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Alterations in brain structure related to breast cancer and its treatment: Chemotherapy and other considerations

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Abstract

Cognitive effects of cancer and its treatment have been a topic of increasing investigation over the past ~30 years. Recent studies have focused on better understanding the neural correlates of these effects, with an emphasis on post-chemotherapy effects in breast cancer patients. Structural MRI studies have utilized both automated and manual approaches to quantify gray and white matter characteristics (e.g., regional volume and density) in breast cancer patients treated with chemotherapy relative to patients who did not receive chemotherapy and/or healthy controls. While most work to date has been retrospective, a small number of baseline (pre-systemic therapy) and prospective longitudinal studies have been conducted. Data have consistently shown lower gray and white matter volume and density in patients treated with chemotherapy, particularly in frontal and temporal brain regions. Host factors and/or the cancer disease process and other therapies (e.g., antiestrogen treatment) also seem likely to contribute to the observed differences, though the relative contributions of these effects have not yet been investigated in detail. These structural abnormalities have been shown to relate to subjective and objective cognitive functioning, as well as to biological factors that may help to elucidate the underlying mechanism(s). This review examines the currently available published observations and discusses the major themes and promising directions for future studies.

Keywords

brain; breast cancer; chemotherapy; frontal lobes; magnetic resonance imaging; neuroimaging; voxel-based morphometry

Introduction

As the literature demonstrating cognitive sequelae of cancer and its treatments has become more established, a growing body of research has utilized advanced neuroimaging techniques to examine the underlying neural mechanisms of these effects, particularly cognitive symptoms attributed to systemic chemotherapy. Other papers in this special issue review the findings from functional MRI (fMRI; de Ruiter and Schagen 2013) and diffusion tensor imaging (DTI; Deprez et al. 2013), and integrate the structural and functional literature (Pomykala et al. 2013). Here we review the current structural MRI literature examining cancer- and treatment-related alterations in brain morphology.

Studies examining brain structure typically implement analytic approaches designed to segment the brain into specific structures (e.g., hippocampus) or tissue compartments (e.g.,

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gray or white matter, GM and WM respectively) of interest, via either manual tracing or automated segmentation or parcellation approaches. Manual tracing techniques typically utilize a standard, manualized approach to delineating regions of interest (ROIs), which most commonly encompass a particular brain structure. Such protocols rely on anatomic landmarks and conventional boundaries to define the ROI, and tracings must meet a defined level of inter-and intra-rater reliability. These methods can be extremely precise for particular ROIs in a given individual, but have the drawback of being time- and labor-intensive. More recent studies tend to rely on automated or semi-automated approaches for delineating ROIs. For example, image processing software packages such as FreeSurfer (Dale et al. 1999; Fischl et al. 1999) are available to automatically parcellate MRI data into specific ROIs (e.g., brain structures or lobar regions of interest) and extract volumetric and cortical thickness values.

Voxel-based morphometry (VBM) is another commonly used method for quantitative evaluation of structural differences on a voxel-by-voxel basis throughout the entire brain (Ashburner and Friston 2000, 2001; Good et al. 2001). As VBM is used in a number of the studies discussed in this review, a brief description of the method is provided, along with some important considerations for its use. Unlike morphological methods that involve manual segmentation of selected structures, VBM is a fully automated procedure for examining tissue integrity, which allows quantification of regional volume and density of brain tissue compartments. VBM implements statistical parametric mapping procedures to assess tissue-specific intensity values across every voxel in the brain relative to a user-defined statistical threshold, providing an unbiased, comprehensive, and highly reliable assessment of tissue characteristics sensitive to local differences. As part of VBM processing, the user can elect to mathematically “modulate” the data by multiplying voxel values by the determinant of the Jacobian matrix, to account for the effects of spatial normalization and preserve the original relative volumes of brain regions. However, a recent validation study suggests that modulation significantly reduces the ability of VBM to detect mesoscopic (i.e., between microscopic and macroscopic) differences (Radua et al. 2013). Without modulation, relative tissue concentration is preserved. Studies using modulated data therefore generally refer to differences in regional brain volume, while those using unmodulated data refer to differences in regional brain density or concentration (Mechelli et al. 2005). Another consideration when using VBM is whether or how to model “global” differences between groups. For example, total intracranial volume can be included in analyses as a covariate of no interest to control for the potential confound of overall brain size when examining regional differences in tissue volume or density. Alternatively, global or local scaling techniques can be utilized to remove overall between-group differences. These approaches can result in significant alterations in data, such that differing findings among VBM studies may be attributable in part to such variations in processing and analytic approaches (Mechelli et al. 2005; Peelle et al. 2012).

This review will focus on studies of patients with breast cancer, where the majority of relevant work has been conducted to date (see Table 1 for a summary of articles reviewed here). As noted in Deprez et al. in this issue (Deprez et al. 2013), for the purposes of this special issue we are most interested in the effects of treatments for non-CNS cancers that are not directly targeting the CNS. We therefore will not review the growing literature documenting GM and WM abnormalities and their cognitive correlates in individuals during and after intrathecal chemotherapy treatment (often with high-dose methotrexate) for acute lymphoblastic leukemia (ALL; e.g., Carey et al. 2008; Ciesielski et al. 1999; Glass et al. 2006; Kesler et al. 2010; Lesnik et al. 1998; Reddick et al. 2006). Similarly, while there are a number of reports of acute or reversible leukoencephalopathy as a neurologic complication linked to chemotherapy in various cancer populations, these are typically qualitative or descriptive in nature, rather than based on statistical comparisons, and so will not be covered

here. Finally, as the focus of this review is on the effects of cancer and its treatments on MRI measures of brain structure, we will not review the small literature examining brain structure in relation to psychiatric symptomatology in breast cancer patients, but not as related to cancer or its treatment (Hakamata et al. 2007; Hara et al. 2008; Inagaki et al. 2004; Matsuoka et al. 2006; Matsuoka et al. 2003; Nakano et al. 2002; Yoshikawa et al. 2006). However, the demonstration of a potential relationship between symptoms of depressive and anxiety disorders and volume of specific brain structures in cancer patients highlights the need to examine these and other psychosocial factors and patient-specific covariates (see discussion of Scherling et al. 2012 below) when conducting this type of research, to explore potential explanatory factors when differences are found.

