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Uniformed Services of the Health Sciences

05/06/2010

ABSTRACT

Title of Thesis: Are fatigue and depressive symptoms related to cognitive limitations in occupationally active breast cancer survivors?

Briana L. Todd, M.A., 2010

Thesis Directed by: Michael Feuerstein, PhD, MPH,

Director of Clinical Training

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Objective: To determine whether fatigue and depressive symptoms are independently and interactively associated with cognitive problems at work, and if so, whether these relationships are specific to cancer survivors.

Method: Breast cancer survivors (BCS; $n = 133$) and a non-cancer comparison group (NCCG; $n = 122$) completed self-report measures of both generic and work-related cognitive limitations (Functional Assessment of Cancer Therapy-Cognitive Scale, Cognitive Symptom Checklist-modified), depression (Hospital Anxiety and Depression Scale), and physical fatigue (Rotterdam fatigue scale).

Results: Three years post-primary treatment, BCS reported higher levels of fatigue ($p < 0.001$), depressive symptoms ($p < 0.001$), and cognitive limitations ($p < 0.001$) than NCCG. Fatigue and depressive symptoms were each independently associated with cognitive limitations. No group by symptom interactions was observed.

Conclusion: Healthcare providers working with BCS need to carefully consider, assess, and monitor the associations of fatigue and depressive symptoms with reported cognitive limitations.

Are fatigue and depressive symptoms related to cognitive limitations in occupationally
active breast cancer survivors?

by

Briana L. Todd

Thesis/dissertation submitted to the Faculty of the
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Introduction

Over 50% of women diagnosed with breast cancer are under the age of 65 (Horner, et al., 2009) indicating that a large number of breast cancer survivors are of a working age. However, the unemployment rate for breast cancer survivors is higher than those not affected by cancer (de Boer, Taskila, Ojajarvi, van Dijk, & Verbeek, 2009). Studies also indicate that for a heterogeneous subset of survivors who do return to work, work productivity and job satisfaction may be reduced (Amir, Neary, & Luker, 2008; Gudbergsson, Fossa, Borgeraas, & Dahl, 2006). A study by Hansen and colleagues (2008) indicates that occupationally active breast cancer survivors report difficulties at work four years post-diagnosis. Breast cancer survivors also report that performance based cognitive functions, observed in 13 to 34% of breast cancer survivors (Wefel, Witgert, & Meyers, 2008), can disrupt working ability (Amir, et al., 2008).

A main component of work involves working memory, executive function, and attention. Executive function is necessary for higher level processing involved in work that includes planning, problem-solving, reasoning, verbal fluency, abstract thinking, and multitasking (Alvarez & Emory, 2006; Grafman, 2007). A number of breast cancer survivors report that impaired cognitive functioning can negatively impact their work ability (Boykoff, Moieni, & Subramanian, 2009; Taskila, Martikainen, Hietanen, & Lindbohm, 2007). For example, Boykoff and colleagues (2009) conducted a qualitative study to investigate cognitive impairment and its impact on work in breast cancer survivors. Breast cancer survivors indicated that difficulties with memory, reduced speed, and efficiency negatively impacted their work performance and also increased stress at work. Similarly, in a sample of cancer survivors, including breast cancer, 19%

reported that cancer decreased their mental work ability two to six years post-diagnosis (Taskila, et al., 2007).

A subset of breast cancer survivors also reports fatigue (34%) and depression (22%) four to ten years after the completion of primary treatment (Bower, et al., 2006; Mehnert & Koch, 2008). Recent research has observed a relationship between fatigue and work ability in breast cancer survivors three to four years post-diagnosis or treatment (Hansen, et al., 2008; Calvio, Peuogeot, Bruns, Todd, & Feuerstein, 2010; Lavigne, Griggs, Tu, & Lerner, 2008). Hansen and colleagues indicated that while breast cancer survivors reported higher levels of both depressive symptoms and fatigue, fatigue attributed more to reduced work output in the cancer survivors while depressive symptoms attributed more to reduced work ability in those not affected by cancer. Similarly, Lavigne and colleagues found that fatigue was associated with decreased work productivity in breast cancer survivors while a measure of non-specific distress was not.

Fatigue and depressive symptoms are associated with cognitive limitations in breast cancer survivors (Fann, et al., 2008; Mehnert, et al., 2007; Vardy, et al., 2008). Mehnert and colleagues found that five years after the completion of standard-dose chemotherapy, fatigue in breast cancer survivors was associated with reduced cognitive functioning. An association between distress and perceived problems with memory and concentration has been reported in breast cancer survivors who previously received adjuvant chemotherapy (Shilling & Jenkins, 2007). Fann and colleagues conducted a systematic review examining the relationship between depression and breast cancer, which indicated that depression, is among the factors (i.e., chemotherapy, anxiety, and fatigue) that are related to cognitive impairments in breast cancer survivors. However,

these studies did not explicitly investigate symptoms and their interrelationships with cognitive limitations in breast cancer survivors and a non-cancer comparison group actively at work.

The overlapping features of depression and fatigue have posed a problem in research (Reuter & Harter, 2004) and clinical practice (Arnold, 2008) for years. Despite the high concordance of fatigue and depressive symptoms in breast cancer survivors, there is difficulty in discerning any differential role these symptoms may have in relation to cognitive limitations. The complexity in differentiating between fatigue and depression has historically been a challenge, which is partially due to their symptom presentation (Holland, 2002). For instance, fatigue is both a factor secondary to cancer and a symptom of depression. Also, not only can fatigue be a result of depression, the functional limitations of fatigue may also result in depression. Research demonstrates that depression is a main factor in fatigue in breast cancer survivors, accounting for about a third of the variance in fatigue (Okuyama, et al., 2000). However, other studies suggest that fatigue and depression are independent (Visser & Smets, 1998). Consequently, fatigue in cancer survivors may not simply represent a symptom of depression.

Proposed mechanisms of fatigue and depression in cancer are suggestive of a shared underlying mechanism of the two symptoms (Cleeland, et al., 2003) in addition to distinct mechanisms for each symptom (Ryan, et al., 2007). In support of a shared underlying biological mechanism is cytokine dysregulation (Cleeland, et al., 2003; Cleeland, et al., 2000). Cancer and its treatment is believed to cause increased levels of proinflammatory cytokines, due to tissue damage, that results in a cluster of behavioral symptoms including fatigue, depression, anxiety, pain, gastrointestinal disturbance, and

decreased appetite. It is hypothesized that cytokine dysregulation is a shared underlying symptom of these behavioral symptoms. However, within the proposed shared cytokine dysregulation mechanism, research indicates that there are two behavioral syndromes, one that includes sadness and the other that includes fatigue (Cleeland, et al., 2003).

Independent mechanisms for both fatigue and depression in cancer have also been proposed. Preliminary hypotheses suggest that cancer and its treatment can lead to an increase in serotonin, which subsequently increases fatigue (Ryan, et al., 2007). This hypothesis is largely based on observations concerning exercise related fatigue. Research indicates that exercise results in increase levels of tryptophan, the precursor of serotonin, which are associated with increased levels of fatigue. Conversely, one hypothesized mechanism of depression is a decrease in serotonin. Additionally, randomized control trials examining the efficacy of Paroxetine for attenuating fatigue and depression in cancer patients indicate that the selective serotonin reuptake inhibitor is effective in reducing depression but not fatigue (Morrow, et al., 2003; Roscoe, et al., 2005). Although etiology cannot be assumed from intervention studies, a possible explanation of these interventions is that decrease levels of serotonin are not involved in cancer related fatigue.

Furthermore, research indicates that individuals with fatigue and depression have differing cortisol slopes in response to an experimental stressor. Bower and colleagues (2005) examined fatigued and non-fatigued breast cancer survivors on average eight years post-treatment. Fatigued breast cancer survivors had a significantly blunted cortisol response to the Trier Social Stress Test as compared to the non-fatigue breast cancer survivors. Conversely, a meta-analysis by Burke and colleagues (2005) indicated that

individuals with depression have a heightened cortisol response to an experimental stressor that remains elevated during a recovery period. While the directionality between fatigue and depression with cortisol is unknown, research does indicate a differential relationship between the two symptoms and cortisol. Although more research is needed within the cancer survivor population to confirm any of the proposed theories, preliminary evidence does suggest independent mechanisms of both fatigue and depression in cancer.

While studies have suggested that fatigue and depression are related to cognitive limitations (Mehnert, et al., 2007; Shilling & Jenkins, 2007) and that cognitive limitations can pose challenges at work (Amir, et al., 2008; Boykoff, et al., 2009), there have been no investigations that consider the specific relationship of these two common symptoms with cognitive limitations in cancer survivors who continue to work years after the completion of primary treatment. The present study aims to clarify the independent and interactive relationships among fatigue, depressive symptoms, and their association with generic and work-specific cognitive limitations in breast cancer survivors. Additionally, the current study will assess whether these relationships differ in breast cancer survivors compared to individuals who are actively working and those working with no history of cancer.

