Coping with Attention, Learning and Memory Challenges after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

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Disclosures

- Dr. Parsons has been a consultant to Monteris Inc., a medical device company that manufactures a device for brain tumor surgery.
- Dr. Parsons is a consultant to Servier Inc. (a pharmaceutical company that develops anti-cancer drugs).
- Dr. Parsons receives royalties from the American Psychological Association for a book authorship

Those relationships have no meaningful impact on the material being discussed today

Coping with Cognitive Changes After Transplant

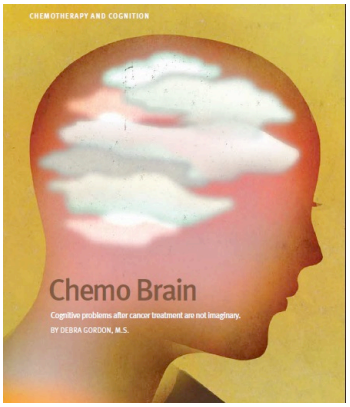
GOALS:

- Discuss cognitive problems that transplant recipients experience and how those problems are related to the functioning of different brain networks and systems.
- Explain neuropsychological evaluation and describe how it may be helpful for an individual who is dealing with cognitive symptoms.
- Describe the science regarding the nature and causes of these problems.
- Provide suggestions for coping with these problems on a day-to-day basis.

Topics

- Cognitive symptoms after transplant
  - Which cognitive functions are affected?
  - The severity and extent of cognitive symptoms
  - Relationship of those symptoms to brain systems/structures
- Causes of cognitive symptoms?
  - Chemotherapy (inflammation, neurotoxicity, demyelination)
  - Fatigue/Sleep problems
  - Stress
  - Side effects/complications
- Evaluation and treatment of cognitive symptoms
  - Medical/Neurologic workup
  - Neuropsychological evaluation
  - Treatment

Chemo Brain: Cognitive problems after cancer treatment are not imaginary.
Neurology Now
April/May 2014; Volume 10(2); p 20–27



Editorials

"Doctor, Will the Treatment You Are Recommending Cause Chemobrain?"

Patricia A. Ganz, *Jonsson Comprehensive Cancer Center at the University of California Los Angeles, Los Angeles, CA*

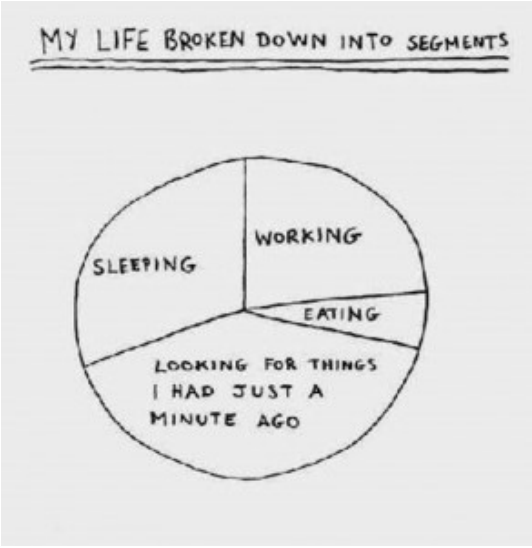
DOI: 10.1200/JCO.2011.39.4288;

Study Confirms 'Chemo Brain' is Real

http://www.newsmax.com/Health/Health-News/chemo-brain-real-memory/2016/08/19/id/744331/

What is Cognition?

