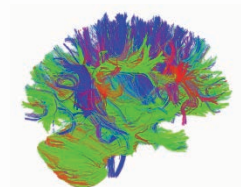
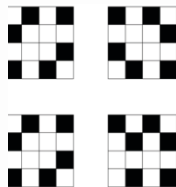


# Influence of Chemotherapy on Cognitive Function

- experience from non-CNS studies -

NETHERLANDS  
CANCER  
INSTITUTE

ANTONI VAN LEEUWENHOEK



# Chemotherapy and Cognition

- Increasing evidence that chemotherapy for non-CNS disease can produce neurobiological changes
- Stressing the importance to assess and manage cognitive functioning in patients with non-CNS disease

# Brain met studies with cognition as an endpoint

Trials have historically been about radiation effects on cognition

Radiation-induced late effects are due to dynamic interactions between multiple cell types in the brain:

- Endothelial cells
- oligodendrocytes - required for formation myelin sheets - and astrocytes - interacting with vascular and parenchymal elements in the brain
- microglia proliferation
- involvement of stem cells in hippocampus

# An example from brain met RT trials:

***Chang et al. Lancet Oncol 2009; 10:1037-44***

## Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

**Table 3:** Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by Hopkins Verbal Learning Test—Revised

# Another example from brain met RT trials:

VOLUME 29 • NUMBER 3 • JANUARY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non–Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis

Alexander Sun, Kyoungwha Bae, Elizabeth M. Gore, Benjamin Movsas, Stuart J. Wong, Christina A. Meyers, James A. Bonner, Steven E. Schild, Laurie E. Gaspar, Jeffery A. Bogart, Maria Werner-Wasik, and Hak Choy

**Table 4.** Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

Component by Time Point	PCI				Observation				P*	Adjusted P†
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%		
3 months										
Recall	28	45	34	55	10	13	66	87	< .001	< .001
Delayed recall	25	44	32	56	7	10	64	90	< .001	< .001
6 months										
Recall	11	19	46	81	3	5	58	95	.02	.045
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

\*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

†Adjusted using the Hommel's method; adjustment is made within time point.

Shift from short term palliation to prolonged control of tumor growth while maintaining/improving neurologic and functional status and avoiding potential toxicity of WBRT

Initiatives to apply chemotherapy/targeted agents for brain metastases call for:

- Exploring the effects of chemotherapy/targeted agents on cognition
- Compare those effects to radiation effects on cognition
- Disentangle these effects

# Very few data out there....

Preservation of Neurocognitive Function and Local Control of 1 to 3 Brain Metastases Treated With Surgery and Carmustine Wafers

*Brem et al. Cancer, 2013*

- Pts received resection and chemowafers while deferring WBRT
- Results indicated that cognitive function could be preserved or improved in the majority of the pts with acceptable rates of local control, similar to surgery and WBRT

# Very few data out there....

Phase II Trial of Erlotinib Plus Concurrent Whole-Brain Radiation Therapy for Patients With Brain Metastases From Non–Small-Cell Lung Cancer  
Welsh et al. JCO, 2013

- No increase in neurotoxicity was observed when compared with a historical control group



# Effects of chemotherapy on cognition in patients with non Central Nervous System cancer

Different setting:

- Less interference of other factors that can impact cognition (tumor progression, radiation)
- No expectation that chemotherapy may be associated with improvement of cognitive function
- Studied in breast cancer, testicular cancer, lymphoma, multiple myeloma, colorectal cancer, ovarian cancer and prostate cancer

# Neuropsychological studies (n=80)

Cognitive problems are typically mild to moderate in nature

- Subgroup of patients exhibit cognitive problems following chemotherapy (varying from 17% to 70%)
- Core impairments: learning and memory, executive function, psychomotor speed
- Arise during treatment and persist well into survivorship period

*Pre-treatment cognitive dysfunction possible*

## **Cognitive effects of chemotherapy in breast cancer patients: a dose–response study<sup>†</sup>**

Barbara Collins<sup>1,2\*</sup>, Joyce MacKenzie<sup>1</sup>, Giorgio A. Tasca<sup>1,2</sup>, Carole Scherling<sup>3</sup> and Andra Smith<sup>2</sup>

<sup>1</sup>The Ottawa Hospital – Civic Campus, Ottawa, ON, Canada

<sup>2</sup>School of Psychology, University of Ottawa, Ottawa, ON, Canada

<sup>3</sup>Memory and Aging Centre, UCLA in San Francisco (UCSF), San Francisco, CA, USA

