Cognitive Function in Survivors of Breast Cancer After Chemotherapy

2018
28-30 JUNE
VIENNA, AUSTRIA
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Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

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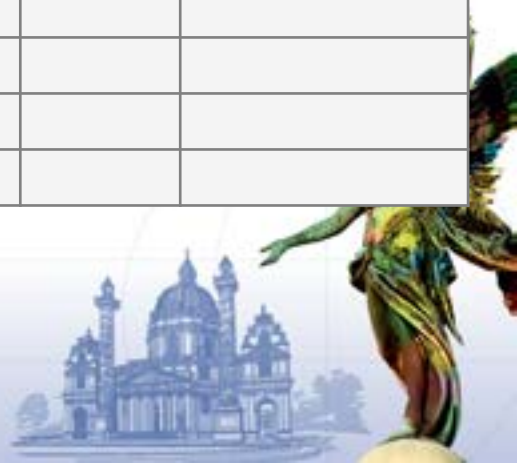

Definitions

- Terms
  - Cancer-related cognitive impairment (CRCI)
  - Chemotherapy-related cognitive impairment
  - “Chemobrain”, “chemofog”

- Problem Areas
  - Visual and verbal memory, learning, concentration, attention, processing ability, executive function, language

Ahles et al., 2018, Annu Rev Clin Psychol

Examples of CRCI

- Trouble with details like names, events, dates
- Trouble with learning new things
- Trouble remembering common words - word is on the ‘tip of the tongue.’
- Trouble remembering things you usually have no trouble recalling like directions
- Trouble focusing on tasks and taking longer to accomplish a task
- Trouble with multi-tasking (at work, at home)

Adapted from ACS, www.cancer.org, 2018

Severity of CRCI

- Mild cognitive impairment: typically a range of -1.5 to -2 standard deviations below population normative scores on standardized cognitive assessments
- CRCI: Generally mild to moderate in nature
- The **pre-treatment (baseline)** level of cognitive function is important for determining **clinically meaningful declines** that are more subtle in cancer patients
  (Wefel et al., 2004, Wefel et al., CA, 2015)

Overall Impact of CRCI

- Negative impact on quality of life and activities of daily living
  (Reid-Ardnt et al., 2010, Psycho-Oncology; Van Oh et al., 2013, Eur J Oncol Nurs; Selamat et al., 2014, PLOS One; Klemp et al., 2018, Support Care Cancer)
- Negative impact on performance in school/work
  (Wefel et al., 2004, Cancer; Van Oh et al., 2018, J Cancer Surviv.)
- Impaired social functioning
  (Reid-Arndt et al., 2009, J Psychoc Oncol.)
- Related to mortality risk
  (Hshieh et al., 2018, JAMA Oncol.)

Who and When?

- **Breast cancer** (most studies)
- Colorectal cancer
- Prostate cancer
- Hematologic malignancy
- Testicular cancer
- Ovarian cancer
- Multiple myeloma

- **Chemotherapy** (most studies)
- Radiation
- Hormone therapy
- Stem cell transplant

Selected References: van Dam et al., 1998, JNCI; Brezden et al., 2000, JCO; Ahles et al., 2002, JCO; Wefel et al., 2004, Cancer; Schagen et al., 2006, JNCI; Bender et al., 2006, Psycho-oncol; Wefel et al., 2011, Cancer; Koppelmans et al., 2012, JCO; Correa et al., 2012, Gynecol Oncol; Jones et al., 2013, Cancer; Ahles et al. 2012, JCO; Ganz et al., 2014, JCO; Hurria et al., 2014, Clin Breast Cancer; Vardy et al., 2015, JCO; Bender et al., 2015; Mandelblatt et al., 2014 JCO, Lange et al., 2016 Oncologist; Merriman et al., 2017, Janelsins et al., 2017, JCO; Sharafeldin N et al., 2018

Current Data on the Trajectory of CRCI Related to Chemotherapy in Patients with Solid Tumors

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• Post Surgery	• 30-40%	• TMT • COWA • HVLT-R • Computerized measures • Self-report (FACT-Cog)
• During Chemotherapy	• 40-80%	
• Post Chemotherapy	• 50-60%	
• Short-term follow-up (6 mo – 1 yr)	• 40-56%	
• Long-term follow-up (1 yr+)	• 35%	

Selected References: van Dam et al., 1998, JNCI; Brezden et al., 2000, JCO; Ahles et al., 2002, JCO; Wefel et al., 2004, Cancer; Schagen et al., 2006, JNCI; Bender et al., 2006, Psycho-oncol; Wefel et al., 2011, Cancer; Koppelmans et al., 2012, JCO; Oncol; Ahles et al. 2012, JCO; Ganz et al., 2014, JCO; Vardy et al., 2015, JCO; Mandelblatt et al., 2014 JCO, Lange et al., 2016 Oncologist; Janelsins et al., 2017, JCO

Study Aims

- Primary and secondary aims
  - To determine the longitudinal change in cognitive function in breast cancer patients compared to controls from pre- to post-chemotherapy and from pre-chemotherapy to six months post-chemotherapy.

- Exploratory aims
  - To identify demographic, biologic, psychologic, and clinical risk factors of cognitive decline.

