



Overview of the Effects of Cancer Treatment on Cognitive Impairment in Children

No Conflicts of Interest to Disclose



Cancer Treatment Effects on Cognitive Impairment in Children

- **Neurocognitive function**
 - **Multidimensional concept comprised of domains reflecting a healthy brain**
 - **Attention**
 - **Learning**
 - **Information processing speed**
 - **Visual-spatial skills**
 - **Psychomotor skills**
 - **Executive function**
 - **working memory**
 - **inhibition & self control**
 - **concept formation**
 - **planning & organization**





2018

28-30 JUNE
VIENNA, AUSTRIA

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

What are the Consequences of CNS-Directed Therapy for Children?



Cancer Treatment Effects on Cognitive Impairment in Children

- **Neurodevelopmental and academic problems**
 - Memory
 - Visual spatial abilities
 - fine motor speed
 - attention
 - processing speed
 - academic achievement
- **Common & challenging consequence of CNS-directed treatment**
 - 20 to 60% of ALL survivors
 - 40 to 100% of brain tumor survivors



Cancer Treatment Effects on Cognitive Impairment in Children

- **Secondary consequences on**
 - behavioral adjustment
 - 41% at risk for internalizing problems
 - psychological well being (anxiety, depression)
 - social & adaptive skills
 - vocational success
 - leadership skills
 - independent living
 - quality of life



2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



**Cancer Treatment Effects on
Cognitive Impairment in Childhood ALL**



**One in 330 children diagnosed with cancer
by age 20**

**One in 530 young adults 20 to 39 years of age is a
childhood cancer survivor**

**Most prevalent cancer among children &
adolescents is acute lymphoblastic leukemia
once fatal
5 year survival approaches 90%**