- All of the skills of thought
  - Memory
  - Concentration
  - Language Skills
  - Visual Skills
  - Executive Functions
    - Reasoning and Problem Solving
    - Judgment
    - Impulse Control
    - Flexibility
    - Planning
    - Sequencing and Organizing

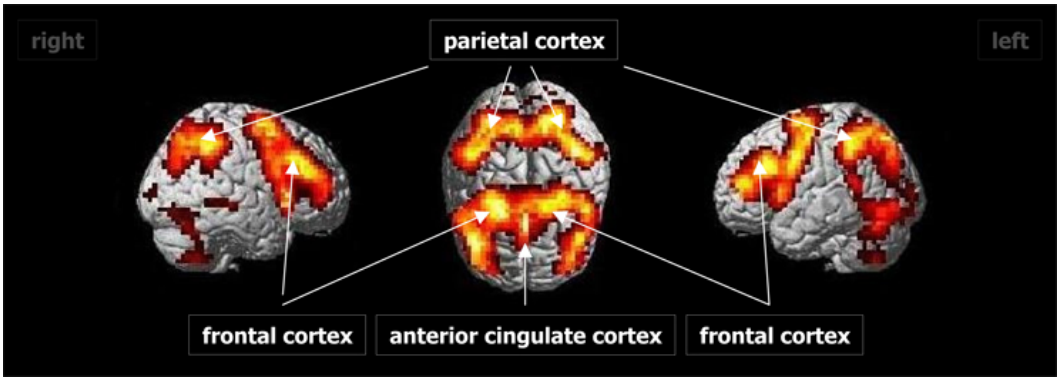


Neuropsychological Evaluation: How do we assess cognition?

- Motor examination
- Visuospatial Function
- Language
- Information Processing Speed
- Recent Memory
- Attention/Working Memory
- Executive Function
- Mood/Quality of Life

Working Memory

- The ability to hold and manipulate information in mind
- Multi-tasking



Memory

Recent Memory:

Encoding

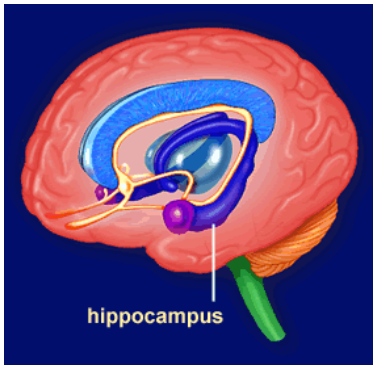
- Bringing information into memory system
- Highly related to attention
- Depends on focus and processing speed

Storage (Consolidation)

- Retention of information over time

Retrieval

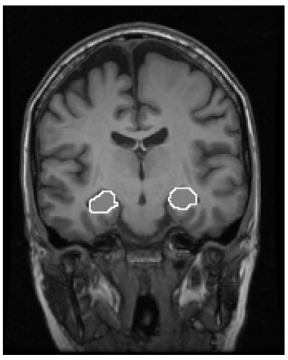
- Ability to recall the specific details later
- Use recognition test (yes/no) to disentangle retrieval from storage based memory deficits.



Brain Structures Affected by Chemotherapy

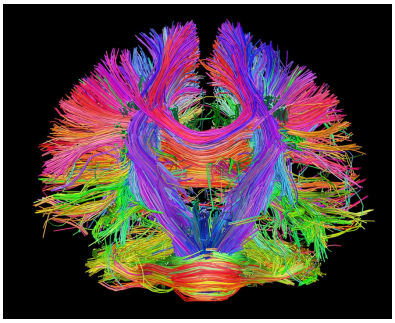
Hippocampus – critical memory area

- Women who had received chemotherapy five years earlier were compared to no-chemotherapy controls
- Chemotherapy reduced hippocampal volume, but not whole brain
- Hippocampal volume correlated with memory scores
- (smaller hippocampus = lower memory scores)



Kessler et al, 2012; Brn, Beh, Immun. 30, S109

Attention and Processing Speed



- Attention
  - Sustained Attention
  - Divided Attention
  - Shifting Attention
- Speed of processing
  - Related to attention
  - Processing automatic material is rapid
  - Interference occurs between competing information
  - Together with working memory is critical for “Multi-tasking”
- Depends on efficient communication and connection between brain areas

