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Yara Alshaabi  
*University of Vermont*

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Interaction of Age and Cancer Treatment on Brain Function and Structure in Breast Cancer Survivors

Yara Alshaabi

In Partial Fulfillment of the Requirements for Graduation from the Honors College with a Bachelor of Science in Biological Sciences

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University of Vermont Committee:

Julie Dumas, Ph.D.

Alison Brody, Ph.D.

Laura Hill, Ph.D.
Abstract

Breast cancer is a common form of cancer that is increasing in its diagnosis among women in the last few decades. Cancer treatments such as chemotherapy, radiation, and hormone therapy are approved forms of treatment for breast cancer that have been shown to cause improvements in long term cancer survival (eg. Hutchinson et al. 2012). However, many cancer survivors report adverse effects of the cancer treatment on their memory and thinking. The research literature shows that despite the improving survival rate, cancer and cancer treatment have detrimental effects on survivors’ brain function. For instance, studies have shown that cancer treatment can cause changes attentional processing, and executive functioning. On the other hand, normal aging also has an adverse effect on brain function. In this study, I examined how age and time since cancer treatment influenced the function and structure of the brain. The main goal of this study was to examine the short and long term effects of cancer treatment on brain structure and function in older women. Twelve women completed one study day. Two groups of cancer survivors who were on average 71.75 years old were examined. One group of women was about two years since the end of their cancer treatment. The other group of women was around 10 years since the end of their cancer treatment. Participants were asked to complete memory tests, attention tests, mood questionnaires, and a magnetic resonance imaging (MRI) session. Results showed greater brain activation in the 10 year survivor group during the working memory task as measured by fMRI. There was also a significant difference in the psychiatric assessment (Older Adult Self Report OASR) between the groups. The 10 year survivor group scored higher on the OASR which indicated having more critical problems such as irritability. Further research with a similar protocol and a larger sample is needed to fully understand the interaction of age and cancer treatment on the brain.

Keywords: Breast cancer, cancer treatment, brain, women, aging.
Introduction

“Chemobrain” is a term used by cancer survivors to describe thinking and memory problems that can occur after cancer and cancer treatment. Cancer treatment has been shown to have diverse side effects on brain structure and function (e.g. Vardy & Dhillon, 2010; Shilling et al., 2005; Kayl et al., 2006; Schagen et al., 2006). As cancer is mainly a disease of aging, we do not currently have a complete understanding of how aging, cancer, and cancer treatment interact to affect the brains of older cancer survivors. The prospective longitudinal studies of cognition after cancer treatment have generally shown that there are negative effects on the brain within one month of treatment and these negative effects appear to resolve one year later (Dumas et al. 2013; McDonald et al. 2012). However, older cancer survivors compared to age-matched comparison subjects who have not had cancer perform more poorly and have worse cognitive outcomes (Nguyen et al. 2012). Thus, this study examined older women who are the same age, but their time since cancer treatment was different.

Several studies show that cancer treatment results in cognitive impairment which has gained more attention in the last decade. Most of the studies examined women who were survivors of breast cancer and have found that women report subjective complaints of cognitive impairment (Hutchinson et al. 2012). Studies also show objective impairment during neuropsychological testing (e.g. Weis et al., 2009). Other studies have suggested that cancer treatment can induce cognitive changes up to more than 20 years after chemotherapy exposure. For instance, a recent study emphasized that survivors of more than 20 years after chemotherapy performed worse than healthy controls on neuropsychological tests (Koppelmans et al. 2012). Thus, the effects of cancer treatment on the brain may be long lasting (Dumas, et al. 2013, Bruno et al. 2012; Hosseini et al., 2012). Studies have also identified structural changes in the brain
after cancer treatment in gray and white matter (Deprez et al., 2012; de Ruiter et al., 2012; Inagaki et al., 2007; McDonald et al. 2012b). Another study suggested that cancer treatment and chemotherapy are associated with the accelerated aging for survivors (Hurria et al., 2017, Jones et al., 2017).

Normal aging has effects on brain function and structure. In fact the frontal cortex of the brain shrinks and causes changes to the brain making it more susceptible to stroke, cognitive impairment, and white matter lesions (Peters, 2006). There is a reduction in brain volume and weight and an enlargement of the brain ventricles in normal individuals over the age of 60 years which affects their cognitive status (Anderton 2002). The most seen cognitive change associated with aging is in memory including the episodic memory, semantic memory, procedural memory, and working memory. A study suggested that normal old adults’ performance is affected in some tasks by slower reaction times, lower attentional levels, slower processing speeds, and potentially a lesser ability to use strategies (Anderton 2002).

