

**ADDRESSING COGNITIVE  
DYSFUNCTION IN PATIENTS  
WITH CANCER**

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UNC RN and Allied Health Lecture  
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**OUTLINE**

- Background
- Causes and underlying mechanisms
- Screening and diagnosis
- Treatment
- LCCC 1921: Memantine for prevention of cognitive decline in patients with breast cancer

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**LEARNING OBJECTIVES**

1. Identify causes of cancer-related cognitive dysfunction
2. Describe the impact of cognitive problems in cancer patients on quality of life and medical outcomes
3. Recognize available treatments for patients with cancer experiencing cognitive dysfunction

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**HISTORICAL PERSPECTIVE**

- Awareness since 1970s - "Serial Cognitive Testing in Cancer Patients Receiving Chemotherapy" (Oxman 1980)
- "Chemobrain" defined in late 1990s in cross-sectional studies in breast CA
- 2002 – Ahles et al. showed long-term effects of chemo
- 2004 – Wefel et al. first prospective longitudinal study
- Growing appreciation for cognitive difficulties resulting from cancer **and** its treatments over the last 15-20 years (i.e. CRCI, CRCD)

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**PREVALENCE OF CRCI**

- Up to 30% with cognitive impairment before chemotherapy
- 75% report cognitive deficits during treatment
- 15-50% exhibit objective impairment after chemotherapy
- Lasts years after treatment

Janelins 2014, Ahles 2018

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**QUALITY OF COGNITIVE PROBLEMS REPORTED POST-TREATMENT**

- Memory
- Concentration
- Executive function
- Ability to learn new material
- Subtle (usually) or dramatic
- Variable course

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### SIGNIFICANCE OF CRCI

- Associations
  - adverse mental health
  - inability to return to work
  - worse emotional and social well-being
  - impaired physical function
  - increased mortality
- Greater influence on chemotherapy prescribing than age or functional status
- One of the most feared problems among cancer survivors

Janelsins 2014, Yang 2018, Von Ah 2021, Von Ah 2015, Klaver 2020, Nakamura 2020, Hsieh 2018, Mohile 2018

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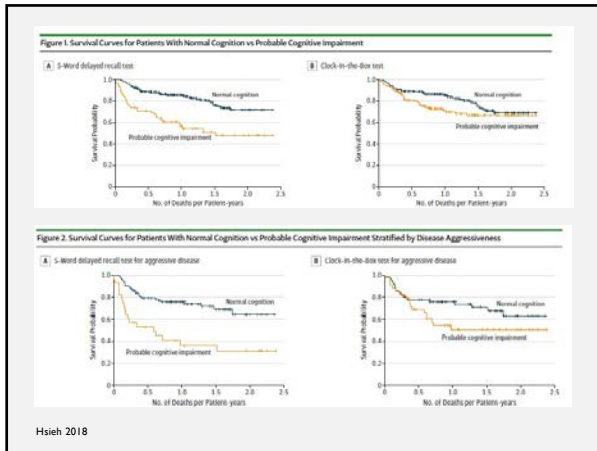
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### OVERARCHING MECHANISMS

- Direct toxicity
- Cytokine-mediated neuroinflammation
- Oxidative stress
- Genetic
  - Survivors w/ APOEε4 with worse cognitive problems
  - Breast CA survivors treated w/ chemotherapy with COMT Val158Met had greater decline
  - BDNF Met/Met genotype protective against chemo-induced cognitive changes

Ahles 2018, Ahles 2014, Wefel 2015, Mandelblatt 2018

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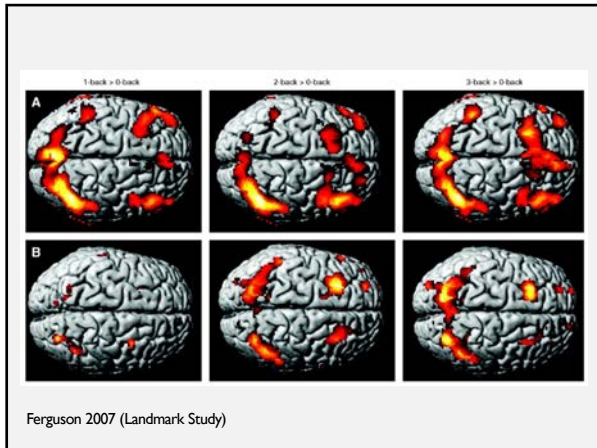
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**IMAGING FINDINGS**

