The background image shows a lighthouse situated on a rugged, rocky cliff. The lighthouse is white with a dark lantern room and a red light visible through its window. It is surrounded by several evergreen trees. The sky is a soft, warm color, suggesting either sunrise or sunset. The overall scene is peaceful and scenic.

Skills of Managing “Chemobrain”

Robert J. Ferguson, Ph.D.

Eastern Maine Medical Center
Lafayette Family Cancer Center

University of Maine Dept. of Psychology,
Cancer Support Now: 2nd Annual Long-Term Effects of Cancer Survivorship
Conference

1. Chemotherapy-associated Cognitive Change-Background
2. The cognitive-behavioral management approach and medications
3. Findings to date
4. Future directions

Acute to Chronic Disease Shift

“We are now living well enough and long enough to slowly fall apart.”

- *Robert Sapolsky, Ph.D.*

Author: Why Zebras Don't Get Ulcers

Cancer is a chronic illness

- Survivorship defined as diagnosis of cancer and forward
(<http://cancercontrol.cancer.gov/ocs/office-survivorship.html>)
- About 12 M living who have had a diagnosis of cancer (NCI, 2007)

Current Knowledge of Chemotherapy-Associated Cognitive Dysfunction

- History: chemo tx associated with measurable decrements in neuropsychological test performance (Silberfarb, 1980, 1983)
 - Acute effects
 - Possible confounds with depression, anxiety and stress responses
 - Normative comparisons vs. Controls/baseline

Evaluation of Cognitive Function

Table 1. Summary of Cognitive Articles

Study	Year	Study Design	Sample Size (N)	Patient Groups, ^a	NP Assessments	Definition of Cognitive Impairment	Cognitive Impairment (%)	Comments	Statistical Methods
Van Dam ³	1998	Cross-sectional	34	BC posthigh-dose CT	Traditional battery, 2 hours	≥ 2 SD below control group; ≥ 3 tests impaired	32	Z scores; impairment score for each test and global impairment score	
			36	BC poststandard CT (IFC)			17		
			34	Controls: BC no CT			9		
Schagen ⁴	1999	Cross-sectional	39	BC post-CT (ICMF)	Traditional battery, 2 hours	≥ 2 SD below control group; ≥ 3 tests impaired	28	Z scores; impairment score for each test and global impairment score	
			34	Controls: BC no CT			12		
Schagen ⁵	2002	Cross-sectional (Follow-up of previous studies)	22	BC posthigh-dose CT	Traditional battery, 2 hours	≥ 2 SD below control group; ≥ 3 tests impaired	14	Z scores; impairment score for each test and global impairment score	
			23	BC poststandard CT (ICMF)			9		
			31	BC poststandard CT (ICMF)			13		
			27	BC no CT			11		
Ahles ⁶	2002	Cross-sectional	71	BC and lymphoma post-CT	Traditional battery, 2 hours	Below lowest quartile on ≥ 40 domains; summary score	39	Z scores, summary score	
			67	Controls: BC and lymphoma but no CT			14		
Bredsen ⁷	2000	Cross-sectional	31	BC on CT	HSCS; time: 25 minutes	Moderate-severe classification	48	Summary score \rightarrow classification	
			40	BC post-CT			50		
			36	Controls: healthy			11		
Tchen ⁸	2003	Cross-sectional	100	BC on CT	HSCS; Trials A and B; CCP	Moderate-severe classification	16	Summary score \rightarrow classification	
			100	Controls: healthy			4		
Mar Fan ⁹	2005	1- and 2-year follow-up of Tchen study	91	BC post-CT (I) and 2 year	HSCS; Trials A and B; CCP	Moderate-severe classification	4.4	Summary score \rightarrow classification	
			83				3.6		
			83				3.8		
			81	Controls: healthy			0		
Verdy ¹⁰	2006	Longitudinal	91	BC and CRC	HSCS; Coghealth (15 min); Headminder (30 min)	Moderate-severe: ≥ 1 SD below norm on ≥ 15 and ≥ 18 domains	HSCS: time I: 30%; time II: 5%; time III: 8%	Summary score \rightarrow classification; RCI \rightarrow summary score	
			28	BC post-CT	Traditional battery, 2.5-3 hours; 9 domains	≥ 2 SD below norm on ≥ 6 domains	75		
Meyers ¹¹	1995	Cross-sectional	21	SCLC pre-CT	Traditional battery, 14 tests	≥ 1 SD below norm on individual tests; no overall definition	70-80% memory impaired in both groups	T scores; compared with published normative data; ANOVA; summary scores	
			25	SCLC post-CT/RT (pre-CD)					
Weefel ¹²	2004	Prospective longitudinal, 0, 6, and 18 months	18	BC to receive CT	Traditional batteries, 14 tests, 7 domains	≥ 1.5 SD on 1 test or ≥ 2 SD on 1 test	38%; 61% decline at 18 months	Z scores; means; RCI	
			19	BC post-CT	Traditional battery and computer test, ~ 2 hours	No definition	N/A		
Castellon ¹³	2004	Cross-sectional	36	BC post-CT				CT worse than non-CT but not different to controls	Z scores; domain scores and summary score; ANOVA
			19	Controls: healthy					
Jacobsen ¹⁴	2004	Prospective longitudinal	77	Mixed solid tumors	Battery, 7 tests	No definition	N/A	Regression analyses comparing memory and cognitive function; change score; means; z scores	
			60	BC post-CT	Traditional battery, 9 tests, 5 domains	> 2 SD below norm on each test but no overall definition	N/A		
Donovan ¹⁵	2005	Cross-sectional	80	BC post-CT				No difference between groups	Z scores; summary score; effect size (d); ANOVA
			83	Controls: BC no CT					
Freeman ¹⁶	2002	Cross-sectional	8	BC on CT	Traditional battery, 20 tests, 3 hours	No definition	N/A	CT worse than post-CT	Means, ANOVA for comparison between groups
			9	BC post- or on CT					
O'Shaughnessy ¹⁷	2005	Longitudinal 0, pre- and 4 and 8 months post-CT	47	BC on CT on epstein alpha	EXIT 25; CLOK; time: 20 min	No definition	N/A	No difference in groups at 8 months	Group mean; difference from baseline; comparison within or between groups
			47	BC on CT on placebo					
Shilling ¹⁸	2005	Longitudinal 0 and 8 months	60	BC who will have CT	Traditional battery, 14 tests	Reliable cognitive decline on $\geq 2/14$ tests	Decline in 34% on CT v 19% controls	Repeated measures ANOVA; RCI with practice effect correction	
			43	Controls: healthy					