Improved Survival from Childhood ALL

Use of multi-agent chemotherapy

Know risk factors for recurrence

minimal residual disease

treatment intensity matched to recurrence risk

Aggressive CNS-directed treatment for subclinical disease in the brain

primary site of initial disease relapse

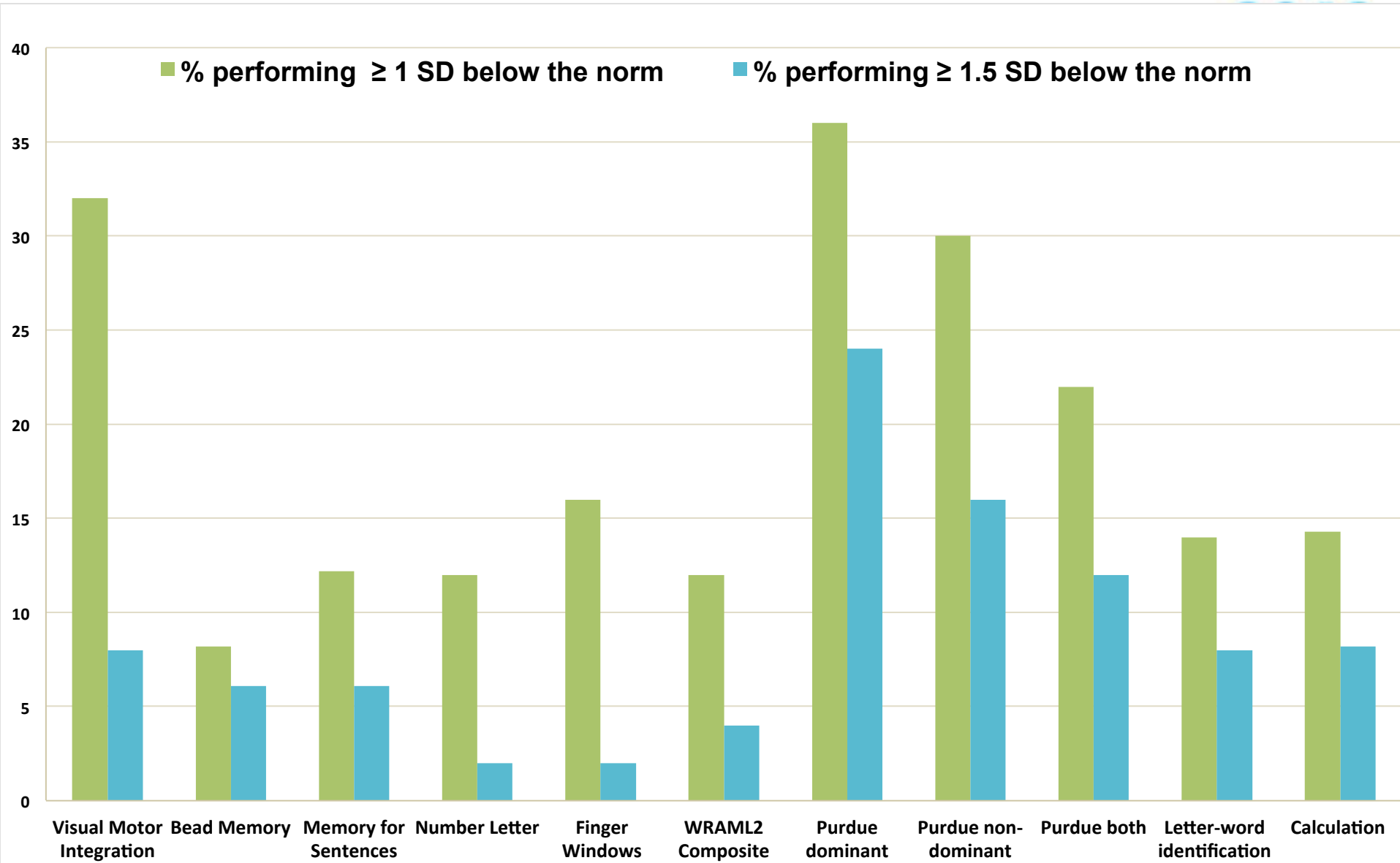


Risk Factors for Treatment-related Cognitive Problems

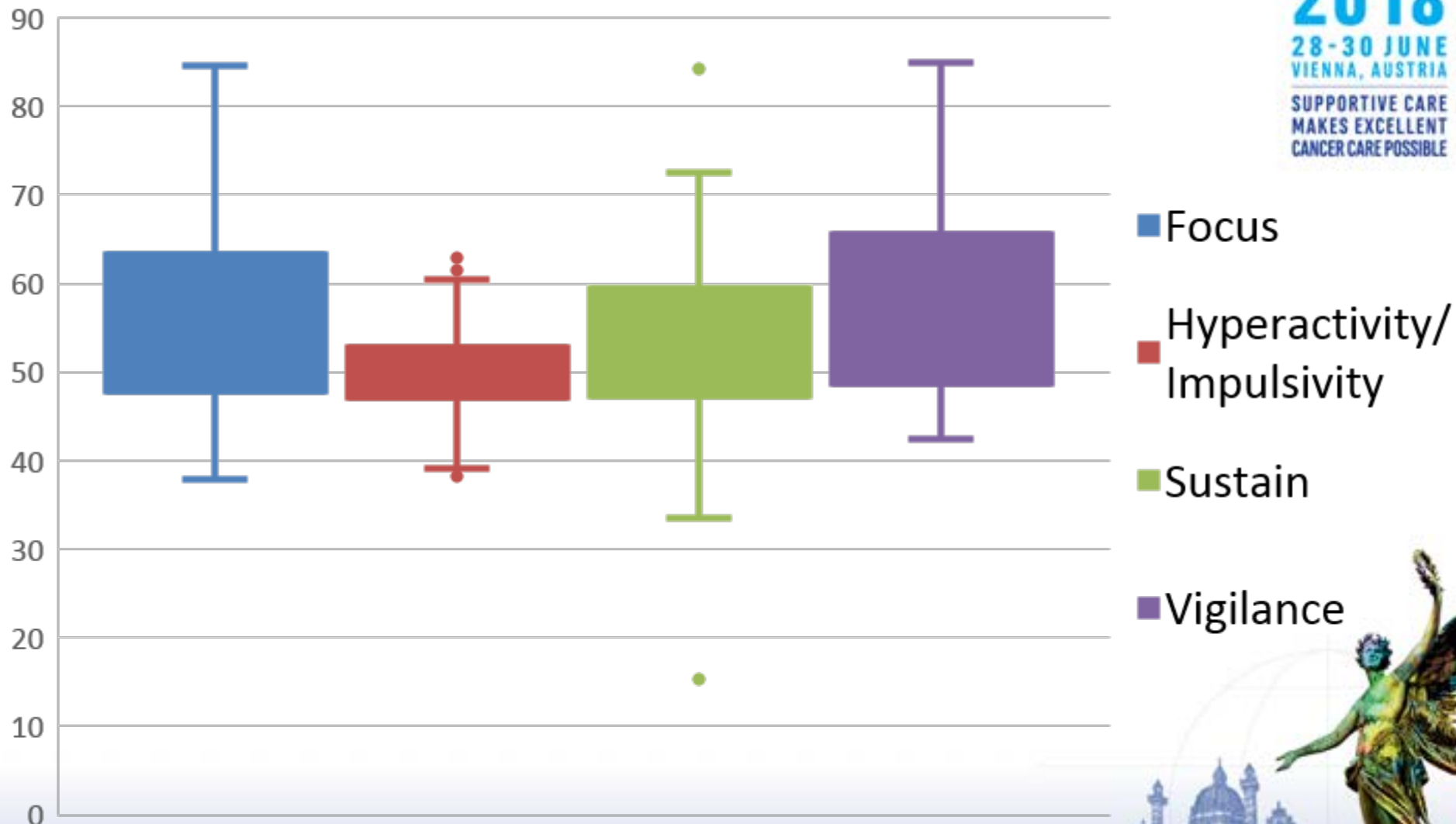
- **Younger age at diagnosis**
 - associated with worse outcomes in some studies
 - Greater decline in verbal working memory among children < 5 years of age at diagnosis
- **Sex differences in rate of development of white matter tracks may → different patterns of cognitive problems**
- **Treatment Intensity**
 - faster rate of decline in visual spatial skills among children treated with intrathecal and intravenous methotrexate compared to those treated with only intrathecal therapy
- **Ethnicity**
 - Hispanic ethnicity robustly associated with neurotoxicity risk after accounting for sex, age at diagnosis, and ALL risk stratification