Longitudinal Cognitive Study in Breast Cancer and Lymphoma Patients and Age- and Gender-Matched Controls (N=1,432)

PI: Janelsins

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Assessment 1 (Within 7 days prior to 1st chemotherapy)	**Assessment 2** (Within one month post-chemotherapy)	**Assessment 3** (At six months following Assessment 2)	**Assessment 4** (At 1 year following Assessment 2)	**Assessment 5** (At 2 years following Assessment 2)
All study subjects	All study subjects	All study subjects	200 patient sub-study	200 patient sub-study
Neuropsychological Assessment	Neuropsychological Assessment	Neuropsychological Assessment	Neuropsychological Assessment	
Self Report	Self Report	Self Report	Self Report	Self Report
Blood collection for cytokine and genetic analyses	Blood collection for cytokine and genetic analyses			

Longitudinal Cognitive Study in Female Breast Cancer Patients and Age-Matched Controls (N=945)

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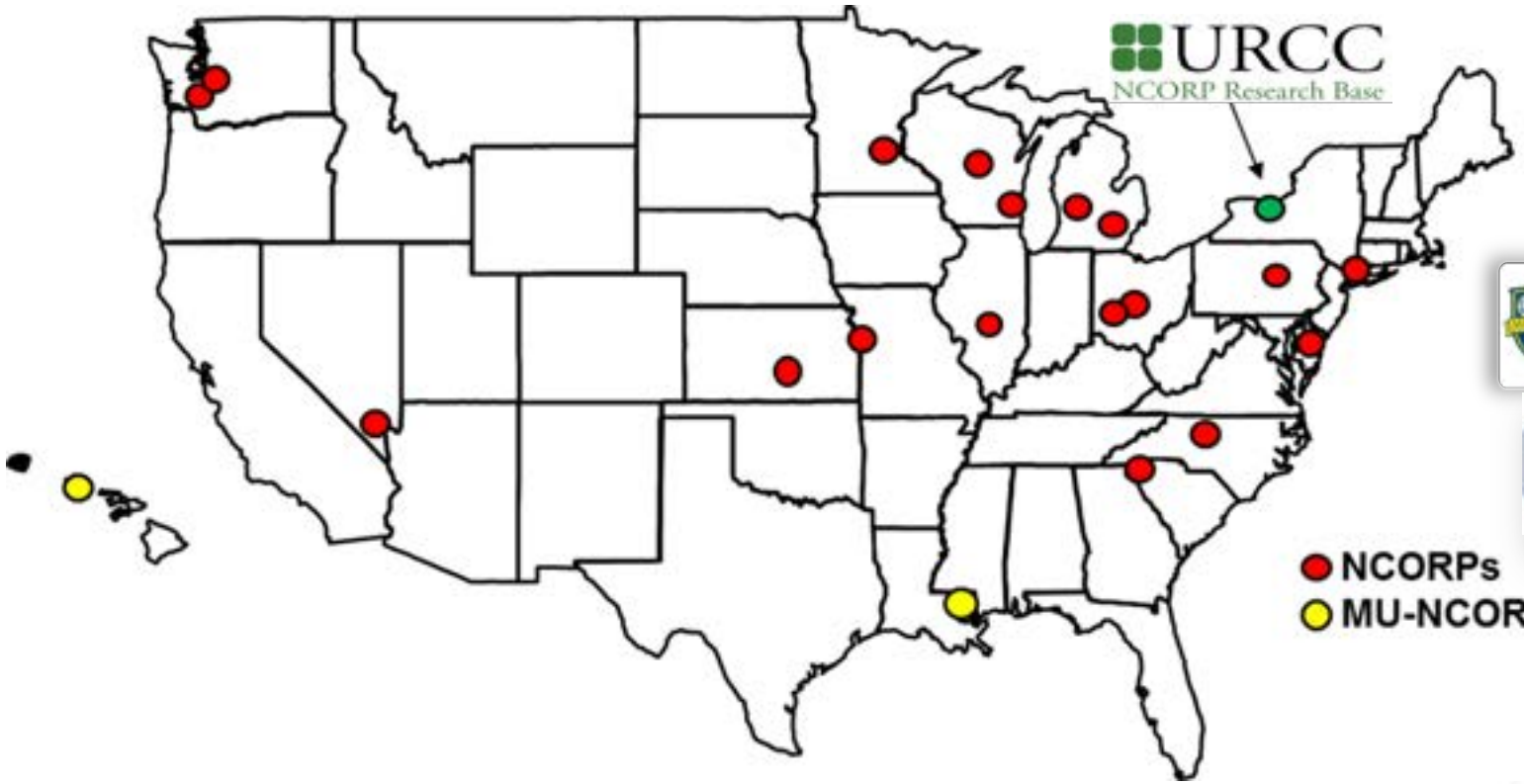
Assessment 1 (Within 7 days prior to 1st chemotherapy)	**Assessment 2** (Within one month post-chemotherapy)	**Assessment 3** (At six months following Assessment 2)
Breast cancer and control subjects	Breast cancer and control subjects	Breast cancer and control subjects
Neuropsychological Assessment	Neuropsychological Assessment	Neuropsychological Assessment
Self Report	Self Report	Self Report
Blood collection for cytokine and genetic analyses	Blood collection for cytokine and genetic analyses	

NCI Community Oncology Research Program



Aurora NCORP, Cancer Research Consortium of West Michigan, Columbus NCORP, Dayton Clinical Oncology Program, Delaware/Christiana Care NCORP, Geisinger Cancer Institute NCORP, Greenville NCORP of the Carolinas, Gulf South NCORP, Hawaii MU NCORP, Heartland Cancer Research NCORP, Kansas City NCORP, Metro-Minnesota NCORP, Michigan Cancer Research Consortium, Nevada Cancer Research Foundation NCORP, Northwell NCORP, Northwest NCORP, Pacific Cancer Research Consortium, SCOR NCORP, Wichita NCORP, Wisconsin NCORP

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Eligibility

Breast Cancer Patient Inclusion:

- Females with invasive non-metastatic breast cancer (stage I-IIIC)
- Be chemotherapy naïve and scheduled to begin a course of chemotherapy
- 21 years of age or older

Breast Cancer Patient Exclusion:

- No major psychiatric illness requiring hospitalization
- No neurodegenerative disease or any CNS disease
- Not to receive concurrent radiation during chemotherapy
- Must not be pregnant

Controls: same age (±5 years) and meet the same (applicable) eligibility criteria