(continued on next page)

<u>Regimen</u>	<u>Number of Breast Cancer Survivors</u>	
cyclophosphamide/methotrexate/5-fluorouracil	12	
cyclophosphamide/methotrexate/5-fluorouracil/ vincristine/prednisone	2	
cyclophosphamide/doxorubicin/5-fluorouracil	10	
cyclophosphamide/doxorubicin	3	
cyclophosphamide/carboplatin	1	
vinblastine/doxorubicin/thiotepa/halotestin	1	
<u>Number of Lymphoma Survivors</u>		
oral cyclophosphamide	3	
cyclophosphamide/bleomycin	1	
cyclophosphamide/etoposide	1	
cyclophosphamide/doxorubicin/vincristine/prednisone	5	
cyclophosphamide/doxorubicin/vincristine/ prednisone/bleomycin	1	
cyclophosphamide/doxorubicin/vincristine/ prednisone/etoposide	2	
cyclophosphamide/vincristine/prednisone/procarbazine	2	
cyclophosphamide/vincristine/doxorubicin/methotrexate/ asparaginase/etoposide/mercaptopurine	1	
prednisone/methotrexate/doxorubicin/cyclophosphamide/ etoposide/cytarabine/bleomycin/vincristine/leucovorin	1	
doxorubicin/bleomycin/vinblastine/dacarbazine	1	
etoposide/vinblastine/doxorubicin	2	
vinblastine	2	
mechlorethamine/vincristine/prednisone/procarbazine	3	
mechlorethamine/vincristine/prednisone/procarbazine/ doxorubicin/bleomycin/vinblastine/dacarbazine	1	
mechlorethamine/doxorubicin/cyclophosphamide/ vincristine/prednisone/bleomycin	1	

