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Subtle hippocampal deformities in breast cancer survivors with reduced episodic memory and self-reported cognitive concerns

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ABSTRACT

Cancer survivors have lingering cognitive problems, however the anatomical basis for these problems has yet to be fully elucidated. Clinical studies as well as animal models of chemotherapy have pinpointed cell and volume loss to the hippocampus, however, few studies have performed shape analysis of the hippocampus on cancer survivors. This study used high-dimensional deformation mapping analysis to test whether localized hippocampal deformation differs in breast cancer survivors who received adjuvant chemotherapy coupled with hormone blockade therapy, and if deformation was related to subjective self-reported concerns and cognitive performance. 3 T MRI images were acquired from 16 pre-menopausal breast cancer survivors and 18 healthy controls without a history of cancer. Breast cancer survivors had undergone chemotherapy within the eighteen months prior to the study, and were receiving estrogen-blockade therapy at the time of the study. Automated high-dimensional deformation mapping was used to compare localized hippocampal deformation differences between groups. Self-reported subjective concerns were assessed using Neuro-QOL Cognitive Function assessment, whereas cognitive performance was evaluated using the NIH Toolbox Cognition Battery. Relative to healthy controls, cancer survivors showed significantly more inward hippocampal deformation, worse self-reported cognitive functioning, and inferior episodic memory test score. This study is the first of its kind to examine the relationship between hippocampal deformity and cognitive impairment in cancer survivors.

1. Introduction

The number of people surviving cancer is increasing each year (Edwards et al., 2014). Although advances made in cancer treatments have significantly improved survival and health outcomes, the side effects of cancer treatment can be troubling (Early Breast Cancer Trialists' Collaborative, G., et al., 2012; Midgley and Kerr, 2005). Up to 75% of survivors receiving chemotherapy experience cognitive impairment or a decline in cognitive ability termed Cancer-Related Cognitive Impairment (CRCI[1]) that cannot be solely attributed to depression, stress, or fatigue (Nelson et al., 2007; Vodermaier, 2009; Dietrich et al., 2008). Further, as many as 35% of cancer survivors continue to experience CRCI for months or years following the completion of treatment (Janelsins et al., 2011). Studies examining cognitive impairment in CRCI have found the most commonly affected cognitive domains include attention, processing speed, executive function, and learning and memory (Janelsins et al., 2014; Janelsins et al., 2011; Vardy et al., 2008). CRCI can have severe negative impacts on cancer survivors. Thus, understanding the neural mechanisms underlying CRCI symptoms is imperative for improving quality of life. Advances made in neuroimaging technology may lead to early detection of CRCI in cancer patients, timely treatment, and novel therapies for CRCI in cancer patients.

CRCI involves functional and structural changes in many regions of the brain, including the temporal cortices (Kaiser et al., 2014). Both animal and clinical studies have shown that the hippocampus is

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[1] CRCI is also known as post-chemotherapy cognitive impairment (PCCI), chemobrain, or chemofog.

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particularly vulnerable to adverse effects of cancer treatments (Nobakht et al., 2009; McDonald et al., 2010). Clinical studies have found damage to the hippocampus and its white matter connections, including an overall volume decrease in these regions in survivors who underwent adjuvant chemotherapy (Inagaki et al., 2007; S. Kesler et al., 2013). Hormonal therapy agents may also play a role in hippocampal neuronal loss, synaptic dysregulation and loss, and accelerated beta amyloid accrual (Zhou et al., 2010; Prange-Kiel et al., 2006; Nobakht et al., 2009). Aberrant hippocampal activation has also been observed in CRCI. While some studies reported increased activation in the hippocampus in cancer patients compared with controls during verbal memory tests (S. R. Kesler et al., 2009; Lopez Zunini et al., 2013), others have found decreased hippocampal and parahippocampal activation in cancer patients during recognition and encoding tasks (de Ruiter et al., 2011; Wang et al., 2015). Although past research has provided evidence for hippocampal structural and functional irregularities in CRCI, much more research is needed to understand how the function of the hippocampus changes during cancer treatment.

