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Brain Structure and Function in Patients with Ovarian Cancer treated with First-Line Chemotherapy: A pilot Study

DD Correa¹, JC Root², M Kryza-Lacombe¹, M Mehta³, S Karimi⁴, ML Hensley⁵, and N Relkin

¹Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY

²Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY

³Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

⁴Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY

⁵Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background—Women with ovarian cancer often undergo chemotherapy involving multiple agents. However, little is known about treatment-related central neurotoxicity in this population. The goal of this cross-sectional study was to assess brain structure and function and neurocognitive abilities in patients with ovarian cancer following first-line chemotherapy.

Methods—Eighteen patients with ovarian, peritoneal and fallopian tube cancer and eighteen healthy controls matched for gender, age and education participated in the study. The patients were evaluated 1–4 months following completion of first-line taxane/platinum chemotherapy. All participants underwent structural and functional magnetic resonance imaging (MRI), and completed neuropsychological tests of attention, memory and executive functions. Neuroimaging

Address correspondence and reprint requests to: Denise D. Correa, PhD, ABPP-CN, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; Telephone number: 212-610-0491; FAX number: 646-888-3175; corread@mskcc.org.

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Conflict of Interest:

Dr. Correa serves on the Editorial Board of *Neuro-Oncology Practice* and on the Neurotoxicity Advisory Board for Juno Therapeutics.

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assessments included voxel-based morphometry (VBM) for measuring gray matter (GM) volume, and functional MRI (fMRI) during the N-back working memory task.

Results—The results of VBM showed that patients had significantly reduced GM volume compared to healthy controls in the right middle/superior frontal gyrus, and in the left supramarginal gyrus and left inferior parietal lobule. fMRI results indicated significantly decreased activation in patients relative to healthy controls in the left middle frontal gyrus and left inferior parietal lobule during the N-back task (1/2/3-back > 0-back). There were no statistically significant differences between the two groups on the neuropsychological tests.

Conclusions—This is the first study showing structural and functional alterations involving frontal and parietal regions in patients with ovarian cancer treated with first-line chemotherapy. These findings are congruent with studies involving women with breast cancer, and provide additional supporting evidence for central neurotoxicity associated with taxane/platinum chemotherapy.

Keywords

ovarian cancer; chemotherapy; cognitive; MRI; fMRI

Introduction

Ovarian cancer is the sixth most common cancer in women with more than 20,000 individuals diagnosed in the United States each year (Siegel et al. 2015). Standard treatment for ovarian cancer often includes cytoreductive surgery followed by taxane and platinum-based chemotherapy (McGuire and Markman 2003; Morrison et al. 2007). Considering that the median survival for patients with ovarian cancer exceeds five years and about one third of patients are cured (Ozols 2002), cognitive dysfunction is of significant concern as it may interfere with quality of life. There is compelling evidence that chemotherapy is associated with neurotoxicity (Rzeski et al. 2004; Ahles and Saykin 2007). While several studies described chemotherapy-induced changes in brain structure and function and cognitive abilities in other cancer populations, little is known about treatment-related central neurotoxicity in women with ovarian cancer.

The majority of cognitive and neuroimaging studies of patients treated with chemotherapy for non-central nervous system (CNS) cancers have been conducted in women with breast cancer (Vardy et al. 2008; de Ruiter et al. 2012). Several cross-sectional studies documented that chemotherapy had a negative impact on cognitive functioning in subgroups of breast cancer survivors (Ahles et al. 2002; Brezden et al. 2000; Wefel et al. 2010), although other studies have reported no detrimental effect (Donovan et al. 2005; Scherwath et al. 2006). Prospective studies suggested that subsets of patients had cognitive dysfunction prior to and after chemotherapy (Wefel et al. 2004b; Collins et al. 2013). The cognitive domains most consistently found to be disrupted by the side effects of chemotherapy include attention and working memory, executive functions, graphomotor speed, and memory (Correa and Ahles 2008; Wefel et al. 2004a), suggesting involvement of frontal-subcortical circuitry (Wefel et al. 2004b; Correa et al. 2007).

To date, only five studies have evaluated cognitive functions in patients with ovarian cancer. In a cross sectional study of long-term survivors of ovarian cancer, a subset of patients met criteria for cognitive impairment (Correa et al. 2010). Two prospective studies (Hess et al. 2010; Hess et al. 2015), using a computerized test battery to assess selected cognitive domains (processing speed, attention, reaction time) in women with newly diagnosed ovarian cancer showed declines during chemotherapy. In one of these studies (Hess et al. 2015), there was evidence of improvement 6 months post-chemotherapy, but subsets of patients had impaired performance during and following treatment in at least one cognitive domain. Two small prospective studies found no evidence of cognitive decline (Mayerhofer et al. 2000; Hensley et al. 2006).