Cancer and cancer treatment, in fact, might accelerate the aging process. However, the interaction between cancer treatment and aging is an ongoing research topic. Cancer survivors are more likely to report changes to their mental health and physical ability. This suggests that cancer treatment such as chemotherapy, radiation, molecular-targeted therapies, and hormonal therapy can indeed accelerate the aging process (Peters, 2006). However, several gaps in knowledge remain, and future research is needed in order to understand the implications of cancer as well as ways to decrease the risk of the treatment itself.

The main goal of this study was to identify the diverse effects of cancer treatment on brain function and brain structure in older women who are breast cancer survivors. This study compared two different groups of women who were breast cancer survivors. One group was
recent cancer survivors who were between 1 and 3 years post cancer treatment, while the other was approximately 10 years post cancer treatment. We examined the effect of age and recent versus remote cancer treatment on brain structure and function. Comparing survivors who are the same age but with different post-treatment time periods has not done before. We hypothesized that the aging process negatively interacts with the recovery from cancer treatment and these negative effects on the brain will be worse for women who are 3 years post their cancer treatment. Furthermore, cancer treatment later in life will be more detrimental to brain structure and function as the brain’s ability to recover from any insult decreases. Specifically, the survivors who are 10 years since their treatment will perform better on the neuropsychological tests, have larger hippocampal volumes, and decreased activation in the working memory network compared to those who are more recent cancer survivors. Both the hippocampal volume and working memory-related brain activation measures have been shown to be related to pathological aging (Fjell 2014). If these changes are detected in these two groups of cognitively normal participants, there may be recommendations for strategies for preventing cognitive decline in the future.

**Methods**

**Participants**

Participants were 12 cognitively normal women, aged 65-75. The 3 year survivor group was on average 71.7 years old while the 10 year survivor group was on average 71.8 years old ($t(11) = - .11, p = .46$) (Table 1). Women were recruited by mailing advertisements to breast cancer survivors who were patients at the University of Vermont Medical Center. Once a potential participant reached out by email or phone, she underwent a phone screening to determine eligibility. During this process, participants were asked to report their basic personal information, including name, age, and address.
They were asked questions about medical history and medications. Participants also were screened for MRI exclusions, including having movable metal in their body like a cardiac pacemaker, an aneurysm clip made of metal, a metal injury to the eye, and claustrophobia. Once the participant was determined to be eligible for the study after the phone screening, a time was set up for her to come to the Clinical Research Center at the University of Vermont Medical Center and complete the experiment procedure.

Inclusion criteria were an age between 65-75, breast cancer survivor, and English speaking. To participate they must also be literate and physically able to complete the questionnaires and tasks. Women must be cancer survivors who have a history of breast cancer (stage 1 or 2). One group of women were cancer survivors who are 2+/-1 years after the completion of cancer treatment. Another group of women were cancer survivors who are 10+/-1 years post a successful cancer treatment.

Exclusion criteria were participants who are unable to see or hear. The majority of the work in cancer and cognition has not found definitive evidence about the effects of chemotherapy regimen on cognition with one exception. Kesler et al. (2016) reported that women who received anthracycline had worse cognitive outcomes compared to those who received nonanthracycline-based chemotherapy. We excluded women who had anthracycline treatment in an effort to examine the ability of the brain to recover from the additional nonspecific cognitive effects of nonanthracycline medications.

Women with movable metal in their bodies were not eligible to participate. This includes pacemakers, aneurysm clips, and metal injury to the eye. Women who reported that they were claustrophobic and unable to tolerate the MRI were not eligible to participate.
Study Visit

Upon the participant’s arrival to the Clinical Research Center at the University of Vermont Medical Center, informed consent was signed. Participants then were asked to perform a number of cognitive, dementia, and psychiatric assessments before the MRI. All women were cognitively and behaviorally assessed using standard tests designed to identify significant cognitive or behavioral impairment including the Mini Mental State Exam (MMSE) (Folstein et al. 1975), Brief Cognitive Rating Scale (Reisberg and Ferris 1988), the Mattis Dementia Rating Scale (Jurica et al. 2001), and the Global Deterioration Scale (GDS; Reisberg et al. 1988). All subjects performed the Wechsler Test of Adult Reading (WTAR) to estimate IQ. They also completed the Beck Depression Rating Scale to test any signs or symptoms of depression (Beck et al. 1961), the Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989) to assess sleep quality over a one month interval. Each woman completed the Older Adult Self Report that assesses a number of aspects of psychological and psychiatric functioning (Achenbach et al. 2004). These procedures are detailed in table 2.

