Breast Cancer: Basic and Clinical Research

REVIEW

Why, After Chemotherapy, is it Necessary to Assess Memory Using Translational Testing?

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Abstract: As the number of cancer survivors rises, so does the importance of understanding what happens post-chemotherapy. The evidence is clear that chemotherapy affects not only cancer cells, but also healthy cells including neurons, leading to long-term cognitive dysfunction in a large portion of survivors. In order to understand the mechanism of action and in the hope of reducing the potential neurocognitive side effects of chemotherapy, pre-clinical testing should be used more effectively. However, the field is lacking translation from clinical studies to animal models. Spatial learning and memory paradigms based on the water maze, the most commonly used rodent model, are available for translational testing in humans and could overcome this weakness. There is an overwhelming need in the field to understand whether the water maze is an adequate model for post-chemotherapy impairments or whether other paradigms should be used. This is of great importance for the understanding of the mechanisms, side effects of new drugs, appropriate pharmacotherapy, and confounding factors related to chemotherapy treatment regiments. This review is very important to both basic scientists and clinicians determining how translational paradigms are critical to future cancer research, as well as what type of paradigms are appropriate in our technically advancing society.

Keywords: water maze, cancer, memory, spatial, translation

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What Factors Affect Memory After Chemotherapy?

The prevalence of cancer has risen to epidemic proportions. Chemotherapy, the main treatment for cancer, is a disease treatment that makes use of chemical toxins that affect more than just cancer cells, leading to various symptoms that includes nausea, vomiting, fatigue, infection, and neuropathy, thus adversely impacting the treated individual's quality of life.[1] Regardless of cancer type, when chemotherapy survivors are asked how their treatments affected their mental processes, the majority report that their powers of recall are diminished and, in addition, they often complain of memory loss.[2,3] Unfortunately, unlike children, adults are not examined for long-term cognitive effects, which may result from the chemotherapeutic agents. Many are not even told that memory loss or cognitive decline is a side effect of treatment.

Regardless of the type of cancer, chemotherapy and surgery are the two main methods of treatment. Adjuvant chemotherapy is generally necessary to battle breast cancer with the administration of the chemotherapeutic agent(s) either orally or intravenously. This type of treatment involves drugs that move through the bloodstream, destroying malignant cells in their different phases of growth.[4] However, chemotherapy drugs do not only attack cancer cells but also cross the blood brain barrier and cause damage in several areas of the brain.[5–7] This effect is variously know as chemo-brain and chemo-fog; both expressions are used to describe the cognitive decline some patients experience post-chemotherapy.[8–10] The majority of studies that exist have been done with breast cancer patients because of their high survival rate, as well as the high rates of younger and middle-aged women who, after having undergone chemotherapy, complain of cognitive decline.

The chemicals used in chemotherapy induce negative effects on neurons, progenitor cells, and neurotransmitters involved in cognitive processing.[7,11] Methotrexate and 5-Flourouracil (5-FU), the two most common chemotherapy drugs used to treat breast, colorectal, head, and neck cancers, have been examined in pre-clinical models because of their neurological effects. In rodent models, systemic 5-FU has been shown to lead to delayed damage of the white-matter tracts, causing damage to the central nervous system.[12] Examinations of the hippocampus from 7 days to up to 1 month after single intravenous injections of methotrexate showed there to be reduced hippocampal cell proliferation.[13,14] One particular regimen, Cyclophosphamide, Methotrexate, and 5-FU (CMF), has also been shown to lead to decreased hippocampus cell proliferation and altered chromatin remodeling in the hippocampus.[15] In addition, carmustine (BCNU), cisplatin, and cytosine arabinoside (cytarabine) injections in mice lead to increased cell death and division in the sub-ventricular zone, dentate gyrus of the hippocampus, and corpus callosum.[7] Injections of cisplatin, cyclophosphamide, thiotepa, or ifosfamide in young rats led to widespread cortical and thalamic lesions.[16] The studies to which we have so far referred agree that chemotherapy drugs are neurotoxic, but how does that translate to humans and how can we assess damage in order to reduce the effects?

