Emerging Targets and Pathways in Cancer-Related Cognitive Impairment (CRCI)

Alex Chan, PharmD, MPH, FCCP, FISOPP, BCPS, BCOP
Deputy Head and Associate Professor
Department of Pharmacy
National University of Singapore
Duke-NUS Medical School
Singapore

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Overview

- A Clinical Conundrum: CRCI
- Review on Known Mechanisms
- Emerging Pathways and Targets

Cancer-Related Cognitive Impairment (CRCI)

- Commonly known as ‘chemobrain’ or ‘chemofog’
  - Memory, concentration, execution function, psychomotor speed, verbal ability are most likely to be affected
- Incidence varies, depending on the cognitive assessments used
- Distinct and heterogeneous trajectories

Ng T,.., Chan A. *Psychooncology* 2018;27(4): 1185-92

CRCI: Unmet Needs

Systematic review of pharmacologic and non-pharmacologic interventions to manage cognitive alterations after chemotherapy for breast cancer

...ventions were effective in improving executive function and self-reported concentration.
Conclusion: Current evidence does not favour the pharmacologic management of cognitive alterations associated with breast cancer treatment. Cognitive training and physical activity interventions appear promising, but additional studies are required to establish their efficacy.

Chan RJ,.., Chan A. *EJC* 2015; 51, 437– 450

Pharmacologic management of cognitive impairment induced by cancer therapy

Cognitive dysfunction is a challenging adverse effect of chemotherapy and radiotherapy that has limited treatmen options. Clinical trials for proposed pharmacotherapeutic interventions to help manage these cognitive symptom have had conflicting results and no standard of care has yet been established. Pharmacotherapeutic approache for cancer therapy-induced cognitive symptoms include CNS stimulants (eg, methylphenidate and modafinil)

Karschnia P, et al. *Lancet Oncol* 2019; 20: e92–102

Currently ‘Known’ Mechanisms

- Inflammation
- Direct neurotoxicity to the brain
  - Mitochondria damage
  - Glucose metabolism
  - Apoptosis
  - Necrosis
- Hypothalamic-Pituitary-Adrenal Axis
- Genetic Polymorphisms

Chung NC,.., Vardy JL. *Oncology (Williston Park)* 2018; 32(12):591-8.

Current Ongoing Trials

	Mechanism of Action of Potential Targets	Clinical Trial Registry Number
Anti-dementia agents		
Donepezil	Protecting the forebrain cholinergic system	NCT02822573
Memantine	Encouraging glutamatergic neurotransmission	NCT02360215 NCT03342443
CNS Stimulants		
Methylphenidate	Activating the frontostriatal network	NCT02970500
Neuroprotective Agents		
Fluoxetine	Protecting cell division in hippocampus	NCT01615055
Docosahexaenoic acid	Reducing microglia infiltration	NCT02517502
Ibuprofen	Protecting against neuronal injury	NCT03186638
Nicotine	Encouraging glutamatergic neurotransmission	NCT02312934

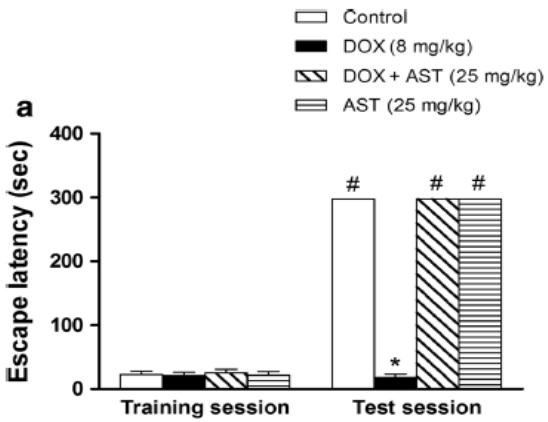
Karschnia P, et al. *Lancet Oncol* 2019; 20: e92–102

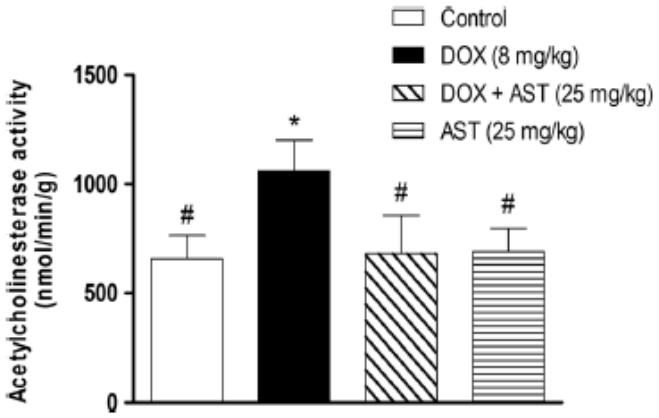
Emerging Pathways and Targets in CRCI

Astaxanthin Ameliorates Doxorubicin-Induced Cognitive Impairment (Chemobrain) in Experimental Rat Model: Impact on Oxidative, Inflammatory, and Apoptotic Machineries

Sara Emad El-Agamy[1] · Amal Kamal Abdel-Aziz[1] · Sara Wahdan[1] · Ahmed Esmat[1] · Samar S. Azab[1]

- A carotenoid (phytochemical) widely found in marine organisms
- Potent antioxidant capacity– currently used as a dietary supplement
- Exhibits anti-inflammatory and anti-apoptotic activities