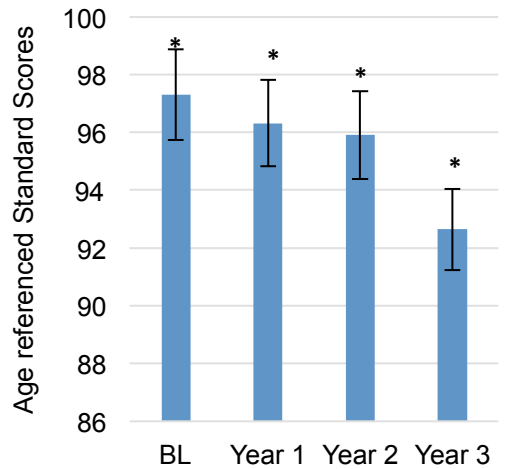
Percent of Subjects Performing 1 or 1.5 Standard Deviation Below Norm



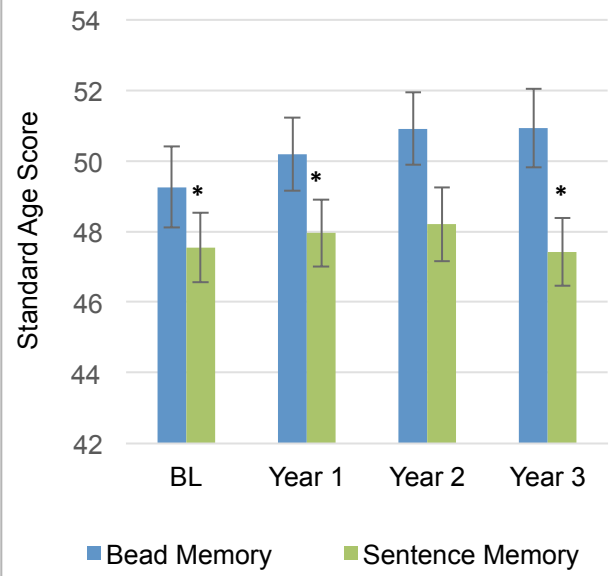
Factors of Attention Score Distribution



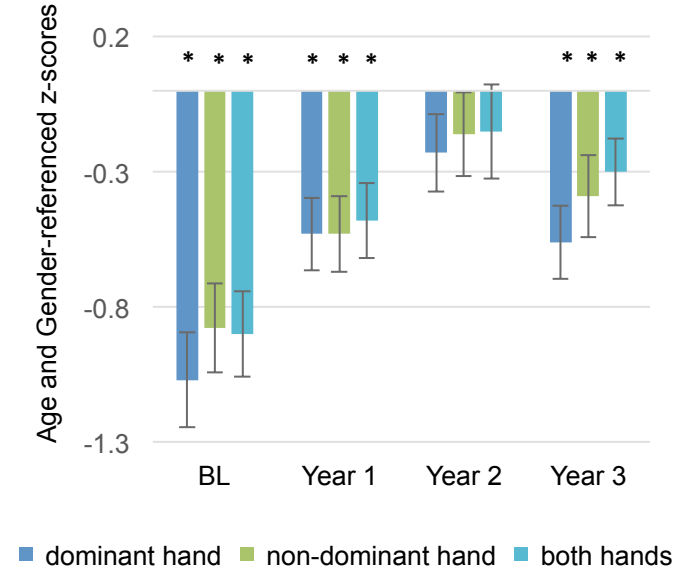
Visual Motor Integration



Short-Term Memory



Fine Motor Dexterity



n = 71; * significantly below age-adjusted norms



Cognitive Abilities Impact Academic Outcomes



| | Visual Motor Integration | Visual Memory | Verbal Memory | Fine Motor Abilities |
|-----------------------------------|---|---|---|---|
| Letter/Word Identification | $r = 0.748$ $p < 0.001$ | $r = 0.624$ $p < 0.001$ | $r = 0.534$ $p < 0.001$ | $r = 0.465$ $p < 0.001$ |
| Calculation | $r = 0.536$ $p < 0.001$ | $r = 0.340$ $p = 0.015$ | $r = 0.321$ $p = 0.020$ | $r = 0.290$ $p = 0.040$ |