Imaging

Post-chemotherapy mental deficits are specific to a given patient and cannot be generalized. Small differences may not be detectable by standardized tests, or indeed the patient may simply be able to compensate for any difference(s).[17] As a result, recent studies have utilized brain imaging as a potential measure of post-chemotherapy neurological damage. Studies in breast cancer survivors have found smaller grey and white matter 1 year after chemotherapy in several areas, including the parahippocampal gyrus and prefrontal regions, both of which are linked to attention, concentration, and visual memory.[18,19] Drugs such as ifosfamide have side effects that include hallucinations, dizziness, confusion, and hemiparesis and have led to comas.[20] Leukoencephalopathy, a disease that destroys the brain's white matter, has also been reported as a neurological complication associated with such chemotherapy drugs as 5-FU, cisplatin, levamisole, methotrexate, and pirarubicin.[20–22] Neuroimaging has led to early detection of leukoencephalopathy, and with subsequent steroid treatment, the effects of leukoencephalopathy are reversible, regardless of the age of the sufferer.[21,23] In support of the idea of tracking, it can be beneficial to use neuroimaging techniques on patients who show any signs of cognitive decline.[24] However, a review of the literature indicates that the histological lesions in human brains that result from these types of neurological conditions are different than those found in animal models,[25] which may limit

the usefulness of such imaging for translation to pre-clinical models.

Standardize Neurocognitive Testing

There are more than 30 reviews that list all of the different tests used and domains tested in the examination of neurocognitive deficits after chemotherapy.[5,11,26–36] Studies vary significantly in terms of the tests used, sample sizes, and whether or not pre-chemotherapy testing was done. In addition, there is a huge variety of confounding factors related to neurocognitive assessments.[37] There are many confounding biological factors to consider in these studies, including types of controls, age, gender, stress levels, menopausal status, and whether or not a given sample group member is undergoing hormone therapy. The list goes on and on.

When assessing post-chemotherapy cognitive status in older individuals, age-associated cognitive decline and the assortment of sensory and memory issues generally linked to aging must also be taken into account.[37] With advances in technology, we are beginning to observe more individuals under 50 years of age being diagnosed with cancer. These individuals still have many years of work ahead of them. Memory is essential to their ability to function properly. These individuals are also more likely to be subjected to more intense treatment regimens to prevent the reoccurrence of their cancer. This may explain why younger individuals appear to be more cognitively affected by chemotherapy than their older counterparts.[2,38] Even when slight, the cognitive effects of chemotherapy can negatively impact work performance and the ability to care for children.[29,39,40] In addition, some individuals become so impaired they are no longer able to maintain their jobs or careers, making the stress of caring for their families that much harder. Very few studies have examined younger patients (those under 40) and the impact of chemotherapy in that group. We need to keep in mind that younger patients are greater users of technology and that the types of assessments for memory that involve computer-based programs can and should therefore be considered.

Recommendations have been made by the International Cognition and Cancer Task Force (ICCTF) to include measures of learning and memory, processing speed, and executive function (Hopkins Verbal Learning Test-Revised [HVLT-R], Trail-Making Test [TMT], Controlled Oral Word Association [COWA], and the Multilingual Aphasia Examination)[41] as standard batteries in the clinical testing of post-chemotherapy patients. The ICCTF recommends that future clinical studies include pre-chemotherapy testing, consider sample size, and use controls appropriately. The ICCTF further recommends that additional standardized methods of analysis need to be developed for use in such studies.[41,42] Even if there is more standardization, what are these tests going to tell us and how can we improve treatments? Are the standard pen/pencil or puzzle-like neurocognitive assessments to measure intelligence, executive function, visual memory, motor coordination, and psychomotor speed really valid to help us understand the mechanism of impairments? All of these tests have one thing in common:—they do not translate to pre-clinical models (Fig. 1). The issue is how sensitive are the measures and how that information can be translated to neuronal functioning and an understanding of the mechanism of action in pre-clinical models.[43]

Why is it Important to Translate Animal Models to Clinical Testing?

An important issue to consider is that not all individuals will display similar cognitive impairments even if undergoing the same regimen. Every individual is unique and his or her response to drugs and the type of cancer they have will alter the treatment received. It should also be noted that chemotherapy drugs are administrated as part of a complete regimen, with other medications included in order to reduce side effects; how these medications interact and effect cognition makes the results of clinical testing almost impossible to interpret. In terms of neurocognitive testing itself, there are many studies that examine the domains and the types of tests used[5,11,27–29,31–33,44,45] for those in the post-chemotherapy phase. In the more than 50 studies that have been conducted to examine the long-term effects of chemotherapy, only a handful have included visual-spatial tasks; these types of tasks are paradigms that can be used to translate between clinical and pre-clinical models. Those tests that have been used have included the Block Design test, which is a subtest of Wechsler's Adult Intelligence Scale-III that uses colored blocks to represent a design (Fig. 1), and the Rey-Osterrieth Complex Figure Test (RCFT),