**Table 5.** Number (and percentage) of chemotherapy patients and controls

	Frequency impairment		$\chi^2$	<i>p</i>
	Chemo	Controls		
T1, <i>n</i> = 60	7 (11.7%)	6 (10%)	0.09	0.77
T2, <i>n</i> = 59	13 (22.0%)	7 (11.9%)	2.17	0.14
T3, <i>n</i> = 60	14 (23.3%)	9 (15%)	1.35	0.25
T4, <i>n</i> = 60	19 (31.7%)	8 (13.3%)	5.78	0.02
T5, <i>n</i> = 59	20 (33.9%)	10 (16.9%)	4.47	0.04
T6, <i>n</i> = 48	15 (31.3%)	6 (12.5%)	4.94	0.03
T7, <i>n</i> = 46	17 (37.0%)	7 (15.2%)	5.64	0.02

# Acute and Late Onset Cognitive Dysfunction Associated With Chemotherapy in Women With Breast Cancer

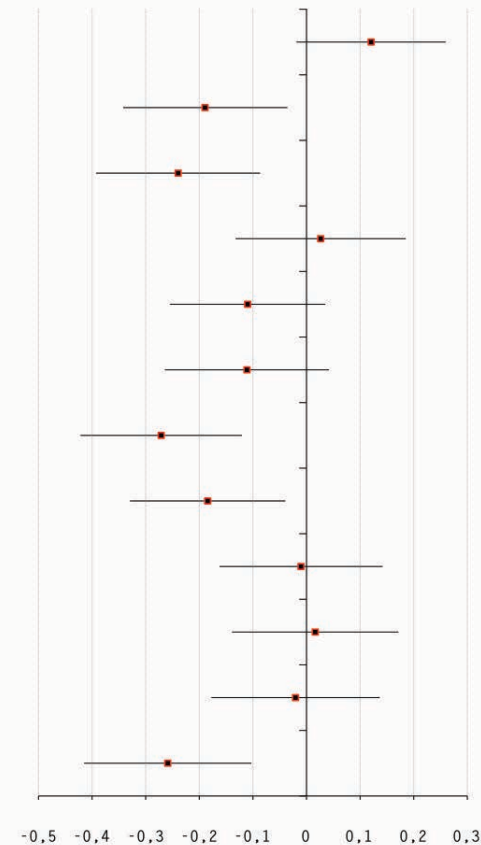
Jeffrey S. Wefel, PhD<sup>1</sup>; Angele K. Saleeba, PhD<sup>1</sup>; Aman U. Buzdar, MD<sup>2</sup>; and Christina A. Meyers, PhD<sup>1</sup>

- Breast cancer pts treated with FAC-Paclitaxel (n=42)
- Acute interval: 65% cognitive decline
- long-term evaluation: 61% cognitive decline
- Within this group of pts:
  - 71% evidenced continuous decline from the acute interval - 29% evidenced new delayed cognitive decline

# NKI-AVL study: BC patients CMF chemotherapy n=196; Reference group n=1509. On average 21 years after completion of treatment

Z-score of the difference (95% CI)

Cognitive Domain -	Testoutcome:	p
Dementia Screener -	MMSE	.090
Verbal Memory -	15WLT: immediate recall	.015
	15WLT: delayed recall	.002
	15WLT: recognition	.744
Processing Speed -	LDST: total correct	.137
Reading Speed -	Stroop: Word card	.154
Attention -	Stroop: Color-card	<.001
Inhibition -	Stroop: Color-word card	.013
Verbal Fluency -	Word fluency: total	.894
Visuo-spatial Functioning -	DOT: total correct	.837
Psycho-motor Speed -	PPB: Dominant hand	.798
	PPB: Non-dominant hand	.001



The magnitude of the effects is comparable to approximately six years of age-related decline in cognitive function

# Risk factors for neurotoxicity

## Treatment-related:

- High dose exposure
- Multi-agent therapy with additive/synergistic effects (ET?)

