Effects of Chemotherapy on Sensory Inhibition and Sensory Memory in Breast Cancer Survivor

Raquel Bibi

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Effects of Chemotherapy on Sensory Inhibition and Sensory Memory
in Breast Cancer Survivors

by

Raquel Bibi

A thesis submitted to the faculty of
City College of the City University of New York,
In partial fulfillment of the requirements for the degree of

Master of Arts

Department of Psychology
City College of the City University of New York
January 2013
I wish to acknowledge Dr. Robert Melara
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Most of all, I wish to thank my husband, Eddie, for putting up with me through the years. Albert, Celia, Sonia, and Elliott, thank you for your understanding and love.
# Table of Contents

List of Tables ........................................................................................................................................... 5

List of Figures ........................................................................................................................................... 6

List of Abbreviations ............................................................................................................................... 7

Abstract ..................................................................................................................................................... 8

Introduction .............................................................................................................................................. 9

Neuropsychological Evidence of Cancer-Related Cognitive Dysfunction .............................................. 11

- Cancer Biology ....................................................................................................................................... 11

- Chemotherapy ......................................................................................................................................... 12

- Hormone Replacement Therapies ......................................................................................................... 14

- Psychological Distress ............................................................................................................................. 16

Neurobiological Evidence of Cancer-Related Cognitive Dysfunction ................................................... 18

Neurophysiological Evidence of Cancer-Related Cognitive Change ...................................................... 19

- Animal Models ....................................................................................................................................... 20

- Imaging .................................................................................................................................................. 21

- Electrophysiology ................................................................................................................................... 22

  - P3b component .................................................................................................................................... 23

  - P50 suppression ..................................................................................................................................... 24

  - Mismatch Negativity Response ........................................................................................................... 26

  - Gating in and gating out ....................................................................................................................... 27

- The Current Study ................................................................................................................................. 29
Methods ................................................................................................................................. 29

Participants............................................................................................................................. 29

Stimuli, apparatus, and procedure ......................................................................................... 30

EEG Recording ....................................................................................................................... 31

Dipole Source Analysis .......................................................................................................... 32

Results .................................................................................................................................... 33

P50 suppression ....................................................................................................................... 33

Dipole analysis of P50 suppression ......................................................................................... 34

Mismatch negativity ............................................................................................................... 35

Correlational analyses ........................................................................................................... 35

Discussion ............................................................................................................................... 37

Relationships between sensory inhibition and sensory memory ............................................ 38

Neurobiological basis of chemotherapy-induced cognitive impairment ............................ 40

Limitations ............................................................................................................................... 42

Future directions .................................................................................................................... 44

Source Localization of MMN ................................................................................................ 44

Stress and the Hippocampus .................................................................................................. 45

Conclusions ............................................................................................................................ 48

References ............................................................................................................................... 49
List of Tables

Table 1. Review of Animal Studies of Chemotherapy-Related impairments.......................... 69-69

Table 2. P50 suppression index (P50_s2/P50_s1) to each pair of age-matched participants in the
     paired click paradigm........................................................................................................ 71

Table 3. Correlation with participant age of P50 suppression (paired-click and oddball
     paradigms) and MMN indices, separately for healthy controls and breast cancer
     survivors................................................................................................................................ 72
List of Figures

Figure 1. Factors that affect assessment of cognitive changes induced by drugs. .................... 73

Figure 2. Postulated mechanisms of chemotherapy-associated cognitive changes.................... 74

Figure 3. Grand Average ERPs and Significant Clusters of P50 Supression............................. 75

Figure 4. Average magnitude of dipole moments in paired-click paradigm by brain region ...... 76

Figure 5. Grand Average MMN at CZ with Significant Clusters ............................................. 77
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>Anastrozole Tamoxifen And Combined trial</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>BCI</td>
<td>brain computer interface</td>
</tr>
<tr>
<td>CFC</td>
<td>contextual fear conditioning</td>
</tr>
<tr>
<td>CRF</td>
<td>cancer related fatigue</td>
</tr>
<tr>
<td>CTC</td>
<td>cyclophosphamide, thiotepa, and carboplatin</td>
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<tr>
<td>ERP</td>
<td>Event Related Potential</td>
</tr>
<tr>
<td>FEC</td>
<td>5-fluorouracil, epirubicin, and cyclophosphamide</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional MRI</td>
</tr>
<tr>
<td>IL-6</td>
<td>cytokine interleukin-6</td>
</tr>
<tr>
<td>ISI</td>
<td>inter-stimulus interval</td>
</tr>
<tr>
<td>MMN</td>
<td>mismatch negativity response</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>N1 (N100)</td>
<td>negative ERP component occurring ~100 ms post-stimulus</td>
</tr>
<tr>
<td>NOR</td>
<td>novel object recognition (task)</td>
</tr>
<tr>
<td>P1 (P50)</td>
<td>positive ERP component occurring ~50 ms post-stimulus</td>
</tr>
<tr>
<td>P50 suppression</td>
<td>Ration of stimulus 2 P50 (P1) / stimulus 1 P50 (P1)</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission topography</td>
</tr>
<tr>
<td>POCD</td>
<td>postoperative cognitive dysfunction</td>
</tr>
<tr>
<td>PTSD</td>
<td>post-traumatic stress disorder</td>
</tr>
<tr>
<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>SERMs</td>
<td>selective estrogen receptor modulators</td>
</tr>
<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-alpha</td>
</tr>
<tr>
<td>WAIS-R</td>
<td>Wechsler Adult Intelligence Scale Revised</td>
</tr>
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</table>
Abstract

Survivors of breast and other cancers often report protracted difficulty in performing tasks involving concentration and memory even years after the completion of adjuvant chemotherapy regimens. The current study investigated whether chemotherapy is associated with deficits in sensory gating and sensory memory. A group of nine breast cancer survivors, and nine age-matched healthy control participants (mean age 54 years), watched silent films while pairs of clicks or streams of tones were presented during electroencephalographic recording. The survivors evinced a relatively weakened ability to inhibit redundant sensory stimulation (P50 suppression), whether to the second of a pair of clicks or to a train of identical auditory tones. Dipole source analysis localized the survivors’ impairment to the hippocampus, with preservation of function in gating mechanisms of the frontal lobe and auditory cortex. Survivors also showed diminished sensory memory needed to register novel or deviant information in an otherwise uniform auditory environment (mismatch negativity). The findings suggest that chemotherapy is associated with a pervasive deterioration of early, automatic mechanisms of sensory gating. Loss of sensory inhibition may trigger a cascade of attention and memory deficits in survivors further down the information processing line, effectively accelerating cognitive aging through disruption of hippocampus-dependent memory functions.
Effects of Chemotherapy on Sensory Inhibition and Sensory Memory in Breast Cancer Survivors

Although breast cancer is the most common form of cancer in women (excluding non-melanoma skin cancer), and a leading cause of cancer death in America, the overall five-year survival rate is now an impressive 88% (Center for Disease Control and Prevention, 2010; American Cancer Society, 2010). Advances in clinical oncology have meant that more women than ever are living after chemotherapy. As the number of survivors increase, the ongoing treatment-related side effects must be addressed. Acute cognitive changes during chemotherapy are common (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008; Wefel & Schagen, 2012), with a significant subgroup of cancer survivors revealing in self report protracted difficulty in performing certain cognitive tasks, months and even years after the completion of adjuvant chemotherapy regimens (Koppelmans et al., 2012; McLachlan, Devins, & Goodwin, 1998; Minisini et al., 2004; Reid-Arndt, 2006). Especially common are reports of impairments in concentration, maintaining performance speed, and remembering prospective chores (Berglund, Bolund, Fornander, Rutqvist, & Sjödén, 1991; Hedayati, Schedin, Nyman, Alinaghizadeh, & Albertsson, 2011), problems that often negatively impact employment after cancer treatment (Ahn et al., 2009; Bradley, Bednarek, & Neumark, 2002; Keith, Wu, Epp, & Sutherland, 2007; Munir, Burrows, Yarker, Kalawsky, & Bains, 2010). Survivors of breast cancer were among the first to report these symptoms and provide recurrent anecdotal evidence of “chemobrain.” Although the prevalence of neuropsychological deficits significantly decreases as time after the end of oncological therapy elapses, a subset of breast cancer survivors remains concerned about their prolonged deficits in memory and concentration abilities.
In 2003, researchers formed The International Cancer and Cognition Task Force to address the growing need for research into long-term cognitive impairments following chemotherapy in order to identify risk factors, treatment options, and preventive actions (Vardy et al., 2008). There has since been an upsurge in research on cognitive deficits following adjuvant chemotherapy, but there still remains a paucity of research into the underlying mechanisms of these purported cognitive deficits.

In the last decade, systematic investigations on the effects of cancer and chemotherapy agents have begun to characterize the subset of survivors who, relative to healthy controls, display in tasks of selective attention and working memory persistent and clinically relevant long-term deficits (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006), even as long as 20 years after treatment (Koppelmans et al., 2012). The study of cognitive decline following cancer therapy is complicated by the use of multiple treatments, side-effects such as cancer related fatigue, and psychiatric changes including depression and anxiety, along with mediators such as age, inflammation, sleep deprivation, and other medications. Figure 1 illustrates the constellation of factors that affect assessment of cognitive change. In addition, methodological confounds such as differences in patient populations, assessment instruments used, and criteria for defining change, complicate understanding of the incidence of post-treatment cognitive change and perhaps explain inconsistencies in reported prevalence (Ahles, 2012). Thus, despite more direct neuropsychological evidence from longitudinal studies of cancer patients before and after chemotherapy, results are inconsistent (Jenkins et al., 2006; Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Nevertheless,
a subset of survivors displays long-term post-treatment cognitive deficits independent of these confounds.