2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

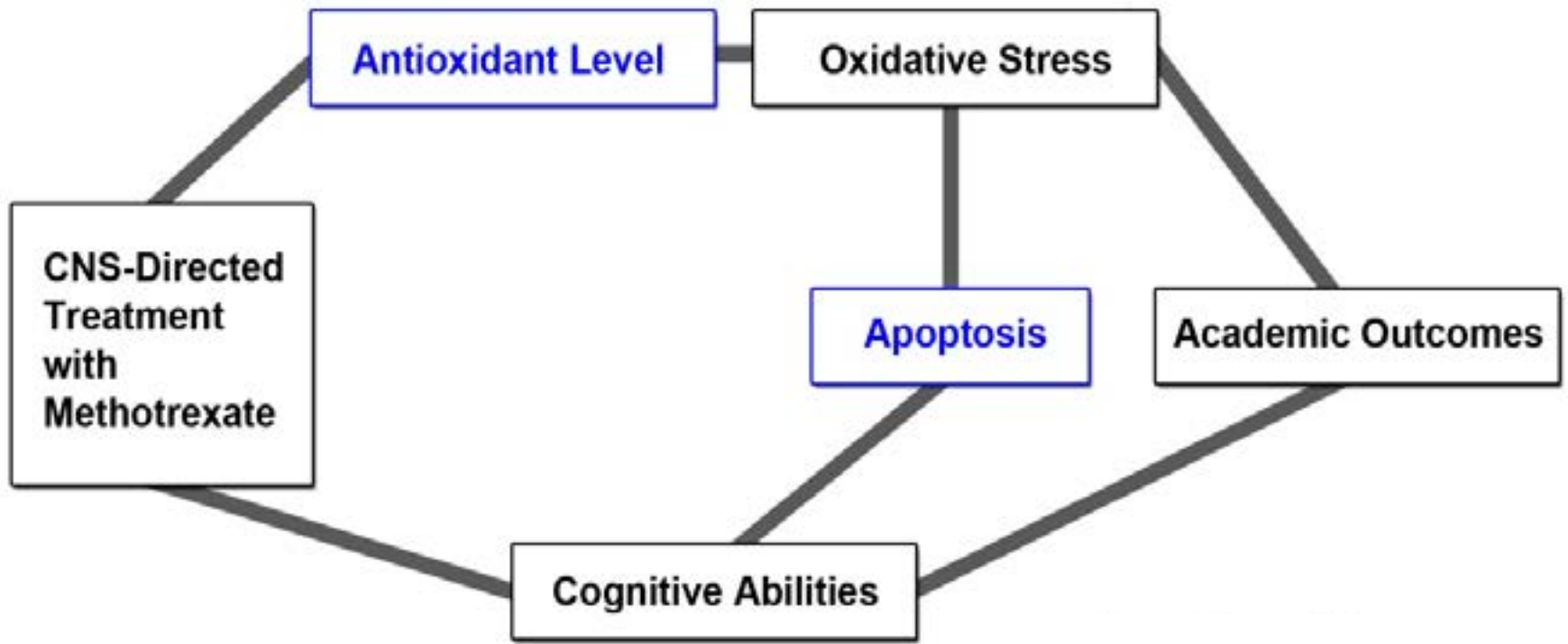
Why do Children with ALL have Long-Term Neurodevelopmental Problems?





2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

CNS Directed Chemotherapy Model of Neurologic Injury: Oxidative Stress & Apoptosis

