

**PART 1: Understanding the cognitive
impact of cancer treatments**

James Wolf, MD

**PART 2: Cognitive Therapy Patients
undergoing Chemotherapy**

Lisa Clossey, MS CCC-SLP

March 22, 2013

The Milton J. Dance, Jr.
Head & Neck Center
Johns Hopkins Voice Center at GBMC

6569 North Charles Street
Physicians Pavilion West, Suite 401
Baltimore Maryland 21204
443-849-2087 fax 443-849-2649

Cognitive Therapy
Lisa Clossey, MS CCC-SLP

The Milton J Dance Jr Head & Neck
Center

***“You start a conversation you can't
even finish it.
You're talkin' a lot, but you're not
sayin' anything. ”***

David Byrne, Talking Heads



Wrong house?

...brain fog!

Overview

- Previously Well Known Neurological Complications
- Historical Overview of Cognitive Dysfunction
- Chemotherapy Drugs cited
- A Documenting Study
- Daily Life Factors
- Biological Factors
- My Own Conclusions

Traditional reasons for seeking neurological consultation

WELL KNOWN COMPLICATIONS

Neurological Complications of Cancer and its Treatment

- Peripheral neuropathy
- Seizures
- Delirium
- Opportunistic infections
- Metastatic Disease
- Paraneoplastic Syndromes
- And an evolving field that does not belong in any of the above classifications

An evolving concept

“CHEMOBRAIN”

Historical overview

- 1995-2004 multiple studies discussed the phenomenon
- 2005: 31 percent of women receiving chemotherapy for breast cancer were said to have cognitive decline

Historical Overview

- 2006: A three year prospective study: Most women receiving chemotherapy did not suffer cognitive complications.
- A small subgroup of women who experienced treatment-induced menopause were at greater risk for decline “mildly” immediately following chemotherapy

Historical Overview

- 2007: PET imaging during neuropsychological testing TREATED 5-10 YEARS EARLIER showed abnormal blood flow in the inferior frontal gyrus and cerebellum
- 2007-2008 Little consensus defining cognitive impairment, the types of tests used, and methods used to analyze data.

Historical Overview

- Incidences of cognitive decline ranged from 12-68.5% in chemotherapy sample and 4.8 to 64.3% in the healthy control sample
- “...need for greater consensus among scientists in developing consistent methods of design and analysis to provide meaningful results.”
- 2007 Six potential mechanisms as to cause

Chemotherapy drugs cited

- Most studies involve patients treated for breast cancer and colon cancer
- Drugs cited include doxorubicin, 5-fluorouracil, adriamycin, cyclophosphamide, methotrexate,
- Animal models and cell culture studies suggest carmustine, cisplatin, cytosine arabinoside

Chemotherapy-associated risk factors

- Exposure to higher doses either by intent or by impaired clearance or by impaired metabolism
- Crossing the blood-brain barrier
- Additive or synergistic effects of multi-agent chemotherapy
- Intrathecal administration
- Non-chemotherapy drugs with potential or real CNS side effects, such as analgesics, steroids, anti-anxiety drugs, sedatives, anti-seizure drugs

Chemotherapy: Other types treatments

- Biological Risk Modifiers, ie interferon-alpha
- Hormonal therapies such as tamoxifen and leuprolide.
- Tamoxifen affects a) neurotransmitters, such as serotonin and dopamine, b) cytokines, c) other neuroimmune systems
- ? Leuprolide. Studies have shown mixed results

**Chemo Brain: Research
Proves It's Real!**



Documenting Studies

- Jeffrey Wefel, Dept of Neuro-Oncology M.D> Anderson in Cancer July, 2010
- “Acute and Late Onset Cognitive Dysfunction Associated With Chemotherapy in Women With Breast Cancer”
- Incidence, Nature, and Chronicity of cognitive dysfunction

Documenting-Wefel Study

- All patients were at least 18 years old, completed >8 years of formal education, and spoke English fluently
- None had previous history of any other cancers, had taken previous chemotherapy.
- None had previous neurological or psychiatric disorder
- None had used any drugs that could affect cognition for three weeks prior to testing.