**Neuropsychological Evidence of Cancer-Related Cognitive Dysfunction**

Approximately one in eight American women will be diagnosed with breast cancer in their lifetime (American Cancer Society, 2010). Treatment of breast cancer most often begins with surgery. Depending on diagnostic features, either a lumpectomy or a mastectomy is performed and surgery is completed with either sentinel (nearby) lymph node dissection or axillary (under armpit) lymph node dissection. Post-surgery, clinical criteria (such as age, cancer type, size, hormone receptor and metastatic status) establish a patient’s adjuvant treatment regimen, including chemotherapy, radiotherapy, endocrine treatment, and immunotherapy, by themselves or in combination with other treatments. Initial investigations of cancer-related cognitive decline focused on chemotherapy drugs and largely ignored the role these multi-modality treatment strategies may have on cognitive function. Today, researchers are cognizant of the possible impact on cognition of cancer biology, chemotherapy, endocrine modulators, and psychological factors.

**Cancer Biology**

Wefel et al. (2004) conducted a small (n=18) prospective study of cognitive impairments before and after chemotherapy. Comprehensive neuropsychological evaluations of breast cancer patients, which included self-report measures of personality traits, affective status and carcinoma-specific quality of life (QOL), were obtained three times over the course of their chemotherapy treatments: at baseline, three weeks after chemotherapy completion (approximately six months after baseline evaluations), and one year post-chemotherapy treatment. Using statistical approaches designed to minimize potential false positives while
maintaining the capacity to determine the frequency of actual impairment, Wefel et al. (2004) classified patients with a cognitive impairment at baseline and/or after treatment into two groups: those who had z-scores above 1.5 on two or more cognitive tests and those that had a z-score of 2.0 on a single cognitive test.

Unexpectedly, 33% of patients were classified as having cognitive impairment at baseline. Shortly after completing their cancer regimens, within-subject analyses revealed that 61% of patients demonstrated cognitive decline from their baseline assessment in one or more cognitive tasks. Of these patients, approximately 50% remained cognitively impaired 18 months after initiation of adjuvant chemotherapy. Declines in performance occurred most often in the digit span and arithmetic subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R) and in the Trail-Making tests. Although these cognitive impairments were subtle, they were nonetheless associated with patients’ inability to return to work.

Chemotherapy

Early investigations of cognitive impairments in breast cancer survivors were cross-sectional studies conducted on women receiving adjuvant chemotherapy after a primary diagnosis of breast cancer (Minisini et al., 2004). In a study of delayed chemobrain (nine years after the end of treatment), Ahles et al. (2002) found significant impairments in cognition and memory on neuropsychological tests. Cancer survivors receiving systemic chemotherapy were more likely to score in the lowest quartile on the Neuropsychological Performance Index (39% vs. 14%, P < .01). Treatment was associated with significantly impaired verbal memory (p<.01) and psychomotor functioning (p<.05).

Schagen et al. (2006) conducted a prospective longitudinal study investigating the cognitive sequelae of chemotherapy using three groups of breast cancer patients and a control
group of healthy women. Two of the three breast cancer groups comprised high-risk breast cancer patients who had participated in a randomized trial receiving either high-dose adjuvant chemotherapy with cyclophosphamide, thiotepa, and carboplatin (CTC “high dose” group) or standard-dose chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC “standard” group), followed by radiotherapy and tamoxifen (40 mg daily for 2–5 years); the third breast cancer group consisted of women with Stage I breast cancer who received radiation treatments without systemic chemotherapy agents (no-CT “no chemo” group).

Participants completed neuropsychological evaluations (10 tests, 24 indices) that measured cognitive functioning in five domains: focused–sustained attention, working–verbal–visual memory, processing speed, executive function, and verbal/motor function. Premorbid intelligence was measured during the initial assessment using the Dutch Adult Reading test. Participants in the high-dose and standard-dose groups were tested before the start of chemotherapy and again six months after completion of therapy (~one year after initial evaluation). The “no chemo” group was re-assessed 12 months after their first assessment and the controls six months later.

A patient was defined as cognitively impaired if she scored two standard deviations below the mean of the healthy group on at least three of the 24 test indices. Controlling for age and IQ, Schagen et al. (2006) found no significant differences among the four groups in neuropsychological test scores or in the percentage of participants who were classified as cognitively impaired at the first and second assessments. However, when the researchers accounted for age, IQ, practice and the magnitude of cognitive changes in test scores between assessments, they found that the percentage of breast cancer patients whose cognitive performance had deteriorated was significantly higher in the high-dose group (25%) - but not the
standard-dose group (12.8%) or no-chemo group (17.5%) - relative to the control group (6.7%). Although the deterioration in cognitive performance over time occurred across a variety of tests measuring several cognitive functions, those most sensitive to executive functions exhibited the strongest effects. The results are consistent with accumulating research evidence that higher chemotherapy doses are linked with more severe and persistent cognitive impairment. This conclusion must be interpreted with caution, however, because the moderating role on cognitive decline of follow-up hormone replacement therapy is unknown in this study, since all participants in chemotherapy treatment received tamoxifen.

**Hormone Replacement Therapies**

Limitations of Schagen et al. (2006) suggest the effects of hormone replacement therapies (HRTs) such as tamoxifen and anastrozole are especially relevant in discussions of chemobrain. These drugs, which prevent cancer growth in estrogen positive cancer tumors, belong to a class of compounds known as selective estrogen receptor modulators (SERMs). The use of SERMs in cancer treatments may contribute to cognitive decline after chemotherapy because of side effects, which include the induction of chemical menopause. Elderly women with low levels of unbound endogenous estradiol (a measure of available estrogen) are more likely than those with high levels to develop cognitive impairments (Yaffe et al., 2000). Menopausal symptoms such as hot flashes, symptoms of the normal aging process, occur more frequently, are more distressing, and are of greater duration in naturally and artificially postmenopausal breast cancer patients (Carpenter, Johnson, Wagner, & Andrykowski, 2002). In addition, patients who report more severe hot flashes endorse moderate to severe interference with sleep (40%), concentration (33%), mood (29%), and sexuality (28%).
Jenkins, Shilling, Fallowfield, Howell, and Hutton (2004) gave a battery of neuropsychological tests to breast cancer patients enrolled in the anastrozole-tamoxifen-and-combined (ATAC) trial for the treatment of breast cancer or post-menopausal healthy controls. Here, patients were assigned randomly into anastrozole alone, tamoxifen alone, or combined anastrozole and tamoxifen groups. Relative to healthy controls, breast cancer patients were found to be impaired on a processing speed task and a measure of immediate verbal working memory task. However, patient performance across groups was not significantly related to the length of hormone replacement therapy.

Falleti et al. (2005) performed a meta-analysis of six cross-sectional breast cancer studies to investigate the effects of HRTs on six cognitive domains (attention, motor function, memory, language, executive function, and spatial ability). The meta-analysis revealed effect sizes of small to moderate magnitude in each domain: attention (.03) motor function (.51) memory (.26), language (.18) executive function (.41) spatial ability (.48). These findings suggest that HRTs may induce a generalized cognitive impairment. Moreover, a significant logarithmic relationship was found between effect size and time since last chemotherapy treatment ($r^2 = .63$) and between effect size and the percentage of patients currently taking tamoxifen ($r^2 = .60$), and a linear relationship was found between effect size and average age ($r^2 = .67$). These analyses indicate that the magnitude of impairment in cognitive function is larger in younger age groups. Interestingly, younger women with breast cancer commonly enter menopause artificially after surgery, chemotherapy, and or HRT.

An open label, randomized study comparing the efficacy of exemestane versus tamoxifen treatments provided the opportunity to explore the effect of adjuvant endocrine treatments on cognitive functioning in post-menopausal breast cancer patients not treated with chemotherapy.
(Schilder et al., 2010). Participants were patients in a exemestane group (n=99), a tamoxifen group (n=80), and a control group (i.e., healthy same-age female friends/relatives of patients included to account test-retest effects of neuropsychological tests; n=120). Comprehensive neuropsychological evaluations that included objective measures in cognitive abilities and self-report measures of anxiety, depression, fatigue, menopausal symptoms, and cognitive functioning were conducted before surgery, before hormone therapy, and one year later. At follow-up, Schilder et al. (2010) found that tamoxifen, but not exemestane, was associated with worse performance in verbal memory, executive functioning, and information processing speed. In a later study, Schilder et al. (2012) found that patients report a lower frequency of cognitive failures than healthy controls, both before and after chemotherapy. The prevalence of cognitive complaints did not differ between the groups at initial testing, but over time, patients receiving tamoxifen reported more attention/concentration complaints than patients receiving exemestane. Although self-reported cognitive functioning showed moderate associations with anxiety/depression, fatigue, and menopausal complaints, it was not associated with actual cognitive test performance.