- ↓gray matter volume
- ↓white matter connectivity
- Altered functional brain activation and connectivity
- Decreased volume and connectivity correlate with worse function

Sousa 2020, Kaiser 2014, Kesler 2020, Kesler 2014, Deprez 2018, Amidi 2019

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**INFLAMMATION**

- Associated with ↑ risk for cancer and neurocognitive disorders
- ↑ cytokine levels in CA pts at baseline relative to controls
- ↑ during chemo and ↓ (but stay elevated) with time
- Correlate with self-reported and objective cognitive function
- Correlated with hippocampal volume and metabolism
- Strongest data for TNF $\alpha$ , IL-6, and IL-1 $\beta$

Patel 2015, Wang 2016, Kesler 2013 (Landmark Study), Lyon 2016, Hoogland 2019

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### CANCER TREATMENT AND AGING

- Chronic inflammation
- Increased oxidative stress
- Accumulation of DNA damage
- Shortening of telomeres
- Increased cell senescence
- Increased expression of p16<sup>INK4a</sup> and ARF in breast cancer patients (estimated 10 yrs of aging)
- Increased activation of ERK and AKT signaling pathways in rats

Sanoff 2014, Salas-Ramirez 2015

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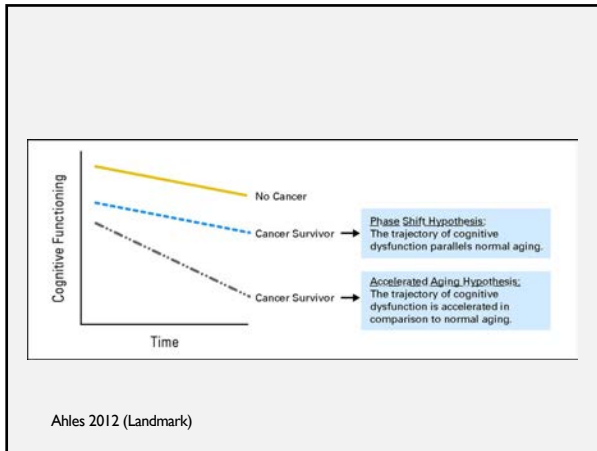
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### CANCER

- Non-CNS Cancers
  - Immune system dysfunction → disrupt brain structure and function
  - Feeling physically ill, fatigued, depressed, etc.
- Primary brain tumors and brain metastases
  - ↑ Intracranial pressure
  - Edema
  - Displacement of brain tissue
  - ↓ blood supply

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**CHEMOTHERAPY**

- Most chemo cannot cross the BBB
  - CA increases BBB permeability
  - Even small amounts can cause significant damage
- Toxic to neural progenitor cells
- Increases levels of pro-inflammatory cytokines
- Cytokines increase BBB permeability
- Elevated cytokines can lead to damage through oxidative stress and DNA damage
- Diminution of neurogenesis
- Disruption of myelin and oligodendrocyte precursors
- Mitochondrial dysfunction
- Accelerates brain aging

Hodgson 2013 (Landmark), El-Agamy 2019, Ren 2019, Lange 2019

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**SURGERY**

- In pts w/ brain tumors, can improve or worsen cognitive function
- Mastectomy implicated in cognitive effects
- May be 2/2 increased inflammation, pain, psychological effects
- Impact of anesthesia (especially in elderly)