Several studies using magnetic resonance imaging (MRI) (Conroy et al. 2013; Inagaki et al. 2007; Koppelmans et al. 2012; McDonald et al. 2013) have documented reductions in gray matter volume, primarily in the prefrontal cortex, in breast cancer survivors treated with chemotherapy. Functional MRI (fMRI) studies have shown alterations in prefrontal activation patterns during the performance of working memory tasks in areas similar to the volumetric changes described (McDonald et al. 2012; Conroy et al. 2013). These data suggest that quantitative neuroimaging techniques in combination with standardized cognitive assessment can be useful in advancing our understanding of chemotherapy-induced cognitive changes. However, there are no studies using structural and functional neuroimaging to assess treatment-related central neurotoxicity in patients with ovarian cancer.

In this cross-sectional pilot study, we measured brain structure and function and neurocognitive abilities in patients with ovarian cancer following treatment with first-line taxane-platinum chemotherapy.

Materials and Methods

Subjects

Eligibility—Patients diagnosed with stage I–IV ovarian, peritoneal and fallopian tube cancer were recruited from a cohort of patients followed on the Gynecologic Medical Oncology service at Memorial Sloan-Kettering Cancer Center (MSKCC) between 2012 and 2014. Study eligibility included: age 21 to 70 years, completion of first-line taxane and platinum-based chemotherapy 1–4 months prior to enrollment, disease remission at study entry, not on hormonal therapy at enrollment, no history of psychiatric or neurological disorders, and fluency in English. Healthy controls that met the same inclusion (except for cancer diagnosis and chemotherapy treatment) and exclusion criteria, and scored at least 26 on the Mini-Mental State Exam (MMSE) were recruited through community fliers. Healthy controls were frequency-matched to patients on age, education, and gender. The MSKCC Institutional Review Board approved the research protocol, and all participants provided written informed consent.

Measures

MRI Scan Acquisition—All participants were imaged on the same Siemens 3T Magnetom Tim Trio scanner (max gradient strength 45 mT/m; max slew rate 200 T/m/s) at the Citigroup Biomedical Imaging Center (CBIC) at Weill Cornell Medical Center. *Structural Imaging*: A high-resolution T1 weighted anatomical image was acquired using a Magnetization Prepared Rapid Gradient Echo MPRAGE sequence: repetition time (TR)=2300, echo time (TE)=2.96msec, flip angle=9, field of view (FoV)=256mm, 176 sagittal slices with thickness=contiguous 1.2mm, number of averages=1, matrix=256×256, voxel resolution=1×1×1.2mm). Fluid attenuated inversion recovery (FLAIR) sequences were also acquired to rule out pathology. *Functional Imaging*: Blood Oxygenation Level-Dependent (BOLD) contrast imaging, which reflects changes in venous deoxyhemoglobin associated with neuronal activity, was used. A series of functional scans was collected using a gradient echo EPI sequence (TR/TE=2250/29msec, flip angle=79, field of view=220mm, 39 axial slices with thickness=contiguous 3.5mm, number of averages=1, matrix=220×220, voxel resolution=2.5×2.5×3 mm).

Image Processing—For *structural image processing*, voxel-based morphometry (VBM) analysis was performed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) under the Statistical Parametric Mapping, version 8 (SPM8) software package (Wellcome Department of Imaging Neuroscience, London, UK) within MATLAB (Version 7, Mathworks, Inc., Natick, MA). Following reconstruction, MPRAGE structural images were AC-PC reoriented, normalized using high-dimensional DARTEL normalization, segmented into gray, white, and CSF compartments and non-linearly modulated, with resulting gray-matter compartment smoothed using an isotropic Gaussian spatial filter (FWHM=8 mm). *Functional image processing* consisted of the following steps using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>): reconstruction of EPI functional images, AC-PC reorientation; realignment to correct for slight head movement between scans and for differential spin excitation history based on intracranial voxels; co-registration of functional EPI images to the corresponding high-resolution anatomical image based on the rigid body transformation parameters of the reference anatomical image to the latter for each individual subject; stereotactic normalization to a standardized coordinate space (Montreal MRI Atlas version of Talairach space) based on the high-resolution anatomical image to normalize for individual differences in brain morphology; spatial smoothing with an isotropic Gaussian kernel (FWHM=8mm) to increase signal-to-noise ratio.