Executive Functions

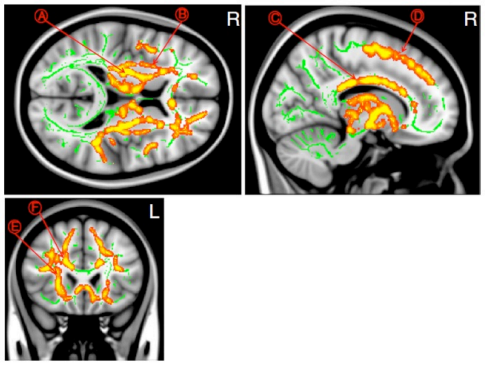
- “Frontal lobe” tests
- Reasoning & problem solving
- Inhibition
- Shifting
- Initiation, cessation, perseveration
- Requires integration of other domains, efficiency
- Other qualitative executive skills
  - Awareness/insight
  - Judgment

What do cognitive tests tell us about how and where chemotherapy affects the brain?

- Multiple brain areas are affected
- Fibers that connect distant brain areas appear to be vulnerable
- Certain brain areas (e.g., hippocampus) may be particularly at risk
- These widespread effects suggest that there is toxicity throughout the brain, with particular areas that may be more vulnerable than others.

Brain Connections are Affected by Chemotherapy

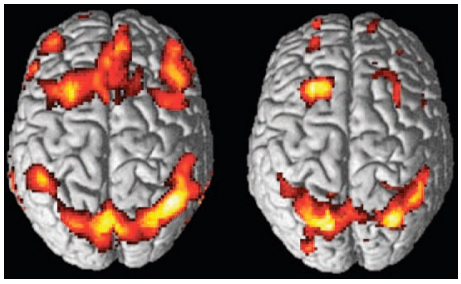
- Patients receiving high dose chemotherapy for hematological disorders and autologous stem cell transplant were compared prior to and 1 year after induction chemotherapy vs controls
- Significant decrease in integrity of brain connections (white matter), which correlated with cognitive test performance



Correa et al, 2016, BIB. 10 (2), 486.

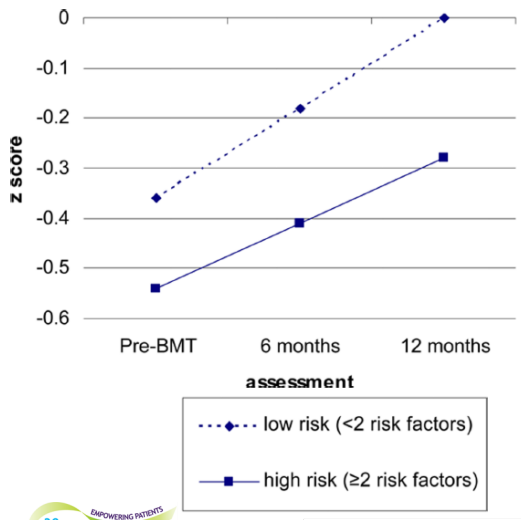
Brain Activity and Chemotherapy

- Functional brain imaging techniques measure brain blood flow while people are performing cognitive tasks
  - FMRI
  - PET
- Twin study, showing differences between a patient treated with chemotherapy and her twin.



Ferguson et al., 2007, J Clin Oncol 25:3866

Variability of Cognitive Problems in People who had a Transplant

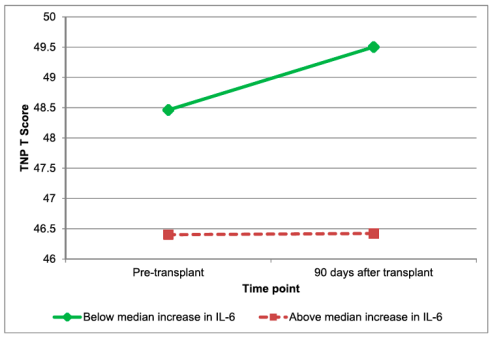


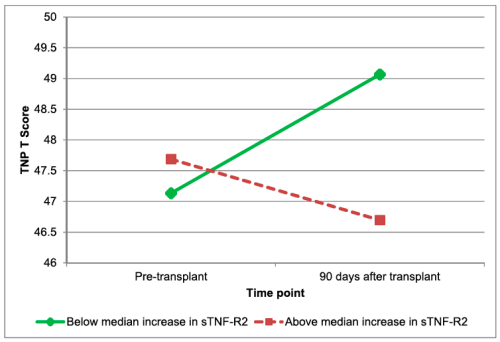
- History of brain disorders or treatment to the brain (e.g., radiation)
- Transplant factors (allogeneic vs autologous)
- Length of hospitalization
- Other signs of toxicity (e.g., enteritis)
- Age
- Pre-existing brain risk factors (e.g., diabetes, heart disease, hypertension, hyperlipidemia)