Wefel Study

- Patients took standardized cognitive tests, mood measures, and a Quality of Life (QOL) study-Functional Assessment of Cancer Therapy-Breast Module
- Cognitive testing was done at baseline, an average of 2.9 months, 7.0 months, and 13.1 months after baseline
- 42 patients were enrolled

42 patients in Wefel Study

- 9/42 (21%) met criteria for having cognitive impairment at baseline. They will be called Group 1
- 33/41 (79%) did not have baseline cognitive impairment. They are Group 2.
- Self reports of depression (Beck Depression Inventory) or anxiety (State Trait Anxiety Inventory) did not correlate with any baseline cognitive test at baseline.
- No significant differences existed in QOL reports between Group 1 and Group 2

Group 1 vs Group 2..mostly similar

- Group 1 was older
- No differences in education, menopausal status, hormone replacement therapy history, tumor stage, or pre-treatment surgery for breast cancer.
- All patients were initially randomized to 5-FU, adriamycin, and cyclophosphamide (FAC) and FAC + paclitaxel but because only 8 patients were in FAC only, both groups were combined. Five patients ended up dropping out of entire study,
- Leaving 37 patients for the entire study

The remaining 37 patients in Wefel's study

- **24/37 (65%)** showed an acute decline in cognitive function in one, two, or three tests either during or shortly after chemotherapy completion (mean months 1.6)
- **24/24 (100 %)** of patients who declined during treatment did not improve shortly after therapy was over.
- Most declines involved learning and memory, psychomotor processing speed and executive functioning (Hopkins Verbal Learning Test and Trail Making Tests)

Wefel Study..Non-factors in 37 patients

- Mood
- QOL
- Ability to work
- Pretreatment cognitive status
- Demographic/clinical characteristics

Wefel Study: Late interval

- Involved **28/37** patients at combined 13 months after baseline and 7.7 months after treatment completion.
- So, **28** patients in this phase
- **17/28 (61%)** showed cognitive decline relative to test performance during acute phase.
- **12/17 (71%)** showed both acute and late cognitive decline
- **5/17 (29%)** showed *new onset* cognitive decline that was not present during acute interval.

Patients without Late Cognitive Decline

- **11/28** did not have late cognitive decline
- **8/11** declined during acute interval and remained stable with significant improvement (except for 2/8 who improved in memory test alone)
- **3/11** did not decline at any time point.
- Progressive and delayed cognitive decline did not correlate with chest wall radiation, hormonal therapy, or progressive disease.

Daily Life Factors

- Fatigue
- Sleep
- Nutrition
- Co-morbid illnesses
- Other medications taken concomitantly
- ? Depression
- Psychosocial support

Biological Factors

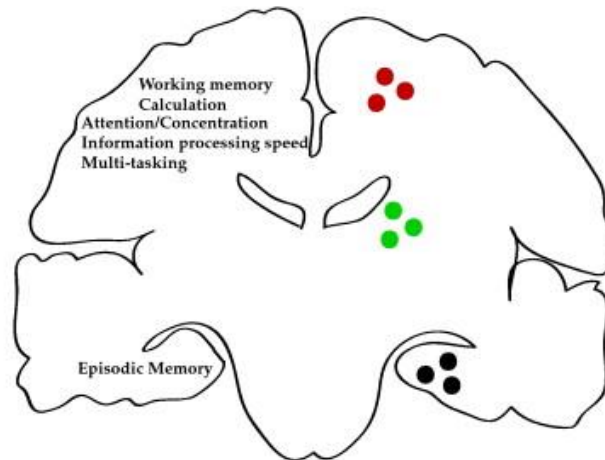
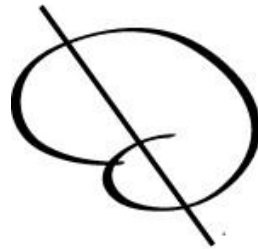
- Injury to parts of brain including hippocampus, frontal lobe
- Possible vascular, inflammatory, and demyelinating (folate antagonists)
- ? Mineralizing microangiopathy in white matter
- NMDA associated excitotoxicity
- Alterations in neurochemistry affecting dopamine, serotonin, and norepinephrine
- Anemia
- Chemotherapy induced menopause