Functional Working Memory Task—To assess attention and working memory during fMRI, the visual N-Back test was administered to all participants. This task has been reported to activate the dorsolateral prefrontal cortex (Ragland et al. 2002; Owen et al. 2005) and has been used in fMRI studies assessing attention and working memory in clinical populations (McAllister et al. 2001), as well as in a studies of breast cancer patients (McDonald et al. 2012). During scanning, participants were presented with series of letters, one letter at a time every 3 seconds. Four conditions were used: 0-back, 1-back, 2-back, and 3-back. The 0-back condition requires the subject to identify a single target letter. The 1-back requires the subject to decide whether the current letter is the same as the one immediately preceding it. The 2-back requires the subject to decide whether the current

letter is the same as the one two back in the sequence. The 3-back requires the subject to decide whether the current letter is the same as the one three back in the sequence. The 0-back assesses attention and only minimally working memory. The 0-back condition assesses attention and only minimally working memory, and the 1-, 2-, and 3-back conditions impose an increasing load on working memory. The subjects were instructed to respond by pressing their thumb for all matches and their index finger for all non-matches. The four conditions were each presented three times in pseudorandom order in a block-like fashion for a total of 12 blocks per scan. Each block consisted of 9 trials, which led to a total of 27 trials per condition. A 30 second fixation was presented between each block. Participants rehearsed a practice version of the task before the scanning to guarantee understanding of the task demands.

Neuropsychological and Psychological Measures—Neuropsychological tests with documented sensitivity to the adverse effects of cancer therapy (Correa et al. 2007; Ahles et al. 2010) were selected to evaluate Attention and Working Memory (Brief Test of Attention – BTA, Schretlen et al. 1996; Symbol Span subtest of the WMS-IV, Wechsler 2009); Executive Functions (Trail Making Test Parts A & B – TMTA, TMTB, Heaton et al. 2004); Controlled Oral Word Association Test – COWA, Benton et al. 1983); and Verbal Memory (California Verbal Learning Test-Second Edition – CVLT-II; Learning – CVLT-L, Long Delayed Recall – CVLT-LD, Discrimination Index – CVLT-DI, Delis et al. 2000). Raw cognitive test scores were compared with published normative values according to age, and when available, to age and education, and subsequently converted into z-scores. Mood and Quality of Life (QoL) was assessed using the Center for Epidemiological Study-Depression scale (CES-D, Radloff 1977), the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-FS Version 4, Cella 1997), and The Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O Version 4, Basen-Engquist et al. 2001).

Imaging and Behavioral Analyses

Descriptive statistics for demographic variables were generated with frequencies for categorical variables and with means and standard deviations, or median and ranges as appropriate, for continuous variables.

Structural and Functional Image Analysis—For structural MRI voxel-based morphometry analysis (VBM), subject level maps were entered into a two-group ANCOVA (patients; healthy controls) with age entered as a covariate. For functional image analysis, at the individual subject level, a voxel-by-voxel whole brain multiple linear regression model was initially applied. Proportional scaling was used to remove temporal global fluctuation, which was estimated as the mean intensity of intracranial voxels of each volume. The regression model at the individual level consisted of the principal regressor—the block onset times convolved with a prototypical hemodynamic response function—and covariates of no interest: realignment parameters, the global fluctuation estimator, scanning periods, and the first-order temporal derivative of the principal regressor. To accommodate the residual intra-subject temporal correlation pattern, an autoregressive model was incorporated. A restricted maximum likelihood estimator using an expectation maximization algorithm was utilized to estimate effects at every brain voxel. Lastly, linear contrasts were used to assess regionally

specific effects. The resultant contrast-effect images were then progressed into a set of group-level models.

A random-effects model was used for whole-brain group analyses. In an analysis of covariance setting, age was entered as a covariate. For both structural and functional contrasts, initial uncorrected voxel-wise threshold was $p = 0.005$ with resulting maps corrected using an empirically derived cluster extent threshold (Structural $k \geq 297$; Functional $k \geq 13$) as determined by random field theory procedures in SPM8 (Hayasaka and Nichols 2004). The cluster extent threshold was determined by the number of contiguous voxels per cluster expected under the null hypothesis (expected number of voxels per cluster) with non-stationary random field theory methods used to adjust expected cluster sizes based on local smoothness (Kluesch et al. 2012; Nenadic et al. 2010; Niedtfeld et al. 2013). For functional n-back contrasts, models were built for the contrast of working memory load (1-, 2-, 3-back) versus simple attention (0-back), as well as individual contrasts of high working memory load (3-back > 0-back; 2-back > 0-back) to determine independent contributions to differences in functional recruitment between groups.