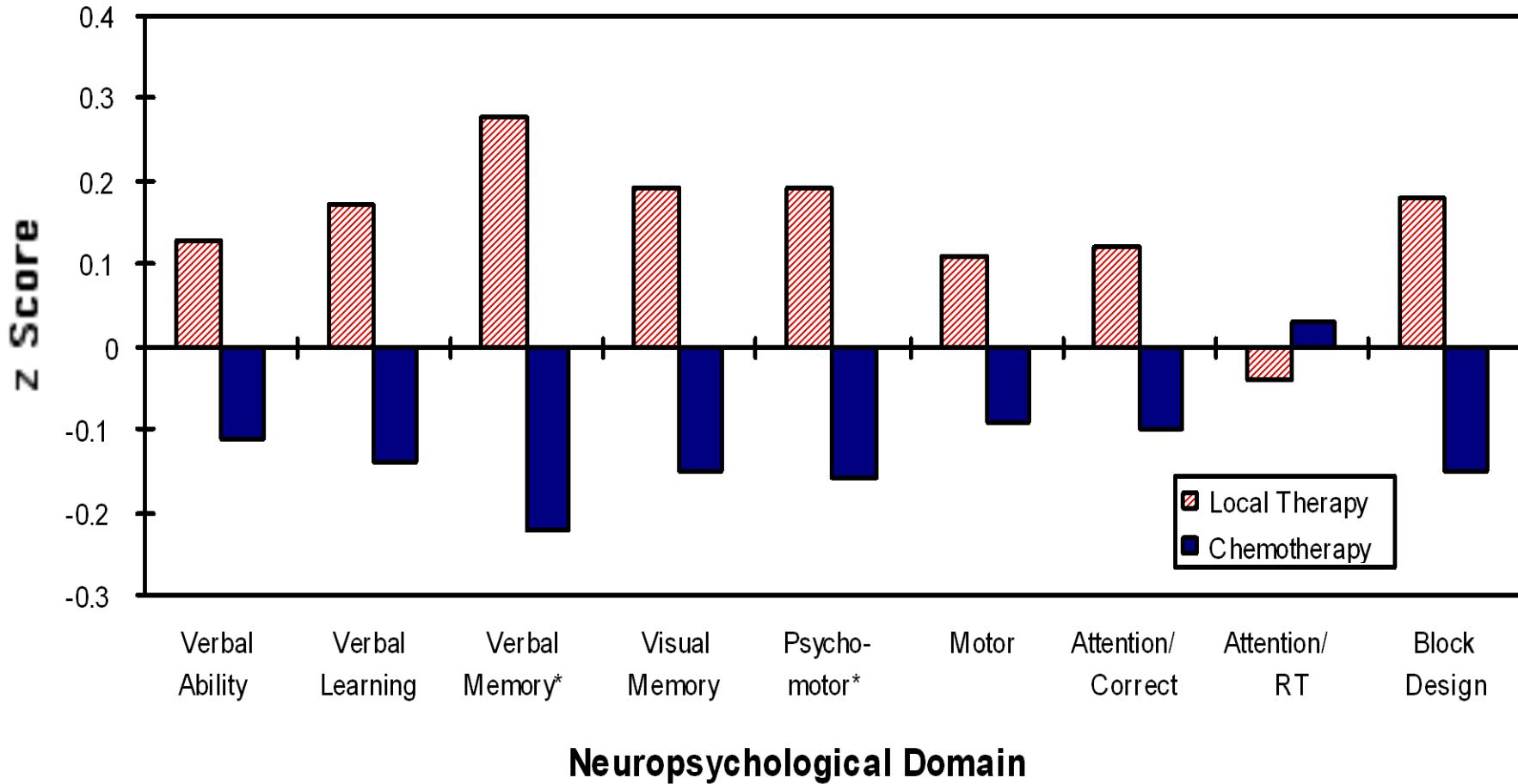
To Summarize....

- About 25 to 40% of participants demonstrate mild-moderate cognitive impairment after chemo
- Areas affected appear to be in verbal recall, working memory and processing speed
- Most individuals recover well after treatment
- Problems appear not to be due only to stress, anxiety or depressive symptoms
- Researchers need better agreement as to what constitutes memory impairment

Probable Mechanisms?