## Patient-related:

- None consistently identified  
(age, cognitive reserve, education, depression, anxiety, fatigue, treatment induced menopause, genetics)

But given the small sample sizes, exploration of risk factors is likely  
Underpowered

# Pre-clinical and imaging studies: potential mechanisms of neurotoxicity

## Direct mechanisms:

- Cellular toxicity
- White matter dysfunction

## Indirect mechanisms:

- Vascular toxicity
- Cytokine release
- Oxidative stress
- Inflammation

## Neurotoxicity +/- cognitive dysfunction

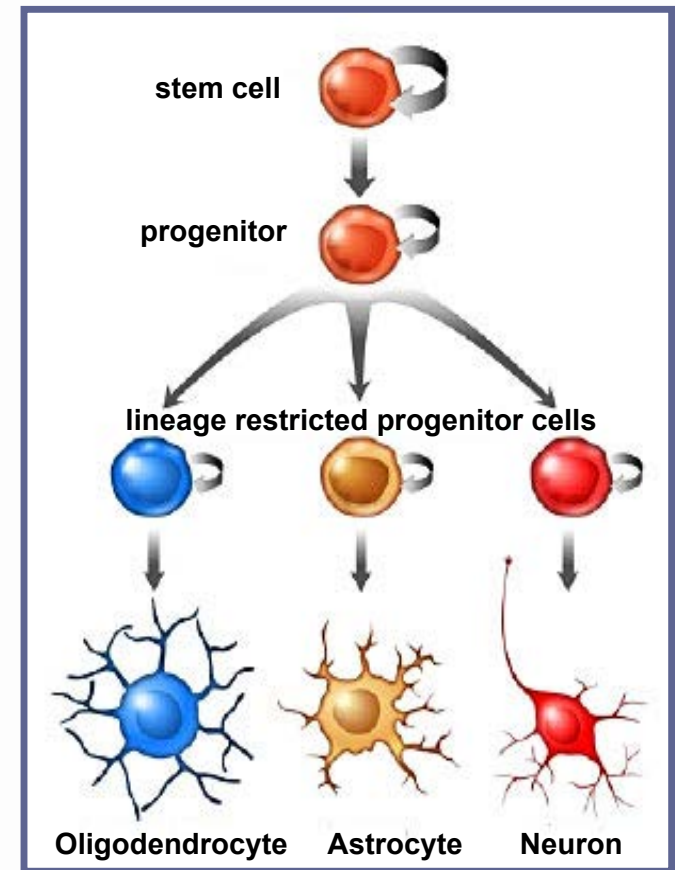
## Global and constitutional factors

- Genetic factors
- Drug resistance, DNA repair
- Metabolism
- Age, cognitive reserve

## Pre-clinical studies

Many common chemotherapeutic agents are associated with adverse effect on neurobiology and behavior

Damage of mature post-mitotic oligodendrocytes and immature progenitor cell populations required for ongoing neurogenesis, gliogenesis, and maintenance of white matter integrity are etiologic factors



*Dietrich et al.*

*J. Biology, 2006, 2008; Cancer Research, 2010*



# Preclinical studies: mechanisms of neurotoxicity

<i><b>Mechanism</b></i>	<i><b>Chemotherapy</b></i>	<i><b>Reference</b></i>
<i>Impaired neurogenesis</i>	<i>Ara-C, BCNU, Cisplatin, Cytosan, Doxorubicin, 5-FU, MTX, Paclitaxel, Thiotepa</i>	<i>Briones &amp; Woods 2011, 2014 Mignose 2006 Seigers, 2008, 2009,2010 Mustafa 2008 Mondie 2010 Janelins 2010 Lyons 2011 Nokia 2012 Christie 2012 Yang 2011, 2012 Elbaltagy 2012 Dubois 2014 Yang 2014 Periera Dias 2014</i>
<i>Impaired gliogenesis &amp; myelin toxicity</i>	<i>Ara-C, BCNU, Cisplatin, 5-FU, cytosan, MTX</i>	<i>Dietrich 2006 Han 2008 Hyrien 2010 Briones 2014</i>
<i>Oxidative damage</i>	<i>Adriamycin, BCNU,Cytosan, Doxorubicin</i>	<i>Manda 2003 Joshi 2005, 2007,2010 Aluise 2011 Obob 2010, 2011</i>
<i>Inflammation</i>	<i>BCNU, Cytosan, Doxorubicin, 5-FU, MTX</i>	<i>Tangpong 2006, 2007, 2011 Helal 2009 Seigers 2010 Christie 2012 Briones 2014</i>
<i>Epigenetic dysregulation</i>	<i>Cytosan, 5-FU, MTX</i>	<i>Briones 2011</i>
<i>Neurotransmitter alterations</i>	<i>MTX</i>	<i>Madhyastha 2002</i>
<i>Vascular damage / blood supply</i>	<i>MTX</i>	<i>Seigers 2010</i>