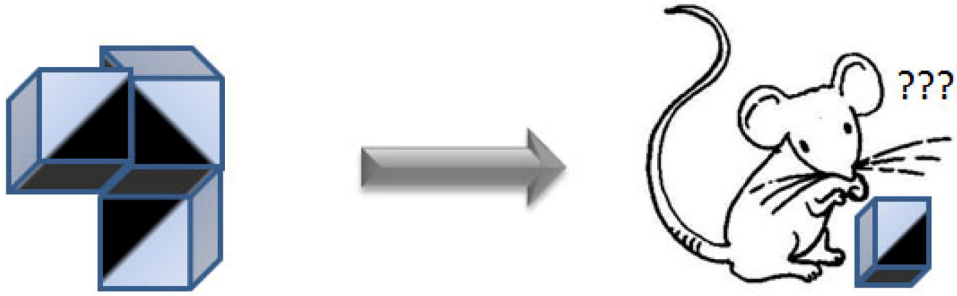

Figure 1. The Block Design task and a mouse unable to understand the task.

a memory test that is used to assess visuospatial construction or Visual Reproduction a subtest of the Wechsler's Memory Scale—Revised (WMS-R) (Table 1).[46–50] The results of these studies do not agree on whether chemotherapy impacts long-term visual-spatial memory, but the tasks used vary significantly and are, it should be noted again, not translatable to pre-clinical models (Table 1).

The Morris water maze (MWM)[51] is the most commonly used and recognized spatial learning and memory test used for the pre-clinical assessment of drug use and various confounding factors such as genetics, age, and gender, assessing these both in terms of acute and long-term learning and memory effects (Fig. 2). This rodent based test has been use for the understanding of the mechanism of neuro-physiological/neuro-anatomical changes and can be used to assess learning and memory in a way that is translatable to humans. The drugs that are part of the CMF regimen have been studied extensively in animals in terms of their acute and long-term cognitive

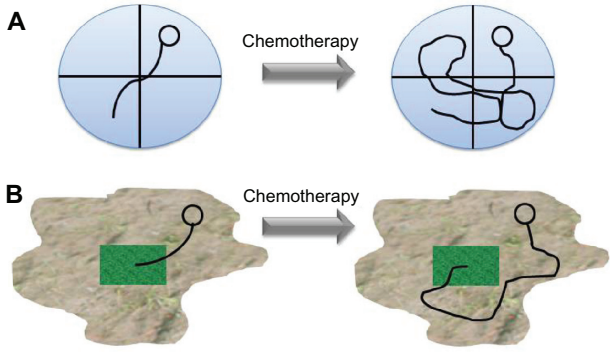

Figure 2. A representation of the Morris Water Maze (MWM) and Memory Island (MI) program translation between rodent and human tasks. (**A**) Diagram of the MWM pool and a representative path that a rodent takes to reach the platform. After chemotherapy treatment, rodents take a longer path to reach the platform. (**B**) Diagram of MI and the pathway a person might use to navigate to the target. After chemotherapy, they take a longer pathway to find the target.

effects using the MWM task. Examination at 7 days and 1 month after a single intravenous injection of methotrexate induced impairments in a MWM probe trial and delayed memory performance and novel object recognition.[13,14] In mice injected intraperitoneally (i.p.) weekly with methotrexate, impairments were apparent in initial hidden spatial memory in a MWM.[52] There have also been studies in pre-clinical models that have not shown there to be long-term cognitive impairments in animals that perform the MWM after repeated treatments with CMF.[53,54] Of all these experiments, time between exposure and testing, number of injections, and type of test varied significantly. More consistency between studies is needed to definitively determine whether this paradigm mimics the cognitive effects seen in humans.

Additional medications are administered for women with estrogen positive cancers, including taxol (tamoxifen), which is an estrogen receptor modulator (SERM). Compared to women on chemotherapy alone, those women who received chemotherapy and tamoxifen scored lower in visual memory and verbal working memory (Table 1).[47,49,55] A follow-up study of women who continued to take taxomifen for at least 5 years after chemotherapy treatment as a prevention measure also found that they faired negatively when compared to non-tamoxifen users, with more complaints of memory problems and reduced scores on narrative writing task.[56] In rodent models, repeated administration of tamoxifen or combinations of methotrexate and 5-FU injections both produced deficits in acquisition and retention in an operant learning paradigm.[57] Although the tests are not comparable, they indicate that secondary treatments are a potential confounding factor to consider when assessing post-chemotherapy neurocognitive side effects. Evidence supports that secondary drugs

Table 1. Chemotherapy and visual spatial impairments in humans.