Examination of brain structure in breast cancer survivors treated with chemotherapy

White matter change after high-dose chemotherapy with bone marrow support

In some of the earliest systematic work in this area, Stemmer, Brown, and colleagues published a series of papers examining WM changes after high-dose chemotherapy for breast cancer (Brown et al. 1995; Brown et al. 1998; Stemmer et al. 1994). This group (Stemmer et al. 1994) initially reported on 13 high-risk breast cancer patients (stage II-IV disease) studied with MRI after high-dose cyclophosphamide, cisplatin, carmustine, and autologous bone marrow support. Eight patients had a single post-treatment MRI scan, while five had serial studies. Five patients had scans prior to bone marrow support chemotherapy (though all had previously received standard-dose systemic chemotherapy and/or induction chemotherapy in preparation for transplant); no abnormalities were apparent on these scans. Based on neuroradiological ratings, four patients had severe WM changes post-transplant, four had moderate changes, and one had mild changes, while four did not demonstrate abnormality. Changes seemed more frequent and severe five or more months post-transplant. However, the authors did not find a relationship between WM changes and neurological status. In a subsequent paper, this group (Brown et al. 1995) compared MRI and magnetic resonance spectroscopy (MRS) findings in 13 similar patients (it was not clear whether this group of patients overlapped with those in the previous report) relative to 13 matched controls, including semi-automated measurement of the degree of WM abnormality. Scans were conducted on average 12 months after treatment completion, and showed WM abnormalities ranging from 1 to 153 cm^3 (mean 49±50 cm^3). MRS measures, including N-acetyl aspartate (NAA)/creatine (Cr) and NAA/choline (Cho) ratios, were not abnormal relative to controls despite these structural differences, nor was there a clear relationship between degree of WM abnormality and neurological status, though about half of the patients experienced some post-treatment neurological complication. To clarify the time course of these WM changes prospectively, Brown et al. (Brown et al. 1998) used serial MRI and MRS to follow eight stage II-IV breast cancer patients over the course of treatment, with baseline scans planned prior to induction chemotherapy (though for some patients after standard-dose chemotherapy), after induction chemotherapy but prior to high-dose chemotherapy and transplant, and at 1, 3, 6, 9, and 12 months after transplant with the same regimen described above. MRI appeared normal in all patients at baseline, and in all six patients for whom scans were available after induction chemotherapy. WM changes were apparent in one of these patients two months post-treatment. At three months post-transplant and later, three of four patients remaining in the study showed an increasing volume of WM changes that stabilized in the 6- to 12-month post-treatment phase, consistent with this group's earlier finding of development of WM abnormalities in the months post-treatment. The highest volumes of abnormal WM for these patients were 73, 151, and 166 cm^3. Despite these WM abnormalities, few neurochemical changes were detected by MRS, although NAA/Cr ratios suggested a transient treatment-related decrease, potentially suggestive of

temporary neuronal dysfunction which subsequently normalizes. Again there was no clear relationship to clinical status; while transient neurological abnormalities were noted, no patient showed persistent CNS symptoms. Overall, this group of studies suggests significant WM abnormalities detectable within a few months of completion of high-dose systemic chemotherapy and bone marrow transplant. However, the clinical significance of these findings is unclear, given the lack of a consistent relationship with neurological status. These investigators studied patients with more advanced disease who received more aggressive treatment than many of the studies discussed below. However, their findings demonstrate significant structural brain changes that appear attributable to chemotherapy, laying a foundation for subsequent work in this area.

Retrospective studies of gray and white matter in breast cancer survivors

In the first published study utilizing VBM to examine brain GM and WM differences in patients after cancer chemotherapy, Saykin and colleagues (Saykin et al. 2003) studied 12 patients treated with chemotherapy (10 breast cancer, two lymphoma) and 12 healthy demographically matched control participants. Patients were all greater than five years post cancer diagnosis. Widespread abnormalities in neocortical GM and cortical and subcortical WM volume were found in patients relative to controls, while no regions were apparent where patients showed greater tissue volume than controls. This finding of both GM and WM abnormalities in patients several years post cancer treatment extended the prior work by documenting that these differences can be observed in patients with less aggressive disease who were treated with standard-dose chemotherapy, and presented evidence that such abnormalities appear to persist over time post-treatment.

Inagaki et al. (Inagaki et al. 2007) subsequently used VBM to compare patients who had been treated with chemotherapy to those who had not and to a healthy control group. At an average of four months post-treatment chemotherapy-treated patients showed lower GM volume in the right middle and superior frontal and parahippocampal gyri and lower WM volume in the bilateral middle frontal gyri, left precuneus and parahippocampal gyrus, and right cingulate gyrus relative to those not receiving chemotherapy. Correlational analyses demonstrated significant positive relationships between superior frontal and parahippocampal GM and precuneus WM volumes and indices of attention/concentration and/or visual memory from the Wechsler Memory Scale, Revised (WMS-R) in the chemotherapy-treated group. At about three years post-treatment no differences were found between the two cancer groups in samples that partially overlapped with the four-month post-treatment analysis. When all cancer patients were compared to healthy controls no significant volume differences were apparent at either time point, though the two cancer groups were not separately compared to the control group. The lack of significant differences between patients who did and did not receive chemotherapy at the three-year time point was consistent with prior work by this group, (Yoshikawa et al. 2005, discussed further below), in which they found no between-group differences in hippocampal volumes in patients greater than three years after treatment completion. However, these findings stand in contrast to other work discussed in this review demonstrating significant structural abnormalities many years after treatment completion (Conroy et al. 2013; de Ruiter et al. 2012; Kesler et al. 2013; Koppelmans et al. 2012b). Advantages of the Inagaki et al. study include large group sizes for this type of study, with 51-55 participants per group at the first time point and 37-73 per group at the second time point, as well as integration of structural MRI and cognitive data. As noted by the authors and in subsequent commentary, however, methodological factors also affect interpretation of the results. As noted by Eichbaum et al. (Eichbaum et al. 2007), groups were confounded by hormonal treatment status (significantly more chemotherapy-treated than nonchemotherapy-treated patients received antiestrogen treatment), and the majority of patients did not receive a currently recommended standard

chemotherapy regimen (data were gathered prior to anthracycline regimens becoming standard treatment). Additional analyses might also have been very informative in this sample, including independent comparison of each cancer group with controls and correlation of brain volume with cognitive performance across all three groups rather than just within the chemotherapy-treated cohort.

To investigate potential factors related to brain structural differences after chemotherapy, Conroy et al. (Conroy et al. 2013) examined the relationship of post-chemotherapy interval (PCI) and oxidative and direct DNA damage in peripheral lymphocytes to GM density from VBM, fMRI activation during working memory processing, cognitive performance, and cognitive complaints in 24 chemotherapy-treated patients (on average six years post treatment completion) relative to 23 matched healthy controls. Within the patient group PCI was found to be positively correlated with GM density in the right frontal and temporal lobes (Fig. 1), caudate, and precuneus, and in the left frontal lobe, cuneus, and putamen. In the right frontal lobe (Brodmann areas 9 and 10) GM density was also positively related to global cognitive functioning as measured by neuropsychological testing, and PCI was found to be negatively correlated with working memory-related fMRI activation (Fig. 1). Between-group analyses showed that patients evidenced lower GM density than controls in distributed brain regions, including left temporal lobe and thalamus and right insula, midbrain, and cerebellum. Mean GM density in these regions showed an inverse relationship with oxidative DNA damage and learning and memory performance. Patients also showed lower fMRI activation in the right precuneus and left temporal lobe, and showed poorer memory functioning, greater cognitive complaints, and greater oxidative DNA damage than the control group. These findings were interpreted as consistent with longitudinal data from this group (McDonald et al. 2010; McDonald et al. 2013, discussed below) suggesting that frontal GM gradually recovers over time following an initial chemotherapy-associated insult, though between-group comparisons indicated that persistent differences were present even several years post-treatment. The relationship of these GM findings to cognitive functioning demonstrates their likely functional significance, while the association with oxidative DNA damage offers clues toward a possible underlying biological mechanism. As the authors noted, DNA damage in cancer patients can be linked to both disease-and treatment-related factors, which merit further investigation.

