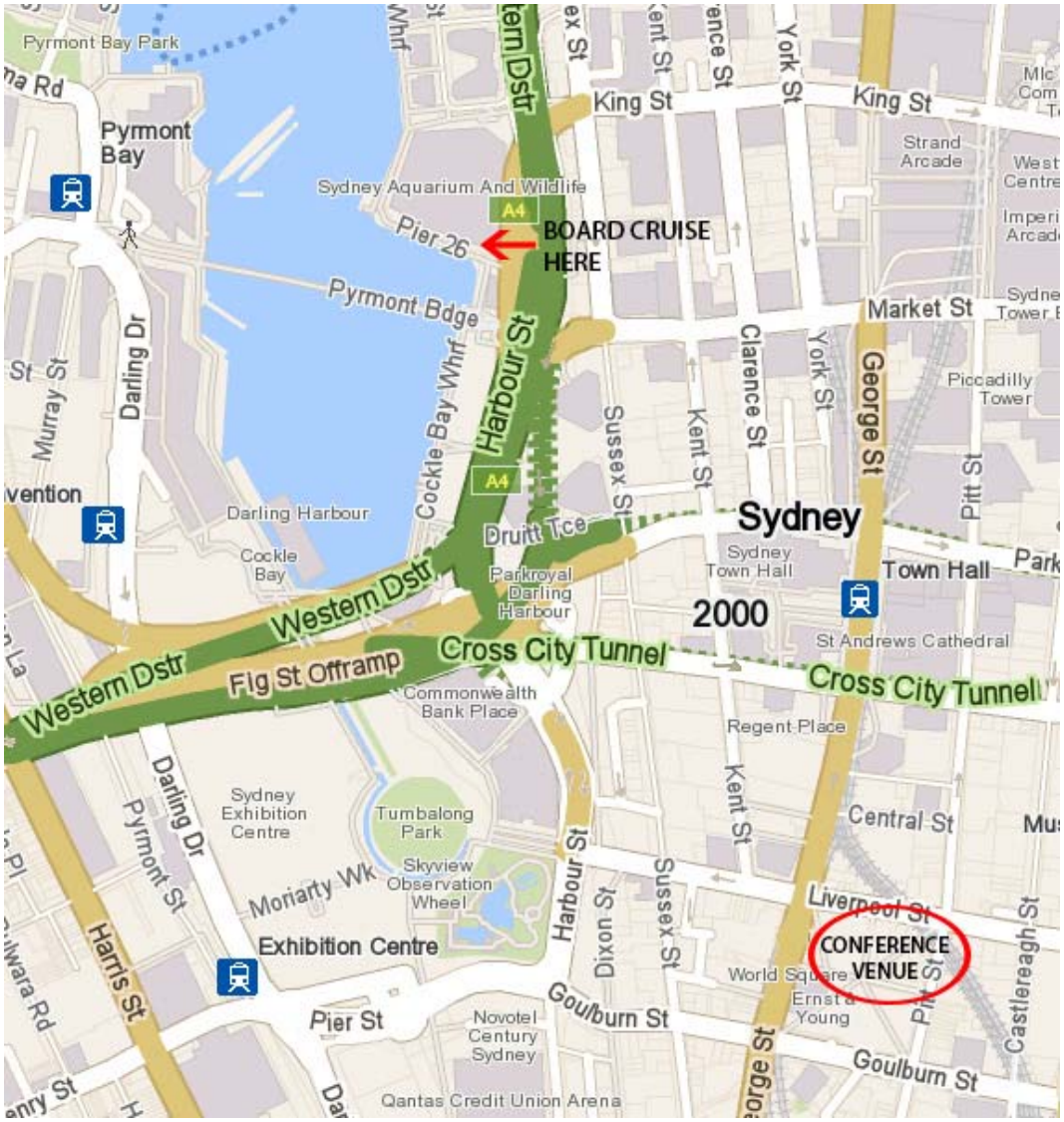
STUDIO, Sydney Tower is Sydney's highest private event space and bar, perched 305 metres above Sydney's CBD with 220 degree views spanning the harbour, Sydney Harbour Bridge and the headlands.

STUDIO is located within comfortable walking distance from the conference venue or a short taxi/Uber trip.

'MEET THE EXPERTS' NETWORKING CRUISE

Wednesday, April 11th from 1.00 – 4.00pm with Captain Cook Cruises

Board the cruise vessel from Pier 26 at Darling Harbour, which is located just to the west of the city centre and next to the SEA LIFE Sydney Aquarium.



This is an opportunity to network and socialise with your colleagues and peers while enjoying a 3-hour cruise on stunning Sydney Harbour on one of Captain Cook Cruises' luxury vessels. A delicious buffet lunch and drinks will be served during the cruise.

If you are attending one of the workshops at The University of Sydney in the morning you can travel to Pier 26 at Darling Harbour by public transport or it is about a 15 minute taxi / Uber trip. The University is situated on several major bus routes which head into the city, either from Parramatta Road or City Road. There are no direct bus routes between the University and Darling Harbour so there is some walking required once you alight in the city. You can plan your trip at: https://transportnsw.info/.


CAPTAIN
COOK III
Captain Cook
Cruises
Captain Cook Cruises
CAPTAIN COOK III

CONFERENCE SPONSORSHIP

CANCER RESEARCH NETWORK, The University of Sydney

We would like to acknowledge the generous support of the Cancer Research Network (CRN), The University of Sydney, in providing funding and administrative assistance for the conference.

The CRN, established in 2006, is a cross-Faculty initiative of the University. The CRN links cancer researchers in the University and its teaching hospitals and affiliated research institutes and institutions to build high quality cancer research capacity and achieve international cancer research excellence in areas of strength.

For further information please visit the CRN's website: http://sydney.edu.au/cancer-research/

POSIT SCIENCE CORPORATION

We would like to acknowledge the generous support of Posit Science Corporation in providing funding for student awards and travel grants for the conference.

Posit Science Corporation is an American company providing brain fitness software and services. The company was founded in 2002 by neuroscientists Dr Michael Merzenich and Dr Henry Mahncke to develop brain health programs based on the latest advances in neuroscience research. The company's flagship product is BrainHQ (www.brainhq.com), a software package designed to improve memory, attention, mental processing speed, interpersonal skills, and overall intelligence. There is also ongoing research in specific clinical conditions. Posit Science helps people be at their best throughout their lives by providing brain-training exercises clinically proven to improve cognitive performance.

PLENARY SESSIONS

IMMUNOTHERAPY AGENTS AND COGNITION

Professor Florence Joly, MD PhD, Medical Oncologist, Centre François Baclesse Comprehensive Cancer Centre, Caen, FRANCE

Over the last decade a tremendous amount of data has been published on how cancers generate immune tolerance. Anticancer immunity is the subject of a multitude of factors that contribute to the generation of activated T Cell immunity or tolerance. A paradigm shift is happening where instead of targeting the tumour cells, new molecules target the immune system to break the cancer tolerance and stimulate the anti-tumour immune response. Checkpoint inhibitors, the most developed immunotherapy agents, are monoclonal antibodies blocking key inhibitory receptors of T Cells such as cytotoxic T Lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 and its ligand (PD-1 and PDL-1). These molecules have led to some long-term responses in advanced cancers, due to polyclonal adaptive anti-tumour immunity with memory.

Due to the immunomodulatory mechanism of action, immunotherapy agents can generate a wide range of adverse events, including neurological toxicities (4-6% with one agent, 12% with combination therapy). Most neurologic adverse events are grade 1-2 and non-specific symptoms such as headache. Chronic fatigue is common and may be linked to cognitive fatigue and complaints. However, no clinical study has focused on the impact of immunotherapy agents on cognitive function. Cognitive impairment (executive functions) has been observed in a preclinical model evaluating the combination of peripheral radiation and immunotherapy agents in mice with peripheral tumours, with an increase of CD 68 + activation in microglia in the hippocampus and changes in CNS pro inflammatory cytokines. However the real impact of immune modulators on the brain is not well known.

BIOGRAPHY: Dr Florence Joly is a medical oncologist in the François Baclesse Comprehensive Cancer Centre in Caen, France. She did her training at the Universities of Grenoble and Caen, in France and a fellowship in 2003 at the Princess Margaret Hospital in Toronto with Prof Ian Tannock. Dr Joly is head of the Clinical Research Department of the François Baclesse Centre and Vice President of the French Research Group on Supportive Care and the GINECO group. She treats patients with gynaecology and urinary cancers and is author of 186 indexed publications. She is a member of the research Unit INSERM U-1086, Anticipe (Lower Normandy University), and leads a large multidisciplinary research program on quality of life: particularly long-term quality of life among survivors and impact of cancer treatments on cognition. She heads the Ligue labelled French cancer platform dedicated to Cancer and Cognition, supported by the North-West Canceropole (www.cancerandcognition.com). This multidisciplinary group of researchers has studies from bench to bedside on chemotherapy in the elderly, targeted therapies, and a new generation of hormone therapy.

COGNITIVE AND NEUROIMAGING OUTCOMES IN COGNITIVE/BRAIN REHABILITATION APPROACHES

Associate Professor Donald Mabbott, PhD, Program Head – Neurosciences & Mental Health, The Hospital for Sick Children, Toronto, CANADA

Quantitative neuro-imaging has allowed us to measure the impact of paediatric brain tumours on brain structure and function and ultimately relate this to thinking and learning. I will discuss how we have used different neuro-imaging approaches to characterize white matter structure and neural function in paediatric brain tumour survivors. I will consider how the tissue properties of white matter structure may affect cognition in these children. Finally, I will present new research regarding white matter plasticity and how such plasticity can be harnessed for brain repair and cognitive restoration in this vulnerable population of patients.

BIOGRAPHY: Dr Donald Mabbott is a psychologist with the Paediatric Brain Tumour Program in the Division of Haematology/Oncology at The Hospital for Sick Children, a senior scientist in the Research Institute at The Hospital for Sick Children, and an associate professor in the Department of Psychology at the University of Toronto. He provides clinical neuropsychology services to children with brain tumours and their families and has a research program in developmental neuropsychology.

Dr Mabbott's research uses innovative brain imaging techniques (i.e. Diffusion Tensor Magnetic Resonance Imaging; Magnetoencephalography) and psychological tests to study the impact of brain injury on how the brain grows and develops in childhood. Specifically, he examines the impact of treatment for paediatric brain tumours on the structure and function of the brain.

The overall goal of his research is to reduce the burden of brain tumours and their treatment to improve the quality of life for children. His work has been instrumental in documenting the thinking and learning difficulties children treated for brain tumours experience and the underlying damage to brain structure and function that cause these problems.

THE USE OF NEW TECHNOLOGIES TO ASSESS COGNITION IN ONCOLOGY: OPPORTUNITIES AND CHALLENGES

Professor Paul Maruff, PhD, Honorary Professor, The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, AUSTRALIA

There are many developments occurring in neuroscience and neuro-psychology that can now provide scientists with new opportunities for understanding the effects on cognition of different cancers and their therapies. Our field is sophisticated with the assessment of cognition using pen and paper or computerised instruments tests applied in formal assessments, however, as with all approaches to measurement of cognition there are issues that warrant consideration with application of new developments for measuring cognition. I will outline recent approaches that have been applied to understanding the effects of disease on cognition in cancer and in other areas of medicine. These will be: a) remote or unsupervised cognitive assessment using web-based tests; b) assessment of daily changes in cognition using smartphone apps; c) assessment of adaptive behaviour using digital technologies; and d) neuropsychological approaches to adaptive behaviour. I will argue that rather than replacing the current assessment methods these new approaches allow us to understand different aspects of cognition and how they can inform models of CNS dysfunction in cancer, as well as providing a basis for optimal patient care. However, used properly, knowledge arising from the use of new approaches to measuring cognition should enhance current understanding of cognition in cancer.

BIOGRAPHY: Dr Paul Maruff is one of the founders of Cogstate. He is a neuropsychologist with expertise in the identification and measurement of subtle behavioural and cognitive dysfunction. Dr Maruff's research integrates conventional and computerized neuropsychological testing with cognitive neuroscientific methods to guide decision making in drug development and in clinical medicine.

He has worked extensively on method to identify subtle neurocognitive impairment, and to assess the efficacy of pharmacological treatment, in Alzheimer's disease, mild cognitive impairment and the HIV dementia complex. He has extended this approach to identify cognitive dysfunction, and monitor treatment efficacy in psychiatric diseases such as schizophrenia, obsessive-compulsive disorder and depression in adults, and attention deficit disorder, developmental dyspraxia and substance abuse in children.

Dr Maruff remains an active researcher. He is Professor at the Florey Institute for Neuroscience and Mental Health. He is clinical co-chair of the Australian Imaging Biomarker and Lifestyle (AIBL) study. He has published over 250 research articles in international peer-reviewed scientific journals, and has co-authored 10 book chapters.

THE INFLUENCE OF CANCER ON COGNITION IN PRECLINICAL MODELS

Dr Adam Walker, PhD, National Breast Cancer Foundation Postdoctoral Fellow, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, AUSTRALIA

Translation is a two way street that requires collaboration between the lab bench and the clinic. Animal models are a necessary piece of that collaboration because they can answer key questions around causal mechanisms not possible in the clinic. Located at Monash Institute of Pharmaceutical Sciences, I am invested in novel drug design and repurposing safe available anti-inflammatories and other drugs to combat cancer-associated cognitive impairment. In my plenary, I will outline how I am using syngenic, orthotopic mouse models of metastatic breast cancer to explore bidirectional communication between the brain and tumour. I will discuss the need for tumour bearing mouse models to accurately identify the mechanisms of cancer-associated cognitive impairment and will identify potential intervention strategies that have emerged from this work. I will also outline how I use tumour bearing mouse models to investigate the impact of post-operative cognitive decline and 'chemobrain' to accurately mimic the cancer patient experience. I will present my mouse model of cancer survivorship, in which 'survivor' mice are created to identify the mechanisms responsible for sustained cognitive impairment in survivors after cancer and cancer treatment.

BIOGRAPHY: Dr Adam Walker's research program investigates the role of neuroinflammation in psychiatric illness and cognitive function. He completed his PhD at the University of Newcastle and undertook a successful postdoctoral fellowship at the prestigious MD Anderson Cancer Center, USA. Now located at Monash Institute of Pharmaceutical Sciences, Dr Walker is invested in novel drug design and repurposing safe available anti-inflammatories and other drugs to combat cancer-associated cognitive impairment.

As a National Breast Cancer Foundation research fellow, Dr Walker is applying his expertise in neuroinflammation to identify novel mechanisms and treatments for chronic central nervous system (CNS)-related side-effects of cancer and cancer treatment. These mechanisms include neuroinflammation, the IDO-kynurenine pathway and blood-to-brain transport mechanisms. To accomplish this he uses syngenic, orthotopic mouse models of breast cancer metastasis to explore bidirectional communication between the brain and tumour. He has pioneered the repurposing of novel drugs and supplements (aspirin, ketamine and leucine) to treat inflammation and cancer-associated cognitive impairment and depression.

ORAL PRESENTATIONS: MONDAY & TUESDAY

Accelerated brain aging in patients with breast cancer post chemotherapy

Authors: Vikram Rao[1], Ashley Henneghan[2], Shelli Kesler[2]

Institutional affiliations: [1]University of Texas MD Anderson Cancer Center, Department of Neuro-oncology, Houston, USA. [2]University of Texas MD Anderson Cancer Center, Department of Neuro-oncology, USA.

Corresponding author: vvrao@mdanderson.org

Background: Breast cancer and chemotherapy are often associated with abnormalities in brain structure that could be attributed to accelerated brain aging. The discrepancy between brain age and chronological age has promising potential as a useful biomarker for cognitive disorders and impairments including cancer related cognitive impairments. We aim here to assess brain aging as predicted by brain anatomical measures in patients with breast cancer (BC) who undergo chemotherapy.

Methods: Structural MRI data were acquired from 43 newly diagnosed patients with BC (mean age = 49.44 +/- 8.92 years) and 50 matched female controls. Patients were imaged at pre-treatment baseline, 1 month post-chemotherapy and 12 months post-chemotherapy (yoked intervals for controls). Freesurfer-based models were used to extract cortical thickness measurements. These features were then used to predict brain age with Brain-Age Regression Analysis and Computation Utility Software (BARACUS). BARACUS employs established machine learning algorithms for characterizing brain age using only neuroimaging measures. The difference in predicted brain age and chronological age was compared between breast cancer and control groups longitudinally with linear mixed modeling and cross-sectionally with t-tests.

Results: There was no significant difference between the two groups at baseline. Brain age discrepancy (predicted minus chronological age) showed a significant increase ($p<0.05$) in the BC group compared to controls from post-chemotherapy to 12 month follow-up ($p = 0.032$). Further, at post-chemotherapy, the BC group showed significantly higher brain age compared to controls ($p = 0.018$).