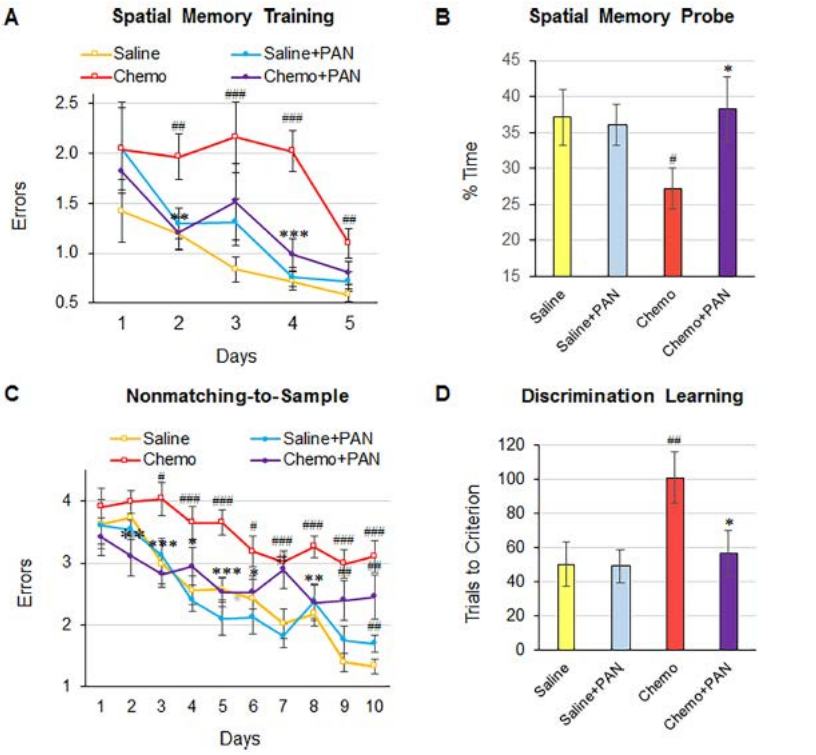
Emad El-Agamy S, et al. *Mol Neurobiol* 2018; 55:5727–5740

RESEARCH ARTICLE

PAN-811 prevents chemotherapy-induced cognitive impairment and preserves neurogenesis in the hippocampus of adult rats

Zhi-Gang Jiang[1]*, Gordon Winocur[2,3,4]*, J. Martin Wojtowicz[5], Olga Shevtsova[5], Steven Fuller[1], Hossein A. Ghanbari[1]

- A ribonucleotide reductase inhibitor, originally designed for cancer therapy.
- Scavenging free radicals and to inhibit H_2O_2-induced neurotoxicity.



Fewer Errors

Less Memory Problems

Jiang ZG, et al. *PLoS One* 2018; 13: e0191866

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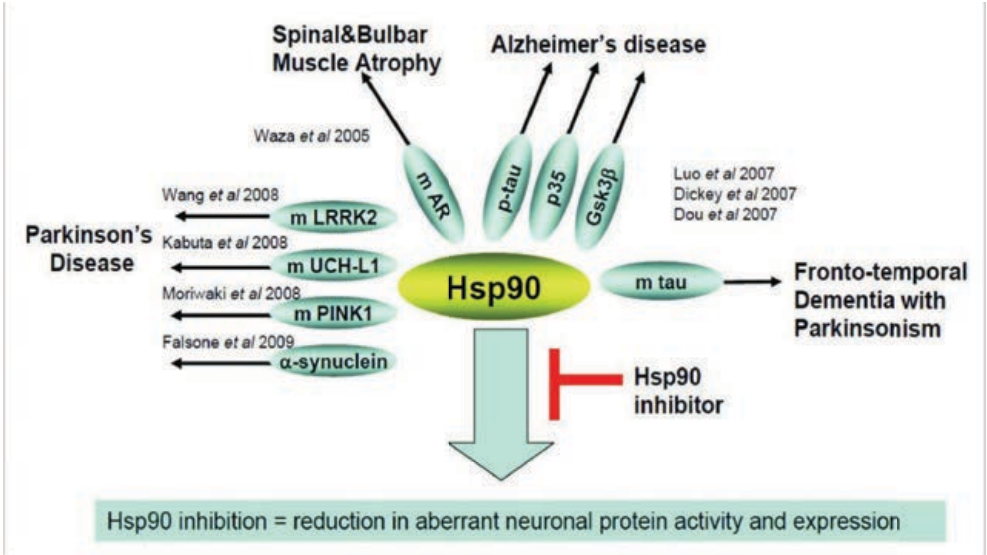
KU-32 Prevents 5-Fluorouracil Induced Cognitive Impairment

Michael J. Sofis, **David P. Jarmolowicz**, **Sam V. Kaplan**, **Rachel C. Gehringer**, **Shea M. Lemley**, **Brian S. Blagg**, and **Michael A. Johnson**
University of Kansas

- KU-32 repairs mitochondrial dysfunction to prevent myelin degradation and protects the cells from damages by cytotoxic drugs



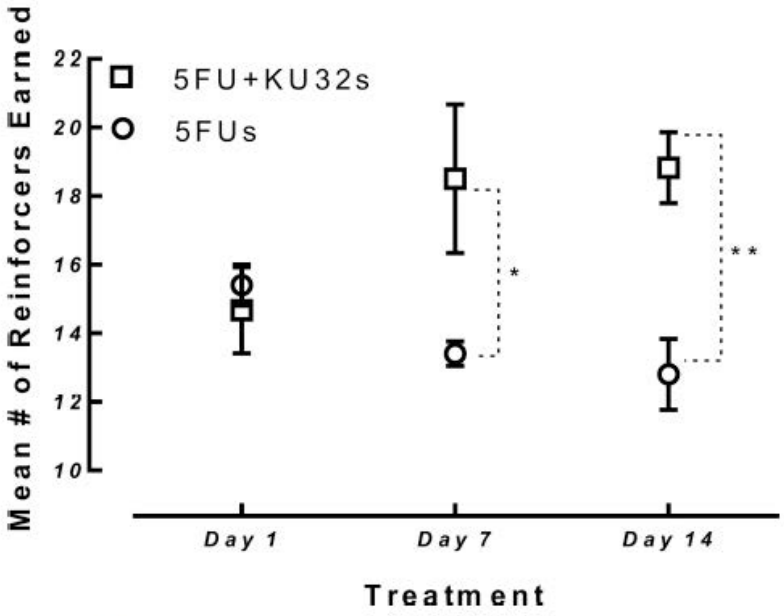


Fig. 1.
Mean number of reinforcers earned (y-axis) for the 5FU + Saline group (cir-cles) and 5FU + KU32 group (squares) across D1, D7, and D14 (x-axis).

Sofis MJ, et al. *Behav Brain Res* 2017;329: 186–90f

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How does Methotrexate (MTX) induce CRCI?