Ref	Groups	Cancer Type	n	Sex	Testing Age	Treatment	Test used	Effect of Chemotherapy
47	Chemotherapy	BC Stage I-IV	19	F	42.6 ± 5.4	Pre/Post (1 week, 1 year)	RCFT – Immediate Recall	No effect
	Chemotherapy + Tamoxifen	BC Stage I-IV	19	F	40.1 ± 6.5	Pre/Post (1 week, 1 year)	RCFT—Delay Recall	No effect
	Surgery only	BC Stage I-II			44.5 ± 4.1	Surgery only		
48	Chemotherapy	BC Stage I-IV Lymphoma	36	F/M	48.6 ± 8.0	CEF (Pre/Post)	RCFT—Copy	No effect
	Cardiac		14	F/M	40.4 ± 9.1		RCFT—Immediate Recall	No effect
	Healthy		17	F/M	39.3 ± 11.7		RCFT—Delay Recall	No effect
49	Chemotherapy	BC Stage I-II	18	F	46.8 ± 4.0*	CMF	Visual Reproduction I (WMS-R)	Effect
	Chemotherapy + Tamoxifen	BC Stage I-II	18	F		ACT	RCFT—Copy Trail	Effect
	Surgery only	BC Stage I-II	17	F	48.3 ± 6.3		Block Design (WAIS-III)	Effect
50	Chemotherapy	BC Stage I-II	18	F	47.1 ± 6.5*	CMF (3 years)	RCFT—Copy	No effect
	Chemotherapy + Tamoxifen	BC Stage I-II	18	F		CMF (3 years)	RCFT—Immediate Recall	Effect
	Surgery only		34	F	46.1 ± 5.2		Visual Reproduction (WMS-R)	Effect
65	Chemotherapy	BC Stage I-IV	22	F	46.7 ± 3.8	Various (Post only)	Memory Island – Immediate Recall	Effect
	Healthy		16	F	52.5 ± 2.0		Memory Island – Delay Recall	Effect
							Block Design (WAIS-III)	No effect

Note: *age was reported for combined Chemotherapy and Chemotherapy + Tamoxifen groups.
Abbreviations: RCFT, Rey-Osterrieth Complex Figure Test; CMF, cyclophosphamide, methotrexate, and 5-FU; ACT,adriamycin, cytoxan and taxol; CEF, cyclophosphamide, epirubicin and 5-FU; Pre/Post, Chemotherapy; BC, Breast Cancer; WMS-R, Wechsler's Memory Scale – Revised; WASI-III, Wechsler abbreviated scale of intelligence.

such as raloxifene, letrozole or exemestane (SERM/aromatase inhibitors) may be better alternatives to the more commonly used tamoxifen, as they appear to have fewer or no confounding side-effects on overall cognitive health.[55,58–62] Although these drugs are newer to the market, they tend to be more expensive and as only a few studies are available, both doctors and patients have to consider options and weigh risks.

Today's technology is advancing and so are the available methods of assessing learning and memory impairments. Using human versions of visual-spatial memory tasks such as the "Memory Island" (MI) program is a useful way of helping to transition from pre-clinical models to a clinical setting (Fig. 2). MI is a virtual reality program designed to mimic the MWM four-quadrant coordinate system. In MI, individuals find both visible (marked) and hidden targets on a virtual island designed by Dr. Jacob Raber (Oregon Health Science University) and Dean Inman (Oregon Research Institute) (Fig. 2).[63] Performance measures are the same as in MWM, wherein distance, latency, velocity, and distance from the target can be assessed. MI examines motor coordination, working memory, picture recognition, visual-spatial memory, and verbal/non-verbal ability.[63–66] MI can also be an appropriate measure of visual-spatial learning and memory suitable for use in multiple (non-English speaking) cultures, as it is considered a non-verbal test.[66] MI adequately assesses depth perception, visual-spatial attention, figure-ground discrimination, spatial perception, and orientation.[63–66] Furthermore, these types of paradigms can be utilized as quantitative and qualitative measures in research projects or for clinical screening following traumatic brain injury, as well as in the assessment of Alzheimer's disease or other neurodegenerative conditions. Additionally, there are other tests that result in data that are easily translatable to clinical settings; these include Novel Image/Novel Location tasks, which examine spatial picture location recognition and are used to model novel object recognition in pre-clinical models.[63,65,66] There have also been significant advances in touch screen technology to translate rhesus monkey working memory tasks into clinical assessments.[67,68] Determining the long-term cognitive deficits that result from chemotherapy remains an urgent need and one that can be fulfilled through the use of translational paradigms.