Reid-Arndt 2012 (Landmark), Cimprich 2010 (Landmark), Su 2020

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**RADIATION**

- Cranial, Head & Neck
  - Radiation necrosis
  - Disrupts creation of new neurons in the hippocampus
- Local
  - Some evidence for adverse cognitive effects
- Mechanisms
  - Chronic oxidative stress and inflammation
  - Neuronal damage
  - Changes to BBB, ischemia, oligodendrocyte function

Wilke 2018, Dong 2015, Carvalho 2018

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**HORMONAL THERAPY**

- Estrogen and testosterone support brain function
- Tamoxifen
  - Smaller hippocampal size
  - Combination with chemo may lead to greater cognitive difficulties
  - Other studies show no association
- Aromatase inhibitors independently associated with cognitive decline
- ADT with adverse cognitive consequences

Ganz 2014, Van Dyk 2019, Le Rhun 2015, Morote 2017, Bender 2015, Gonzalez 2015

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**IMMUNOTHERAPY**

- Checkpoint inhibitors increasingly important treatment for many cancers
  - May lead to neuroinflammation, which in combination with radiation or other immunotherapies could cause cognitive impairment
  - Reports of cognitive impairment in clinical trials, but further research needed
- CART cell therapy associated with a profound, immune-mediated encephalopathy in ~30%, but long-term effects not known

Topalian 2012 (Landmark), McGinnis 2017, Goldberg 2016, July 2020

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**TARGETED THERAPIES**

- Monoclonal antibodies and small-molecule tyrosine kinase inhibitors also increasingly common
- Anti-VEGF antibody bevacizumab associated with objective global cognitive decline
- Improvement in cognitive function in patients with metastatic RCC or GIST tumors receiving sorafenib or sunitinib
- Chronic encephalopathy in some MM patients exposed to proteasome inhibitors
- Long-term sequelae not studied

Fathpour 2014, Gilbert 2014, Ng 2018, Mulder 2014, Wick 2016

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**COMORBIDITIES AFFECTING COGNITIVE FUNCTION**

- Sleep disorders (insomnia, sleep apnea)
- Depression, anxiety, distress
- Pain and pain medications
- Other physical illnesses
- Fatigue
- Anemia

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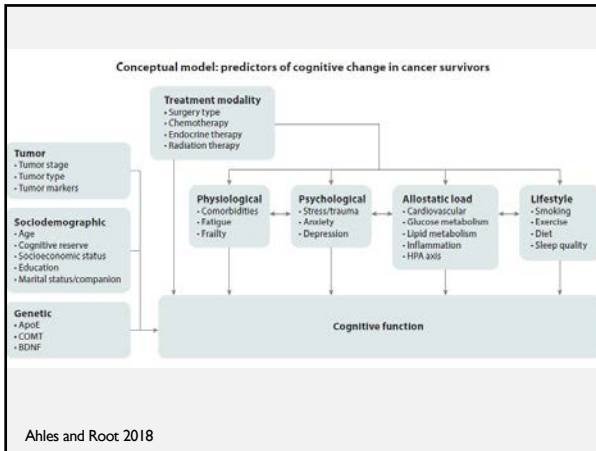
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**SELF-REPORT VS. OBJECTIVE MEASUREMENT**

- Self-reported problems more common
- Self-report limitations
  - Is it really measuring cognitive impairment?
- Objective measurement limitations
  - Is it sensitive enough?
  - Logistically feasible?

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**MEASUREMENT OF CRCI**

- No standard for screening, monitoring
- Self-report measures: PROMIS Cognitive Function, FACT-Cog, EORTC-QLQ-30, PRO-CTCAE
- Objective screening instruments: MMSE, MOCA, RBANS, BOMC
- Neuropsychological Assessment (NPA) \* Gold Standard
  - ICCTF recommends: Hopkins Verbal Learning Test, Trail Making Test, Controlled Oral Word Association Test

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**MEASUREMENT IN THE CLINIC**

- Self-report screeners
  - Primary care
  - Oncology
- Screening Instruments
  - Psychiatry, Psychology, Neurology
  - Occupational Therapy
  - Speech Therapy
- Neuropsychological Assessment
  - Neuropsychology