Conclusion: We demonstrated evidence of accelerated brain aging in middle-aged, post-chemotherapy patients with BC. Increased brain age might make the brain more susceptible to other neurocognitive disorders and could be one of the important factors contributing to cognitive impairment in BC survivors. Our results also have broader implications of using brain aging as a potential biomarker of general neurodegeneration in other populations.

Association of frailty and cognitive function in older breast cancer survivors

Authors: Tim Ahles[1], Elizabeth Schofield[1], Yuelin Li[1], Elizabeth Ryan[1], James Root[1], Sunita Patel[2], Katrazyna McNeal[1], Heidi Tan[2], Vani Katheria[2], Arti Hurria[2]

Institutional affiliations: [1]Memorial Sloan Kettering Cancer Center, New York, USA. [2]City of Hope Comprehensive Cancer Center, Duarte, USA.

Corresponding author: ahlest@mskcc.org

Background: The purpose of this study was to examine the association between frailty and cognitive function in older (>60 years) breast cancer survivors.

Methods: Breast cancer survivors 55 or older at the time of diagnosis and were 5-15 year, disease-free survivors (N=298, age range 62-89) and age and education matched non-cancer controls (N=153, age range 60-91) were evaluated with standardized neuropsychological measures grouped into domains (attention, processing speed, and executive function [APE], learning and memory [LM], and visual spatial [VS]). Frailty was assessed using the Deficit Accumulation Frailty Index (DAFI). Propensity analysis was used to control for stage and tumor characteristics that could influence treatment choice.

Results: Cancer survivors scored lower on the LM domain compared to controls (p=0.004), but no differences were seen for the APE and VS domains. Using frailty as a continuous measure pooled across groups, higher frailty scores were strongly associated with lower levels of cognitive function across all domains: APE (p=0.002), LM (p=0.001), and VS (p=0.009). Inclusion of group (chemotherapy, no chemotherapy, and non-cancer controls) revealed that the inverse association between frailty and cognitive function was observed in the cancer survivor groups for the APE and LM domains but not in the non-cancer group. Interestingly, the strongest associations were observed in the no chemotherapy group, perhaps related to the fact that less fit older adults are less likely to treated with chemotherapy.

Conclusion: As our population ages, there are multiple factors that can influence cognitive aging, including the diagnosis of cancer and exposure to cancer treatments. The results of this study suggest that the development of frailty in the context of a history of breast cancer diagnosis and treatment influences the pattern of cognitive aging and demonstrates the importance of the assessment of frailty in studies of cognition in older breast cancer survivors.

The effect of endocrine therapy (ET) on neuropsychological functioning in breast cancer survivors (BCS) over time

Authors: Kathleen Van Dyk[1], Catherine M. Crespi[2], Julienne E. Bower[3], Laura Petersen[4], Patricia A. Ganz[5]

Institutional affiliations: [1]UCLA - Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, Los Angeles, USA. [2]UCLA - Jonsson Comprehensive Cancer Center, Dept. of Biostatistics Fielding School of Public Health, Los Angeles, USA. [3]UCLA - Jonsson Comprehensive Cancer Center, Depts. of Psychology and Psychiatry/Biobehavioral Sciences, Los Angeles, USA. [4]UCLA - Jonsson Comprehensive Cancer Center, Los Angeles, USA. [5]UCLA - Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, Fielding School of Public Health, Los Angeles, USA.

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Background: In contrast to the effects of primary cancer treatments on cognition, the adverse cognitive effects of ET are less well-studied in BCS. Evidence from available neuro-psychological and self-report studies raise concern about the risks of ET, but are often limited to the months following primary cancer treatment. Since ET is often taken for years, we aimed to address this gap by evaluating the neuropsychological effects of ET over time.

Methods: BCS underwent neuropsychological assessments after primary cancer treatment and before ET if indicated (n=189; mean age = 51.35 ±8.34), at 6-months (n=174), 12 months (n=172), and were invited for an additional follow-up approximately 4 years later (n=103). Standard neuropsychological domain scores were derived from sample-based z-scores. We developed linear mixed models testing the main effects and interaction terms of ET and chemotherapy exposure over time on domain scores. ET was modeled as a time varying factor and all models included age and IQ as fixed effects.

Results: No effects of ET or chemotherapy were observed in models of learning, memory, visuospatial, and attention domains. ET x chemotherapy and ET x chemotherapy x time terms significantly contributed to the model of executive function ($F(1,322.413)=5.76, p=.02$, $F(7,238.537)=3.25, p=.003$), driven by improvement observed only in those who were not on ET and never received chemotherapy. An ET x chemotherapy x time term marginally contributed to the model of processing speed ($F(9,197)=1.925, p=.05$), also suggesting improvement in those not on ET with no chemotherapy history.

Conclusion: ET dampens improvement over time in executive functioning and processing speed among those without chemotherapy exposure. This may reflect reduced practice effects, a marker of cognitive compromise. Although the magnitude of effects are small, follow-up study of implications for functioning and quality of life are critical.

Sleep disturbances and cognitive decline in older cancer patients: Interaction with *APOE* e4 and *BDNF* genotype

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Background: Sleep disturbance is a risk factor for cognitive decline in non-cancer populations, but its role is less clear among cancer survivors, and there is little data on whether effects vary by genotype.

Methods: Newly diagnosed stages 0-3 female breast cancer patients (n=333) ages 60+ without dementia or neurological disease were recruited at six US sites from August 2010-December 2015. Participants completed surveys and neuropsychological tests before systemic therapy, and 12 and 24 months later; biospecimens were obtained for genotyping. Sleep disturbance was characterized by self-report of restless sleep and not sleeping well and was separated into two time-varying components: within-person changes and between-person differences. Standardized neuropsychological test scores were grouped into domains (attention, processing speed, and executive function [APE] and learning and memory [LM]). Fluctuation models tested the effect of sleep disturbances and interactions of sleep with *APOE* (e4 vs. other) or *BDNF* (Val/Val vs. any Met) on cognition, considering covariates.

Results: Among patients, 36% reported sleep disturbances. Within-person sleep disturbances affected APE scores, with participants performing more poorly at times when they had sleep disturbance vs. not (Est [SE]=-.08 [.04], P=0.04), but genotype and genotype-sleep interactions in predicting APE were not significant. Between-person sleep disturbance was associated with lower LM scores (-0.29 [.1], P=0.03), with a significant *APOE* e4 genotype interaction (P=0.002). *APOE* e4 carriers with sleep disturbances had lower LM scores than the other groups. The interaction of sleep with *BDNF* was not significant (P=0.12).

Conclusion: Sleep disturbances are prevalent and a risk factor for cognitive decline among older breast cancer patients, especially learning and memory decline among those with vulnerability based on the *APOE* e4 genotype. Sleep assessment may be important in survivorship care and as an intervention target.

Systematic light exposure and cognition in hematopoietic cell transplant survivors: A pilot study

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Background: Hematopoietic cell transplant (HCT) survivors may experience a range of co-occurring cancer-related symptoms including cognitive impairment (CRCI). Systematic light exposure using bright white light (BWL) has shown promise as a treatment for cancer-related symptoms (e.g, fatigue). This study investigated the preliminary efficacy of BWL to treat CRCI and assessed treatment satisfaction.

Methods: Fifty-six HCT survivors 1-5 years post-transplant (mean age 60) screened for mild cognitive impairment using computerized neuropsychological tests (i.e., ≥1 SD below the mean on ≥1 subtest) were randomized to BWL or an established comparison dim red light (DRL) condition. Participants were instructed to use the light box for 30 minutes/morning for 28 days. Standardized measures of objective (primary outcome) and self-reported cognitive functioning (secondary outcome) were administered at baseline, the end of the intervention, and 3-weeks post-intervention. Preliminary efficacy was examined using linear mixed models. Treatment satisfaction was assessed using an established 4 point Likert-scale question.

Results: There were statistically significant improvements over time in both groups in objective ($p<.0001$) and self-reported cognition ($p=.034$). Linear mixed models indicated no significant time by group effects for objective ($p=.20$) nor self-reported cognition ($p=.41$). Seventy-two percent of participants were satisfied with the intervention to some extent (scores between 2 and 4) with no significant difference between groups ($p=.87$).

Conclusion: Although improvements to objective and self-reported cognition were evident in both groups, there was no specific hypothesized effect of BWL over DRL. It is unclear whether changes over time were due to placebo effects, real therapeutic effects of both light conditions, changes unique to each group and unrelated to the intervention, or in the case of objective cognitive functioning, whether both groups were simply displaying practice effects. Due to the small sample size, follow-up research is warranted potentially with a usual care group.

Predicting chemotherapy-related brain injury using connectomics and machine learning

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Background: Identifying cancer survivors at risk for developing cognitive impairment is critical, but challenging. Applying machine learning analyses to neuroimaging data may address this challenge. We aimed to provide a foundation for using machine-learning algorithms in combination with neuroimaging data to predict outcomes reflecting chemotherapy-related brain injury.

Methods: We evaluated 31 female patients with breast cancer (BC) prior to treatment and 1 year after treatment completion and categorized them as impaired or not based on changes in cognitive performance compared to healthy controls. Connectome properties (acquired from fMRI imaging with a 3.0 Tesla) and relevant individual and medical variables were used to determine the most accurate random forest classification (RFC) algorithm for predicting cognitive impairment. RFC was also used to calculate probability of Alzheimer's Disease (AD) diagnosis from connectome properties, demographic and APOE genotype obtained from 47 female AD converters and 47 matched controls. The algorithm was then applied to data from 78 female BC survivors.

Results: A connectome-based algorithm predicted 1-year post-treatment cognitive impairment with 100% accuracy ($p < 0.0001$) and was more accurate than models of individual and medical variables ($p = 0.005$). Chemotherapy-treated BC survivors showed higher predicted probability of AD compared to controls ($p < 0.0001$) and chemotherapy naïve survivors ($p = 0.007$) even after stratifying for APOE e4 genotype.

Conclusion: Machine-learning algorithms applied to neuroimaging data may accurately predict both the risk for cognitive impairment following breast cancer treatment and the probability of breast cancer survivors developing AD later in life.

Changes in the executive functioning network in breast cancer patients: Preliminary results from a prospective fMRI study with 6 month and 3 year follow up

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Background: Breast cancer (BC) and treatment are associated with alterations in brain function during executive functioning. There is a paucity of knowledge on the trajectory of these changes and the contribution of systemic treatments. We evaluated BC patients receiving systemic treatment (anthracycline-based chemotherapy +/- endocrine treatment = BC+SYST), patients not exposed to systemic treatment (BC-SYST) and women without a cancer (NC). Participants were evaluated before, and 6 months and 3 years after completion of chemotherapy, or matched intervals.

Methods: We used an fMRI version of The Tower of London to probe the executive functioning network. fMRI analyses were performed with FSL FEAT after careful removal of artefacts with independent component analysis. Only participants with data for all timepoints were included in the analyses. Here we report cross-sectional analyses.

Results: Evaluable data were used from 16 BC+SYST patients, 14 BC-SYST patients and 22 NC. At baseline, we found hyperactivation of the executive functioning network with increasing task load, compared to NC. After 6 months, activation for BC+SYST (and NC) remained/was further elevated compared to BC-SYST. After 3 years, NC was elevated compared to BC-SYST whereas BC+SYST did not differ from the other groups.

Conclusion: These preliminary results confirm previous findings of hyperactivation of the executive functioning network in breast cancer patients before treatment (Menning et al., 2015) that persisted 6 months (Menning et al, 2017) but not 3 years after treatment. This might reflect increased effort after neurotoxicity from treatment with normalization of network activation after 3 years. BC-SYST show a persistent pattern of hypoactivation after initial hyperactivation at BL. These results confirm that deviations in brain function in breast cancer patients differ according to treatment type. Longitudinal analyses will be performed to further clarify this pattern of results.

High levels of inflammatory markers in breast cancer survivors 20 years after cessation of chemotherapy are associated with impaired cognitive performance

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Background: Increased inflammation is an important candidate mechanism underlying cancer- and cancer treatment-related cognitive impairment. Inflammatory markers are often dysregulated in patients receiving chemotherapy. Less is known about the inflammation status in cancer survivors and its effect on long-term cognitive performance. To target this knowledge gap, we investigated levels of inflammatory markers in breast cancer survivors more than 20 years after cessation of chemotherapy and explored the relation of these markers to cognitive functioning.

Methods: 166 chemotherapy-exposed breast cancer survivors were compared with 1,444 cancer-free women from a population-based sample (aged 50-80 years). Inflammation status was assessed by neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). Participants underwent a cognitive test battery, from which the g-factor was derived assessing general cognitive function. We examined the association between cancer, inflammatory markers, and g-factor using linear regression models.

Results: Breast cancer survivors had higher inflammatory markers compared to controls (mean difference for log NLR=0.29;95% confidence interval (CI)0.22;0.35, log PLR=0.17; 95%CI0.11;0.22, log SII=0.30;95%CI0.22;0.38. G-factor was lower in cases compared to controls (mean difference=-0.12;95%CI-0.27;0.03). In cases, higher levels of inflammatory markers were associated with decline in g-factor (per standard deviation (SD) increase NLR=-0.14;95%CI-0.28;0.00, PLR=-0.13;95%CI-0.26;0.01, SII=-0.15;95%CI-0.29;-0.02). The interaction between cancer status and inflammatory markers showed an additional decline in g-factor per SD increase in inflammatory markers in cancer survivors (β-coefficient for interaction for NLR=-0.14;95%CI-0.28;-0.01, PLR=-0.17,95%CI-0.29;-0.05, SII=-0.16;95%CI-0.30;-0.03).

Conclusion: Breast cancer survivors have more than 20 years post-chemotherapy increased inflammatory markers compared to controls. High inflammatory markers were associated with poorer cognitive performance. This association was more pronounced in breast cancer survivors than in controls, suggesting a role for inflammation in long-term cognitive impairment in cancer survivors.

Nicotinamide mononucleotide prevents and reverses doxorubicin and oxaliplatin-induced fatigue and memory impairments in the laboratory rodent

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Background*:* Whilst chemotherapy agents show promising results as a robust cancer treatment, patients often experience cognitive impairments known as 'chemobrain'. The loss of nicotinamide adenine dinucleotide (NAD +), important for the regulation of gene expression, mitochondrial function and metabolic efficiency may be responsible for these neurotoxic side effects. This may further propagate the loss of sirtuin 1 (SIRT1), a protein believed to be neuroprotective against cognitive ageing, leading to subsequent oxidative stress and apoptosis.

Methods*:* In experiment 1 rats were given a single injection of doxorubicin (DOX, 4mg/kg) with nicotinamide mononucleotide (NMN), a permeable NAD + precursor, in their water (500mg/L) for 48 hours. To follow, rats underwent voluntary wheel running to determine levels of fatigue and short-term memory testing in the novel object recognition (NOR) task. In experiment 2, rats were given a single injection of DOX (6mg/kg) with NMN in their water (2g/L) for 7 days followed by the NOR and novel location recognition (NLR) tasks. In experiment 3, rats were given a chronic course of oxaliplatin (OXP, 6mg/kg) for 3 weeks. After a 1-week recovery period, rats were administered NMN (3g/L) for 7 days in their water followed by the NOR task. Rats were then taken off NMN for 10 days and tested again in the NOR task to determine if the effects of NMN were long lasting.

Results*:* NMN treatment prevented the development of DOX-induced fatigue and recognition memory impairments and reversed OXP-induced recognition memory impairments. Furthermore, OXP treated rats taken off NMN for 10 days still showed intact recognition memory.

Conclusion*:* Treatment with NMN alleviates chemobrain with the effect of NMN still persistent even when rats were off treatment. Understanding the mechanisms of chemobrain is vital to implement behavioural and pharmacological strategies to inhibit acute chemotherapy-induced neurotoxicity.

Bone marrow is critical for brain repair after radiation injury

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Background: Central nervous system (CNS) injury caused by cranial irradiation results in damage to the neurovascular niche, neural progenitor cells and cerebral white matter, resulting in progressive brain volume loss and cognitive dysfunction. There are no available treatment options for affected patients and novel strategies to promote brain repair after CNS injury are urgently needed. We here ask whether hematopoietic cells and cytokine regulators of hematopoietic function could alter the negative impact of irradiation on the CNS, both on a structural and functional level.

Methods: Using mouse models of focal and diffuse radiation injury, in combination with bone marrow transplantation, serial neurocognitive behavioral assays and magnetic resonance imaging, we studied the effects of Granulocyte Colony-Stimulating Factor (G-CSF) and bone marrow derived hematopoietic cells on neural repair.

Results: We demonstrate that G-CSF enhances neurogenesis and gliogenesis after cranial irradiation. Using a G-CSF receptor knockout mouse model in combination with bone marrow transplantation, we further show that bone marrow-derived monocyte-macrophage populations home to the injured brain where they mature and integrate into the existing cellular microenvironment in various brain regions. Our studies further reveal that this process is critical for altering neural progenitor cells and brain repair mechanisms, including regeneration of cerebral white matter and improvement in neurocognitive function.