de Ruiter et al. (de Ruiter et al. 2012) also undertook a multimodality imaging approach to the examination of differences in brain structure and function in a group of breast cancer survivors on average 9.5 years post-chemotherapy (N=17) relative to breast cancer patients not treated with chemotherapy (N=15). The chemotherapy-treated group consisted of high-risk breast cancer patients treated with the same standard- and high-dose chemotherapy regimens followed by autologous peripheral blood hematopoetic progenitor-cell transplantation rescue and subsequent tamoxifen treatment. Of note, except for one participant who took tamoxifen, the nonchemotherapy group in this study did not receive antiestrogen treatment. In addition to examination of brain GM using VBM, de Ruiter et al. included DTI, MRS, and fMRI activation during memory encoding. VBM analysis showed lower GM volume in chemotherapy-treated patients relative to those who did not receive chemotherapy in left occipital and lateral posterior parietal cortex and bilateral precuneus and cerebellum. When examined relative to previously reported fMRI activation during memory encoding (de Ruiter et al. 2011), GM volume loss in left parietal cortex colocalized with fMRI hypoactivation in the same region (Fig. 2). DTI abnormalities relative to the nonchemotherapy group, including greater mean and radial diffusivity, were also observed in posterior parietal regions in chemotherapy-treated patients, adjacent to the regions in which VBM and fMRI differences were noted. These findings point toward persistent brain structural and functional abnormalities many years after chemotherapy (though with a more intensive treatment regimen than is in common use today), and demonstrate the presence of

GM and WM abnormalities that relate to differences in brain function and metabolites, illustrating potential underlying neural mechanisms for cognitive symptoms after cancer treatment.

In the largest study of this kind to date, that notably included patients at the longest time interval after chemotherapy completion, the same group (Koppelmans et al. 2012b) examined brain structural differences in a group of 184 breast cancer survivors relative to 368 age-matched women who had never had cancer from a population-based cohort study (Hofman et al. 2009). All patients were treated with the same chemotherapy regimen (cyclophosphamide, methotrexate, and 5-fluorouracil), had not received adjuvant antiestrogen therapy, and completed chemotherapy on average 21 years prior to MRI scanning. Dependent measures included total brain volume (TBV), total GM and WM volumes, and hippocampal volume, as well as whole-brain examination of focal differences in GM using VBM. The patient group showed significantly smaller TBV and total GM volume relative to reference subjects, with no differences in other imaging metrics. The relative reduction of GM in patients was found to be comparable to the effect of almost four years of age-related GM decline. Differences in this study from others discussed here include the use of a population-based reference sample rather than a healthy control group for comparison, as well as adjustment of analyses for a large number of covariates previously shown to be related to brain volume (age, education, intracranial volume, height, blood pressure, presence of diabetes, smoking status, and symptoms of depression). As this group had previously demonstrated cognitive impairments in this group of patients (Koppelmans et al. 2012a), the imaging findings may be indicative of neural correlates of these symptoms.

Given the commonly reported finding of episodic memory difficulties in breast cancer patients after chemotherapy, studies have focused on examination of differences in hippocampal structure as well as their relationship to memory functioning in this population. Bergouignan et al. (Bergouignan et al. 2011) examined 16 patients after breast cancer treatment (surgery, chemotherapy, and local radiation, four also had antiestrogen treatment, studied 18-36 months after radiation treatment) relative to 21 matched healthy controls to examine differences in hippocampal GM as measured by an automated segmentation procedure and relate hippocampal integrity to autobiographical memory performance. Breast cancer patients were found to have significantly smaller hippocampi than controls (8% volume reduction on average), as well as poorer autobiographical memory retrieval. Analysis of anterior versus posterior hippocampus showed that posterior hippocampus was on average 11% smaller in cancer patients than controls, while no group differences were apparent in anterior hippocampus. Posterior hippocampal volume was also related to autobiographical memory performance. This finding was demonstrated in breast cancer patients without significant psychiatric comorbidity, leading the authors to infer that the observed hippocampal and memory differences were likely attributable to the experience of breast cancer (i.e., cancer and its treatment), rather than to any associated psychiatric symptomatology. The authors also noted that volume reduction specific to posterior hippocampus has previously been shown in stress-related psychiatric disorders (e.g., depression, anxiety, posttraumatic stress disorder). In their own sample, preliminary analyses also suggested a relationship between distressing memories, posterior hippocampal volume, and autobiographical memory. As this study was retrospective and did not include patients who did not receive chemotherapy, the hippocampal and memory differences cannot be conclusively attributed to chemotherapy, though such findings are consistent with those observed prospectively by other groups and specifically attributed to chemotherapy (see discussion of McDonald et al. 2010; McDonald et al. 2013 below).

Kesler et al. (Kesler et al. 2013) also examined hippocampal volume in chemotherapy-treated breast cancer survivors (N=42, on average nearly five years post-treatment) relative to matched healthy controls (N=35), and looked at the relationship to memory functioning and serum cytokine levels, to assess the potential relationship of inflammatory processes to brain structure and function after chemotherapy. Patients showed significantly lower left hippocampal volume relative to controls, with a trend for lower right hippocampal volume. Patients also showed lower objective and subjective memory than controls. In those for whom cytokine data were available interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) were significantly elevated in patients relative to controls. Levels of other cytokines did not show between-group differences. Across groups left hippocampal volume was associated with verbal memory performance and cytokine levels. In patients lower left hippocampal volume was associated with higher levels of TNFα and lower levels of IL-6, with a significant interaction between these, which the authors interpreted as suggestive of a modulatory effect of IL-6 on TNFα. Older age was associated with higher levels of both IL-6 and TNFα, and shorter time since treatment was also associated with higher TNFα levels. Hippocampal volume was not associated with time since treatment, suggesting that volume loss may remain stable over time. In controls left hippocampal volume was not significantly associated with cytokine levels, though stronger verbal memory performance was associated with lower TNFα levels and higher left hippocampal volume. Findings were not accounted for by levels of mood symptoms or other host, disease or treatment variables (e.g., menopausal status, tamoxifen or radiation treatment, disease stage). Based on prior literature, the authors proposed that chemotherapeutic agents may show varying levels of neurotoxicity and/or may differentially affect cytokine expression, which has been linked to hippocampal damage in animal studies. Their findings therefore offer clues to potential mechanisms underlying chemotherapy-related changes in brain structure and function.