Jim et al, Cancer (2012)

Inflammation Contributes to Cognitive Problems after Transplant

- Those who have signs of greater inflammation (Interleukin-6, tumor necrosis factor, C-reactive Protein) have more cognitive problems after BMT

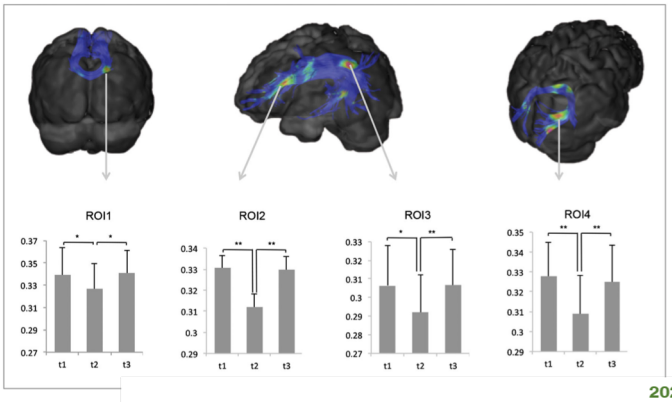




Hoogland et al, Brn Beh & Immun (2019)

Some Good News

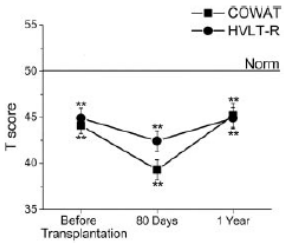
- Numerous studies have shown that cognition improves over time after chemotherapy.
- Brain activity can normalize
- Even integrity of brain connections has been shown to return to normal



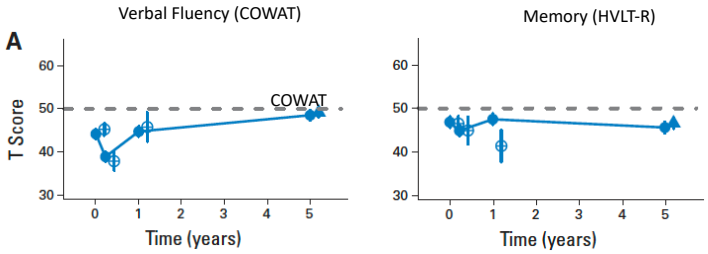
Deprez et al, Brain Imaging and Behavior (2018)

Cognitive Recovery after Transplant

- Syrjala and colleagues followed allogenic transplant recipients 1 year and 5 years after transplant
- They saw changes in memory, word-finding, and processing speed after transplant
- The patients returned to their pre-transplant baseline by 1 year
- These changes remained stable when followed up at 5 years from transplant.



Syrjala et al, Blood (2004)



Syrjala et al, JCO (2011)

More Good News

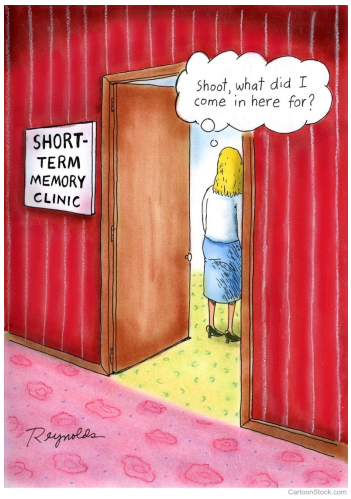
- Chemotherapy cognitive effects tend to be mild
- Only a subset of individuals experience these problems
- There are a number of factors that you CAN control that can improve cognition
  - Sleep
  - Pain
  - Stress
  - Mental Stimulation
  - Supportive and Compensatory Strategies

