Does Chemotherapy Influence Cognitive Functioning?

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Importance of Studying Cognitive Decline Secondary to Cancer Therapy

- A challenge facing cancer survivors as identified by the National Coalition for Cancer Survivorship
- Negative impact on work/school performance and QOL
- Informed decision-making
- Similar pediatric research resulted in treatment modifications that reduced negative cognitive effects while maintaining treatment efficacy
- Development of interventions to prevent or treat cognitive decline

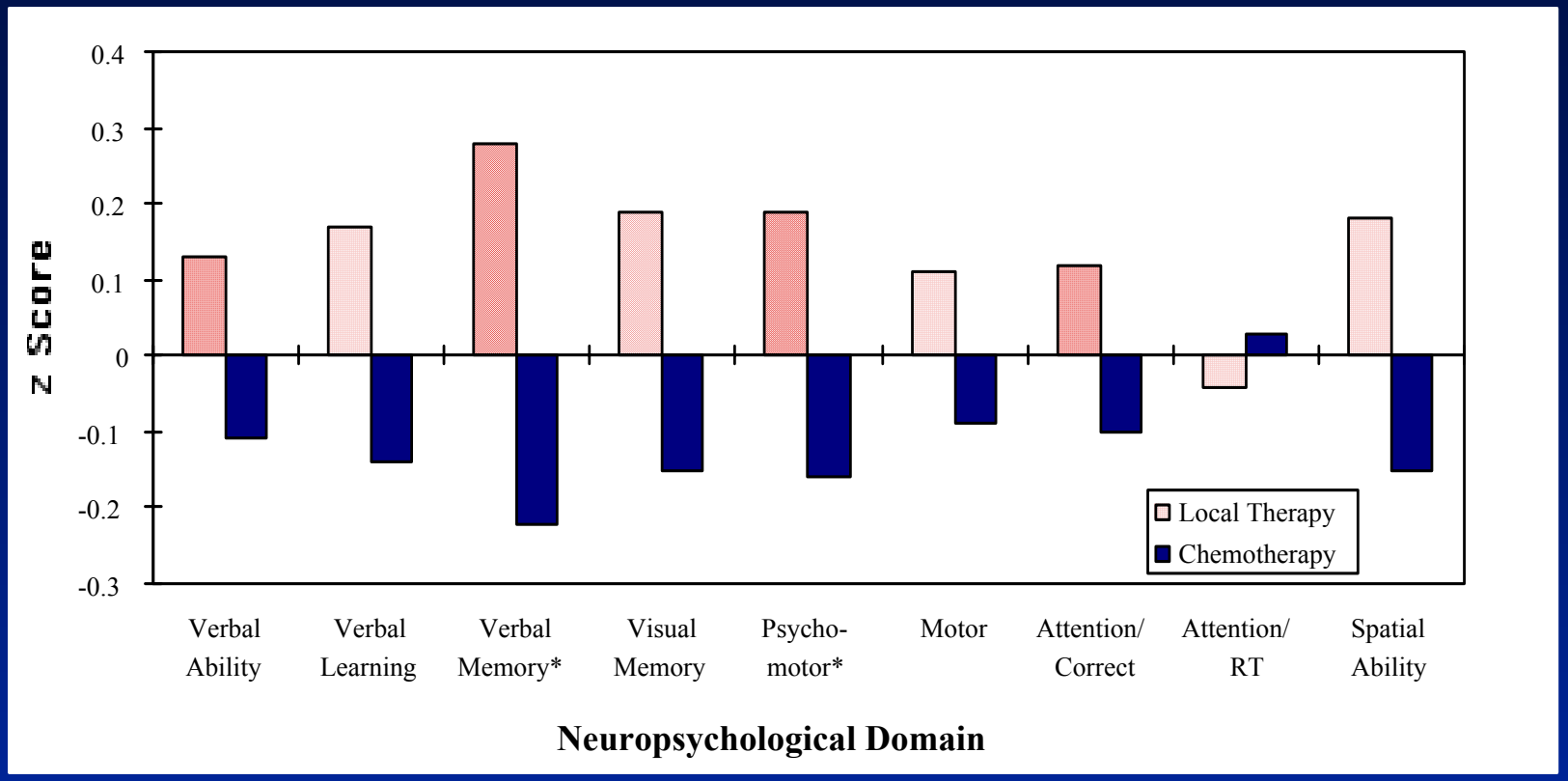
Common Cognitive Problems Reported Post-Chemotherapy