**Psychological Distress**

A breast cancer diagnosis interrupts an individual’s daily life and brings their mortality into focus (Saegrov & Halding, 2004). Typically, cancer diagnoses cause greater distress and trauma than other serious diseases and illnesses; it is a potential death sentence and a serious threat to one’s wellbeing. Despite the fact that the prognosis for breast cancer is generally quite good, breast cancer survivors must live with the ever-present threat of a relapse. In view of current knowledge regarding the links between emotion and cognition, stress induced by the cancer diagnosis may represent one source of cognitive impairment (Reid-Arndt & Cox, 2012).
Schilder et al. (2012) noted that many studies fail to find a relationship between subjective and objective measures of cognitive impairment following treatment for cancer (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). Psychological stress may be a reason: Perceived impairment may be an indicator of psychological distress rather than cognitive impairment (Hutchinson et al., 2012) or may increase vulnerability of breast cancer patients to cognitive impairment after chemotherapy (Vearncombe et al., 2009). In fact, recent research suggests that psychological distress is significantly related to cognitive impairment in breast cancer patients (Ando-Tanabe et al., 2012; Antoni et al., 2012). Ando-Tanabe et al. (2012) found that chemotherapy patients had significantly lower baseline performance in digit symbol and verbal fluency relative to healthy controls, with task performance correlated negatively with anxiety. Since patients showed significantly higher anxiety at baseline, the authors proposed that anxiety could underlie the reported baseline impairments.

Andreano, Waisman, Donley, and Cahill (2012) investigated the effect on cognitive dysfunction of glucocorticoid responses in survivors following long-term treatment of Lupron, a gonadotropin-releasing hormone agonist used in the treatment of estrogen receptor positive tumors. Glucocorticoid responses to a physiological stressor were not significant in Lupron-treated survivors, but elevated cortisol levels in controls. Narrative recall was worse in survivors than controls, independent of stress treatment. Yet controls exposed to post-training stress showed significant enhancement of emotional recall and a significant relationship between cortisol release and subsequent memory, effects not observed in survivors. The results suggest that stress may contribute to cognitive difficulties in survivors by disrupting enhancement of memory.
Neurobiological Evidence of Cancer-Related Cognitive Dysfunction

As clinical evidence of cancer-related cognitive loss accumulates, identification of the neural mechanisms at play in vulnerable patient subgroups becomes essential. Several candidate mechanisms have been suggested, but pinpointing the precise cause of cognitive loss following cancer treatment remains elusive (Ahles & Saykin, 2007; Seigers & Fardell, 2011). Viable molecular outcomes of chemotherapy include three primary mechanisms: (1) oxidative stress to DNA repair processes (Blasiak J. et al., 2004; Nadin, Vargas-Roig, Drago, Ibarra, & Ciocca, 2006), (2) elevated levels of inflammatory cytokines in brain tissue (Burstein, 2007; Janelinsins et al., 2012; Seigers & Fardell, 2011), and (3) genetic susceptibility to breakdowns in neural repair processes (Ahles et al., 2003). The brain is susceptible to oxidative stress due to its limited antioxidant capacity. Oxidative stress is created when excessive free radicals react with proteins, cell walls and DNA, causing damage to cell structures ultimately leading to cell death.

Cancer tumors may indirectly disturb cognitive functioning through tissue release of cytokines and chemokines, regulatory molecules that foster communication among cells in the immune system (Ahles, 2012; Janelinsins et al., 2012; Walker, Drew, Antoon, Kalueff, & Beckman, 2012). Abnormal concentrations of cytokines in neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease, multiple sclerosis and traumatic brain injury, have been implicated in the pathogenesis of cognitive impairments (Janelinsins et al., 2012). Recent literature suggests that elevated levels of cytokines and chemokines may play a role in cognitive deficits observed in chemobrain. For example, Janelinsins et al. (2012) conducted an investigation of inflammatory processes by assessing the effects of two different chemotherapy regimens on cytokine IL-6 and chemokines MCP-1 and IL-8. They found significant differences in cognitive functioning between treatment regimens and significant negative correlations
between MCP-1 and the cognitive domains of concentration and forgetfulness for patients receiving adriamycin. Better-powered, longitudinal studies can in the future provide additional insight into cognitive sequelae following chemotherapy treatments by exploring the distinct inflammatory responses elicited by different chemotherapy regimens.

Finally, genetic susceptibility to DNA damage may alter signaling pathways that act as master regulators of aging and thus control age-related brain pathology (Bishop, Lu, & Yankner, 2010), thus contributing to the pathogenesis of chemotherapy-induced cognitive decline (Ahles, 2012). In particular, the epsilon 4 allele of APOE may be a potential genetic marker for increased vulnerability to chemotherapy-induced cognitive decline (Ahles et al., 2003).

The three molecular candidates – oxidative stress, neuro-inflammation, and genetic susceptibility – in no way create an exhaustive list (Ahles, 2012; Ahles & Saykin, 2007; Seigers & Fardell, 2011; Walker et al., 2012). For example, it is conceivable that the concurrent administration of several cytotoxic agents could combine to have a negative synergistic effect on cognition. At present, though, there is insufficient clinical evidence to evaluate the relationships among types of chemotherapy regimens, dose intensities, and degree of cognitive impairment (Cheung, Chui, & Chan, 2012). Thus, more research is needed to understand the role of pharmacological factors in chemotherapy-associated cognitive changes.

**Neurophysiological Evidence of Cancer-Related Cognitive Change**

The neurotoxic effects of chemotherapy agents target cells in the hippocampus (Dietrich, Han, Yang, Mayer-Proschel, & Noble, 2006; Seigers, Schagen, Beerling, et al., 2008) and prefrontal cortex (Ferguson, McDonald, Saykin, & Ahles, 2007; Hakamata, Matsuoka, Inagaki, et al., 2007; Inagaki, Yoshikawa, Matsuoka, et al., 2006), two brain regions critical to normal
memory and attentional functioning. However, emerging evidence indicates impairment may be more widespread than previously believed (Winocur et al., 2012).

**Animal Models**

Animal models can be utilized for systematic investigations into underlying physiological mechanisms of cognitive dysfunction in cancer (Seigers & Fardell, 2011). Animal models can be utilized for specific investigations into cause and effect relationship between drug treatments and cognition in breast cancer. Table 1 lists a summary of these findings. Moreover, they have the potential to identify therapeutic targets to prevent and treat cognitive impairments. However, this method of inquiry is underutilized and only a few chemotherapeutic agents have been studied for their neurocognitive effects.

Chemotherapy treatments in rodents are associated with increased cell death and decreased cell division in the dentate gyrus of the hippocampus, a region in which generation of new neurons continues into adult life, far beyond the point of neurogenesis in most other brain regions. These agents cause a dose-dependent negative effect on hippocampal cell proliferation and increase oxidative stress in the brain (ELBeltagy et al., 2012).

Several animal reports have established a negative impact on hippocampus-dependent behaviors in learning and memory tasks of the chemotherapy drugs cyclophosphamide, methotrexate, methotrexate, 5-fluorouracil (5-FU), and thioTEPA (J. E. Fardell, Vardy, Logge, & Johnston, 2010; Joanna E. Fardell, Vardy, Shah, & Johnston, 2012; Wilson & Weber, 2013; Yang et al., 2012). Moreover, an investigation on cognitive function of two widely used cytotoxic agents -- cyclophosphamide and doxorubicin -- revealed disruption of hippocampal neurogenesis (Christie et al., 2012; Wilson & Weber, 2013). Here, rats that were chronically exposed to clinically relevant doses of chemotherapy drugs were impaired on the novel place
recognition (NPR) task and the contextual fear conditioning task (CFC). Both groups of chemotherapy treated rodents exhibited a significant decline (80%-90%) in hippocampal neurogenesis. Nevertheless, the functionality of hippocampal neurogenesis is still hotly debated (Seigers & Fardell, 2011).

**Imaging**

Studies utilizing functional and anatomical magnetic resonance imaging (MRI) and positron emission tomography (PET) have examined structural and functional changes in the brain associated with chemotherapy. Reduction in the volume of brain regions important for executive functioning (e.g., frontal cortex) and changes in the integrity of white matter tracks have been associated with changes in cognitive functioning in patients treated with chemotherapy (Saykin et al., 2003; Stemmer et al., 1994). Reduced activation in frontal cortex during a working memory task in patients treated with chemotherapy has also been reported (Saykin et al., 2006). A study using [O-15] PET demonstrated that breast cancer patients treated with chemotherapy showed decreased metabolic activity in the prefrontal cortex during short- and long-term memory tasks, relative to both breast cancer patients who did not receive chemotherapy and healthy controls (McDonald, Conroy, Ahles, West, & Saykin, 2010). McDonald, Conroy, Ahles, West, and Saykin (2012) reported evidence for compensatory activations in a prospective fMRI examination of brain alterations during a working memory task in breast cancer patients at baseline and one year after chemotherapy treatment. These results suggest that even before adjuvant treatment patients with breast cancer engage in compensatory hyperactivation of frontal cortices in response to the cancer disease process and raise the possibility that performance on neuropsychological testing may remain in the normal range through an altered activation of brain patterns.
Electrophysiology

Few studies have sought to link chemotherapy treatment in humans to functional changes in electrophysiological (EEG) processing. One aim of the current study was to pinpoint electrophysiological correlates of breakdowns in specific cognitive processes in the aftermath of breast cancer treatment. Event-related potentials (ERPs), waveforms derived from EEG recordings time locked to individual stimuli and signal averaged across repeated trials, offer a noninvasive physiological measure of the time course and functional integrity of specific cognitive processes as a result of chemotherapy. Providing excellent resolution in the temporal domain, ERPs provide accurate voltage change in the millisecond range, and can help to distinguish and localize sequential stages of information processing in the brain. By comparison, PET and fMRI are considerably more sluggish in their temporal resolution, and are less cost efficient. ERPs provide independent measures of memory and information processing, two of the most commonly affected areas of cognitive functioning post-chemotherapy.