Treatments for Cognitive Problems: Medications

- Memory enhancers (donepezil, memantine)
  - Have been used primarily in other neurologic disorders, such as Alzheimer's Disease
  - Aricept was found to have a positive effect on people with brain tumors in terms of mood, cognition, and quality of life
  - Memantine has been shown to protect the brain from toxicity of radiation therapy
- Attention enhancers (e.g., Ritalin, Provigil, etc)
  - These medications can improve attention, alertness, arousal
  - Were found to reduce symptoms of cognitive problems after brain tumor
  - May or may not help with fatigue
- The pattern on neuropsychological assessment can help to decide what the most useful treatment may be

Non-Medical Treatment: Cognitive Rehabilitation

- Compensatory strategies are most effective method
  - Identify the goal you'd like to achieve or the thing you'd like to do better
  - Work with someone to develop a strategy to achieve that goal
- Cognitive rehabilitation specialists
  - Speech specialists
  - Occupational therapy specialists
- Success is contagious!



Compensatory Strategies for Cognitive Problems

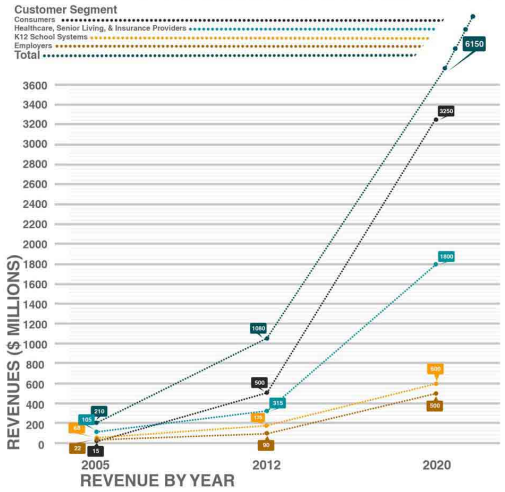
- Associative Strategies for Memory – Use *meaning* to improve memory for labels that are difficult to recall
  - Face-Name associations
  - Object-Place associations, a.k.a, "Method of Loci"
- Organizational/Technology Aids
  - Calendars, medication organizers, reminders
- Environmental changes
  - Reducing distractions - e.g., noise cancelling headphones
- Enhancing attention
  - Example – reading and listening to a book/audiobook simultaneously

Interventions for Chemotherapy-Related Cognitive Impairment

Does 'brain exercise' help (e.g., computerized brain training)?

- It's better than nothing…
- …but not necessarily better than anything else
- Cognitive "exercise" improves performance on the specific tasks
  - Attention related activities
  - Semantic network type activities
- Generalizability of results mixed
- Buyer beware

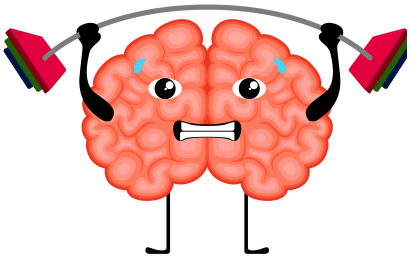
Buyer Beware!



ftc.gov/news-events/press-releases/2016/01/lumosity-pay-2-million-settle-ftc-deceptive-advertising-charges

