

Bone Marrow Failure Disease and The Brain

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GOALS:

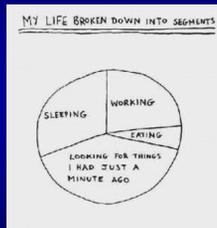
1. Discuss the types of cognitive problems that patients experience and how those problems are related to the functioning of different brain networks and systems.
2. Explain the process of neuropsychological evaluation and describe how it may be helpful for an individual who is dealing with cognitive symptoms.
3. Describe the (very limited) scientific literature regarding the nature and causes of these problems.
4. Provide suggestions for coping with these problems on a day-to-day basis.



Cognitive Functions

What is 'Cognition'

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



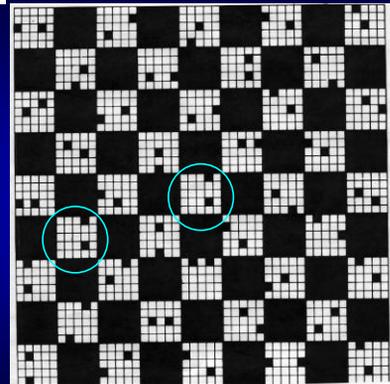
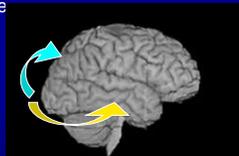
Movement and Coordination

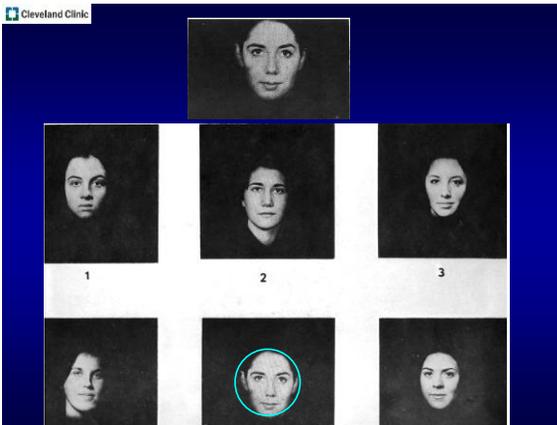
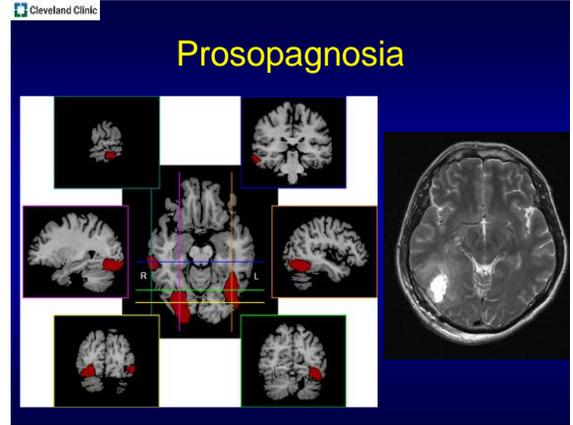
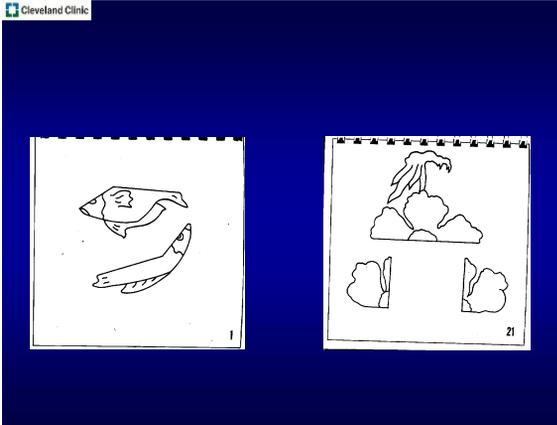
- Quantify speed and dexterity
- Adds a quantitative element to examination of movement
- Tests progress from proximal/gross to distal/fine
 - Grip strength
 - Finger tapping
 - Grooved pegboard



Visuospatial

- “Where” pathway (blue)
 - Visual search
 - Location of objects in space
- “What” pathway (yellow)
 - Object identification
 - Facial recognition
- Integration/construction
 - Image rotation
 - Drawing
 - Block design





Language

- Language Production
 - Fluency
 - Phrase Length
 - Prosody
- Naming (Word Finding)
- Comprehension
- Reading
 - Word recognition
 - Comprehension
- Writing

Memory

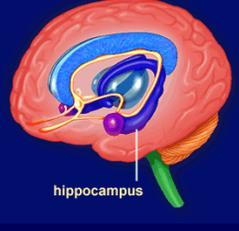
Recent memory:

- 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 paradigm (yes/no) to disentangle retrieval from consolidation based memory deficits.