Baseline Characteristics

Attribute	Characteristic	Statistic	All (%) (N=945)	Breast Cancer/ Chemotherapy (N=581)	Non-Cancer Control (N=364)	P Value
Age		Mean	53.1	53.4	52.6	p=0.167
		SE	0.34	0.44	0.54	
		Range	[22-81]	[22-81]	[27-81]	
Race	Black	N	64 (6.8%)	47 (8.1%)	17 (4.7%)	p=0.017
	Other	N	20 (2.1%)	16 (2.8%)	4 (1.1%)	
	White	N	861 (91.1%)	518 (89.1%)	343 (94.2%)	
Ethnicity	Hispanic or Latino	N	12 (1.3%)	7 (1.2%)	5 (1.4%)	p=0.999
	Not Hispanic or Latino	N	920 (97.3%)	566 (97.4%)	354 (97.3%)	
	Unknown	N	13 (1.4%)	8 (1.4%)	5 (1.3%)	
Education	<8thGrade	N	1 (0.1%)	1 (0.2%)	0 (0%)	P<0.001
	Some High School	N	10 (1.1%)	10 (1.7%)	0 (0%)	
	HSGED	N	174 (18.4%)	131 (22.5%)	43 (11.8%)	
	Part College	N	351 (37.2%)	194 (33.4%)	157 (43.1%)	
	College	N	248 (26.2%)	140 (24.1%)	108 (29.7%)	
	Graduate	N	161 (17.0%)	105 (18.1%)	56 (15.4%)	
Marital Status	Widowed	N	45 (4.8%)	28 (4.8%)	17 (4.7%)	p=0.276
	Divorced	N	106 (11.2%)	69 (11.9%)	37 (10.2%)	
	Separated	N	20 (2.1%)	17 (2.9%)	3 (0.8%)	
	Single	N	75 (7.9%)	45 (7.8%)	30 (8.2%)	
	Long term relationship	N	43 (4.5%)	28 (4.8%)	15 (4.1%)	
	Married	N	656 (69.4%)	394 (67.8%)	262 (72.0%)	
Menopausal Status	Pre-Menopausal	N	287 (30%)	182 (31.3%)	105 (28.9%)	p=0.136
	Peri-Menopausal	N	88 (9.3%)	45 (7.7%)	43 (11.8%)	
	Post-Menopausal	N	481 (51%)	303 (52.2%)	178 (48.9%)	
	Medically-Induced	N	89 (9.4%)	51 (8.8%)	38 (10.4%)	

Janelsins et al., 2017 JCO

Baseline Characteristics

Attribute	Characteristic	Statistic	Breast Cancer/ Chemotherapy (N=581)
Stage of Disease	Stage 1	N	158 (27.2%)
	Stage 2	N	285 (49.1%)
	Stage 3	N	108 (18.6%)
	Unknown	N	30 (5.1%)
Chemotherapy	Anthracycline	N	279 (48.0%)
	Non-Anthracycline	N	302 (52.0%)
Radiation Therapy (A2 to A3)*	Yes	N	287 (57.5%)
	No	N	205 (41.3%)
	Unknown	N	13 (2.6%)
Hormone Therapy (A2 to A3)*	Yes	N	172 (34.0%)
	No	N	324 (64.2%)
	Unknown	N	9 (1.8%)

*N from A2 to A3 = 505

Janelsins et al., 2017 JCO

Cognitive Complaints in Female Breast Cancer Patients and Age-Matched Controls (N=945)

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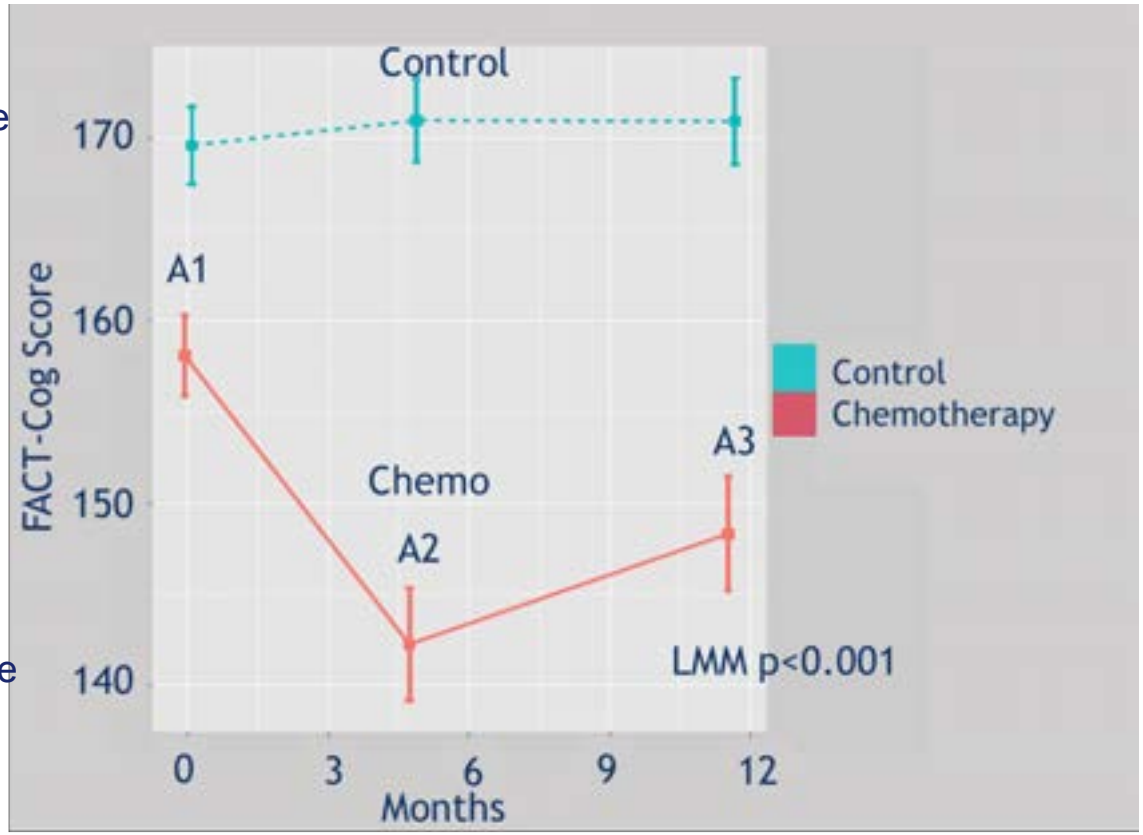
Better Cognitive Function