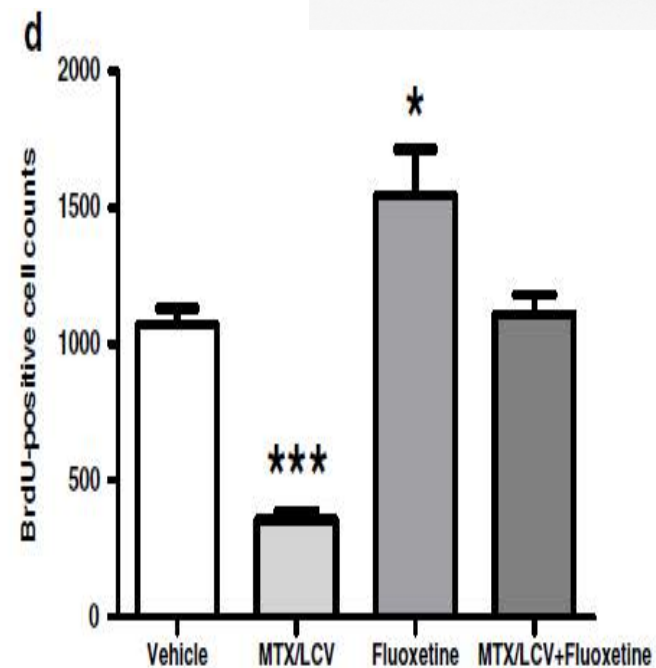
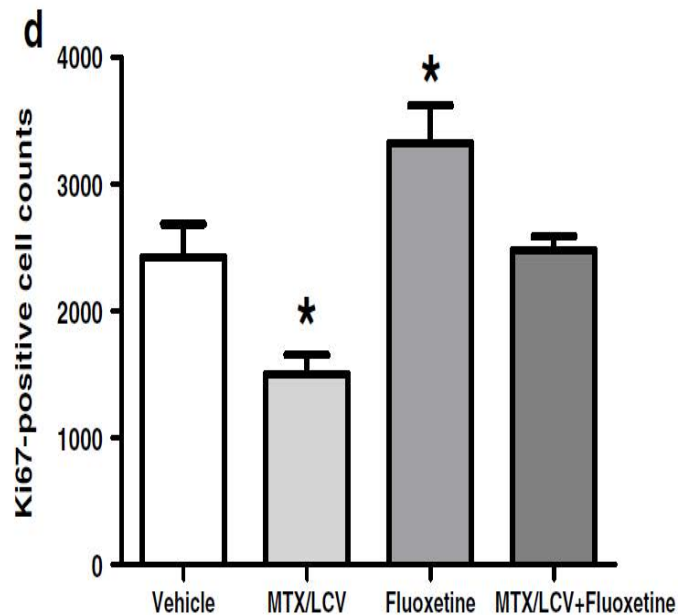
*As reviewed by Dietrich*

# Preclinical studies: cognitive dysfunction

<i>Category of Agents</i>	<i>Agents</i>
<i>Anti-metabolites</i>	<i>Ara-C, 5-FU, MTX</i>
<i>DNA cross linking agents</i>	<i>Platinum, Nitrosureas, Cytosine, TMZ, Thiotepa</i>
<i>Mitotic and microtubule inhibitors</i>	<i>Vincristin, Paclitaxel, Docetaxel</i>
<i>Topoisomerase inhibitor</i>	<i>Doxorubicin, topotecan</i>
<i>Targeted agents</i>	<i>Anti-VEGF</i>
<i>Hormonal agents</i>	<i>Steroids, tamoxifen, AIs</i>