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Memory

Recent memory



hippocampus

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Neuropsychological Evaluation: Attention, Processing Speed & Working Memory

- Attention
 - Sustained Attention
 - Divided Attention
 - Shifting Attention
- Working Memory = mental RAM
 - Information you “hold in mind”
 - Has a maximum capacity
 - Sets limits on amount of material you can process at one time
- Speed of processing is related to attention
 - Processing automatic material is rapid
 - Interference occurs between competing information
 - “Multi-tasking”

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Processing Speed

1	2	3	4	5	6	7	8	9
—	⊥	⊓	⊔	⊕	⊖	⊗	⊘	⊙

Sample items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4
5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3
7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4
6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7
9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6
2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5
7	1	8	2	9	3	6	7	2	6	5	2	3	1	4	8	4	2	7	6

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Sustained attention/working memory

Practice 1



Trial 1



Practice 2



Trial 2



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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



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Stroop Color Word Test

read word

Red	Green	Blue
Blue	Red	Green
Green	Red	Blue
Blue	Green	Blue
Red	Red	Green
Red	Blue	Red
Green	Blue	Blue

Name color of X's

XXX	XXX	XXX

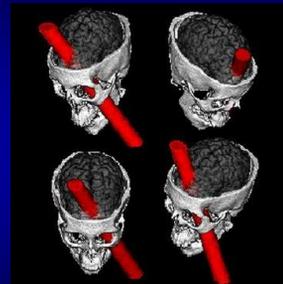
Name color of font

Red	Green	Blue
Blue	Red	Green
Green	Red	Blue
Blue	Green	Blue
Red	Red	Green
Red	Blue	Red
Green	Blue	Blue

Personality/emotion

- Clinical interview
- Standardized measures
 - Mood measures (BDI, BAI, Hamilton, etc)
 - Personality measures (PAI, MMPI)

Phineas Gage



Damasio et al., Nature 1994

Phineas Gage

- "The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is . . . irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires . . . obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others. . ." (John Harlow, MD, 1868)

How common are cognitive problems in bone marrow failure disease

- All studies to date use combined samples
- Include individuals with MDS along with more common conditions such as Acute or Chronic myelogenous leukemia (AML or CML)
 - In a study of 106 patients with either CML (n=91) or MDS (n=15), ~25% had low scores on one or more cognitive test at the time of diagnosis (Meadows et al., 2013).
 - The %age of people with low test scores *improved* at 18 months after treatment (15%).

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How do bone marrow failure diseases affect cognition?

- Anemia and related Fatigue
- Immune Response Activity
- Complications
- Cancer Treatment
 - Chemotherapy
 - Hematopoietic Stem Cell Transplantation

How do bone marrow failure diseases affect cognition?

Anemia and cognition

- Low blood hemoglobin levels can lead to decreased oxygen to the brain
- In a sample of 88 patients with AML (n= 41) or MDS (n=47), hemoglobin levels were correlated with neuropsychological test scores (Wood et al, 2011).
 - Used cutoff scores:
 - Mild anemia = 10-12.5 mg/dl
 - Moderate = 8-10 mg/dl
 - Severe = < 8 mg/dl

How do bone marrow failure diseases affect cognition?

Wood et al, 2011

- Those with mild anemia had no relationship between Hgb and cognitive performance.
- Moderate – Severe anemia led to decreased performance on tests of recent memory, working memory, and fine motor speed.
 - 25% of patients with mod-sev anemia were had impairments on multiple tests in this battery

How do bone marrow failure diseases affect cognition?

Anemia

- Fatigue
 - Results in a reduction in arousal
 - <Attention
 - <Working Memory
 - <Processing speed
 - People experience a memory problem
 - Due to reduced **encoding**

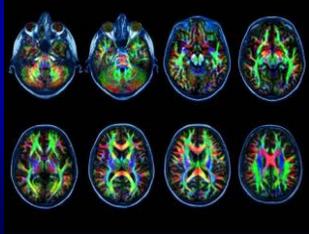
Other causes of Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Gave neuropsychological tests to 54 people with AML (n=19) or MDS (n=35) before chemotherapy
 - 26 returned for follow up testing 1 mo after treatment
- **Age:** Average = 60 years (range = 21-84)
- **Gender:** 30 male/24 female
- **Response: (1 month)**
 - Complete = 19 (14 seen for follow up)
 - Partial or no response = 23 (8)
 - Not evaluated = 12 (4)
- Hypothesized that these symptoms may have to do with *cytokine-immunologic activation*.