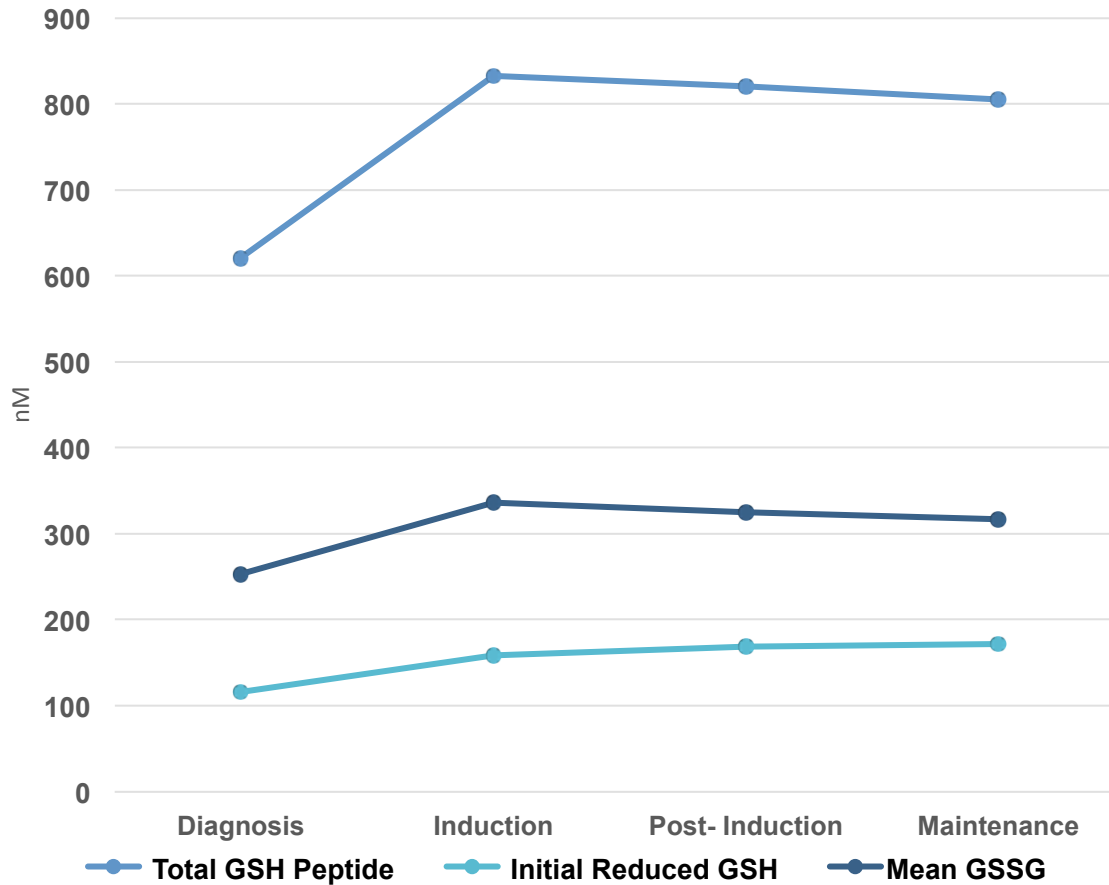


Glutathione (GSH)

- **Predominant anti-oxidant synthesized within cell (cytosol)**
- **Present in**
 - reduced (GSH) form
 - major brain antioxidant
 - oxidized (GSSG) form
- **Ratio of GSH/GSSG normally >100 but can be < 4 during oxidative stress**
- **GSH efflux from cell occurs in response to increase in ROS**



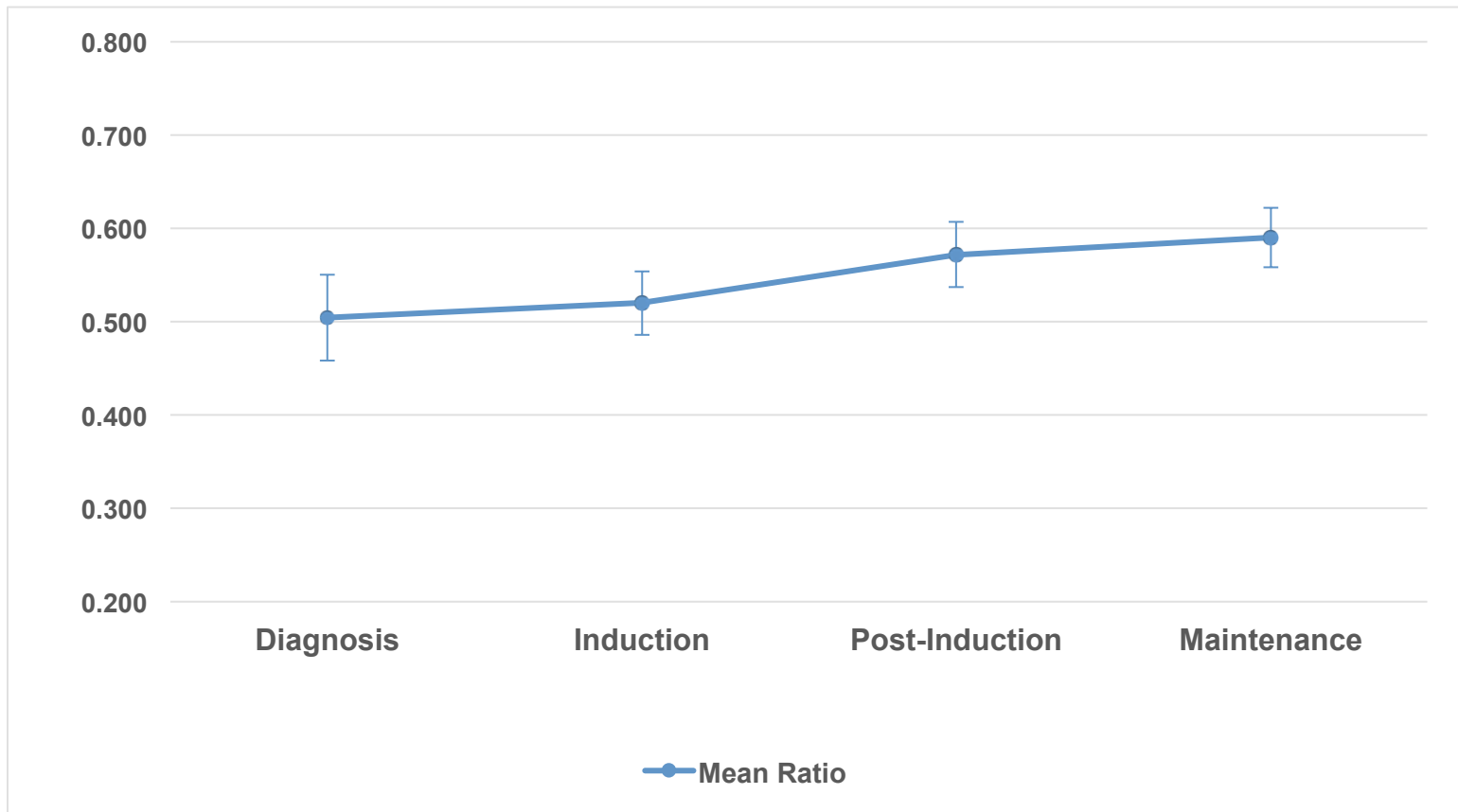
Changes in CSF GSH during CNS Directed Treatment