Preclinical studies have also found hippocampal changes associated with cancer treatments. Christie and colleagues have shown that mice treated with cyclophosphamide and doxorubicin, chemotherapy agents commonly used in breast cancer treatment, performed worse than control mice on cognitive tests of learning and memory that are specifically sensitive to hippocampal function (Christie et al., 2012). Furthermore, adjuvant chemotherapy drugs have been found to be a major cause of hippocampal blood vessel damage (Seigers et al., 2010). A recent preclinical study showed that agents commonly used in chemotherapy decreased neurogenesis and increased cell death in the dentate gyrus of the hippocampus, among other brain regions (Dietrich et al., 2006). Furthermore, Acharya and colleagues found reductions in dendritic complexity, spine density in the granule and pyramidal cells of the dentate gyrus, and CA1 in mice treated with cyclophosphaminde (Acharya et al., 2015).

Advances in neuroimaging techniques have allowed us to study brain morphometry in great detail. Deformation-based analysis such as shape analysis has been utilized to identify local morphological abnormalities of the hippocampus in several disorders including Alzheimer disease, mild cognitive impairment, and schizophrenia (Styner et al., 2004; Costafreda et al., 2011; Csernansky et al., 2005). As a measure of macroscopic volume change, precise localization can be important in detecting early changes in structure and may aid in determining prognosis. To the best of our knowledge, there has been no prior report of detailed deformation analysis of the hippocampus morphology in cancer survivors. The current study applied high-dimensional deformation mapping analysis to test whether hippocampal shape differs in individuals with breast cancer who underwent adjuvant therapy, as compared with healthy controls. We hypothesized that breast cancer survivors would demonstrate more inward hippocampal deformation. We also examined relationships between these deformation abnormalities and cognitive battery performance thought to be hippocampal dependent as well as those that reflect domains implicated in CRCI. Because the hippocampus is primarily involved in episodic memory, our association analysis focused primarily on the relationship between hippocampal deformation and cognitive domains involved in memory. We hypothesized that breast cancer survivors would demonstrate worsened cognitive performance on measures of memory, and that this would be correlated with greater inward shape deformation of the hippocampus. Working memory, attention, processing speed, and executive functioning are domains reported to be impaired in CRCI and/or involve the hippocampus and its connected cortical circuitry. Therefore, we also assessed the relationship between hippocampal deformation and cognitive performance pertaining to these domains. We hypothesized that cancer survivors would demonstrate worse performance on these tests, and that poor performance score would be correlated with greater inward hippocampal shape deformation. Finally, we examined associations between hippocampal shape deformation and self-reported cognitive concerns.

2. Materials and methods

2.1. Participants

The Institutional Review Board at Northwestern University as well as the Robert H. Lurie Comprehensive Cancer Center Scientific Review Committee provided approval for this HIPAA-compliant study. All subjects gave written, informed consent and were compensated for their participation. Sixteen female pre-menopausal breast cancer survivors were recruited from the Northwestern Medicine Enterprise Data Warehouse or via physician referral. Eighteen female healthy controls were recruited from Research Net and community advertisements (posters, craigslist.com).

All cancer survivors had histologically confirmed invasive ductal carcinoma (metastatic and/or localized), metastatic lobular carcinoma or inflammatory breast cancer without brain metastases. All cancer survivors had been diagnosed as stages I-IV at time of treatment. All survivors underwent and had completed systemic chemotherapy interventions within 18 months prior to the study, and were receiving estrogen blockade therapy (Tamoxifen) at the time of the study. Chemotherapeutic drugs used included Anthracycline, Taxane, and Cyclophosphamide. Participants included in the study were between the ages of 18 and 45 years and had normal or corrected vision. Breast cancer survivors were included only if they had a physician-rated Eastern Cooperative Oncology Group (ECOG) performance grade of 0 or 1, (0 – good functional status, 1 – symptomatic and restricted in physically strenuous activity but otherwise ambulatory, 2 – capable of all self-care but requiring rest up to half of the waking day, 3 – requiring rest more than half of the waking day, 4 – bedridden) (Oken et al., 1982). All participants were right handed, reported no history of current or past neurological or psychiatric disorders, and denied having used psychoactive drugs (not including drugs prescribed as part of their estrogen blockade therapy) at the time of the study, and demonstrated MRI safety compatibility. This study recruited only premenopausal women for two important reasons: to avoid potential confounding effect of older age on cognition, and to exclude certain chemical regimens that are often prescribed in older breast cancer patients (e.g. aromatase inhibitors which lower the amount of estrogen in the body).