Conclusion: Our study uncovers an unanticipated link between bone marrow and brain and identifies G-CSF responsive cells and bone-marrow derived monocyte-macrophage populations as critical mediators of brain plasticity and regeneration following diffuse CNS injury secondary to irradiation. We here report a novel repair strategy that could be readily tested in patients.

Cannabidiol as an effective treatment against oxaliplatin-induced memory impairments and peripheral neuropathies

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Background: Oxaliplatin treatment is associated with severe peripheral and central nervous system neurotoxicities both during treatment and subsequently from treatment, which present as abnormal pain sensitivity (touch and cold allodynia) and cognitive impairments. In a rat model, we examined whether cannabidiol, a non-psychoactive component of cannabis, would be an effective preventative and remedial treatment against these neurotoxicities.

Methods: The first experiment examined whether cannabidiol (CBD; 30mg/kp/i.p.) given prior to a single injection with Oxaliplatin (OXP; 10mg/kg i.p.) tactile and cold allodynia, and memory impairments in the novel object (NOR) and novel location recognition (NLR) tests. The second experiment examined whether CBD (20mg/kg i.p.) would reverse established tactile and cold allodynia and memory impairments when given 14 days after 3 cycles of treatment with OXP (6mg/kg/week for 3 weeks i.p.).

Results: In the first experiment, OXP treated rats showed significant reductions in tactile allodynia ($p<0.001$) and cold allodynia ($p< 0.05$) if treated with CBD. Rats treated with a single injection with OXP showed no significant reduction in memory in the NOR but were impaired in the NLR ($p<0.05$). Treatment with CBD reduced the effect of OXP in the NLR ($p<0.01$). In the second experiment, CBD treatment reversed tactile and cold allodynia and memory impairments in both the NOR and NLR for up to 45 days after CBD treatment.

Conclusion: CBD both prevents and reverses peripheral neuropathies and memory impairments caused by oxaliplatin treatment. Moreover, a single dose of CBD provided a long-lasting treatment of established neuropathies and memory impairments.

Cognitive functions and dopaminergic polymorphisms in brain tumor patients

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Background*:* Cognitive dysfunction is common in patients with brain tumors treated with radiotherapy (RT) and chemotherapy (CT). We reported previously that single nucleotide polymorphisms (SNPs) in the *APOE*, *COMT* and *BDNF* genes may influence cognitive outcome in this clinical population. In this study, we assessed whether additional gene variants in the dopaminergic (DA) system may contribute to cognitive dysfunction in brain tumor survivors.

Methods*:* One hundred and fifty patients with brain tumors participated in the study: ninety had been treated with RT ± CT, fifty-seven had CT alone, and three had no therapy. All patients completed neuropsychological tests of attention, executive functions and memory, and provided a blood sample for genotyping. We used a Bayesian penalized multivariate regression approach to estimate the associations between the SNPs and cognitive outcome, adjusting for age, education, tumor location, treatment with RT ± CT, time since treatment completion, and *APOE* epsilon ϵ-4 allele. We quantified the strength of association between a SNP and a cognitive test score using a novel measure referred to as the posterior association summary (PAS) that takes value between 0 (= no association) and 1 (= very strong association).

Results*:* SNPs in the *DRD1* (rs4532), *DRD2/ANKK1* (rs1554929), *DRD4* (rs3758653), and *ANKK1* (rs34863235) genes were strongly associated with attention and executive functions (PAS>0.90). Additional SNPs in the *COMT* gene (rs174696; rs2073748; rs740603) were also strongly associated with the cognitive outcomes (PAS>0.90).

Conclusion*:* The findings provide new evidence that polymorphisms in the dopamine metabolic pathway may be functionally relevant and influence cognitive outcome in patients with brain tumors.

Impact of a mindfulness-based intervention on chemotherapy-induced cognitive dysfunction and brain alterations: A pilot study

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Background: This pilot study focuses on breast cancer patients who finished chemotherapy treatment and experience cognitive complaints. Research and expert opinions suggest that attention, memory and executive functioning are most often compromised and that cognitive deficits can persist up to 20 years post-treatment. This study aims to assess the impact of a mindfulness-based intervention (MBI) on the cognitive complaints and cognitive impairment after cancer treatment.

Methods: Participants were 34 breast cancer patients who completed treatment and had cognitive complaints assessed with the cognitive failure questionnaire. They were randomized to a mindfulness condition or waitlist control condition (TAU). Assessments took place at three points in time, one week before the intervention, one week after the intervention and at three months follow-up. Primary outcomes are objective measures on cognitive functioning using cognitive tests and brain imaging (MRI) and subjective measures using (self-report) questionnaires. Symptoms of emotional distress, fatigue and mindfulness skills are secondary outcomes.

Results: Multilevel modelling showed 1) no significant changes in cognitive functioning collected via cognitive tests, and 2) a significant reduction in the subjective measure of cognitive failure, emotional distress and fatigue. Further analyses showed that improvement in mindfulness skills was correlated with a reduction of subjective cognitive failure.

Conclusion: While MBI significantly reduced cognitive complaints, MBI in the current format did not improve outcomes on objective measures of cognitive functioning in this small sample size. Positive effects, however, were observed for subjective cognitive complaints and related distress, which suggests that participants after the MBI related in a different way to their cognitive complaints.

Neurocognitive and neuroimaging outcomes of anesthesia exposure in long-term survivors of childhood acute lymphoblastic leukemia

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Background: Studies on the long-term effects of anesthesia on brain integrity are limited, especially in childhood cancer survivors, who undergo numerous anesthesia procedures following diagnosis.

Methods: Data were abstracted for cumulative dose and administration duration for 5,699 anesthesia procedures performed in 212 survivors of childhood acute lymphoblastic leukemia (ALL; mean [SD] age 14.4 [4.8] years; 7.7 [1.7] years post-diagnosis) treated with chemotherapy only. At >5 years post-diagnosis, neurocognitive testing and structural brain MRI were conducted. General neurocognitive impairment was defined as ≥3 tests with age-adjusted scores <2 SD below norms (5% likelihood in general population with 40 measures). Performances were also examined for test-specific measures that fell below population norms, correcting for false discovery rate. Associations of anesthesia exposure with general neurocognitive impairment, test-specific performances, brain volumes, and white matter integrity were examined using log-binomial or general linear models, adjusting for age, sex, and intrathecal and high-dose intravenous methotrexate.

Results: 43% of survivors exhibited general neurocognitive impairment. Higher risk of impairment was associated with higher propofol dose (RR=1.43 per 100 mg/kg, 95% CI 1.09-1.89), higher pentobarbital dose (RR=1.25 per 10 mg/kg, 95% CI 0.99-1.58), and longer anesthesia duration (RR=1.03 per hour, 95% CI 1.00-1.06). Longer duration was associated with worse performance on Letter Sequencing ($p<0.01$), Number-Letter Switching ($p=0.03$), and Letter Fluency ($p=0.04$), and with smaller pallidum volume ($p<0.01$) and abnormal corpus callosum diffusivity ($p=0.03$). Higher propofol dose was associated with worse performance on Spatial Span Forward ($p=0.04$), Letter Sequencing ($p=0.04$), and Number-Letter Switching ($p=0.04$). Higher pentobarbital dose was associated with more Omissions ($p=0.04$) and Perseverations ($p=0.01$), and smaller subcortical grey matter volumes ($p=0.03$).

Conclusion: Higher cumulative anesthesia dose and duration contribute to neurocognitive impairment and neuroimaging abnormalities in long-term survivors of childhood ALL, beyond the known effects of neurotoxic chemotherapies.

Cerebellar volumes and neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy alone

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Background: Disruption of the glutathione antioxidant pathway by chemotherapy may cause cerebellar volume loss and associated neurocognitive problems in survivors of childhood ALL treated with chemotherapy alone.

Methods: Brain MRIs and neurocognitive tests were obtained in 176 survivors (49% male, mean age at diagnosis 6.8 years, 14.5 years at evaluation). MRIs were also obtained in 82 community controls (57% male, 14.6 years at evaluation). General linear models were used to compare cerebellar volumes between survivors and controls. Among survivors, sex-stratified multivariate linear models were used to test associations among neurocognitive function, cerebellar and cortical measurements, serum concentration of dexamethasone, and number of intrathecal injections of methotrexate, hydrocortisone and cytarabine (IT) received, adjusting for age at diagnosis and intracranial volume.

Results: Cerebellar volume was smaller in survivors than controls ($p<0.01$). In females, smaller cerebellums were associated with more ITs. Controlling for intracranial volume, increased chemotherapy exposures and younger age at diagnosis, smaller cerebellar volume was associated with thinner cortex in the rostral and caudal middle frontal gyri (p's < 0.0001), precuneus ($p <0.0001$), and superior frontal areas ($p<0.0001$) among survivors. Smaller bilateral cerebellar volumes and more ITs were associated with poorer initiation and cognitive flexibility (p's<0.05). Smaller cerebellums and higher dexamethasone exposures were associated with poorer organization and planning in female survivors (p's<0.05). Smaller bilateral cerebellar volumes were associated with worse visual processing speed ($p=0.02$) and poorer working memory was associated with smaller right cerebellar volumes in males ($p<0.05$). Smaller left cerebellums in males and bilateral cerebellar volumes and higher dexamethasone exposure in females were associated with worse motor processing ($p<0.04$).

Conclusion: Compared to community controls, long-term survivors of childhood ALL demonstrated smaller cerebellums associated with cognitive impairment. Results support hypothesis of antioxidant pathway disruption, particularly in females.

Genome-wide association study of attention problems and executive dysfunction in adult survivors of childhood leukemia

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Background: To examine genetic predictors of attention problems and executive dysfunction in adult survivors of childhood acute lymphoblastic leukemia (ALL).

Methods: 728 survivors of ALL (mean [SD] current age=31.6 [7.7] years, time since diagnosis=25.0 [7.5] years) completed standardized assessment of attention (Conners' Continuous Performance Test; Trails A) and executive function (Trails B, Verbal fluency, Digit Span Backwards). Age-adjusted z-scores and impairment frequencies ($\geq$2SD below the normative mean) were calculated. Single nucleotide polymorphisms (SNPs) associated with impairment were identified through a genome-wide association study (Affymetrix 6.0 GeneChip with imputation to the 1000 Genomes Project) using a 2-stage resampling approach with a type 1 error rate of 1×10^{-6}. Clinical and genetic factors associated with neurocognitive impairment were examined in multivariable logistic regression models.

Results: Twenty percent of survivors were impaired on at least one measure of attention; 24% on at least one measure of executive function. Prevalence of impairment increased by cranial radiation (CRT) dose (e.g., attention impairment: no CRT=13%; $\leq$20Gy=20%; >20Gy=28%). Three SNPs were internally validated as associated with attention impairment and 3 SNPs with executive dysfunction. In multivariable models adjusted for ancestry and clinical factors, an interaction between CRT dose and SNP rs11200297 (intron region of NSMCE4A, associated with telomere maintenance) was associated with impaired executive function. Survivors treated with $\leq$20Gy CRT had 156% increased risk of executive dysfunction with each minor allele (RR=2.56, 95% CI 1.54-2.86), those treated with >20Gy CRT had 34% increased risk with each minor allele (RR=1.34, 95% CI 1.04-1.73). The SNP was not associated with dysfunction in survivors treated without CRT.

Conclusion: Genetic variants related to telomere maintenance may modify risk of executive dysfunction in aging adult survivors of childhood ALL treated with CRT; however, interactions between polymorphisms and treatment exposures may have a threshold effect.

POSTER PRESENTATIONS: MONDAY

Chemotherapy is associated with altered immediate early gene expression and oxidative damage in the hippocampus

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Background: Systemic chemotherapy is associated with cognitive impairment in some cancer survivors. Evidence derived from clinical longitudinal studies and animal models of this 'chemobrain' phenomenon have suggested several mechanisms related to treatment including inflammation and oxidative damage. In a previous study we have reported that female rats injected with doxorubicin/cyclophosphamide chemotherapy display deficits in spatial memory tasks and exhibit altered expression of signaling and synaptic plasticity-related molecules in the hippocampus. The purpose of the present study is to examine the potential role of oxidative stress and identify the downstream molecular players involved in the pathogenesis of cognitive decline after chemotherapy treatment.

Methods: Ovariectomized female rats were injected intravenously once a week for three weeks with the combination of cyclophosphamide and doxorubicin. Dissected hippocampi were evaluated for expression of immediate early genes and oxidative stress responsive genes by western blot and qPCR analysis. Immuno-northern blot and Dot blot analysis was conducted to evaluate the relative levels of the oxidative damage marker 8-hydroxyguanine (8-OHdG). Brain sections from a separate cohort of animals were processed for immunohistochemistry to assess the expression and localization of 8-OHdG in the hippocampus.

Results: We found that the activation (cJun) and expression (Arc, Bdnf, Creb, Homer1a) of some immediate early genes were significantly higher in the chemotherapy group. Real-time qPCR analysis revealed that the levels of GPx, NFkB, and TNFa were upregulated. Moreover increased immunohistochemical staining and dot blot detection of 8OHdG in treated animals indicates increased oxidative damage.

Conclusion: These results indicate that chemotherapy may lead to oxidative damage in nucleic acids and induce alterations in the expression profile of stress responsive and plasticity-related genes in the CNS.

Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review

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Background: In addition to the burden of a life-threatening diagnosis, cancer patients are struggling with adverse side-effects from cancer treatment. Chemotherapy has been linked to an array of cognitive impairments and alterations in brain structure and function ("chemobrain"). In this review, we summarize the existing evidence that evaluate the changes in cognitive functioning and brain with chemotherapy, as assessed using structural and functional MRI-based techniques in a longitudinal design.

Methods: This review followed the latest PRISMA guidelines using Embase, Medline, PsychINFO, Scopus, and Web of Science databases with date restrictions from 2012-2017. Fourteen research articles met the key inclusion criteria: (i) the studies involved adults cancer patients (mean age>18); (ii) the use of chemotherapy in the treatment of cancer; (iii) pre-post assessment of behavioural and brain-based outcomes; and (iv) abstracts written in English. Effect sizes of subjective and objective cognitive impairments from the reviewed studies were estimated using Cohen's *d* or z-scores. We calculated percentage of mean change or effect sizes for main neuroimaging findings when data were available. Strength of the correlations between brain alterations and cognitive changes was obtained using squared correlation coefficients.

Results: We showed small to medium effect sizes on individual tests of attention, processing speed, and verbal memory; and medium effect sizes on self-report questionnaires. In addition, we demonstrated changes in brain morphology, perfusion, and brain activation in frontal, parietal, and temporal brain regions. Finally, we observed moderate-to-strong correlations between worsening cognitive function and morphological changes in frontal brain regions.

Conclusion: While MRI is a powerful tool for detection of longitudinal brain changes in the 'chemobrain', the underlying biological mechanisms are still unclear. Continued work in this field will hopefully detect MRI metrics to be used as biomarkers to help guide cognitive treatment at the individual cancer patient level.

Cancer treatments on cognition: Building translational research to optimize the design of preclinical animal studies

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Background: The evaluation and understanding of the cognitive decline in patients treated for a cancer are complex and need a multidisciplinary approach in human sciences with a strong link between clinicians and neurobiologists.

Methods: Our work mainly involves research and clinical groups of Normandie developing programs in patients and animal models, to improve our understanding of the impact of cancer and its treatments on cognitive functions.

Results: The clinical Cog-Age study showed that a pathological cognitive decline is detected 6 months after chemotherapy in breast cancer elderly patients. In a mirror study, chemotherapy administration in young and aged mice resulted in altered behavioral flexibility and neural precursor proliferation in the hippocampus. The clinical COG-ANGIO study demonstrated that antiangiogenics exert a direct negative impact on cognitive functions and fatigue in kidney cancer patients. In mice, the anti-angiogenic mTOR inhibitor everolimus led to weight loss and modification of cell metabolism in sleep/wake cycle or food intake-involved brain areas, suggesting asthenia. In addition, immunoneutralizing VEGF impaired spatial learning performance and neuronal activity of CA3 hippocampus neurons, indicating learning memory deficits induced by anti-VEGF. Our Cog-Pro study currently aims to prospectively evaluate the incidence of cognitive functions among elderly men treated by new homono-therapy for a metastatic prostate cancer. A specific behavioral preclinical model is here proposed to evaluate emotional reactivity and cognitive functions of castrated aged (19-20 month old) C57B/l6 male mice in the presence of two different androgen axis inhibitors. The first results demonstrate a significant impact of one therapy compared with the other one on spontaneous activity sustaining a reduced welfare.

Conclusion: Careful and systematic evaluation of new cancer therapy on cognitive functions in translationally designed preclinical models provide a strong impact on mechanism understanding and on the strategy of prevention by selection of treatments exhibiting minimum brain co-morbidities.