Functional n-back performance analysis—Behavioral data from the in-scanner, functional n-back task was assessed for group differences in accuracy and in reaction time. For reaction time analysis, independent sample t-tests were used to compare patients and healthy controls performance for each condition (0-, 1-, 2-, 3-back) separately. For accuracy analysis, given nonparametric qualities of the data, Mann-Whitney U tests were conducted for each condition separately.

To assess potential associations of structural and functional imaging data with neuropsychological test performance, neuropsychological test z-scores were entered into an ANCOVA model within SPM and identified as covariates of interest.

Neuropsychological tests and self-report scales—Two sample T-tests were used to compare neuropsychological test z-scores and self-report mood and QoL raw scores between patients and healthy controls. Post-hoc non-parametric analysis was used to compare the proportion of low z-scores between the two groups. The relation between neuropsychological test and QoL scores was assessed using Pearson's correlation.

Results

Table 1 presents demographic and treatment characteristics of the study participants. There were no significant differences between the 18 patients and the 18 healthy controls in age, education, and estimated IQ. Most patients were diagnosed with ovarian cancer (83%), had stage III disease (72%), and were treated with paclitaxel and carboplatin regimens (67%). All patients underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and completed chemotherapy at a median of 80 days prior to study participation. Twelve patients (70%) developed peripheral neuropathy following chemotherapy, which is overall consistent with prior studies reporting peripheral neuropathy in association with taxane and platinum regimens (Brewer et al. 2016). One patient was excluded from the imaging analyses due to scanner malfunction and missing data for all sequences.

Structural Imaging

Patients had significantly reduced gray matter (GM) volume compared to healthy controls in frontal cortical regions including the right middle/superior frontal gyrus and left inferior frontal operculum, together with parietal areas including the left supramarginal gyrus extending into the left angular gyrus ($p < 0.005$, cluster extent > 297). No significant findings were exhibited in which patients had increased gray matter volume compared to healthy controls (Table 2, Figure 1a). GM volume of the anatomical regions showing between group differences was not associated with neuropsychological test performance.

Functional Imaging

To focus on activations associated specifically with working memory load, all working memory load conditions were contrasted with the 0-back condition (1/2/3-back $>$ 0-back) in the initial model followed by specific contrasts of higher working memory load conditions (3-back; 2-back) individually contrasted with the 0-back condition. In the contrast of 1/2/3-back $>$ 0-back, patients had significantly decreased activation relative to healthy controls in the left middle frontal gyrus and left inferior parietal lobule ($p < 0.005$, uncorrected, cluster extent > 13) (Table 3, Figure 1b). In the contrast of 3-back $>$ 0-back, patients showed significantly decreased activation relative to healthy controls only in the left superior parietal lobule ($p < 0.005$, cluster extent > 16) extending into the left inferior parietal lobule. In the contrast of 2-back $>$ 0-back, patients had significantly decreased activation relative to healthy controls only in left middle frontal gyrus ($p < 0.005$, cluster extent > 16).

Examination of structural and functional findings showed regionally adjacent and partially overlapping structural and functional differences between healthy controls and patients in the left inferior parietal lobule, with patients exhibiting both decreased functional recruitment and reduced GM volume than healthy controls (Figure 1c).

In-scanner working memory (N-Back) performance

The analysis of N-back reaction time performance per condition between subjects (Figure 2), showed trend significance for 0-back ($t(33) = 1.96$, $p = 0.059$) and 2-back conditions ($t(33) = 1.95$, $p = 0.059$), with slower reaction time for patients relative to healthy controls. There were no differences in reaction time for 1-back ($t(33) = 1.66$, $p = 0.106$) and 3-back conditions ($t(33) = .919$, $p = 0.365$) between groups. Non-parametric analysis of n-back accuracy performance per condition between subjects found no significant difference in accuracy scores between patients and healthy controls. There were no significant correlations between regional functional activation and fMRI task performance.

Neuropsychological Assessment and QoL

Results of two sample T-tests on continuous cognitive test variables comparing patients and healthy controls on tests of attention, memory, and executive functions showed no significant differences on any of the tests. Group mean test z-scores ranged from $+ 0.19$ to $+ 1.58$ on all tests based on published normative data (Table 4). However, 22% of patients but none of the healthy controls had two or more z-scores ≥ 1 standard deviations below normative values, and the results of non-parametric z-score test for two population proportions showed a significant difference ($z = 2.07$, $p = 0.019$). The low test z-scores among patients relative to

healthy controls were on tests of attention and executive function (BTA; Trails-A; COWA), and memory (short delay free recall-CVLT-II).