Unfortunately, spatial resolution of ERPs is limited and very different source arrangements can lead to the same EEG measurements (Scherg & Von Cramon, 1986). This is known as the inverse problem. To address this problem, one must localize the supposed electric sources in the brain by introducing a priori assumptions on the generation of EEG signals (Michel et al., 2004). Advances in EEG analysis and computing capabilities have enabled spatial source reconstruction of ERP components. Michel et al. (2004) emphasized the important distinctions among different approaches of source reconstruction available in terms of their a priori constraints and assumptions and favor those that are heavily influenced by physiological principles over those that are influenced by the experimenter. In addition, the authors state that the more appropriate the assumptions the more trustworthy the source estimations.
**P3b component.** Several recent ERP studies suggest impairments from chemotherapy in the timing and/or efficiency of auditory memory and attentional processes. For example, Kreukels and her colleagues (Kreukels, Schagen, Ridderinkhof, et al., 2005, 2006; Kreukels, Hamburger, de Ruiter, et al., 2008; Kreukels, van Dam, Ridderinkhof, et al., 2008) have tested breast cancer survivors and control participants in auditory or visual oddball paradigms to measure the relative amplitude and latency of the P3b ERP component, which has neural sources in the posterior cingulate and parahippocampal gyrus (Halgren, Baudena, Clarke, Heit, Liegeois, et al., 1995; Halgren et al., 1998; Knight, Scabini, Woods, & Clayworth, 1989).

In one study, Kruekels, Hamburger, de Ruiter et al. (2008) compared survivors who had undergone different chemotherapy regimens (i.e., FEC and CTC) with Stage I breast cancer patients who had not received chemotherapy (control). Auditory P3b amplitude and latency were reduced in each of the chemotherapy groups relative to controls, with no concomitant effect of tamoxifen treatment. The authors additionally found that chemotherapy had no effect on the earlier N1 ERP component, a measure of perceptual integrity. The results suggest that chemotherapy undermines the speed and distinctiveness of stimulus encoding in working memory, leaving mechanisms of perceptual encoding intact.
**P50 suppression.** The auditory P3b component is generated during active attention to rare deviant sounds within a stream of repetitive sounds. The chemotherapy-induced disruption of these active attentional processes may in fact have an earlier sensory basis in automatic information processing. One candidate source is sensory gating measured as suppression to the auditory P50 ERP component in a passive paired-click paradigm. Here, two brief auditory signals are presented 500 ms apart; the normal inhibitory response automatically activated to the first click is measured as a reduction in the P50 ERP amplitude to the second click (Clementz, Geyer, & Braff, 1997). P50 suppression is presumably a feature of normal sensory gating, instrumental in managing information overload (Nabor, Kathmann, & Enge, 1992). Indeed, P50 suppression is significantly reduced in schizophrenia (Nashaat N. Boutros, Overall, & Zouridakis, 1991; Freedman et al., 1987)(Boutros, Zouridakis, & Overall, 1991; Freedman, Adler, Gerhardt, et al., 1987), a psychiatric syndrome marked by sensory flooding (McGhie & Chapman, 1961).

P50 suppression has been traced in part to the inhibitory activity of α7-nicotinic neurons in the CA3 region of hippocampus (Adler et al., 1998; Bickford-Wimer et al., 1990)(Adler, Olincy, Waldo, Harris et al., 1998; Bickford-Wimer, Nagamoto, Johnson et al., 1990), suggesting a role of sensory memory in the gating response. Noteworthy in this regard is the recent finding of a deficit in P50 suppression in Alzheimer’s dementia (Thomas, vom Berg, Rupp, et al., 2010). Other putative P50 generators include the thalamus (Jennifer Court et al., 1999) (Court, Spurden, Lloyd et al., 1999; Hinman & Buchwald, 1983), auditory cortex (Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001; Huang, Edgar, Thoma et al., 2003), and dorsolateral prefrontal cortex (Boutros, Gjini, Urbach, & Pflieger, 2011; Knight, Scabini, &
Woods, 1989). One analytic advantage of using the P50 gating paradigm is that the methods employed to study human subjects can be matched in studies of other animals.

Gandal, Erlichman, Rudnick, and Siegal (2008) investigated in a mouse model the effects on P50 suppression of the breast cancer agents methotrexate and 5-fluorouracil. Mice injected with either low or high doses of the combined agents were compared electrophysiologically with placebo-injected control mice. Gandal et al. recorded from electrodes implanted in hippocampal CA3. This paradigm, reflecting whole brain electrical activity characteristically similar to human ERPs, revealed significant loss of suppression (defined as the ratio of P1 minus N1 amplitude of the second click to that of the first click) in both drug groups five weeks after treatment relative to controls. Importantly, chemotherapy had no effect on the amplitude of either the P1 or N1 component to the first click, suggesting that perceptual encoding was preserved.

Gandal et al. (2008) also implemented two behavioral tasks – novel object recognition (NOR) and contextual fear conditioning (CFC) – to clarify the role of hippocampal (memory) and amygdala (emotional) processing with respect to P50 sensory gating. In the NOR task chemotherapy-treated animals showed longer total exploration over both training and testing sessions in comparison to control animals. Gandal et al. suggested that chemotherapy-treated animals suffer an underlying memory deficit to novelty. In the CFC task, which is sensitive to hippocampus and amygdala function, chemotherapy-treated animals displayed significantly increased freezing ratios across time during the behavioral paradigm. Freezing ratios (CFC) were significantly correlated (r=0.57, p<0.02) with exploration time (NOR), demonstrating that performance in the two tasks were linked. The authors suggested that increased freezing ratios at initial training (CFC baseline) and decreased sensory gating are due to deficiencies in habituation. Overall, the results pointed to a hippocampus-based impairment in sensory
inhibition resulting from breast cancer treatment. One goal of the current study is to investigate the possible effects on P50 suppression of chemotherapy in breast cancer survivors several years after treatment.

**Mismatch Negativity Response.** The results of several recent studies have suggested a functional link between P50 suppression and the mismatch negativity response (MMN), an ERP measure of the automatic detection of stimulus change (deviants) within an otherwise homogeneous stimulus environment (standards) that indexes the *gating in* of contextually important stimulus information (Naatenen, 1992). The MMN component has been successfully used to assess integrity of auditory memory in both healthy and clinical populations (Naatanen et al., 2011). Increases in P50 suppression co-vary with decreases in MMN responses in the elderly, patients with frontal lesions, and alcoholics, suggesting an interrelationship between the two processes. Moreover, both P50 suppression and MMN amplitude are impaired in schizophrenics and in their unaffected family members (Adler, Hoffer, Wiser, & Freedman, 1993; Adler, Hoffer, Griffith, Waldo, & Freedman, 1992)(Adler, Hoffer, Griffith, et al., 1992; Adler, Hoffer, Wiser, & Freedman, 1993; Jessen, Fries, Kucharski et al., 2001; Michie, Innes-Brown, Todd, & Jablensky, 2002), implying that P50 and MMN are endophenotypes of preattentional deficits (Braff & Light, 2004).
Gating in and gating out. Both P50 suppression and MMIN amplitude can be measured in a single paradigm, known as the oddball paradigm. Here, participants are engaged in an attention-occupying task while standard and deviant auditory stimuli are presented. MMN is an increased negativity in the ERP wave to the deviant wave (relative to the standard) that peaks approximately 250 ms after stimulus onset. P50 suppression is seen as increased P50 (positive) amplitude to the deviant wave (relative to the standard). On one interpretation, increases in the amplitude of the MMN to deviant stimuli reflect pre-attentive recognition of novel stimuli, or gating in, whereas increases in P50 suppression to deviant stimuli reflect automatic exclusion of novelty, or gating out (Boutros, Torello, Barker, et al., 1995; Boutros & Belger, 1999). In line with this interpretation, sensory gating in the MMN oddball paradigm can be operationally defined as: 1) the ratio of the amplitude of the response to the infrequent stimulus (deviant) divided by amplitude of the response to the frequent stimulus (standard), where higher ratios can either reflect stronger inhibition with repetition (gating out) or a stronger response to rare stimuli (gating in); and 2) as the differences between the deviant minus the standard (P50d), where higher values indicate more suppression. Investigating the P50 evoked response in a modified oddball paradigm, Boutros, Torello et al. (1995) proposed that with either interpretation of the P50 suppression response, higher standard/deviant ratios reflect a more active sensory gating mechanism subserved by distinct neuronal processes (i.e., gating in vs. gating out).

Overlapping systems in frontal cortex are responsible in part for generating the P50 and MMN responses (Kisley, Noecker, & Guinther, 2004). Functional linkage implies a more general purpose gating system (Boutros, Torello, Barker, et al., 1995). Ermutlu, Demiralp, and Karamursel (2007) employed an oddball paradigm in healthy participants to investigate interactions among the P50, N1, and MMN components. Using 1.5 s, 2.5 s, and 3.5 s
interstimulus intervals (ISIs), the authors found that the N1 component increased significantly with increasing ISIs for both standards and deviants, with N1 to deviants significantly larger than N1 to standards at 1.5 s ISI. In the 2.5 s ISI condition, MMN responses were significantly smaller, and amplitude of P50 suppression (P50d) significantly larger, than in the 1.5 s ISI or 3.5 s ISI conditions, suggesting increased gating in and decreased gating out at this ISI. Furthermore, MMN amplitude increased with P50 suppression across ISIs. Ermutlu et al. concluded that the inhibition of repeated stimuli (P50d) aids the detection of deviant stimuli (MMN) (see also Kisley, Noecker, & Guinther, 2004; cf. Gjini, Arfken, & Boutros, 2011).