Worse Cognitive Function



- Anxiety
- Depression
- Cognitive Reserve

Controlled for: age, education, race, menopausal status, and baseline reading ability, anxiety, and depression

Janelsins et al., 2017 JCO

Prevalence of Clinically Meaningful CRCI

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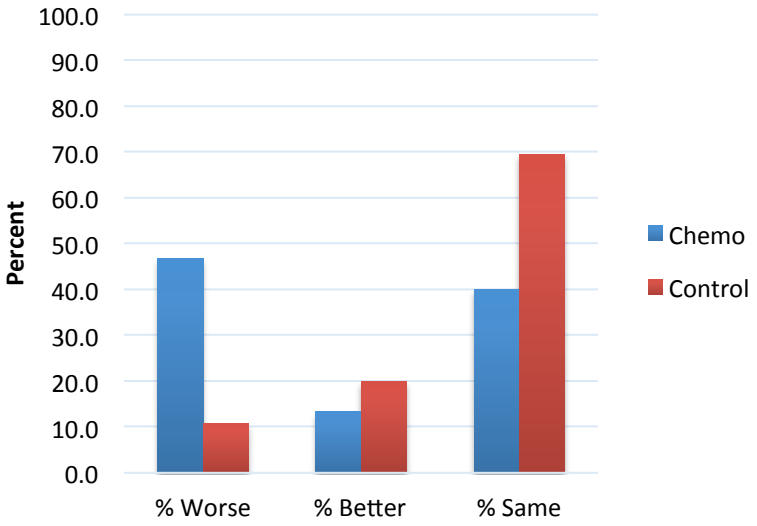
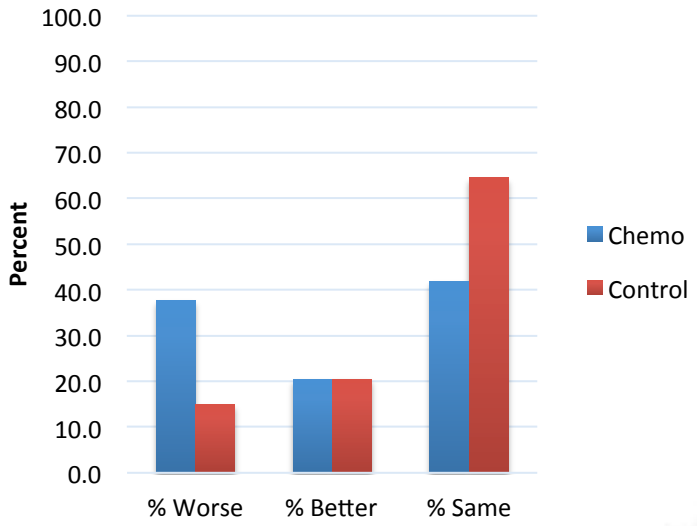
- Pre- to post-chemotherapy*



- Pre-chemotherapy to 6 months post-chemotherapy*



*p<0.001

Janelsins et al., 2017 JCO

Trajectory of CRCI

Domain and Test	Directionality of Better Score	Chemotherapy (A1) - Control (A1)	p value	Chemotherapy (A2-A1) – Control (A2-A1)	p value	Chemotherapy (A3-A1) - Control (A3-A1)	p value
		Adjusted β (SE)		Adjusted β (SE)		Adjusted β (SE)	
Memory							
CANTAB Delayed Match to Sample Visual Memory (Primary)	higher	1.08 (1.21)	0.373	0.76 (1.44)	0.597	**-3.81 (1.59)**	**0.017**
CANTAB Verbal Recognition Memory	higher	0.13 (0.12)	0.277	**-0.40 (0.13)**	**0.003**	0.09 (0.13)	0.480
CANTAB Verbal Recognition Memory	higher	0.12 (0.15)	0.432	-0.14 (0.20)	0.505	-0.03 (0.20)	0.895
Hopkins Verbal Learning Test-Revised Immediate Recall	higher	0.12 (0.10)	0.244	-0.03 (0.09)	0.738	0.07 (0.09)	0.453
Hopkins Verbal Learning Test-Revised Delayed Recall	higher	-0.02 (0.15)	0.920	-0.05 (0.12)	0.691	0.12 (0.13)	0.369
Attention							
CANTAB Rapid Visual Processing Speed	higher	**-3.11 (0.53)**	**0.039**	-1.12 (0.68)	0.098	**-2.44 (0.70)**	**<0.005**
Trail Making Test-A	lower	-0.01 (0.01)	0.433	**0.02 (0.01)**	**0.039**	0.02 (0.01)	0.059
Executive Function							
CANTAB One touch stockings of Cambridge	lower	-0.01 (0.02)	0.066	0.02 (0.02)	0.310	0.004 (0.02)	0.810
Controlled Oral Word Association	higher	0.25 (0.23)	0.285	**-0.80 (0.16)**	**<0.005**	-0.19 (0.19)	0.318
Trail Making Test-B	lower	**-0.03 (0.01)**	**0.030**	0.02 (0.01)	0.119	0.01 (0.01)	0.380

Controlled for: age, education, race, reading (cognitive reserve), anxiety, depression

Janelsins et al., In Revision

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Longitudinal Trajectory of Cancer-Related Cognitive Impairment: Visual Memory (CANTAB DMS)