Method

Participants

One hundred and forty-nine female breast cancer survivors (BCS) and 132 females with no history of cancer (non-cancer comparison group; NCCG) were recruited. BCS had completed primary treatment (i.e., surgery, chemotherapy, radiation therapy) at

least one year but no more than ten years prior to the time of the study. Inclusion for both groups in the study was contingent upon being female, between the ages of 18 and 65, working full-time at the time of the assessment, and having computer/Internet access higher than dial-up. Exclusion criteria for both groups included attention deficit hyperactivity disorder (ADHD), epilepsy, drug or alcohol abuse, dementia, or metastatic cancer. Sixteen BCS and ten participants from the NCCG did not complete at least one full measure and therefore were excluded from the final analysis. Final analysis included 133 BCS and 122 NCCG. Analyses indicated that among the non-completers there was no significant difference between being a BCS and being in the NCCG ($\chi^2 = 0.83$, $df = 1$, $p = 0.36$). Analyses also indicated no significant difference between completers and non-completers concerning age ($t(268) = 0.94$, $p = 0.75$), education ($\chi^2 = 5.44$, $df = 5$, $p = 0.36$), primary occupation ($\chi^2 = 9.19$, $df = 4$, $p = 0.06$), marital status ($\chi^2 = 3.37$, $df = 4$, $p = 0.50$), race ($\chi^2 = 0.94$, $df = 3$, $p = 0.82$), or ethnicity ($\chi^2 = 0.97$, $df = 1$, $p = 0.32$).

Procedures

Participants were recruited through advertisements and flyers distributed to cancer clinics/centers, primary care clinics, support groups, hospital bulletin boards, newspapers, and websites. Recruitment material directed participants to a secure website to complete screening material. Eligible participants were counterbalanced to one of two test conditions that first assessed either perceived cognitive limitations or performance based cognitive limitations to account for any fatigue related to the task or order effects. The current study, which is part of a larger study, only includes the measures of perceived cognitive limitations because research from a collateral study indicated a lack of relationship between performance based measures and work in the BCS (Calvio, et al.,

2010). After logging onto a main website and completing an informed consent, participants received the links and instructions on how to complete the study's measures. Demographics, health history, work history, substance use prior to testing, and measures of emotional and physical health were also collected.

Measures

Demographics, Medical, and Work Status. Participants provided information regarding demographics, medical history, and work status. Demographic information included ethnicity, race, age, marital status, household income, and education. Medical information collected from BCS included location of tumor, stage of tumor, treatment received, and time since completion of treatment. Both groups were asked questions concerning their medications, menopausal status, and perceived pain via a visual pain analogue scale (Scott & Huskisson, 1979).

Hospital Anxiety and Depression Scale (HADS). The HADS (Zigmond & Snaith, 1983) assesses depression and anxiety in a general medical population. The HADS includes 14 items that are divided into two subscales, Anxiety (A-scale) and Depression (D-scale), which are separately scored. The HADS has been shown to be a valid and reliable measure to assess depression and anxiety in cancer patients (Hopwood, Howell, & Maguire, 1991) and is widely used in this population (Poppelreuter, et al., 2004; Spiegel & Giese-Davis, 2003). The HADS was selected because the D-scale focuses on affective symptoms rather than somatic symptoms, which overlap with fatigue. Although the HADS-D primarily excludes somatic symptoms, item eight on the D-Scale, "I feel as if I am slowed down" may share variance with a component of fatigue, lethargy. Exploratory analyses within the current study address this issue.

Fatigue. Three questions were extracted from the Rotterdam Symptom Checklist (de Haes, van Knippenberg, & Neijt, 1990) to form a unidimensional measure of physical fatigue. After reviewing twenty fatigue measurement tools, Jean-Pierre and colleagues (Jean-Pierre, et al., 2007) concluded that this unidimensional measure of fatigue was a good measure of cancer-related fatigue. A unidimensional measure of fatigue is believed to be a more valid measurement as opposed to a multidimensional measure of fatigue because it reduces the possibility that other factors, such as depression, are contributing to the measure's score. The Rotterdam physical fatigue measure includes questions that assess tiredness, lack of energy, and difficulty sleeping.

Functional Assessment of Cancer Therapy Cognitive Scale Version two (FACT-Cog). The Fact-Cog (Wagner, Cella, & Doninger, 2003) is a 50-item self-report measure that assesses cognitive limitations in cancer survivors. Participants rank the frequency each statement occurred in the past seven days on a five-point likert scale that ranges from 0 ("never") to 4 ("several times a day"). The current study used the Perceived Cognitive Impairment (PCI) subscale. Lower scores on the PCI subscale are indicative of poorer functioning. Jacobs and colleagues (2007) assessed the Fact-Cog's psychometric properties on 101 cancer survivors and found it to have an internal consistency with a range of 0.97 (total score) to 0.58 (concentration subscale). The Fact-Cog also was shown to have similar psychometric properties as the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning scale (EORTC-CF), which is commonly utilized to examine attention and memory. Jacobs and colleagues suggest that the Fact-Cog measures cognitive impairments more broadly than other scales.

Cognitive Symptom Checklist- modified (CSC). O'Hara and colleagues (1993) developed the CSC as a tool for providers to examine patient reported cognitive complaints. A modified version of the CSC was constructed to assess work task impairment due to specific cognitive functions. The CSC assesses patient reported cognitive limitations involving attention/concentration, memory, executive functions, and visual processes in those with neurological insults such as brain tumors and head injuries. Feuerstein and colleagues (2007) reduced the measure from 100 to 59 items to assess perceived cognitive limitations in working memory, executive functioning, and attention influencing work. This adapted version of the CSC was included in the present study because at the time no work related measure of cognitive limitations was available. While the Fact-Cog does mention work within one of the questions, the main focus of the scale is not associated with work.

Substance use. Substance use can influence cognitive function (Newhouse, Potter, & Singh, 2004; Peeling & Dawson, 2007; Weissenborn & Duka, 2003) and, thus, is a potential confounder of perceived cognitive limitations. Questions derived from the caffeine consumption questionnaire (accessed online from <http://www.drkeddy.com/client/caffeine.pdf>), the Behavioral Risk Factor Surveillance System Questionnaire (accessed online from <http://www.cdc.gov/brfss/questionnaires/pdf-ques/2007brfss.pdf>), and the Centers for Disease Control website (accessed online from: http://www.cdc.gov/NCHS/data/nhanes/nhanes_01_02/sp_smq.pdf) were used. The current study utilized questions concerning alcohol consumption, caffeine consumption, and smoking status.

Results

BCS ranged in age from 26 to 62 (mean 44.89 years, SD = 9.11), as seen in Table

1. Among BCS, 87% (n = 116) identified themselves as Caucasian, 6% as African American (n = 8), 5% as Asian American/Pacific Islander (n = 7), and 2% as Other (n = 2). The majority of BCS identified themselves as cohabitating with a partner (76%, n = 101), as having a household income of \$100,000 or more (52%, n = 69), that their highest education level was a graduate degree (47%, n = 62), and that their primary occupation was in the category of professional/technical/science (46%, n = 61). BCS most commonly indicated that they were post-menopausal (41%, n = 55). BCS typically received chemotherapy (83%, n = 110), radiation therapy (74%, n = 98), and surgery (97%, n=129). The mean time since treatment was 3 years (SD = 2.39), as seen in Table 2.

The NCCG ranged in age from 21 to 61 (mean 39.16 years, SD = 11.42). About 66% of the NCCG identified themselves as Caucasian (n = 80), 21% as African American (n = 26), 7% as Asian American/Pacific Islander (n = 8), and 7% as Other (n = 8). The NCCG most commonly indicated that their highest education level was a graduate degree (43%, n = 52), that they cohabitated with a partner (55%, n = 67), had a household income of \$100,000 or more (31%, n = 38) and that their primary occupation was in the category of professional/technical/science (48%, n = 58). The majority of the NCCG indicated that they were pre-menopausal (76%, n = 93).

Chi-square analyses and t-tests indicated that the groups differed on age ($t(252) = 9.19, p < 0.001$), race ($\chi^2 = 19.37, df = 3, p < 0.001$), ethnicity ($\chi^2 = 5.98, df = 1, p < 0.05$) marital status/living arrangement ($\chi^2 = 12.23, df = 1, p < 0.001$), annual household income ($\chi^2 = 20.49, df = 6, p < 0.01$), and menopausal status ($\chi^2 = 60.99, df = 2, p < 0.001$). BCS tended to be older, Caucasian, less ethnically diverse, married/cohabitating

with a partner, and had a higher annual household income. Groups did not differ on education, primary occupation, or years at current job.

A Hotelling's Trace multivariate test was conducted to compare differences in symptom burden (i.e., depression, fatigue, anxiety, pain) between BCS and NCCG. Anxiety and pain were examined due to the potential influence they can have on fatigue, depressive symptoms, and cognitive limitations. We controlled for age, household income, marital status/living arrangement, ethnicity, race, and menopausal status because the groups differed on these factors. An overall significant difference was detected between the two groups ($F(4,244) = 6.01, p < 0.001$). The multivariate analysis indicated that BCS reported higher levels of fatigue ($F(1,247) = 21.72, p < 0.001$), depressive symptoms ($F(1,247) = 12.36, p < 0.01$), anxiety ($F(1,247) = 5.85, p < 0.05$), and pain ($F(1,247) = 6.01, p < 0.05$) (Figure 1).