Cognitive Tests

Mini Mental State Exam (MMSE)

All subjects were cognitively evaluated using the Mini Mental State Exam (MMSE) (Folstein et al., 1975) as the initial cognitive status screening questionnaire. A higher score on the MMSE indicate better cognitive functioning. Participants were asked questions such as the date, perform commands, and to redraw an image. To be an eligible participant where her data included in the study, participants were required to have a score equal to or greater than 24.
Brief Cognitive Rating Scale (BCRS)

Subjects were also cognitively evaluated using the Brief Cognitive Rating Scale (Reisberg and Ferris 1988) BCRS, a higher score was related to a greater degree of cognitive impairment.

Global Deterioration Scale (GDS)

All subjects were evaluated by the Global Deterioration Scale (GDS; Reisberg et al. 1988) which rated the degree of cognitive impairment (Reisburg et al., 1993). A higher score was related to greater global cognitive functioning.

Mattis Dementia Rating Scale (DRS)

Mattis Dementia Rating Scale (Jurica et al. 2001) was also performed. A score above 130 on the Mattis scale was required. DRS was used to assess the participant’s level of cognitive functioning.

Behavioral Tests

Pittsburgh Sleep Quality Index (PSQI)

Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989) was filled by every subject in order to assess sleep quality over a one month interval.

Beck Depression Rating Scale

Beck Depression Rating Scale assessment which is a self-report rating inventory was done to measure the symptoms of depressions.

Cognitive Tasks

Letter-Number Sequencing Task (LNST)

Letter Number Sequencing task was also completed by the participants to measure verbal working memory (Wechsler, 1997). Task consist of reading aloud a series of letters and numbers
to the subject and they were asked to repeat them back with the numbers first in order and then the letters in alphabetical order. Four practice items were done before starting the actual task. Participants’ scores were calculated by counting the number of correct successful trials.

**Buschke Selective Reminding Test (BSRT)**

The BSRT is a measure of episodic memory (Buschke & Fuld, 1974) that was completed by every subject. It measures the encoding and retrieval of information from episodic memory as it is a multi-trial verbal list-learning task. Sixteen unrelated words were read to the subject and the subject was asked to recall as many words as possible. It consisted of eight trials and one delayed trial that was administered around 30 minutes after the last trial. The dependent variables of this task were total recall, consistency, recall failure, and delayed recall. Total recall represents the total recalled number of words by the participant. Consistency represents when the subject recalled a word for two trials in a row. Intrusions were words that the participant said and were not one of the 16 words. Recall failure represents failure to recall a word for two trials in a row.

**Wechsler Test of Adult Reading (WTAR)**

Wechsler Test of Adult Reading WTAR was also used to evaluate the premorbid intelligence and the intellectual functioning of participants.

**The Older Adult Self Report (OASR)**

The Older Adult Self Report (OASR) is a psychiatric assessment that was completed by each participant (Achenbach et al., 2004). It yields seven syndromes, including anxious/depressed, worries, memory/cognition problems, and thought problems.
**fMRI Task**

**N-back Task**

The N-back Task is a measure of verbal working memory. The subject completed four different conditions which were 0-back, 1-back, 2-back and 3-back. In each of these conditions, the goal was to decide if the presented letter matched a letter 1, 2, or 3-back that appeared before in the sequence. Subject was required to press the “match” button when the letter matched the letter in every condition and the “mismatch” button for any other letters. In the 0-back condition, the subject was asked to make a “match” response whenever she sees a given target letter (Figure 1). In the one-back condition, the subject required to press the “match” button when the letter matched the letter that appeared one item back (Figure 1). In the two-back condition, subjects made a response when the presented letter matched the letter two items back (Figure 1). In the three-back condition, subject pressed the “match” button when the letter appeared three items back (Figure 1). Subjects practiced this task by doing two different rounds of each condition on a computer before doing it in the MRI scanner. In general, the task lasted around 8 minutes where each of the 0-, 1-, 2-, and 3-back conditions were presented three times in a pseudorandom order. Between every condition, a rest break was presented with a plus sign (+) fixation for about 12 seconds. In the MRI scanner, subjects used a fiber optic button to make a response. During the task, accuracy measures and reaction times were recorded.