Cognitive limitation and emotional distress among occupationally active breast cancer survivors in mainland China

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Background: Residual symptoms such as fatigue, cognitive limitations, and emotional distress can be experienced by cancer survivors. These symptoms may impact their abilities at work and quality of life (QOL). The objectives of this study were to determine whether cognitive limitations and emotional distress at work are related to work productivity and QOL in Chinese breast cancer survivors (BCS), the most prevalent cancer survivor group in mainland China.

Methods: A sample of 159 occupationally active BCS and 253 women served as non cancer comparison (NCC) group were recruited. They completed questionnaires related to depression, anxiety, cognitive limitations, work limitations, and quality of life. Demographic variables, type of job, stage at diagnosis, and treatment exposure were also measured as potential confounders.

Results: According to the univariate analyses, BCS reported higher levels of anxiety and depression ($p < 0.001$) but lower global QOL than women in NCC group ($p < 0.001$). BCS also indicated higher levels of work productivity loss than NCC group (3.7% versus 2.4%; $p < 0.001$), especially in the domain of time management, mental-interpersonal demands, and output demands ($p < 0.001$). Multiple regression analyses showed that higher anxiety was associated with work limitations (B=.005, p=0.014) and QOL (B=-2.417, p<0.05) in BCS. In addition, cognitive limitations at work were associated with work limitations (B=.002, p<0.001) and QOL (B=-1.022, p<0.05) in BCS only.

Conclusion: Returning to work is an important component of QOL in employed patients who survive cancer. Work-related cognitive limitation and emotional distress are related to work ability of the cancer survivors. Healthcare professionals should be aware of cancer survivors' cognitive limitations and emotional distress while at work and the relationship between them and the work challenges they can experience if they remain in the workplace.

Development of an animal model of breast cancer survivors to test novel interventions to treat cognitive impairment

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Background: Currently there is a dearth of understanding of the biological mechanisms responsible for cognitive impairment in cancer survivors, and no pharmacological strategies to treat cognitive impairment in patients or survivors are available. Here we present the first mouse model of cancer survivorship that evaluates the contribution of key treatment events and produces "cancer survivor" mice. We have confirmed that both tumour and chemotherapy alone cause cognitive impairment. We have identified that inflammation is responsible for breast cancer-induced cognitive impairment but not chemotherapy (paclitaxel)-induced cognitive impairment. We have developed appropriate mouse models to mimic surgical stress from breast tumour resection (lumpectomy vs mastectomy).

Methods: Our model of cancer survivorship combines three key components, breast cancer, surgical resection of the primary tumour and adjuvant chemotherapy, to mimic the clinical phenomenon of breast cancer survivors. We use syngeneic, orthotopic models of mammary adenocarcinoma in mice. Tumour cells are transduced with luciferase, which allows us to use bioluminescence imaging to track tumour growth, metastasis and recurrence. Memory, learning and cognitive flexibility are assessed using validated behavioural tests at each stage of treatment and throughout the survivorship phase.

Results: We expect that there will be a cumulative effect of these three key stages (cancer, surgery and chemotherapy) on cognitive impairment during treatment and a substantial proportion of mice that exhibit sustained cognitive impairment after treatment (ie. during survivorship). We are using this model to identify biological mechanisms of sustained cognitive impairment in "survivor mice" and develop novel pharmacological treatment strategies

Conclusion: We are currently using this model to identify biological mechanisms of cognitive impairment after cancer and determine if there is a cumulative burden of cancer and cancer treatment on cognitive function during treatment. This will drive development of novel pharmacological treatments to alleviate cognitive impairment in cancer survivors.

Multi-center reproducibility of structural, diffusion tensor and resting state functional magnetic resonance imaging measures

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Background: To assess multi-center reproducibility and longitudinal consistency of MRI imaging measurements, as part of a phase III longitudinal multi-center study comparing the neurotoxic effect following prophylactic cranial irradiation with hippocampal avoidance (HA-PCI), in comparison with conventional PCI in patients with small cell lung cancer.

Methods: Harmonized MRI acquisition protocols from 6 participating sites and 2 different vendors were compared using both physical and human phantoms. We assessed variability across sites and time points by evaluating various phantoms and data from two healthy volunteers, including hippocampal volume, diffusion metrics and resting-state fMRI.

Results: We report average coefficients of variation (CV) below 5% for intra-scanner, intravendor and intervendor reproducibility for both structural and diffusion imaging metrics, except for diffusion metrics obtained from tractography with average CVs ranging up to 7.8%. Additionally, resting-state fMRI showed stable temporal SNR and reliable generation of subjects DMN across vendors and time points.

Conclusion: These findings indicate that the presented multi-site MRI acquisition protocol can be used in a longitudinal study design and that pooling of the acquired data as part of the phase III longitudinal HA-PCI project is possible with careful monitoring of the results of the half-yearly QA assessment to follow-up on potential scanner-related longitudinal changes in image quality.

Examining the feasibility of an online cognitive rehabilitation program in haematology survivorship care to reduce chemotherapy-related cognitive impairment

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Background: Chemotherapy-associated cognitive impairment can adversely impact cancer survivors. Knowledge about its aetiology and therapy is limited. An online cognitive rehabilitation program (CRP) has been reported to improve self-reported cognitive function in cancer survivors. This pilot study examines the feasibility and sustainability of a CRP in survivorship care post-autologous stem cell transplantation (ASCT).

Methods: This was a multi-site collaborative pilot study. Patients were evaluated at four time points using a neuropsychological tool (CogState) and validated questionnaires.
T1 = Baseline cognitive assessment performed prior to ASCT.
T2 = Post-ASCT cognitive assessment performed on day 40±5 from the ASCT. At this assessment patients were introduced to the online CRP.
T3 = Post-CRP cognitive assessment performed ten weeks post-CRP commencement.
T4 = Final cognitive assessment performed 6-months post-CRP commencement.
Patients were asked to use the CRP for 120-minutes per week for nine consecutive weeks

Results: Thirty-two patients consented to the study; the recruitment rate was 68%. At interim analysis, 16 participants had completed the CRP intervention. The mean age was 58 years (SD=10.7), 10 (63%) were male, 10 (63%) had multiple myeloma and the mean time since diagnosis was 3.4 years (SD=4.3).
Patients reported high satisfaction and usability with the CRP. Despite efficacy not being a primary endpoint, there was a trend demonstrating an increase in cognitive function post-CRP, although no definite conclusion can be made in this pilot study.
No patient reported clinically significant anxiety or depression scores during the study.

Conclusion: This research supports the feasibility and sustainability of online CRPs in survivorship care post-ASCT. The results aid in the design of a future randomized controlled trial and suggest that further research regarding the efficacy of CRPs is warranted. This represents a positive step forward in addressing the need for interventions targeting chemotherapy-related CI for cancer survivors.

Conducting small group cognitive rehabilitation in the clinical cancer setting: Lessons from a translation feasibility trial

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Background: Multiple trials from independent research groups have demonstrated that small group cognitive rehabilitation can reduce cancer-related cognitive impairment. However, applicability of such interventions in clinical practice has not been reported previously. In this translation feasibility study, a group cognitive rehabilitation intervention was offered to patients who attended a specific cancer centre. The aim was to evaluate the feasibility and effect size when implementing small group cognitive rehabilitation in a clinical cancer setting.

Methods: Participants were 27 women who had been treated with chemotherapy for breast cancer at Mater Cancer Care Centre, Brisbane, completing chemotherapy 6-60 months before study participation. All participants received the Responding to Cognitive Concerns (ReCog) cognitive rehabilitation intervention, over 4 sessions of two hours duration conducted weekly in groups of 3 to 9 participants. The intervention was provided by occupational therapy staff from the centre. Primary outcomes were recruitment rate and participant satisfaction. Secondary outcomes were self-reported cognition (Functional Assessment for Cancer Therapy version 3), neuropsychological performance (WebNeuro online cognitive battery), quality of life, and distress.

Results: Thirty-one volunteers responded to a mailout to 225 patients and a further 25 were invited by treating staff. Of these 56 volunteers, 27 enrolled, 25 were unable to attend, and 4 were ineligible. All participants endorsed at least moderate satisfaction with ReCog and believed their cognitive problems had improved. Statistically significant improvements associated with small to moderate effect sizes were found in perceived cognitive impairment; information processing and executive function from WebNeuro; distress; and several quality of life subscales.

Conclusion: Results showed it was feasible to deliver group cognitive rehabilitation within clinical practice. Participants were highly satisfied and improved significantly on self-reported and externally assessed neuropsychological performance. Consideration could be given to providing CR intervention earlier than 6 months post treatments, since returning to work precluded participation for many.

Childhood cancer, age at diagnosis and educational attainment: A meta-analysis

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Background: Developments in childhood cancer treatment over the past 40 years have resulted in improvements in health outcomes and mortality rate. However, a variety of cognitive and psychosocial sequelae remain. Impairments in processing speed, attention, working memory and executive function are common in survivors, with associated challenges to academic achievement and final educational attainment. The relationship between childhood cancer diagnosis and educational attainment is potentially moderated by a range of factors including; treatment type, cancer type, treating country and age at diagnosis. In particular, survivors diagnosed early may be more prone to the cognitive consequences arising from treatment. This meta-analysis has three aims. Firstly, to determine whether childhood cancer survivors have worse educational attainment than those not treated for cancer. Secondly, to determine whether diagnosis before adolescence is associated with poorer educational attainment than diagnosis during adolescence. Thirdly, the study aims to identify the disease and treatment factors which moderate or mediate the relationship between age at diagnosis and educational attainment.

Methods: A systematic search based on the key concepts "cancer", "neoplasms", "paediatric" and "educational attainment" retrieved 4777 records from the online databases Embase, Medline and PsychINFO. Eligible studies were appraised as excellent quality with a high level of inter-rater reliability. The results of approximately 20 studies will be synthesised. Effect sizes for university graduation rates in those diagnosed during pre-adolescence (ages 0 to 10), those diagnosed during adolescence (ages 11 to 21), and non-cancer controls, will be compared. Additionally, subgroup analyses will examine the influence of treatment type, cancer type and treating country.

Perceived cognitive impairment in haematological cancer patients who have undergone allogeneic stem cell transplantation and its correlates.

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Background: Cognitive impairment is a major concern for cancer patients and has been observed in breast, colorectal, ovarian, and testicular cancer patients. However, few studies have examined cognition in haematological cancer patients. This study aimed to determine whether haematological cancer patients who had undergone allogeneic stem cell transplantation (SCT) report greater cognitive impairment than healthy controls. A secondary objective was to assess potential correlates of perceived cognitive impairment (PCI) in this population.

Methods: Participants were 30 haematological cancer patients who had undergone allogeneic SCT in the past 1-5 years and 30 age-matched healthy controls. Participants completed questionnaires assessing PCI, psychological distress, sleep quality and fatigue as well as an assessment of premorbid IQ.

Results: There were no significant differences between patients and controls in terms of age, gender, education or premorbid IQ. However, patients reported significantly greater PCI than controls, and this difference constituted a large effect. There were no differences in PCI in patients who had undergone myeloablative and non-myeloablative conditioning therapy or in those who had received chemotherapy only and those who had received chemotherapy and radiotherapy. Anxiety was associated with increased PCI in patients and fatigue was associated with PCI in both patients and controls. Hierarchical multiple regression found that sleep quality, fatigue and mood explained 82% of the variance in PCI in the patient group.

Conclusion: Haematological cancer patients who had undergone allogeneic SCT reported greater PCI than controls. Furthermore, this was associated with anxiety and fatigue. Future research should determine the direction of these effects. For example, if anxiety is a predictor of PCI, as opposed to an outcome, interventions could target mood in order to alleviate PCI in allogeneic SCT recipients. Alternatively, treatment of PCI may result in improvements in a number of domains including mood and fatigue if these outcomes follow cognitive impairment.

Neurotransmitter, inflammation, and growth factor pathway single nucleotide polymorphisms (SNPs) related to perceived cancer-related cognitive impairment

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Background: Mechanisms related to the etiology of cancer-related cognitive impairment (CRCI) need to be uncovered. SNPs related to CRCI may provide insight into etiology of biologic pathways that may be dysregulated, as well as provide information on susceptibility to developing CRCI. Previous research suggests that inflammation, growth factors, membrane transport proteins, and neurotransmitter alterations may be related to CRCI, or more broadly related to cognitive impairment.

Methods: As part of a large longitudinal study of CRCI in 449 Caucasian breast cancer patients through the University of Rochester Cancer Center NCI Community Oncology Program Research Base, we investigated a set of 111 candidate tag SNPs representing 14 genes purported to be involved in CRCI or in cognitive impairment. Genomic DNA was isolated from whole blood samples from patients at pre-chemotherapy and SNPs were genotyped at Roswell Park using Illumina Sequenom. Using linear regression with an additive model, we assessed relationships between SNPs and FACT-Cog scores (post-chemotherapy – pre-chemotherapy) after adjusting for baseline age and education. We then applied a Benjamin-Hochberg (BH) false discovery rate (FDR) correction to the p-values within genes.

Results: SNPs in genes of IL-6, COMT, MRE11A, ABCB1, IGF, IGFBP2, IGFBP3 were all significantly related to worse FACT-Cog score ($p<0.05$ for all except MRE11A $p=0.06$). ABCB1 was most strongly related to FACT-Cog score, with the minor allele related to a decrease in score of 13.39 points ($p=0.01$). After utilizing the BH FDR adjustment for multiple SNPs, these pathways remained significant at $p<0.20$.

Conclusion: While further confirmatory work is needed, our research preliminarily suggests that SNPs in several pathways may be related to CRCI, with the strongest evidence for the minor allele SNP in the ABCB1 drug transporter gene being most strongly related to decline in perceived CRCI.

Cognitive flexibility and selective and sustained attention in cancer survivors: A preliminary evaluation of functional near-infrared spectroscopy application

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Background: Patients and survivors of non-central nervous system cancers have reported experiencing cognitive difficulties (e.g., problems in attention and memory) related to cancer and its treatments. We tested the applicability of functional near-infrared spectroscopy (fNIRS) to evaluate cognitive processing, brain hemodynamics and neuronal activities in cancer survivors vs. younger and older healthy adults.

Methods: We assessed 18 adult females. We used fNIRS to assess prefrontal cortex (PFC) activation under cognitive stimuli (i.e., Stroop and Go/NoGo) designed to assess cognitive flexibility and selective and sustained attention. We completed hemodynamic response analysis using general linear model (GLM) and computed beta values for oxygenated and deoxygenated hemoglobin concentrations, which we plotted as images (using MATLAB) to illustrate cognitive stimuli-evoked activation responses in the prefrontal cortex.

Results: Our analysis revealed significant task sub-levels and channel location activation in the PFC for the Stroop test ($p<0.05$). The Go/No-Go showed diffused and bilateral patterns of activation in VLPFC for older adults. The findings showed significant activation in the R-VLPFC for the Go tasks ($p<0.05$), suggesting possible VLPFC support for inhibitory control. The results showed significant differences between cancer and healthy participants on channels 14 and 1 for the NoGo tasks, and channel 4 for the Go tasks.

Conclusion: These preliminary findings support the application of fNIRS to assess mental processing, cognitive flexibility, and selective and sustained attention for cancer patients and survivors.

Cognitive impairment in breast cancer patients before surgery?

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Background: Memory and attention dysfunction is a common complaint among breast cancer patients after chemotherapy. Nevertheless, 20-30% of women have cognitive impairment after surgery and before any adjuvant treatment. These disorders may be explained by the impact of breast cancer surgery anesthesia. However, very few studies focused on cognitive functions before any treatment. In the French national cohort CANTO, a subgroup of patients had cognitive assessment before any treatment (surgery or neo-adjuvant treatment).

Methods: Breast cancer patients without metastasis were eligible. Episodic, working memory, executive functions, processing speed, attention, cognitive complaints, anxiety, depression and fatigue were assessed with neuropsychological tests (HVLT, digit and spatial span, letter-number sequencing, TMT, verbal fluencies, Stroop, d2, symbol search) and self-reported questionnaires (FACT-Cog, HADS), before any treatment. Cognitive impairment was defined according to ICCTF recommendations.

Results: Results concern 264 women (54±10.8 years), with breast cancer diagnosis (stage I-II, 69%) within 37 days in average (SD: 70.3). Only six patients (2.3%) had a cognitive impairment in at least one cognitive domain (episodic memory and working memory). Twenty percent (n=52) had significant cognitive complaints (PCI, FACT-Cog). Significant anxiety or depression symptoms were observed respectively in 46% and 13% of patients. They were related to cognitive complaints ($p<0.001$).

Conclusion: This study is the first which assessed cognition before any breast cancer treatment, using a large national cohort. Twenty percent had significant cognitive complaints, however very few patients had objective cognitive impairment, contrasting with the rate of cognitive impairment observed before adjuvant treatment and after surgery in breast cancer patients. These results suggest that surgical procedure itself, possibly by general anesthesia, could be involved in cognitive impairment in breast cancer patients.