In breast cancer survivors who were a minimum of 1 year post-chemotherapy (mixed regimens), a study found reduced performance in MI performance measures in terms of both immediate and delayed spatial memory when compared to health controls (Table 1).[66] The breast cancer survivors were able to learn the tasks to a similar degree as the controls, but took longer to find the targets once the visible cues were gone (hidden trials).[66] After 15 minutes in the delayed memory trial, only 50% of the breast cancer survivors were able to find the target compared to the 82% of healthy controls that were able to do so (Table 1).[66] The results are similar to those found in the rodent model of long-term chemotherapy exposure.[14,15]

The study also found that particular coping strategies were associated with MI performance. Those that use emotional coping displayed reductions in learning and immediate MI performance when compared to those who use more problem-focused coping.[66] Those that used problem-focused coping also performed better in delayed spatial memory performance, had higher general intelligence scores, and showed an increased ability to perform psychomotor speed tasks. Understanding the link between coping and cognition can help in the development of behavioral therapies to help patients resume normal functioning. Although this was only a pilot study and did not account for pre-chemotherapy differences, it does help to validate the use of MWM in pre-clinical testing for the assessment of the cognitive effects of chemotherapy drugs. Future longitudinal studies will include more subjects to assess different chemotherapy regimen effects as well as genetic, age-related, and other potential confounders.

Conclusion

In the era of technology, scientists and clinicians alike need to adapt to the tools available. The overall goal has always been translation of bench to bedside, but we have to know if the bench is truly examining what is actual taking place as a result of a disease and/or treatment for that disease. Although, cancers such as breast cancer do not affect the brain per se, there is clear evidence that the treatments do have an effect on a significant proportion of patients. We have to consider a patient's overall health, well-being, and ability to function after treatment, which includes reintegration into daily function and/or work environments. We need to make it a

priority to reduce the side effects of the drugs used and to optimize the use of appropriate animal models. MWM is the most widely used behavioral paradigm in rodents and is used for the examination of all manner of treatments and diseases models, but is it really the best model for every condition that affects the brain? Does it truly examine what happens in humans? These questions are critical for the future of model system research. Most chemotherapy drugs have never been tested with respect to long-term cognitive effect in rodents and need to be in order to help identify those with minimal side-effects. MWM is the old standby with respect to examining long-term cognitive side effects post-pharmacotherapeutic intervention; however there are other translational paradigms such object recognition[63] and fear conditioning[69,70] rodent-based paradigms that have recently been adapted for clinical studies. Researchers and clinicians alike need to determine how and what paradigms should be used in both pre-clinical and clinical settings.

There is also a serious lack of communication between clinicians, neuropsychologists, and neuroscience researchers. When examining cancer patients post-treatment, clinicians take advantage of neuropsychologists' advice to design testing batteries, and basic scientists for pharmacological efficacy; however, they do not take advantage of what a behavioral neuroscience animal model researcher could bring to the table. I propose that when batteries are constructed in clinical studies for the purpose of examining neurocognitive status (post-pharmacotherapeutic intervention), a behavioral neuroscience animal model researcher needs to be involved in the development, in order to help insure that translational testing is used, thus aiding in the study of the mechanism. Translational testing should be the norm, not an afterthought. Behavioral neuroscience researchers understand that the point of the treatment is to cure the disease first and foremost, but they also understand how detrimental the neurocognitive side effects of the treatments can be on a patient's functioning post-treatment. Only by working together can we help make the patient diseases free while also increasing the probability of them regaining normal functioning.