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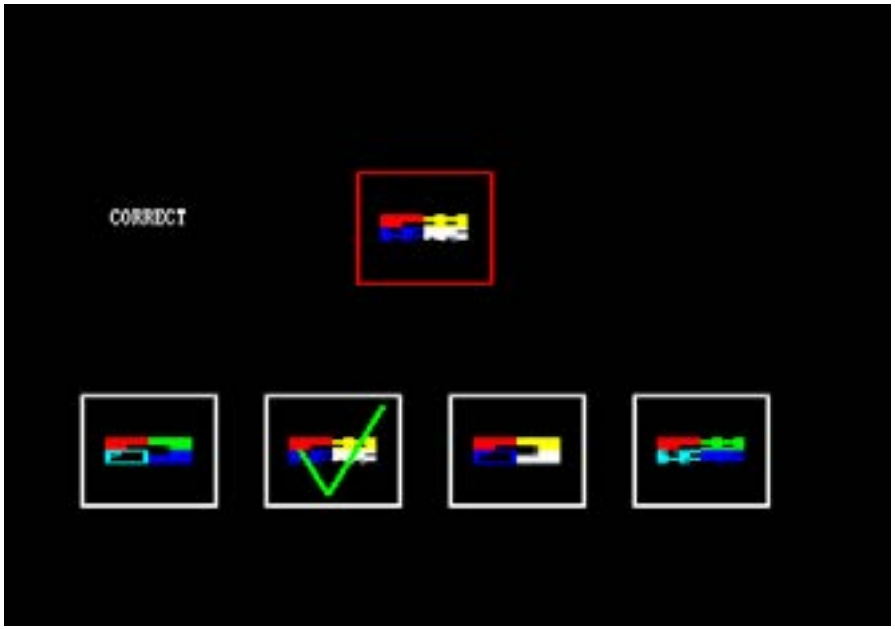

0, 4, 12 second delays

Longitudinal Trajectory of Cancer-Related Cognitive Impairment: Visual Memory (CANTAB DMS; N=943)

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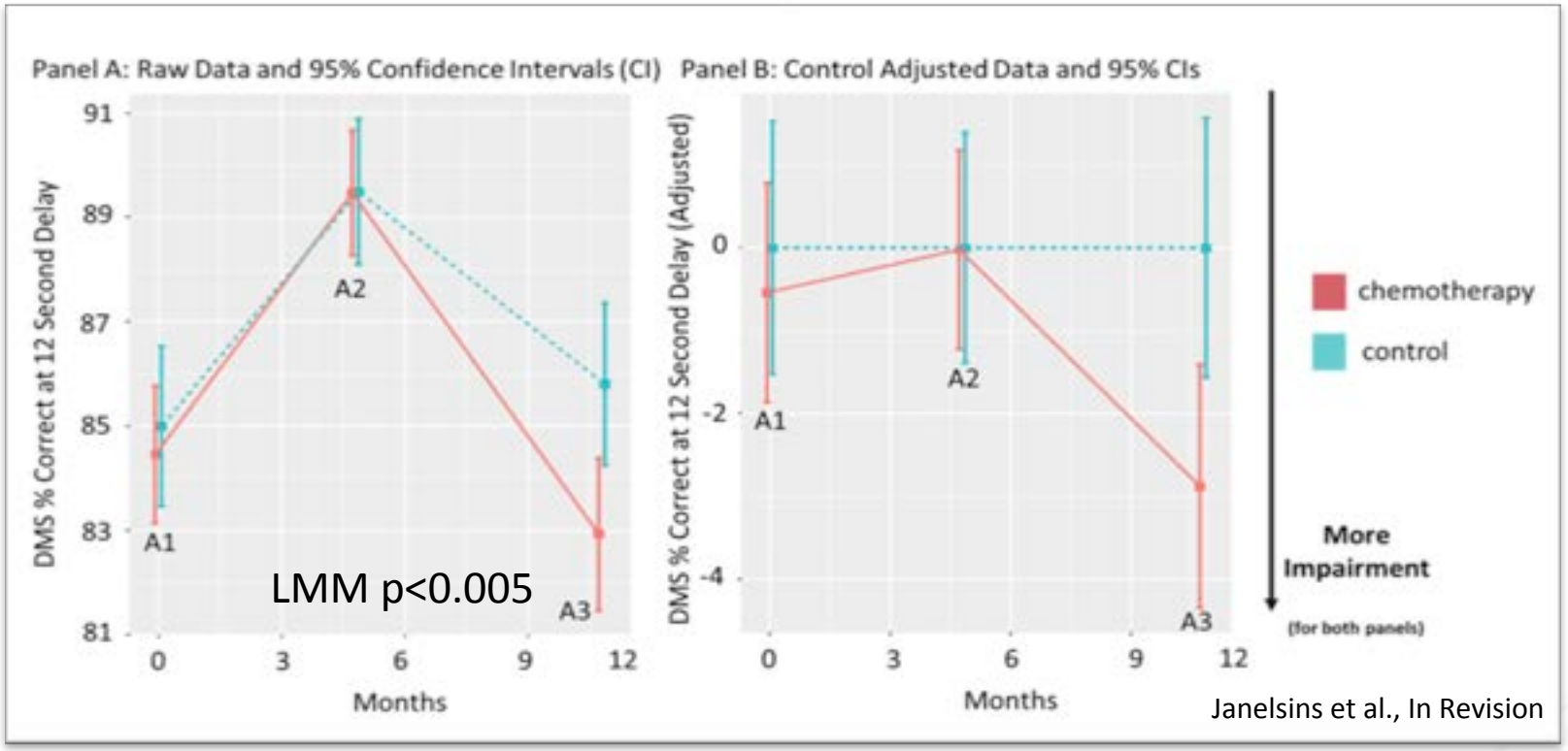

Janelsins et al., In Revision

LMM controlled for: age, education, reading (cognitive reserve), anxiety, depression

The Big Picture

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Diagnosis Treatment Survivorship