**Faces Encoding and Recognition Tasks**

The Face-Name Encoding task was done during the MRI and the Face Recognition was completed after the MRI. Subjects were shown two faces with names before the MRI session. These two pictures were then used during the MRI task as “familiar” pictures since the face-name pair was presented to the subject previously. New pictures with names were introduced
during the MRI task which were considered as “novel” pictures since they were not presented to
the subject previously. This task lasted around 8 minutes as the “familiar” and “novel”
conditions were presented in balanced order. Subject was asked to make a subjective decision by
pressing the “match” button if she thought that the name was a good fit for the face and to not
make a response if the she thought that the name did not match face. After the MRI session was
finished, the face recognition task was introduced to the subject on a computer with the same
faces that were presented in the MRI session but with two different names. Subjects were
required to choose the face-name pair that was presented during the MRI task. During the
recognition task, accuracy measures and reaction times were recorded.

MRI Information

Subjects were scanned using a Philips 3T Achieva full body scanner. Standard protocols
for the Dumas lab were performed. The following sequences were performed in order: 1) N-
back task that had 36,900 DICOM files (615 dynamics X 60 slices) (8 minutes) 2) Faces-name
encoding task that had 35,820 DICOM files (597 dynamics X 60 slices) (8 minutes) 3) T1
weighted images that are used to evaluate the normal anatomy (5 minutes) where fat is
represented in white because it has a high signal intensity and water is represented in black
because it has a low signal intensity. In total, the MRI session lasted for about 60 minutes and all
images were viewed by a neuroradiologist to exclude any abnormalities.

fMRI Analyses

Statistical analyses were performed for the n-back task using a 2(groups: 3 years, 10
years) X 4(Working Memory Load: 0-back, 1-back, 2-back, 3-back) random effects ANOVA
using standard ANOVA procedures in Brain Voyager (Brain Voyager QX). For the Face-Name
Encoding task, statistical analyses were performed using a 2(groups: 3 year, 10 year) x
2(Recognition: Novel, Familiar) random effects ANOVA using standard ANOVA procedures in Brain Voyager (Brain Boyager, QX). I did not perform corrections for multiple comparisons because the sample size was too small. The hippocampus volume measures were analyzed using FreeSurfer program.

Data Analysis

While the sample was small, statistical tests were performed to examine any differences between the groups. An independent groups $t$-test was run on all cognitive, behavioral and psychiatric measures in order to determine whether there was a statistically significant difference between the two groups.

Results

Participants

A total number of 12 subjects were recruited. Subjects ranged from 68 to 75 years old. The 3 year survivor group was on average 71.7 years old while the 10 year survivor group was on average 71.8 years old ($t(11) = -.11, p = .46$) (Table 1). Table 1 shows the means and standard deviations of both groups. Subjects were well educated women with a mean education of 15.65. There was no difference between the level of education between the groups ($t(11) = -.54, p = .30$). Most of the women received surgery, radiation and hormonal therapy. In fact, out of 12 participants 8 women received radiation and hormonal therapy and only three received radiation with one year course of chemotherapy. Along with that only one subject out of the 12 received only chemotherapy. The means of the behavioral tests (Table 2), screening tests (Table 3), cognitive tasks (Table 4) and fMRI performance were recorded and reported.
Activation: Working Memory

Working-memory related brain activation was examined during N-back task. All subjects showed activation in the bilateral frontal, parietal, and cerebellar regions (Figure 2). When the groups were compared directly, greater activation was seen in the 10 year group (0, 1, 2, 3-back conditions minus 0, 1, 2, 3-back) (Figure 3, 4).

Activation: Episodic Memory

Episodic-memory related brain activation was examined during face-name encoding task. All subjects showed activation in the occipital and temporal lobes during the encoding task (Figure 5). However, no activation differences were found when comparing the two groups (Novel minus Familiar) (Figure 6).