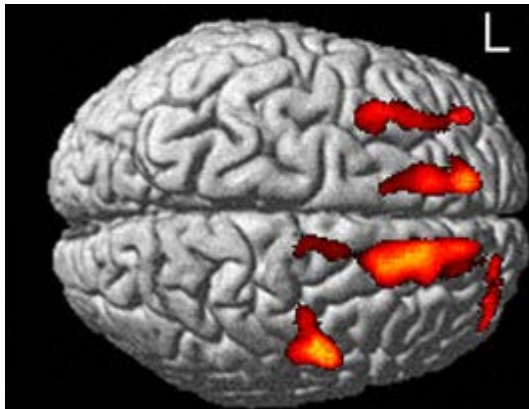
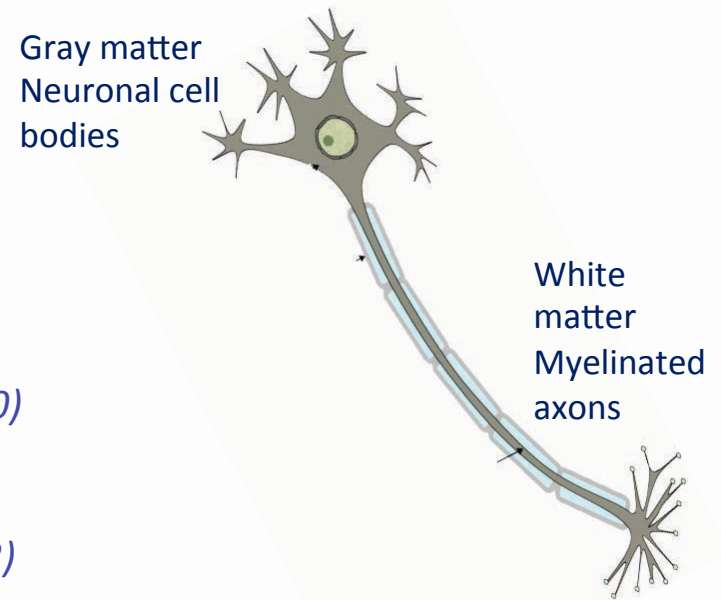
## Fluoxetine reverses the memory impairment and reduction in proliferation and survival of hippocampal cells caused by methotrexate chemotherapy

Laura Lyons • Maha ElBeltagy • Jariya Umka •  
Rachel Markwick • Carla Startin • Geoffrey Bennett •  
Peter Wigmore



# Gray matter volume: Early and late effects

- 1 month and after anthracycline-based CT (n=17) (*McDonald, Breast Cancer Res Treat, 2010*)
- 21 years after CMF CT (n=184) (*Koppelmans, Breast Cancer Res Treat, 2012*)



1 month

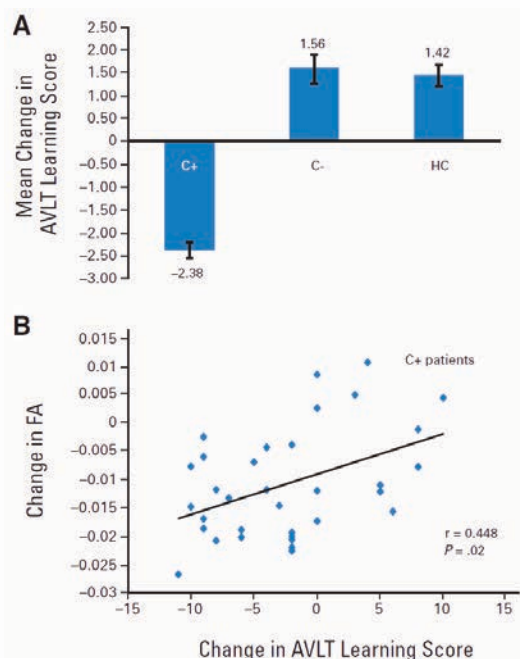
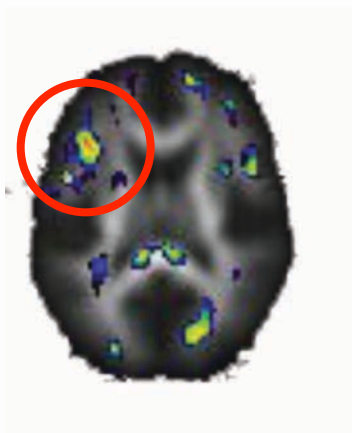
	Chemo n=184		Reference n=368			
	Mean ml	SD	Mean ml	SD	$\beta$ ml	p
Gray matter	617	16	620	21	-3	.003

21 years

Comparable to  
decline in gray  
matter volumes of  
4 years of age

# Patients with non-CNS disease after CT

Prospective imaging studies indicate structural brain changes from pre- to post chemotherapy - white matter particularly vulnerable (Deprez et al. JCO 2012)