Kisley et al. (2004) investigated the functional significance of sensory gating by examining covariation among the P50, N100, and MMN components in an age-restricted (18-35) sample of healthy adults. The investigators used an abbreviated version of the Sensory Gating Inventory to characterize quantitatively each individual’s daily experience regarding passive attention switching and associated perceptual phenomena in three different domains: perceptual modulation, distractibility, and over-inclusion.

Kisley et al. (2004) found that P50 suppression was associated with participants’ ratings of perceptual modulation, whereas N100 suppression (N100s2 / N100s1) was associated with their ratings of over-inclusion. Further analysis revealed that P50 suppression was especially related to the rating items involving difficulties in excluding irrelevant stimuli (filtering), whereas N100 suppression was related to a heightened awareness of background sounds. No significant correlations were reported between ratings and MMN amplitude.

Kisley et al. (2004) found no association between P50 and N100 suppression, supporting the notion that these components correspond to different processing systems. Similarly, there was no relationship between N100 suppression and MMN amplitude. However, the authors
found that P50 suppression and MMN amplitude correlated negatively: stronger P50 suppression during the paired-click paradigm was associated with weaker MMN amplitude in the oddball paradigm. The latter finding is consistent with a dual-use model, which may arise from either temporal or frontal cortical circuits believed to be involved in the generation of both P50 and MMN components.

The Current Study

Here, we measure both P50 suppression and MMN in two groups of participants (survivors and healthy controls) to assess the role of chemotherapy on the coordination between gating in and gating out processes. Within each group we explore whether the efficiency of sensory gating varied with age, to probe possible similarities between chemotherapy and normal aging in their effects on gating in and gating out (Pekkonen et al., 2005). We employed two separate measures of gating out: (1) the ratio of P50 amplitude to two clicks (paired-click paradigm) and (2) the ratio of P50 amplitude to standard and deviant tones (oddball paradigm).

Methods

Participants

Eighteen women (40-66 years old), nine breast cancer survivors (average age =53.78 years) and nine healthy controls (average age = 54.44 years), recruited from ads and referrals, volunteered to participate in the study. Each survivor was paired with an age-matched control participant (see Table 2); the average age of participants was equal across groups, $t(16) = 0.16, ns$. Standard audiometry was performed to screen participants for normal hearing, defined as pure tone sensitivity better than or equal to 20 dB HL bilaterally for octave frequencies between 250 Hz and 8 kHz. All were right-hand dominant as determined by the Edinburgh handedness
survey (Oldfield, 1971). Exclusion criteria included: (1) metastasis or relapse; (2) history of or current neurological or primary psychiatric disorder; (3) head trauma; (4) alcohol or drug abuse; (5) lack of fluency in English. One further exclusion criterion for controls was previous history of cancer or treatment with chemotherapy. Inclusion criteria for survivors included: (1) diagnosis of invasive breast cancer; (2) treatment with standard-dose chemotherapy; (3) no cancer treatment except tamoxifen for two or more years; (4) currently disease free; (5) greater than 18 years old when diagnosed. The nature of the procedures was explained fully, and informed consent was obtained from each participant. The Institutional Review Board of the City College of New York approved the protocol.

**Stimuli, apparatus, and procedure**

Each participant completed three blocks of trials: one block of the MMN oddball paradigm (800 trials) between two blocks of the P50 paradigm (150 trials each). The study was carried out in an electrically and acoustically shielded Industrial Acoustics Company (New York) chamber. The stimuli were delivered over Nova-40 headphones. Stimuli were created using Adobe Audition, digitized to eight bits at a sampling rate of 48 kHz. In both paradigms, participants were instructed to ignore the auditory stimuli and to watch a silent movie, as they sat in a comfortable chair at a distance of 60 cm from a Dell Model P1130 RGB computer monitor.

Stimuli used in the P50 paradigm were 150 pairs of identical clicks presented binaurally at an intensity of 72 dB HL and a duration of .035 ms. Each pair was separated by an inter-stimulus interval of 500 ms. The inter-trial interval varied randomly between 9 s and 10 s in rectangular distribution. Stimuli used in the MMN paradigm were 800 pure tones presented binaurally at an intensity of 72 dB HL and duration of 100 ms, including 10 ms rise/fall. Deviant tones (1030 Hz) appeared pseudorandomly within a stream of standard tones (1000 Hz); at least
two standards separated the deviants in the stream. Stimulus probability was 80% for standards and 20% for deviants. The inter-stimulus interval varied between 1080 ms and 1320 ms in rectangular distribution.

Participants were given short breaks throughout testing. The entire experiment, including EEG preparation, lasted approximately three hours.

**EEG Recording**

Continuous recordings of the EEG were collected at a sampling rate of 512 Hz using a BioSemi Active-Two system in a high-density (160 electrodes) montage arranged in an elastic cap. Blinks and other eye movements were monitored by electrooculogram (EOG) from two electrode montages, one on the infra and supra-orbital ridges of the right eye (VEOG), the other on the outer canthi of each eye (HEOG). Fieldtrip™ was used to process EEG data to perform automatic muscle artifact rejection (Oostenveld, Fries, Maris, & Schoffelen, 2011). To accumulate evidence of artifacts the Fieldtrip algorithm z-normalizes and averages time points across electrodes, based on calculations of the Hilbert envelope (amplitude of the signal) on each electrode over time and each electrode’s mean and standard deviation over samples. Trials contaminated by blinks or eye movements were removed using independent-components analysis (Blasiak et al., 2004; Jung et al., 1998). Prior to signal averaging, waveforms were inspected individually for movement artifacts; rejected channels from a trial were interpolated using a linear nearest-neighbor algorithm (Bastiaansen & Knosche, 2000). On average, approximately 25% of trials were rejected because of movement, eye, or jump artifacts.

Sweep time in the paired-click paradigm was 450 ms, including a 50 ms pre-stimulus baseline; signal-averaged waveforms referenced to linked mastoids were digitally band-pass filtered between 6 and 50 Hz (de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007). Peak
amplitude and peak latency of the P50 ERP component to each click were measured at each scalp location within a 40-80 ms post-onset search epoch. P50 suppression was measured as the ratio of P50 peaks to the two clicks (P50_{S2}/P50_{S1}). A second measure of P50 suppression was derived in the passive oddball task by comparing the ratio of P50 peaks to the standard and deviant tones (P50_{standard}/P50_{deviant}). S1 peak amplitude, measured as baseline to peak, was determined by implementing peakdet.m, a public domain Matlab function (Billauer, 2012). The function exploits the alternating nature of the derivatives along a user-defined threshold to robustly identify local maxima or minima (peaks or valleys) in a noisy vector. Peak and latency for S2 were determined in a similar manner, constrained to be within 10 ms of S1.

Sweep time in the oddball paradigm was 1100 ms, including a 100 ms prestimulus baseline; signal-averaged waveforms referenced to the nasion were band-pass filtered between .1 and 20 Hz. MMN was measured as the peak amplitude and peak latency of the difference wave (standard minus deviant waveforms) at each scalp location within a 175-250 ms post-onset search epoch. For ease of comparison, all analyses of ERP (P50 and MMN) amplitudes, including correlational analyses, were performed at the Cz electrode location. To identify the scalp topography of group differences in P50 suppression or MMN, we report cluster analyses (Oostenveld et al., 2011) conducted on P50 or MMN group contrasts, thus controlling for multiple comparisons.

**Dipole Source Analysis**

We employed Brain Electrical Source Analysis (BESA; Scherg & Von Cramon, 1986; Weisser R. et al., 2001) to isolate the relative contribution of four putative neural generators of the P50 suppression response: hippocampus (Rosburg et al., 2004), thalamus (Williams, Nuechterlein, Subotnik, & Yee, 2011), superior temporal gyrus (STG; Thoma et al., 2005), and
dorsolateral prefrontal cortex (DLPFC; Grunwald et al., 2003). Eight dipoles, seeded bilaterally, were fit as regional sources: hippocampus (right: 30.0, -17.3, -12.0; left: -30.0, -17.3, -12.0 with x, y, z coordinates in Talairach space), thalamus (right: 9.3778, -31.30, 8.7978; left: -9.3778, -31.30, 8.7978), STG (right: 61.0, -27.0, 16.0603; left: -61.0, -27.0, 16.0603), and DLPFC (right: 50.0, 39.0, 17.0; left: -50.0, 39.0, 17.0).

The P50 peak was defined as the maximum of the regional source activity at the first orientation within a time interval identified individually for each participant and separately to each stimulus, S1 and S2. The P50 interval was determined by visual inspection to exclude the P30 and N40 components while falling within an epoch 40-80 ms after stimulus onset. We used a four-shell model, fixing the electrical conductivities of cerebrospinal fluid, skin, bone, and brain to 1.0, 0.33, 0.0042, and 0.33 S/m, respectively. The four dipole moments to each stimulus were then subjected to a mixed-model analysis of variance (ANOVA), with anatomical location (4 levels: thalamus, hippocampus, STG, DLPFC), hemisphere (2 levels: left, right), stimulus type (2 levels: S1, S2), and group (2 levels) as within-subject factors. All main effects and interactions reported as significant were reliable after Greenhouse-Geisser correction if appropriate (Greenhouse and Geisser, 1959).