Biological factors II

- Pharmacogenetic
- Blood-brain barrier penetration
- Dosage of drug
- Nutritional status
- Decreased clearance or impaired metabolism

Past, Present, and Future

- 2012 Monje and Dietrich in Behavioural Brain Research
- Neurogenesis, or the production of new cells in the brain
- Involving neurons in the hippocampus
- Dividing stem and progenitor (similar in type) cells in hippocampus, under the ventricular system and may be vulnerable to chemotherapy
- Oligodendrocyte precursor cells in subcortical white matter



From Bench Research to Chemobrain

- Injury to these areas can produce slowed information processing and impaired attention, and difficulty storing new memories

Conclusions

- Cognitive dysfunction secondary to both cancer and its treatment is a real entity
- Its incidence varies according to different articles.
- Different measures are used to conceptualize it.
- No medications have emerged to eliminate it.
- Some common threads exist between it and subcortical dementia.
- Effective screening measures are needed so it can be validated and addressed.
- Its understanding and treatment are multi-disciplinary.

Cognitive Therapy
Lisa Clossey, MS CCC-SLP

The Milton J Dance Jr Head & Neck
Center

Cognition

- “Act or process of knowing. Cognition includes every mental process that may be described as an experience of knowing (including perceiving, recognizing, conceiving, and reasoning), as distinguished from an experience of feeling or of willing.”

Roles of SLPs -

- *Speech sound production
 - *Resonance
 - *Voice
 - *Fluency
- *Language (comprehension and expression)
 - *Cognition
- *Feeding and swallowing

SLP Role (continued)

- Services Include:
 - Prevention and pre-referral
 - Screening
 - Assessment/evaluation
 - Consultation
 - Diagnosis
 - Treatment, intervention, management
 - Counseling
 - Collaboration
 - Documentation
 - Referral

Assessments

**Burns Brief Inventory of Communication and Cognition (Burns Inventory)*

**Cognitive Linguistic Quick Test (CLQT)*

**Mini Inventory of Right Brain Injury, Second Edition (MIRBI-2)*

**Repeatable Battery of Neuro Assessment (RBANS)*

**Ross Information Processing Assessment: Second Edition (RIPA-2) and the Geriatric (RIPA-G)*

**Scales of Cognitive Ability for Traumatic Brain Injury (SCATBI)*

www.ASHA.org

Assessment/Treatment areas

Memory

*Immediate

*Delayed

Attention

Reasoning/Problem Solving

Visuospatial

Executive Functioning

Language

Sequencing

Information Processing Speed

Approaches to Therapy

- Strategy Training (Compensatory)
 - Applying strategies to cope with cognitive deficits
 - Examples: planning ahead, minimizing distractions, mnemonics: acronyms
- Retraining (Restorative)
 - Frequent/repetitive exercises (restoring attention, memory, executive functioning)
 - Examples: word list, *Parrot Software*, *Luminosity*