2.2. Cognitive assessment

The NIH Toolbox for Cognition (www.nihtoolbox.org), a computerized cognitive battery, was administered to participants on site. This battery targets several cognitive domains, including attention, language, processing speed, episodic memory, executive function, and working memory (Weintraub et al., 2013) which are measured by seven subtests. The Toolbox provided standardized scores (SS) for each participant on each subtest, normalized to the NIH Toolbox reference groups by demographic variables: age, ethnicity, gender and level of education. These standardized scores use a T-score matric of 50 as the mean of the reference population and 10 as the standard deviation. Such normalized scores allow quick interpretation of symptoms in comparison to others in the reference population.

Picture Sequence Memory Test is a measure of episodic memory thought to be related to hippocampal functioning (Bauer et al., 2013) and it was used in our primary analysis when testing for group differences and correlation with imaging and self-report measures. For the secondary analysis, we analyzed Flanker Inhibitory Control and Attention Test, Pattern Comparison Processing Speed Test, Dimensional Change Card Sort Test, and List Sorting Working Memory Test because these tests reflect cognitive domains implicated in CRCI such as working memory, attention, processing speed, and executive functioning. Finally, we analyzed the composite measures of fluid, crystalized and overall

cognition. Fluid intelligence composite score was calculated based on an average of the following subtests: Flanker (measure of executive function, attention and inhibitory control), Dimensional Change Card Sort (measure of executive function and set shifting), Picture Sequence Memory (measure of episodic memory), List Sorting (measure of working memory), and Pattern Comparison (measure of processing speed). Crystallized Cognition Composite Score included Picture Vocabulary Test, and Oral Reading Recognition Test (both measures of language). The overall NIH Toolbox Cognitive Function Composite Score is the average of the Crystalized and Fluid Composite Scores (Slotkin et al., 2012).

2.3. Self-reported cognition

Participants completed two computerized adaptive tests to assess subjective daily cognitive function and impairment. Neuro-QOL questionnaires gathered self-reported impairment information surrounding general cognitive concerns, executive function concerns, as well as concerns about anxiety, depression, fatigue, and sleep (www.neuroqol.org) (Cella et al., 2012). Self-reported outcome measures enable "real-time" monitoring of symptoms and quality of life, facilitate comparative research, and improve communication between patients and their healthcare providers. The self-reported general cognitive concerns section consisted of questions related to perceived difficulties in memory, attention and decision making. The executive function concerns section consisted of questions surrounding applications of mental function related to planning, organizing, calculating, working with memory and learning. Participants also completed the PROMIS pain interference scale (www.nihpromis.org) to assess the extent to which pain effects functioning (Cella et al., 2012). Neuro-QOL measurement and PROMIS pain interference instrument yielded standardized T-scores for each participant.

2.4. MRI data acquisition and brain mapping

All participants were pre-screened for MRI safety and were scanned in a single session on a Siemens TIM TRIO scanner with a 32-channel dedicated head coil. Structural imaging was acquired using MPRAGE T1-weighted scans (TR = 2400 ms, TE = 3.16 ms, voxel size = 1 mm^3, FOV = 25.6 cm, flip angle = 8°, 176 sagittal slices). Participants' structural images were processed with the atlas-based Free Surfer and high-dimensional, large-deformation diffeomorphic metric mapping (FS + LDDMM) pipeline (Khan et al., 2008) to produce hippocampal surfaces for each subject. FS + LDDMM consists of Freesurfer (version 5.3) subcortical labeling (Fischl et al., 2002), initial alignment with intensity normalization, and LDDMM (Beg et al., 2005). We have demonstrated that diffeomorphic mapping of structural MRI produced maps between anatomical atlases and subject scans with sub-mm precision that were valid and reliable (Csernansky et al., 2004). We have also demonstrated that surface-based representation of anatomical structures based on these maps were valid, reliable and led to deformation patterns as biomarkers that were disease-specific (Csernansky et al., 1997; Csernansky et al., 2004; Joshi et al., 1997; Miller et al., 2003; Wang et al., 2007; Wang et al., 2006).