We can also use technology in memory based rehabilitation programs. First of all, as standard of care all patients undergoing chemotherapy should have neuropsychological assessments completed before treatment is initiated; therefore, a neuropsychologist can assess pre-morbid functioning. Patients that display reduced cognitive functioning post-treatment have several options of rehabilitation measures, depending on the type of impairment. For example, there are computer memory exercise programs, memory practice drills (repeating word list), spaced retrieval interventions (SR) and applied neurocognitive interventions (Mnemonic training, Prospective Memory Process Training (PROMPT), errorless training, Assisted Mirror Reading) available for to help patients in restoration (rebuilding lost abilities), reorganization (substituting current abilities for those lost). There are also tools to help the patient during treatment work for both acute and long-term disorienting side-effects, including memory notebooks, electronic organizers, and environmental modifications. Most critical of all is keeping the patient brain active and helping patients maintain normal day to day activities.

Future Prospective

Considering the diversity of treatments and symptoms, the wonder drug that can cure all cancers and has no side effects will not be found. What we can do is reduce the impact and intensity of cognitive side-effects by taking into account an individual's genetics. Genetic studies involving genes such as Apolipoprotein E (ApoE), which has three common alleles (*ApoE2*, *ApoE3* and *ApoE4*), suggest *ApoE4* carrier status as a potential genetic risk factor in the early-onset of breast cancer and neurocognitive impairments post-chemotherapy.[46,71] *ApoE4* carriers displayed several impairments, specifically in visual memory and spatial ability,[46] providing at least primary evidence that *ApoE* genotype may be a confounding factor when assessing cognitive status. The clinical study is consistent with rodent models, where transgenic mice expressing human *ApoE4* display behavioral abnormalities such as deficits in MWM performance,[51] as well as significant alterations in the hippocampus and cortex.[72,73] Several studies conducted in the last few years, have consistently found that the response to particular chemotherapies and hormone therapies appear to be *ApoE* genotype dependent.[59] This strongly suggests that future studies must address the confounding factor of an individual's genetics. The future of medicine will require tailoring a patient's treatment based not only on the type of cancer and tumor profile, but also that individual's genetics and how that will affect the potential side-effects of the treatments.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Author Contributions

Conceived and designed the experiments: SFA. Analysed the data: SFA. Wrote the first draft of the manuscript: SFA. Contributed to the writing of the manuscript: SFA. Agree with manuscript results and conclusions: SFA. Jointly developed the structure and arguments for the paper: SFA. Made critical revisions and approved final version: SFA. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References

1. Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. *Curr Oncol*. 2007;14:173–9.
2. Myers JS, Sousa VD, Donovan HS. Predictors of self-reported memory problems in patients with ovarian cancer who have received chemotherapy. *Oncol Nurs Forum*. 2010;37:596–603.