The two groups did not differ significantly on the self-report depression scale (CES-D), and mean scores were below the cutoff for clinical depression (Lewinsohn et al. 1997) (Table 4). The patients' mean scores on the fatigue (FACIT-FS) and QoL (FACT-O) self-report scales were generally comparable to the findings in other cancer populations (Yellen et al. 1997) and in patients with ovarian cancer (Basen-Engquist et al. 2001). There were no significant correlations between scores on the self-report scales and the neuropsychological tests.

Conclusions

This is the first study reporting reduced gray matter volume and alterations in regional brain activity in patients with ovarian cancer following completion of first-line taxane-platinum chemotherapy. Our preliminary findings showed that in comparison to age and education matched healthy controls, patients had reduced gray matter volume primarily in frontal regions, including the right superior and middle frontal gyrus and left inferior frontal operculum, as well as in the left inferior parietal lobule. Several studies involving women with breast cancer treated with various chemotherapy regimens (with and without taxane/platinum), described reductions in gray matter volume, predominantly in prefrontal and temporal brain regions (Conroy et al. 2013; Inagaki et al. 2007; Koppelmans et al. 2012; McDonald et al. 2013). Two prospective studies (McDonald et al. 2010; McDonald et al. 2013) reported decreased gray matter density in bilateral frontal and temporal lobe areas one month following chemotherapy relative to the pre-treatment baseline in breast cancer patients, but not in patients who did not receive chemotherapy or in healthy controls, with partial recovery over time, suggesting that the observed changes were likely related to chemotherapy adverse effects. However, pre-treatment structural brain abnormalities have also been described in two studies (Scherling et al. 2011, 2012). Our results are overall consistent with the post-chemotherapy structural abnormalities observed in breast cancer, and suggest that chemotherapy-related central neurotoxicity is also of concern for women with ovarian cancer.

The functional neuroimaging findings indicated that in comparison to healthy controls, patients with ovarian cancer had decreased activation in the left middle frontal gyrus and left inferior parietal lobule during the visual N-back task. This pattern of results was evident when all working memory load conditions were contrasted with the 0-back condition, and were specifically evident in the 2- and 3-back contrasts. Our findings are in agreement with cross-sectional fMRI studies of breast cancer survivors treated with chemotherapy (de Ruiter et al. 2011; Ferguson et al. 2007; Kesler et al. 2011; Kesler et al. 2009) showing a consistent pattern of altered activation in prefrontal and parietal areas during working memory and executive function tasks, as compared with patients not treated with chemotherapy and healthy controls. McDonald et al. (2012) conducted a prospective study involving patients with breast cancer using fMRI, and found frontal and parietal lobe hyperactivation during a working memory task (N-back) before treatment, decreased activation one month post-chemotherapy, and a return to pretreatment hyperactivation at one year post-treatment. The decreased activation was interpreted as representing difficulty maintaining compensatory

activation due to the adverse effects of chemotherapy. More recent work has found associations of functional recruitment of frontal and temporal areas with verbal working memory in breast cancer patients (Lopez Zunini et al. 2013), and two studies showed a positive correlation with fMRI task performance and regional brain activation (de Ruiter et al. 2012; Kesler et al. 2011). In our study, patients showed slower reaction time on the N-Back task as compared to healthy controls, but there were no significant group differences in accuracy, suggesting that patients may have required more time to perform the working memory task. We found no significant associations between performance on the N-back task and regional brain activation. In the context of prior studies, our preliminary results support findings of reduced functional activity and gray matter volume in brain regions involved in executive functions, which may be at least in part associated with treatment-related central neurotoxicity.

Our neuroimaging findings also showed regionally adjacent and partially overlapping areas of reduced gray matter volume and decreased functional recruitment in the left inferior parietal lobule. This brain region has been shown to be involved in spatial memory and working memory, and to be recruited during the performance of the N-Back task (Petersen et al. 1988; Posner et al. 1988; Leung and Alain 2011). Prior studies have suggested that the inferior parietal lobule is involved in integrating information across brain networks, and may represent an intermediate node between executive and default mode networks (Braga et al. 2013; Philip et al. 2016), and may participate in higher order aspects of cognitive control such as temporal order of information (Marshuetz et al. 2000). Interestingly, a reduction in gray matter volume that overlapped with fMRI hypoactivation in the left posterior parietal region was described in breast cancer survivors treated with high-dose chemotherapy (de Ruiter et al., 2012).