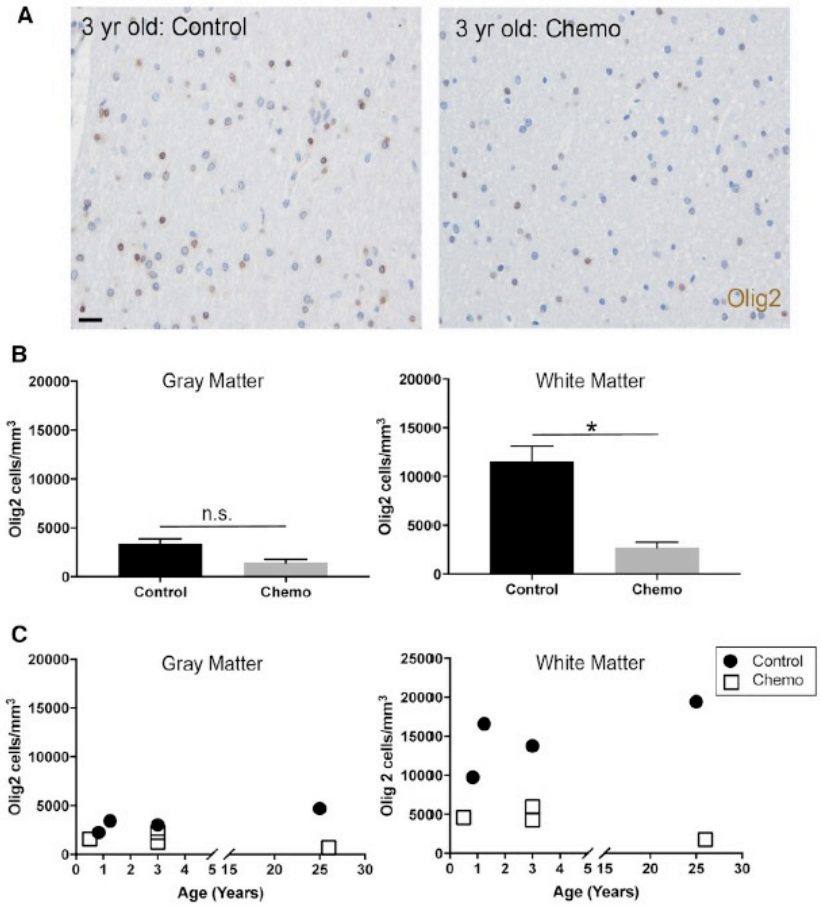

Figure 1. Frontal Lobe White Matter Depletion of Oligodendrocyte Lineage Cells following Chemotherapy

(A) Representative photomicrographs of Olig2$^+$ (brown) cells in frontal lobe white matter of a 3-year-old child exposed to chemotherapy and a non-chemotherapy exposed, age-matched control subject.
(B) Chemotherapy exposure selectively depletes Olig2$^+$ cells in frontal lobe white matter ($p = 0.0211$; $n = 4$), but not in gray matter ($p = 0.0913$; $n = 4$).
(C) Frontal lobe Olig2$^+$ cells throughout early life and young adulthood following chemotherapy treatment, compared to age-matched controls.

Gibson EM, et al. *Cell* 2019; 176: 46-55.

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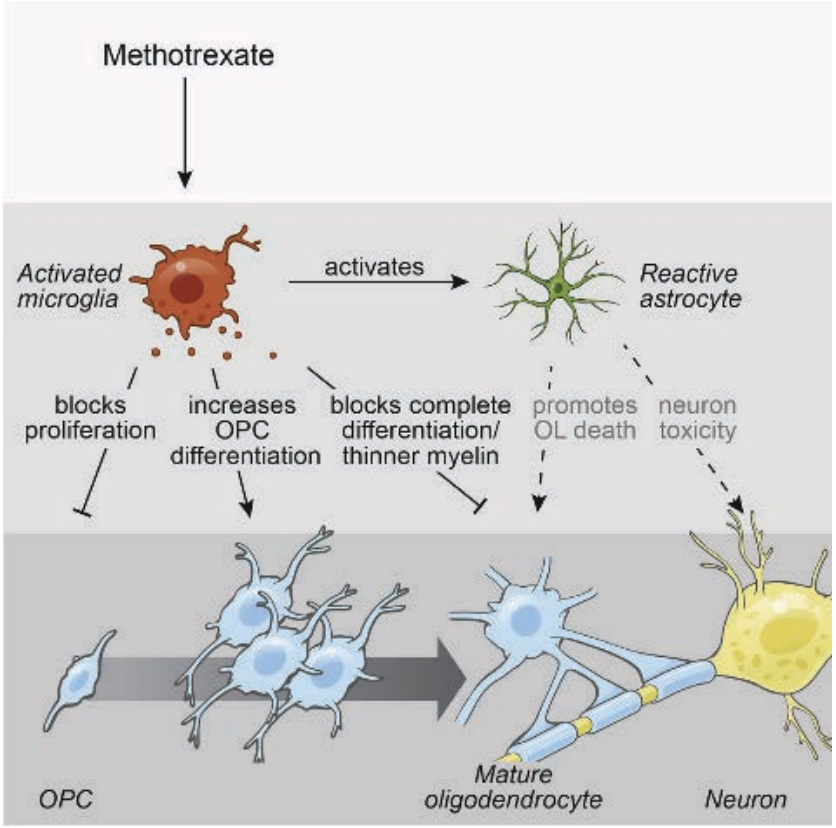
Methotrexate-Induced Oligodendrocyte Damage



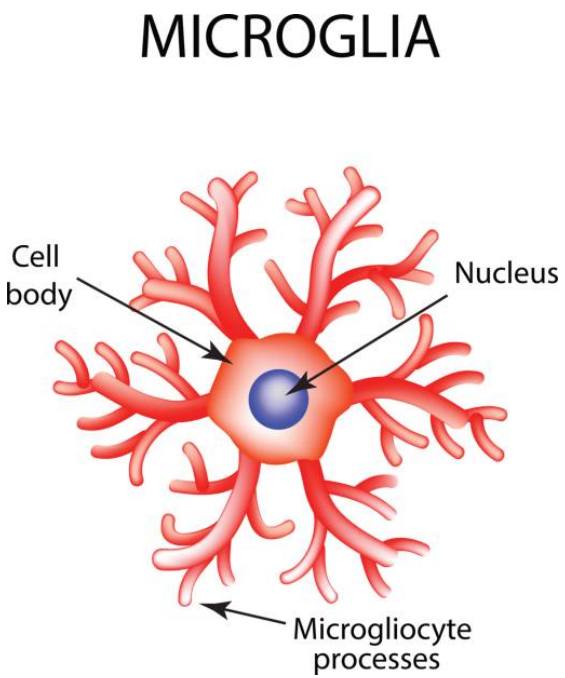
- Microglial activation is necessary for the persistent dysregulation of oligodendrocyte lineage cells, myelin and astrocytes, causing CRCI after MTX exposure.