- Memory and Concentration
- Executive Function
- Ability to Learn New Material /Reading Comprehension
- Ability to Work with Numbers

Studies Examining Cognitive Effects of Chemotherapy in Breast Cancer Patients

Study	Diagnosis	Sample Size	Assessment Timing Post-Tx	Chemo-Therapy	Local Therapy
Wieneke & Dienst (‘95)	Breast Ca	28	Ave. 6.6 mo.	75%	N/A
van Dam et al (‘98)	Breast Ca	36 chemo 34 local	Ave. 2 yrs	17%	9%
Schagen et al. (‘99)	Breast Ca	39 chemo 34 local	Median 1.9 yrs	28%	12%
Brezden et al. (‘00)	Breast Ca	Grp A: 31 Grp B: 40 Grp C: 36 (healthy contols	Grp A: After min. of 2 cycles Grp B: Median 2 yrs	Grp A: 48% Grp B: 50% Grp C: 11%	N/A
Ahles et al. (‘02)	Breast Ca & Lymphoma	71 chemo 57 local	Ave. 10 yrs	39%	14%
Tchen et al (03)	Breast CA	100 chemo 100 controls	During chemo	Chemo 16% Controls 4%	N/A

Adjusted z-Transformed Domain Scores for the Chemotherapy vs. Local Therapy Groups



*p<.05, adjusted for age and education

Longitudinal Assessment of Cognitive Functioning

- Importance of pretreatment assessments
- Importance of appropriate controls given the same test battery over similar time frames

Longitudinal Assessment

- 18 breast cancer patients treated with FAC were tested at pretreatment and 1 and 12 months post-treatment
- 33% exhibited cognitive impairment at pretreatment compared to 61% at 1 month post-treatment
- At 1 year, 45% of patients impaired at 1 month demonstrated stable performance 45% improved, and 10% had mixed results

– Wefel et al. (2004)

Dartmouth Longitudinal Cognitive Assessment Study

- Prospective neuropsychological assessment of breast cancer and lymphoma patients treated with systemic chemotherapy or local therapy (and matched healthy controls)
- Assessed prior to treatment, and 1, 6 and 18 months post-treatment

Predictors of Cognitive Deficits

- Type of chemotherapy
- Education level and IQ
- History of traumatic brain injury
- History of learning disability
- Genetic variables
- Hormonal factors

Genetic Factors

- APOE -ε4 has been implicated in cognitive decline associated with cardiac surgery, head trauma, and aging, both normal and with associated chronic illnesses
- APOE-ε4 and cognitive deficits secondary to chemotherapy

Z-Transformed Domain Means by APOE Status

Domains	APOE E4 Positive	APOE E4 Negative	p value*
	Mean (SD)	Mean (SD)	
Visual Memory	-0.30 (1.12)	0.04 (0.81)	0.03
Spatial Ability	-0.38 (1.17)	-0.13 (0.97)	0.05
Psychomotor Function	-0.24 (0.80)	0.05 (0.66)	0.08
Verbal Ability	0.10 (0.68)	-0.16 (0.86)	0.83
Verbal Learning	-0.20 (1.16)	-0.03 (0.94)	0.48
Verbal Memory	0.21 (0.90)	-0.15 (0.89)	0.21
Motor Functioning	-0.01 (0.72)	-0.11 (0.73)	0.93
Attention CR	-0.14 (0.97)	-0.01 (0.87)	0.33
Attention RT	-0.19 (0.69)	-0.05 (0.67)	0.30

*Controlling for age, gender, education, diagnosis, and WRAT-R (reading subset)

Potential Mechanisms

- Reduction in microvascular or neuronal repair processes associated with the APOE -ε4 allele
- Pre-existing morphologic differences (e.g., smaller hippocampal volume) associated with the APOE -ε4 allele