- Neurotoxicity to cns and pns (Keime-guibert, et al., 1998)
- crossing blood brain barrier? (Troy,et al., 2000)
- Neurotoxicity producing demyelination
- Immunologic response producing autoimmune vasculitis
- Microvascular injury--leading to obstruction, thrombosis, ischemia (Tuxen & Hansen, 1994)
- COMT
- Apolipoprotein E (APOE)
 - Alzheimer's, brain injury (Parasuraman, Greenwood, & Sunderland, 2002)
 - Chemo/cog. dysfunction (Ahles, Saykin, Noll, et al., 2003)

Adjusted Z-transformed domain scores for chemotherapy vs. local therapy groups.



Normal neuropsych
testing scores?

What Impairment?!

So? How Does Cognitive Dysfunction Affect Daily Life?

- Cognitive dysfunction one of the most feared symptoms among the healthy population (Anderson, Rothenberg, & Kaplan, 1998)
- Cognitive dysfunction is recognized as a target problem by the President's Cancer Panel and by the National Coalition for Cancer Survivorship

Employment function

www.huricanevoices.org

Their experiences fell into several categories:

- :: Having to shift or relinquish employment:
 - inability to function in a work environment,
 - going on disability,
 - premature retirement,
 - downsizing to a job with fewer responsibilities and less pay.
- :: Being overwhelmed by tasks assigned, unable to multi-task, or organize daily work load.

Home function

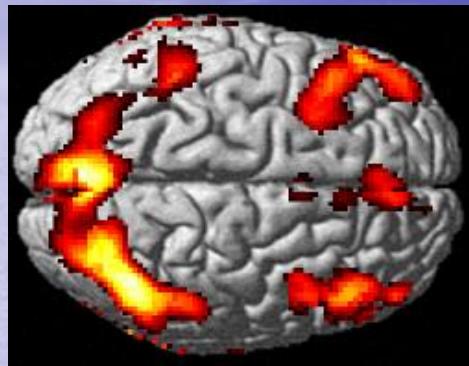
At home respondents report:

- :: Being teased, criticized, or 'supervised' by family members.
- :: Children prematurely taking on increased responsibility.
- :: Spouses who feel the cancer patient is acting irresponsibly.
- :: Respondents won't go to social functions due to embarrassment.
- :: Inability to maintain personal responsibility for household or financial tasks.

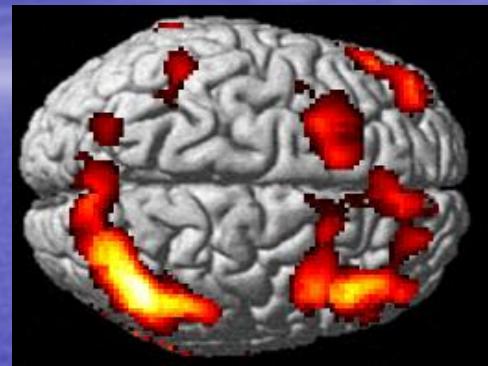
Diathesis-Stress Model

- Diatheses: Biological vulnerabilities, learning history, etc.
- Stress: Increased demands, challenges, threats (e.g., cancer diagnosis, time demands, adjustment in work/social life)

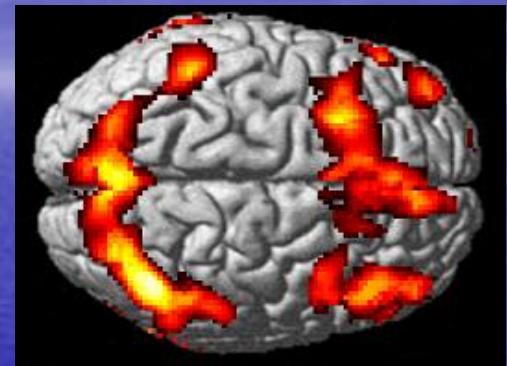
1-back>0-back



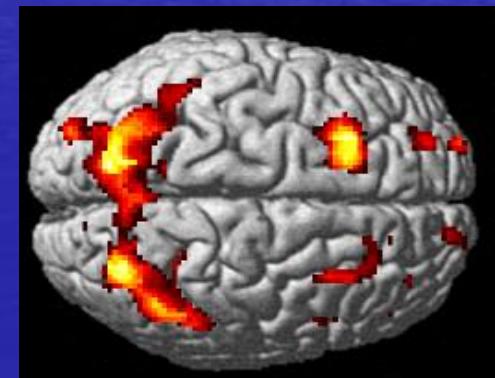
2-back>0-back



3-back>0-back



Chemotherapy-treated Twin-Twin A



Non-cancer Twin-Twin B

Cognitive-Behavioral Approach to Management of Cognitive Problems

–“compensatory strategies vs. mental muscle”