2.5. Hippocampal surface processing

The hippocampal surfaces for each participant were rigidly registered to atlas space to compute a population average (Csernansky et al., 2004). Deformation was calculated for each participant from the population average of all participants by quantifying the perpendicular amplitude between surfaces on a vertex-to-vertex level. This amount of perpendicular change between the surfaces was given a positive (outward deformity from population average) or negative (inward deformity) sign. Deformation at each vertex was summed across the entire hippocampal surface and compared between the survivor and control groups. Three subfield boundaries were delineated for visualization purposes as CA1, subiculum, and combined CA2, CA3, CA4 and dentate gyrus (CA2–4 + DG) as previously described (Wang et al., 2003; Duvernoy, 1988). Finally, overall hippocampal volume for each participant was calculated using the volume enclosed within the hippocampal surfaces (Csernansky et al., 2004).

2.6. Statistical analysis

Independent sample *t*-test was used to compare participant demographics. Because the survivors were significantly younger than the controls, all statistical analyses (excluding age-adjusted NIH Toolbox data) were performed with age as a covariate to reduce its potential confounding effect. Univariate ANOVA was used to examine group differences in self-report and cognitive performance measures, controlling for age. To analyze volume and deformation measures, repeated-measures ANOVA was used to examine group (between-subjects factor) and hemisphere (within-subjects repeated factor) differences, controlling for age. Partial correlations between self-report, cognitive performance and deformation measures were calculated using Pearson's product-moment correlation coefficient, controlling for age. All statistical analyses were performed in SPSS (v.21). Further, surface-based analysis was performed using SurfStat (http://www.math.mcgill.ca/keith/surfstat/) to localize significant group differences on deformation. In this procedure, we performed vertex-wise linear mixed effects model analyses. Deformation was used as the dependent variable and discrete group membership was used as the independent variable while age was included as a covariate. This model produces a parameter estimate on the group variable, accounting for age, from which significance (*p* value) was calculated. To control for multiple comparisons, Random Field Theory (RFT) (Robert J. Adler and Society for Industrial and Applied Mathematics., 2010; R. J. Adler and Hasofer, 1976; Worsley, 2005) was applied (within SurfStat). Since signals (i.e., deformations) at adjacent vertices on the surface are necessarily correlated therefore may be spatially continuous (i.e., forming clusters), multiple comparison correction methods such as Bonferroni or false discovery rate (FDR) (Genovese et al., 2002) that only consider the peak of significance at individual vertices are not appropriate (Perneger, 1998). RFT considers both peaks and spatial extent of the signal by modeling the noise as Gaussian random fields (Chumbley and Friston, 2009). This approach produced significant clusters of vertices at a desired family-wise error rate (FWER) (e.g., $p < 0.05$). In addition, the average deformation within the clusters was also calculated for each participant.

3. Results

3.1. Demographics, cognitive performance and self-report measures

Demographic information, as well as cognitive performance and self-report results are presented in Table 1. Survivors (mean age 38.3 years) and controls (mean age 27.2 years) differed significantly in age [$t(32) = 7.00$, $p = 0.001$]. There was no significant difference in years of education [$t(31) = 0.83$, $p = 0.413$] or ethnicity [chi-squared $(5) = 5.29$, $p = 0.382$] between the groups. Time since treatment for the survivors ranged from 6 to 18 months with a mean of 14.43 months. Of the 16 survivors and 18 control participants, one survivor did not complete the cognitive battery or self-report battery and one control participant did not complete the cognitive battery, therefore cognitive performance data represent 15 survivors and 17 controls, self-report data represent 15 survivors and 18 controls and neuroimaging data include all 34 original participants. On Neuro-QOL measures, survivors reported more general cognitive concerns when compared to controls [$F(1,30) = 4.71$, $p = 0.038$]. However, there were no statistically significant differences on Neuro-QOL executive function, anxiety, depression, fatigue, sleep disturbance or pain between groups.

Table 1
Patient demographics, self-report and cognitive performance.