2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



Glutathione (GSH/GSSG) Ratio over Time



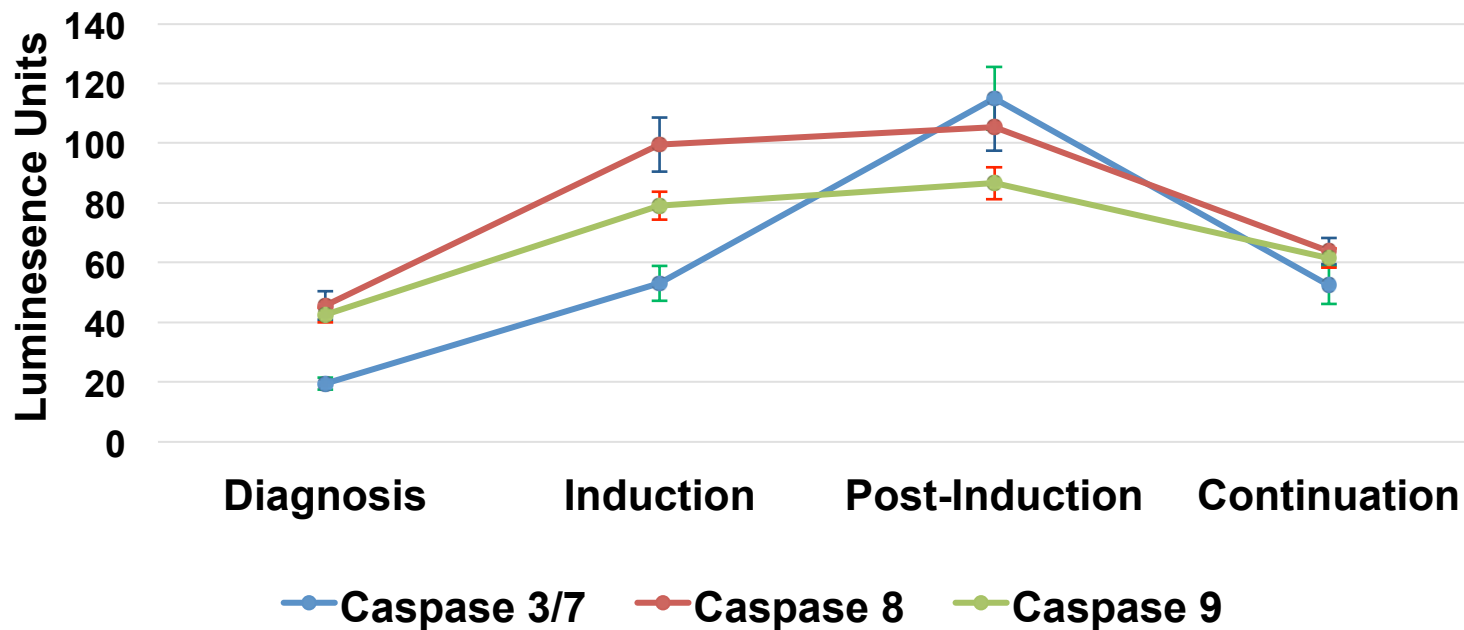
Caspase Enzymes

- **Cysteine-dependent aspartate-specific protease enzymes**
 - 14 have been identified
- **Initiate or execute apoptosis**
 - caspase 8 (extrinsic pathway)
 - caspase 9 (intrinsic pathway)
 - both activate caspase 3
- **Caspase 3 and 7 execute apoptotic cell death**



CSF Caspase Activity by Treatment Phase


2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



Caspase 3/7 is Associated with Cognitive Abilities at End of Treatment



| Mean Caspase 3/7 | Beery VMI | Bead Memory | Sentence Memory | WRAML2 attention/concentration | WRAML2 finger window | WRAML2 number letter |
|-----------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Induction | r = -.354 p = 0.006 | r = -.430 p = 0.001 | r = -.381 p = 0.003 | r = -.330 p = 0.010 | r = -.144 p = 0.158 | r = -.274 p = 0.027 |
| Post Induction | r = -.41 p = 0.002 | r = -.189 p = 0.097 | r = -.290 p = 0.022 | r = -.324 p = 0.011 | r = -.248 p = 0.041 | r = -.196 p = 0.087 |

Active GSH export from the cell an early event in apoptosis through intrinsic or extrinsic pathways
Increase in extracellular GSH initiating event for caspase activation
Increases in caspase 8 (extrinsic pathway) and caspase 9 (intrinsic pathway) activity activates caspase 3/7





2018

28-30 JUNE
VIENNA, AUSTRIA

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Can Cognitive and Academic Abilities be Preserved in Children with ALL?