- “De-emphasize drill and practice”
- Improve adaptation to memory dysfunction or impairments that may not change
- Build on strengths
- Emphasize coping and stress resilience



NORRIS COTTON CANCER CENTER
DARTMOUTH-HITCHCOCK MEDICAL CENTER

Memory and Attention Adaptation Training (MAAT): A Brief Behavioral Skills Program for Cancer Survivors with Attention and Memory Problems Associated with Chemotherapy

Robert J. Ferguson, Ph.D.*

Behavioral Medicine Section

Dartmouth Medical School

RUNNING HEAD: Memory and Attention Training

*This is not a published document. Please do not reproduce or distribute
without permission of the author.

Cognitive-Behavioral Approach to Management of Cognitive Problems

- Education “reattribution”
- Self-awareness training
- Self-regulation, stress management
- Compensatory strategies

To Do:

Buy fresh lime for the fiesta tonight

Pick up the cat's medicine at vet's

Buy a new bike helmet for Jr.

Outline of Brief Cognitive-Behavioral Treatment Schedule

VISIT	CONTENT
1	<ul style="list-style-type: none">• TREATMENT OVERVIEW & PROVISION OF BOOKLET• EDUCATION ON MEMORY AND ATTENTION AND EFFECTS OF CHEMOTHERAPY• SELF-MONITORING INSTRUCTION• RELAXATION TRAINING• HOMEWORK
PHONE CONTACT 1	<ul style="list-style-type: none">• REVIEW HOMEWORK, PROBLEM SOLVE
2	<ul style="list-style-type: none">• HOMEWORK REVIEW• COMPENSATORY STRATEGY(IES) SELECTION, INSTRUCTION, AND REHEARSAL• HOMEWORK
PHONE CONTACT 2	<ul style="list-style-type: none">• REVIEW HOMEWORK, PROBLEM SOLVE
3	<ul style="list-style-type: none">• HOMEWORK REVIEW• COMPENSATORY STRATEGY SELECTION, INSTRUCTION, AND REHEARSAL• ACTIVITY PACING AND SCHEDULING• HOMEWORK• OVERVIEW
PHONE CONTACT 3	<ul style="list-style-type: none">• REVIEW HOMEWORK, PROBLEM SOLVE
4	<ul style="list-style-type: none">• HOMEWORK REVIEW• COMPENSATORY STRATEGY REVIEW• ACTIVITY PACING AND SCHEDULING REVIEW• PLAN FOR RELAPSE PREVENTION• WRAP-UP

Compensatory Strategies

- Self-Instructional Training
- Verbal and “Silent” Rehearsal
- Schedule Making
- External Cueing
- Visual Imagery
- Memory Routines
- The Name-Face Mnemonic (“Name-Face-Association”)

Cognitive-Behavioral Treatment of Chemotherapy-Related Attention and Memory Problems Among Breast Cancer Survivors: A Pilot Study

PI: Ferguson, R. J. Co- PI: Ahles, T.A.

NCI: 1 R03 CA090151-02; Lance Armstrong Foundation

- One group pilot design (feasibility, satisfaction)
- Baseline, post-treatment, 2-month follow-up
- N = 29, Stage I, II BCA, no CNS tx, intrathecal tx, or psychiatric, substance abuse, neurologic
- Mean Age = 56 (7.81), mean IQ, est: 112.82, 15 yrs edu
- Years-post chemotherapy: 8.2 (4.4)
- OUTCOMES:
 - Improved Multiple Abilities Self-report Questionnaire (MASQ)
 - Improved CVLT-II Total Score (54, 55, 61, 59)
 - Digit Symbol, Stroop, Trail-making improvements
 - High Satisfaction 7.14 (1.09) 0-8 rating

“Behavioral Management of Cognitive Impairment Associated with Chemotherapy”

Lance Armstrong Foundation

R. Ferguson, PI

INCLUSION

- diagnosis of stage I and II breast cancer;
- at least 18 months post-treatment currently disease free (not excluding individuals on hormonal therapies such as selective estrogen receptor modulators);
- treatment involved standard dose adjuvant chemotherapy;
- complaint of memory and attention following chemotherapy;
- able to speak read English;
- at least 18 years of age at diagnosis and able to provide informed written consent.