While all the studies described above found significant reductions in brain GM and/or WM in chemotherapy-treated patients relative to control groups, it should be noted that one study has failed to find such differences. Yoshikawa et al. (Yoshikawa et al. 2005) studied 44 breast cancer patients who had received chemotherapy compared to 31 who had not. Thirty-one patients in the chemotherapy group had also received tamoxifen (and may still have been taking it, though this was unclear), while none of the patients in the comparison group took this medication. Patients were on average 3.5 years post chemotherapy completion. The hippocampi were traced manually, and participants also completed subtests of the WMS-R. While chemotherapy-treated patients showed poorer scores on attention/concentration measures, there were no between-group differences in hippocampal volume or memory scores. This study stands in contrast to the literature discussed above showing lower GM in breast cancer patients treated with chemotherapy, as well as to findings of smaller hippocampal volume in patients treated with tamoxifen but not chemotherapy (see discussion of Eberling et al. 2004 below).

In an alternative approach to examination of differences in brain volume, Hosseini et al. (Hosseini et al. 2012) utilized graph theoretical analysis to examine differences in GM networks between chemotherapy-treated breast cancer patients (N=37, on average 4.5 years post-treatment) and matched healthy controls (N=38). In brief, this approach uses computational methods to examine correlational relationships between data points, in this case between regional brain GM volumes. Characteristics of these relationships help to elucidate brain organization, and have previously been described in terms of the nature and strength of connections between brain regions, using terminology related to the relative “small-world” properties of brain networks, including factors such as the number and length of regional connections (Bassett and Bullmore 2006; Petrella 2011; Sporns et al. 2004). Arguing that prior studies had shown a diffuse pattern of brain structural abnormalities after breast cancer chemotherapy suggestive of effects on large-scale brain networks, these

authors examined GM network connectivity across a range of network densities, and found that overall network correlation strength was significantly lower in patients than controls. While networks in both groups showed characteristics of small-worldness, patients showed lower clustering coefficient and small-world index, indicative of relative reduction in small-world properties, though the overall difference in small-worldness was at trend level of significance (p=0.08). Examination of regional network measures showed reduced interactivity (i.e., nodal betweenness/degree) of frontotemporal regions in patients relative to controls, with higher values in more posterior regions (parieto-occipital) as well as anterior cingulate and left thalamus. A smaller number of network hubs was also found in the patient group relative to controls (three versus six hubs), with hubs in the patient group primarily in parietal and cingulate regions while those of controls were largely in frontotemporal regions. The authors interpret these findings as indicative of lower regional connectivity as well as global network organization and integration in breast cancer patients after chemotherapy. In particular, they describe the differences observed in frontotemporal regions as consistent with prior literature noting abnormalities in GM volume and density in these areas, and hypothesize that these network differences may be related to deficits noted in related cognitive domains (i.e., executive functions and memory) in breast cancer patients after treatment. Unfortunately this hypothesis could not be directly tested in this dataset as the network measures extracted are at the group rather than the individual level. Although highly novel, this study does not appear to have included correction for multiple comparisons. While this is an issue common to many neuroimaging studies, given the methodology used here such correction might be of particular utility, given the large number of brain regions tested for significant relationships. Overall, however, Hosseini et al. interpret their findings as suggestive of reduced robustness and efficiency of network organization after chemotherapy. This demonstration of abnormal interconnectivity in distributed brain regions, particularly those which have been identified in other work as showing structural and functional abnormalities related to cancer and treatment (e.g., frontotemporal circuitry), offers further support for the hypothesis that alterations in the structural integrity of these regions may underlie the cognitive symptoms observed in this population.

Prospective and baseline studies of brain structural alterations related to breast cancer and treatment

Prospective longitudinal examination of gray matter changes

The cross-sectional studies discussed above focused on analysis of residual structural abnormality in the brains of patients successfully treated for breast cancer at varying intervals post-treatment. Without baseline data, however, it is impossible to know with certainty how much these differences are attributable to cancer treatments, including chemotherapy, versus potential effects of the cancer disease process itself or other factors. A small number of prospective, longitudinal studies have begun to address this question. In the first such study, McDonald et al. (McDonald et al. 2010) compared women treated with chemotherapy for breast cancer (N=17), breast cancer patients who did not receive chemotherapy (N=12), and matched healthy controls (N=18). Participants completed MRI scans at three time points: the baseline visit was conducted after surgery but prior to adjuvant treatment (radiation, chemotherapy, or antiestrogen treatment), a second visit was scheduled about one month after chemotherapy completion (or yoked intervals for the other two groups), and a final visit was completed one year after the second scan. VBM was used to compare GM density between groups and over time. No between-group differences in GM were seen at baseline, and within-group analyses of controls and patients who did not receive chemotherapy did not show any regions of GM decline over time. One month post-treatment, however, the chemotherapy-treated group showed significantly reduced GM

density compared to baseline in bilateral frontal, cerebellar, and medial temporal regions, including hippocampus, and right thalamus (Fig. 3). Group-by-time interaction analyses demonstrated that chemotherapy-treated patients showed significant reductions in bilateral middle frontal and right cerebellar GM density relative to controls from baseline to one month post-treatment, while patients who did not receive chemotherapy showed decreased GM density in the right cerebellum relative to controls. Further longitudinal analyses demonstrated that some of the regions where GM density decreases were observed in the chemotherapy-treated group showed recovery to baseline values one year later, while other regions showed persistently diminished GM density over time. Covariate analyses demonstrated that these reductions in GM density were not attributable to time since cancer surgery, disease stage, psychiatric symptoms, psychotropic medication use, or length of time on antiestrogen treatment. In subsequent work this group (McDonald et al. 2012) reported alterations in working memory-related fMRI activation that overlapped with these GM changes in frontal regions, demonstrating potential functional significance to these structural alterations. These prospective study findings (McDonald et al. 2010) confirmed those of prior retrospective work, and suggest that the observed reductions in GM density were likely primarily attributable to chemotherapy rather than other cancer- or host-related factors. However, the finding of milder GM changes over time in patients not treated with chemotherapy relative to controls indicates that the potential effects of other cancer treatments must also be investigated.