	Oncology group	Control group	*t*-test (df)	*p* value
Demographics Mean (SD) [range]	($n = 16$)	($n = 18$)		
Age	37.93 (5.20) [28–45]	27.17 (4.08) [21–37]	7.0 (32)	0.001[b]
Years of education	16.64 (1.65) [13−20]	16.22 (1.86) [13−21]	0.83 (32)	0.431
Handedness (R/L)	100% R	100% R		–
Gender	100% F	100% F		–
			chi-squared (df)	*p* value
Ethnicity (C;AA;O)	12;1;3	10;2;5	5.29 (5)	0.382
Self-report Mean T-score (SD)	($n = 15$)	($n = 18$)	ANOVA *F* (df)	*p* value
Neuro-QOL				
Applied cognition - general concerns[a]	36.96 (5.96)	42.09 (5.58)	4.71 (1,30)	0.038[b]
Applied cognition - executive function[a]	40.55 (5.93)	43.57 (5.58)	0.76 (1,30)	0.389
Anxiety	53.95 (4.78)	51.37 (4.66)	2.58 (1,30)	0.119
Depression	48.24 (6.08)	44.77 (4.51)	0.38 (1,30)	0.543
Fatigue	47.86 (7.76)	46.30 (6.01)	0.72 (1,30)	0.402
Sleep disturbance	50.37 (9.72)	46.50 (6.10)	0.002 (1,30)	0.965
PROMIS				
Pain interference	47.91 (10.22)	42.71 (5.81)	1.43 (1,30)	0.241
NIH toolbox cognition Mean standard score (SD)	($n = 15$)	($n = 17$)	*t*-test (df)	*p* value
Primary cognitive variables				
Picture sequence memory test (EM)	96.96 (12.73)	107.05 (13.01)	2.13 (30)	0.041[b]
Secondary cognitive variables				
Flanker inhibitory control and attention test (Att., EF)	95.61 (7.68)	95.29 (12.02)	0.09 (30)	0.930
Pattern comparison processing speed test (PS)	88.51 (12.21)	82.65 (10.03)	1.49 (30)	0.147
Dimensional change card sort (EF)	95.92 (8.57)	98.72 (11.84)	0.76 (30)	0.455
List sorting working memory test (WM)	101.84 (12.29)	107.03 (13.43)	1.10 (30)	0.282
The following are included subtests and composites from the NIH toolbox				
Picture vocabulary test (lang.)	134.54 (20.24)	136.02 (17.49)	0.22 (30)	0.824
Oral reading recognition test (lang.)	111.61 (10.93)	118.77 (15.11)	1.52 (30)	0.140
Cognition total	120.64 (18.45)	129.43 (16.59)	1.42 (30)	0.166
Fluid intelligence composite	96.70 (13.55)	98.30 (16.95)	0.29 (30)	0.773
Crystalized intelligence composite	127.63 (17.29)	134.24 (17.25)	1.08 (30)	0.289

Demographic and self-report information for oncology survivors and control participants. Group comparisons of self-report measures were controlled for age. NIH Toolbox measures are reference adjusted for age, ethnicity, gender and level of education. Additional tests (picture vocabulary, oral reading recognition) and composite scores included in the NIH Toolbox are also listed here. Lower scores indicate worse performance on NIH toolbox tests.

C = Caucasian, AA = African American, O = Other/Declined to Answer, EM = episodic memory, EF = executive function, Att. = attention, WM = working memory, PS = processing speed, lang. = language.

[a] Lower scores signify worse perceived functioning, in all other self-report (including pain interference), lower scores signify fewer symptoms (i.e. less anxiety).

[b] Statistically differs between groups.

Survivors demonstrated significantly lower scores on the episodic memory subtest of the age-adjusted NIH Toolbox Cognitive Battery (Picture Sequence Memory test, $t(30) = 2.13$, $p = 0.041$). No group differences in demographically corrected cognitive performance were observed in our secondary analyses which included the attention, processing speed and executive functioning subtests. No group differences were observed in our tertiary analysis which included the remaining subtests and composite scores of cognitive performance obtained with the NIH Toolbox Cognition Battery.