A Hotelling's Trace multivariate test was also conducted to compare differences between the groups on the CSC subscales (executive function, memory, attention) and the Fact-Cog subscale (PCI). We controlled for group demographic differences (i.e., age, marital status/living arrangement, race, ethnicity, household income, and menopausal status). An overall significant difference was detected between the two groups ($F(4,244) = 18.14, p < 0.001$). Examination of the CSC indicated that BCS reported significantly greater impairment in executive function ($F(1,247) = 30.60, p < 0.001$), memory ($F(1,247) = 61.54, p < 0.001$), and attention ($F(1,247) = 13.67, p < 0.001$) than the NCCG. The Fact-Cog also indicated that BCS reported higher levels of general cognitive impairment on the PCI ($F(1,247) = 52.62, p < 0.001$) than the NCCG (Figure 2).

Due to the large number of possible confounding variables we employed a data

reduction technique (Tabachnick & Fidell, 1996). Univariate regressions were conducted with all potential confounders (i.e., age, education level, marital status/living arrangement, household income, ethnicity, race, menopausal status, primary occupation, years at current job, pain, anxiety, caffeine consumption, smoking status, and alcohol consumption). All measures that met $p < 0.10$ criteria were entered into the first step of the multivariate regressions. The final multivariate regression was conducted for BCS and NCCG combined, with the dependent variables being the CSC and Fact-Cog subscales. All regressions included the following steps: (1) confounding variables, (2) cancer, fatigue, depressive symptoms, (3) fatigue x depressive symptoms, cancer x fatigue, cancer x depressive symptoms. Interaction terms were calculated by multiplying cancer status (breast cancer = 0, non-cancer = 1) by the variable of interest.

Cognitive Symptom Checklist Executive Function. As Table 3 indicates, the first step of the model was significantly associated with 22% of the variance in work related executive function ($R^2 = 0.216, p < 0.001$), with anxiety ($\beta = 0.33, p < 0.001$), pain ($\beta = 0.16, p < 0.01$), and education ($\beta = -0.11, p < 0.05$) as significant confounders. Both fatigue ($\beta = 0.17, p < 0.05$) and depressive symptoms ($\beta = 0.25, p < 0.001$) were independently associated with perceived deficits in executive function at work for both groups and along with the main effect of Cancer ($\beta = -0.21, p < 0.001$) accounted for 15% of the variance ($R^2 \text{ Change} = 0.147, p < 0.001$). There were no significant interactions.

Cognitive Symptom Checklist Working Memory. The second model examined the independent and interactive associations of fatigue and depressive symptoms with perceived working memory limitations at work. As seen in Table 3, the covariates were

significantly associated with 23% of the variance to the model ($R^2 = 0.226, p < 0.001$). Anxiety ($\beta = 0.32, p < 0.001$), pain ($\beta = 0.22, p < 0.001$), and race ($\beta = -0.13, p < 0.05$) were all significant in the first step. Fatigue ($\beta = 0.19, p < 0.01$) and depressive symptoms ($\beta = 0.23, p < 0.001$) were independently associated with perceived deficits in memory for both groups and along with Cancer ($\beta = -0.33, p < 0.001$) accounted for about 23% of the model's variance ($R^2 \text{ Change} = 0.227, p < 0.001$). Analyses did not reveal any significant interactions.

Cognitive Symptom Checklist Attention. When examining perceived limitations in attention at work, step 1 of the model revealed that the confounders significantly accounted for 22% of the model's variance ($R^2 = 0.22, p < 0.001$). Further examination indicated that anxiety ($\beta = 0.31, p < 0.001$), pain ($\beta = 0.19, p < 0.01$), menopausal status ($\beta = -0.13, p < 0.05$), and race ($\beta = -0.14, p < 0.05$) were all significantly related to perceived attention problems at work in both groups. Cancer ($\beta = -0.11, p < 0.05$), fatigue ($\beta = 0.17, p < 0.05$), and depressive symptoms ($\beta = 0.15, p < 0.05$) significantly contributed to 7% of the model's variance ($R^2 \text{ Change} = 0.07, p < 0.001$). No significant interactions were revealed.

Fact-Cog Perceived Cognitive Impairment. As Table 3 indicates, the confounders significantly contributed to step 1 of the model ($R^2 = 0.27, p < 0.001$). Anxiety ($\beta = -0.34, p < 0.001$), pain ($\beta = -0.25, p < 0.001$), race ($\beta = 0.12, p < 0.05$), and age ($\beta = -0.13, p < 0.05$) were all significant in the first step. Fatigue ($\beta = -0.27, p < 0.001$) and depressive symptoms ($\beta = -0.15, p < 0.05$) were each independently associated with perceived deficits for both groups and along with cancer ($\beta = 0.29, p < 0.001$) accounted for about 20% of the model's variance ($R^2 \text{ Change} = 0.20, p < 0.001$). Analyses did not

reveal any significant interactions.

Exploratory Analyses. To determine the amount of variance shared between fatigue and depressive symptoms in the BCS, a regression line with the two variables was plotted (Figure 3). The analysis indicated that for BCS, fatigue and depressive symptoms shared 27.5% variance, suggesting that while the two symptoms share some variance there is a large amount of independence between the two symptoms. Item eight on the HADS-D scale, “I feel as if I am slowed down” may have accounted for some of the shared variance between fatigue and depressive symptoms. The regression line was plotted again removing item eight from the HADS-D scale (Figure 4). Results indicated that without item eight, fatigue and depressive symptoms shared 19% variance in BCS. This finding suggested that item eight on the depression inventory may have some shared variance with fatigue. Therefore, the previously conducted linear regressions were conducted again with the removal of item eight from the HADS-D.

As shown in Table 4, the analyses did not produce any changes in the first step of the model for any of the dependent variables. Concerning the second step, fatigue remained independently associated with both generic (PCI) and work-specific (CSC attention, executive function, and working memory) cognitive limitations. Depressive symptoms remained independently associated with work specific cognitive limitations in executive function ($\beta = 0.20, p < 0.01$) and working memory ($\beta = 0.16, p < 0.01$). However, the depressive symptoms independent associations with work-specific cognitive limitations in attention ($\beta = 0.11, ns$) and generic cognitive limitations ($\beta = -0.09, ns$) were no longer significant. As depicted in Table 4, all interactions remained not significant.

Discussion

Breast cancer survivors who are working on average three years post-treatment report a higher level of fatigue, depressive symptoms, and both generic and work-specific cognitive limitations than a non-cancer comparison group. Both fatigue and depressive symptoms (i.e., when considering the full depression inventory) were each independently associated with perceived work-specific and generic cognitive limitations in the two groups. In fact, fatigue and depressive symptoms contributed between 7% and 23% of the variance in perceived cognitive limitations when considered together with the group main effect. There was no group by fatigue or group by depressive symptoms interactions. The analyses also did not reveal any significant fatigue by depressive symptom interactions.

The findings are consistent with prior research, which indicates that both fatigue and depressive symptoms can be present in a subgroup of breast cancer survivors years after the completion of primary treatment (Von Ah, et al., 2009; Ahn, et al., 2007; Bower, et al., 2006; Mehnert & Koch, 2008). The current study extends this finding by demonstrating the occurrence of higher levels of fatigue and depressive symptoms in actively working breast cancer survivors three years post-treatment. The complex relationship between fatigue and depression (e.g., fatigue is among the DSM-IV criteria for diagnosis of depression) can make it difficult to distinguish between the two in practice (Arnold, 2008) and in research (Reuter & Harter, 2004). Our study demonstrated that both fatigue and depressive symptoms were each independently associated with perceived cognitive limitations at work and in general. Past research had demonstrated the independent occurrence of fatigue and depression in breast cancer survivors

(Goldstein, et al., 2006). However, the distinction between these two symptoms has not previously been studied in relation to cognitive limitations in breast cancer survivors, which can have important treatment applications.

Careful consideration needs to be taken when assessing a breast cancer survivor who reports symptoms that are both related to fatigue and depression. As seen by the current study, both fatigue and depressive symptoms can be independent. Proper diagnosis is needed to prevent the mismanagement of symptoms. It is important that when assessing symptoms in cancer survivors, especially in the context of reported functional limitations, that careful consideration is given to the distinction between fatigue and depression as different treatments have been shown to be effective for these symptoms during primary cancer treatment (Morrow, et al., 2003; Roscoe, et al., 2005). This may also apply in the management of these symptoms post-treatment. Additional support for the careful distinction between fatigue and depressive symptoms is provided by our finding that a removal of an item on the depression inventory that shares variance with fatigue alters the independent associations that depressive symptoms has with cognitive limitations.

Furthermore, it is currently difficult to remediate cognitive limitations in breast cancer survivors. Therefore, if a breast cancer survivor presents with cognitive limitations it may be helpful to assess for fatigue and depressive symptoms, as well as other modifiable factors such as anxiety and pain. Although the current study did not address causality, at this point efforts to alleviate symptoms such as fatigue and depression may be helpful in attenuating cognitive limitations. Future studies are needed to test this relationship.