This group subsequently replicated these findings of decreased frontal GM density using VBM in an independent, larger, more heterogeneous cohort of 27 breast cancer patients who received chemotherapy, 28 who did not, and 24 matched controls (McDonald et al. 2013). Participants were studied at the same intervals as described above, though analyses included only the first two study visits, as the study was ongoing and only partial data was available for the final study visit at the time of that report. In this second cohort patients who did not receive chemotherapy showed lower GM density in the left cingulate gyrus at baseline relative to controls. This finding was of uncertain significance; it seemed unlikely to be related to cancer per se, as no such difference was seen between chemotherapy-treated patients and controls. In addition, this region did not evidence significant change over time in within-group or interaction analyses. Consistent with the prior study (McDonald et al. 2010), interaction analyses showed that patients treated with chemotherapy had decreased GM density in the left middle frontal gyrus at one month post-treatment relative to controls. Within-group analyses showed decreased left middle and superior frontal GM density in the chemotherapy-treated group at one month post-treatment relative to baseline. Such changes were again not evident in patients who did not receive chemotherapy or controls. Within the chemotherapy-treated group GM density in the left middle frontal gyrus was found to correlate with self-reported difficulties in executive functions as measured by the Behavioral Rating Inventory of Executive Function-Adult Version (BRIEF-A), with reduced GM density at one month post-treatment showing an association with greater complaints in terms of ability to initiate problem-solving or activity. In order to evaluate possible risk factors for chemotherapy-related changes GM density and BRIEF-A scores were compared between patients with and without the apolipoprotein (*APOE*) ε4 allele, a known risk factor for cognitive changes. No between-group differences were found based on *APOE* ε4 status, though it was noted that a relatively higher percentage of chemotherapy-treated patients carried this allele. These findings provided confirmatory evidence that the observed reductions in GM density were most likely attributable to chemotherapy treatment, as such changes were not observed in patients who did not receive chemotherapy or controls. In addition, the finding of a relationship between frontal GM density and self-reported executive functioning was consistent with a prior fMRI study (Kesler et al. 2011) reporting a correlation between brain activation during an executive functioning task and BRIEF-A ratings in the same frontal regions (Brodmann areas 8, 10, and 46). Likewise, the GM

changes observed are consistent not only with these researchers' other studies (Conroy et al. 2013; McDonald et al. 2010, 2012), but with those of other groups demonstrating structural and functional brain abnormalities prior to adjuvant treatment (Scherling et al. 2011; Scherling et al. 2012) and post-treatment (de Ruiter et al. 2011; Kesler et al. 2009; Kesler et al. 2011; Silverman et al. 2007).

Pre-treatment examination of gray and white matter differences

One other published paper to date has examined GM and WM prior to planned chemotherapy for breast cancer (Scherling et al. 2012). These authors studied 23 patients prior to initiation of chemotherapy compared to 23 demographically matched healthy controls. Patients were studied post-surgery but prior to adjuvant treatment, and VBM was conducted on both GM and WM, using whole-brain and ROI-based analyses. These authors were particularly interested in examining the potential effects of possible confounding variables on group differences in brain structure, including demographic, psychological, and biological factors such as time since surgery, diurnal cortisol levels, estrogen, symptoms of depression or anxiety, and estimated intellectual ability. Of note, while patient and control groups did not differ in terms of measured cognitive functioning, estrogen, or cortisol levels, patients did show significantly higher mean scores on measures of depression and anxiety symptoms, though group means remained within the nonclinical range for these scales. Comparisons of GM values revealed no between-group differences for either whole-brain or ROI analyses, and inclusion of covariates did not significantly modify these results. For WM, no significant between-group differences were apparent in whole-brain analyses, though ROI analyses showed smaller WM volumes in patients than controls in bilateral inferior frontal, left pre- and post-central, insula, striatum, inferior parietal, precuneus, and corpus callosum, and right supramarginal and middle temporal regions. Interestingly, addition of some covariates to the analyses (depression and anxiety symptoms, time since surgery) resulted in significantly higher WM values in patients than controls in right parahippocampal and left occipital ROIs, while inclusion of other covariates continued to demonstrate lower WM in patients relative to controls in ROI-based analyses, but altered which regions demonstrated significant differences. For both GM and WM, regression analyses showed relationships between regional brain volume and the variables of interest, including symptoms of depression and anxiety, estimated intellect, time since surgery, and cortisol levels. These relationships differed depending on whether the whole sample or individual groups (breast cancer patients or controls) were examined, and varied in directionality depending on the analysis. For example, level of depression symptoms was associated with larger or smaller GM volumes, depending on brain region and group examined. Results from this study were generally consistent with the baseline findings of the longitudinal studies described above (McDonald et al. 2010; McDonald et al. 2013), which showed little to no pre-treatment difference in GM between breast cancer patients and healthy controls. Scherling et al. did demonstrate pre-chemotherapy abnormalities in WM in patients relative to controls; while these were not apparent in whole-brain analyses, they were evident when specific ROIs were examined. As the authors note, these findings can therefore be thought of as reflecting more subtle differences in brain structure than those typically detected by whole-brain analytic approaches.

Potential effects of disease process and other treatments

It is also important to consider the potential role of the cancer disease process itself and other treatments (e.g., surgery, local radiation, antiestrogen treatment, etc.) in the brain structural abnormalities observed in cancer patients. While the studies noted above have found only limited structural differences prior to adjuvant treatment, post-chemotherapy findings are to some degree confounded with additional treatments which have also been implemented. In a study focusing on the role of estrogen in brain structure and function in

postmenopausal women, Eberling et al. (Eberling et al. 2004) examined healthy women who either were (ERT+, N=15) or were not (ERT-, N=15) taking estrogen and breast cancer patients taking tamoxifen (TAM, N=10), five of whom had received radiation, but none of whom had received chemotherapy. Participants underwent FDG PET, structural MRI with manual segmentation of the hippocampus, and cognitive evaluation. The authors hypothesized that estrogen would have a neuroprotective effect in this context, such that estrogen use would be related to greater hippocampal volume, while tamoxifen use would be associated with lower volume (and lower glucose metabolism on PET). Consistent with this hypothesis, after removal of one outlier from the TAM group, hippocampal volumes were significantly smaller in the TAM group relative to ERT+ bilaterally, with ERT-participants showing intermediate volumes. While the TAM group also showed significantly poorer performance than the other two groups on a semantic memory task, task performance was not directly related to hippocampal volume. There was no relationship of hippocampal volume to hippocampal glucose metabolism, nor were group differences in hippocampal glucose metabolism observed, though significant differences in frontal glucose metabolism were found between all groups (i.e., ERT+>ERT-, ERT+>TAM, ERT->TAM). Given the study design, the contribution of cancer versus its treatments to the observed findings cannot be separated, but these results suggest that the potential effects of cancer itself or of other cancer treatments must be carefully considered when studying presumed effects of chemotherapy on brain structure.