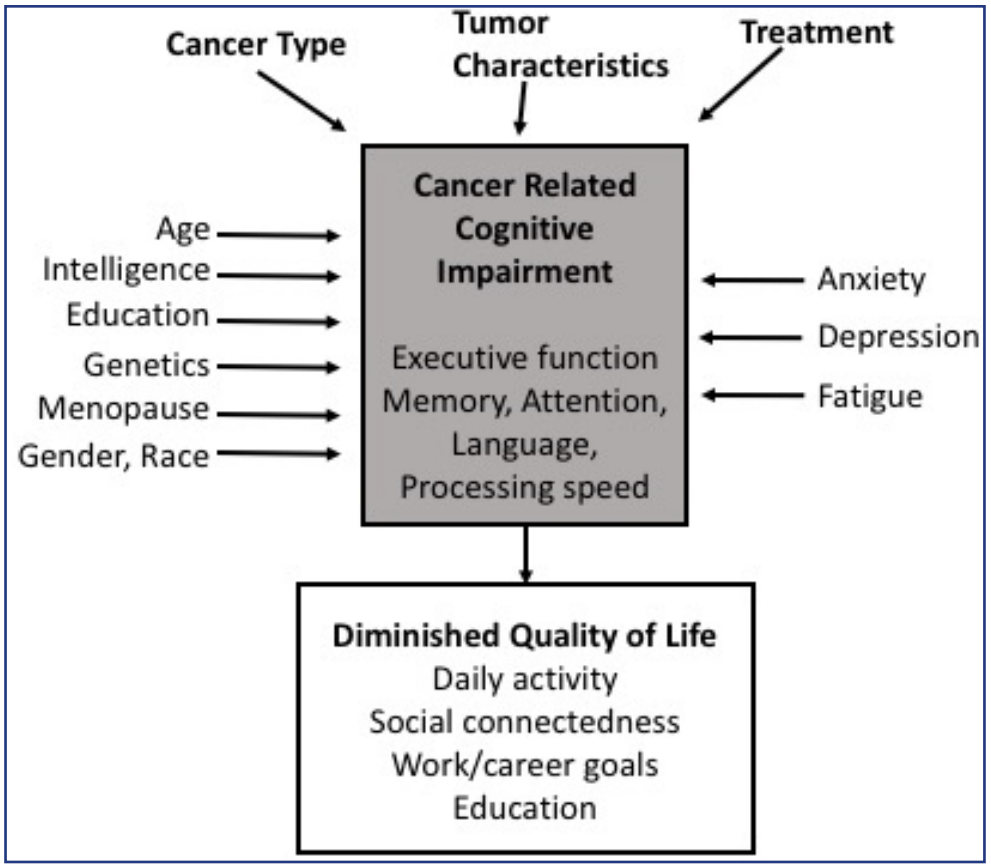
Long-term problems?

What treatments?

CRCI

Host, disease, medical, psychological, biologic (protein and genetic)?

CRCI Risk Factors



Williams et al., 2017

- Older age
- Minority race
- Lower education level
- Lower cognitive reserve
- Postmenopausal
- Comorbidities
- Higher baseline anxiety
- Higher baseline depression

Selected References: Cimprich et al., 2005; Ahles et al., 2010; JCO; Magnuson et al., Curr Geriatr Rep; Janelsins et al., 20017, JCO

Biologic Etiology of CRCI is Likely Multifactorial

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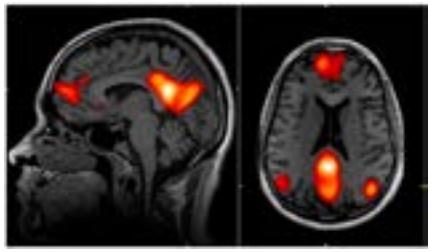
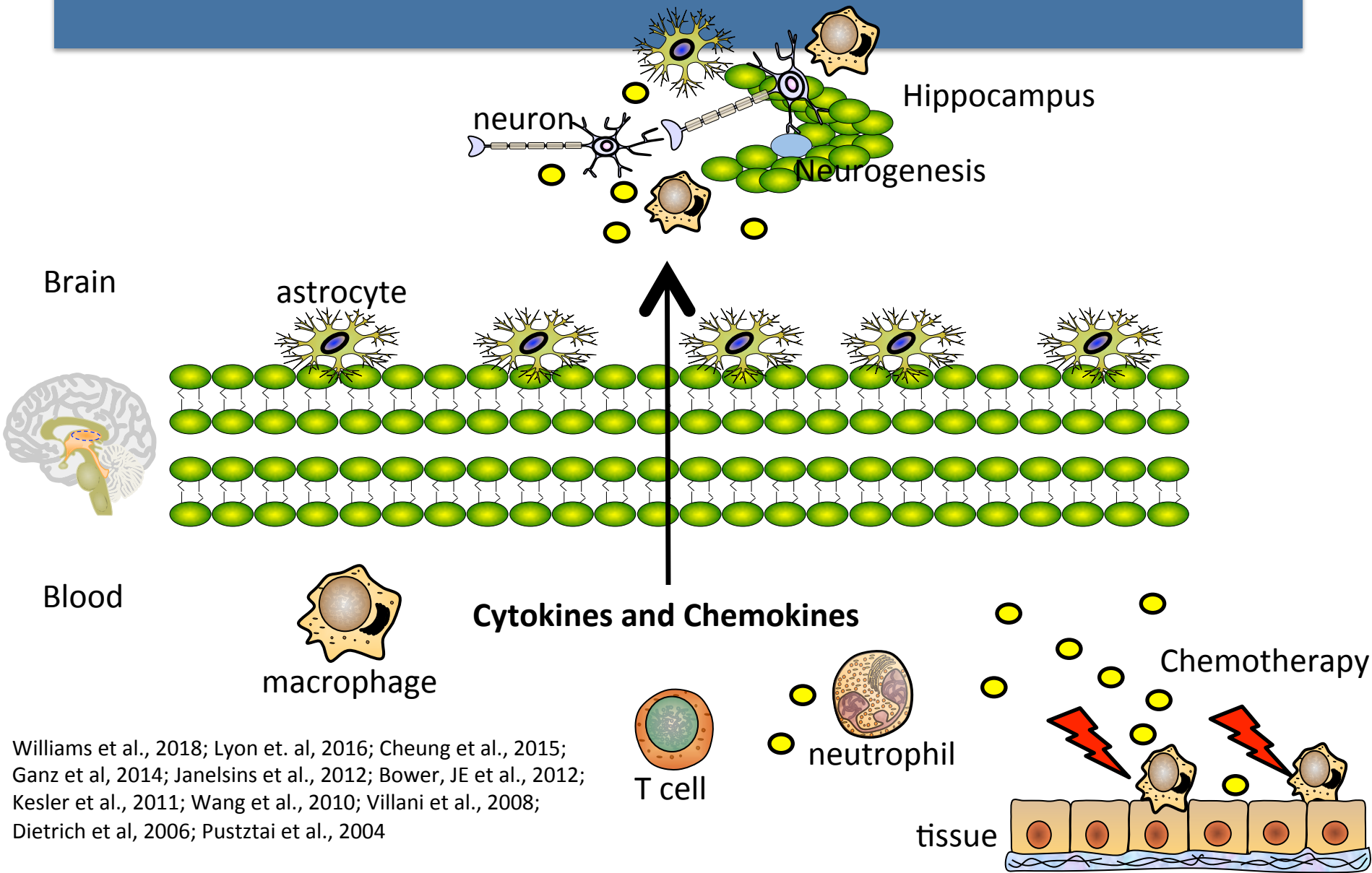
- Methods and advances
  - Blood-based biomarker studies have helped our understanding of relationships between CRCI and potential biologic mechanisms
    (Reviewed in: Castel et al., 2017, Front Pharmacol.)
  - Neuroimaging studies have helped our understanding of CNS neurotoxicity
    (Reviewed in: Deprez et al., 2018, JCNI)