Gibson EM, et al. *Cell* 2019; 176: 46-55.

Microglia in the CNS

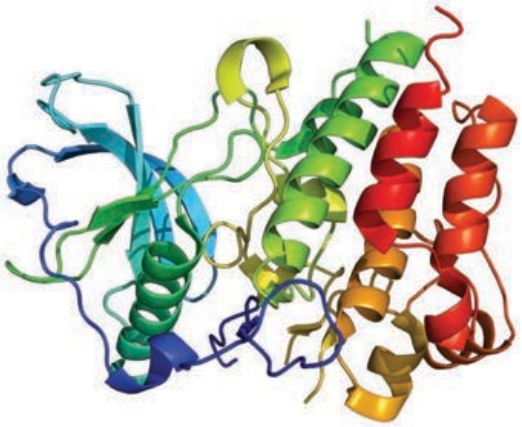
- Innate immune cells of the CNS

- Microglia serve as resident phagocytes that dynamically survey the CNS
  - ✓ Protect against Alzheimer's Disease
  - ✓ However, activated microglia can also secrete inflammatory factors that injure neurons directly or via activation of neurotoxic astrocytes



Colony-stimulating factor-1 receptor (CSF-1R)

- PLX5622, a CSF1R inhibitor
  - May inhibit the activity of microglia and restore astrocyte reactivity in the CNS



Elimination of microglia improves cognitive function following cranial irradiation

Munjal M. Acharya[1], Kim N. Green[2], Barrett D. Allen[1], Allison R. Najafi[2], Amber Harutyun Minasyan[1], Mi T. Le[1], Takumi Kawashita[1], Erich Giedzinski[1], Vipan K. Brian L. West[3], Janet E. Baulch[1] & Charles L. Limoli[1]

Research Article

MOLECULAR PAIN

Targeting macrophage and microglia activation with colony stimulating factor 1 receptor inhibitor is an effective strategy to treat injury-triggered neuropathic pain

SeungHwan Lee[1,2], Xiang Qun Shi[1,2], Anni Fan[1,2], Brian West[3] and Ji Zhang[1,2,4]

Molecular Pain
Volume 14: 1–12

DOI: 10.1177/1744806918764979
journals.sagepub.com/home/mpx
SAGE

Minocycline prevents microglia activation

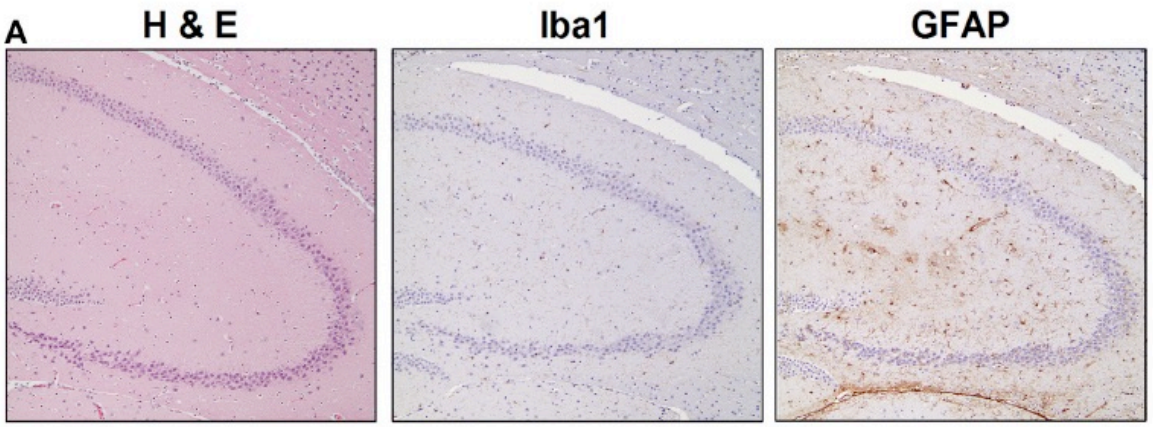
Minocycline, a putative neuroprotectant, co-administered with doxorubicin-cyclophosphamide chemotherapy in a xenograft model of triple-negative breast cancer

Lauren E. Himmel[a,b], Maryam B. Lustberg[c], A.Courtney DeVries[d], Ming Poi[e], Ching-Shih Chen[b,f], Samuel K. Kulp[b,*]

[a] Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA
[b] Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA
[c] Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, OH 43210, USA
[d] Department of Neuroscience, College of Medicine, The Ohio State University, Columbus, OH 43210, USA
[e] Division of Pharmacy Practice and Science, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA
[f] Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan

Representative partial sections of mice hippocampus and dentate gyrus are shown for H&E, Iba1, and GFAP stains from the AC treatment group

In vivo studies



No detection of activated microglia and astroglial scars

Himmel LE, Lustberg MB, et al. *Experimental and Toxicologic Pathology* 2016; 505–515

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December 4th 2015,
Today & Straits Times

COGNITIVE IMPAIRMENT AFTER CHEMOTHERAPY LINKED TO BDNF GENE

Protein gene may protect from 'chemobrain': Study

SINGAPORE – Researchers are a step closer to understanding why some breast cancer patients develop cognitive impairment after chemotherapy and whether some high-risk patients could benefit from early intervention.

A local study has found that early-stage breast cancer patients with a variation of the brain-derived neurotrophic factor (BDNF) gene are less likely to get "chemofog" or "chemobrain" — cognitive impairment, such as memory loss and difficulty in decision-making and multi-tasking, after chemotherapy..

Such cognitive changes "affect patients' quality of life, prevent them from returning to work or school, and inhibit their social activities", said Associate Professor Alexandre Chan, who co-led the study with PhD candidate Terence Ng. Both are from the National University of Singapore's Department of Pharmacy.

"Hence, gaining a better understanding of how 'chemobrain' occurs and how to prevent it is crucial," said Assoc Prof Chan.

The BDNF gene is responsible for producing a protein that controls the growth and function of nerve cells in the brain and spinal cord. Previous studies have linked the gene to cognitive impairment in patients with Alzheimer's disease and other neuropsychological disorders, but this is the first time the BDNF gene is associated with cognitive changes in cancer patients. The discovery was reported in the international scientific journal Neuro-Oncology in August.