Hippocampus

Differences in the hippocampus volumes were measured using the FreeSurfer program. However, no significant differences between the groups’ hippocampus volumes were found ($t(11) = 1.74, p = .11$) for the left hippocampus and ($t(11) = 1.22, p = .25$) for the right hippocampus.

Performance: Working Memory

Data were analyzed with a 2(groups: 3 years, 10 years) X 4(Working Memory Load: 0-back, 1-back, 2-back, 3-back) mixed model ANOVA for the proportion hits, the proportion of false alarms and reaction time separately (Figures 7-9). No significant group effect differences between the both groups were found ($F(1,9)=3.911, p=.08$) and no significant interaction between the groups was found ($F(3,9)=.10, p=.93$).
**Performance: Episodic Memory Performance**

Accuracy and reaction time measures were recorded and analyzed for the face-name task using 2(groups: 3 year, 10 year) x 2(Recognition: Novel, Familiar) model. However, no significant differences between the groups were found (Table 5).

**Behavioral Measures**

Participants completed Older Adult Self Report (OASR), Beck Depression Rating Scale, and Pittsburgh Sleep Quality Index (PSQI) as subjective measures of their mood and physical symptoms. The Older Adult Self Report yields seven syndromes, including anxious/depressed, worries, memory/cognition problems, and thought problems. To examine any significant differences an independent samples t-test was run. There were statistically significant differences between the subjective measures of the two groups (Table 6). The 10 year group was more irritable than the 3 year group ($t(11) = -2.33, p = .02$) and reported more critical problems ($t(11) = -1.92, p = .05$). Furthermore, the 10 year group had a higher score in the total problems portion ($t(11) = -2.69, p = .02$) (Table 6). There were no significant differences between the subjective measures in the Pittsburgh Sleep Quality Index (PSQI) and in the Beck Depression Rating Scale between the two groups (Table 2).

**Cognitive Measures**

Participants completed the Mini Mental State Exam (MMSE), Brief Cognitive Rating (BCRS), Mattis Dementia Rating (DRS), Global Deterioration Scale (GDS), Wechsler Test of Adult Reading (WTAR), Buschke Selective Reminding Test (BSRT) and the Letter-Number Sequencing Task as a cognitive measure of their mental status. No significant differences in measures between the two groups were found in Mini Mental State Exam ($t(11) = 0, p = .5$),
Brief Cognitive Rating \( t(11) = -0.89, p = 0.20 \), Mattis Dementia Rating \( t(11) = -0.66, p = 0.26 \), and the Global Deterioration Scale \( t(11) = -0.06, p = 0.27 \). (Table 3)

However, there was a significant difference between the Wechsler Test of Adult Reading (WTAR) measure \( t(11) = -0.24, p = 0.03 \) (Table 3).

There were no significant differences in the 4 dependent measures of the Buschke Selective Reminding Test. The statistic results for the variables in the BSRT were \( t(11) = 0, p = 0.50 \) for the total recall measure, \( t(11) = 0.21, p = 0.42 \) for the total consist measure, \( t(11) = 0.08, p = 0.47 \) for the total recall failure measure and \( t(11) = 0.21, p = 0.42 \) for the delayed recall measure.

Letter-Number Sequencing Task \( t(11) = -0.54, p = 0.30 \) between the two groups (table 4).

**Discussion**

This pilot study was the first to examine the interaction of age and cancer treatment on brain function in breast cancer survivors. Data were collected from the 12 participants. Participants’ age ranged from 68-75 years old. All subjects were well educated white women who were recruited mostly from Chittenden County. All women were healthy breast cancer survivors and not demented. Results showed that varying post cancer treatment times did have an effect on brain activation in the working memory N-back task. We tested the hypothesis that the aging process negatively interacts with the recovery from cancer treatment and these negative effects will be worse for women who are 3 years post their cancer treatment. More specifically, decreased activation on the N-back task, larger hippocampal volumes, and better performance on the neuropsychological tests were expected to be seen in the 10 year group. However, our data did not support these hypotheses.
In the N-back task, greater activation in the working memory network was seen in the bilateral frontal and parietal regions for women who are in the 10 year survivor group. Neuroimaging studies have shown that greater activation during the N-back task is associated with decreased neural efficiency and is associated with less efficient thinking patterns (Neubauer & Fink, 2009). Other studies have also shown that the parietal region in the brain has been involved in retrieval during working memory tasks (Berryhill & Olson, 2008). While there were no statistically significant differences in performance between the groups in the N-back, there was a higher hits scores in the 3 year survivor group compared to the 10 year survivor group which indicated better performance. The 3 year survivor group tended to have higher scores in the reaction time which indicated a slower speed compared to the 10 year survivor group. However, these results were not significant. The interaction between aging process and the recovery time from cancer treatment had negative effects that were worse for women who are 10 years post their cancer treatment. Results could be explained by the small sample size and by the difference in the recovery time after cancer treatment. Cancer and cancer treatment cause negative effects that are long lasting on the brain. This study may have observed these effects getting worse over time. Cancer treatment may have contributed to accelerating the aging process and caused an early cognitive decline that worsened over time. A bigger sample size is needed to fully understand the effects of cancer treatment on the brain during aging.