Memory

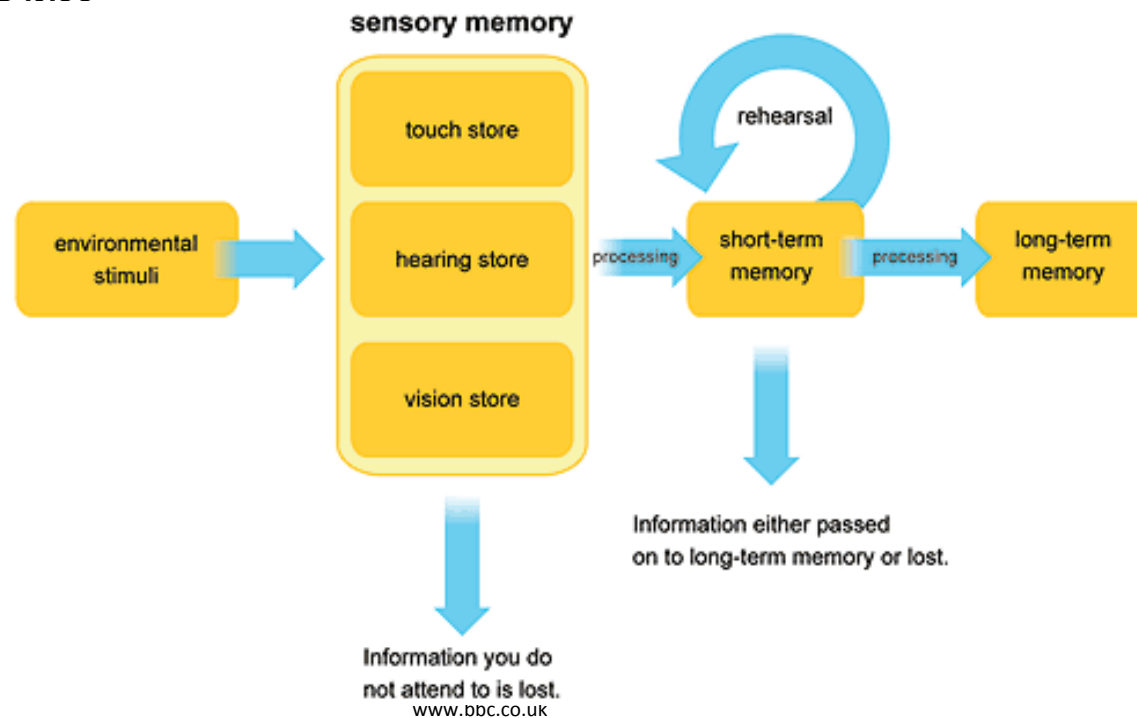
“the power or process of reproducing or recalling what has been learned and retained especially through associative mechanisms”

Memory

- 4 stages of the Memory Process:
 - Attention
 - Encoding (visual, auditory, kinesthetic)
 - Consolidation
 - Retrieval

Memory (cont)

- 3 stages of memory storage
 - Sensory
 - Working
 - Long-term



Memory (cont)

Two types of memory retrieval

- *Immediate
- *Delayed

Why we forget:

- *Trace decay
- *Displacement
- *Interference
- *Poor consolidation
- *Change over time

Memory and Therapy:

Goal: Improve and/or expand a Pt's memory through systematic training using strategies to assist with recall (i.e. categorization, association, repetition)

Techniques/Activities:

Selecting Information

Coding/Grouping

Using Aids: Internal vs. External

Attention

“the act or state of applying the mind to something ”

www.merriam-webster.com

Attention and Therapy

- Goal: Improve attention/concentration skill building while using functional activities.

- Techniques/Activities:

- Attention Process Training (APT)

- helps retrain attention and concentration deficits in adolescents and adults (computer base)

- Strategies Training (i.e. time management)

- Word Searches
 - Crossword puzzles
 - Visual Scanning

Mark all E's.

W	E	D	E	T	Y	E	N	G	E	E	C	E	O	U
O	E	E	D	F	G	E	H	E	E	E	S	C	V	B
E	E	B	Y	N	E	D	X	S	E	Z	A	E	E	S
L	E	C	U	D	E	N	M	E	L	W	S	E	E	S

- Selective: maintaining your attention despite distractions.

- Talking on the phone while your favorite T.V. show is on.
 - Using external noise while completing a task

- Alternating: shifting focus between tasks that have different mental requirements.