Discussion

Examination of brain structural alterations related to breast cancer and its treatment has progressed dramatically over the past two decades. Initial studies demonstrating overt WM abnormalities (Brown et al. 1995; Brown et al. 1998; Stemmer et al. 1994) laid a foundation for more sophisticated analytic approaches using advanced image analysis techniques. Since this earliest work, several studies (Bergouignan et al. 2011; Conroy et al. 2013; Inagaki et al. 2007; Kesler et al. 2013; Koppelmans et al. 2012b; de Ruiter et al. 2012; Saykin et al. 2003) have consistently demonstrated lower volumes of GM and WM in chemotherapy-treated breast cancer survivors relative to comparison groups (breast cancer patients not treated with chemotherapy and/or healthy controls) using both manual and automated analytic techniques, with only one published study failing to document such differences (Yoshikawa et al. 2005). However, it should also be noted that investigators may not seek to publish negative findings, leading to a bias in the literature toward studies demonstrating significant between-group differences. Abnormal GM connectivity characteristics have also been demonstrated in regions overlapping with those showing volumetric differences (Hosseini et al. 2012). These retrospective studies have examined patients from several months to >20 years post-treatment, and have found volumetric differences in diffuse brain regions, though changes in frontal and temporal regions, including medial temporal structures such as the hippocampus, have been among the most consistent findings across studies. The limited data examining patients at baseline (post-surgery but prior to adjuvant treatment) have generally not demonstrated significant abnormalities in GM between breast cancer patients and controls (though baseline differences in the left cingulate were noted in one study (McDonald et al. 2013)). Reduced WM at baseline has likewise been reported using some analytic approaches but not others (Scherling et al. 2012). Prospective longitudinal investigations (McDonald et al. 2010; McDonald et al. 2013) have shown significant reductions in GM after chemotherapy relative to baseline, again prominently in frontal and temporal lobe regions, which appear to demonstrate partial but not complete recovery over time, consistent with the residual differences noted in the retrospective literature. Limited evidence suggests that antiestrogen treatment may also contribute to these alterations in brain structure (Eberling et al. 2004; McDonald et al. 2010), though the effects of chemotherapy appear much more pronounced.

These reductions in brain volumes in chemotherapy-treated patients, particularly in the frontal lobes (e.g., Brodmann areas 8, 9, and 10), have been demonstrated to correlate with objective and subjective cognitive functioning, subject-specific demographic and treatment variables (e.g., PCI), and/or biological factors which may point toward underlying etiology, including oxidative DNA damage and cytokine and brain metabolite levels (Bergouignan et al. 2011; Conroy et al. 2013; Inagaki et al. 2007; Kesler et al. 2013; McDonald et al. 2013; de Ruiter et al. 2012). Regional differences in brain structure have also been demonstrated to correlate or colocalize with brain activation as measured by fMRI (Conroy et al. 2013; McDonald et al. 2012; Michiel B. de Ruiter et al. 2012), further demonstrating the functional significance of these structural abnormalities. Frontal abnormalities have also been demonstrated in the limited available DTI literature in this population, and have demonstrated correlations with cognition in some work (Deprez et al. 2012; Deprez et al. 2011; de Ruiter et al. 2012). This indicates a potential WM correlate for the GM changes discussed here, as well as further evidence for a neural substrate of cancer- and treatment-related functional changes. While baseline comparisons show some structural differences potentially attributable to host factors and/or the cancer disease process, much more dramatic group abnormalities are evident post-treatment, particularly after systemic chemotherapy. Taken in combination, these data offer consistent support for reductions in brain gray and white matter after cancer chemotherapy, even therapy which does not target the CNS, in a non-CNS cancer. Furthermore, where focal findings have been noted, the frontal and temporal brain regions most typically affected are also those which subserve cognitive functions commonly reported to show cancer- and treatment-related effects, including executive functions and episodic memory.

The consistency of brain regions found to demonstrate reductions in GM and WM density and/or volume after breast cancer chemotherapy is noteworthy, with frontal and temporal regions repeatedly demonstrating such abnormalities in studies with differing comparison groups (i.e., patients treated without chemotherapy or healthy controls) and at different magnet field strengths (i.e., 1.5 versus 3 Tesla). While such regional differences have been most prominent in several studies, more diffuse changes are noted in others. As cancer treatments, including chemotherapy, can be conceptualized as a diffuse insult, treatments administered systemically might be predicted to lead to diffuse rather than focal brain effects. The focal findings described above in may be related to both methodological and biological factors. Imaging analyses utilize different approaches to selection of statistical thresholds. It is therefore the case that while focal changes are noted at a particular level of statistical rigor, more diffuse findings may be observed at a more lenient threshold. Therefore, more varying patterns of brain changes related to cancer and its treatment may be found depending upon the analytic approach taken. In addition, as noted above, variations in image preprocessing steps (e.g., use of modulated or unmodulated VBM data) can directly impact the ability to detect regional group differences. However, it also seems plausible that frontal and temporal brain regions may be more vulnerable to cancer- and treatment-related effects. As noted above, an extensive literature has documented cognitive effects in neuropsychological functions primarily subserved by frontotemporal systems, but has not typically found global cognitive impairment in this population. As discussed further below, the link between cancer and aging has prompted increased examination of commonalities between cognitive and brain changes related to cancer and its treatment and those related to the aging process, including both “normal” age-related cognitive change and pathological processes such as Alzheimer's disease and its precursors. For example, frontal regions have been demonstrated to show age-related GM and WM changes prior to more posterior regions (Gunning-Dixon et al. 2009; Peelle et al. 2012), and atrophy of medial temporal regions is among the earliest structural changes apparent in Alzheimer's disease, and one of the best predictors of conversion from prodromal to more advanced disease (Risacher et al. 2009; Risacher et al. 2010). Of note, in cancer survivors those studies examining older

patients (who are also those further out from cancer treatment) have found more diffuse GM changes, rather than focal differences (e.g., Koppelmans et al. 2012b). This prompts the question of whether more regional changes may be present in younger individuals or those in earlier stages relative to cancer diagnosis and treatment, with perhaps more diffuse effects becoming apparent over time as a result of an interaction between cancer- and treatment-related effects and the aging process. The biological mechanisms underlying these changes are under active investigation, and proposed etiologies in cancer populations have included chemotherapy-induced DNA damage (directly or through increases in oxidative stress), individual variation in genes related to neural repair and/or plasticity, and chemotherapy-induced hormonal changes (Ahles and Saykin 2007). The studies discussed above offer preliminary support for some of these hypothesized etiologies, particularly in terms of oxidative DNA damage and inflammatory process involvement.

As mentioned above, multiple lines of evidence also suggest that there may be an interaction between cognitive and brain changes related to cancer and its treatment and cognitive disorders of aging, including Alzheimer's disease and its precursors. Convergent data from cognitive, imaging, genetic, and other biomarker studies suggest that older breast cancer patients may be more vulnerable to structural and functional brain changes after chemotherapy, and that these abnormalities may be related to alterations in immune functioning after breast cancer treatment (Mandelblatt et al. in press). As discussed by Ahles et al. (Ahles et al. 2012), while the mechanisms leading to increased cancer risk with age are incompletely understood, both the aging process and chemotherapy treatment are associated with biological factors such as DNA damage, oxidative stress, inflammation, and decreased telomere length. As outlined by these authors, the commonality of underlying biological processes related to cancer- and treatment-related cognitive changes and cognitive disorders of aging suggests the possibility that cancer treatments may accelerate the aging process in vulnerable individuals, either by shifting the trajectory of cognitive dysfunction to an earlier point in the lifespan, or accelerating this trajectory altogether (Ahles et al. 2012). As different mechanisms may contribute to this process for different individuals, and as these potential effects are not mutually exclusive, research focusing on older patients will be important to address these questions, as most studies to date have focused on younger breast cancer patients (in their 40s-50s).