3. Ferguson RJ, McDonald BC, Saykin AJ, et al. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. *J Clin Oncol*. 2007;25:3866–70.
4. Verstappen CC, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs*. 2003;63:1549–63.
5. Nelson CJ, Nandy N, Roth AJ. Chemotherapy and cognitive deficits: mechanisms, findings, and potential interventions. *Palliat Support Care*. 2007;5:273–80.
6. Wigmore PM, Mustafa S, El-Beltagy M, et al. Effects of 5-FU. *Adv Exp Med Biol*. 2010;678:157–64.
7. Dietrich J, Han R, Yang Y, et al. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. *J Biol*. 2006;5:22.
8. Hurria A, Somlo G, Ahles T. Renaming "chemobrain". *Cancer Invest*. 2007;25:373–7.
9. Meyers CA. How chemotherapy damages the central nervous system. *J Biol*. 2008;7:11.
10. Scherwath A, Mehnert A, Schleimer B, et al. Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects. *Ann Oncol*. 2006;17:415–23.
11. Ahles TA, Saykin A. Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Invest*. 2001;19:812–20.
12. Han R, Yang YM, Dietrich J, et al. Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. *J Biol*. 2008;7:12.
13. Seigers R, Schagen SB, Beerling W, et al. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. *Behav Brain Res*. 2008;186:168–75.
14. Seigers R, Schagen SB, Coppens CM, et al. Methotrexate decreases hippocampal cell proliferation and induces memory deficits in rats. *Behav Brain Res*. 2009;201:279–84.
15. Briones TL, Woods J. Chemotherapy-induced cognitive impairment is associated with decreases in cell proliferation and histone modifications. *BMC Neurosci*. 2011;12:124.
16. Rzeski W, Pruskil S, Macke A, et al. Anticancer agents are potent neurotoxins in vitro and in vivo. *Ann Neurol*. 2004;56:351–60.
17. Raffa RB. Is a picture worth a thousand (forgotten) words?: neuroimaging evidence for the cognitive deficits in 'chemo-fog'/'chemo-brain'. *J Clin Pharm Ther*. 2010;35:1–9.
18. Inagaki M, Yoshikawa E, Matsuoka Y, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer*. 2007;109:146–56.
19. Deprez S, Amant F, Smeets A, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *J Clin Oncol*. 2012;30: 274–81.
20. Minisini A, Atalay G, Bottomley A, et al. What is the effect of systemic anticancer treatment on cognitive function? *Lancet Oncol*. 2004;5:273–82.
21. Choi SM, Lee SH, Yang YS, et al. 5-fluorouracil-induced leukoencephalopathy in patients with breast cancer. *J Korean Med Sci*. 2001;16:328–34.
22. Israel ZH, Lossos A, Barak V, et al. Multifocal demyelinative leukoencephalopathy associated with 5-fluorouracil and levamisole. *Acta Oncol*. 2000;39:117–20.
23. Fujimoto C, Ito K, Iwasaki S, et al. Reversible impairment of auditory callosal pathway in 5-fluorouracil-induced leukoencephalopathy: parallel changes in function and imaging. *Otol Neurotol*. 2006;27:716–9.
24. Taillibert S, Voillery D, Bernard-Marty C. Chemobrain: is systemic chemotherapy neurotoxic? *Curr Opin Oncol*. 2007;19:623–7.
25. Gold R, Hartung HP, Toyka KV. Animal models for autoimmune demyelinating disorders of the nervous system. *Mol Med Today*. 2000;6:88–91.
26. Castellon SA, Silverman DH, Ganz PA. Breast cancer treatment and cognitive functioning: current status and future challenges in assessment. *Breast Cancer Res Treat*. 2005;92:199–206.
27. Cheung YT, Chui WK, Chan A. Neuro-cognitive impairment in breast cancer patients: Pharmacological considerations. *Crit Rev Oncol Hematol*. Jul 2012;83(1):99–111.
28. Correa DD, Ahles TA. Neurocognitive changes in cancer survivors. *Cancer J*. 2008;14:396–400.