Internet based work-related cognitive rehabilitation for cancer survivors: Design of a randomised controlled trial

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Background: Cognitive problems are common in non-central nervous system cancer survivors. These problems are perceived as an important contributor to affect job performance and work ability. Various interventions for cancer-related cognitive impairment have been proposed, but effectiveness concerning work-related outcomes is not yet established. The aim of the current study is to develop and evaluate the (cost-) effectiveness of an internet-based cognitive intervention programme for occupationally active cancer survivors.

Methods: A three-armed randomized controlled trial will be conducted with six months of follow-up, including two intervention groups (i.e., high-intensity and low-intensity cognitive rehabilitation) and one waitlist control group. In total, 300 cancer survivors (18 – 65 years) who have returned to work and who experience cognitive problems will be recruited. Patients with and without cognitive dysfunction established in a neuropsychological assessment will be eligible; stratification will take place based on the presence of this cognitive dysfunction. The high-intensity arm will contain a comprehensive training programme (including psycho-education, fatigue management, and cognitive strategy training) with individual guidance (blended intervention). The low-intensity arm will contain a brief cognitive training programme (including psycho-education and fatigue management) without individual guidance. The primary outcome will be accomplishment of an individually defined work-related treatment goal. Secondary outcomes include self-perceived and tested cognitive functioning, work-related outcomes, and quality of life.

Discussion: About 40-50% of the cancer patients worldwide are of working age at time of diagnosis. Many of the occupationally active cancer survivors experience cognitive problems. An effective treatment to alleviate cognitive decline and to improve work ability is needed. Therefore, up to September 2021, we will develop and evaluate a cognitive internet-based intervention programme. Both from an individual and a societal perspective, it is essential to sustain cancer survivors' employability.

Work after breast cancer: Identification of cognitive difficulties using the Perceive, Recall, Plan Perform System of Task Analysis

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Background: A high proportion of women report subtle cognitive changes that negatively impact their capacity to participate in work after breast cancer treatment. Few ecologically valid assessment tools are available to evaluate the cognitive demands and performance of women with breast cancer in the workplace. This study aims to identify difficulties in work related cognitive strategy use experienced by women with breast cancer using the Perceive, Recall, Plan and Perform (PRPP) System of Task Analysis.

Methods: Deductive content analysis was used to code secondary data from ten women (42 – 54 years) who were previously interviewed about cognitive changes they experienced after treatment and had returned to work. Interview transcripts were coded using the 34 PRPP cognitive strategy items (relative to attention, sensory perception, memory, planning, and performance monitoring) to identify and quantify specific cognitive work related difficulties described by the women.

Results: The 10 women experienced particular difficulty with cognitive strategy use at work related to the "Programming", "Continuing" and "Attending" PRPP processing categories. While all women rated themselves competent with their work performance, they all experienced high level cognitive strategy application disturbance which impacted their ability to work to the level they desired relative to amount, effort, or quality. They likened the disturbance to 'a hidden disability' which was experienced by them, but often not observable to others.

Conclusion: Women with breast cancer may experience difficulties with cognitive strategy application upon return to work. The PRPP System of Task Analysis was identified as a potentially useful measurement and interview tool for this purpose. However, this pilot study indicated the need for further research to establish the PRPP as a valid and reliable tool for assessing the cognitive demands of work and identifying cognitive strategy problems for women with breast cancer.

A critical review of the quality of instruments to measure cancer-related cognitive changes (CRCC) in women with breast cancer

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Background: The purpose of this critical review was to determine what assessment instruments are potentially available for clinicians to use in evaluating identifying cancer related cognitive changes (CRCC) in women with breast cancer. The review also aimed to determine the psychometric properties of the embedded in assessment tools identified for clinical use in this population.

Methods: A critical review design was undertaken following PRISMA guidelines. Searches were conducted in the following databases: MEDline, CINAHL, Web of Science Core Collections, OT Seeker, Scopus and PsychInfo. Selected articles were appraised using a standardised evaluation form. Each identified assessment tool was further evaluated according to its psychometric properties, and data were independently extracted from the selected articles by two researchers. An extension of a scoping review (originally conducted in February 2013) was performed to identify potential instruments. Searches were completed in eight databases to: (a) identify any new literature from January 2013 to December 2016, (b) identify instruments that may have clinical utility for practitioners and (c) extract evidence about the psychometric properties of the identified measures. Critical analysis of both the studies and the instruments identified within the studies were undertaken in order to assess the quality of the instruments.

Results: Twenty-three studies were identified, with a total of 20 assessment instruments potentially available for use with the breast cancer population. Four instruments were identified as having the strongest psychometric properties and potential clinical utility.

Conclusion: Results indicate a lack of information about psychometric properties when selecting an instrument for the assessment of CRCC in research studies. This has an impact on the ability of clinicians to identify issues relating to CRCC in a standardised way, impeding the development of evidence-based care plans for individuals recovering from breast cancer.

Differences in white matter microstructure between postmenopausal women with and without breast cancer before aromatase inhibitor therapy

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Background: Others previously identified reduced white matter microstructure in mixed samples of pre-and post-menopausal women with breast cancer before systemic therapy; fatigue was an important covariate. These relationships may differ in women with breast cancer after menopause. Therefore, the purpose of this study was to compare white matter microstructure between postmenopausal women with and without breast cancer before aromatase inhibitor therapy (without chemotherapy), and to consider the relationship between white matter microstructure and fatigue.

Methods: Post-surgical breast cancer patients (n=11) completed 3 Tesla diffusion MRI before beginning aromatase inhibitor therapy without chemotherapy. We scanned controls (n=11) without breast cancer, frequency matched on age and years of education. We used FSL for preprocessing and tract-based spatial statistics, identifying significant differences in fractional anisotropy (FA) between groups using the non-parametric randomise routine (with 500 permutations) with threshold-free cluster enhancement (TFCE), adjusting for age and education. We compared white matter microstructure by level of fatigue from the Profile of Mood States Fatigue-Inertia subscale. Atlas-based analysis was performed using the JHU White-Matter Tractography Atlas.

Results: Adjusting for age and education, we found higher FA in patients versus controls in the right superior longitudinal fasciculus, left inferior longitudinal fasciculus, and left corticospinal tract (TFCE $p<.05$). No FA comparisons survived TFCE correction for controls>patients. The relationship between FA and fatigue was stronger in patients than controls in diffuse tracts (TFCE $p<.05$); this relationship held for the corpus callosum at TFCE $p<.01$.

Conclusion: Postmenopausal women with breast cancer demonstrate significant differences in white matter microstructure in diffuse tracts before aromatase inhibitor therapy. Our findings suggest that elevated white matter microstructure in patients compared to controls is related to fatigue. It is possible that cancer-related mechanisms for fatigue, such as systemic inflammation, may play a role in white matter health.

International online assessment of cognitive problems associated with cancer and cancer treatment: An American validation study of the Amsterdam Cognition Scan

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Background: The Amsterdam Cognition Scan (ACS) is an online tool for unsupervised cognitive testing, developed to facilitate large-scale data collection for oncology research. The original version is in Dutch. In order to enable international data-pooling, we have created an American version of the ACS as well. The primary focus of the current study was to assess the usability and validity of this version for use in American populations.

Methods: All ACS elements (7 neuropsychological tests included) were translated and audio-visual materials were prepared using an American English speaking spokesperson. Non-central nervous system cancer patients were recruited at MSKCC Counseling Center; a total of 35 patients (54% female; mean age 57.1 years; 86% high education level) completed both the ACS (unsupervised) and a traditional (supervised) neuropsychological assessment. Usability of the ACS was assessed through participant feedback and technical reports. Convergent validity was assessed using Spearman/ Pearson correlations. Validity results were compared to results from a Dutch validation study (n=201; 56% female; mean age 53.5 years; 61% high education), using Fischer-*z* tests.

Results: Ninety-five percent of the participants indicated to prefer an online over a traditional neuropsychological assessment. Comparing ACS and traditional test scores, we observed moderately-high to high convergent validity (r/ρ= .51 to .79). Correlations were generally stronger than in the Dutch validation study (r/ρ= .36 to .70), potentially due to the more homogenous American sample, although this difference was only significant for one test (Wordlist Delayed Recall: Fischer-*z*=2.01; *P*=.04).

Conclusion: Usability of the American ACS was high, as participants were able to successfully complete the tests in an unmonitored setting. Validity results indicate that the American ACS tests sufficiently measure the cognitive constructs of interest. After establishing American norm data, the ACS would allow us to gather large-scale research data on cognitive functioning of cancer patients internationally.

Neurocognitive impairment in adult survivors of soft tissue sarcoma

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Background: Limited data are available regarding neurocognitive outcomes in survivors of pediatric soft tissue sarcomas (STS). We examined neurocognitive performance and social attainment in this population.

Methods: Survivors of STS (n=150; 61% rhabdomyosarcoma [14% with a chest/abdomen tumor, 20% extremities, 43% head/neck, 23% genitourinary]; 41% female; mean [SD] age 33 [8.9] years; 24.3 [8.7] years since diagnosis) and 349 community controls (56% female; age 35 [10.2] years) completed neuropsychological testing. Chronic conditions were categorized using Common Terminology for Adverse Events and dichotomized as grades 0-1(asymptomatic) vs. grades 2-4(moderate to life-threatening). Associations between treatments and neurocognitive outcomes and between chronic conditions and neurocognitive outcomes (adjusting for age at diagnosis, race, and cranial radiation) were examined using linear models. Associations between neurocognitive outcomes and social attainment were examined using log binomial models.

Results: Compared to normative data and controls, survivors showed lower performance on 12 of 17 cognitive measures, including vocabulary (mean[SD] z=-0.45[1.15], p<0.001) and cognitive flexibility (-0.52, p<0.001). Survivors had lower college graduation rates (31% vs. 55% for controls, p<0.001). Treatment with doxorubicin was associated with lower scores on vocabulary (β=-1.47, p=0.026) and cognitive flexibility (β=-2.23, p=0.028). Impaired cognition was not associated with tumor location or cranial radiation exposure. Neurologic morbidity was associated with lower scores on arithmetic (β=-0.70, p=0.008) and attention (β=-1.14, p<0.001). Musculoskeletal morbidity was associated with lower scores on visual memory (β=-0.73, p=0.018) and cognitive flexibility (β=-1.26, p=0.007). Better cognitive performance was associated with college graduation (Relative risk [95% CI]: verbal reasoning = 1.11 [1.07-1.16], processing speed = 1.11 [1.05-1.16]).

Conclusion: In survivors of STS, treatment with doxorubicin and presence of chronic health conditions are associated with lower neurocognitive performance, which is associated with lower social attainment.

Classifying cancer-related cognitive impairment (CRCI) using the Functional Assessment of Cancer Therapy – Cognitive (FACT-Cog) and Multidimensional Fatigue Symptom Inventory – Mental scale (MFSI-Mental)

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Background: CRCI can be characterized using existing ICCTF research criteria based on neuropsychological assessment, and measured using continuous subjective instruments. Identifying useful cut-points for subjective instruments can help capture CRCI in both research and clinical settings. In this study, we generated receiver operating characteristic (ROC) curves with commonly used instruments in cancer survivorship, the FACT-Cog and MFSI-Mental, defining CRCI based on neuropsychological or self-report methods.

Methods: In 134 breast cancer survivors (BCS; age=56.75 ±4.43, mean years since treatment=4.43 ±.64) we collected neuropsychological data and five measures of interest: the MFSI-Mental and 4 FACT-Cog measures: Perceived Cognitive Ability (PCA), Perceived Cognitive Impairment (PCI), Comments from Others (CO) and Impact on Cognitive Quality of Life (QoL). The Patient's Assessment of Own Functioning Inventory (PAOFI) cognitive complaint measure was collected in this sample and compared to a sample of normal controls (n=63, age = 51.97±9.35). We operationalized CRCI based on ICCTF criteria or PAOFI Total ≥2SD above the mean for normal controls. We generated ROC curves based on each CRCI definition using the five measures of interest.

Results: None of the five measures exhibited good classification power for CRCI based on ICCTF criteria, the best being the FACT-Cog PCA with 63.4% area under the curve (AUC), p=.02. Good classification power for CRCI based on elevated PAOFI total was observed for FACT-Cog PCI, PCA, and QoL (AUCs 85%, p<.01; 84.2%, p<.01; 87.2%, p<.01, respectively) and MFSI-Mental (AUC 88.7%, p<.01). The following cut-points emerged (cut-point, % sensitivity - % specificity): PCI <57, 80.6% - 75.5%; PCA <18, 80.6% - 79.4%; QoL <14, 83.9% - 76.5%; MFSI-Mental >4, 87.1% - 72.5%.

Conclusion: FACT-Cog PCI and MFSI-Mental are useful for classifying CRCI defined by self-report but not ICCTF criteria. Further validation of cut-points is warranted.

Multimodal cross-sectional studies of hippocampal-prefrontal network dysfunction in breast cancer survivors after chemotherapy

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Background: Cognitive impairments are frequently reported following adjuvant chemotherapy. The potential neuropathological substrates of impairments remain uncertain. Studies indicate that the hippocampus may be particularly vulnerable to cancer treatments. We performed a series of studies examining hippocampal-prefrontal network structure, function and connectivity in breast cancer survivors and controls.

Methods: We studied 17 pre-menopausal breast cancer survivors and 18 healthy controls. Survivors had undergone chemotherapy within the previous 18 months, and were presently receiving estrogen-blockade therapy. The NIH Toolbox Cognition Battery and Neuro-QOL Cognitive Function were used to assess objective and subjective cognition. 3T Structural MRI and a specialized functional MRI of long-term memory processing sensitive to covert hippocampal impairment through eye-movement tracking were collected. Measures of hippocampal-prefrontal structure, function, and task-related functional connectivity were analyzed and compared to objective and subjective measures of cognition.

Results: Relative to healthy controls, breast cancer survivors demonstrated elevated subjective cognitive concerns, lower episodic memory performance, and impaired eye-tracking behavior in the absence of any impairment in standard task recognition during the fMRI covert-memory task. Survivors showed significant, co-localized hippocampal-prefrontal structural (reduced hippocampal volume & shape, left PFC thinning) and functional network abnormalities (reduced hippocampal activation). Survivors also showed increased task-related hippocampal-cortical functional connectivity. The increased task-related functional connectivity was related to elevated cognitive concern in the survivors. There was no relationship between hippocampal-prefrontal network structure, task activity and any of the standard and self-reported cognitive testing measures.

Conclusion: We report for the first time brain network structure, function, and connectivity in the same breast cancer survivors. We identified hippocampal and memory abnormalities in survivors that were not evident using standard testing approaches. Our results suggest that the structural and functional abnormalities, combined with a potential compensatory response through increased functional connectivity, could explain, in part, the subjective concerns for cognitive abilities experienced by the survivors.

Subcomponent processes underlying learning and memory decline associated with cancer and cancer therapy in women with breast cancer

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Background: Reduced learning/memory has been observed in women with breast cancer (BC) after chemotherapy. Little is known about subcomponent cognitive processes and learning/memory strategies underlying this profile. Serial position patterns consistent with greater reliance on working (ie, recency) than episodic (ie, primacy) memory and less use of semantic clustering were reported in MCI/AD.

Methods: Female patients (≥50yo) with stage I-III HER2/neu- BC treated with adjuvant chemotherapy and healthy controls (HC) were recruited. Participants completed neuropsychological assessment including HVLT-R prior to chemotherapy (baseline [B]) and one month after chemotherapy (follow up [FU]).

Results: BC (n=24) patients and HC (n=51) completed testing at B and FU. At B groups did not differ in age or mood; HC had more education, higher WRAT-4 Reading, HVLT-R (TR, DR, serial clustering) and Neuro-QOL, and, lower fatigue. At FU, RCI-defined decline on HVLT-R TR (21% vs 2%) and DR (17% vs 2%) was more frequent in BC compared to HC. Decline was not associated with age, education, WRAT-4, endocrine therapy, mood, or fatigue. At FU, BC patients recalled more recency (d=.37) and fewer primacy (d=.26) words during encoding, and showed less semantic clustering (SC) over time (d=.35). Within the BC patient group, HVLT-R TR decliners compared to non-decliners evidenced lower SC (d=.52) and SC ratio (d=1.06) at B; at FU, decliners evidenced lower SC (d=.38), greater recency (d=.28), and greater shift in the serial position curves from primacy to recency (d=.11) and middle to recency (d=.39).

Conclusion: BC patients treated with chemotherapy evidenced more frequent decreases in learning and memory compared to HC. BC patients' failure to use semantic clustering and shifts in serial position curves toward greater reliance on working compared to episodic memory are consistent with MCI/AD populations.