Potential Candidate Gene

- Repair / Plasticity
- Neurotransmitters
- Blood Brain Transporters

Hormones and Cognitive Functioning

- Reduced estrogen and testosterone levels have been associated with cognitive decline
- Chemotherapy and hormonal levels may interact to increase cognitive decline in cancer survivors

Mechanisms

- Vascular injury
- Direct injury to cerebral parenchyma / demyelination
- Immunologic / autoimmune mechanism

Imaging Techniques

- Structural MRI
- Functional MRI
- MR Spectroscopy
- Diffusion Tensor Imaging
- PET

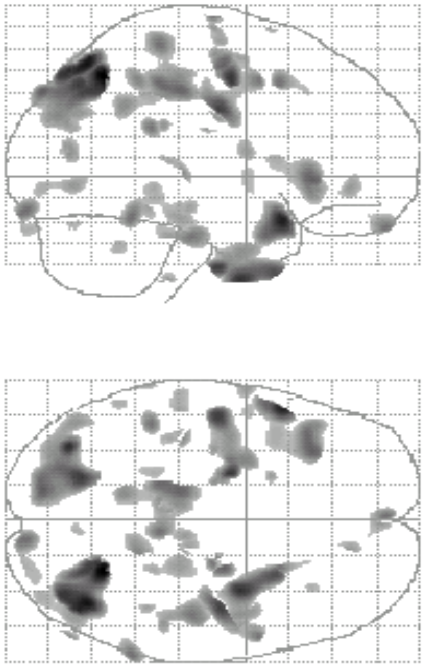
Pilot Study of Structural and Functional MRI in the Assessment of Chemotherapy-Induced Cognitive Problems

- Compared 10 survivors who received chemotherapy to 10 matched healthy controls
- Evidence for structural differences in both gray and white matter

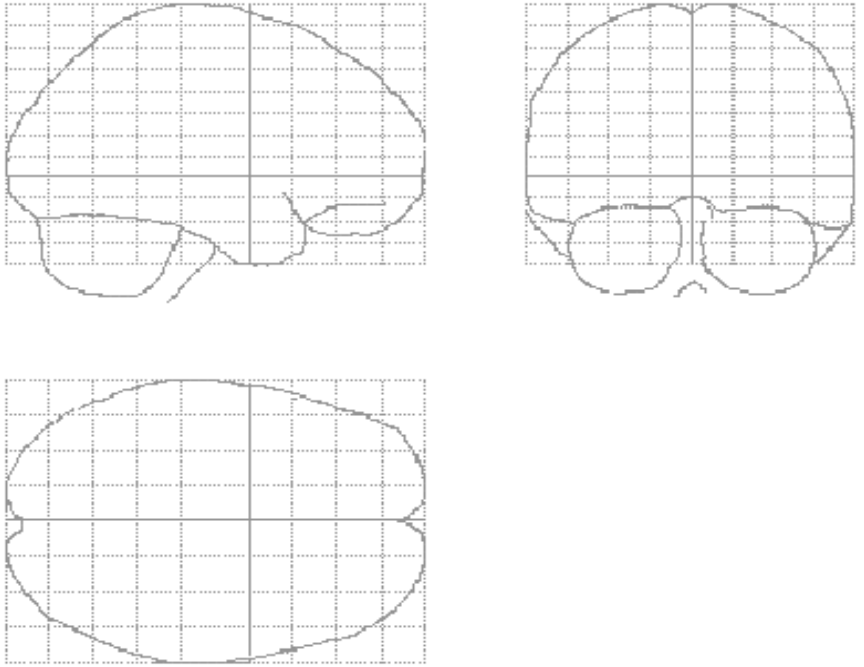
Regions of Local Gray Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