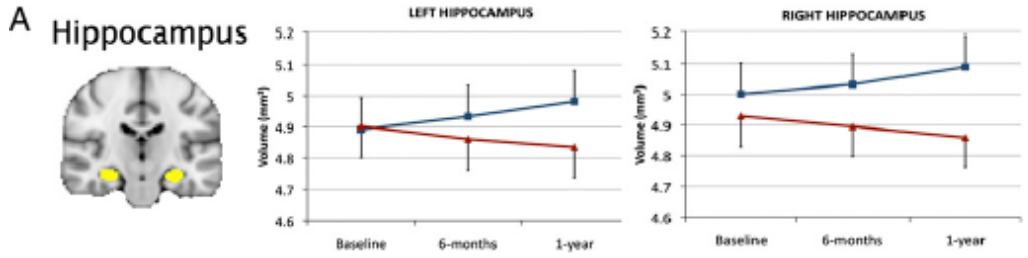
Maintaining Brain Health

- Physical exercise
  - Promotes the growth of new nerve cells in the brain
  - Reduces inflammation
  - Improves efficiency of blood supply to the brain
  - Helps promote overall brain health
- Talk to your doctor about the level of exercise that is safe
  - general guidelines are similar to those for heart health



Maintaining Brain Health

- The Value of Exercise: Can help reduce brain loss of aging



Kramer et al., 2011, PNAS

Directions for the Future

- Innovative therapies that address the underlying neuropathology of chemobrain
- Interventions to prevent impact of inflammatory cytokines on brain health
- Management of *modifiable* contributors to cognitive symptoms
- Further expansion of cognitive therapeutic approaches with well designed trials

Directions for the future: Medication Trials

Intervention	Putative Mechanism/Interventions	Clinical trial registry numbers
CNS stimulants		
Methylphenidate	Dopaminergic agonism	NCT02970500
Anti-dementia drugs		
Donepezil	basal forebrain cholinergic system protection	NCT02822573
Memantine	glutamatergic neurotransmission, neuroprotection	NCT03342443; NCT02360215
Neuroprotective drugs and interventions		
Lithium	hippocampal neuroprotection	NCT01486459
Pioglitazone	protection from oxidative neuronal injury	NCT01151670
Ramipril	protection from oxidative neuronal injury	NCT03475186
Fluoxetine	protection of dividing cells in hippocampus	NCT01615055
Ibuprofen +/- exercise	anti-inflammatory interventions	NCT03186638; NCT01238120
Nicotine	glutamatergic neurotransmission	NCT02312934

Directions for the Future: Non-Medical Trials

Intervention	Putative Mechanism/Interventions	Clinical trial registry numbers
Cognitive rehabilitation	Computerized cognitive training +/- exercise	NCT03285048; NCT03094026
Trans-cranial direct current stimulation	Enhancement of neuroplasticity	NCT03487601; NCT03143894
Psychotherapy	Meditation Based Stress Reduction	NCT02786797; NCT03253627; NCT02518308
Exercise +/- behavioral interventions	Specific supervised physical exercise programs in patients with cancer, tailored to physical capabilities, some in combination with behavioral therapy	NCT03049124; NCT02999074; NCT02934880; NCT02793921; NCT02533947; NCT03191968; NCT03169075;
Light therapy	Correction of circadian rhythm abnormalities	NCT02677987; NCT02661308
Alternative Therapies	Acupuncture, Tai Chi	NCT02457039; NCT03196037

Summary

- There are reasons to believe that chemotherapy has toxic side effects on the brain – chemobrain is “real”
- Other factors also contribute to problems with cognition in some people after BMT
- Primary issues include attention, memory, processing speed and executive function
- Fortunately, problems tend to be relatively mild and usually recover
- Treatment for cognitive problems is available:
- Neuropsychological evaluations can help understand the problem
- Strategies range from simple compensations to medications

QUESTIONS?

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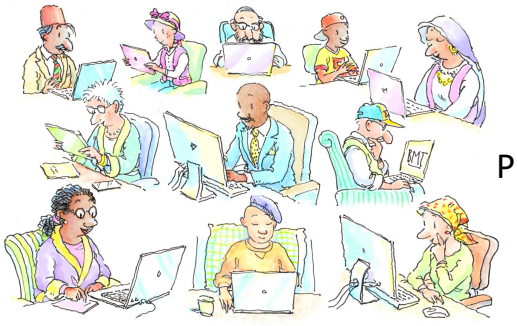
LET US KNOW HOW WE CAN HELP YOU



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