Cognitive Sequelae of Chemotherapy

- Chemotherapy
 - The concept of ‘chemobrain’ is controversial
 - Chemo agents damage the white matter
 - Brain’s fibers of connection
 - Reduces attention, processing speed (encoding), working memory



Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Interferon-alpha
 - Increases the level of interleukins and TNF-alpha
 - Related to problems with memory, motor dexterity, problem solving, and mood
 - These increased cytokine levels are caused by MDS/AML
 - Treatment with multi-agent chemotherapy increases them

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Cognitive domains tested:
 - Attention
 - Speed of Information Processing
 - Recent Memory
 - Cognitive Flexibility
 - Motor Dexterity
- Other areas assessed:
 - Activities of daily living
 - Fatigue
 - Quality of Life

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Biological variables
 - Levels of various Cytokines in blood
 - Interleukins 1, 6, 8
 - Tumor Necrosis Factor – Alpha
 - Hemoglobin levels

Cytokines and Cognitive Impairment in MDS (& AML)

Meyers et al., 2005

- Results
 - Before treatment, > 40% had low performance on 1 test
 - Cognitive function **declined** 1 month after treatment

Test	Baseline (n = 54)	Follow-up (n = 26)
Attention	7	8
Psychomotor speed	8	13
Total recall	44 ^b	50
Immediate recognition	7	25
Delayed recall	41 ^b	58
Verbal fluency	17 ^c	25
Visual scanning	28 ^b	38
Executive	29 ^b	46
Dexterity	37 ^b	54 ^d

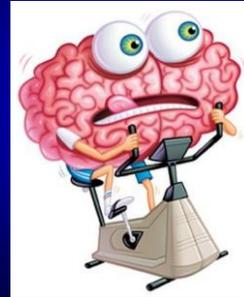
Cognitive Sequelae of Chemotherapy

- Risk factors for cognitive decline:
 - Some agents are more neurotoxic than others
 - Method of delivery (intrathecal)
 - Age
 - Total dose
 - Vascular risk factors (diabetes)
 - Genetic polymorphisms/individual factors?
 - Apolipoprotein E (APoE)
 - Brain derived neurotrophic factor (BDNF)
 - Catecholomine-o-transferase (COMT)
 - C-reactive Protein (CRP) ... and others

Scientific studies of Cognitive Impairment in MDS (& AML)

- Take home points
 - The rate of cognitive problems is somewhere from 25-45% at disease onset
 - Hgb levels <10 mg/dl may increase the likelihood of cognitive symptoms and fatigue
 - There is also a relationship between cytokine levels and cognitive symptoms
 - Fatigue did not have as strong a relationship with cognitive test scores as did cytokine levels
 - Cognitive symptoms may get worse during treatment (e.g., at 1 month), but seem to improve after treatment is complete and recovery occurs (e.g., 12-18 months).

Maintaining Brain Health



Maintaining Brain Health

- Does brain 'exercise' help?
 - 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**

Maintaining Brain Health

- 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 therapy
 - Occupational therapy
 - Success is contagious!



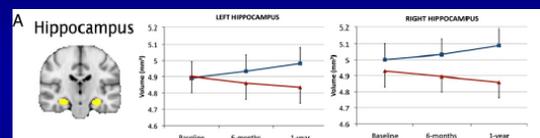
Maintaining Brain Health

- Physical exercise
 - Helps promote overall brain health
 - Improves blood flow to the brain
 - Can help reduce the loss of brain with aging
- 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



Kramer et al., 2011, PNAS

Maintaining Brain Health

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Summary

- The brain is not considered a primary site of pathology in AA, MDS and PNH
 - Despite that, many factors combine to effect brain function and cognition in some people with these disorders
- Primary issues include fatigue, immune system processes, chemotherapy side effects
- Treatment for cognitive problems is available:
 - maintaining good general brain health
 - developing strategies on an individual basis
 - Some medications can help
- Neuropsychological evaluation and cognitive rehabilitation are useful to understand the cause of a cognitive problem and develop strategies to deal with it

Questions?