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Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: A replication and extension study

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ABSTRACT

Cognitive changes related to cancer and its treatment have been intensely studied, and neuroimaging has begun to demonstrate brain correlates. In the first prospective longitudinal neuroimaging study of breast cancer (BC) patients we recently reported decreased gray matter density one month after chemotherapy completion, particularly in frontal regions. These findings helped confirm a neural basis for previously reported cognitive symptoms, which most commonly involve executive and memory processes in which the frontal lobes are a critical component of underlying neural circuitry. Here we present data from an independent, larger, more demographically diverse cohort that is more generalizable to the BC population. BC patients treated with ($N = 27$) and without ($N = 28$) chemotherapy and matched healthy controls ($N = 24$) were scanned at baseline (prior to systemic treatment) and one month following chemotherapy completion (or yoked intervals for non-chemotherapy and control groups) and *APOE*-genotyped. Voxel-based morphometry (VBM) showed decreased frontal gray matter density after chemotherapy, as observed in the prior cohort, which was accompanied by self-reported difficulties in executive functioning. Gray matter and executive symptom changes were not related to *APOE* ε4 status, though a somewhat greater percentage of BC patients who received chemotherapy were ε4 allele carriers than patients not treated with chemotherapy or healthy controls. These findings provide confirmatory evidence of frontal morphometric changes that may be a pathophysiological basis for cancer and treatment-related cognitive dysfunction. Further research into individual risk factors for such changes will be critical for development of treatment and prevention strategies.

Cognitive changes related to breast cancer and its treatment have been an area of increasing study, with numerous reports demonstrating cognitive impairment in patients relative to controls. These changes have been differentially attributed to chemotherapy, radiation, and anti-estrogen treatment (Agrawal et al., 2010; Ahles et al., 2010; Collins et al., 2009; Jim et al., 2009; Quesnel et al., 2009), and have been reported most prominently in executive functions (e.g., working memory) and processing speed, cognitive processes largely subserved by frontally mediated brain systems (impairment in other cognitive domains has also been noted; for review and meta-analysis see (Anderson-Hanley et al., 2003; Correa and Ahles, 2008; Stewart et al., 2006)). A higher than expected incidence of impaired cognitive performance has also been found in patients prior to systemic treatment (Ahles et al., 2008; Wagner et al., 2006; Wefel et al., 2004), suggesting that host factors and/or the cancer disease process itself may play a role. This prior work demonstrates the continued need for further investigation of the effects of cancer treatment and the disease process on cognition in vulnerable individuals (McDonald and Saykin, 2011; Vardy et al., 2008).

The neural mechanisms underlying these cognitive changes have likewise been the subject of increasing investigation. Several cross-sectional, retrospective structural MRI studies have utilized voxel-based morphometry (VBM) to assess gray matter changes after breast cancer treatment quantitatively, in an automated, unbiased manner (de Ruiter et al., in press; Hakamata et al., 2007; Inagaki et al., 2007; McDonald et al., 2008; Saykin et al., 2003; Yoshikawa et al., 2006). Those studies comparing gray matter between patients who did and did not receive chemotherapy have demonstrated residual gray matter deficits in the chemotherapy-treated group, even several years after treatment completion (de Ruiter et al., in press; Inagaki et al., 2007; McDonald et al., 2008; Saykin et al., 2003). We recently reported the first prospective VBM study examining such gray matter changes relative to pre-treatment baseline (McDonald et al., 2010). We predicted that

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these changes would be detectable in the short-term but would recover at least partially over time, given prior cognitive studies suggesting longitudinal improvement in brain function after chemotherapy (Ahles et al., 2010; Collins et al., 2009; Jansen et al., 2011; Jenkins et al., 2006; Schagen et al., 2002). Findings were consistent with study hypotheses, demonstrating reduced gray matter in chemotherapy-treated patients one month after chemotherapy completion in bilateral frontal, medial temporal, and cerebellar regions. One year later gray matter density had returned to baseline levels in some regions, though not all. No between-group differences were found at baseline, and changes were not seen in patients who did not receive chemotherapy or healthy controls.

The purpose of the current investigation was to assess gray matter alterations related to breast cancer and its treatment prospectively in an independent cohort of patients treated with and without standard-dose systemic chemotherapy and demographically matched healthy controls, in order to replicate our previous findings. Given the prominence of executive function changes among the cognitive domains affected in cancer patients after treatment (Anderson-Hanley et al., 2003), and the recent finding of a relationship between self-reported executive functioning and altered brain activation after breast cancer chemotherapy (Kesler et al., 2011), we also sought to examine the relationship of these gray matter changes to self-reported executive functioning. Finally, a large body of research has shown a significant relationship between the apolipoprotein E (*APOE*) ε4 allele and Alzheimer's disease and its precursors, and has demonstrated a role for *APOE* in other neurocognitive disorders (for reviews see (Bookheimer and Burggren, 2009; Smith, 2000)). Given prior work demonstrating decreased cognitive functioning in cancer survivors treated with chemotherapy who carried the ε4 allele vs. those who did not (Ahles et al., 2003), we further evaluated possible risk factors for gray matter changes after chemotherapy by investigating their relationship to presence or absence of the *APOE* ε4 allele.