29. Janelsins MC, Kohli S, Mohile SG, et al. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Semin Oncol*. 2011;38:431–8.
30. Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. *J Clin Oncol*. 2007;25:2455–63.
31. Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. *Br J Cancer*. 2004;90:1691–6.
32. Quesnel C, Savard J, Ivers H. Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. *Breast Cancer Res Treat*. 2009;116:113–23.
33. Vearncombe KJ, Rolfe M, Wright M, et al. Predictors of cognitive decline after chemotherapy in breast cancer patients. *J Int Neuropsychol Soc*. 2009;15:951–62.
34. Correa DD, Hess LM. Cognitive function and quality of life in ovarian cancer. *Gynecol Oncol*. 2012;124:404–9.
35. Koppelmans V, Breteler MM, Boogerd W, et al. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol*. 2012;30:1080–6.
36. Morse R, Rodgers J, Verrill M, et al. Neuropsychological functioning following systemic treatment in women treated for breast cancer: a review. *Eur J Cancer*. 2003;39:2288–97.
37. Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. *J Am Geriatr Soc*. 2006;54:925–31.
38. Baker F, Denniston M, Smith T, et al. Adult cancer survivors: how are they faring? *Cancer*. 2005;104:2565–76.
39. Wefel JS, Lenzi R, Theriault RL, et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004;100:2292–9.
40. Reid-Arndt SA, Yee A, Perry MC, et al. Cognitive and psychological factors associated with early post-treatment functional outcomes in breast cancer survivors. *J Psychosoc Oncol*. 2009;27:415–34.
41. Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12:703–8.
42. Shilling V, Jenkins V, Trapala IS. The (mis)classification of chemo-fog—methodological inconsistencies in the investigation of cognitive impairment after chemotherapy. *Breast Cancer Res Treat*. 2006;95:125–9.
43. Tannock IF, Ahles TA, Ganz PA, et al. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol*. 2004;22:2233–9.
44. Phillips KA, Bernhard J. Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. *J Natl Cancer Inst*. 2003;95:190–7.
45. Whitney KA, Lysaker PH, Steiner AR, et al. Is "chemobrain" a transient state? A prospective pilot study among persons with non-small cell lung cancer. *J Support Oncol*. 2008;6:313–21.
46. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*. 2003;12:612–9.
47. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. *Psychooncology*. 2006;15:422–30.
48. Mehlsen M, Pedersen AD, Jensen AB, et al. No indications of cognitive side-effects in a prospective study of breast cancer patients receiving adjuvant chemotherapy. *Psychooncology*. 2009;18:248–57.
49. Castellon SA, Ganz PA, Bower JE, et al. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol*. 2004;26:955–69.
50. Schagen SB, van Dam FS, Muller MJ, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer*. 1999;85:640–50.
51. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. *J Neurosci Methods*. 1984;11:47–60.
52. Winocur G, Vardy J, Binns MA, et al. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. *Pharmacol Biochem Behav*. 2006;85:66–75.
53. Lee GD, Longo DL, Wang Y, et al. Transient improvement in cognitive function and synaptic plasticity in rats following cancer chemotherapy. *Clin Cancer Res*. 2006;12:198–205.
54. Long JM, Lee GD, Kelley-Bell B, et al. Preserved learning and memory following 5-fluorouracil and cyclophosphamide treatment in rats. *Pharmacol Biochem Behav*. 2011;100:205–11.
55. Collins B, Mackenzie J, Stewart A, et al. Cognitive effects of hormonal therapy in early stage breast cancer patients: a prospective study. *Psychooncology*. 2009;18:811–21.
56. Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat*. 2000;64:165–76.
57. Walker EA, Foley JJ, Clark-Vetri R, et al. Effects of repeated administration of chemotherapeutic agents tamoxifen, methotrexate, and 5-fluorouracil on the acquisition and retention of a learned response in mice. *Psychopharmacology (Berl)*. 2011;217:539–48.
58. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353:2747–57.
59. Acevedo SF. The confounding factor of apolipoprotein E on response to chemotherapy and hormone regulation altering long-term cognition outcomes. In: Kostner G, Frank S, editors. *Lipoproteins—Role in Health and Diseases*. Rijeka, Croatia: InTech; 2012.
60. Phillips KA, Ribi K, Sun Z, et al. Cognitive function in postmenopausal women receiving adjuvant letrozole or tamoxifen for breast cancer in the BIG 1-98 randomized trial. *Breast*. 2010;19:388–95.
61. Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med*. 2001;344:1207–13.
62. Agrawal K, Onami S, Mortimer JE, et al. Cognitive changes associated with endocrine therapy for breast cancer. *Maturitas*. 2010;67:209–14.
63. Rizk-Jackson AM, Acevedo SF, Inman D, et al. Effects of sex on object recognition and spatial navigation in humans. *Behav Brain Res*. 2006;173:181–90.
64. Acevedo SF, Piper BJ, Craytor MJ, et al. Apolipoprotein E4 and sex affect neurobehavioral performance in primary school children. *Pediatr Res*. 2010;67:293–9.
65. Piper BJ, Acevedo SF, Edwards KR, et al. Age, sex, and handedness differentially contribute to neurospatial function on the Memory Island and Novel-Image Novel-Location tests. *Physiol Behav*. 2011;103:513–22.
66. Ayala-Feliciano M, Pons-Valerio JJ, Pons-Madera J, et al. The relationship between visuospatial memory and coping strategies in breast cancer survivors. *Breast Cancer (Auckl)*. 2011;5:117–30.
67. Verrico CD, Liu S, Asafu-Adjei JK, et al. Acquisition and baseline performance of working memory tasks by adolescent rhesus monkeys. *Brain Res*. 2011;1378:91–104.
68. Maki Y, Yoshida H, Yamaguchi H. Computerized visuo-spatial memory test as a supplementary screening test for dementia. *Psychogeriatrics*. 2010;10:77–82.
69. Milad MR, Goldstein JM, Orr SP, et al. Fear conditioning and extinction: influence of sex and menstrual cycle in healthy humans. *Behav Neurosci*. 2006;120:1196–203.
70. Milad MR, Wright CI, Orr SP, et al. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry*. 2007;62:446–54.
71. Porrata-Doria T, Matta JL, Acevedo SF. Apolipoprotein E allelic frequency altered in women with early-onset breast cancer. *Breast Cancer (Auckl)*. 2010;4:43–8.
72. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *J Lipid Res*. 2009;50 Suppl:S183–8.
73. Struble RG, Cady C, Nathan BP, et al. Apolipoprotein E may be a critical factor in hormone therapy neuroprotection. *Front Biosci*. 2008;13:5387–405.

Supplementary Data

A video abstract by the authors of this paper is available. video-abstract10293.mov