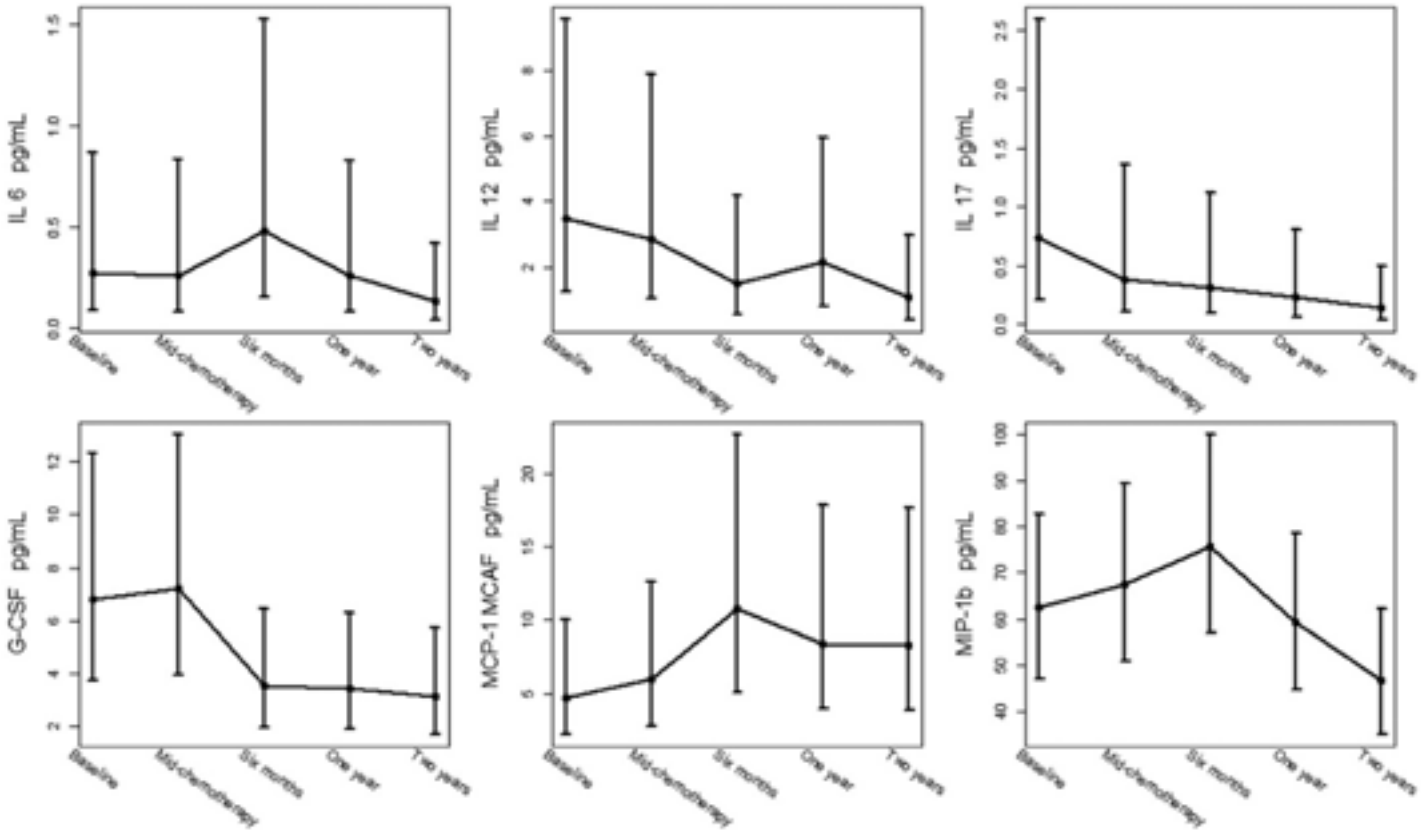
  - Animal models have helped our understanding of the peripheral and CNS impact of cancer treatments on inflammation, oxidative stress, and mitochondrial function
    (Reviewed in: Dietrich et al., 2015, Neuroscience)

Does Inflammation Contribute to CRCI?