The current study did not find an interaction between fatigue and depressive symptoms in relation to cognitive limitations. Several past studies that demonstrated a strong relationship between fatigue and depression utilized a multi-dimensional measure of fatigue (Jean-Pierre, et al., 2007), where the conceptual basis of the fatigue measure includes many elements of distress and fatigue. It is possible that we did not observe the interactive relationship between fatigue and depressive symptoms because we limited our measure to the physical dimension of fatigue. Potentially the previous relationships between fatigue and depression may have been a result of their overlap in the affective domain. In fact, when removing overlapping questions between fatigue and depression measures, the correlation between the two symptoms is attenuated (Stone, Richards, A'Hern, & Hardy, 2001). The lack of significant interactive relationships between fatigue and depressive symptoms may also be a result of differing underlying mechanisms.

In a prior study we observed that a stronger relationship between fatigue and perceived work productivity was evident in breast cancer survivors, while a stronger relationship between depressive symptoms and perceived work productivity occurred in a non-cancer comparison group (Hansen, et al., 2008). The current study indicated the relationships between fatigue, depressive symptoms, and cognitive limitations occurred the same in both groups. Potentially we did not observe group differences in the relationships between fatigue, depressive symptoms, and cognitive limitations due to the study's unique sample. A large proportion of the breast cancer survivors were employed in professional, technical, science, management, or administration professions. These are typically jobs that require high functions. The breast cancer survivors may have learned

to compensate for their fatigue and depressive symptoms so that they could perform optimally at work.

A power analysis indicated that we were powered at 80% to detect the interactions when they collectively explained an additional 2.7% of the variance in the dependent variable (nQuery Advisor 6.01; Statistical Solutions, Boston, MA, USA). Our analyses revealed an R^2 change that explained less than 2.7% of the variance for the interactions. However, we do not believe that limited power for the interactions hinders our ability to interpret the results. Even if our analyses produced statistically significant results that added 2.7% variance to the model, it would not have been a clinically significant effect.

The current findings need to be considered with respect to certain methodological limitations. Due to the cross-sectional nature of the study we cannot determine the directionality between symptom burden (e.g., fatigue and depressive symptoms) and cognitive limitations. While performance based neuropsychological measures could have been included, and have been considered the gold standard for measuring cognitive function, a collateral study demonstrated a lack of sensitivity of neuropsychological testing in relation to cognitive limitations and work function (Calvio, et al., 2010). Additionally, self-report of medical histories (e.g., stage of tumor) were used in the present study. However, past work indicates a positive relationship between survivor recall of medical information and actual data from medical records (Maunsell, Drolet, Ouhoummane, & Robert, 2005). The current study utilized a convenience sample and the breast cancer survivors were mostly Caucasian, middle class, educated, had high functioning jobs, and access to the Internet. Therefore, the results of the current study

cannot be generalized to all breast cancer survivors.

As reviews indicate (Brown & Kroenke, 2009) there is a correlation between depressive symptoms and fatigue. The current study also shows that depressive symptoms and fatigue each account for unique variance in relation to cognitive limitations. Therefore, careful consideration needs to be given when assessing fatigue and depressive symptoms as they often have overlapping symptoms but can also exhibit their own influence. While directionality must await prospective studies, these findings highlight the need to consider both fatigue and depressive symptoms as independent factors related to perceived cognitive limitations.

Table 1. Participant Characteristics

	BCS			NCCG		
	n	%		n	%	
Age**						
≤ 40 years old	40	30.1%	M=44.89	76	62.3%	M=39.16
41-50 years old	51	38.3%	SD = 9.11	20	16.4%	SD=11.42
51-65 years old	42	31.6%		26	21.3%	
Race***						
Caucasian	116	87.2%		80	65.6%	
Non-Caucasian	17	12.8%		42	34.4%	
Ethnicity*						
Hispanic	4	3.0%		13	10.7%	
Non-Hispanic	129	97.0%		109	89.3%	
Education						
Some College or less	30	22.6%		27	22.1%	
Associates or Bachelors Degree	41	30.8%		43	35.2%	
Graduate Education	62	46.6%		52	42.6%	
Marital/Living Arrangement***						
Cohabiting with a partner	101	75.9%		67	54.9%	
Single/Not Cohabiting	32	24.2%		55	45.1%	
Primary Occupation						
Clerical/Sales/Service	25	18.8%		23	18.9%	
Management/Administration	47	35.3%		41	33.6%	
Professional/Technical/Science	61	45.9%		58	47.5%	
Years at current job						
Less than 6 years	74	55.6%	M=7.32	76	62.3%	M=5.89
6 to 15 years	42	31.6%	SD=6.90	34	27.9%	SD=6.81
16 years or more	17	12.8%		12	9.8%	
Annual Income**						
0-39,000	8	6.0%		23	18.9%	
40-59,000	15	11.3%		22	18.0%	
60-79,000	22	16.5%		26	21.3%	
80-99,000	19	14.3%		13	10.7%	
100,000 or more	69	51.9%		38	31.1%	
Menopausal Status***						
Currently going through menopause	40	30.1%		6	4.9%	
Pre menopausal	38	28.6%		93	76.2%	
Post menopausal	55	41.4%		23	18.9%	

*p<0.05, **p <0.01, ***p<.001

BCS = Breast Cancer Survivors (n=133), NCCG = Non Cancer Control Group (n=122)

Table 2. Breast Cancer Survivors: Medical History
(n= 133)

	n	%
Tumor Location		
Right Breast	68	51.1
Left Breast	59	44.4
Both Breasts	5	3.8
Tumor Stage		
I	47	35.9
II	62	47.3
III	22	16.8
Treatment		
Chemotherapy	110	82.7
Radiation Therapy	98	73.7
Surgery	129	97.0
Tamoxifen or Ralozifene	59	44.4
Herceptin (Trastuzumab)	18	13.1
Other Treatment	31	23.3
Years Since Primary Treatment		
1 year	45	33.8
2-5 years	67	50.4
6-10 years	17	12.8
Mean (S.D.)	3.07	2.39
Note: Not all participants responded to all questions		

Table 3. Fatigue and depressive symptoms in relation to self-reported measures of cognitive limitations (n = 255)

	CSC Attention	CSC Executive Function	CSC Memory	PCI
	Beta (β)			
	Step 1: Covariates			
Anxiety	0.31***	0.33***	0.32***	-0.34***
Pain	0.19**	0.16**	0.22***	-0.25***
Menopausal Status	-0.13*	-0.10	-0.04	0.11
Race	-0.14*	-0.10	-0.13*	0.12*
Age				-0.13*
Education		-0.11*		
	$R^2=0.22***$	$R^2=0.216***$	$R^2=0.226***$	$R^2=0.27***$
	Step 2: Symptom Burden			
Cancer	-0.11*	-0.21***	-0.33***	0.29***
Fatigue	0.17*	0.17*	0.19**	-0.27***
Depressive Symptoms	0.15*	0.25***	0.23***	-0.15*
	$R^2=0.29***$	$R^2=0.364***$	$R^2=0.454***$	$R^2=0.47***$
	$R^2 \Delta=0.07***$	$R^2 \Delta=0.147***$	$R^2 \Delta=0.227***$	$R^2 \Delta=0.20***$
	Step 3: Interactions			
Fatigue x Depressive Symptoms	-0.09	0.25	0.15	-0.01
Cancer x Fatigue	-0.06	-0.02	-0.02	0.03
Cancer x Depressive Symptoms	0.01	-0.12	-0.07	0.11
	$R^2=0.29***$	$R^2=0.378***$	$R^2=0.459***$	$R^2=0.47***$
	$R^2 \Delta=0.001$	$R^2 \Delta=0.015$	$R^2 \Delta=0.006$	$R^2 \Delta=0.01$

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

CSC: Cognitive Symptom Checklist; PCI: Functional Assessment of Cancer Therapy Cognitive Scale Perceived Cognitive Impairment subscale

Table 4. Fatigue and depressive symptoms[†] in relation to self-reported measures of cognitive limitations (n = 255)

	CSC Attention	CSC Executive Function	CSC Memory	PCI
	Beta (β)			
	Step 1: Covariates			
Anxiety	0.31***	0.33***	0.32***	-0.34***
Pain	0.19**	0.16**	0.22***	-0.25***
Menopausal Status	-0.13*	-0.10	-0.04	0.11
Race	-0.14*	-0.10	-0.13*	0.12*
Age				-0.13*
Education		-0.11*		
	R ² =0.22***	R ² = 0.216***	R ² =0.226***	R ² =0.27***
	Step 2: Symptom Burden			
Cancer	-0.12*	-0.22***	-0.33***	0.30***
Fatigue	0.19*	0.19**	0.22**	-0.29***
Depressive Symptoms	0.11	0.20**	0.16**	-0.09
	R ² =0.283***	R ² = 0.352***	R ² =0.437***	R ² =0.46***
	R ² Δ=0.06***	R ² Δ= 0.136***	R ² Δ=0.211***	R ² Δ=0.187***
	Step 3: Interactions			
Fatigue x Depressive Symptoms	-0.12	0.23	0.11	-0.01
Cancer x Fatigue	-0.08	-0.08	-0.08	0.03
Cancer x Depressive Symptoms	0.04	-0.07	-0.04	0.11
	R ² =0.286***	R ² = 0.366***	R ² =0.442***	R ² =0.462***
	R ² Δ=0.003	R ² Δ= 0.014	R ² Δ=0.005	R ² Δ=0.004

*p<0.05 **p<0.01 ***p<0.001

[†] Excluding item 8 from Hospital Anxiety Depression Scale ; CSC: Cognitive Symptom Checklist; PCI: Functional Assessment of Cancer Therapy Cognitive Scale Perceived Cognitive Impairment subscale

Figure 1. Self-report measures of fatigue, depressive symptoms, anxiety, and pain (+SE) for BCS and NCCG.