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**INTERVENTIONS FOR CRCI**

- Behavioral: Cognitive rehabilitation, Cognitive Training, Combination
- Physical activity: Yoga, Exercise programs
- Mind-Body: Meditation, Mindfulness, Acupuncture
- Pharmacotherapies: Donepezil, Memantine, Modafinil, Methylphenidate, Epostimulating agents, Vitamin E, Ginkgo biloba, SSRIs

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### INTERVENTION RESEARCH FOR CRCI

- Mostly limited to breast CA
- Generally years after completion cancer treatment
- Small sample sizes
- Prevention trials are rare
- Challenges with access, cost, patient participation

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### COGNITIVE TRAINING

- Repetitive, increasing challenging tasks (often via computer) to improve, maintain, or restore cognitive function
- Start out with 4-5, 30-60 min sessions per week for at least 6 weeks
- Research
  - ~ 10 studies
  - Primarily in early stage breast CA survivors
  - Completed adjuvant therapy and were reporting cognitive concerns

Fernandez 2019, Mayo 2020

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### COGNITIVE REHABILITATION

- ↑ self-awareness to support problem-solving and compensatory strategies
- Initially developed in TBI and stroke populations
- Usually weekly therapy for 30-60 min with neuropsychologist, occupational therapist, speech/language pathologist
- Research
  - ~10 studies
  - Individual and group delivery (in person or online)
  - 4-7 sessions
  - Improved cognitive symptoms > neuropsychological performance

Fernandez 2019, Mayo 2020

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**PHYSICAL ACTIVITY**

- ↑ new neurons in the hippocampus, BDNF levels, reduces inflammation
- ↓ risk of Alzheimer's and slows age-related cognitive decline
- Moderate intensity exercise at least 150 min/week OR vigorous exercise at least 75 min/week
- Local Resources
  - Get REAL & HEEL
  - Health Coaching
  - LIVESTRONG at the YMCA
  - Yoga

Campbell 2018, Zimmer 2016, Myers 2018, Campbell 2020

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**MIND-BODY**

- Bring an awareness of individual potential for healing or restoration
- Guided imagery, meditation, mindfulness-based stress reduction, neuro/biofeedback, and acupuncture
- Mindfulness
  - UCLA MAPS classes
  - Apps: The Mindfulness App (I&II), Sitting Still, Headspace, Insight Timer, Mindfulness Bell
  - Local courses through UNC-Chapel Hill Program on Integrative Medicine and Duke Integrative Medicine
- Acupuncture
  - UNC Family Medicine Acupuncture Clinic
  - NC Society of Acupuncture and Asian Medicine

Freeman 2014, Milbury 2013, Hoffman 2012, Johns 2016, Alvarez 2013, Johnston 2011, Cimprich 1993, Cimprich and Ronis 2003, Van der Gucht 2020

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**PHARMACOTHERAPIES**

- Stimulants (methylphenidate and modafinil)
- Alzheimer's drugs (donepezil and memantine)
- SSRIs (sertraline and paroxetine)
- Ginkgo biloba
- Vitamin E
- Erythropoietin-Stimulating agents\*
- Weigh risk/benefit

Karschnia 2019, Miladi 2019, Mayo 2020

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MEDICATIONS  
FOR CRCI

- Fewer than 10 published RCTs
- Only 3 agents that have been studied as prevention
  - Epo-stimulating agents: not effective + adverse effects
  - Methylphenidate: closed prematurely due poor recruitment
  - Ginkgo Biloba: Large study, not effective

Karschnia 2019, Mayo 2020

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INFLAMMATORY HYPOTHESIS OF CRCI

Inflammatory cytokines:

- 1.) elevated in cancer
- 2.) increase during chemotherapy
- 3.) correlate with cognitive deficits

Memantine (NMDA receptor antagonist) binds the NMDA receptor-operated calcium channels, inhibit the prolonged influx of Ca<sup>2+</sup> ions.

Olsson and Liabo 2014

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CAN MEMANTINE HELP?

What is it?