Episodic memory was tested during the face-name encoding task. Neuroimaging studies have shown that successful performance on this task is associated with greater activation in the brain and especially in the hippocampus (Kirwan & Stark 2004; Sperling et al., 2001). In this study, no statistically significant differences in activation were seen between the groups and there were no statistically significant group differences in the hippocampal volume measures.
Other cognitive testing measures were performed in this study included the BSRT which is a measure of episodic memory and the letter-number sequencing task which is considered a measure of working memory. There were no statistically significant differences in performance between the groups. Other cognitive measures that showed no significant group effect differences included Mini Mental State Exam, Brief Cognitive Rating Scale, Global Deterioration Scale and Mattis Dementia Rating Scale. Furthermore, the 10 year survivor group scored higher on the IQ test (Wechsler Test of Adult Reading, WTAR) compared to the 3 year survivor group. However, one of the participants in the 3 year survivor group scored 74 on the WTAR because she is not a native English speaker. Because of this, this subject data was excluded ($t(11) = -2.05, p = .04$). A significant group difference was still observed.

There was no significant group difference in the Beck Depression Rating Scale or the Pittsburgh Sleep Quality Index (PSQI). There are a variety of variables that may have affected the data gathered in this study. However, results illustrated a few significant differences between some of measures of the Older Adult Self Report (OASR). In general, the OASR task provides ratings of specific problems, strengths, adaptive functioning, and descriptive information from each participant. The 10 year survivor group scored higher on the OASR total problems, critical items, and irritability measures. Results could be explained by a small sample size. One subject in the 10 year survivor group had a critical item score that was close to the borderline clinical range. This likely explains the group difference in this small sample. Since none of the scores went above the clinical range, the significant findings between the groups represented the group effect difference rather than actual critical problems of individuals within the groups.

Furthermore, the relationship between aging, cancer treatment, and psychological health is an important findings to focus on in the future research. Specifically, why the “critical
items”, “total problems” and “irritability” measures in particular found to be more affected by
cancer treatment and aging process than any of the other measures in the OASR assessment.

The problems portion of the OASR addresses psychological problems indicating higher levels critical problems such as having irritability. However, cancer itself can increase the risk of developing psychological problems. In fact, a study suggested that cancer survivors are more than twice as likely to have psychological problems compared with adults without cancer (Hewitt, 2003). In general, health care providers have focused more largely on cancer patients’ physical health status, and less on psychological and mental health issues (Page, 2008). Another study suggested that the first three years of cancer treatment are considered critical period and patients’ psychological and mental health is monitored. However, long-term survivors face psychological challenges associated with cancer recurrence as well as continuation of mental health problems that occurred during diagnosis and treatment. In fact, long term survivors experience loss of emotional support from their providers, family and friends (Stanton, 2012). Another reason that could explain why the 10 year survivor group scored higher on some the OASR measure is being diagnosed with cancer in early age. A study suggested that patients diagnosed with cancer in early age face additional stressors and challenges and are at higher risk for poorer mental health outcomes compared with those who receive cancer diagnoses at older ages (Kroenke 2004, Kornblith 2007). Moreover, cancer diagnosis in late 50s is less common and is more unexpected since cancer incidence increases with age (Taylor, 2014). Other factors that might also contribute for having psychological problems in early diagnosed survivors are disruptions in family, concerns about caring for children, work-related difficulties, and financial issues (Kornblith 2007). Researchers are still studying the impact of cancer diagnosis and treatment on the lives of adults. Our results indicated that aging process might have interacted
with recovery time from cancer treatment and impacted women who are 10 years post their cancer treatment. This was shown in the fMRI brain activation during working memory task.