Although chemotherapy-related central neurotoxicity would be expected to be associated with a more diffuse pattern of brain abnormalities, most neuroimaging studies in breast cancer show a relatively consistent pattern of gray matter reductions and altered functional activation in frontal and temporal regions, suggesting that these areas may be more vulnerable to chemotherapy adverse effects. The findings of neurocognitive studies of patients with breast cancer described predominantly executive and memory dysfunction, consistent with involvement of these brain regions. However, it has been noted that methodological factors pertaining to imaging analyses, such as selection of statistical thresholds, may in part influence the pattern and extent of regional findings when different analytic approaches are used (McDonald and Saykin 2013). We derived our cluster extent threshold empirically taking into account the voxel size used in the structural and functional MRI data, which is equally or more conservative than other imaging studies in cancer survivors (de Ruiter et al. 2011; Deprez et al. 2014; Stouten-Kemperman et al. 2015; Nudelman et al. 2016). The validity of our reported findings is further strengthened by the fact that structural and functional differences overlapped or were regionally adjacent, suggesting structural differences may have contributed to functional differences between groups. That these findings represent true differences between groups is further supported by the fact that no differences were found in the reverse contrast of patients and controls.

When analyzed continuously with parametric tests, neuropsychological test results showed no significant differences between patients and healthy controls, with group mean test scores within the average range across both groups. However, the results non-parametric sub-group analysis showed a significant difference in proportion of decreased test performance, with 22% of the patients but no healthy controls having two or more scores at or below one standard deviation relative to normative values. There were no group differences in depression and scores were not indicative of mood disturbance; fatigue and QoL scores were comparable to other cancer groups. In a prior study of neuropsychological function in long-term survivors of ovarian cancer who were 5 to 10 years from diagnosis (Correa et al. 2010), mean cognitive test scores were within the average range, but 28% of patients met criteria for cognitive impairment. Two small prospective studies found no significant cognitive decline in ovarian cancer patients treated with taxane-based chemotherapies (Mayerhofer et al. 2000; Hensley et al. 2006). Hess et al. (2010) used a computerized test battery to assess selected cognitive domains in twenty seven patients with advanced ovarian and primary peritoneal cancer prior to chemotherapy, and after the third and sixth cycle of chemotherapy. The findings showed that more than 80% of patients declined in attention, processing speed and reaction time during chemotherapy, and about 40% had cognitive impairment. On a recent multi-center prospective study, Hess et al. (2015) assessed cognitive functions using the same computerized test battery in 231 patients with ovarian cancer at baseline (pre-treatment), during chemotherapy and six months after treatment. The results showed statistically significant improvement in attention and processing speed, but not in reaction time, from baseline to the 6-month follow-up; however, impaired performance in at least one domain was evident in approximately 25% of patients at cycle 4, 21% post-cycle 6, and 17% at 6 months post-chemotherapy. These findings suggest that, similar to the literature on breast cancer patients, subsets of patients with ovarian cancer treated with chemotherapy experience mild decrements on aspects of attention and executive functions. We also expanded these findings to show that ovarian cancer patients show alterations in brain structure and function, and that quantitative neuroimaging approaches may complement neuropsychological assessments and provide greater sensitivity to detect chemotherapy adverse effects.

The mechanisms of chemotherapy-induced cognitive dysfunction are not well understood, but there is evidence that it may produce neurotoxicity through demyelination, secondary inflammatory response, and microvascular injury (Tuxen and Hansen 1994). Recent studies have documented that chemotherapy can disrupt hippocampal neurogenesis (Dietrich et al. 2006), and is associated with alterations in white matter integrity (Inagaki et al. 2007; Deprez et al. 2013). Recent rodent studies have shown that cisplatin inhibits neurogenesis and disrupts cognitive function (Manohar et al. 2014; Vichaya et al. 2015), and that metformin may prevent cisplatin-related central neurotoxicity (Zhou et al. 2016). Additional studies addressing the neurotoxicity of specific chemotherapeutic agents would contribute to our understanding of the underlying mechanisms, and the development of preventive interventions.

In addition, variation in genetic polymorphisms (e.g., APOE; COMT) may influence the vulnerability to cognitive changes associated with cancer treatment (Ahles et al. 2003; Correa et al. 2014; Correa et al. 2016). Other factors such as cancer-related anemia and

fatigue secondary to treatment may also interfere with cognitive functioning (Kayl and Meyers 2006). A recent study reported higher oxidative DNA damage in a sample of breast cancer survivors than in healthy controls, and associations of oxidative DNA damage with gray matter density (Conroy et al. 2013). Surgically-induced menopause has been associated with an increased risk of cognitive impairment and dementia (Shuster et al. 2008), and recent studies have shown that hormonal therapy can disrupt cognitive functions in women with breast cancer (Schilder and Schagen 2007; Schilder et al. 2010). A study assessing the influence of estrogen in brain structure and function (Eberling et al. 2004) reported reduced hippocampal volume in women with breast cancer on antiestrogen therapy, compared to postmenopausal women taking estrogen; postmenopausal women not on estrogen showed intermediate volumes. Therefore, hormonal changes may also contribute to alterations in brain structure and function, and should be considered in the context of studying the adverse effects of chemotherapy.