- A pill taken by mouth
- Decades of safety data
- Most studied for Alzheimer's disease, but effective in many medical conditions

Why for Chemo Brain?

- Blocks harmful inflammation in the brain
- Helpful for patients during brain radiation
- Prevented chemo brain in animal studies

McShane 2006 (Landmark), Brown 2013 (Landmark), Cole 2013 (Landmark)

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**ABOUT THE STUDY**

**What is the purpose of the study?**  
 We want to learn if giving memantine can prevent cognitive changes in people with breast cancer who are receiving chemotherapy.

**What will be done?**

- Patients will be given memantine during chemotherapy. This is a pill taken two times each day.
- Cognition will be tested with cognitive tasks and surveys over ~1 hour.
  - Before starting chemotherapy
  - 4 weeks after ending chemotherapy.
- Patients will receive a \$25 gift card for each survey.

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**MORE INFORMATION IF YOU ARE INTERESTED**

Eligibility Criteria

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Contact us

- Are 18 years old or older
- Have stage I, II, or III breast cancer
- Are scheduled to begin chemotherapy at
  - UNC Chapel Hill,
  - UNC Hillsborough, or
  - UNC REX
- Speak English

  
 e-mail:  
 Zev Nakamura, MD  
 zev\_nakamura@med.unc.edu  
 Or  
 Yesy Lopez, BA  
 yesy\_lopez@med.unc.edu

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**FUTURE DIRECTIONS**

- Complete single-arm, pre-post study of memantine
- RCT of memantine vs. placebo to mitigate chemotherapy-related cognitive changes
  - Multi-site trials, including community-based trials (i.e., NCORP)
  - Translational models
- Other cancers, cancer treatments

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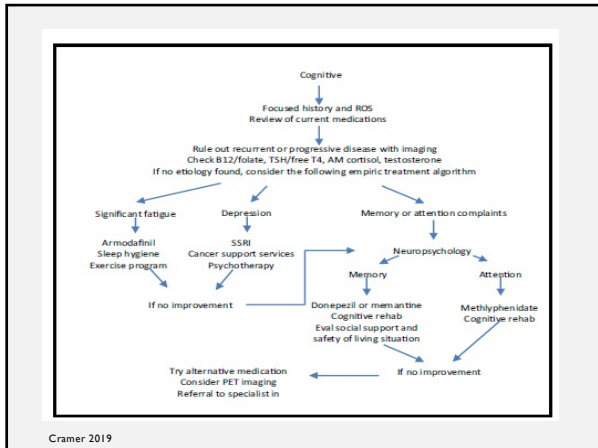
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### FOR ALL PATIENTS

- Active journaling
  - Describe an experience, why it was important, what it meant for you, what you learned from it
  - Goal to increase "idea-density"
- External aids
  - Day planner
  - Alerts/reminders on smart phone or tablet
  - Sticky notes, whiteboards
- Routine
- Workplace accommodations
  - Examples and procedural information available at [www.eeoc.gov/policy/docs/accommodation.html](http://www.eeoc.gov/policy/docs/accommodation.html)

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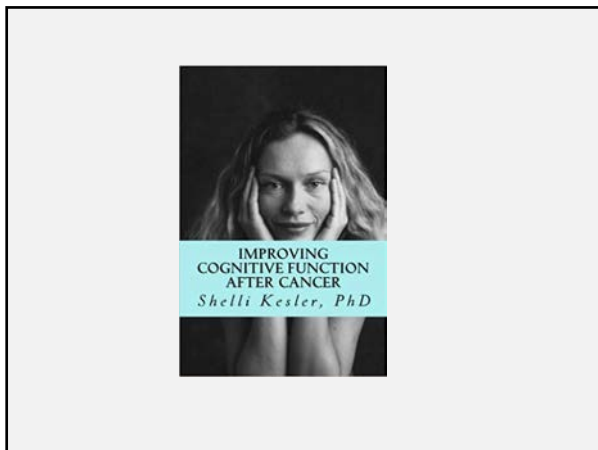
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