**Limitations**

The main limitation in this pilot study was the small sample size of 12 women. Because of this, the results of this small sample size might be unreliable. It may be possible to observe a significant interaction between age and cancer treatment with more participants. The sample of the 12 participants does not accurately represent the larger population of older breast cancer survivors. Since most participants received radiation and hormonal therapy, this might explain why there was no group effect difference in the cognitive testing. In fact, radiation has large impacts on the treatment region rather than on the brain. However, chemotherapy does have an effect on the brain. In fact, chemotherapy sides’ effects are results of the treatment crossing the blood brain barrier and killing cancer cells (De Vries 2006). About 66.70% of women in this study had radiation and hormonal therapy while only 33.3% had 1 course of chemotherapy along with radiation. Chemotherapy drugs are known to cause healthy brain cells to die off and may be one of the underlying biological causes of the cognitive side effects “chemo brain” that many cancer survivors report. Another limitation was the difficulty of getting women who received chemotherapy in the 65-75 age range. Young women tend to have chemotherapy more in early diagnosed cancer.

**Future Directions**

This was a study that examined the interaction of age and cancer treatment on the brain of breast cancer survivors. A similar protocol should be completed in the future with bigger sample of cancer survivors considering only chemotherapy treatment in order to further understand the interaction of these two factors on the brain. Additionally, future direction for this study should
be focused mainly on the cognitive decline differences between the groups in general. Research relevant to this finding could investigate further in the different cancer treatments and their effects on the brain. Another future direction is to compare the two groups with a control wellbeing group of the same age.
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### Tables

#### Table 1

Demographic data (means and standard deviations) for all study participants (n=12)

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Table 2

Behavioral Tasks Means and Standard Deviations

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<td>PSQI</td>
<td>2</td>
<td>12</td>
<td>6</td>
<td>3.79</td>
</tr>
</tbody>
</table>
Table 3

Screening Tasks Means and Standard Deviations. There was a significant difference in the WTAR task measure (p<0.026).

<table>
<thead>
<tr>
<th>Cognitive Assessment</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>27</td>
<td>30</td>
<td>27.67</td>
<td>1.21</td>
</tr>
<tr>
<td>WTAR</td>
<td>74</td>
<td>113</td>
<td>98</td>
<td>14.54</td>
</tr>
<tr>
<td>3 years Mattis (DRS)</td>
<td>132</td>
<td>141</td>
<td>137</td>
<td>4.43</td>
</tr>
<tr>
<td>Mood (GDS)</td>
<td>1</td>
<td>2</td>
<td>1.67</td>
<td>0.52</td>
</tr>
<tr>
<td>BCRS</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>0.89</td>
</tr>
<tr>
<td>MMSE</td>
<td>26</td>
<td>29</td>
<td>27.67</td>
<td>1.37</td>
</tr>
<tr>
<td>WTAR</td>
<td>101</td>
<td>122</td>
<td>113.2</td>
<td>7.52</td>
</tr>
<tr>
<td>10 years Mattis (DRS)</td>
<td>131</td>
<td>144</td>
<td>137.8</td>
<td>5.49</td>
</tr>
<tr>
<td>Mood (GDS)</td>
<td>1</td>
<td>2</td>
<td>1.83</td>
<td>0.41</td>
</tr>
<tr>
<td>BCRS</td>
<td>11</td>
<td>8</td>
<td>905</td>
<td>1.05</td>
</tr>
</tbody>
</table>
Table 4

Buschke SRT and the Letter-Number Sequencing tasks scores (means and standard deviations) of both groups. No significant difference was found in any of these measures.

<table>
<thead>
<tr>
<th>Task</th>
<th>3 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Recall</td>
<td>61.8(18.5)</td>
<td>61.8(14.2)</td>
</tr>
<tr>
<td>Total Consistency</td>
<td>27.3(13.3)</td>
<td>25.7(14.2)</td>
</tr>
<tr>
<td>Total Recall Failure</td>
<td>29.3(21.90)</td>
<td>28.5(11.3)</td>
</tr>
<tr>
<td>Total Delayed Recall</td>
<td>6.33(2.58)</td>
<td>6(2.55)</td>
</tr>
<tr>
<td>Total Correct Letter-Number</td>
<td>8.67(3.67)</td>
<td>9.5(1.05)</td>
</tr>
</tbody>
</table>
Table 5

Accuracy and reaction time (ms) (mean and standard deviations) for recognition memory task of faces and names. No significant differences were found among these groups (p>0.097).