NOTE: Higher scores indicate poorer functioning

*** $p < 0.001$

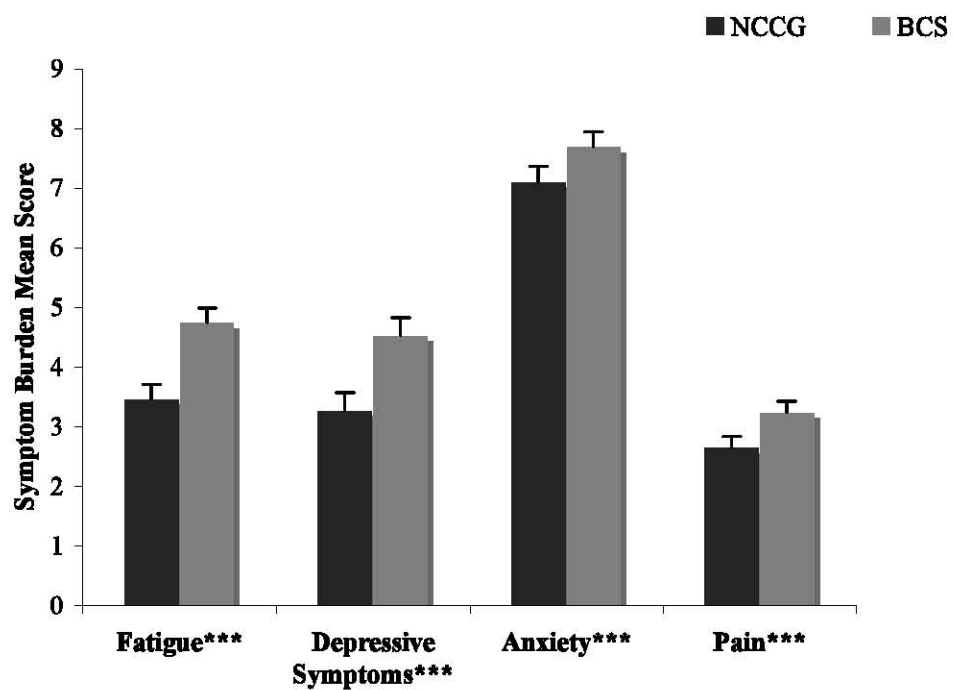


Figure 2. Self-report measures of work-specific and general cognitive limitations (+SE) for BCS and NCCG

Note: PCI , lower score indicates poorer functioning

*** $p < 0.001$

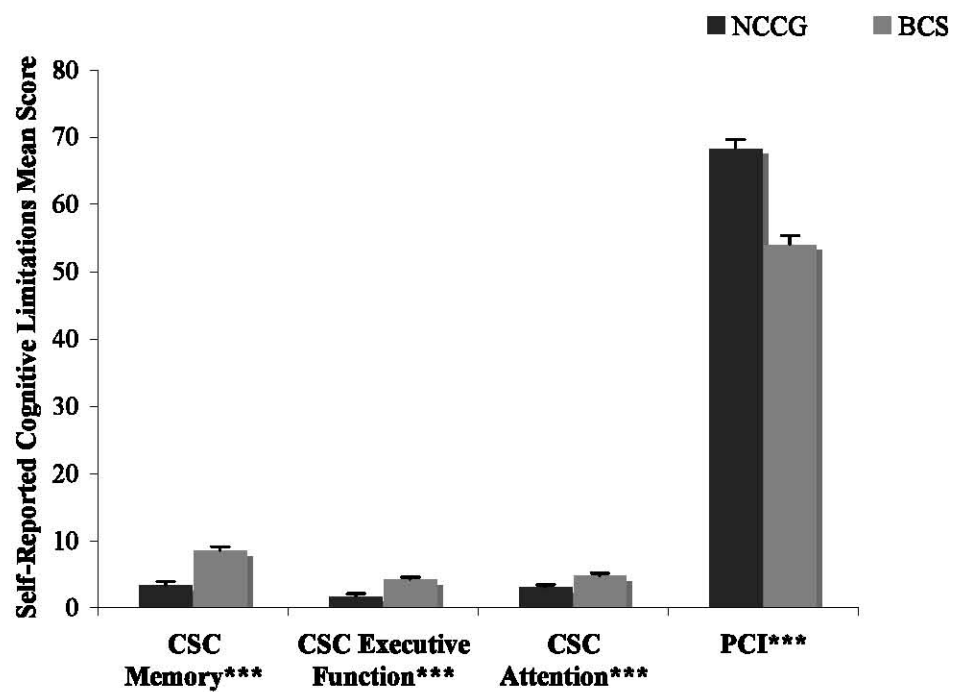


Figure 3. Regression Line Fatigue and Depressive Symptoms

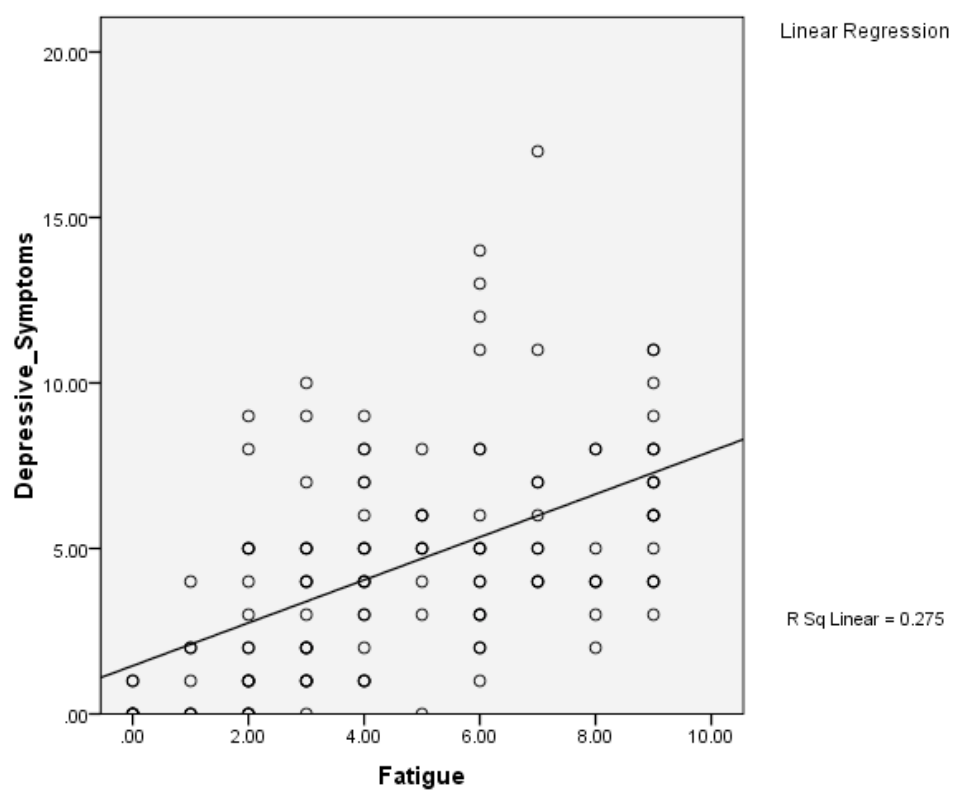
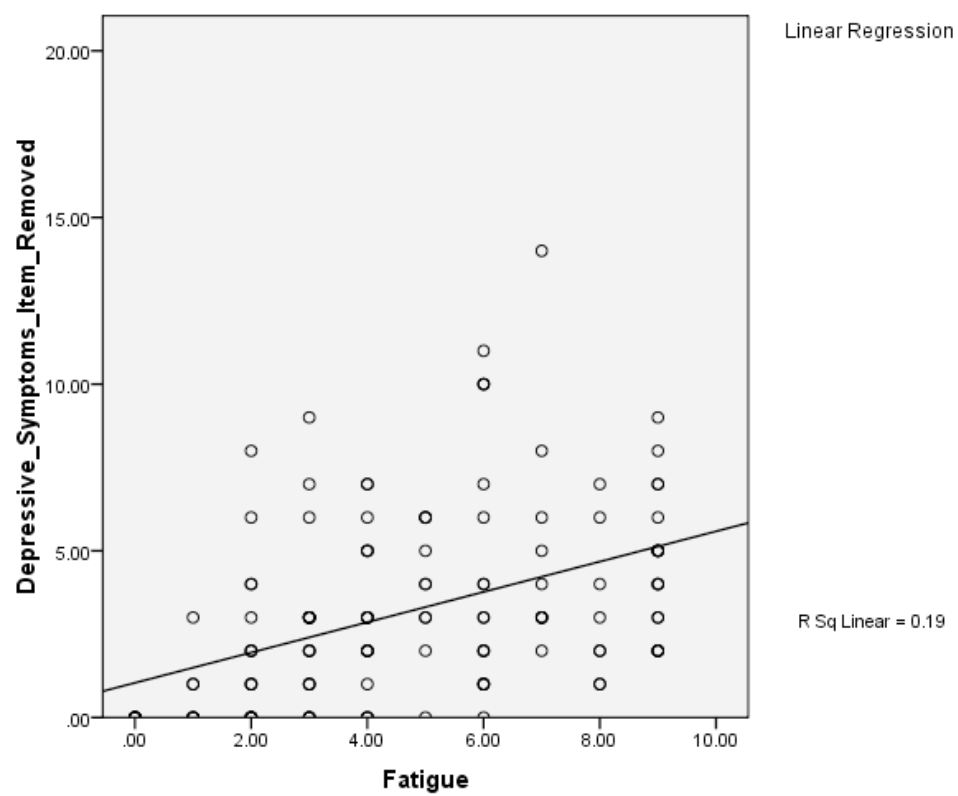