3.2. Group comparison of hippocampal deformation and volume

Hippocampal deformation results are listed in Table 2. Survivors showed significantly more inward deformation across both hemispheres when compared to controls, covarying for age (survivors mean = −0.068 mm, std = 0.13; controls mean = 0.026 mm, std = 0.12; $F(1,31) = 5.76$, $p = 0.023$). There was no significant difference in localized deformity between hemispheres [$F(1,31) = 0.402$, $p = 0.31$)], however, the right hippocampus was more inwardly deformed compared to controls after controlling for age [$F(1,31) = 8.156$, $p = 0.008$], whereas the left was not [$F(1,31) = 2.421$ $p = 0.130$]. Surface analysis yielded three significant clusters (Fig. 1) of vertex-wise differences in hippocampal deformation in survivors compared to controls after controlling for age. The colors represent parameter estimates on the group variable (t-values) of deformation amplitudes with blue and purple representing inward deformation and red and orange colors represent outward deformation of survivors compared with controls.

Total average hippocampal volume (left and right combined) was significantly smaller in survivors (mean = 2102 mm^3, std = 192) compared to controls (mean = 2247 mm^3, std = 173) after controlling for age [$F(1,31) = 6.90$, $p = 0.013$]. We found no significant mean volume difference between left and right hemispheres.

3.3. Correlations of self-report, cognitive performance and deformation

No significant correlations were found between age-adjusted inward hippocampal deformity and Picture Sequence Memory Test, nor with remaining NIH toolbox subtests, i.e., measures of fluid, crystalized, or total composite cognition in survivors or controls (see Table 3, significance level set at $p < 0.001$ to account for multiple comparisons). No significant correlations were found between inward hippocampal deformity and any of the self-report outcome measures after controlling for age. No correlations were found between any of the age-adjusted self-report outcome and NIH toolbox measures.

4. Discussion

Previous animal studies have indicated that adjuvant chemotherapy and hormone depletion may inhibit neurogenesis of the hippocampus, alter blood supply through vessel damage, and cause white matter damage (Christie et al., 2012; Seigers et al., 2008; Inagaki et al., 2007; de Ruiter et al., 2012). Consistent with these previous results, we find that breast cancer survivors had smaller total hippocampal volume than healthy controls. Complementary to the difference in total hippocampal volume, we found that survivors demonstrated more inward deformation in several locations along the hippocampus (see Fig. 1) when compared to controls. We used high-dimensional deformation mapping to localize this change in volume to specific regions of the hippocampal surface. As hypothesized, we found that breast cancer

Table 2
Local hippocampal deformations in mm^3, mean (SD).

	Oncology group ($n = 16$)	Control group ($n = 18$)	*F* test (df)	*p* value
Hippocampal deformation				
Combined right and left	−0.068 (0.13)	0.026 (0.12)	5.76 (1,31)	0.023[a]
Right	−0.083 (0.13)	0.032 (0.13)	8.16 (1,31)	0.008[a]
Left	−0.053 (0.18)	0.020 (0.11)	2.42 (1,31)	0.130

Total combined, right and left hippocampal deformation (in mm^3) for breast cancer survivors and control participants after controlling for age.

[a] Statistically different between groups.