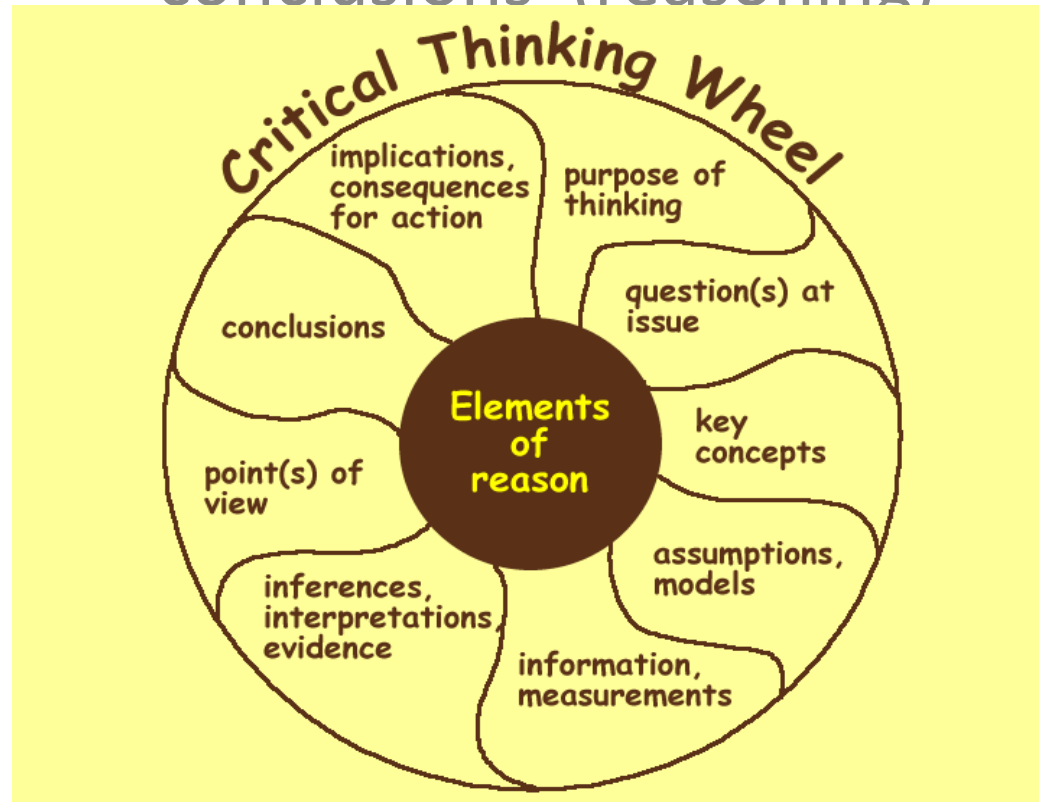
- Completing a puzzle while the clinician is in the background asking questions.

- Divided Attention Tasks: maintaining your attention while completing two activities simultaneously.



Reasoning

“the drawing of inferences or conclusions (reasoning)”



Reasoning and therapy

- Goal: Improve the ability to organize information, reason, and develop interpersonal insights, starting at a concrete level and progressing to an abstract level.
- Techniques/Activities:
 - overt reasoning (word deduction, similarities/difference, analogies)
 - covert reasoning (sequencing sentences of an activity, determining part/whole relationships)
 - Abstract: focus on figurative vs. literal language

Problem Solving

- using generic or *ad hoc* methods, in an orderly manner, for finding solutions to problems.
- Mayer and Wittrock (2006) distinguished among four major cognitive processes in problem solving: *representing*, in which the problem solver constructs a cognitive representation of the problem; *planning*, in which the problem solver devises a plan for solving the problem; *executing*, in which the problem solver carries out the plan; and *self-regulating*, in which the problem solver evaluates the effectiveness of cognitive processing during problem solving and adjusts accordingly.