Figure 4. Regression Line Fatigue and Depressive Symptoms Excluding Item 8



LIST OF APPENDICES

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Appendix A: Advertisements

Advertisement for Newspaper and Craig's list
Advertisement for Flyer

Are You a Working Breast Cancer Survivor OR Would You Like To Help Breast Cancer Survivors?

Women breast cancer survivors, 1 to 10 years after primary cancer treatment, whose breast cancer has not spread AND women without cancer history are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of adult ADHD (prior to cancer), dementia, brain injury, epilepsy, drug or alcohol abuse. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

<http://cim.usuhs.mil/cancerstudy>

For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Are You A Working Breast Cancer Survivor?

Women breast cancer survivors, **1 to 10 years** after primary cancer treatment, whose breast cancer has not spread are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of adult ADHD (prior to cancer), dementia, brain injury, epilepsy, drug or alcohol abuse. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

<http://cim.usuhs.mil/cancerstudy>

For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Do You Want To Help Breast Cancer Survivors?

Women without cancer history are needed for on-line study on cognitive function and work. Must be currently working full-time, ages 18 through 65, and without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD. You will need Internet access with connection speed faster than dial-up. Study includes completing questionnaires and a short online test of memory. The study will take approximately 60 to 75 minutes to complete. To see if you are eligible for our study, go to:

<http://cim.usuhs.mil/cancerstudy>

For more information call Lisseth Calvio at (301) 295-9660 or email cogworkstudy@gmail.com.

Are You a Working Breast Cancer Survivor?

An investigation into working and cognitive function after primary treatment for cancer

In order to participate, you must be:

- 1) Female breast cancer survivors between 1 and 10 years since primary treatment (surgery, chemotherapy, and/or radiation) whose breast cancer has not spread**
- 2) Currently working full-time**
- 3) Between the ages of 18 and 65**
- 3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD (prior to cancer diagnosis)**
- 4) Have access to the Internet (any connection speed other than dial-up)**

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time. The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

<http://cim.usuhs.mil/cancerstudy>

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

This research project is being run by the Uniformed Services University of Health Sciences, Bethesda M.D.

Want To Help Breast Cancer Survivors?

An investigation into working and cognitive function after primary treatment for cancer

In order to participate, you must be:

- 1) Female who has never been diagnosed with cancer**
- 2) Currently working full-time**
- 3) Between the ages of 18 and 65**
- 3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD**
- 4) Have access to the Internet (any connection speed other than dial-up)**

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time. The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

<http://cim.usuhs.mil/cancerstudy>

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

*This research project is being run by the Uniformed Services University of Health
Sciences, Bethesda M.D.*

Are You a Working Breast Cancer Survivor **OR** **Would You Like To Help Breast Cancer Survivors?**

An investigation into working and cognitive function after primary treatment for cancer
In order to participate, you must be:

- 1) Female breast cancer survivors between 1 and 10 years since primary treatment (surgery, chemotherapy, and/or radiation), whose breast cancer has not spread
OR Female who has never been diagnosed with cancer**
- 2) Currently working full-time**
- 3) Between the ages of 18 and 65**
- 3) Without a history of dementia, brain injury, epilepsy, drug or alcohol abuse or adult ADHD (for breast cancer survivors, no ADHD diagnosis prior to cancer diagnosis)**
- 4) Have access to the Internet (any connection speed other than dial-up)**

We will ask you to take a short online questionnaire and test of memory, attention and organization that will require 60 to 75 minutes of your time. The study is 100% online and can be taken from any computer that does not use dial-up connection.

To see if you are eligible for our study, please go to:

<http://cim.usuhs.mil/cancerstudy>

For more information, you may contact Lisseth Calvio at (301)295-9660 or via email at: cogworkstudy@gmail.com

This research project is being run by the Uniformed Services University of Health Sciences, Bethesda M.D.

Appendix B: Random Number List

Random Number List

018	101	140	095	139	060
077	106	066	057	072	011
049	002	104	045	079	013
005	006	132	015	053	117
105	051	014	092	116	009
149	073	123	097	093	131
058	046	020	059	100	080
107	087	004	023	150	138
038	062	068	125	047	144
136	034	130	081	076	098
052	024	056	063	007	090
035	040	111	121	145	050
070	010	026	091	033	135
096	124	126	108	075	012
148	094	120	082	074	067
029	054	003	008	114	142
083	019	027	103	088	044
032	146	055	085	028	031
030	122	089	110	021	042
048	016	086	141	036	113
127	147	064	133	001	118
128	017	084	025	065	041
137	102	134	078	069	109
112	039	037	043	119	022
099	071	129	115	061	143

Appendix C: Informed Consent Form

Consent for Participation in a Research Study

The following information is provided to inform you about the research project and your participation in it. Please read this form carefully and feel free to ask any questions you may have about this study and/or about the information given below.

It is important that you understand that your participation in this study is totally voluntary. You may refuse to participate or choose to withdraw from this study at any time. If, during the course of the study, you should have any questions about the study or your participation in it, you may contact:

Lisbeth C. Calvio, M.S. at 301-295-9660
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799
cogworkstudy@gmail.com

Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799
mfeuerstein@usuhs.mil

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814
cogworkstudy@gmail.com

1. INDICATED BELOW ARE THE FOLLOWING:

- a. THE PURPOSE OF THIS STUDY
- b. THE PROCEDURES TO BE FOLLOWED
- c. THE APPROXIMATE DURATION OF THE STUDY

1a. THE PURPOSE OF THIS STUDY:

- Over 80% of breast cancer survivors return to work within months of diagnosis and treatment.
- Some survivors experience memory or concentration problems that may impact their ability to work.

- This study will look at how tests and questionnaires of memory, attention, and organization might relate to each other and to your performance at work.
- If you agree to participate in this study, you will be asked to take an online questionnaire and a short test of your memory, organization and attention. The study will take approximately one hour to one hour and fifteen minutes to complete.

1b. THE PROCEDURES TO BE FOLLOWED:

Individuals meeting qualifications below may be asked to participate in the study.

You may **qualify** for this study based on the following:

- Adult female ages 18 to 65 years old
- Currently working full-time
- Computer/Internet access and usage; computer speed faster than dial-up (Only people with an Internet speed connection faster than dial-up will be able to continue with the study.)
- **Breast Cancer Survivors Only**: Between 1 and 10 years since completion of primary treatment (surgery, chemotherapy, radiation); working 1 year prior to diagnosis of cancer, and currently working.

You are **not qualified** if you have any of the following:

- Metastasized Cancer
- Dementia or Brain Disorder (For Example: Traumatic Brain Injury or Epilepsy)
- Drug and/or Alcohol Abuse
- Existence of adult Attention Deficit Hyperactivity Disorder (ADHD) prior to Cancer treatment

Participation in this study includes completing

1. online questionnaire (approximately 30 minutes to complete)

and

2. a short online test of memory, organization and attention (approximately 30 minutes to complete)

1c. DURATION OF THE STUDY

Approximately 1 hour to approximately 1.25 hours

2. THIS STUDY IS BEING DONE SOLELY FOR THE PURPOSES OF RESEARCH

There will be no direct benefit to you by participating in this study. It is the goal of this research to help other cancer survivors in the future related to their ability to work.

3. DISCOMFORTS AND/OR RISKS THAT CAN BE REASONABLY EXPECTED ARE:

- The risks associated with this study are minor
 - You may find the questionnaires ask questions that may make you uncomfortable
 - You may skip questions at any time
 - Also, you may decline to participate at any time and/or withdraw your participation at any time
- You may experience discomfort or fatigue while completing the test segment
 - There will be ample opportunities to take a break built into the study, in between sections and after each test
- If you have any questions or concerns, you can reach the principle investigators:
 - By telephone (301)295-9660
 - By email: cogworkstudy@gmail.com
 - A researcher will get back to you within one business day

4. POSSIBLE BENEFITS TO YOU THAT MAY BE REASONABLY EXPECTED ARE:

- You may gain a better understanding of the relationship between your memory, organization and attention (perceived and actual) and your productivity at work.
- Through completing this study, you will be providing information that will be helpful in expanding scientific knowledge about work productivity and memory, organization and attention function in breast cancer survivors.
- Our long-term goal is to gain a better understanding of the measurement of memory, organization and attention limitations and its impact on work productivity, and ultimately, work towards improving work productivity in cancer survivors.