1. Participants

Written informed consent was obtained from all participants according to the Declaration of Helsinki under a protocol approved by the Indiana University Institutional Review Board. Participants were female breast cancer patients treated with (CTx+, $N = 27$) and without (CTx−, $N = 28$) systemic chemotherapy and healthy controls ($N = 24$). Patients had non-invasive (stage 0) or non-metastatic invasive (stages I, II, or III) disease, and were treated with common standard-dose chemotherapy regimens which all included a taxane (see Table 1 for demographic and treatment data). Exclusion criteria for all groups were: (1) prior treatment with cancer chemotherapy, CNS radiation, or intrathecal therapy; (2) current or past alcohol or drug dependence; (3) neurobehavioral risk factors including neurologic, medical, or psychiatric conditions known to affect brain structure or function, except history of depression or anxiety in breast cancer patients. Potential participants for all groups were excluded for current diagnosis of any DSM-IV Axis I disorder or a history of any psychiatric disorder requiring hospitalization. Anxiety and depression symptoms were assessed at each study visit with the Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff, 1977) and the State-Trait Anxiety Inventory-State subscale (STAI-S) (Spielberger, 1983).

2. Methods

Study measures were completed at baseline (after surgery but before radiation, chemotherapy, and/or anti-estrogen treatment) and approximately one month following the completion of chemotherapy (M1), or yoked intervals for the CTx− and control groups, for all participants except nine CTx+ patients who received neoadjuvant chemotherapy prior to surgery and additional treatment. For these nine participants the baseline study visit was prior to both cancer surgery and systemic treatment, and the second study visit was approximately one month after chemotherapy completion. For CTx+ patients the baseline visit was conducted on average 9.9 days (SD 11.0) prior to the start of chemotherapy (range 1–43 days). One CTx− participant began tamoxifen about three weeks prior to her baseline scan. Of note, data reported here are drawn from a larger study in which participants undergo a comprehensive assessment including structural and functional neuroimaging, objective and subjective cognitive evaluation, and genetic and other biomarkers at three time-points. Data collection is ongoing, particularly for the final study visit (not reported here, given our current partial sample), and the present findings therefore represent an interim analysis of a subset of the larger study.

2.1. Self-reported executive function

Self-report of executive functioning was obtained with the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) (Roth et al., 2005), which includes an overall composite score (the Global Executive Composite, or GEC) and two major index scores: the Behavioral Regulation Index (BRI), composed of the Inhibit, Shift, Emotional Control and Self-Monitor scales, and the Metacognition Index (MI), which includes the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials scales. Between-group differences on BRIEF-A scale and index T-scores were compared using the general linear model in SPSS (SPSS Statistics 19, IBM Corporation, Somers, NY) to examine differences in self-reported executive function at M1 controlling for baseline levels. Of note, higher T-scores on this measure indicate greater levels of executive complaints.

2.2. APOE genotyping

APOE alleles were determined using standard assays for the two single nucleotide polymorphisms (SNPs) coding for the ε4 (rs429358) and ε2 (rs7412) vs. more common ε3 allele of *APOE*. Participants who were carriers of one or two copies of the ε4 allele were considered *APOE* ε4 positive. Within the CTx+ group, differences between *APOE* ε4 positive and negative patients for significant gray matter clusters and BRIEF-A scales were compared using the general linear model in SPSS (SPSS Statistics 19, IBM Corporation, Somers, NY) to examine differences at M1 controlling for baseline levels.

2.3. MRI scan acquisition

All scans were acquired on the same Siemens Tim Trio 3T scanner using a 12-channel head coil. A T1-weighted three-dimensional magnetization prepared rapid gradient echo (MPRAGE) volume was used for VBM, with the following parameters: TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm, FA = 9 deg, 160 1.2 mm thick sagittal slices with no skip, 256×256 matrix, in-plane resolution of 1 mm^2. This MPRAGE sequence has been extensively tested and validated via the multicenter, international Alzheimer's Disease Neuroimaging Initiative (ADNI) study (see http://adni.loni.ucla.edu/ for additional information). T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences were also acquired to rule out incidental pathology.

2.4. Image analysis

Locally developed MATLAB (R2009b, Mathworks, Inc., Natick, MA) scripts were used to implement optimized VBM methods