Problem Solving and Therapy

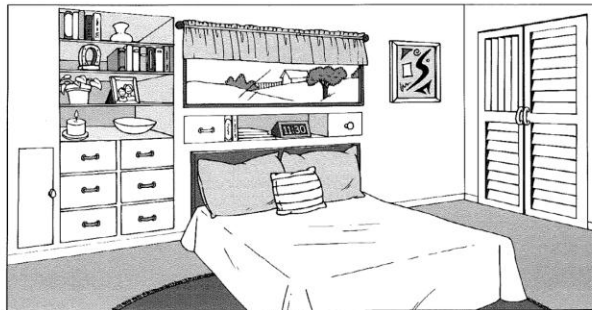
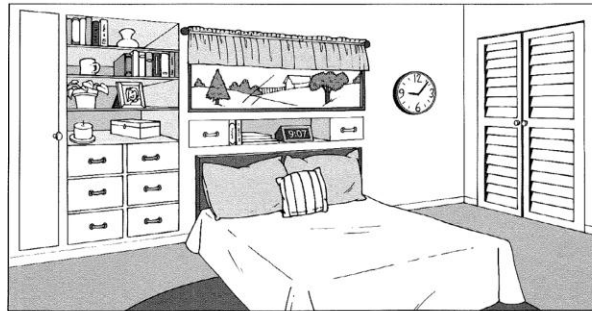
Goal: To improve Pt's ability to solve functional problems within everyday living experiences.

Techniques/Activities:

*Auditory and/or visual

Auditory: short stories covering topics such as medical, household, financial, and community.

Visual: pictures, news videos, prescriptions, orders (i.e. retail)



Visuospatial Skills

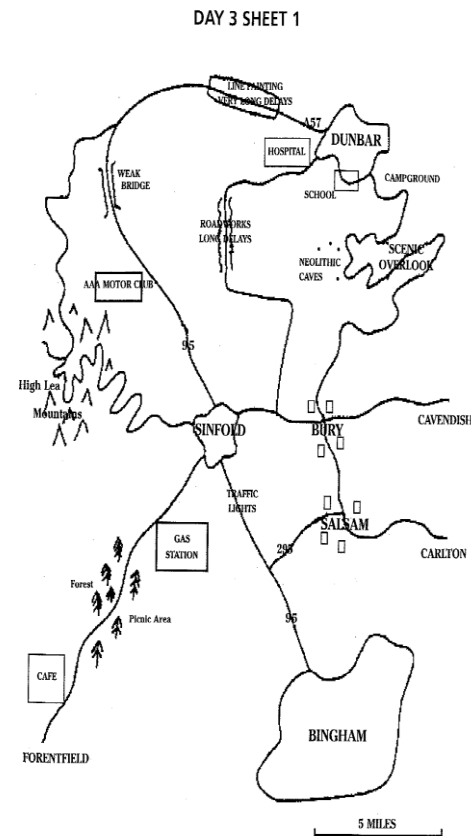
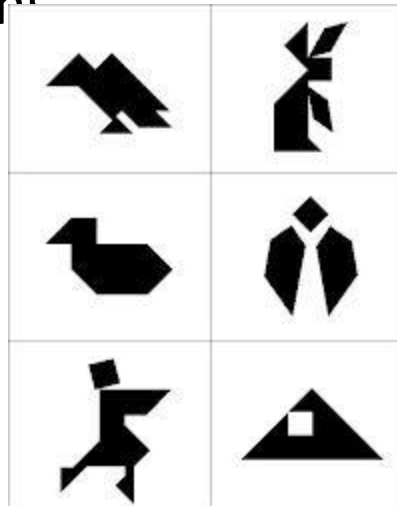
“ability to process and interpret visual information regarding where things are situated in space.”

“This group of cognitive functions analyzes and understands space (i.e., the world around you) in two and three dimensions. They include mental imagery and navigation, distance and depth perception, and visuo-spatial construction. Visuo-spatial functions represent the brain's highest level of visual processing, and requires the proper functioning of your parietal cortex, in the upper part of the brain.”

Visuospatial Skills and Therapy

- Techniques/Activities:

- Mazes
- Maps
- Tangrams



Executive Functioning

“processes that include initiation, planning, hypotheses generation, cognitive flexibility, decision making, self-regulation, judgment, feedback utilization, and self-perception.”

Components:

Initiation
Planning
Cognitive Flexibility
Self-Monitoring
Self-Regulation

Executive function can be divided into two categories:

- *organization
- *regulation

Executive Functioning and Therapy

- Goal: Improve a Pt's ability to manage time and attention, switch focus, plan and organize, remember details, curb inappropriate speech or behavior, and integrate past experience with present action
- Techniques/Activities:
 - Self-Organize
 - Plan
 - Simplify Information
 - Organize Information

Sequencing

“the order in which things happen or should happen”

www.merriam-webster.com

Information Processing Speed

“the ability to rapidly process simple and complex information.”