5. PRIVACY AND CONFIDENTIALITY:

- All information you provide as part of this study will be confidential and will be protected to the fullest extent provided by law.
- Information that you provide and other records related to this study will be accessible to those persons directly involved in conducting this study and members of the Uniformed Services University of the Health Sciences Institutional Review Board (IRB), which provides oversight for protection of human research volunteers.
- All questionnaires, results and forms will not have identifying information and will be kept in a restricted access, password protected computer, in a locked office. Data from questionnaires will be entered into a database in which individual responses are not identified.
- Paper copies of the data will not be kept.
- Personal information will be collected for payment purposes. This information will be kept separate from the database, in a password protected computer in a locked office at the Uniformed Services University of the Health Sciences.
- If you are a military member, please be advised that under Federal Law, a military member's confidentiality cannot be strictly guaranteed.

Note: YOU ARE FREE TO WITHDRAW THIS CONSENT AND TO STOP PARTICIPATING IN THIS STUDY OR ANY ACTIVITY AT ANY TIME FOR ANY REASON.

6. COMPENSATION

- You will be given the option of receiving a book on stress reduction for completing both phases of this study
- At the end of the study, you will be asked for some personal information (e.g., name, address, social security number, phone number) in order to receive the book.
- This information is collected for tax tracking information by our institution. We must receive this information in order to render compensation.
- This information will be stored separately from the study data and will be stored in a secure, password protected computer in a locked office with restricted access.

7. RECOURSE IN THE EVENT OF INJURY:

COMPENSATION TO YOU IF YOU ARE INJURED AND LIMITS TO YOUR MEDICAL CARE: This study should not entail any physical or mental risk beyond those described above. It is believed that complications arising from participation should not occur. If, for any reason, you feel that continuing this study would constitute a hardship for you, you may end your participation in the study at any time.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, contact the Director of Human Subjects Protection Program at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301)295-9534. This office can review the matter with you. They can provide information about your rights as a research volunteer. They may also be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301)295-3028.

Should you have any questions at anytime about the study you may contact the principal investigator, Lisbeth C. Calvio, M.S., Department of Medical and Clinical Psychology, USUHS, Bethesda, Maryland 20814-4799, at 301-295-9660.

**STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS
RESEARCH PROJECT:**

I have read this consent form and I understand the procedures to be used in this study and the possible risks, inconveniences, and/or discomforts that may be involved. All of my questions have been answered. I freely and voluntarily choose to participate. I understand that I may withdraw at any time. By clicking on the "yes" button, you are agreeing that you have read the consent form and understand the procedures to be used in this study. You also agree that you freely and voluntarily choose to participate and understand that you may withdraw at anytime. If you wish you may print out a copy of this form for your records.

- ☐ Yes, I agree to participate in this study.**

Appendix D: Screening Questions

Screening Questions:

Thank you for your interest in participating in our study. The following is a list of questions that will determine your eligibility for this study. We will email you within a few days after your completion of this screener.

- 1. Are you within the ages of 18 and 65?**
- 2. What is your gender?**
- 3. Are you able to access the Internet when needed?**
- 4. Are you able to use the Internet by yourself (without help/assistance)?**
- 5. Are you currently working full-time or self-employed? (Full-time is considered to be on average 40 hours of work or more a week)**
- 6. On average, how many hours do you work a week?**
- 7. Have you ever been diagnosed with any of the following: Dementia, Brain Injury, Adult Attention Deficit Hyperactivity Disorder (Adult ADHD), Epilepsy, Drug or Alcohol Abuse?**

- 1. Have you ever been diagnosed with any form of cancer?**
 - If yes, please specify the type of cancer you were diagnosed with:

- 9. Have you ever been diagnosed with breast cancer?**

*****The following questions are specific cancer questions- Only for those who answered yes to having a history of cancer****

- 1. Were you diagnosed with stage IV (metastasized) cancer?**
- 2. Did you complete primary cancer treatment (defined as surgery, radiation therapy and/or chemotherapy) between 1 and 10 years ago?**
- 3. Where did you receive primary cancer treatment?**
- 4. What type of treatment have you received for your cancer (for example, lumpectomy, 3 rounds of chemotherapy)?**

For all participants:

1. What is an email address where you can be contacted for the purpose of this study?

Please note that within the next few days, we will be emailing you from the following email address: cogworkstudy@gmail.com. Please ensure that your email address allows this email address to bypass any filter settings on your email. Thank you for your interest in our study.

Appendix E: Participant Instructions

Instructions (Condition I):

Thank you for your interest and participation in our study. The information that you provide will be looked at very carefully and be used in future efforts to help cancer survivors at work.

This study will be conducted in two parts and will require you to access two separate websites:

- o One website will contain questionnaires
- o One website will consist of some short tests of memory, attention, and organization (CNSVS).

This study will take one hour to one hour and fifteen minutes to complete. It must be completed continuously. Once you begin the first portion, you must also complete the second portion during the same time period. Also, please ensure that you complete the study in a quiet area with no or little distractions. You will be allowed to take breaks in between the short tests and in between logging into the two websites. You will be required to have a connection speed that is faster than dial-up.

Your Identification Number is:

You will be asked this number several times, including when you log on to the website with the test of memory, attention, and organization.

Please follow the order of events that is provided to you:

Click the link below:

[Click Me](#)

Or copy and paste the following website to your browser:

https://www.surveymonkey.com/s.aspx?sm=9J5uaGoq_2fhYErTylDmeycg_3d_3d

1. The first pages that you will see are the informed consent forms. Please read it carefully. You must agree to participate in the study in order to proceed.
2. You will then be presented with a series of questionnaires.
3. Upon completing the questionnaires, when you will click on the link it will open up the test in another window. **DO NOT CLOSE THE INITIAL BROWSER as you will need to return after finishing the test portion.**
4. When you log on to the test portion (CNSVS Web Agent), you will be asked for a test administrator and password. Please put “usuhs” for both.
5. The next window will ask for your “Subject ID and birthdate.
6. Your Subject ID is your participant number (provided above).

7. At the end of the study, you will be asked a few more questions for compensation purposes and given online support resources.
8. You will be done once you see the following message and click the link to end the questionnaire:
This concludes the questionnaire. You may close your browser window now. Thank you again for your participation, if you have any questions you can contact the principle investigators as listed below:

Email: cogworkstudy@gmail.com

Liseth C. Calvio, M.S. 301-295-9660
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814

Thank you for your participation.

Sincerely,
Liseth C. Calvio, M.S.
LT MSC USN
Principle Investigator
Uniformed Services University of the Health Sciences

Instructions (Condition II):

Thank you for your interest and participation in our study. The information that you provide will be looked at very carefully and be used in future efforts to help cancer survivors at work.

This study will be conducted in two parts and will require you to access two separate websites:

- o One website will consist of a short test of memory, attention, and organization (CNSVS)
- o One website will consist of questionnaires

This study will take one hour to one hour and fifteen minutes to complete. It must be completed continuously. Once you begin the first portion, you must also complete the second portion during the same time period. Also, please ensure that you complete the study in a quiet area with no or little distractions. You will be allowed to take breaks in between the short tests and in between logging into the two websites. You will be required to have a connection speed that is faster than dial-up.

Your Identification Number is:

You will be asked this number several times, including when you log on to the website with the test of memory, attention, and organization.

Please follow the order of events that is provided to you:

Click the link below:

[Click Me](#)

Or copy and paste the following website to your browser:

https://www.surveymonkey.com/s.aspx?sm=9J5uaGoq_2fhYErTylDmeycg_3d_3d

1. The first pages that you will see are the informed consent forms. Please read it carefully. You must agree to participate in the study in order to proceed.
2. You will take the test portion of the study first. You will be asked to click on a link that will open up the CNSVS test in another window. **DO NOT CLOSE THE INITIAL BROWSER as you will need to return after finishing the test portion.**
3. On the CNSVS site, you will be asked to log in. When you log in to the test portion (CNSVS Web Agent), you will be asked for a test administrator and password. Please put “usuhs” for both.
4. The next window will ask for your “Subject ID” and birthdate.
2. Your Subject ID is your participant number (provided above).