EXCLUSION

- history of CNS disease;
- history of CNS radiation, intrathecal therapy or CNS-involved surgery;
- neuro-behavioral risk factors such as traumatic brain injury, history of neurological disorder, learning disability or substance addiction;
- current psychiatric disorder.

Outcome Measures

- Multiple Abilities Self-Report Questionnaire (MASQ)

(Seidenberg, Haltiner, Taylor, Hermann, & Wyler, 1994)

- 48 items, 5 pt Likert scale, almost always/never
- Language, visual-perceptual, visual memory, attention, verbal memory

- Quality of Life-Cancer Survivor Scale (QOL-CS)

(Ferrell, Dow, & Grant, 1995)

- 41 items, physical, psychological, social, spiritual scales
- 0-10 Likert scale

- CES-D-State-Trait Anxiety

Outcome Measures

Satisfaction

- General (0 = not at all satisfied; 8 = completely satisfied)
- *Improving* or helping to compensate for problems of memory and attention (0 = not at all helpful; 8 = completely helpful)

Outcome Measures

Neuropsychological

Verbal Domain

CVLT-2 Total Score

Processing Speed

Trail Making Number-Letter Switching

Stroop Color-Word

Stroop Color-Word Switching

Digit Symbol

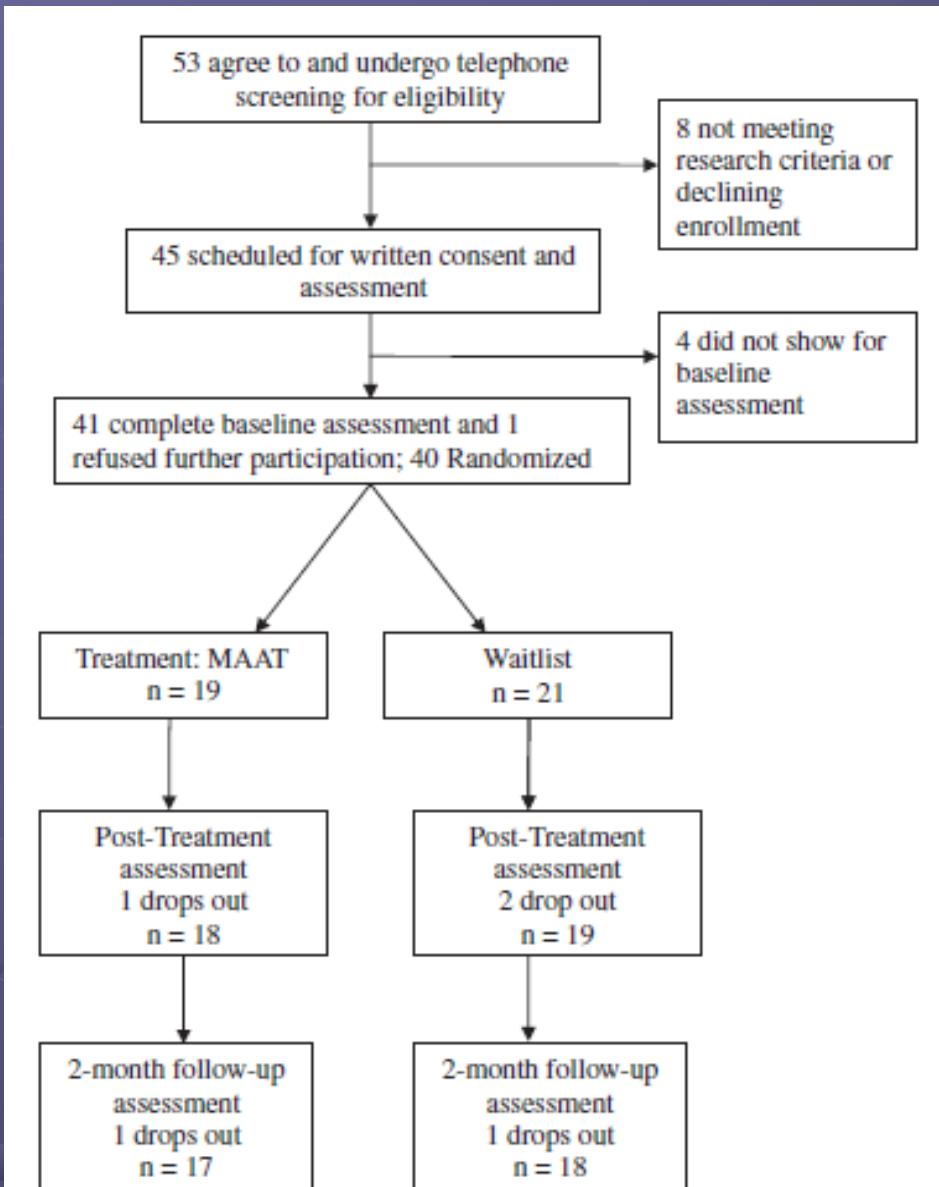


Figure 1. Study flowchart. Note: MAAT = Memory and Attention Adaptation Training

Table I. Background characteristics of participants

	Group		
	Total (n = 40)	MAAT (n = 19)	Waitlist (n = 21)
Variable			
Age	50.28 (6.4)	51.21 (7.3)	49.43 (5.1)
Education (in years)	16.38 (2.4)	16.95 (1.9)	15.86 (2.7)
Estimated IQ	114.72 (4.2)	115.61 (4.1)	113.92 (4.1)
Marital status			
Currently married		76.2%	63.2%
Caucasian	97.5%		
Other	2.5%		

Note: No factor was significantly different between groups ($p > 0.05$).

Table 2. Group comparisons of principal outcomes

	Baseline Mean (SD)	Post-Tx Mean (SD)	D	2-Month f/u Mean (SD)	d	F	p
Functional/quality of life outcomes							
MASQ total score ^a							
Treatment n = 19	120.05 (21.42)	107.03 (17.25)	0.67	108.95 (18.98)	0.55	1.24	0.30
Waitlist n = 21	111.90 (28.01)	105.69 (24.43)	0.24	104.93 (22.46)	0.28		
Treatment-control difference			0.43			0.27	