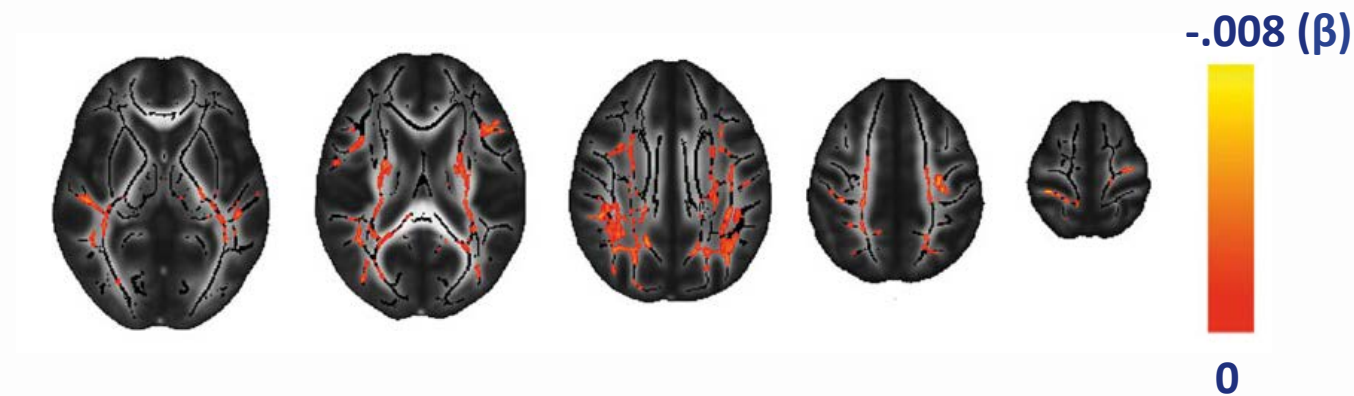
“Doctor, Will the Treatment You Are Recommending Cause Chemobrain?”

Patricia A. Ganz, Jonsson Comprehensive Cancer Center at the University of California Los Angeles, Los Angeles, CA

See accompanying article on page 274

# White matter integrity: very late effects

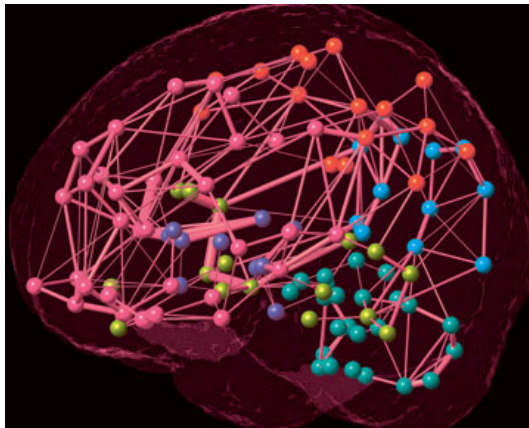
- 20 years post CMF chemotherapy
- Lower white matter integrity over time in chemotherapy-exposed survivors



FA decreases over time

# Brain connectivity

- Altered brain structure reduces the brain network's ability to stabilize and support the dynamic functional networks that underlie various cognitive processes
- Multiple fMRI studies have shown altered functional brain activation and connectivity associated with non-CNS cancer and its treatments



# The rationale of assessing cognitive function in brain met chemotherapy/targeted agent trials

- To provide supporting evidence for the clinical benefit of the treatment approach
- To assess the risk of neurotoxicity of the treatment

Treatment of brain metastases must balance local and distant control in the CNS with neurotoxicity

Cognitive assessments may be helpful in this process, when conducted properly





# Chemotherapy in adult CNS cancers

Improvement due to disease control vs neurotoxicity of CT

- Temozolomide (SD or DD) in new GBM, 30% cognitive decline (Hilverda 2010, Wefel 2011)
- PCV in anaplastic glioma and GBM, 35-50% cognitive decline (Levin 2002, Gorves, 1999: did not distinguish between chemoradiation and adj CT)
- PCNSL pts improvement in cognitive functioning after rituximab, mtz, procarbazine and vincristine followed by reduced-dose brain radiation and high-dose cytarabine (Correa 2007, 2009)
- GBM pts treated with standard chemoradiation, maintenance temozolomide and bevacizumab showed higher level of cognitive decline than those receiving a placebo (RTOG 0825 Wefel 2013)