Some potential confounding factors will require further investigation, though treatment patterns make this a challenge. For example, it is typically the case that patients receiving chemotherapy have higher stage disease than those not treated with chemotherapy, while those not receiving chemotherapy tend to skew slightly older. The issue of menopausal status and chemotherapy-induced amenorrhea (see Conroy et al. 2013 in this issue)) is also likely important when considering structural and functional brain changes in this population, but may be confounded with treatment status. Likewise, it is difficult to disentangle effects of antiestrogen treatments from those of other modalities, given current practice patterns. While the retrospective studies described above have been critical for advancing our understanding of post-treatment effects, additional prospective work continues to be needed to discriminate cancer- versus treatment-related effects on brain structure and function, and to monitor the course of these changes over time. It will also be critical to further examine the relationship of observed changes to brain function (e.g., cognitive and behavioral measures, fMRI and other neurophysiological markers), to assess the functional significance of these findings. As discussed above, consideration must also be given to inclusion of appropriate covariates, as these can significantly affect the observed findings. Given the challenges inherent in recruiting participants to these types of studies, multicenter collaborations will likely be the most effective way to gather enough data to meaningfully answer mechanistic and biological questions regarding the etiology of these changes, particularly when consideration is given to factors like genetic risk. In addition, such larger

studies will be needed to obtain sufficiently heterogeneous samples to adequately address the many potential risk factors of interest (e.g., socioeconomic and other medical and mental health variables, cognitive reserve, effect of specific chemotherapy regimens, etc.). Future research along these lines will be able to build upon the knowledge gained to date, with the overarching goal of elucidating biological mechanisms underlying these brain changes, in order to advance work in the areas of effective treatment and compensatory strategies, as well as possible approaches to prevent cancer- and treatment-related changes in brain structure and function.

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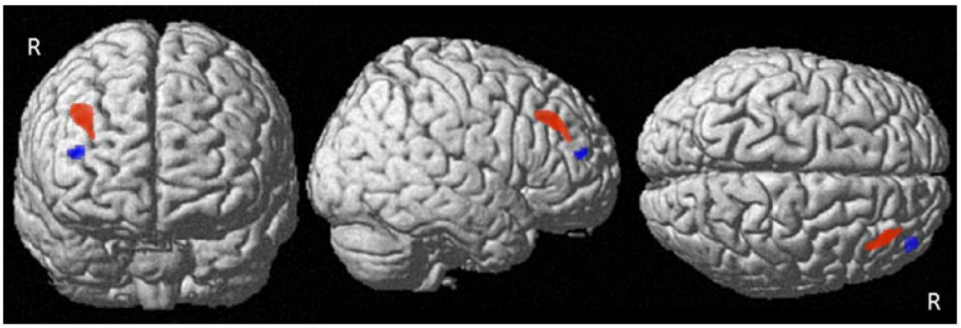

Fig. 1.

Functional and structural overlap in the right anterior middle frontal gyrus. Gray matter density as measured by VBM (red) was positively correlated with post-chemotherapy interval, while working memory-related fMRI activation (blue) was negatively correlated with post-chemotherapy interval (voxelwise p uncorrected=0.001, cluster size=10 for both modalities; from Conroy et al. 2013).

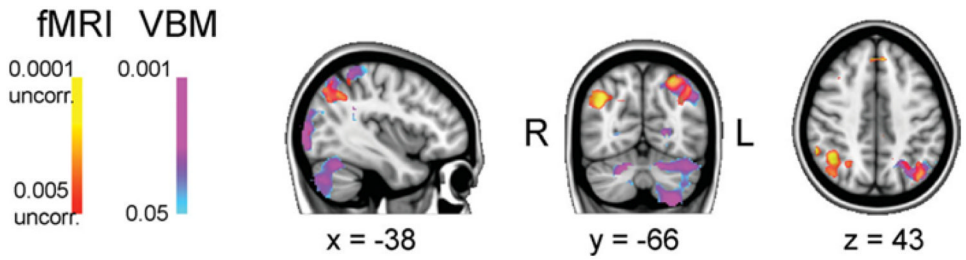

Fig. 2.

Lower regional gray matter volume as measured by VBM in chemotherapy- compared to no-chemotherapy patients overlaps with fMRI hypoactivation during a paired associates task in left posterior parietal cortex. Right posterior parietal cortex shows hypoactivation but no volume reduction. Bilateral cerebellum shows volume reduction but not task-related activation. Color bars show range of corrected (VBM) and uncorrected (fMRI) p values (from de Ruiter et al. 2012).

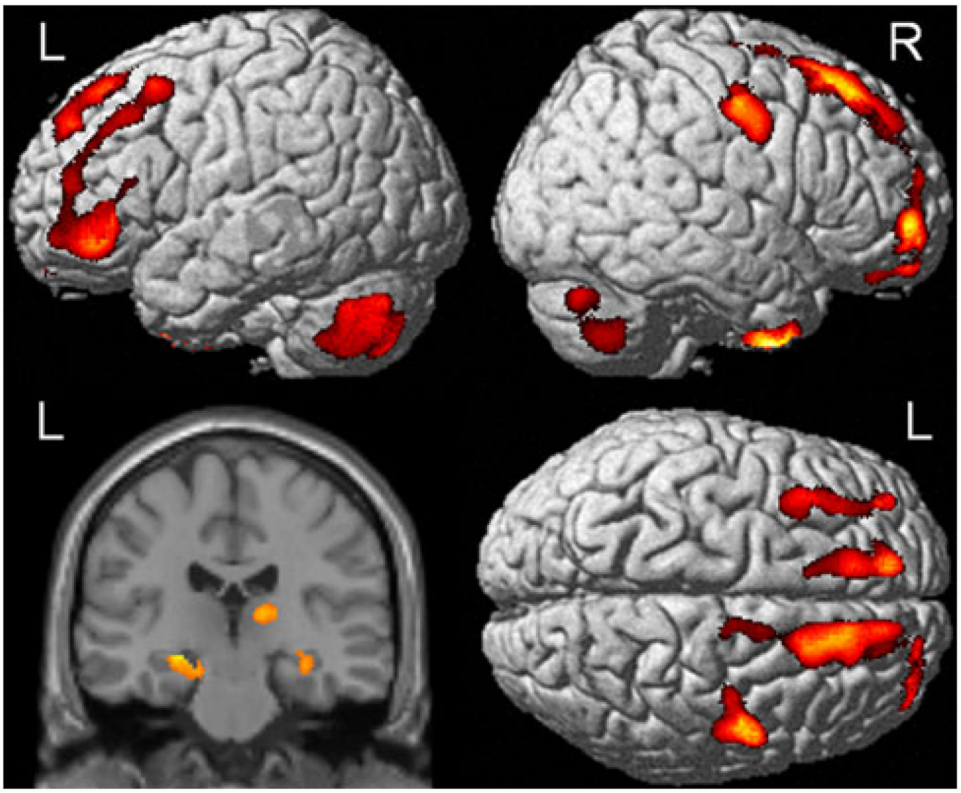

Fig. 3.