Improving Academic Outcomes: Math Intervention

Determine if
Math
Intervention
prevents
declines in
academic
math scores
in children
with ALL



2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

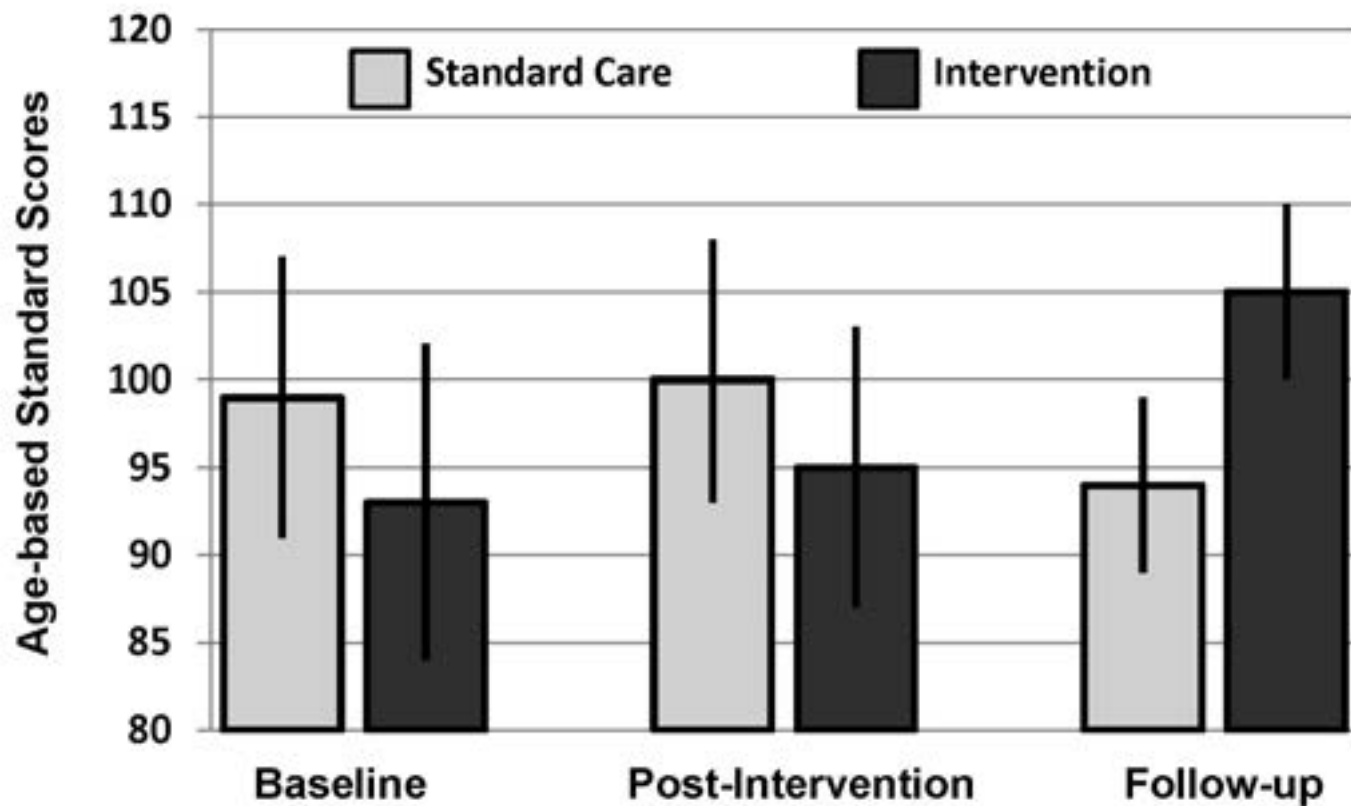


Improving Academic Outcomes: Math Intervention

- Children consented after diagnosis confirmed and therapy initiated
- Random assignment to intervention or standard care
- Neurocognitive evaluations completed for all subjects at baseline, post-intervention and 12 months later
- Children in intervention group received 40 hours of math enhancement skills using a “multiple representations” approach over 12 months
- Parents of children in both groups received feedback on child’s neurocognitive evaluation performance