**Results**

**P50 suppression**

Figure 3 (left panels) depicts the grand averaged ERP waveforms evoked at Cz by each click in the breast cancer survivors (middle panel) and healthy age-matched controls (top panel). No differences between groups were found in the amplitude of either the P1 or N1 ERP components to the first click (p’s>.10). However, the breast cancer survivors showed significantly weaker P50 suppression than controls at this electrode location, $t(8) = 2.51, p<.05$. 
The average suppression index (P50$_{S2}$/P50$_{S1}$) at Cz was .72 for survivors and .45 for controls, comparable to differences found between healthy controls and patients diagnosed with schizophrenia (Clementz et al., 1997) and Alzheimer’s disease (Thomas et al., 2010). Cluster analysis controlling for multiple comparisons revealed that the group differences predominated over central and parietal electrode sites in the right hemisphere (see Figure 3, bottom left panel). Table 2 summarizes the suppression index to each pair of age-matched participants, revealing consistently weaker suppression in cancer survivors compared with controls.

As shown in the right panels of Figure 3, the group effect was replicated in the oddball measure of P50 suppression (P50$_{\text{standard}}$/P50$_{\text{deviant}}$), with significantly weaker suppression at Cz for survivors (.93) than controls (.81), $t(8) = 2.48, p<.05$. Cluster analysis of this measure (Figure 3, bottom right panel) indicated significant clusters over left temporal locations.

**Dipole analysis of P50 suppression**

Figure 4 illustrates the average magnitude of dipole moments to S1 and S2 at each of the four bilateral neural structures thought to contribute to P50 suppression in the paired-click paradigm: hippocampus, thalamus, STG, and DLPFC. This model accounted for 89.69% of the variance in the control participants and 90.41% of variance in the survivors. ANOVA of dipole magnitudes yielded a significant main effect of location, $F(3, 24) = 12.45, p<.001$, $MS_e = 41.08$, a main effect of stimulus type, $F(1, 8) = 17.47, p<.01$, $MS_e = 18.59$ and, most important, a significant interaction of location, type, and group, $F(3,24) = 3.71, p<.05$, $MS_e = 3.29$.

As shown in Figure 4, the magnitude of dipole moments in the thalamus, STG, and DLPFC was comparable between groups. However, survivors showed significantly weaker dipole activity than controls in the hippocampus, across both hemispheres. Our finding with
survivors is reminiscent of that recently reported by Williams et al. (2011) on a group of young schizophrenics (average age = 27.6 years).

**Mismatch negativity**

Figure 5 depicts the average ERP at Cz to standard and deviant tones in the cancer survivors (left middle panel) and healthy controls (left top panel). MMN area is represented with shading in each panel. ERP difference waves (deviant minus standard) for each group appear in the bottom panel. There were no differences in the onset of the MMN component in the two groups, \( t(8) = .47, \text{ ns} \). However, the magnitude and duration of MMN were significantly weaker at Cz in the survivors than in the control participants, \( t(8) = 4.18, p<.01 \). Moreover, cluster analysis revealed that the difference between groups was widespread across scalp locations (see Figure 3, right panel).

**Correlational analyses**

Table 2 summarizes correlations of participants’ age with the three ERP measures: \( P50_{S2}/P50_{S1} \), \( P50_{\text{standard}}/P50_{\text{deviant}} \), and MMN. We found at Cz that \( P50_{S2}/P50_{S1} \) was associated with age in the control group (\( r = .63 \)), with older participants revealing weaker P50 suppression. Importantly, this relationship was not observed in the survivor group (\( r = .08 \)), suggesting that chemotherapy had disrupted effects of normal aging on sensory gating (Pekkonen et al., 2005). However, we found that the relationship between \( P50_{\text{standard}}/P50_{\text{deviant}} \) and age was roughly the same in survivors (\( r = .37 \)) and controls (\( r = .59 \)). Interestingly, \( P50_{S2}/P50_{S1} \) and \( P50_{\text{standard}}/P50_{\text{deviant}} \) were associated positively in controls (\( r = .56 \)), but negatively in survivors (\( r = -.43 \)). MMN amplitude (greater amplitude = more negative voltage) was found to decline significantly with age (\( r = .46 \); controls, \( r = .54 \), survivors, \( r = .53 \)). MMN and
P50\textsubscript{standard}/P50\textsubscript{deviant} were correlated positively in the oddball paradigm ($r = .37$; controls, $r = .20$, survivors, $r = .24$).
Discussion

A group of breast cancer survivors and a group of age-matched healthy control participants watched silent films while pairs of clicks or streams of tones were presented over headphones. The experiment revealed for the first time in survivors significant chemotherapy-dependent deficits in processes of both sensory inhibition (as measured by P50 suppression) and sensory memory (as measured by MMN). The survivors exhibited a relatively weakened ability to inhibit redundant sensory stimulation, whether to the second of a pair of clicks or to a train of identical auditory tones. The scalp topography of group differences in P50 suppression differed by paradigm, peaking over the right hemisphere in the paired-click paradigm and over the left hemisphere in the oddball paradigm. Dipole source analysis localized the survivors’ loss of P50 suppression to the hippocampus, with relative preservation of function in the gating out mechanisms of the frontal lobe and auditory cortex. Survivors also showed a diminution in the sensory memory processes needed to register novel or deviant information in an otherwise homogenous auditory environment. The fact that deficits in both gating in and gating out were observed within the same (oddball) paradigm indicates an especially strong linkage between these processes as modulated by chemotherapy agents. Nevertheless, correlational analyses suggested that the paired-click paradigm is particularly sensitive to the detrimental effects of chemotherapy on sensory gating; here, we found that the effects of normal aging on P50 suppression seen in healthy controls were superseded by chemotherapy-related changes in an age-matched group of cancer survivors. Collectively, our findings suggest that cancer/cancer treatments are associated with a pervasive disruption of early, automatic mechanisms of sensory gating.
**Relationships between sensory inhibition and sensory memory**

A central motivation of the current study was to extend to humans the results reported by Gandal et al. (2008) revealing a significant reduction in P50 suppression in a mouse model. As in their study, we found that the difference in P50 electrophysiological activity between chemotherapy and control groups was restricted to the second click; in both studies, chemotherapy left largely unaffected the P1 and N1 ERPs to the first click (see Figure 3), suggesting that in both mice and humans agents used to treat breast cancer leave untouched early stages of perceptual processing. Instead, these agents targeted processing of the repeated click, indicating that the disruption to stimulus processing from chemotherapy begins with a breakdown in the normal buildup of sensory inhibition to redundant information.

The close correspondence in P50 suppression between chemotherapy-treated mice and human cancer survivors tested in the paired click paradigm suggests that breast cancer treatment is perhaps sufficient to damage sensory inhibition, although additional effects on cognitive function may arise from the cancer itself (Kesler et al., 2011; McDonald et al., 2012), radiation treatment, hormone replacement therapy used to treat the cancer (Falleti et al., 2005; Jenkins et al., 2004), or the emotional reactions to the cancer diagnosis or its treatment (Amir & Ramati, 2002; Smith et al., 2011).

To be sure, self-reports from survivors in the breast cancer community underscore the fact that cognitive loss from chemotherapy includes more than simply disruptions to sensory function, but also (and predominantly) poorer attention, memory, and executive functions (Schagen et al., 2006; Wefel et al., 2004). What is the relationship between the current findings and the types of functional loss typically reported by survivors? One hypothesis is that early sensory deficits trigger a chain reaction affecting later functions along the stream of cognitive
processes, thereby accounting for the broad range of deficits associated with chemobrain. Previous investigators have already pointed (in healthy participants) to a possible linkage in the processing chain between sensory inhibition and sensory memory, the former employed to minimize redundant information, the latter to flag non-redundant (novel) information (Ermutlu, Demiralp, & Karamursel, 2007). Our second goal in the current study was to probe whether these two types of gating are linked as dual consequences of chemotherapy. We found that both P50 suppression and MMN amplitude were reduced in breast cancer survivors relative to controls, suggesting a connection between the inhibitory processes active 50 ms after stimulus onset and the comparison processes evident 150 ms later. We also found in the oddball paradigm a modest positive correlation ($r = .37$) between P50 suppression and MMN amplitude. What psychophysiological processes tie these two ERP components together in the context of chemotherapy treatment? Two possibilities present themselves.

First, perhaps chemotherapy-induced damage to inhibitory mechanisms disrupts the quality of information handed off to later sensory memory mechanisms. On this account, chemotherapy’s harmful effects are limited to the neural generators driving P50 suppression, leaving intact those responsible for the MMN response. One downstream consequence of inefficient gating out – here, the failure to properly inhibit repeated (standard) events – is inadequate gating in, specifically, failure to readily detect novel (deviant) events in the environment (Ermutlu et al., 2007). Chemotherapy-induced loss of P50 inhibition could thus itself explain the drop in MMN amplitude seen in survivors. Variants on this account might also explain the associations between P50 suppression and MMN amplitude reported in other clinical populations, including individuals with schizophrenia or Alzheimer’s disease (Adler et al., 1993;
Adler et al., 1992; Jessen et al., 2001) Michie et al., 2002; but see Gjini et al., 2010; Turetsky et al., 2009).

A second possibility is that chemotherapy damages neural structures common to gating in and gating out activities. Both P50 suppression and MMN responses tap stimulus memory processes: In the former, the evoked memory of a recent stimulus triggers an inhibitory response, whereas in the latter a response is evoked when the current stimulus deviates from recent memory. Both P50 suppression and MMN responses are disrupted when healthy participants are administered scopolamine (a muscarinic receptor antagonist), suggesting a common cholinergic pathway (Callaway, Halliday, Naylor, & Brandeis, 1991; Pekkonen et al., 2001). Finally, both responses are heavily dependent on neural generators localized to the temporal and frontal lobes, suggesting common pre-attentive auditory mechanisms (Giard et al., 1990; Godey et al., 2001; Knight et al., 1989a; Näätänen and Michie, 1979). On this second account, then, chemotherapy agents target the memory comparison mechanisms of the frontal or temporal lobes that subserve the two types of gating. As we discuss later, however, dipole analysis performed in the current study makes this account the less likely.