Chemobrain In Motion (CIM) – The impact of different chemotherapy accompanying aerobic exercise programs on cancer related cognitive impairments in patients with breast cancer

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Abstract

Up to 80% of breast cancer patients suffer from cancer related cognitive impairments (CRCI), often with persisting symptoms after completion of medical treatments. Systemic inflammation and decreased neurotrophic factor levels are discussed as underlying mechanisms. Studies indicate that aerobic exercise and especially high-intensity interval endurance training (HIT) might increase anti-inflammatory cytokines and neurotrophic factors. Moreover, HIT seems to be feasible and beneficial in breast cancer patients. However, RCTs testing the effects of HIT during chemotherapy on CRCI and associated biomarkers in breast cancer patients are lacking.

The aim of the planned study is to investigate the effects of HIT compared to moderate-intensity continuous endurance training, supervised myofascial release training (placebo control group) and a passive waitlist control group on CRCI in breast cancer patients undergoing chemotherapy. The primary endpoint is cognitive function assessed via neuropsychological tests considering different cognitive domains such as verbal memory, verbal fluency, task switching, response inhibition and spatial memory. Secondary endpoints comprise self-perceived cognitive functioning, inflammatory and neurotrophic serum markers as well as the physical capacity. Measurement time points will be immediately before, 1-3 days after and 6 months after completion of chemotherapeutic treatment.

The planned study will be the first RCT that investigates the effects of HIT on CRCI. Applying also a moderate-intensity continuous training group will provide important information on the efficacy of different endurance training methods in alleviating CRCI. Comparisons of both training groups against placebo and waitlist control allow reliable attribution of potential effects to the physiological adaptations and a distinction related to unspecific factors like social attention on CRCI. Capturing physiological markers will provide valuable information about the underlying mechanisms of potential effects/potential lack of effects of HIT on CRCI.

Does self-esteem impact subjective cognitive functioning? Cross-sectional and longitudinal data of patients undergoing high-dose chemotherapy for hematologic neoplasms

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Background: It has been questioned whether cancer related cognitive impairment (CRCI) is a result of structural, biological changes through cancer treatment or rather a result of psychological distress. Patients with hematologic neoplasms undergoing high-dose chemotherapy are subject to several factors potentially influencing self-esteem, including a feeling of guilt, losing functional capacity, losing one's role in family and society or a change in appearance. Therefore, we investigated possible associations between subjective cognitive functioning and self-esteem.

Methods: 35 patients with hematologic neoplasms completed the German versions of the Functional Assessment of Cancer Therapy – cognitive function (FACT-Cog) and the Rosenberg Self-Esteem Scale (RSES) questionnaires before and after undergoing high-dose chemotherapy. For this analysis, the FACT-Cog subscales perceived cognitive impairments (CogPCI), perceived cognitive abilities (CogPCA) and impact of perceived cognitive impairments on quality of life (CogQOL) were examined. RSES consists of only one scale comprising 10 questions, measuring both positive and negative feelings about oneself. Baseline data and differences (post-pre) of all outcomes were analyzed using explorative correlation analysis.

Results: Baseline analysis revealed significant associations between RSES and CogPCI ($r=.481$, $p=.003$) and CogPCA ($r=.476$, $p=.004$), respectively. Changes over time (deltas) showed significant correlations between RSES and CogPCA ($r=.706$, $p=.001$) and RSES and CogQOL ($r=-.548$, $p=.023$).

Conclusion: These results suggest, that psychological factors like self-esteem might be associated with CRCI, especially with subjective cognitive functioning. For future studies, self-esteem should be added as a covariate to further elucidate differing outcomes in objective and subjective cognitive impairment.

Aerobic exercise increases verbal memory in leukemia patients undergoing high dose chemotherapy – interim analysis of a randomized placebo controlled trial

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Background: Supervised exercise programs are known to reduce several side effects of cancer and its treatment (e.g. fatigue), thereby increasing patients` quality of life. Moreover, a vast body of literature suggests positive effects of exercise on structural and functional adaptions of the central nervous system. Against this background, we have implemented a randomized placebo controlled trial, investigating the influence of aerobic exercise on cognitive performance in 83 leukemia patients undergoing high-dose induction chemotherapy.

Methods: In this interims-analysis the first 24 patients who were either randomized to a supervised aerobic exercise group (n=11) or a supervised control group (stretching and relaxing training, n=13) were investigated in view of their verbal memory before and after completing chemotherapy. Verbal memory was assessed using the Hopkins Verbal Learning Test – Revised (HVLT-R).

Results: No group differences were detected for anthropometric data, and baseline levels of intelligence (MWT-B), fatigue (MFI-20), quality of sleep (PSQI), self-perceived cognitive impairments (FACT-Cog) and HVLT-R performance. A 2 (groups) x 2 (pre/post chemotherapy) ANCOVA controlling for baseline levels indicated a significant group x time interaction in total recall performance of the HVLT-R. Participants of the exercise group improved, whereas those of the control group worsen.

Conclusion: These preliminary results further support the hypothesis that exercise could serve as effective strategy to counteract cancer related cognitive impairments. Further analysis of this work may also provide important information on mediators and underlying mechanisms, since a large panel of potential psychological and biological factors will be assessed as well.

POSTER PRESENTATIONS: TUESDAY

Using a computational model to extract more information from the trail making test

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Background: The Trail Making Test is one of the standard tests that is used in clinical neuropsychology, and has been for decades. On this test, a patient connects circles containing numbers in part A, and connects circles containing alternating letters and numbers in part B. This test is sensitive to cognitive impairment, but is aspecific, as a variety of cognitive abilities are involved in performing well on this test.

Methods: A sample of participants with and without cancer were tested in a previously conducted study, using the version of the Trail Making Test as presented in the Amsterdam Cognition Scan (N=202 and 248; Feenstra et al., 2016). This computerized version allows us to not only look at the completion time of the entire test, but also at the time it takes participants to click each of the different circles during the test. This higher resolution of data allows for more detailed process analyses.

A Shifted-Wald model was fitted to the "reaction" times. This model partitions reaction times into measures of ability/difficulty, carefulness/conservativeness, and motor speed/clicking speed. We included the distance between circles, and the difference between parts A and B.

Preliminary Results: A number of results from the model are as expected: Both participants with and without cancer find part B more difficult than part A, are more careful/conservative during part B than during part A, and are slower when the distance to the next circle is longer. Group differences arise in motor speed, with the cancer group being slower.

Conclusion: Our model suggests that groups with and without cancer are similar in ability and carefulness on the Trail Making Test, but that those with cancer are slower to move and click. The combination of computerized testing with computational modeling provides more information than is possible with paper-and-pencil versions.

Long-term cognitive functioning in patients treated for grade I-III brain tumors: The role of radiotherapy

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Background: After neurosurgery, radiotherapy (RT) is the main treatment for many brain tumors. Irradiation, however, may have detrimental effects on cognitive functions. So far, most studies investigating radiation-induced cognitive impairments have used healthy participants as comparison. This approach, however, does not account for tumor-related impairments. In the present cross-sectional study, we compared cognitive functioning in patients with grade I-III brain tumours who received surgical resection with and without RT.

Methods: Adult patients with specified grade I-III brain tumors treated at Aarhus University Hospital between 2006-2016 underwent neuropsychological assessment. Standardized tests included Trailmaking Test (TMT); Hopkins Verbal Learning Test (HVLT); Controlled Oral Word Association Test (COWAT) – Animals/S-words; Coding and Digit Span from WAIS-IV; Paced Auditory Serial Addition Test (PASAT); Stroop Test. Outcomes were converted to z-scores using adjusted normative data and analyzed with one-sample and independent sample t-tests. Test-specific and overall cognitive impairment (OCI) frequencies were determined using ICCTF criteria, and between-group differences were tested with Fisher's exact test.

Results: Ninety-five participants were recruited at the time of analysis. Sixty-six had RT (RT+), while 29 had not (RT-). Mean age was 54.7 years with an average time since diagnosis of 7.8 years. Compared with normative data, lower average scores were observed for the entire group on HVLT-total ($p<0.001$), HVLT-delayed ($p<0.001$), PASAT ($p<0.001$), and Stroop ($p<0.001$). Further indication of lower scores was noted for TMT-B ($p=0.06$), and Coding ($p=0.07$). General OCI frequency was 57.9%. Compared with RT-, RT+ scored lower on COWAT-Animals ($p=0.045$) with indication of lower scores on Coding ($p=0.07$), and Stroop ($p=0.06$). No OCI between-group difference was observed. Higher impairment frequency was observed in RT+ (17%) on COWAT-Animals.

Conclusion: Long-term cognitive impairment was evident in the majority of patients. Our results indicate that radiotherapy may have additional detrimental effects on cognitive functions.

Sex differences in insomnia symptoms and attention and memory problems in adult survivors of childhood cancer

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Background: Long-term survivors of childhood cancer are at risk of developing sleep and neurocognitive problems. Few studies have examined the contribution of insomnia to attention and memory function in this population, particularly with reference to sex differences.

Methods: 642 adult survivors of childhood cancer (52.8% female, mean[SD] age of 34.5[9.2] years, 25.9 [9.1] years since diagnosis) completed standardized questionnaires of sleep disturbance, fatigue and sleepiness, as well as objective testing of sustained attention (Conners' Continuous Performance Test) and memory (California Verbal Learning Test). Age- and sex-adjusted z-scores were calculated for neurocognitive tests. Insomnia was defined as difficulty falling asleep within 30 minutes and nighttime/early morning awakenings ($\geq$3 times per week). Multivariable regression models examined associations between sleep and attention and memory, stratified by sex and adjusted for age, age at diagnosis, and primary treatment exposures (e.g., cranial irradiation, methotrexate).

Results: More females than males reported insomnia (25% vs. 16%, P=0.004). Males performed better on measures of attention (omissions: P<0.001; detectability: P=0.02). No sex differences were observed on measures of memory. In multivariable models adjusted for cancer therapies, insomnia combined with excessive daytime fatigue/sleepiness was associated with worse short-term (P=<0.01, P=0.01) and long-term memory (P=0.01, P=0.02) in females and males, respectively. However, in females only, insomnia without excessive daytime fatigue/sleepiness was associated with lower verbal learning (β = -0.46, P=0.01), short-term (β = -0.50, P=0.01), and long-term memory (β = -0.51, P=0.01). In females, insomnia with significant daytime fatigue/sleepiness was associated with greater omissions (β = -0.52, P=0.02) and poorer detectability (β = -0.43, P=0.01).

Conclusion: Female survivors appear more vulnerable to the adverse effects of insomnia on attention and memory function. Interventions targeting insomnia may confer benefit for neurocognitive problems in adult survivors of childhood cancer.

Improved processing of diffusion tensor imaging data increases sensitivity to detect brain white matter changes in breast cancer patients

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Background: To assess side effects of chemotherapy on brain white matter integrity in breast cancer patients as a neural correlate of cognitive problems. We implemented an enhanced approach for processing brain magnetic resonance imaging (MRI) diffusion tensor imaging (DTI) data in a longitudinal setting. We used an improved registration algorithm and omitted white matter 'skeletonization' within the widely used tract-based spatial statistics (TBSS) framework.

Methods: Twenty-six breast cancer patients scheduled to receive adjuvant chemotherapy with or without endocrine treatment (Ch+), 23 breast cancer patients who did not require chemotherapy or endocrine treatment (Ch-), and 30 age-matched healthy controls (HC) received a T1-weighted scan and a DTI scan at two time points. Baseline data for Ch+ was collected after surgery but before receiving chemotherapy (t0). A follow-up session took place 6 months after chemotherapy and at matched intervals for Ch- and HC (t1). After eddy current correction and diffusion tensor model fitting, a T1-weighted group-wise template was built to warp the fractional anisotropy (FA) maps. We used the ANTs Symmetric Normalization (SyN) registration algorithm.

Results: Ch+ showed a significant decrease in mean FA from t0 to t1 compared to the HC group. Voxel-wise between group analysis showed that both Ch+ and Ch- had significant decreases in FA compared to the HC group, with Ch+ showing more affected voxels than Ch- (5203 vs 230).

Conclusion: These findings suggest a decrease of brain white matter integrity in breast cancer patients, with a possible added effect of chemotherapy treatment. The improved processing pipeline within the TBSS framework increases sensitivity to detect brain white matter changes in breast cancer patients and demonstrates the feasibility of using this pipeline for DTI data in this population.

Cutting through the fog: Nurses' perceptions of cancer-related cognitive impairment

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Background: Cognitive impairment after cancer and chemotherapy occurs frequently and is one of the most distressing symptoms reported by cancer survivors. While impairments are often subtle, typically affecting learning and memory, processing speed and executive function, impacts on quality of life and functioning can be profound. However, little is known about health professionals' perceptions of this problem.

Aim: The current study aimed to explore oncology nurses' awareness and knowledge of cancer-related cognitive impairment (CRCI) and patient care and education offered around this topic.

Methods: Semi-structured interviews were conducted with oncology nurses working acute healthcare in Australian hospitals. Transcribed interviews were analysed based on interpretative phenomenological analysis.

Results: A total of 17 oncology nurses were interviewed. Six themes were identified: the role of oncology nurses, knowing the person, tension in the acute healthcare system, incorporation of evidence, awareness and knowledge of CRCI, and patient care. Participants described using patient-centred approaches to care and education, such as providing holistic care, tailoring information to patient need, and offering reassurances and empathy for patients who raised problems with cognition. Nurses' observations of patients' impairments were highly consistent with prior research. While participants felt that CRCI was a real phenomenon frequently affecting patients, many expressed uncertainty about its cause, duration, impact, and management. Perceptions of low impact and uncertainty about its management reduced discussion about CRCI with patients, lowering the quality of education offered. Nurses also raised issues within the healthcare system that impacted the delivery of care and education and articulated the need for increased resources and training to improve patient support in this area.

Conclusion: These findings extend current understanding of nurses' perceptions of CRCI, providing deeper understanding of factors contributing to nurses' awareness and knowledge of this impairment. Recommendations are proposed to enhance patient care and education related to CRCI.

Acute and long-term effects on brain connectivity in the juvenile brain after cranial irradiation

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Background: Cranial irradiation (IR) is an effective treatment for paediatric brain tumours but it has also detrimental effects on developing young brains, especially in the hippocampus, where neurogenesis occurs throughout life. Furthermore, the risk of cerebrovascular diseases in later life rises as a result of exposure to ionizing irradiation at an early age. Little is known about the impact of IR on functional brain connectivity. To our knowledge, this is the first study to explore this phenomenon by using resting state functional magnetic resonance imaging (rsfMRI) and analysed using a novel method called Quantitative Data-driven Analysis.

Methods: 24 Sprague-Dawley rats were lightly sedated and scanned three times in a 9.4T MRI scanner. The first scan was at postnatal day 20 (P20), one day prior to a single dose of 8 Gy whole brain IR (P21; N=12) or sham IR (N=12). The second scan was 24h after the IR/sham treatment (P22). The third scan was one month after the treatment (P52-56). The fMRI was conducted using an echo planar imaging sequence with a slice plan covering the whole brain from the olfactory bulb to the caudal part of cerebellum. The haemodynamic response was assessed using subcutaneous electrical stimulation (2mA) with 3ms pulses at a frequency of 10Hz. After the last scan, the brains of all rats were analysed using immunohistochemistry, including assessment of neurogenesis.

Results: The results obtained from the non-irradiated rats after the electrical stimulation showed a more pronounced haemodynamic response in the region of motor/sensory cortex compared to the irradiated rat.

Conclusion: The medetomidine protocol for sedation of small rats was successfully established and allowed us to see the BOLD response to electrical paw stimulation. Results from the haemodynamic response indicated that the irradiated rats had a lower response in the corresponding motor/somatosensory cortex. This implies that vascular regulation is disrupted after IR.

Utilizing random forest regression to identify cytokine predictors of cognitive performance in breast cancer survivors

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Background: The neurotoxic effects of cytokine dysregulation initiated by cancer pathology and treatments may result in cancer related cognitive impairments (CRCI). Clinical studies have linked cytokines and cognitive performance in breast cancer survivors (BCS), but the findings have been heterogeneous. It is likely that the relationships between peripheral cytokines and cognitive performance are complex and require multivariate, non-parametric analyses. This study aims to examine cytokine predictors of CRCI in BCS 6 months to 10 years after chemotherapy completion using random forest regression.

Methods: Women with a history of non-metastatic breast cancer and without inflammatory comorbidities were recruited for the study. Data collection included completion of self-report surveys (psychosocial factors), cognitive testing (COWA, HVLT-Immediate & Delay, TMT A & B), anthropometric measures, and non-fasting blood draws (12 cytokines). Data were analyzed using random forest regression, a machine learning analysis, to identify the most significant predictors for each of the cognitive test scores.