Linked to all cognitive domains thru:

tactile

auditory

verbal

visual

Myers, Jamie S.

Language

“System of conventional spoken or written symbols used by people in a shared culture to communicate with each other. A language both reflects and affects a culture's way of thinking, and changes in a culture influence the development of its language.”

Language and Therapy

- Goal: To improve language skills (comprehension and/or expression) for completion of everyday living experiences.
- Techniques/Activities:
 - Functional Communication Training (i.e. listening to directions, asking for help)
 - Yes/no questions
 - Incongruities (i.e. “She drank of glass of turpentine.”)

“Chemo-Brain” and Cognition

- “multidimensional phenomenon that follows cancer diagnosis and chemotherapy tx and involves the Pt’s perception of change in his or her cognitive abilities.”
- significant difference in the genu of the corpus callosum after chemotherapy
- “15-50% of patients with cancer experience changes in their cognitive functioning following chemotherapy.”

- Kanaskie, Mary Louise
 - Abraham et al., 2005
- Hutchinson, Amanda D et al., 2012

Case Study

- ## is a 54 y.o. female
 - Education/Social:
 - Attended ** College x3/yrs with a major in Philosophy and Religion
 - Graduated from ** with a BS in liberal arts
 - ** (teaching basic math to trigonometry)
 - Supervisor of ***
 - District Manager for the **
 - Past Medical Hx:
 - Surgeries: lumpectomy of R breast, sentinel node removal, reduction of both breasts (2011)
 - Removal of remaining lymph nodes near right breast while implanting a Port (2012)
 - Radiation (x2 months) in 2012
 - Chemotherapy/Targeted Therapy
 - Lymphedema Clinic therapy (RUE)
 - Medications/Devices:
 - Chemotherapy: Adriamycin and Cytoxan, Taxol, Herceptin
 - Letrozole
 - Prednisone
 - Lymphedema vest, arm sleeve, gauntlet, and home pump

** - Assessment

- Date of Assessment: 1/23/2013
 - RBANS and executive functioning subtest from the CQLT
- **Complaints:**
 - Inability to multi-task
 - attention span has become much shorter
 - processing speed has decreased
 - greater difficulty with learning new information.
- **Results:**
 - RBANS: Total Score of 73 = borderline, demonstrating greatest difficulties with memory (immediate/delayed) as well as attention.
 - CLQT: WNL for executive functioning skills.
- **Recommendations:**
 - therapy 2x/week for 6 weeks with reassessment at that time.

** - Therapy

- LTG:
 - Beginning: Complete functional tasks at an independent level (i.e. grocery shopping, paying bills).
 - Now: Return to working and driving

- STGs:
 - Memory (Immediate/Delayed):
 - Visual: 80% accuracy
 - Verbal: 60% accuracy
 - Attention