**Neurobiological basis of chemotherapy-induced cognitive impairment**

Animal models of cancer treatment commonly implicate the hippocampus in chemotherapy-induced cognitive impairments. Dietrich et al. (2006) reported that the therapeutic agents carmustine, cisplatin, and cytosine arabinoside disrupt neurogenesis of progenitor cells and oligodendrocytes in the dentate gyrus in vitro and in vivo. Seigers et al. (2008) demonstrated that the breast cancer agent methotrexate interfered in a dose dependent fashion with hippocampal cell proliferation. Gandal et al. (2008) linked the methotrexate-induced crippling of hippocampal cells with reductions in the P50 gating response. Other research teams have shown
poorer performance in rodents after administration of chemotherapy agents on various hippocampally-dependent cognitive tasks, including the Morris water-maze task (Winocour et al., 2006) and the fear avoidance task (Reiriz et al., 2006).

By contrast, neuroimaging studies often identify activity in the frontal lobe as differentiating human cancer survivors from healthy controls. For example, Silverman et al. (2007) using [O-15] water PET found significantly greater metabolic output in inferior frontal gyrus in breast cancer survivors (5-10 years post chemotherapy) performing a short-term memory task compared with age- and education-matched control participants. The authors offered as one interpretation increased compensatory activity in survivors to cope with functional loss from chemotherapy (cf. McDonald et al., 2012). This view suggests that neuroimaging techniques tap the consequences of chemotherapy-induced neural damage, but perhaps not the actual sources.

Results from the current study, conducted with humans, align closely with animal models of chemotherapy. As discussed earlier, previous evidence suggests that four different neural loci contribute to the human P50 suppression response: hippocampus, thalamus, DLPFC, and STG. The mouse model tested by Gandal et al. (2008) localized chemotherapy-dependent loss of P50 suppression to hippocampal CA3 cells. Similarly, here dipole analysis of P50 suppression revealed that group differences in humans are confined to the hippocampus (see Figure 4). Activity in the STG and DLPFC, neural generators common to the P50 suppression and MMN responses, were roughly comparable between survivors and controls.
Limitations

The current study demonstrated that breast cancer patients treated with chemotherapy suffer sensory gating deficits similar to those found in accordance with animal models. Yet, certain methodological issues limit the generality of our conclusions. First, it is possible that effect sizes reported here were influenced by sample selection bias. In particular, perhaps the individuals that we recruited for our study agreed to participate precisely because they had begun to notice difficulties in performing everyday cognitive tasks. Indeed, several of our participants mentioned spontaneously their own cognitive struggles in the workplace. It is conceivable that such individuals represent only a minority of breast cancer survivors, thus yielding an elevated estimate of the true effect size. Of course, it remains a challenge for researchers to avoid this sort of bias in cancer and other forms of biomedical research, implying that the true effect size may be unknowable.

Second, the sample size used in this study – nine individuals in each group – was somewhat smaller than the standard used in this field. Although our success in matching participants in the two groups in age strengthened the robustness of statistical analyses, the higher P50 suppression ratios and reductions in MMN amplitude we found must now be replicated in breast cancer patients using larger sample sizes, in depth neuropsychological assessments, and cognitive tests beyond those employed in the present study.

Finally, although we were able to account for over 90% of the variance in our dipole source model, it is possible that our use of many brain sources (four bilateral sources, eight in total) ensured the excellent outcome. Performing additional analyses with four bilateral random sources might provide baseline evidence as to how likely we were to obtain these results.
Correlational analysis of ERP P50 suppression and P50 suppression using dipole sources could further our supposition that deficits are attributable to hippocampal activity.
Future directions

It is unlikely that a single mechanism can explain most of the major cognitive impairments observed in cancer patients following chemotherapy. While the analyses presented here point toward hippocampal sources of cognitive loss, clinical studies have demonstrated cancer-related cognitive impairment in non-hippocampal dependent tasks (Ahles et al., 2008). In addition, neuroimaging studies provide evidence for bilateral reductions in gray matter in frontal, temporal, cerebellar, thalamic, and cingulate brain region (Inagaki et al., 2007; McDonald et al., 2010) as well as deficits in integrity in frontal, and temporal white matter tracts (Deprez et al., 2012). The goal of future research is to explore further the constellation of factors that contribute to cancer-related cognitive impairments.

Source Localization of MMN

The current study performed source analysis solely on the P50 response. P50 suppression reflects only one stage of information processing that can be assessed in the auditory evoked response elicited in the paired click and oddball paradigm (Lijffijt et al., 2009). Perhaps the P50 component, being a measure of pre-attentive automatic processing, would not reveal frontal differences in frontal activations. It is possible that early (N100) and late (P200) attentive processes, which depend more heavily on frontal (and other regional) processes, are also affected by cancer treatment. Boutros, Gjini, Urbach and Pflieger (2011) found that several prefrontal, cingulate, and parietal lobe region displayed stronger response suppression than primary auditory cortex when mapping the N100 response.

Repeatedly, deficits in the MMN response, expressed as deficient auditory discrimination and orienting, have been used to assess objectively cognitive decline in clinical populations (Naatanen et al., 2011). The MMN receives bilateral contributions from the supra-temporal
plane, in addition to right-hemisphere frontal activity (Naatanen, Paavilainen, Rinne, & Alho, 2007). It is recommended that future studies seek to source localize three separate components – N100, P200, and MMN – to identify possible temporo-frontal deficiency from cancer treatment.

**Stress and the Hippocampus**

Psychological stress reduces neurogenesis in the dentate gyrus (Wilson & Weber, 2013) and damages apical dendrites of pyramidal neurons located in the CA3 region of the hippocampus (Watanabe, Gould, & McEwen, 1992). Stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis and elevates circulating glucocorticoids. Chronic exposure to stress or corticosteroids can inhibit proliferation and survival of new cells and induces depression-related behavior in animals. Interestingly, chemotherapy treatments similarly reduce hippocampal cell proliferation and neurogenesis, producing cognitive impairments in laboratory animals (Christie et al., 2012). Moreover, Wilson and Weber (2013) found that daily restraint stress triggered suppression of cell proliferation in the dentate gyrus, independent of chemotherapy treatment. Future research should examine the interrelationships among stress and cancer treatments in cognitive decline.

Recent animal studies suggest that stress may affect a region of hippocampus separate from that regulating cognition. The dorsal (septal) hippocampus is preferentially involved in cognitive processes while the ventral (temporal) hippocampus is involved in anxiety regulated behaviors and emotion (Bannerman et al., 2004; Tanti, Rainer, Minier, Surget, & Belzung, 2012). For example, (Tanti et al., 2012) found that stress selectively disrupted cell proliferation and neurogenesis in the rodent ventral hippocampus, whereas environmental enrichment selectively increased neurogenesis in the dorsal hippocampus.
One measure of physiological response to stress is increases in inflammatory immune signals called cytokines. Evidence suggests that cognitive dysfunction following breast cancer chemotherapy may be mediated by the cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In animals, Terrando et al. (2010) found that increases in TNF-α after surgery induced peripheral and central inflammation, which led in turn to hippocampal-dependent reductions of freezing in their contextual fear response. In humans, Kesler et al. (2012) found that breast cancer survivors displayed significantly elevated concentrations of IL-6 and TNF-α and that these elevations were associated with significant reductions in left hippocampal volumes and memory performance. The extent of harm of this inflammatory response is far reaching, with the regulatory functions of TNF-α and IL-6 actually promoting tumor inflammation and genesis (Grivennikov & Karin, 2011). Conversely, breast cancer patients who undergo stress reduction interventions have reduced risk for breast cancer recurrence and death compared with patient controls (Andersen et al., 2008). Similarly, mitigation of co-occurring symptoms including stress, anxiety, hot flashes, depression, fatigue, and insomnia - either as a result of treatment side-effects or as a result of enduring the major medical threat that comes with a cancer diagnosis - improves memory and executive function in affected cancer patients (Carpenter et al., 2002; Desai et al., 2013; Reid-Arndt & Cox, 2012). Effective coping strategies have enabled patients to overcome side effects such as fatigue and cognitive impairment (Fitch, Mings, & Lee, 2008; Myers, 2012).

Anxiety and negative affect in cancer patients are associated with changes in immune responses and upregulated expression of pro-inflammatory and metastasis-related genes (Antoni et al., 2012). Recent results reported by Grigsby et al. (2012) found that changes in blood inflammatory proteins may be important predictors of working memory and fine motor skills.
Behavioral interventions, such as cognitive-behavioral stress management (CBSM), reverse anxiety-related leukocyte transcriptional dynamics including downregulation of pro-inflammatory and metastasis-related genes (Antoni et al., 2012).