Regional gray matter density declines as measured by VBM in chemotherapy-treated breast cancer patients from baseline to 1 month after chemotherapy (voxelwise p uncorrected=0.001, cluster size=1,400; from McDonald et al. 2010).

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Table 1

Summary of Studies Reviewed

Authors	Participants	Mean age (SD)	Structural MRI method	Structural MRI finding
Stemmer et al., 1994	13 CTx+ BC patients	43.9 (7.5)	Visual rating of WM abnormality	Mild to severe WM changes in 9 of 13 patients.
Brown et al., 1995	13 CTx+ BC patients 13 healthy controls	47.3 (8.0) 42.0 (10.0)	Semi-automated segmentation of WM abnormalities	WM changes ranging from 1-153cm^3 across all patients, without clear relationship to neurologic status.
Brown et al., 1998	8 CTx+ BC patients	47.4 (9.2)	Semi-automated segmentation of WM abnormalities	WM changes ranging from 73-166cm^3 in 3 of 4 patients remaining in study ≥3 months post-treatment, without clear relationship to neurologic status.
Saykin et al., 2003	12 CTx+ BC and lymphoma patients 12 healthy controls	53.7 (10.5) 55.8 (12.9)	Voxel-based morphometry (modulated)	Reduced volume of GM and WM in distributed brain regions bilaterally.
Eberling et al., 2004	10 BC patients on tamoxifen (TAM); 15 healthy women on estrogen (ERT+); 15 healthy women not on estrogen (ERT-)	64.7 (6.7) 67.3 (7.1) 66.5 (6.4)	Manual hippocampal tracing	Decreased hippocampal volume bilaterally in TAM relative to ERT +; ERT- intermediate.
Yoshikawa et al., 2005	44 CTx+ BC patients 31 CTx- BC patients	48.3 (5.7) 48.2 (5.7)	Manual hippocampal tracing	No between-group hippocampal volume differences.
Inagaki et al., 2007	<1 year post-treatment 51 CTx+ BC patients 54 CTx- BC patients 55 healthy controls ~3 years post-treatment 73 CTx+ BC patients 59 CTx- BC patients 37 healthy controls	47.3 (5.2) 46.3 (6.1) 46.2 (6.7) 48.2 (5.6) 48.4 (4.8) 48.0 (6.4)	Voxel-based morphometry (modulated)	Decreased GM and WM volume in CTx+ relative to CTx- <1 year post-treatment, no difference ~3 years post-treatment. Regions of decreased volume in CTx+ correlated with attention/concentration and visual memory scores. No volume differences between controls and combined cancer group at either time point.
McDonald et al., 2010	17 CTx+ BC patients 12 CTx- BC patients	52.4 (8.5) 52.7 (7.2)	Voxel-based morphometry (unmodulated)	No between-group GM differences pre-chemotherapy. CTx+ patients showed reduced bilateral frontal, temporal, and cerebellar GM density 1 month after treatment relative to controls. Changes improved in some regions 1 year later but persisted in others. CTx-

Authors	Participants	Mean age (SD)	Structural MRI method	Structural MRI finding
	18 healthy controls	50.6 (6.5)		patients showed reduced right cerebellar GM density relative to controls at the 1 month scan.
Bergouignan et al., 2011	16 CTx+ BC patients 21 healthy controls	48.7 (5.0) 47.7 (5.3)	Automated hippocampal segmentation	Hippocampal volume reduced by 8% in patients relative to controls overall, and by 11% in posterior hippocampus. Autobiographical memory also reduced in patients relative to controls and related to posterior hippocampal volume.
de Ruiter et al., 2012	17 CTx+ BC patients 15 CTx- BC patients	56.5 (5.1) 58.2 (5.8)	Voxel-based morphometry (modulated)	CTx+ showed reduced GM volume relative to CTx- in posterior cortical regions and cerebellum. GM reduction in left parietal cortex colocalized with reduced task-related brain activation during memory encoding on fMRI, and was adjacent to alterations in WM as measured by DTI.
Hosseini et al., 2012	37 CTx+ BC patients 38 healthy controls	54.2 (6.1) 55.5 (9.0)	Graph theoretical analysis of GM structural networks	Relative to controls BC patients showed reduced small world characteristics, altered interactions in frontotemporal regions, and fewer network hubs.
Koppelmans et al., 2012	184 CTx+ BC patients 368 female non-cancer reference subjects	64.0 (6.5) 64.0 (6.5)	Automated segmentation and voxel-based morphometry (modulated)	BC patients showed smaller total brain and GM volume relative to reference subjects ~21 years post-treatment.
Scherling et al., 2012	23 BC patients prior to CTx+ 23 healthy controls	51.0 (8.5) 50.0 (9.0)	Voxel-based morphometry (modulated)	No between-group GM differences. Patients showed lower WM volumes than controls in ROI but not whole-brain analyses. Inclusion of covariates modified findings.
Conroy et al., 2013	24 CTx+ BC patients 23 healthy controls	57.8 (9.6) 61.2 (9.9)	Voxel-based morphometry (unmodulated)	Patients showed decreased GM density in several brain regions relative to controls, which was negatively related to oxidative DNA damage and learning and memory performance. Post-chemotherapy interval was positively related to right frontal GM density, which was related to global cognition.
Kesler et al., 2013	42 CTx+ BC patients 35 healthy controls	54.6 (6.5) 55.5 (9.3)	Automated hippocampal segmentation	BC patients showed reduced left hippocampal volume relative to controls, which was related to higher levels of TNFα and lower levels of IL-6, with an interaction between these. In both patients and controls left hippocampal volume was related to verbal memory.
McDonald et al., 2013	27 CTx+ BC patients 28 CTx- BC patients 24 healthy controls	49.9 (7.6) 52.4 (9.1) 47.0 (9.2)	Voxel-based morphometry (unmodulated)	CTx- patients showed reduced left cingulate GM density relative to controls pre-chemotherapy. CTx+ patients showed reduced left frontal GM density 1 month after treatment relative to controls. In CTx+ patients left frontal GM density related to self-reported executive function but not APOE ε4 status.

APOE ε4 = Apolipoprotein E ε4 allele
BC = Breast cancer
CTx+ = Chemotherapy-treated
CTx- = Not chemotherapy-treated
DNA = Deoxyribonucleic acid
DTI = Diffusion tensor imaging
fMRI = Functional MRI

GM = Gray matter
IL-6 = Interleukin-6
ROI = Region of interest
TNFα = Tumor necrosis factor-α
WM = White matter