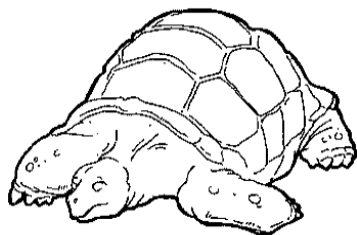
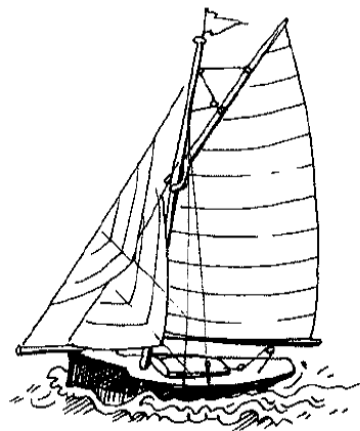
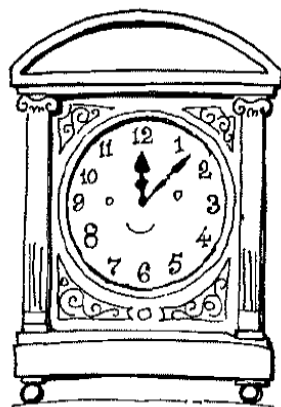
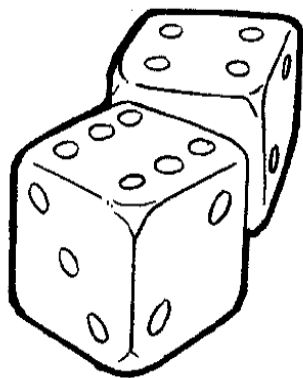
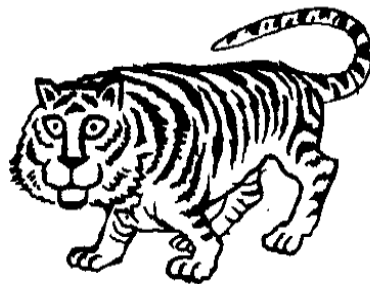
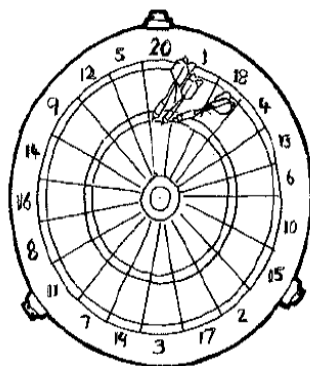
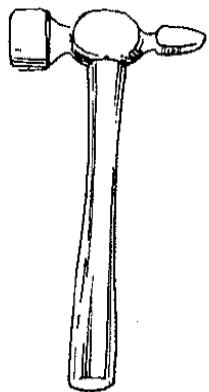
- Activities:
 - During Therapy:
 - Word List: repetition, first-letter mnemonic
 - Objects: categorizing, size
 - Pictures: Memory
 - Paragraphs: key elements, irrelevant information, “short-hand”
 - Selective/Alternating Attention
 - Templates

 - Carry-Over:
 - External Aids (Memory): calendar, planner, business card holder
 - Luminosity
 - Talk to Text
 - YouTube/BBC lectures

** - Today

- Immediate/Delayed Memory:
 - Visual: 100%
 - Verbal: 80%
- Attention: 100%
- Techniques:
 - Short-hand
 - Repetition
 - Tapping
 - Visualizing

“I actually listen to music again. I find that it helps me concentrate better.”



References

- Gehring, Karin, Roukema, Jan Anne, & Sitskoorn, Margriet M. Review of recent studies on interventions for cognitive deficits in patients with cancer. *Expert Reviews* (2012); 12(2): 255-269.
- Hutchinson, Amanda D., Hosking, Jessica R., Kichenadasse, Ganessan, Mattiske, Julie K., Wilson, Carlene. Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. *Cancer Treatment Reviews* (2012); 38: 926-934.
- Lazzari, Andrea M. (1996) HELP for MEMORY. LinguiSystems: East Moline, IL.
- Kit, Malia B., Bewick, Kristin C., Raymond, Michael J., Bennett, Thomas, L. Brainwave-R, Memory, (2002). Pro-Ed.
- Mayer, R. E., & Wittrock, R. C. (2006). Problem solving. In P. A. Alexander & P. H. Winne (Eds.), *Handbook of educational psychology* (2nd ed., pp. 287–304). Mahwah, NJ: Erlbaum
- Myers, Jamie S. Neuropsychologic Testing for Chemotherapy-Related Cognitive Impairment, edited by Robert B. Raffe and Ronald J. Tallarida. (2010) Landes Bioscience and Springer Science + Business Media.
- Tomlin, Kathryn J. (2007) WALC10 – Memory. LinguiSystems: East Moline, IL.
- Tomlin, Kathryn J. (2002) WALC 2 – Language and Cognition. LinguiSystems: East Moline, IL.
- Tomlin, Kathryn J. (2007) WALC 9 – Verbal and Visual Reasoning. LinguiSystems: East Moline, IL.
- www.ASHA.org
- www.merriam-webster.com