In this study, 145 early-stage breast cancer patients from the National Cancer Centre Singapore (NCCS) and KK Women's and Children's Hospital were asked to assess their self-perceived cognitive function. Based on their scores, they were separated into two groups: Those with cognitive impairment after chemotherapy (54 patients) and those without. There was a higher proportion of patients with the variation in their BDNF gene — a change in position of an amino acid in the gene — in the group without cognitive impairment..

Using statistical analysis, researchers found that patients with the gene variation had 74 per cent lower odds of developing self-perceived cognitive impairment. They were also less likely to experience impairment in verbal fluency and/or multitasking ability.

"This novel discovery can certainly help researchers better understand the underlying mechanisms that lead to the development of this chemotherapy-induced side effect," said Assoc Prof Chan. "More importantly, this will provide us with information on whether certain patients who are at high risk for cognitive impairment post-chemotherapy may benefit from early intervention."

The study, conducted from December 2011 to April 2014, followed an earlier study co-led by Assoc Prof Chan, which found that almost one-third (29.3 per cent) of 99 breast cancer patients reported cognitive impairment after chemotherapy.

Breast cancer is currently the top-ranked cancer among females in Singapore, representing 29.2 per cent of all cancer diagnosed among females between 2010 and 2014.

More than 90 per cent of patients with stage 1-4 breast cancer will undergo chemotherapy, said Dr Raymond Ng, a senior consultant medical oncologist at the NCCS, who was involved in the study.

Mr Terence Ng, who was the study's lead investigator, said the exact cause of chemobrain remains unknown, but studies have identified numerous biological, clinical and demographic factors that may contribute to it, such as age, anxiety, baseline intelligence and depression.

The types and dose intensity of chemotherapy regimens may also contribute to cognitive changes, he added.

There's still some way to go before the study findings can result in treatments for cognitive impairment. The team is now collecting additional patient samples for further studies to validate their findings. More studies on the impact of the gene variation among breast cancer patients are needed.

While chemobrain has been observed in patients with other types of cancer, including colorectal cancer and prostate cancer, more studies are needed to confirm if the findings can be extrapolated to other cancer types.

WHAT IS CHEMOBRAIN?
- Cognitive impairment, such as memory loss and difficulty in decision-making and multi-tasking, after chemotherapy.

WHAT CAUSES IT?
- The exact cause of chemobrain remains unknown, but studies have identified numerous biological, clinical and demographic factors that may contribute to it, such as age, anxiety, baseline intelligence and depression.
- The types and dose intensity of chemotherapy regimens may also contribute to cognitive changes.

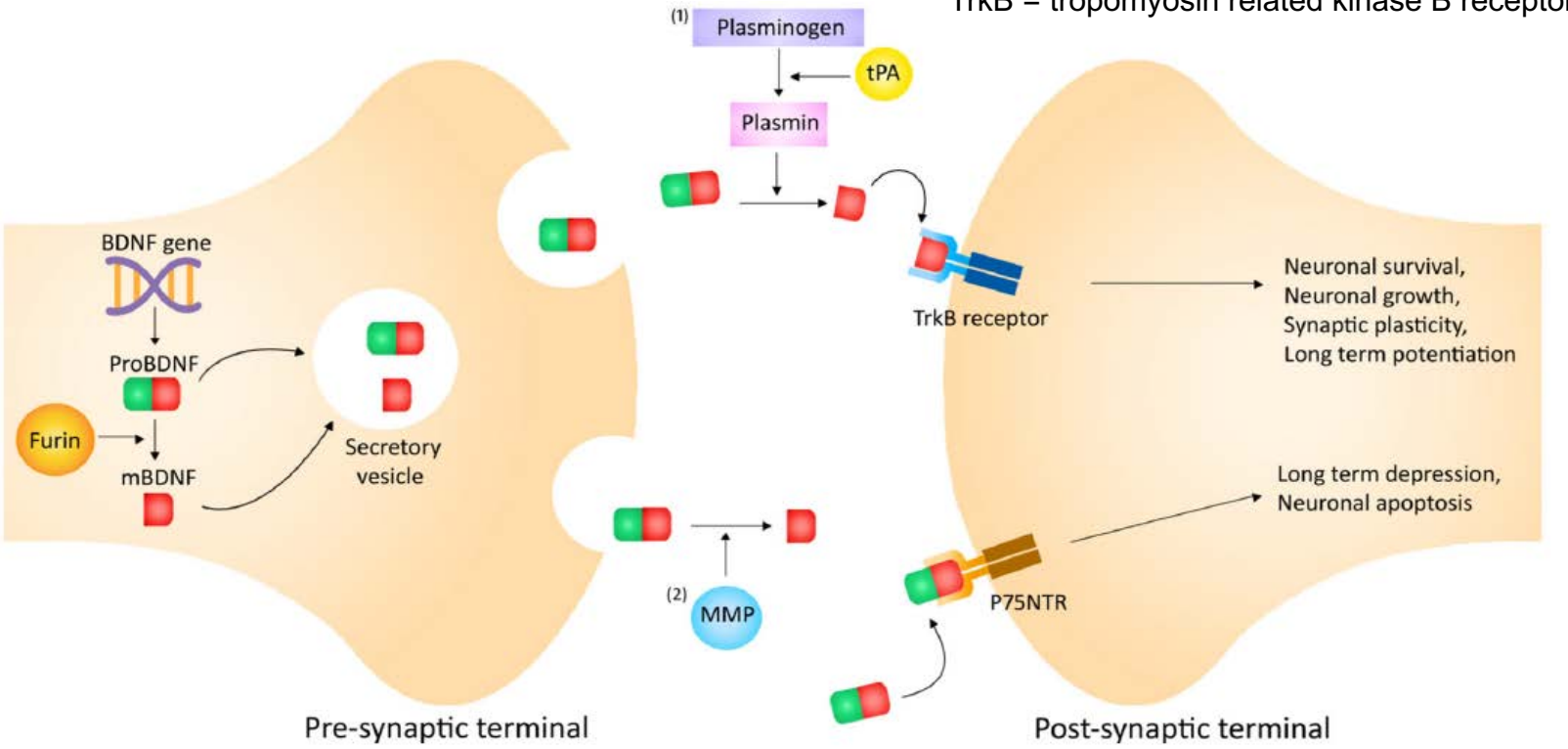
MORE STUDIES NEEDED
- While chemobrain has been observed in patients with other types of cancer besides breast cancer, more studies are needed to confirm if the findings can be extrapolated to other cancer types.