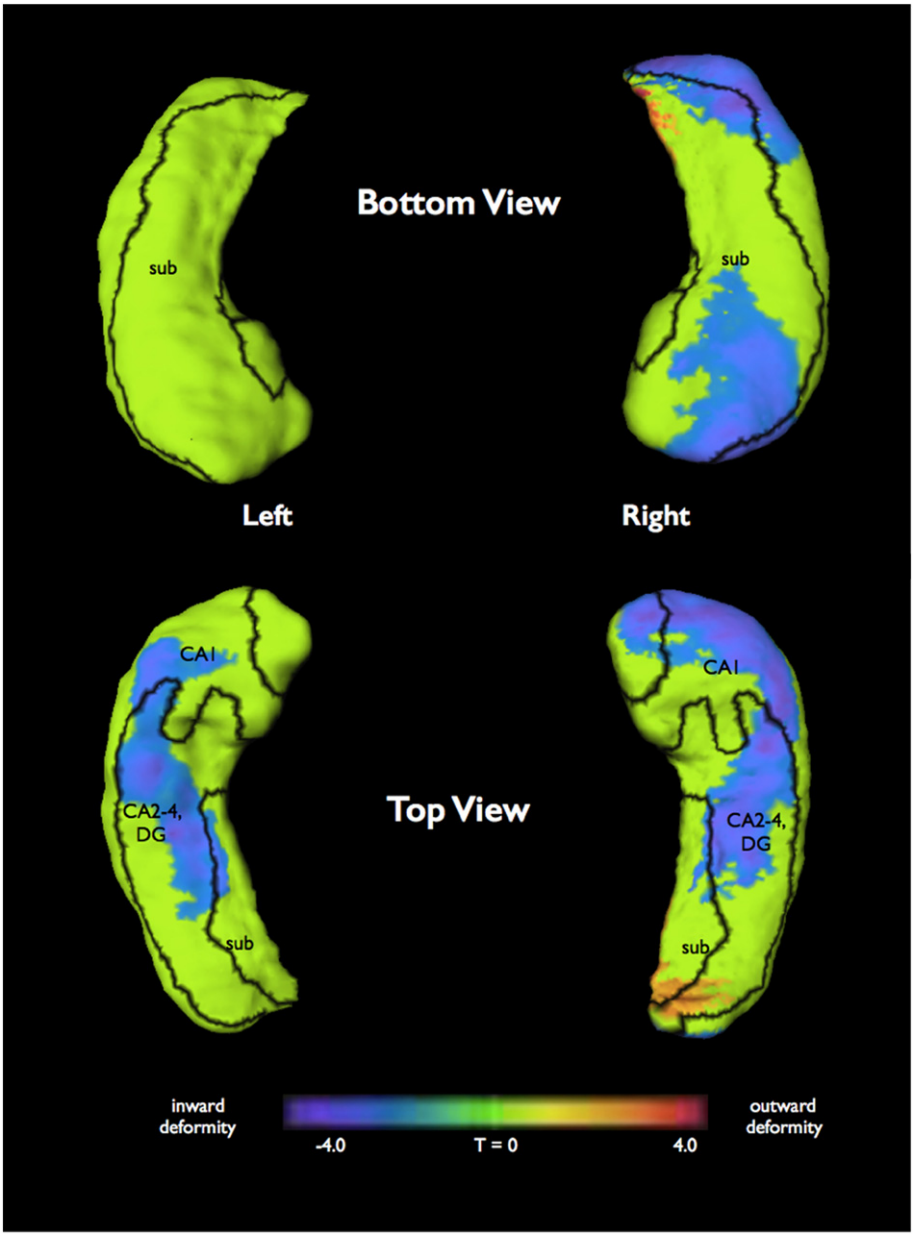

Fig. 1. Hippocampal deformity clusters after controlling for age. Inward deformation (blue and purple) as calculated from parameter estimates (t-values) of a vertex-wise difference in the deformation amplitude between controls and survivors (multiple comparison correction by Random Field Theory, FWER $p < 0.05$). Surface analysis yielded three significant clusters. The first cluster had 1651 vertices (out of 13,322), the second 576, and the third 714, with cluster-level p values of 5.503e-06, 0.000606, and 0.00385, respectively (SurfStat results data).

Table 3
Correlations between age-adjusted cognitive performance measures and age-adjusted average inward hippocampal deformation across the significant clusters in the cancer survivors ($n = 15$).

NIH toolbox measures	Hippocampal deformation	
	R^2	p value
Picture sequence memory test (EM)	−0.377	0.166
Flanker inhibitory control and attention test (Att., EF)	0.159	0.588
Pattern comparison processing speed test (PS)	0.552	0.033*
Dimensional change card sort (EF)	0.097	0.732
List sorting working memory test (WM)	−0.295	0.285
Picture vocabulary test (lang.)	0.148	0.599
Oral reading recognition test (lang.)	−0.030	0.915
Cognition total	−0.019	0.947
Fluid Intelligence composite	−0.024	0.933
Crystalized Intelligence composite	0.089	0.207

* $p < 0.05$.

survivors receiving adjuvant chemotherapy and estrogen blockade therapy exhibit more inward deformation of the hippocampus, with significant inward deformation in the right hippocampus relative to controls. This finding is consistent with previous studies that found right hippocampal grey matter reductions (Lepage et al., 2014), however, it is in contrast to several studies that found the left hippocampus and para-hippocampus to be affected to a greater extent (S. Kesler et al., 2013; Inagaki et al., 2007). Still, another group has reported that left and right hippocampi are affected equally by breast cancer (Bergouignan et al., 2011).