Results: We found a different profile of cytokine predictors for each of the cognitive tests. Adjusted R^2 for each of the models ranged from 0.71-0.77 (p's<9.50^{-10}). The most important variables for COWA scores were IL-10, IL-7, and IL-4, for HVLT-I in were IL-1β, IL-2, and years of education, for HVLT-D IL-4, IL-1β, TNF-α, for TMT A GM-CSF, IL-8, and IL-2, and for TMT B IL-1β and IL-2. The relationships between all the cytokine predictors and cognitive test scores were non-linear.

Conclusion: Our findings suggest that specific cytokines are more important predictors of cognitive performance than BMI, age, psychological variables, and time since end of chemotherapy. Cytokine predictors vary depending on cognitive domain assessed. Our findings are unique to the field of CRCI and suggest non-linear cytokine specificity to neural networks underlying cognitive functions assessed in this study.

Longitudinal observation of objective neuropsychological performance changes in people treated with adjuvant 5FU/oxaliplatin chemotherapy for colon cancer: Pilot study findings

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Background: Declines in cognitive function following chemotherapy has been described in 15–75% of people with cancer. Changes in cognitive function in people undergoing chemotherapy treatment for colon cancer has not been studied extensively. This study described the trajectory of objective neuropsychological performance in people receiving 5FU/oxaliplatin chemotherapy for colon cancer.

Methods: Participants were tested within 3 weeks of starting chemotherapy (T1), end of chemotherapy (T2), and 6-months post-chemotherapy (T3). Objective measures included a neuropsychological (NP) test battery (Trail Making Task A&B; Controlled Oral Word Association; Animal Naming; Hopkins Verbal Learning Test-Revised [HVLT-R]), and a sustained-attention-to-response task (SART) that paired subjective reports of on- vs. off-task attentional states with electroencephalogram (EEG) recordings during this task. NP performance changes were assessed using Friedman's Test ($p<0.05$) with Wilcoxon Signed Ranks Test for post-hoc comparisons (Bonferroni Corrections, $p<0.017$). Changes in EEG-based P300 event-related potentials (ERP) elicited by target events during the SART were assessed using mean amplitude measures from midline central-parietal scalp electrode sites and compared between on- and off-task reports.

Results: Ten participants were recruited (51.0±7.8 years). Nine completed NP testing; seven completed SART with EEG. Overall mean performance in NP tests remained stable throughout all three timepoints, with near statistical significant increase in HVLT-R Retention T-Score from T2 (45.1±6.9) to T3 (52.0±7.1). The trend in HVLT-R subscales showed no change from T1 to T2, and non-statistical improvements at T3. Mean P300 amplitudes during on- and off-task attentional states were near-zero at T1 and T2, but showed a numerical increase in amplitude specifically during on-task attentional states at T3.

Conclusion: Preliminary observations in neuropsychological performance using NP test battery and EEG recording during SART supports the need of larger studies to further investigate patterns of change with chemotherapy treatment.

Cognitive complaints in cancer survivors and expectations for management: Results from a national survey

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Background: Complaints of memory and attention dysfunction are common among cancer survivors. Few studies have assessed cognitive complaints using large sample and information on patients' expectations for management of cognitive disorders are scarce. We aimed to assess cognitive complaints using a large national survey.

Methods: This online survey was proposed by the association the *Seintinelles* to cancer survivors, except brain primary or metastasis cancer and without progressive psychiatric or neurological disease. Cognitive complaints were assessed by a list of questions. Patients were further asked about their expectations for management of cognitive difficulties, the impact on work resumption and knowledge about chemotherapy-associated cognitive problems.

Results: Among 1 610 eligible participants (median age 52 [21-84]), >85% were breast cancer survivors. Median post-cancer treatment time (excluding hormone therapy) was 2.83 years [0.8-33]. Eighty two (5%) had a neurological antecedent and 273 (17%) had a weekly consumption of psychotropic medications. 1 379 participants (86%) had cognitive complaints whose 1214 (88%) related to cancer treatments. Cognitive difficulties started during chemotherapy (419 (35%)), after chemotherapy (360 (30%)) and during hormone therapy (186 (15%)) and lasted a median of 2 years [0.08-32]. For 387 participants (32%), cognitive difficulties had an important impact on work resumption. 618 (40%) had pre-existing knowledge about chemotherapy-associated cognitive problems and this was significantly associated with their cognitive complaints (p=0.01). Among survivors with cognitive complaints related to cancer treatments, 909 (75%) would like to receive cognitive rehabilitation, 439 (48%) psychological support and 294 (32%) physical activity.

Conclusion: Using a national survey of cancer survivors, we observed a large proportion of participants with cognitive complaints. For the majority of them, complaints were due to cancer treatments. Most participants would like to receive management and especially cognitive one. Cognitive program should be included in the portfolio of oncology supportive care.

The tripartite relationship of cognition, depression and fatigue for children with cancer

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Background: Cognitive dysfunction is a common late effect for children with cancer. Cognition reported by parents (PCF-p) and/or children with cancer (PCF-c) have been used by clinicians to refer children for formal cognitive testing. Yet literature indicated a significant relationship between PCF and fatigue & depression. This study aimed to explore the relationship among cognition reported by parents and children and fatigue and depression in children with cancer.

Methods: Data from 515 patients aged 7-21 (mean=14 yrs; 56% males) were analyzed. 34% received radiation therapy, 72% chemotherapy, 71% surgery. Average time since last treatment was 3.3 years. PCF was measured using a validated 43-item pediatric PCF item bank (pedsPCF-p and pedsPCF-c for PCF-p and PCF-c, respectively). Patients completed NeuroQOL Depression, PedsQL Fatigue & neuropsychological tests. Z-scores were created for all scales (mean=0; SD=1): 1) normal: z-scores within 0.5 SD around mean; 2) mild: 0.5-1 SD, 3) moderate: 1-1.5; and 4) severe: > 1.5 SD worse than mean. Latent class analysis was used to classify patients based on depression, fatigue, pedsPCF-p and pedsPCF-c. Logistic regression was used to identify significant predictors of these classes.

Results: Three latent classes were identified: 1) normal PCF-p (z=0.194), PCF-c (z=0.139), non-fatigue (z=-0.296) and non-depression (z=-0.451); 2) mild PCF-p (-0.968) and PCF-c (z=-0.696), moderate fatigue (z=1.331), and severe depression (z=3.141); 3) mild PCF-p (z=-0.565), normal PCF-c (z=-0.373), mild fatigue (z=0.909) and moderate depression (z=1.118). Working memory (class 1 vs. 3), gender (class 1 vs. 3), parent-reported QOL of the child (class 1, vs. 2 & 1 vs. 3), and Hispanic origin (class 1 vs. 2 & 1 vs. 3) were significantly associated with class membership.

Conclusion: This study identified three classes among these symptoms and identified predictors of these classes. Future studies should be done to explore clinical implications of these results

Interventions for cancer-related cognitive change intervention: A systematic review with meta-analysis

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Background: Up to 75% of cancer survivors experience cognitive difficulties that impact daily functioning. Despite the existence of intervention trials for cancer-related cognitive change (CRCC), the prevention and management of CRCC is rarely discussed with cancer patients or survivors. Further, there are few services available to cancer survivors that provide management or support for cognitive concerns. What has been lacking is a comprehensive analysis of the effectiveness of published studies on cognitive interventions that are available to cancer patients. This is important for the development of effective cancer rehabilitation programs to support survivors through short-term, and long-term recovery.

Methods: This study presents a systematic review with meta-analysis. A search of databases Medline, CINAHL, OTSeeker, AMED, and PsychINFO was completed, including years 2007-2017 and limited to randomised control trials (RCTs) published in English. Quality analysis of studies was completed using the Joanna Briggs Institute Critical Appraisal Checklist for RCTs. Meta-analysis was accomplished using Comprehensive Meta-Analysis software.

Results: A total of 23 studies were identified that presented interventions for CRCC and met selection criteria. Interventions fell into three categories: cognitive training based intervention, cognitive behaviour therapy (CBT), and alternative/complementary therapies. Overall, CBT interventions had no significant impact on cognitive functioning, while the other categories significantly improved cognitive performance. The majority of research was completed in the US and was limited to breast cancer populations.

Conclusion: Findings suggest that current research into intervention options for the management of CRCC is limited in scope, however alternative and complementary therapies are both effective and accessible to cancer survivors. Based on current research, CBT should not be recommended as an effective CRCC intervention. The findings are significant for clinical decision making by practitioners recommending interventions for CRCC. There is need for further, high-quality research in this area that addresses the broader population of cancer survivors.

An APOE knock-in mouse model of chemotherapy effects on cognitive behavior and brain structure

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Background: Chemotherapy appears to accelerate aging and produce cognitive decline in some breast cancer survivors. Having an APOE4 allele, a known risk for Alzheimer's disease, also appears to increase risk of cancer-related cognitive decline in older cancer survivors. We developed a novel preclinical model using APOE knock-in mice to study the effects of cancer therapy and aging on cognition and brain structure.

Methods: Three-month old congenic C57BL/6 female mice expressing human APOE3 (n=11) or APOE4 (n=13) alleles underwent baseline behavioral and cognitive assessment with the Barnes maze (spatial learning), and then were exposed to doxorubicin (10 mg/kg) or saline via tail-vein injection. Assessments were repeated one week and six weeks post-exposure. Toxicity was evaluated by overt behaviors, weight loss, and open-field exploration at each assessment. Brain MRI was performed at autopsy eight weeks post-exposure.

Results: Tail injections resulted in minor local inflammation in 20%. There was <5-10% weight loss in both groups, and no morbidity or deaths. Both groups showed reduced exploratory and vigilance behaviors one week post-exposure; this continued at six weeks in APOE4 but not APOE3 mice. APOE4 and APOE3 mice had similar learning on the Barnes's maze at baseline with decrements one week post-exposure. However, at six weeks, APOE4 mice failed to improve and had reduced learning behavior compared to APOE3 mice, taking significantly longer to find the target hole (latency) ($p<0.001$). MRI using voxel-based morphometry revealed that doxorubicin-exposed APOE4 mice had significantly smaller hippocampal regions than exposed APOE3 mice.

Conclusion: An APOE knock-in mouse model is a promising model for studying cancer-related cognitive decline. Future experiments will expose older mice, change the administration mode, vary doses and agents, and include long-term follow-up. This model may generate novel data about treatment-genotype-aging interactions and suggest mechanisms whereby APOE pathways affect cancer-related cognitive decline.

Blood-based biomarkers of cancer-related cognitive impairment in non-central nervous system cancer: Preliminary results from a scoping review

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Background: Given the potentially detrimental effects of cancer-related cognitive impairment (CRCI) on quality of life, there is growing need for the development of large prospective studies to interrogate underlying mechanisms that may guide the design of effective treatments. As a source of multiple biological markers, peripheral blood may serve as a rich source of data that can shed light on potential hypotheses that can be pursued on a large scale. We are currently conducting a scoping review to summarize the extant literature regarding blood-based biomarkers of CRCI among adults with non-central nervous system (CNS) cancers.

Methods: The scoping review follows the six-stage methodology of Arksey and O'Malley. A comprehensive search was conducted for studies published between January 2006-February 2017 that tested an association between any blood-based biomarker and cognitive functioning among adult non-CNS cancer patients. After confirming strong interrater reliability, study selection was conducted in duplicate and data charting of study characteristics was conducted using a standardized form.

Results: Initial results from this analysis will be presented to identify dominant lines of research regarding potential blood-based biomarkers of cognitive functioning, emerging topics and gaps in the current body of evidence, and implications of the design of future work in this area. In addition, analytic issues will be discussed, including the utility of the scoping review methodology for interrogating CRCI literature.

Conclusion: The identification of biological markers of CRCI in peripheral blood promises to provide important insights into underlying mechanisms and potential tools for the early prediction of poor outcomes. Scoping review methodologies that have been designed to characterize heterogeneous and emerging fields of research, provide a structured approach to mapping this growing evidence base.

Episodic memory activation prior to systemic treatment in older breast cancer patients

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Background: Lower than expected cognitive functioning has been reported in breast cancer patients prior to systemic treatment. The literature has primarily focused on younger breast cancer patients, and there have been few pretreatment neuroimaging studies. Older patients may be at higher risk for cancer-related cognitive declines due to aging processes. We used fMRI to examine brain activation patterns during episodic memory encoding in older breast cancer patients prior to systemic treatment.

Methods: Sixteen patients (mean age 68.3 years, mean education 15.3 years) studied post-surgery but prior to systemic therapy and 16 matched healthy controls (mean age 68.2 years, mean education 15.6 years) were recruited at a single site as part of a larger multi-site longitudinal cognitive study. All participants completed a blocked-design episodic memory scene encoding fMRI task. Encoding accuracy was assessed with an out-of-scanner recognition test. Between-group differences in brain activation and correlations between activation and task performance were analyzed using SPM12 and SPSS, respectively.

Results: Task performance accuracy and reaction time did not differ between patients and controls. During scene encoding, patients demonstrated significantly ($p<0.01$) reduced activation in left parahippocampal, insular, and precuneus regions relative to controls. Left parahippocampal activation was significantly ($p<0.05$) positively correlated with task performance across the whole cohort and in patients alone (higher parahippocampal activation was seen with more accurate recognition of new stimuli).

Conclusion: These results are consistent with the limited neuroimaging literature demonstrating altered brain function prior to systemic treatment for non-CNS cancer, and extend the previous work by examining episodic memory processing in older patients. Data acquisition to increase the cohort size is ongoing, and participants will be followed longitudinally to examine the course of these pre-treatment functional alterations post-treatment, to advance understanding of the relationship between cognitive effects of cancer and treatment and risk for age-related cognitive declines.

Is olfactory dysfunction associated with cognitive impairment in recently treated testicular cancer patients?

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Background: Olfactory dysfunction (OD) is a common side-effect of chemotherapy (CT) with negative impact on patients' quality of life. Furthermore, OD has been associated with cognitive decline in neurodegenerative disorders. We have previously reported a high prevalence of cognitive impairment among testicular cancer (TC) patients receiving cisplatin-based CT. In the present study, we aimed to explore whether cisplatin-based CT is associated with OD and whether patients with indications of cognitive impairment are at an increased risk of OD.

Methods: Of 66 TC patients assessed at six months' post treatment, data from 43 patients were included in the present study. Twenty-nine patients (67.4%) underwent orchiectomy, while 14 (32.6%) received additional CT. All patients completed the Brief Smell Identification Test (B-SIT) and standardized neuropsychological tests. Cognitive impairment status was determined using the International Cancer and Cognition Task Force recommendations while osmia categories were based on published B-SIT norms: anosmia (score <6.0), microsmia (6.0-10.0), and normosmia (10.25-12.0).

Results: Overall, 25 patients (58%) were categorised as normosmic, while 18 (42%) were categorised as microsmic. There was no statistically significant association between CT and osmia categories (OR: 0.43, p=0.22). Furthermore, patients with cognitive impairment were not at an increased risk of OD (OR: 1.2, p=0.78).

Conclusion: Neither treatment group nor cognitive impairment status were associated with olfactory dysfunction. However, our preliminary findings suggest that recently treated TC survivors, irrespective of treatment, may exhibit microsmia and, thus, a decreased olfactory functioning. More research is needed to corroborate these findings.

Genetic variation associated with changes in cognitive performance in older breast cancer patients

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Background: Cancer- and treatment-related cognitive dysfunction has become an increasing concern, particularly among older cancer survivors. We hypothesized that a genome-wide association study (GWAS) would identify novel genetic factors interacting with breast cancer diagnosis to influence cancer-related cognitive dysfunction in older women.

Methods: White non-Hispanic participants included older breast cancer patients with non-metastatic disease (BC; N=186) and healthy controls (N=238) with baseline pre-treatment and one year cognitive and GWAS data. Genotyping employed the Affymetrix AXIOM array. Data was imputed using the Haplotype Reference Consortium dataset. Analyses were performed using plink and SPSS software. Cognitive performance measures included longitudinal z-scores normalized by age and education to controls for Learning and Memory (LrnMem) and Attention, Processing speed, and Executive function (APE) domains at baseline and one year later. Case/control differences in regression coefficients from GWAS quantitative trait association analyses with LrnMem and APE change over time were analyzed to identify genetic loci differentially associated with cognitive change by cancer diagnosis. The threshold for genome-wide significance was set to $p<5e-08$.

Results: Participants ranged from age 60-98 (mean 68). Two loci on chromosomes 17 (rs74878829) and 20 (rs11696130, rs56372104 including gene *EDEM2*) were associated with decreases in APE in BC but not controls. One locus on chromosome 10 in gene *INPP5A* (rs188791200) was associated with decrease in LrnMem in BC but not controls.

Conclusion: Two loci not previously associated with cognitive dysfunction were identified, an intergenic region on chromosome 17, as well as a chromosome 20 locus including *EDEM2*, involved in the degradation of glycoproteins. Additionally, a locus was identified in gene *INPP5A*, which was previously associated with cerebellar ataxia in mice. More research is needed to replicate these findings, as well as to identify the potential mechanism(s) linking *EDEM2* and *INPP5A* to cancer-related cognitive dysfunction.