A patient receives chemotherapy treatment. Researchers have linked some side effects to the BDNF gene. PHOTO: REUTERS

30% of breast cancer patients in one study reported cognitive impairment after chemotherapy

Brain-derived neurotrophic factor (BDNF)

TrkB = tropomyosin related kinase B receptors



Ng T,.., Chan A. *BMC Cancer* 2017; 17:867

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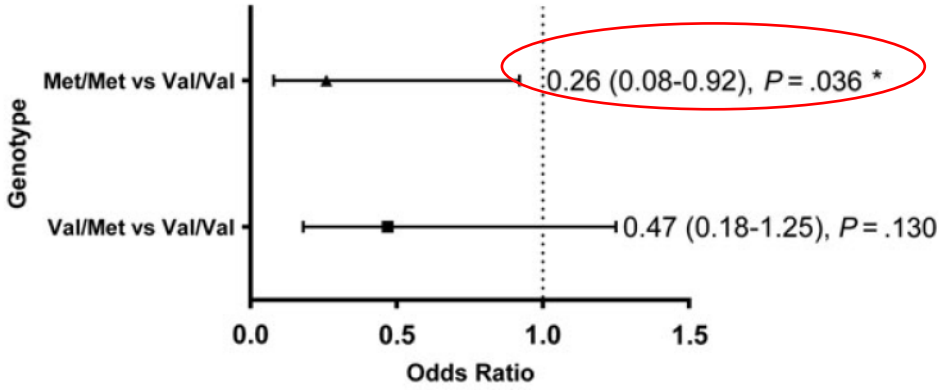
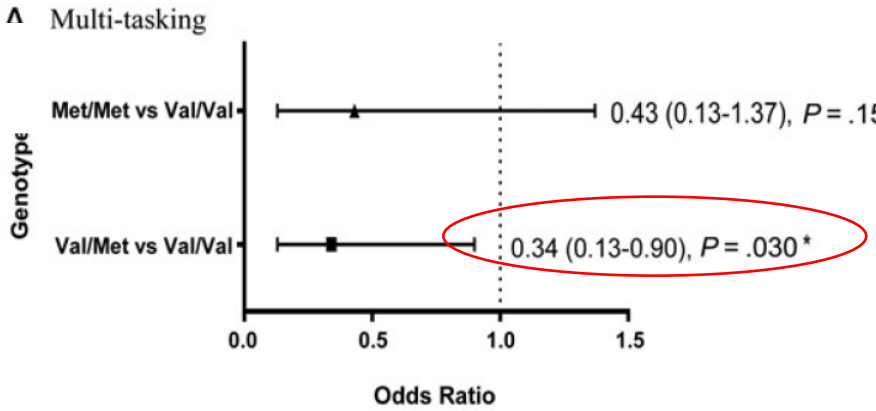
BDNF Val66Met polymorphism and CRCI

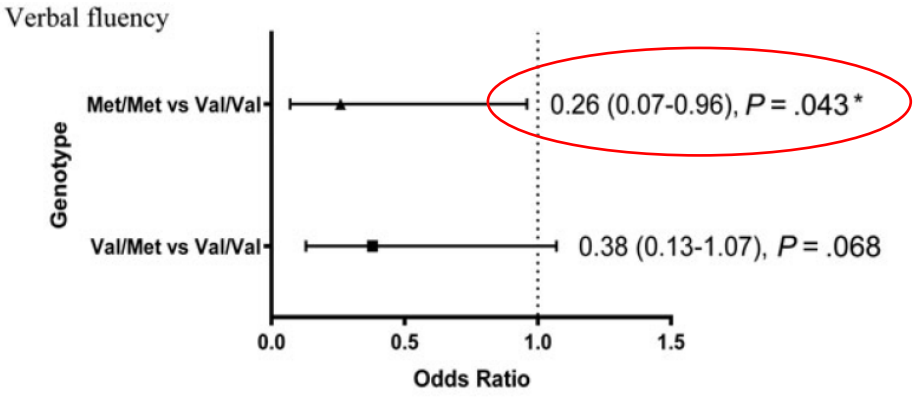
Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer

Terence Ng, Shu Mei Teo, Hui Ling Yeo, Maung Shwe, Yan Xiang Gan, Yin Ting Cheung, Koon Mian Foo, Mooi Tai Cham, Jung Ah Lee, Yee Pin Tan, Gilbert Fan, Wei Sean Yong, Madhukumar Preetha, Wei-Jen Kiley Loh, Si-Lin Koo, Amit Jain, Guek Eng Lee, Mabel Wong, Rebecca Dent, Yoon Sim Yap, Raymond Ng, Chiea Chuen Khor, Han Kiat Ho, and Alexandre Chan

Ng T,.., Chan A. *Neuro Oncol* 2016; 18(2):244-51







Carriers of at least one Met allele were associated with lower odds to develop impairment in the multi-tasking and verbal fluency domains.

Ng T,..,Chan A. *Neuro Oncol* 2016; 18(2):244-51

BDNF Val66Met polymorphism and CRCI

Table 6 Pooled odds ratios of CRCI among patients carrying BDNF Met allele (Val/Met or Met/Met) compared to Val/Val genotype