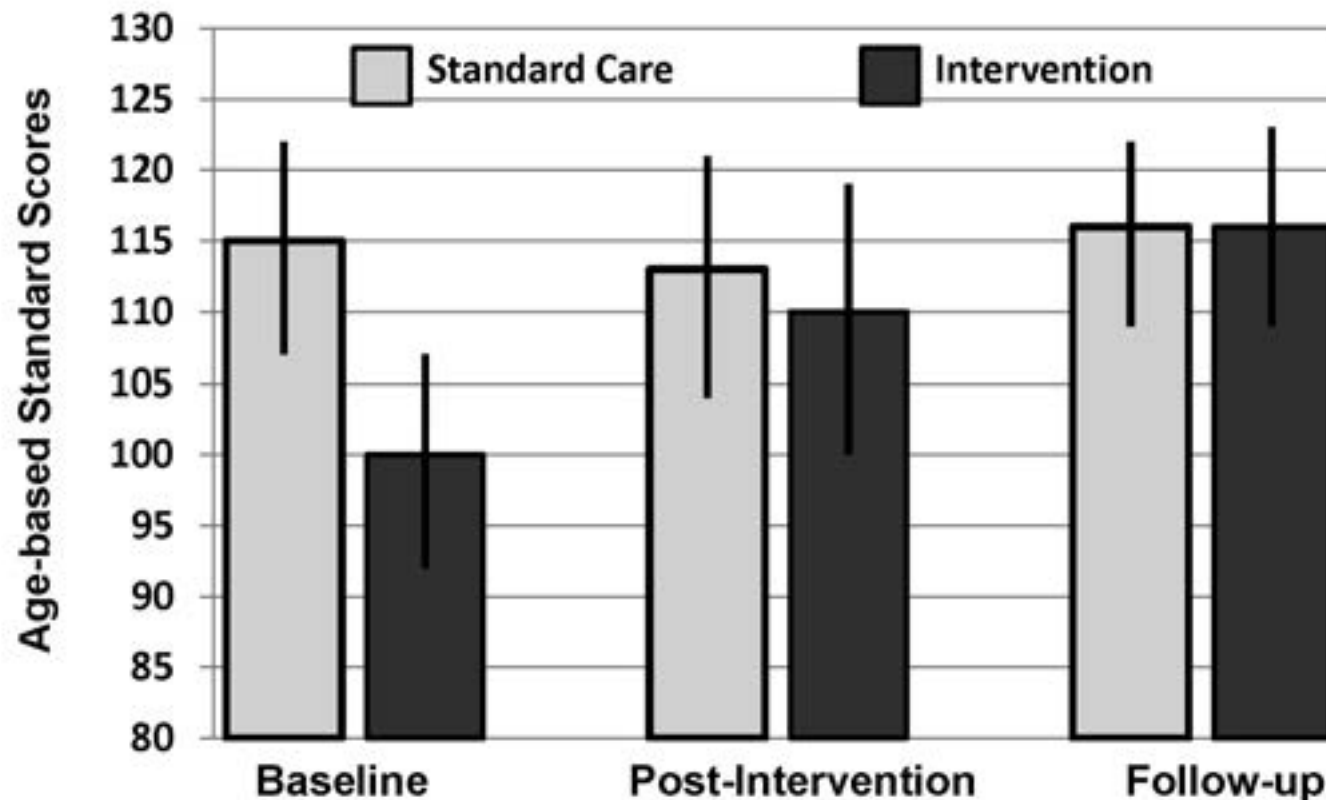
Change over Time in Nonverbal Working Memory



$F [2, 29] = 5.53, p < =.009$



Change over Time in Applied Mathematical Problem Solving Skills



Significant group by time interaction
 $F [2, 29] = 12.47, p < 0.001$


2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



| | | | |
|------------------------|--|---|--|
| <p>Conklin, et al.</p> | <p>Investigate efficacy and adverse effects of methylphenidate (MPH) among survivors of ALL or a brain tumor with learning impairment.</p> | <p>Childhood cancer survivors (n = 122) treated with chemotherapy and/or CNS-directed radiation</p> | <p>Therapeutic effect of MPH relative to placebo significant only for the ink naming time of the Stroop Word-Color Association Test</p> |
| <p>Butler, et al.</p> | <p>Test Cognitive Remediation Program (CRP) efficacy on academic achievement, brief focused attention, working memory, memory recall, and vigilance</p> | <p>Survivors of a childhood malignancy (n = 161) that involved CNS disease and/or treatment to the CNS</p> | <p>Significant improvement in academic achievement; modest effect size; subjects in intervention group incorporated more metacognitive strategies and manifested improved attention (parent report)</p> |





2018

28-30 JUNE
VIENNA, AUSTRIA

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

| | | | |
|----------------------|--|--|--|
| Patel, et al. | Evaluate an intervention teaching compensatory learning and problem solving skills to improve cognitive, academic, and social functioning | Children (n = 12; 6 males and 6 females) treated with CNS-directed therapy for brain tumors (9), leukemia (2) or CNS histiocytosis (1). | Statistically significant improved scores on the WJR Writing Samples standard score and the Social Skills Rating System standard score. Scores on all measures changed approximately ½ SD indicating improved performance |
| Hardy, et al. | Pilot test a computerized cognitive training program for feasibility, acceptability, and effect on attention and working memory | Survivors (n = 9) of ALL (3) or brain tumors (6) between 10 and 17 years of age | Significant increase in Digit-Span Forward subscale of the working memory index and significant decrease in Cognitive Problems Index (parent report) |



Conclusions/Future Directions

- **Apoptosis and oxidative stress have a role in CNS treatment-related neurologic injury**
- **Caspase enzymes serve as a biomarker of neurocognitive decline**
- **Potential efficacy of behavioral neuro-protective interventions**
- **Growing evidence for “accelerated aging” in some pediatric cancer survivors.**
- **Could cognitive decline represents an accelerated aging cognitive aging phenotype?**



2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



Co-Investigators/Collaborators

University of Arizona

Kari Koerner, MPH
Kathie Insel, PhD
Patricia Gundy, MS
Susie Whitman
David Montgomery, PhD
Alice Pasvogel, PhD

Baylor College of Medicine

Lynnette Harris, PhD
Kristin Adkins, MS
Olga Taylor, BS

Duke School of Nursing
Marilyn Hockenberry, PhD

Funding

R01 NR010889-01A1 National Institute for Nursing Research
R01 04905 National Institute of Nursing Research
Alex's Lemonade Stand Foundation Discovery Award