There are several limitations to the present preliminary study. The interpretation of post-treatment differences in brain structure and function is qualified given the cross-sectional design with no pre-treatment baseline, and the absence of a disease specific control group not treated with chemotherapy. As some structural and functional alterations prior to initiation of chemotherapy treatment have been described in breast cancer patients (Scherling et al. 2011, 2012), we cannot exclude the possibility that decreased gray matter volume and reduced functional activation observed in our patients were in part related to disease or to hormonal changes associated with menopause or surgically-induced menopause. While the research design limits a causal interpretation of our findings, we note that the majority of prospective, longitudinal studies in breast cancer described post-treatment differences when controlling for baseline differences in both structure and function, and most included healthy controls as comparison groups (McDonald and Saykin 2013; Ahles et al. 2012). The cross-sectional approach with evaluations at relatively short intervals post-chemotherapy does not allow for any inferences about the stability or possible long-term improvement of the reported findings. The small sample size in our study may have reduced the power to detect structural and functional differences between patients and healthy controls beyond the findings reported here. There were no significant associations between regions showing group differences in gray matter volume and neuropsychological test performance, or any significant group differences in neuropsychological outcomes, which may be in part related to limited power together with potential restriction of range in test performance. In addition, our fMRI paradigm focused on working memory, a domain reported to be sensitive to the adverse effects of cancer treatment, but paradigms assessing other cognitive domains, such as memory may also be considered in future studies. Nevertheless, this is the first study suggesting that ovarian cancer patients treated with first-line chemotherapy may be at increased risk for developing alterations in brain structure and function. To further clarify these preliminary findings, a large prospective study including pre- and post-treatment structural and functional imaging in ovarian cancer patients would be required to assess the contribution of disease, hormonal changes, chemotherapy, and other risk factors to cognitive outcome. The investigation of potential mechanisms of treatment-related central neurotoxicity and susceptibility factors could ultimately lead to the development of targeted preventive or therapeutic interventions.

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Figure 1.

(1a) Regional gray matter volume reductions in patients relative to healthy controls in the right middle/superior frontal gyrus, left supramarginal gyrus, right precentral gyrus, frontal inferior operculum, left inferior parietal region. Voxel-wise height threshold: $p = 0.005$; $k \geq 297$

(1b) Increased regional activation during the N-back functional task (3, 2, 1 > 0) in patients relative to healthy controls in the left middle frontal gyrus and left inferior parietal region. Voxel-wise height threshold: $p = 0.005$; $k \geq 13$.

(1c) Regionally adjacent and partially overlapping areas of decreased functional activation (red) and decreased gray matter volume (blue) in patients relative to controls.
OC=Ovarian cancer; HC=Healthy Controls; Color bar values are in units of T.

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* $p = 0.059$

Figure 2.
N-Back Mean Reaction Time for Patients and Healthy Controls

Table 1**Demographic Characteristics and Treatment History**

	Patients (n=18)	Controls (n=18)
Handedness (R/L)	18/0	17/1
Mean Education (SD)	15.6 (3.8)	15.9 (1.3)
Mean Est.VIQ	109 (8.6)	111 (8.1)
Age at study entry		
Mean (SD)	56.1 (8.2)	56.2 (9.1)
Median (range)	57 (39–69)	59 (35–67)
Age at diagnosis		
Mean (SD)	55.3 (8.2)	N/A
Median (range)	56.5 (38–68)	N/A
Diagnosis		
Ovarian	15	N/A
Fallopian Tube	2	N/A
Peritoneal	1	N/A
Disease Stage		
I	1	N/A
II	0	N/A
III	13	N/A
IV	4	N/A
Chemotherapy regimen		
Paclitaxel, Carboplatin	12	N/A
Paclitaxel, Cisplatin	4	N/A
Paclitaxel, Cisplatin, Carboplatin	2	N/A
Mode of chemo administration		
IV	10	N/A
IV/IP	8	N/A
Number of cycles completed		
Mean (SD)	6.3 (0.9)	N/A
Median (range)	6 (4–8)	N/A
Time since chemo completion (days)		
Mean (SD)	81 (21)	N/A
Median (range)	79.5 (28–119)	N/A
Menopausal at diagnosis (Y/N)	11/7	N/A
Menopausal at study entry (Y/N)	18/0	13/5

SD= standard deviation; Est.VIQ= Estimated Verbal IQ (NAART (Blair and Spreen 1989), or Barona Index (Barona et al. 1984); IV= intravenous; IP=intraperitoneal