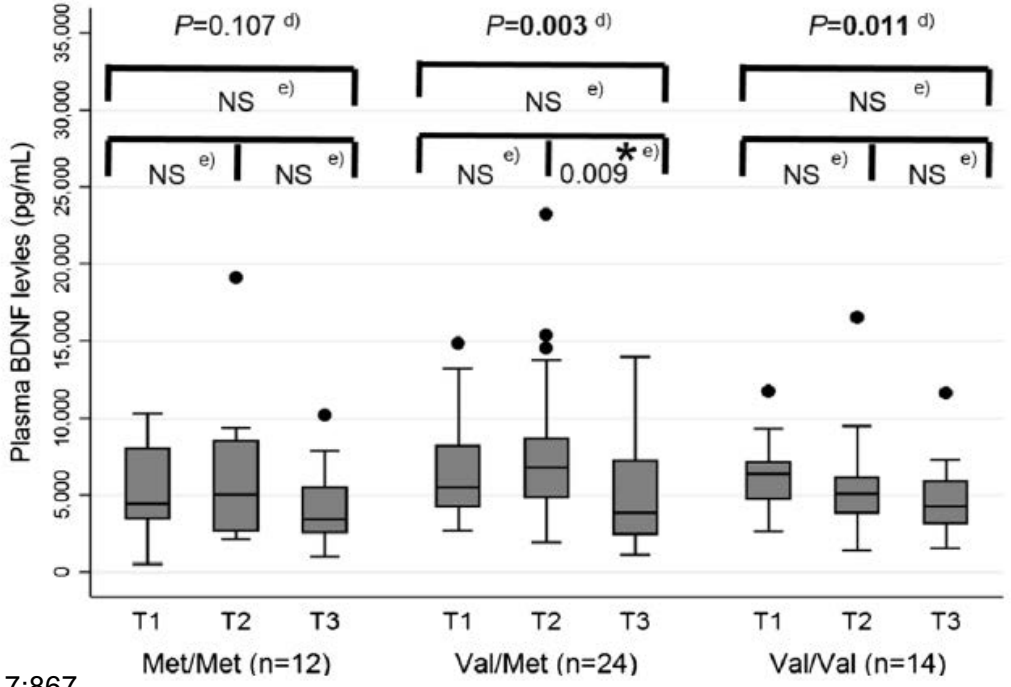
Domain	Cohort	OR (95% CI)	Weight	Pooled OR (95% CI)	*p* value	I^2 (%)
Summation	Previous	0.40 (0.16–1.04)	39.1	0.52 (0.29–0.94)	0.03[a]	0
	Current	0.62 (0.29–1.30)	60.9			
Memory	Previous	0.53 (0.19–1.53)	45.7	0.34 (0.17–0.70)	0.003[a]	17
	Current	0.24 (0.09–0.61)	54.3			
Multitasking	Previous	0.37 (0.15–0.91)	43.0	0.33 (0.18–0.59)	<0.001[a]	0
	Current	0.30 (0.14–0.67)	57.0			
Verbal ability	Previous	0.34 (0.12–0.90)	43.0	0.46 (0.24–0.88)	0.02[a]	0
	Current	0.57 (0.24–1.38)	57.0			
Concentration	Previous	0.61 (0.23–1.59)	40.9	0.75 (0.40–1.39)	0.36	0
	Current	0.86 (0.38–1.90)	59.1			
Mental acuity	Previous	1.03 (0.37–2.86)	36.5	0.62 (0.33–1.15)	0.13	34
	Current	0.46 (0.21–0.99)	63.5			
Functional interference	Previous	0.38 (0.13–1.14)	42.6	0.54 (0.26–1.09)	0.08	0
	Current	0.69 (0.27–1.75)	57.4			

[a] $p < 0.05$

Tan CJ,…, Chan A. *Mol Neurobiol* 2018. doi: 10.1007/s12035-018-1410-4

Evaluation of plasma brain-derived neurotrophic factor levels and self-perceived cognitive impairment post-chemotherapy: a longitudinal study

Terence Ng[1,2†], Ying Yun Lee[1†], Jung-woo Chae[1,2], Angie Hui Ling Yeo[1], Maung Shwe[1], Yan Xiang Gan[2], Raymond C. H. Ng[3,4], Pat Pak Yan Chu[5], Chiea Chuen Khor[6], Han Kiat Ho[1] and Alexandre Chan[1,2,3*]



Ng T,.., Chan A. *BMC Cancer* 2017; 17:867

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Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients

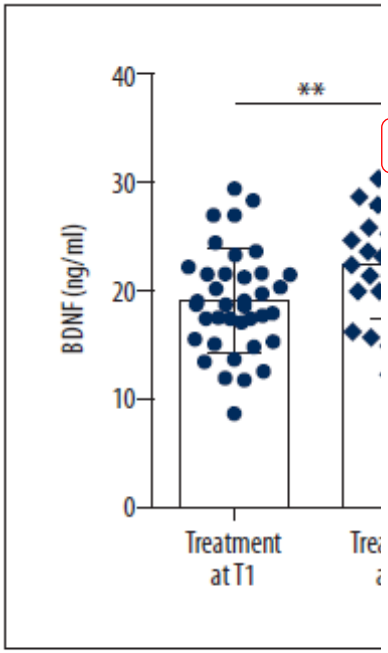

Figure 2. Levels of BDNF in s

Table 2. Summary of neuropsychologic assessment.

Metabolites	Treatment (n=39)			Control (n=36)			Repeated measures ANOVA	
	T1	T2	T value	T1	T2	T value	F	P
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD			
FACT-COG	98.75±12.94	102.38±13.78	4.840**	99.60±11.05	99.80±10.77	1.489	5.77	0.001
PCI	55.42±10.95	56.29±11.49	3.494**	57.55±8.43	57.35±8.99	0.721	3.21	0.027
QOL	11.33±3.42	11.75±3.38	2.632*	11.70±2.41	11.55±2.24	0.326	1.30	0.279
OTH	11.63±2.89	12.54±3.31	2.991**	11.10±2.65	11.30±1.92	1.189	0.48	0.697
PCA	20.38±4.19	21.79±4.40	2.298*	19.25±3.31	19.60±3.33	1.285	3.75	0.014
AVLT1	9.13±1.48	9.17±1.55	0.440	9.25±1.55	9.50±1.82	1.561	0.23	0.873
AVLT2	9.42±1.61	9.63±1.50	2.005	9.45±1.36	9.65±1.50	1.453	0.14	0.936
AVLT3	10.92±1.44	11.42±1.18	2.202*	10.75±1.59	10.70±1.49	0.357	5.21	0.002
VFT	17.88±3.33	18.21±3.74	1.163	18.50±3.38	19.15±2.83	1.412	0.56	0.642
SDMT	34.75±5.15	35.71±5.54	1.558	36.70±5.50	38.05±6.62	2.077	1.33	0.269
CDT	8.08±1.50	8.54±1.14	2.696*	8.10±1.21	8.05±1.36	0.438	5.50	0.002
TMT-B	95.58±26.67	95.46±26.80	0.901	92.35±27.06	90.40±26.19	1.698	0.19	0.901