Subfield boundaries were drawn on the surface of the hippocampus to assess whether deformation is restricted to a particular subfield; we found no such restriction with clusters of deformation bridging all three subfield demarcations, especially in the right hippocampus. This does not necessarily contradict animal studies that identified volume loss in the dentate gyrus since no other subfields of the hippocampus were examined (Dietrich et al., 2006).

Consistent with many studies of CRCI, cancer survivors in this study reported a significant increase in global cognitive concerns when compared to controls. It is suggested that the number of subjective cognitive complaint is higher than the number of cognitive impairment identified by cognitive battery (for a comprehensive review see Hutchinson et al., 2012). In fact, the National Cancer Institute recently issued a statement suggesting that traditional cognitive performance tests designed to detect more severe impairments (e.g. dementia, or traumatic brain injury) may not be suitable to detect more subtle cognitive impairments found in CRCI (FOA PAR-16-212: Leveraging Cognitive Neuroscience to Improve Assessment of Cancer Treatment-Related Cognitive Impairment). However, in the current study, consistent with subjective reports of increased general cognitive concerns, worse episodic memory performance on the NIH Toolbox battery was observed in breast cancer survivors when compared to controls. Contrary to our hypothesis, no group differences were observed in other cognitive domains including working memory, attention, processing speed, and executive functioning. Additionally, no reliable differences were observed between groups on other cognitive performance subtest or composite measures of cognition.

The NIH toolbox Picture Sequence Memory Test subtest targets episodic memory, which is more often implicated in left hippocampal function, whereas the right hippocampus is associated with spatial memory and recalling locations within an environment (Burgess et al., 2002). Future studies should explore the relationship between CRCI and cognitive performance that are thought to be dependent on right-hippocampal functioning such as the Rey Osterrieth Complex Figure Test or the Brief Visuospatial Memory Test-Revised. Tests that rely less on verbal memory and more on spatial memory may help further our understanding of the relationship between hippocampal structure and cognitive difficulties found in CRCI.

Although no association was observed between hippocampus deformation and cognition, it is possible that the demonstrated structural change in the hippocampus may elicit functional changes in breast cancer survivors. A study by Ryals et al. (2015) found that these survivors exhibit deficits in overt and covert spatial familiarity-based recognition, which corresponded to decreased hippocampal activity during memory testing. Interestingly, the location of the functional hypo-activity aligns with the right dentate gyrus/CA2–4 deformation location. Therefore, vertex-wise deformities reported in the present study would allow for structural-functional co-localization (i.e. providing sub-regional seeds for functional analysis such as resting state intrinsic connectivity or task based activity) which may be useful for characterizing more precise structure-function mechanisms.

A limitation of the current study is that the observed changes in localized hippocampal volume may be due to the survivors' chemotherapy regimen, the effects of ongoing Tamoxifen treatment, or a combination of the two; future studies should record and analyze differences in stage, specific type of cancer, and chemotherapy regimen to ascertain their effects on CRCI. Additionally, although the effect of age has been controlled for in all statistical analysis, recruiting aged-matched controls would be beneficial for future studies. Due to the cross-sectional study design, we cannot determine whether breast cancer survivors have cognitive decline relative to their baseline, and whether volume and/or deformation differences were present prior to cancer treatment. The small sample size in this study is another limiting factor which warrants cautious interpretation of the study findings. Future research direction should focus on parsing apart the effects of hormonal therapy from chemotherapy and replicate current study findings using a larger sample size and a longitudinal design.

5. Conclusions

To our knowledge, this study is the first of its kind to analyze hippocampal deformity in subjective CRCI in breast cancer survivors. We observed significant morphological differences in hippocampal structure, increased level of self-reported cognitive difficulties and worse episodic memory performance in breast cancer survivors. Identifying the mechanism by which brain structural changes affect cognitive functions and understanding why CRCI symptoms persist after completion of treatment may lead to early detection of CRCI in cancer patients, timely treatment, and informed therapeutic options for CRCI in cancer patients, thus significantly improve quality of life for cancer survivors.

Compliance with ethical standards

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Conflicts of interest

Alexandra C. Apple, Anthony J. Ryals, Kate I Alpert, Lynne I. Wagner, Pei-An Shih, David Cella, Frank J. Penedo, Joel L. Voss, and Lei Wang declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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