Novel targeted therapies in drug development and cognitive function: A review of the literature

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Background: The development of novel anti-cancer targeted therapies (TTs) represents a paradigm shift in cancer treatment. Toxicities of these novel TTs are first identified during Phase I trials. It is suspected that some agents tested within early trials may lead to cognitive impairment (CI), however as the focus in Phase I is on safety, cognitive function is not formally assessed. Current literature suggests there is a concern CI may be underreported in early clinical trials, with the risk TT's move into standard practice without CI being identified. Therefore there is a need to evaluate what evidence is available and consider gaps in knowledge with regards to novel TTs. Understanding the scope and nature of the problem will assist in developing interventions to ameliorate the effects of CI in this context.

Methods: Evidence was collected from PubMed, Embase, and Medline using a systematic review framework then extended to grey literature databases and clinicaltrials.gov due to limited yield of results.

Results: There are a limited number of reports of CI as a drug related effect of Phase I trials. The symptoms included difficulty word finding loss of memory and concentration. Emerging data on some new targeted TT's as they become standard treatments has meant further research has been required to define the cognitive effects. Putative mechanisms of CI such as cytokine dysregulation and altered DNA repair mechanisms can be aligned with some of the mechanisms and effects of the TT's. There is a lack of objective measurement of cognitive function within Phase I trials.

Conclusions: The lack of formal objective cognitive assessment in early clinical trials highlights the need for a more consistent and valid way of defining and assessing such symptoms in patients receiving novel TT's. Research is currently in progress at the Royal Marsden UK investigating CI in this context.

Pre-treatment symptom clusters and their association with longitudinal cognitive function in older breast cancer survivors

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Background: Symptom clusters can affect cancer survivors' functional outcomes. Older survivors may be especially vulnerable to functional decline but there is little research on symptoms and cognition in older survivors.

Methods: Survivors with newly diagnosed non-metastatic breast cancer (n=320) ages 60+ without dementia or neurological disease were recruited at six US sites from August 2010-December 2015. Participants completed surveys and neuropsychological tests before systemic therapy, and 12 and 24 months later. Latent class analysis was used to identify symptom clusters based on baseline self-reported depression, anxiety, fatigue, sleep disturbance, and pain. The FACT-Cog measured self-reported cognition. Standardized neuropsychological tests measured cognitive function in two domains: attention, processing speed, and executive function [APE] and learning and memory [LM]). Linear mixed-effects models examined the effects of symptom-cluster group on cognitive scores over time, controlling for age, WRAT, race, site, stage, and comorbidity.

Results: Survivors were 68 years of age on average, 79% were White, and 67% had DCIS or Stage 1 cancers. Two non-overlapping symptom clusters were present: high symptom burden (n=48; 15%) and low symptom burden (n=272; 85%). Compared to the low symptom group, survivors with high burden had lower adjusted APE across all time points (Est[SE]=-0.20[.10], P=0.04). The high burden group had lower adjusted baseline LM (-0.34[.13], P=0.009) and more self-reported cognitive problems (-16.28[3.13], P<0.0001); over time, scores tended to continue to be lower for the high vs. low burden group.

Conclusion: Only a small proportion of older breast cancer survivors have high symptom burden at diagnosis, but they have meaningful decrements in cognition. Symptom burden prior to systemic therapy may be a risk-marker for lower cognitive function. If confirmed, symptom management may improve cognitive and other survivorship outcomes. Biological pathways related to symptoms and cognition may suggest shared mechanisms.

Mild cognitive impairment and dementia show contrasting associations with risk of cancer

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Background: Dementia and cancer are major public health concerns. Previous studies showed an inverse relation between dementia and cancer. However, it is uncertain whether this observation is based on biological mechanisms or if it is due to epidemiological limitations. Mild cognitive impairment (MCI) represents the earliest clinical features of dementia. We investigated the relation between MCI and cancer in addition to the association between dementia and cancer to better understand the nature of this finding.

Methods: 13,207 persons from the Rotterdam Study were followed between 1990 and 2013 for the onset of dementia and cancer. Between 2002 and 2005, a subset of 5,181 persons underwent extensive cognitive testing for MCI and subsequently were followed up for cancer until 2013. We used Cox proportional hazard models to determine the association between dementia and cancer and MCI and cancer. We repeated analyses lagged by two and five years to minimize potential effects of reverse causality.

Results: In total 1,404 patients were diagnosed with dementia, and 2,316 developed cancer (63 among dementia cases). Dementia was associated with a decreased risk of cancer (hazard ratio (HR) 0.53; 95%CI 0.41-0.68). 513 persons were diagnosed with MCI and during follow-up 670 persons developed cancer (81 among MCI cases). In contrast to individuals with dementia, those with MCI tended to have an increased risk of cancer (HR 1.25; 95%CI 0.99-1.58). Using a lag interval of two and five years did not affect the difference between dementia and MCI with respect to cancer risk.

Conclusion: We found that persons with MCI seem to be at an increased risk of cancer, whereas those with dementia have a decreased risk. These findings call into question a biological explanation for the inverse link between dementia and cancer, instead suggesting methodological bias.

Does colorectal cancer cause long term cognitive impairment or accelerate cognitive ageing? An extension of a longitudinal study

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Background: Our previous longitudinal study in colorectal cancer (CRC) found cognitive impairment in 43% (125/281) of localised CRC patients versus healthy controls (HC) 15% (10/72) (OR=4.51, 95%CI 2.28-8.93; $p<0.001$) at baseline, and in 50% of CRC patients at 1-2 years, compared to 13% of controls (OR=5.67, 95%CI=2.67-12.03). The trajectory beyond that remains unknown.

Aim: To evaluate patterns of longer-term cognitive function in CRC survivors by extending our original study, determining the impact on functional tasks, and investigating accelerated cognitive ageing.

Methods: Australian participants from the original cohort who remained cancer free were eligible. Subjects completed cognitive and daily-task functional assessments (shopping, financial, cooking, driving tasks) and questionnaires for perceived cognitive function, fatigue, QOL, anxiety/depression. Blood tests included: 10 cytokines, clotting factors, sex hormones. Neuroimaging (MRI, resting state functional connectivity MRI, DTI, proton magnetic resonance spectroscopy) was optional.

Primary analysis will compare proportion of survivors with cognitive impairment with controls using Fisher's exact test. Regression models accounting for baseline characteristics will be evaluated. Secondary analyses using mixed regression models will evaluate outcomes over time. Comparison will be made between patients not eligible or not consenting and those completing long-term follow-up.

Results: Overall 178 participants were reviewed for eligibility for long-term follow-up: 62 were excluded due to death/recurrence/second primary. We assessed 49: localised CRC n=25 (9 had previously received chemotherapy; 16 no chemotherapy) and HC n=23. Mean age: 68.2 (range 34-83) years, 24 (50%) male. Mean time since baseline 7.5 (range 5.6-11.7) years. Neuroimaging was completed in 18. Full results will be available in April 2018.

Conclusion: Data will provide novel information about longer-term effects of cancer and its treatment on cognitive function. It will determine impacts on daily function, identify factors predisposing to longer term cognitive impairment, and explore occurrence of accelerated cognitive ageing.

Cancer-related cognitive impairment (CRCI) and effects of acupuncture on CRCI among Chinese gynaecological cancer patients: A pilot cohort study

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Background: Gynaecological cancers are the second most common types of cancer, followed by breast cancer, among women in China. Cancer-related cognitive impairment (CRCI) has emerged as a significant problem affecting gynaecological cancer survivors. While acupuncture has been used in different aspects of cancer care, the possible preventative effects of acupuncture on cognitive impairment have received little attention. This study hypothesises that acupuncture may be potentially effective in preventing and managing CRCI in cancer patients.

Methods: This prospective cohort study was conducted to assess gynaecological cancer patients' neurocognition, brain structural connectivity, and neurochemical properties at pre- and post-acupuncture intervention.

Results: This study found that the prevalence of cognitive impairment in Chinese gynaecological cancer patients at diagnosis was 26.67%. When investigating the microstructural white matter in the brain, diffusion tensor imaging data in this study indicated that premorbid cognitive functioning (before clinical manifestations become evident) has already existed, as the global and local connectome properties in the entire patient group were lower than in the healthy control group. Using magnetic resonance spectroscopy, this study indicated there was a statistically significant reduction of relative concentration of NAA (N-acetylaspartate) in the left hippocampus ($P < 0.05$). Regarding the effects of acupuncture on preventing or reducing CRCI, patients in the acupuncture group reported better neurocognitive test performance after matching for age, menopausal status, cancer stage, and chemotherapy regimen dosage. On a microstructural level, acupuncture's ability to prevent or reduce CRCI may be attributed to a reduction in demyelination and an enhancement of the neuronal viability of white matter in the hippocampus.

Conclusion: This study found that acupuncture appears effective in preventing CRCI in gynaecological cancer patients undergoing chemotherapy. Additionally, this pilot study provides novel insights into the neurobiological mechanism of cognitive impairment on the human brain, induced by cancer and/or cancer treatment.

Brain metabolism in occipital cortex during endocrine therapy for breast cancer is associated with protection from decline in visual learning ability and predicts one year trajectory of neuropsychologic performance

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Background: We previously found that endocrine therapy for breast cancer is associated with a highly significant increase in occipital cortical metabolism that is absent in breast cancer patients not undergoing endocrine therapy. We now describe relationships between the magnitude of those occipital metabolic changes with changes in neuropsychological performance occurring over the course of a year, and between initial occipital metabolism and subsequent neuropsychologic performance.

Methods: Thirty patients (av. 52 ±9 years) with breast cancer were assessed by both neuropsychological testing and brain PET with [F-18] fluorodeoxyglucose (FDG) at baseline and after 1 year; 19 subjects underwent endocrine therapy (14 after adjuvant chemotherapy), while 11 subjects did not (8 after adjuvant chemotherapy). Eight cognitive domains were assessed by neuropsychological testing. PET scans were analyzed using both standardized volumes of interest (sVOI) and statistical parametric mapping (SPM) methods. Metabolism in occipital regions was measured and assessed for significance of relationships with neuropsychological performance by treatment group, following statistical adjustment for multiple comparisons.

Results: After initial (surgical ± adjuvant chemotherapy) management, patients underwent therapy with aromatase inhibitors (n=8), tamoxifen (n=11), or neither (n=11). The most significant change in regional cerebral metabolism associated with one year of endocrine therapy was increased medial occipital activity, and this change was significantly correlated with concomitant protection from decline of visual learning (r=0.68, p=0.003) in patients undergoing tamoxifen or aromatase inhibitor therapy. Moreover, the level of lateral occipital metabolism prior to initiation of endocrine therapy was a significant predictor of the magnitude of improvement in neuropsychologic performance occurring in the ensuing year (r=0.66, p=0.003 overall; r=0.74, p=0.0003 for verbal memory improvers).

Conclusion: Brain metabolism in occipital cortex of breast cancer patients initiating endocrine therapy is a highly significant advanced predictor, and concurrent correlate, of changes in learning and memory performance over the ensuing year.

Associations between physical capacity (strength/endurance), spatial orientation and response inhibition in leukemia patients undergoing chemotherapy

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Background: Physical capacity and increased activity are associated with decreased risk for neurodegenerative disorders and improved cognitive performance. Moreover, research of the past decades suggest positive effects of physical exercise on cancer risk, and prognosis as well as on side effects of diseases and their medical treatments such as cancer related cognitive impairments (CRCI). Here we investigated potential associations between physical capacity and cognitive performance in leukemia patients before and after induction-chemotherapy.

Methods: Strength (hand grip dynamometer) and endurance capacity (incremental exercise test) were assessed in 29 patients suffering from acute myeloid leukemia before and after completing induction chemotherapy. Spatial orientation (3D orientation task) and response inhibition (INHIB) was measured using a computer based test battery.

Results: At baseline, strength and endurance capacity were positively associated with correct responses within the orientation task ($r=.434$; $p<.05$ and $r=.369$; $p<.05$ respectively). Additionally, strength negatively correlated with omission mistakes during the response inhibition test ($r=.-316$; $p=.10$). Regarding changes over time (pre to post therapy) strength was positively associated with correct responses of the orientation task ($r=.677$; $p<.05$) and the overall performance in the INHIB ($r=.770$; $p<.05$).

Conclusion: Despite the yet small sample size, these results already highlight the potential benefits of supportive exercise interventions in order to counteract and prevent CRCI. The direct relationship between exercise interventions and CRCI still needs to be investigated.

Trail Making Test (TMT-A/-B) performance of leukemia patients compared to age matched norm data

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Background*:* Limitations of executive functions were frequently reported in patients` suffering from cancer related cognitive impairments (CRCI). In order to standardize testing procedures, the ICCTF recommended to use the Trail Making Test-A/-B to assess executive function subdomains attention and set shifting.

Methods*:* Here, we investigated the TMT performance of 38 patients suffering from acute myeloid leukemia before (to) and after (t1) receiving high-dose chemotherapy. The TMT was applied using the computer-based Wiener Testsystem® (Schuhfried, Austria). The primary outcome of TMT-A and -B is the time needed to complete the task. Additionally to the raw scores, percent ranks were compared to an age- and education-matched norm sample (n=419).

Results*:* Mean test performance in TMT-A and -B did not significantly change over time (pre to post chemotherapy). However, an empirical decrease was observed in both parts of the test. Compared to the norm data, leukemia patients indicated low percent ranks, especially in the TMT-A after completing chemotherapy (median PR to = 25; t1 = 14).

Conclusion*:* These preliminary data suggest that leukemia patients have impairments in executive function subdomain attention. Larger sample sizes may be needed to detect potential changes over time.

Cancer related fatigue and cancer related cognitive impairments – different names for one symptom? Cross-sectional and longitudinal data of leukemia patients undergoing high-dose chemotherapy

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Background: Cancer related fatigue (CRF) and cancer related cognitive impairments (CRCI) are two of the most frequently reported side effects of oncological diseases and their medical treatments. Although both symptoms are defined separately, they reveal a certain overlap in view of biological mediators (e.g. increased inflammation), and self-perceived functioning. Here, we investigated potential associations between self-perceived cognitive impairments and CRF in patients suffering from acute myeloid leukemia (AML) undergoing high-dose chemotherapy.

Methods: 35 patients with AML completed the German version of the Functional Assessment of Cancer Therapy – cognitive function (FACT-Cog) and the Multidimensional Fatigue Inventory-20 (MFI-20) questionnaires before and after undergoing high-dose chemotherapy. For this analysis FACT- Cog subscales perceived cognitive impairments (CogPCI) and impact of perceived cognitive impairments on quality of life (CogQOL) were used. Moreover, MFI scales global fatigue (GF), physical fatigue (PF), reduced activity (RA), reduced motivation (RM) and mental fatigue (MF) were used. Baseline data and differences (post-pre) of all outcomes were analyzed using explorative correlation analysis.

Results: Baseline analysis revealed significant associations between CogPCI and all subscales of the MFI-20 (r=-.426 – r=-.726), while MF indicated the strongest correlation (r=-.726, p=<.001). CogQOL negatively correlated only with RA (r=-.366) and MF(r=-.426). Changes over time (deltas) revealed significant correlations between CogPCI and MFI-20 subscales PF (r=-.609), RA (r=-.653), RM (r=-.545), and MF (r=-.568), whereas CogQOL was significantly associated with GF (r=-.577) and RA (r=-.579).

Conclusion: These results suggest, that CRF and CRCI have a severe overlap in the investigated population. Of course, one cannot conclude from these data that CRCI and CRF are similar symptoms with different specifications. However, following research investigating CRCI and CRF should assess both in order to measure an obvious confounding or predictive variable.

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ICCTF YOUNG INVESTIGATOR AWARD

The ICCTF Steering Committee and the local convenors of the 2018 ICCTF Cognition and Cancer Conference would like to congratulate the following winners of the Young Investigator Award:

NICHOLAS PHILLIPS	St. Jude Children's Research Hospital
Oral presentation, Tuesday April 10th Cerebellar volumes and neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia (ALL) treated with chemotherapy alone	
ASHLEY HENNEGHAN	University of Texas MD Anderson Cancer Centre
Oral presentation, Monday April 9th Predicting chemotherapy-related brain injury using connectomics and machine learning	
KIMBERLY VAN DER WILLIK	Netherlands Cancer Institute
Oral presentation, Monday April 9th High levels of inflammatory markers in breast cancer survivors 20 years after cessation of chemotherapy are associated with impaired cognitive performance	
ANTIGONE MATSOS	The University of Sydney
Oral presentation, Tuesday April 10th Nicotinamide mononucleotide prevents and reverses doxorubicin and oxaliplatin-induced fatigue and memory impairments in the laboratory rodent	

The recipients receive a travel grant of US$500, sponsored by Posit Science Corporation.