Quality of life—CS psychological well-being							
Treatment n = 19	5.25 (1.26)	5.63 (1.35)	-0.29	5.37 (1.22)	-0.10	0.516	0.60
Waitlist n = 21	6.42 (1.45)	6.51 (1.20)	-0.07	6.40 (1.38)	-0.01		
Treatment-control difference			-0.22			-0.11	
Quality of life—CS spiritual well-being							
Treatment n = 19	5.91 (2.02)	6.57 (1.79)	-0.35	6.14 (1.99)	-0.11	3.44	<0.05
Waitlist n = 21	6.31 (2.10)	6.02 (1.94)	0.14	6.02 (1.81)	0.15		
Treatment-control difference			-0.49			-0.26	
Quality of life—CS physical well-being							
Treatment n = 19	7.68 (1.95)	7.59 (1.82)	0.05	7.04 (1.79)	0.34	1.72	0.19
Waitlist n = 21	7.79 (1.27)	8.01 (1.32)	-0.17	7.91 (1.10)	-0.10		
Treatment-control difference			-0.22			0.44	
Quality of life—CS social well-being							
Treatment n = 19	6.26 (2.05)	6.48 (1.91)	-0.15	6.75 (1.78)	-0.26	0.618	0.54
Waitlist n = 21	7.31 (1.21)	7.54 (1.18)	-0.27	7.47 (1.59)	-0.19		
Treatment-control difference			0.12			-0.07	
Neuropsychological outcomes							
CVLT-II-Total (T-score)							
Treatment n = 19	60.00 (11.17)	63.63 (9.07)	-0.36	68.47 (9.71)	-0.81	3.161	<0.05
Waitlist n = 21	62.10 (12.12)	60.62 (8.76)	0.14	64.21 (11.52)	-0.18		
Treatment-control difference			-0.50			-0.63	
Digit symbol-coding							
Treatment n = 19	1253 (3.31)	14.05 (2.95)	-0.46	14.42 (2.98)	-0.60	0.9	0.41
Waitlist n = 21	1200 (2.63)	13.07 (2.16)	-0.45	13.33 (2.95)	-0.48		
Treatment-control difference			-0.01			-0.12	
Color word trial ^a							
Treatment n = 19	55.76 (15.30)	50.18 (10.51)	0.43	49.53 (9.65)	0.50	1.56	0.22
Waitlist n = 21	55.50 (12.13)	51.41 (8.78)	0.39	50.26 (8.67)	0.50		
Treatment-control difference			0.04			0.00	
Color word ^a switching trial							
Treatment n = 19	58.82 (9.55)	57.18 (11.12)	0.16	56.63 (8.08)	0.25	1.28	0.29
Waitlist n = 21	58.10 (12.43)	56.14 (11.68)	0.16	56.10 (14.9)	0.15		
Treatment-control difference			0.00			0.10	
Trail making number-letter trial ^a							
Treatment n = 9	63.99 (20.41)	60.68 (23.45)	0.15	54.53 (19.34)	0.48	0.23	0.80
Waitlist n = 21	62.05 (19.36)	59.07 (17.03)	0.16	51.31 (16.22)	0.60		
Treatment-control difference			-0.01			-0.12	