<table>
<thead>
<tr>
<th></th>
<th>3 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>0.629(0.04)</td>
<td>0.706(0.081)</td>
</tr>
<tr>
<td>Reaction time</td>
<td>3369.45(600.66)</td>
<td>3585.32(983.09)</td>
</tr>
</tbody>
</table>
Table 6

OASR Task Measures Means and Standard Deviations

<table>
<thead>
<tr>
<th>OASR</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>50.5</td>
<td>0.577</td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td>52.6</td>
<td>3.975</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>52.8</td>
<td>4.856</td>
</tr>
<tr>
<td>思 3 Years 思 3 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thought Problems</td>
<td>52.6</td>
<td>4.856</td>
</tr>
<tr>
<td>Irritability</td>
<td>50.6</td>
<td>0.894</td>
</tr>
<tr>
<td>Critical Items</td>
<td>51.5</td>
<td>1.915</td>
</tr>
<tr>
<td>Total Problems</td>
<td>41.5</td>
<td>4.796</td>
</tr>
<tr>
<td>Anxiety</td>
<td>54.6</td>
<td>4.336</td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td>51</td>
<td>1.732</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>55.3</td>
<td>3.948</td>
</tr>
<tr>
<td>思 10 Years 思 10 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thought Problems</td>
<td>51.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Irritability</td>
<td>56.4</td>
<td>5.505</td>
</tr>
<tr>
<td>Critical Items</td>
<td>55.8</td>
<td>4.087</td>
</tr>
<tr>
<td>Total Problems</td>
<td>49.25</td>
<td>3.202</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1  N-back Task Conditions Rules.

Figure 2  Activation map for the N-back task for all participants showing an increase in working memory load during 0, 1, 2, 3-back conditions. Blue represents greater activation for the 10 years group and orange greater activation for the 3 years group.

Figure 3  Activation map for the 3 year group compared to the 10 year group. fMRI shows an increase in the working memory load in the bilateral frontal regions in the 10 year group. Blue represents greater activation for the 10 years group and orange greater activation for the 3 years group.

Figure 4  Activation map for the 3 year group compared to the 10 year group. fMRI shows an increase in the working memory load in the parietal region in the 10 year group. Blue represents greater activation for the 10 years group and orange greater activation for the 3 years group.

Figure 5  Activation map for the Face-Name encoding task for all participants. Blue represents greater activation for the 10 years group and orange greater activation for the 3 years group.

Figure 6  Activation map for the Face-Name encoding task comparing the novel minus familiar faces conditions in the 3 year group compared to the 10 year group. No significant activation differences were found between the groups. Blue represents greater activation for the 10 years group and orange greater activation for the 3 years group.

Figure 7  Proportion of hits for each N-back conditions in the 3 year group compared to the 10 year group. There were no significant differences between the measures of the groups.

Figure 8  Proportion of false alarms for N-back conditions in the 3 year group compared to the 10 year group. There were no group effect differences.
**Figure 9** Reaction time (ms) for each N-back condition in group 1 compared to group 2. There were no significant differences between the measures of the groups.
Figures

Figure 1

0 back *(target=C)*

C Q Z G C R D C G S J F C H P T

1 back

B X X A G G L F G N N T C P P H

2 back

K S B S Q M M G M R C J C F Q F

3 back

B R N B Q M S G M R G G C F Q C
Figure 2
Figure 3
Figure 4
Figure 5
Figure 7

![NBack Hits](image-url)
Figure 8

The figure illustrates the NBack False Alarm rates across different conditions. The x-axis represents the N-back conditions (0backFA, 1backFA, 2backFA, 3backFA), and the y-axis shows the proportion of false alarm. The conditions are differentiated by colors: blue for 3 Years and purple for 10 Years. The error bars indicate the variability in the data.
Figure 9

NBack Reaction Time

Hit Reaction Time (ms)

0backHmed 1backHmed 2backHmed 3backHmed

N-back Conditions
- 3 Years
- 10 Years