Williams et al., 2018; Lyon et. al, 2016; Cheung et al., 2015; Ganz et al, 2014; Janelsins et al., 2012; Bower, JE et al., 2012; Kesler et al., 2011; Wang et al., 2010; Villani et al., 2008; Dietrich et al, 2006; Pusztai et al., 2004

Changes in Cytokines from Pre-Chemotherapy to Two Years Follow-Up in Breast Cancer Patients



- Cytokines fluctuate over time
- Different patterns

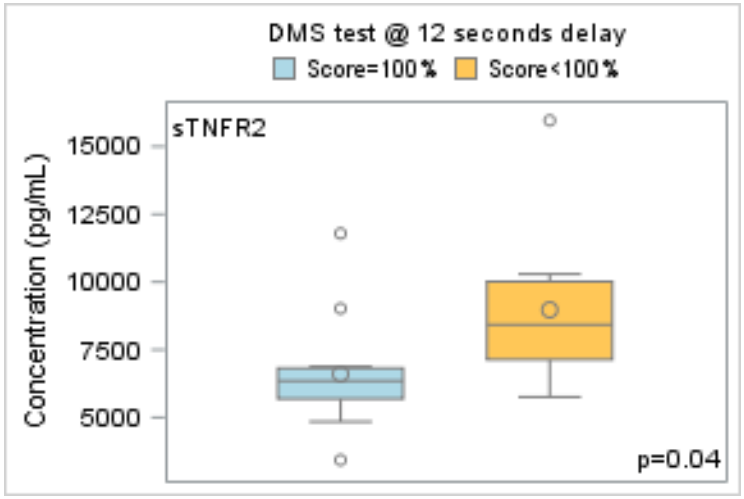
Lyon et al., J Neuroimmunol., 2016

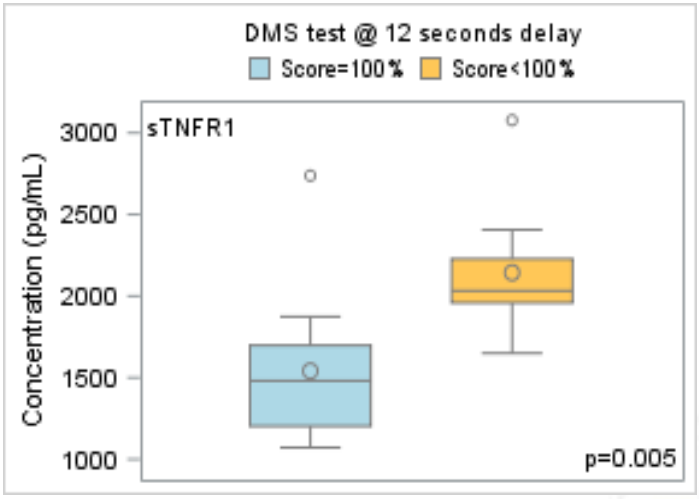
Inflammation and CRCI

- **TNF-α/TNFRI/II**
  - Memory and processing speed, cognitive complaints
  - Prior to surgery and adjuvant therapy (Patel et al., 2015, JNCI)
  - During chemotherapy (Williams et al., 2018, J Neuroimmunol.)
  - Post-chemotherapy (Ganz et al., 2013, Brain Behav Immun.; Kesler, Janelsins et al., 2013, Brain Behav Immun.; Lyon et al., 2016, J Neuroimmunol.)
- **IL-6**
  - Processing speed (Cheung et al., 2015, Ann Oncol.)
- **IL-1β**
  - Processing speed (Cheung et al., 2015, Ann Oncol.)

TNFRs and Visual Memory (DMS)

- Pilot (N=22)
  - Breast Cancer
  - During Chemotherapy





Williams et al., 2018, Journal of Neuroimmunol.

Genetic Risk Factors of CRCI

- *APOE* (Ahles et al., Psycho-oncology, 2014)
  - One copy of an e4 allele associated with deficits in visual memory in patients receiving chemotherapy
- *COMT* rs4680 (Small et al., Cancer, 2011)
  - *Val*^{158}*Met*, Val allele had poorer attention, motor speed, and verbal fluency compared to healthy controls
- *BDNF* rs6265 (Ng et al., Neuro-oncology, 2016)
  - *Val*^{66}*Met,* Met/Met protective for both perceived function, verbal fluency and multitasking

Biomarkers: Beyond Etiology

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- Baseline or early treatment level assessment of biomarkers may help determine who is most likely to develop CRCI
- Biomarker levels may help determine what intervention **modality** may work best

?

Conclusions: Trajectory of CRCI

- CRCI is an important clinical problem that develops prior to and over the course of treatment and persists for a subset of survivors post-treatment.
- CRCI can be assessed by multiple measurement modalities: self-report, neuropsychological assessment, computerized assessment.
- Computerized batteries may be helpful for assessing long-term trajectories (pre-chemotherapy to 6 months post-chemotherapy) of cognitive components of attention and visual working memory.
- Older age, minority race, lower education level, lower reading score, higher baseline anxiety and higher baseline depression were independently associated with cognitive decline.

Conclusions: Mechanisms

- Inflammation is associated with CRCI.
- Promising genetic variants in growth factor, neurotransmitter signaling and aging are also associated with CRCI.
- These pathways are important for our understanding of etiology and also informing risk prediction and intervention research.

Future Directions: Expanding Impact

- Well-controlled, longitudinal studies with long-term outcomes are needed.
- Understanding the relationships between deficits in attention, memory and other cognitive functions in specific disease groups receiving different treatments is needed.
- The role of clinical, demographic, and biologic risk factors need to be assessed to help identify patients at risk for cognitive decline.
  - *What are the interactions between the periphery and CNS?*
- **These data will help further our knowledge of CRCI and be helpful for developing interventions, and ultimately, overall treatment decision making as treatment becomes more complex and tailored to the patient.**

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www.mascc.org/meeting