3. Upon completing the CNSVS test, return to the original window, and continue to fill out a few questionnaires.
4. At the end of the study, you will be asked a few more questions for compensation purposes and you will be provided a list of online support resources.
5. You will be done once you see the following message and click the link to end the questionnaire:
This concludes the questionnaire. You may close your browser window now. Thank you again for your participation, if you have any questions you can contact the principle investigators as listed below:

Email: cogworkstudy@gmail.com

Liseth C. Calvio, M.S. 301-295-9660
Department of Medical & Clinical Psychology,
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Michael Feuerstein, Ph.D., MPH at 301-295-9677
Department of Medical & Clinical Psychology,
USUHS, Bethesda, MD 20814-4799

Institutional Review Board Office at (301) 295-9534
USUHS, Bethesda, Maryland 20814

Thank you for your participation.
Sincerely,

Liseth C. Calvio, M.S.
LT MSC USN
Principle Investigator
Uniformed Services University of the Health Sciences

Appendix F: Self-Report Questionnaires

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)
Cognitive Symptoms Checklist-Modified (CSC; Feuerstein,
Hansen, Calvio, Johnson, Ronquillo, 2007; O'Hara, Harrell,
Bellingrath, & Lisicia, 1993)
Rotterdam Symptom Checklist (Jean-Pierre et al., 2006; de Haes et al.,
1990)
Pain Visual Analogue Scale (Scott & Huskisson, 1979)
Fact-Cog Functional Assessment of Cancer Therapy Cognitive Scale
Version 2 (FACT-Cog; Wagner, Cella, & Doninger, 2003; Cella et al.,
1993)

Hospital Anxiety and Depression Scale (HADS)

Please answer the following questions about how you would describe your feelings as of this moment. Please click only one response for each question.

1. I feel tense or wound up

Most of the time	A lot of the time	Occasionally	Not at all
☐	☐	☐	☐
2. I still enjoy the things I used to enjoy

Definitely as much	Not quite as much	Only a little	Hardly at all
☐	☐	☐	☐
3. I get sort of frightened feelings as if something awful is about to happen

Quite badly	Not too badly	A little	Not at all
☐	☐	☐	☐
4. I can laugh and see the funny side of things

As much as always	Not quite so much now	Definitely not so much now	Not at all
☐	☐	☐	☐
5. Worrying thoughts go through my mind

A great deal of the time	A lot of the time	From time to time	Only on occasion
☐	☐	☐	☐
6. I feel cheerful

Not at all	Not often	Sometimes	A lot
☐	☐	☐	☐
7. I can sit at ease and feel relaxed

Definitely	Usually	Not often	Not at all
☐	☐	☐	☐
8. I feel as if I am slowed down

Nearly all the time	Very often	Sometimes	Not at all
☐	☐	☐	☐
9. I get a sort of frightened feeling like butterflies in my stomach

Not at all	Occasionally	Quite often	Very often
☐	☐	☐	☐
10. I have lost interest in my appearance

Definitely	I don't take so much care as I should	I may not take quite as much care	I take just as much care as ever
☐	☐	☐	☐
11. I feel restless as if I have to be on the move

Very much	Quite a lot	Not very much	Not at all
☐	☐	☐	☐
12. I look forward with enjoyment to things

The Rotterdam Symptom Checklist

Have you during the last 3 days (week), been bothered by:

Tiredness	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Lack of energy	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Difficulties sleeping	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Pain Visual Analogue Scale

Please rate the severity of your pain during the *past week*.

No pain				Severe pain
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Fact-Cog

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred during the past 7 days.**

FC1 – FC13

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts.....0....0	1	2	3	4	
CogA3	My thinking has been slow 0....0	1	2	3	4	
CogC7	I have had trouble concentrating.....0....0	1	2	3	4	
CogM9	I have had trouble finding my way to a familiar place 0....0	1	2	3	4	
CogM10	I have had trouble remembering where I put things, like my keys or my wallet.....0....0	1	2	3	4	
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions 0....0	1	2	3	4	
CogV13	I have had trouble recalling the name of an object while talking to someone 0....	1	2	3	4	
CogV15	I have had trouble finding the right word(s) to express myself 0....0	1	2	3	4	
CogV16	I have used the wrong word when I referred to an object.....0....0	1	2	3	4	
CogV17b	I have had trouble saying what I mean in conversations with others 0....0	1	2	3	4	
CogF19	I have walked into a room and forgotten what I meant to get or do there 0....0	1	2	3	4	
CogF23	I have had to work really hard to pay attention or I would make a mistake 0....0	1	2	3	4	
CogF24	I have forgotten names of people soon after being introduced 0....0	1	2	3	4	

FactCog Questions: Past 7 Days

FC14 – FC20

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow.....0....0	1	2	3	4	
CogC31	I have had to work harder than usual to keep track of what I was doing.....0....0	1	2	3	4	
CogC32	My thinking has been slower than usual.....0....0	1	2	3	4	
CogC33a	I have had to work harder than usual to express myself clearly.....0....0	1	2	3	4	
CogC33c	I have had to use written lists more often than usual so I would not forget things.....0....0	1	2	3	4	
CogMT1	I have trouble keeping track of what I am doing if I am interrupted 0....0	1	2	3	4	
CogMT2	I have difficulty shifting back and forth between different activities that require thinking.....0....0	1	2	3	4	

FactCog Questions: Past 7 Days

FC21-24

		Not at all	A little bit	Some- what	Quite a bit	Very much
CogQ35	I have been upset about these problems.....0.. 0	1	2	3	4	
CogQ37	These problems have interfered with my ability to work.....0.. 0	1	2	3	4	
CogQ38	These problems have interfered with my ability to do things I enjoy.....0.. 0	1	2	3	4	
CogQ41	These problems have interfered with the quality of my life 0 0	1	2	3	4	

FactCog Questions: Past 7 Days

FC25 – FC29

Below is a list of statements that other people with your condition have said are important. By circling the (1) number per line, please indicate how often each of the following has occurred during the past 7 days.

By circling during the

	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
PC30 Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
PC31 Other people have told me I seemed to have trouble speaking clearly					
PC32 Other people have told me I seemed to have trouble thinking clearly					
PC33 Other people have told me I seemed confusedÉ É É É É ...	0	1	2	3	4
	Not at all	A little bit	Some-what	Quite a bit	Very much
PC34 Other people have told me my mind seemed really sharp	0	1	2	3	4

Cognitive Symptoms Checklist – Modified (CSC)

Please read each of the following items below. They describe problems that you may or may not experience at work.

<u>Item:</u>	<u>Yes</u>	<u>No</u>
1. I have difficulty doing math in my head		
2. I have difficulty answering questions quickly		
3. I have difficulty seeing and correcting mistakes on my own		
4. I have difficulty seeing and correcting mistakes pointed out to me by others		
5. I have difficulty focusing on a task when there is too much detail or clutter		
6. I have difficulty making decisions		
7. I have difficulty understanding what I read without rereading it		
8. I have difficulty understanding what I hear the first time I hear it		
9. I have difficulty seeing mistakes that I make as they occur		
10. I have difficulty seeing mistakes after I have completed the task		
11. I have difficulty trying new ideas or actions		
12. I have difficulty planning a speech		
13. I have difficulty shifting my attention among two or more things		
14. I have difficulty staying with a task until completion		
15. I have difficulty planning what to discuss when I meet someone		
16. I have difficulty following directions to a specific place		
17. I have difficulty shifting from 1 task or activity to another		
18. I have difficulty completing all steps of a task or activity		
19. I have difficulty following step-by-step instructions		
20. I have difficulty putting steps in order such that the most important steps are done first		
21. I have difficulty setting up a routine or system to approach tasks		
22. I have difficulty understanding what a problem is when it occurs and clearly stating what the problem is		
23. I have difficulty starting a task or activity on my own		
24. I have difficulty remembering where my car is parked		
25. I have difficulty focusing on a task when there is a sudden movement around me		
26. I have difficulty knowing where to look for information to solve a problem		
27. I have difficulty using new information to re-evaluate what I know		
28. I have difficulty choosing a solution to a problem from several possible sources		
29. I have difficulty focusing on a task when there is a lot of movement happening around me		
30. I have difficulty focusing on a task when there is a sudden loud noise		
31. I have difficulty following written instructions		
32. I have difficulty writing to other people in an organized manner		
33. I have difficulty organizing information to be remembered		
34. I have difficulty focusing on a task when more than one person is speaking at a time		
35. I have difficulty focusing on a task when a radio or TV is playing in the background		
36. I have difficulty following or retracing steps to solve a problem		
37. I have difficulty remembering to perform daily routines		
38. I have difficulty remembering things someone has asked me to do		
39. I have difficulty remembering the content of telephone conversations		
40. I have difficulty focusing on a task when I feel hot or cold		
41. I have difficulty remembering the content of conversations and/or meetings		
42. I have difficulty remembering a word I wish to say		
43. I have difficulty acting on a decision that I made		
44. I have difficulty putting together the materials needed for a task		
45. I have difficulty understanding a system		
46. I have difficulty remembering my train of thought as I am speaking		
47. I have difficulty remembering the name of a familiar object or person		
48. I have difficulty understanding graphs or flowcharts		
49. I have difficulty understanding how a task fits into a plan or system		
50. I have difficulty understanding systems and models		
51. I have difficulty remembering information that is "on the tip of my tongue"		
52. I have difficulty remembering what I intended to write		

- 53. I have difficulty figuring out how a decision was reached
- 54. I have difficulty following the flow of events
- 55. I have difficulty considering all aspects of what I hear or see instead of focusing on only one part
- 56. I have difficulty remembering to schedule appointments
- 57. I have difficulty staying focused in places where there are many sights and sounds
- 58. I have difficulty remembering to keep appointments once they are scheduled
- 59. I have difficulty focusing on a task when I am in a large area

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