Tong T, et al. *Med Sci Monit* 2018; 24: 2919-2927

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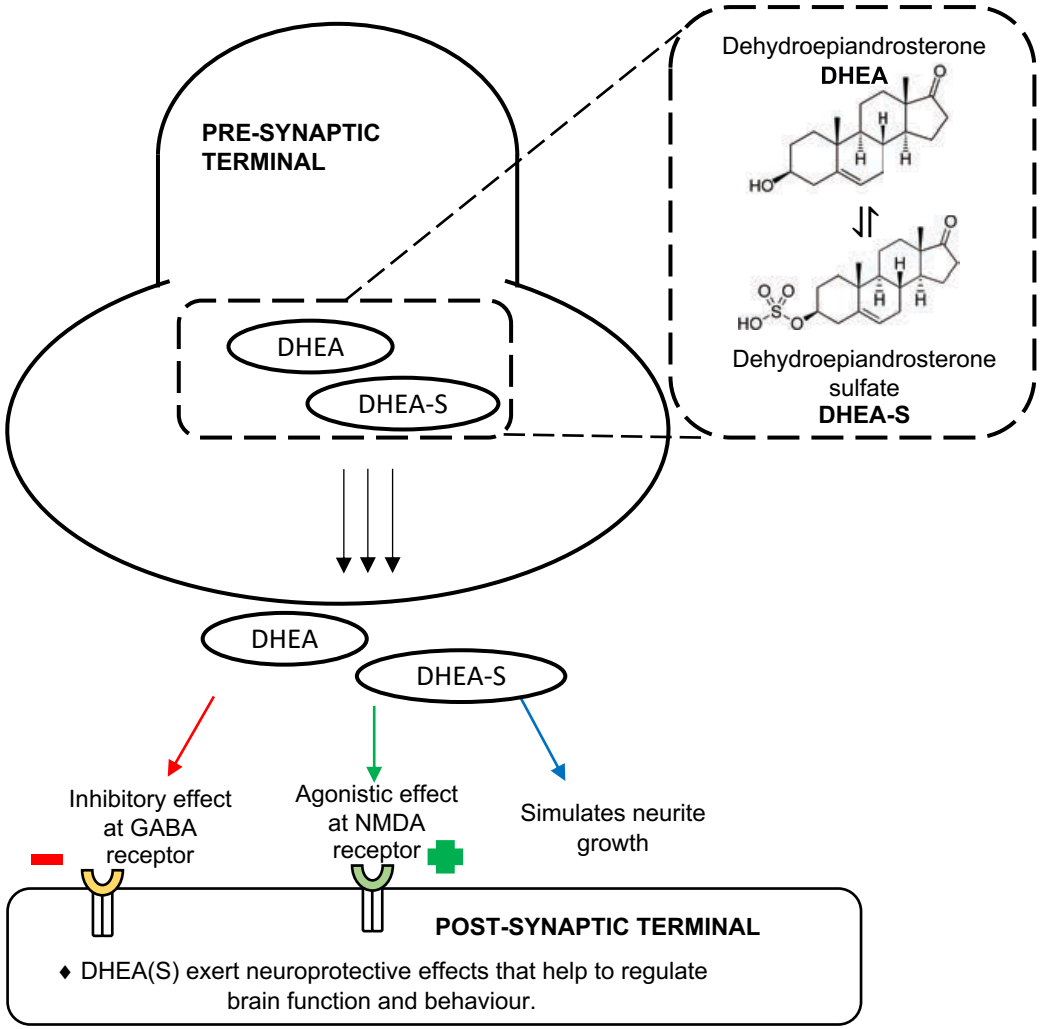
Dehydroepiandrosterone (DHEA)



Prechemotherapy Levels of Plasma Dehydroepiandrosterone and Its Sulfated Form as Predictors of Cancer-Related Cognitive Impairment in Patients with Breast Cancer Receiving Chemotherapy

Yi Long Toh,[1] Juliana Shariq Mujtaba,[1] Sumit Bansal,[1] Angie Yeo,[1] Maung Shwe,[1,2] Aik Jiang Lau,[1,3] and Alexandre Chan[1,2,4*]

[1]Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore; [2]Department of Pharmacy, National Cancer Centre Singapore, Singapore; [3]Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [4]Oncology Academic Clinical Program, Duke-National University of Singapore Medical School, Singapore

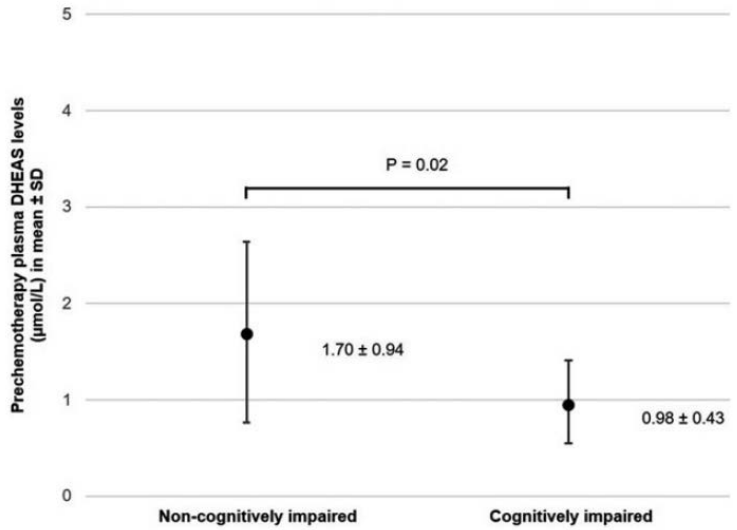


Figure 2. Box plots of mean ± SD baseline plasma dehydroepiandrosterone sulfate (DHEAS) levels for the non–cognitively impaired and cognitively impaired groups defined by the verbal fluency domain.

More details on June 22nd (Saturday) 3:50pm @ Station 3!

Toh YL,.., Chan A. *Pharmacotherapy* 2019;39(5):553-563

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Take home messages

- CRCI is a debilitating adverse effect of cancer and cancer therapy, yet effective management strategies are still lacking.

- Emerging targets and pathways, such as anti-inflammation, anti-oxidant, microglia activation, BDNF and DHEA, are being investigated for their roles in CRCI.

- Increase understanding of basic mechanisms is vital for the development of therapeutics that will mitigate this debilitating side effect of chemotherapy.

THANK YOU

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Presented by
Alex Chan, PharmD, MPH; phaac@nus.edu.sg