Note: d = Cohen's d. Each d in the table is the within group size of effect reflecting change from baseline at post-treatment, and 2-month follow-up, respectively. The treatment-control difference in effect size is the control group effect size subtracted from the treatment group effect size. Negative or positive signs in front of effect sizes do not affect magnitude of effect (larger integer = greater effect).

^aLower MASQ scores indicate fewer cognitive problems and lower scores for both Color-Word Interference and Trail Making Tests indicate better performance. By contrast, higher QOL-CS scores, CVLT-II, and Digit Symbol-Coding scores indicate clinical improvement.

Satis



- Mean General Satisfaction rating

- 7.0 ($SD = 1.05$; 0 = not at all satisfied; 8 = completely satisfied)

- *compensating* for daily memory failures
($M = 6.7$; $SD = 1.54$)

- *improving* memory ($M = 5.2$; $SD = 1.59$)

(0 = not at all helpful; 8 = completely helpful)

5 Top-rated strategies included:

0 = Not at all helpful; 4 = Completely helpful

1. applied relaxation methods (self-regulation, arousal reduction) **3.6**
2. using a schedule or day planner/organizer
3. verbal rehearsal methods
4. activity pacing and scheduling
5. self-instructional training **3.0**

What were the 3
items you were
assigned to
remember?



Future Directions

- MAAT should be electronic; on line, I-phone based, I-Pad
- Applied to –
 - Other cancer treatments that contribute to cognitive impairment
 - CNS disease-related cognitive impairment

Medications

- dexmethylphenidate (d-MPH; Focalin)
 - N = 152 double-blind placebo control
 - 27.7 mg/day, patients with various cancers (non-CNS)
 - Improvements in fatigue and memory in tx
 - 40.8% headaches; 27.6% nausea
- (Lower, et al., 2005)

Medications

- Modafinil (Provigil)
 - N = 68 Breast cancer survivors double-blind placebo control
 - 22.8 months after chemotherapy
 - Improvements in speed of memory on computerized neurocognitive measure
(Kohli, et al., 2007)

What to do- Certainly eat right and exercise...



What to do

1. Rule out Depression, anxiety disorders
 - If there is a tendency to worry, does anxiety play a large role in coping?
 - If so, consider cognitive-behavioral therapy (CBT)
 - Talk to your PCP or other provider, antidepressant medications such as SSRI's can help

What to do

2. Consider consultation with a neuropsychologist

- Testing may detect problems, but often times not sensitive
- Lengthy and costly
- But can identify other neurological problems if occurring

What to do

3. Consider consultation with psychiatrist for medications such as anafranil or methylphenedate
 - Medications can be a simple solution
 - But side effects are a consideration

What to do

4. Consider consultation with a clinical psychologist
 - Ask about evidence-based practices, usually cognitive-behavioral therapies have good research support
 - Ask if they have experience with treating individuals with cancer
 - If they are familiar with the problem chemotherapy-related cognitive effects

What to do

- On-line:
yourbrainafterchemo.com
- Good books:
 - “Where Did I Leave My Glasses?: The What, When, and Why of Normal Memory Loss” Martha Weinman Lear
 - The Memory Workbook

Questions– please remind me to...