Exploration of the relationship of neuropsychological tests of long-term cognitive impairments indexed by the pre-attentive electrophysiological responses to risk factors such as stress, inflammation, sleep disturbance, and anemia is warranted. Extending this investigation using both neuropsychological tests and cognitive tasks that produce ERPs sensitive to attention will provide new information about the brain-behavior relationships in cancer-related impairments.
Conclusions

Our findings suggest that chemotherapies used to treat breast cancer in humans preferentially target hippocampal mechanisms of sensory inhibition. Probable damage to α7-nicotinic cells in the CA3 subfield hinders buildup of inhibition to initial sensory input, yielding abnormally strong sensory activity to recurrent stimulation. Consequent sensory flooding triggers a cascade of attention and memory deficits further down the information processing line, including disruptions to gating in (MMN) and inhibitory control (executive function) functions. On this view, then, chemotherapy effectively accelerates cognitive aging (Ahles et al., 2012; see also Ahles and Saykin, 2007; Papazoglu and Mills, 1997) through disruption of hippocampally-dependent memory functions (cf. J. Court et al., 2001). Increased compensatory activity in the frontal lobe (Ferguson et al., 2007; Silverman et al., 2007) may serve in a subgroup of cancer survivors to partially offset cognitive dysfunction from chemotherapy, which could account for instances of preserved performance on certain neuropsychological tests (Ahles et al., 2002; Tager et al., 2009). Survivors may nevertheless be acutely aware of loss, at least in higher cognitive functions, and a need for greater mental effort to compensate; hence, the consistent self-reports of cognitive impairment following chemotherapy (Berglund et al., 1991; Shilling and Jenkins, 2007). If our account is accurate, ideal therapies for cognitive deficits after cancer and cancer related treatment would aim to restore the early inhibitory processes, such as those gauged by P50 suppression.
References


SENSORY INHIBITION AND MEMORY AFTER BREAST CANCER


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10.1017/S0140525X00058027

10.1016/j.brainresbull.2012.05.005


10.1016/j.bandc.2005.05.001


SENSORY INHIBITION AND MEMORY AFTER BREAST CANCER


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Sensory inhibition and memory after breast cancer


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Schilder, C. M., Seynaeve, C., Beex, L. V., Boogerd, W., Linn, S. C., Gundy, C. M., . . .


Schilder, C. M., Seynaeve, C., Linn, S. C., Boogerd, W., Beex, L. V., Gundy, C. M., . . .

Schagen, S. B. (2012). Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the


SENSORY INHIBITION AND MEMORY AFTER BREAST CANCER


### Table 1

**Review of Animal Studies of Chemotherapy-Related impairments.**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Cytostatic(s)</th>
<th>Cognitive assessment</th>
<th>Cognitive outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konat</td>
<td>Cyclophosphamide + doxorubicin</td>
<td>Passive avoidance + open field</td>
<td>Impaired passive avoidance learning</td>
<td>No effect on anxiety behavior</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide or 5-fluorouracil</td>
<td>MWM + Stone 14-unit T-maze</td>
<td>No impairment</td>
<td>Transient improvement in MWM and Stone 14-unit T-maze seven to nine weeks post treatment</td>
</tr>
<tr>
<td>Macleod</td>
<td>Cyclophosphamide + doxorubicin</td>
<td>Cued and contextual fear conditioning</td>
<td>Impaired contextual fear memory</td>
<td>No effect on cued-fear or acquisition of fear response</td>
</tr>
<tr>
<td>Mondie</td>
<td>thioTEPA</td>
<td>NOR + OLR</td>
<td>Impairment in NOR and OLR</td>
<td>No effect on depressive behavior</td>
</tr>
<tr>
<td>Reiriz</td>
<td>Cyclophosphamide</td>
<td>Step-down inhibitory avoidance</td>
<td>Impaired inhibitory avoidance</td>
<td>No effect on anxiety behavior</td>
</tr>
<tr>
<td>Yang</td>
<td>Cyclophosphamide</td>
<td>Passive avoidance + NOR</td>
<td>Impaired passive avoidance learningImpaired NOR</td>
<td></td>
</tr>
<tr>
<td><strong>Cisplatin and analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fardell</td>
<td>Oxaliplatin + 5-fluorouracil</td>
<td>MWM + NOR + fear conditioning</td>
<td>Impairment in MWM, NOR and contextual fear memory</td>
<td>No impairment in cued-fear memory</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbeltagy</td>
<td>5-Fluorouracil</td>
<td>Fear conditioning + OLR</td>
<td>Impairment in recall of fear conditioning memory and OLR</td>
<td></td>
</tr>
<tr>
<td>Foley</td>
<td>Methotrexate + 5-fluorouracil</td>
<td>Operant conditioning</td>
<td>Combined MTX + 5-FU impairment acquisition and retrieval of an operant response</td>
<td>No impairment due to MTX5-FU failed to impair operant conditioning except at high doses</td>
</tr>
<tr>
<td>Li</td>
<td>Cytosine arabinoside</td>
<td>MWM</td>
<td>Impairment in remote recall of MWM</td>
<td>No impairment in MWM learning or recent recall</td>
</tr>
<tr>
<td>Li</td>
<td>Methotrexate</td>
<td>NOR + OLR</td>
<td>Impaired OLR</td>
<td>No impairment in NOR + open field activity</td>
</tr>
<tr>
<td>Madhyastha</td>
<td>Methotrexate</td>
<td>Conditioned avoidance test</td>
<td>Impaired conditioned avoidance learning and memory</td>
<td>No effect on anxiety behavior</td>
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<tr>
<td>Mustafa</td>
<td>5-Fluorouracil</td>
<td>OLR</td>
<td>Subtle impairment in OLR</td>
<td></td>
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<tr>
<td>Seigers</td>
<td>Methotrexate</td>
<td>MWM + NOR + contextual fear conditioning</td>
<td>Impairment in MWM and NOR after MTXWhen trained prior to MTX treatment, impairment in MWM and fear conditioning memory</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Seigers et al. (2011)*
Table 1 cont

Review of Animal Studies of Chemotherapy-Related impairments.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Cytostatic(s)</th>
<th>Cognitive assessment</th>
<th>Cognitive outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sieklucka-Dziuba</td>
<td>Methotrexate</td>
<td>Passive avoidance task</td>
<td>Impaired passive avoidance learning</td>
<td></td>
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<tr>
<td>Stock</td>
<td>Methotrexate</td>
<td>Appetitive Pavlovian discrimination + conditioned taste aversion</td>
<td>No impairment in either appetitive or aversive conditioning</td>
<td></td>
</tr>
<tr>
<td>Yanovski</td>
<td>Methotreat</td>
<td>Conditioned emotional response + conditioned taste aversion</td>
<td>Impaired conditional emotional response learning Impairment in conditioned taste aversion acquisition</td>
<td></td>
</tr>
<tr>
<td>Winocur</td>
<td>Methotrexate + 5-fluorouracil</td>
<td>Spatial MWM, cued memory, discrimination learning, NMTS, dNMTS</td>
<td>Impairment in spatial MWM, NMTS and dNMTS</td>
<td>No impairment in cued memory or discrimination learning</td>
</tr>
<tr>
<td>Topoisomeraseinteracti ve agents</td>
<td>Doxorubicin</td>
<td>Inhibitory avoidance conditioning</td>
<td>Impairment of memory retention</td>
<td></td>
</tr>
<tr>
<td>Sieklucka-Dziuba</td>
<td>Doxorubicin</td>
<td>Passive avoidance task</td>
<td>No impairment</td>
<td></td>
</tr>
<tr>
<td>Antimicrotubule agents</td>
<td>Paclitaxel</td>
<td>Five choice serial reaction time task</td>
<td>No impairment</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Seigers et al. (2011)
Table 2

*P50 suppression index (P50\textsubscript{S2}/P50\textsubscript{S1}) to each pair of age-matched participants in the paired click paradigm.*

<table>
<thead>
<tr>
<th>Pair Number</th>
<th>Survivor Age</th>
<th>Control Age</th>
<th>Survivor S2/S1</th>
<th>Control S2/S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>40</td>
<td>1.00</td>
<td>0.43</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>47</td>
<td>0.83</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>47</td>
<td>0.66</td>
<td>0.36</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>51</td>
<td>0.20</td>
<td>0.46</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>55</td>
<td>0.74</td>
<td>0.34</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>60</td>
<td>0.67</td>
<td>0.43</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>60</td>
<td>0.78</td>
<td>0.73</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>64</td>
<td>0.59</td>
<td>0.61</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>66</td>
<td>1.00</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Average 53.78 54.44 0.72 0.45
Table 3

Correlation with participant age of P50 suppression (paired-click and oddball paradigms) and MMN indices, separately for healthy controls and breast cancer survivors.

<table>
<thead>
<tr>
<th></th>
<th>P50_{S2}/P50_{S1}</th>
<th>P50_{standard}/P50_{deviant}</th>
<th>MMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td>0.63</td>
<td>0.37</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td>0.08</td>
<td>0.59</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Figure 1. Factors that affect assessment of cognitive changes induced by drugs.

*Adapted from:* (Minisini et al., 2004)
Figure 2. Postulated mechanisms of chemotherapy-associated cognitive changes.

Adapted from: (Vardy et al., 2008)
Grand averaged ERP waveforms evoked at Cz by each click (S1 and S2) in the paired-click paradigm (left panels) and each tone (standard and deviant) in the oddball paradigm (right panels), separately for breast cancer survivors (middle panels) and healthy age-matched controls (top panels). Cluster analysis controlling for multiple comparisons revealed that the group differences over central and parietal electrode sites in the right hemisphere in the paired-click paradigm (bottom left panel) and over left temporal locations in the oddball paradigm (bottom right panel).
Figure 4. Average magnitude of dipole moments in paired-click paradigm by brain region

Average magnitude of dipole moments to S1 and S2 in the paired-click paradigm for each group at each of four bilateral neural structures: hippocampus, thalamus, STG, and DLPFC.
Figure 5. Grand Average MMN at CZ with Significant Clusters

Average ERP at Cz to standard and deviant tones in cancer survivors (left middle panel) and healthy controls (left top panel). MMN area is represented with shading in each panel. Bottom panel: ERP difference waves (deviant minus standard) for each group. Right panel: Cluster analysis revealed that the difference between groups was widespread across scalp locations.