Controls > Chemotherapy

L R



Chemotherapy > Controls



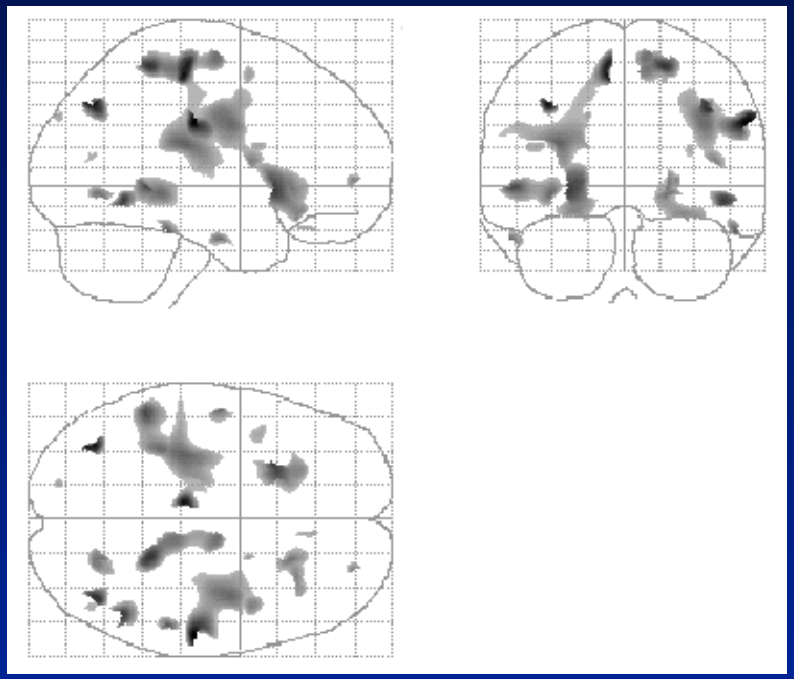
Patients (n=12)
Controls (n=12)

p < .01, k=24

Regions of Local White Matter Volume Reduction in Chemotherapy Treated Cancer Survivors Compared to Healthy Controls on Voxel Based Morphometry

Controls > Chemotherapy

L R



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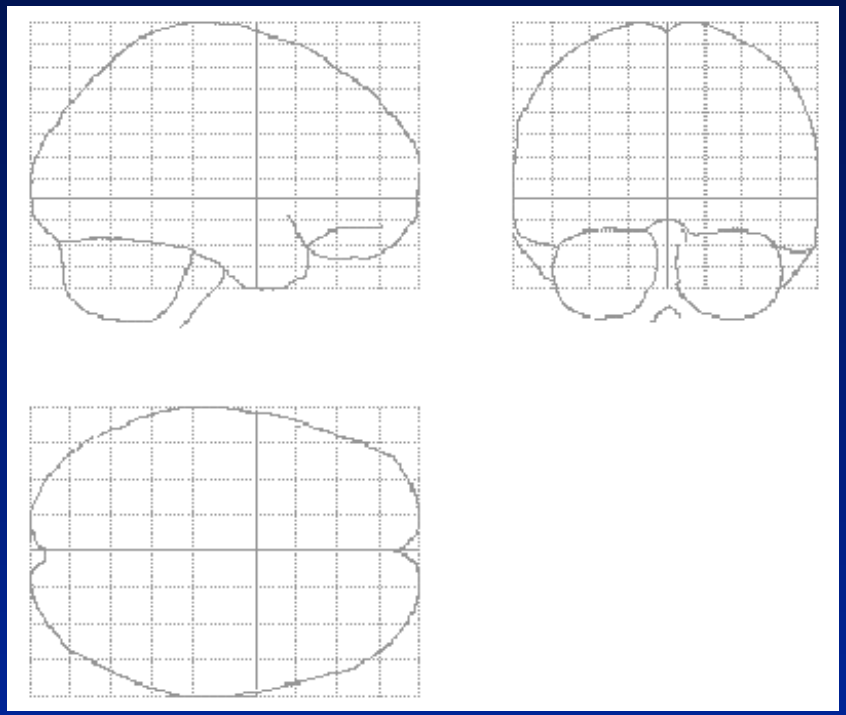

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Controls (n=12)

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Interventions

- Changes in chemotherapy regimens
- Pharmacologic Interventions (erythropoietin, methylphenidate)
- Cognitive Rehabilitation

Summary

- Evidence suggests that cognitive decline can be long-term post-chemotherapy in a subgroup of survivors
- Imaging research suggests that structural and metabolic changes occur in the brain
- Genetic and hormonal factors may be important determinants of vulnerability

Future Directions

- Large scale prospective studies
- Study of factors that increase vulnerability to cognitive decline
- Impact of cognitive changes on QOL
- Use of imaging techniques and development of animal models
- Evaluation of interventions