Table 2

Structural VBM OC < HC

Cluster Level [†]				Voxel-wise Peak Level [‡]			
x	y	z	k (extent)	Cluster p	Peak T	Peak Z	Peak p Region
20	60	27	480	0.189	4.34	3.81	<0.001 R MFG/SFG
-48	-45	34	871	0.084	4.20	3.71	<0.001 L SMG
22	-36	64	305	0.292	4.18	3.69	<0.001 R PCG
-60	3	2	436	0.21	4.04	3.59	<0.001 L FIO
-34	-40	54	343	0.264	3.51	3.19	0.001 L IP

VBM: Voxel Based Morphometry; OC: Ovarian Cancer patients; HC: Healthy Controls; R: Right; L: Left; MFG: Middle Frontal Gyrus; SFG: Superior Frontal Gyrus; SMG: Supramarginal Gyrus; PCG: Postcentral Gyrus; FIO: Frontal Inferior Operculum; IP: Inferior Parietal.

[†] Cluster level extent threshold: $k = 297$

[‡] Voxel-wise height threshold: $p = 0.005$

Table 3

Functional N-back OC < HC

		Cluster Level [†]			Voxel-wise Peak Level [‡]					
		x	y	z	k (extent)	Cluster p	Peak T	Peak Z	Peak p	Region
1/2/3> 0 back		-36	29	46	22	0.171	3.7	3.35	<0.001	L MFG
		-39	32	31			3.21	2.96	0.002	L MFG
		-33	-55	55	29	0.119	3.54	3.23	0.001	L IP
		-36	-52	46			3.46	3.16	0.001	L IP
		-22	-46	40			2.98	2.78	0.003	L IP
3 > 0 back		-30	-58	58	42	0.096	3.97	3.55	<0.001	L SP
		-36	-52	49			3.59	3.27	0.001	L IP
2 > 0 back		-36	29	43	24	0.152	3.64	3.3	<0.001	L MFG

OC: Ovarian Cancer patients; HC: Healthy Controls; R: Right; L: Left; MFG: Middle Frontal Gyrus; FIO: IP: Inferior Parietal; SP: Superior Parietal

[†]Cluster level extent threshold: $k = 13$

[‡]Voxel-wise height threshold: $p = 0.005$

Table 4

Neurocognitive, Mood and Quality of Life Scores

Measure	Patients		Healthy Controls	
	Mean	SD	Mean	SD
Attention and Executive (z-scores)				
TMT-A	0.44	0.84	0.66	0.99
TMT-B	0.49	0.97	0.47	0.64
Symbol Span (WMS-IV)	0.56	0.81	0.41	0.84
COWA	0.19	0.88	0.34	0.80
BTA	0.04	0.74	0.14	0.66
Verbal Memory (z-scores)				
CVLT-II				
CVLT-L	1.57	0.94	1.58	0.73
CVLT-SDFR	0.97	0.83	1.17	0.64
CVLT-SDCR	0.86	0.54	0.75	0.62
CVLT-LDFR	1.03	0.76	0.94	0.59
CVLT-LDCR	0.86	0.61	0.83	0.64
CVLT-DI	0.72	0.88	0.75	0.62
Mood/Quality of Life (raw scores)				
CES-D	8.78	8.41	10.11	9.70
FACIT - FS	41.06	11.34	N/A	N/A
FACT-O	126.94	17.05	N/A	N/A
SWB	24.50	4.81	N/A	N/A
FWB	23.22	4.53	N/A	N/A
PWB	23.78	4.73	N/A	N/A
EWB	19.94	2.94	N/A	N/A
OCS	35.50	3.94	N/A	N/A

SD = Standard Deviation; TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B; WMS-IV = Wechsler Memory Scale - Fourth Edition; COWA = Controlled Oral Word Association Test; BTA = Brief Test of Attention; CVLT-II = California Verbal Learning Test - Second Edition; CVLT- L = California Verbal Learning Test- Learning; CVLT-SDFR = California Verbal Learning Test- Short Delay Free Recall; CVLT-SDCR = California Verbal Learning Test- Short Delay Cued Recall; CVLT-LDFR = California Verbal Learning Test- Long Delay Free Recall; CVLT-LDCR = California Verbal Learning Test- Long Delay Cued Recall; CVLT-DI = California Verbal Learning Test- Discrimination Index; FACT-O = Functional Assessment of Cancer Therapy-Ovarian; SWB = Social/Family Well-Being; FWB = Functional Well-Being; PWB = Physical Well-Being; EWB = Emotional Well-Being; OCS = Ovarian Cancer Subscale.