

Hippocampal functional connectivity is related to self-reported cognitive concerns in breast cancer patients undergoing adjuvant therapy



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ABSTRACT

Nearly three out of four survivors experience Cancer-Related Cognitive Impairment (CRCI) for months or years following treatment. Both clinical and animal studies point to the hippocampus as a likely brain region affected in CRCI, however no previous study has investigated the functional connectivity of the hippocampus in CRCI. We compared hippocampal connectivity in cancer survivors and healthy controls and tested the relationship between functional connectivity differences and measures of objective and subjective cognition. Exploratory analysis of inflammatory markers was conducted in a small subset of participants as well. fMRI data were acquired during a memory task from 16 breast cancer survivors and 17 controls. The NIH Toolbox was used to assess cognitive performance and Neuro-QoL was used to measure self-reported cognitive concerns. Whole-brain group-level comparisons identified clusters with different connectivity to the hippocampus in survivors versus controls during task. Average connectivity was extracted from clusters of significant difference between the groups and correlated with cognitive performance and subjective report. Survivors performed worse on a test of episodic memory and reported greater cognitive concern than controls. Exploratory analysis found higher IL6 in cancer survivors compared to controls. Cancer survivors demonstrated higher connectivity of hippocampus with left cuneus, left lingual, left precuneus, and right middle prefrontal gyrus compared with controls. In survivors, higher task-related hippocampal-cortical connectivity was related to worse subjective measures of cognitive concern. Of the four significant clusters, higher connectivity of the precuneus with hippocampus was significantly associated with worse cognitive concern in survivors. The observed greater hippocampal-cortical connectivity in survivors compared to controls is the first reported fMRI biomarker of subjective concern, and may represent a compensatory response to cancer and its treatments. This compensation could explain, in part, the subjective feelings of cognitive impairment that were reported by survivors.

1. Introduction

Up to 75% of survivors experience Cancer-related Cognitive Impairment (CRCI) for months or years following treatment (Ahles et al., 2012; Janelins et al., 2014). CRCI can have significant negative impacts on survivors, including problems with treatment adherence and decreased quality of life (Janelins et al., 2014). Developing methods to detect and mitigate CRCI is essential to improving cancer survivors' quality of life.

Both objective and subjective cognitive impairment have been reported in survivors following cancer treatment (Biglia et al., 2012; Hurria et al., 2006; Hutchinson et al., 2012; Jenkins et al., 2006; O'Farrell et al., 2013; Scherling and Smith, 2013; Shilling and Jenkins, 2007); the most frequently impaired cognitive domains include

working and long-term memory, executive functioning, processing speed and attention (Ahles et al., 2010; Bender et al., 2006; Debes et al., 2010; Hermelink et al., 2007; Janelins et al., 2011; Wefel et al., 2010). However, most studies have found that objective cognitive deficits measured through laboratory tests did not represent and could not explain the subjective cognitive complaints reported by cancer survivors (Hutchinson et al., 2012; Jansen et al., 2011; O'Farrell et al., 2013). It would be important to understand the neural mechanisms related to CRCI, identify the neurophysiological correlates of CRCI, and develop neuroimaging biomarkers of both objective and subjective deficits in CRCI.

Chemotherapy, hormone therapy and other cancer treatments are thought to impair cognitive functioning by altering specific brain structures and/or impairing connectivity between brain regions

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<https://doi.org/10.1016/j.nicl.2018.07.010>

Received 17 December 2017; Received in revised form 28 June 2018; Accepted 10 July 2018

Available online 12 July 2018

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(Meyers, 2008). Collectively, neuroimaging studies suggest that adjuvant cancer therapies induce dysregulations to the brain's network hubs, including the hippocampus, prefrontal cortex, and the default mode network (Bruno et al., 2012; Chen et al., 2017; de Ruiter et al., 2011; Dumas et al., 2013; Ferguson et al., 2007b; Kesler et al., 2009; Kesler et al., 2013b; Meyers, 2008). The hippocampus, which is of critical importance to memory, has been shown to be vulnerable to the effects of cancer treatments (Inagaki et al., 2007; Kesler et al., 2013a). Both human and animal studies have shown associations between chemotherapeutic treatments with common chemotherapeutics and a variety of abnormal changes to the hippocampus, including loss of gray and white matter, decreased neurogenesis, increased cell death, and blood vessel damage (Dietrich et al., 2006; Inagaki et al., 2007; Nobakht et al., 2009; Seigers et al., 2010).

Recent work by our group revealed a localized loss of hippocampal volume in breast cancer survivors undergoing adjuvant therapy as compared with healthy controls (Apple et al., 2017). Moreover, the hippocampal structural loss co-localized to a region of decreased activity in the same survivors during a covert spatial memory task using functional magnetic resonance imaging (fMRI) (Ryals et al., 2015a). Most interestingly, survivors and controls did not differ in cognitive task performance, and that none of the measures of structural loss or reduced activity were correlated with objective tests or subjective Patient Reported Outcomes (PRO) of cognition in the survivors. To gain deeper insight into a potential brain-based mechanism in the context of CRCI, we sought to explore ways in which the brain may compensate for structural and functional deficits while maintaining cognitive task performance.

In fMRI studies reported in the literature (Bruno et al., 2012; de Ruiter et al., 2011; Kesler, 2014), no increases in task-related activity has explained a compensatory response in CRCI, such as ones reported by Dickerson and colleagues in individuals with mild cognitive impairment (Dickerson et al., 2005). Functional connectivity, on the other hand, could be investigated for its potential role in compensation. Research has shown that improved cognitive performance can be attributable to increased resting-state network functional connectivity. Specifically, research on healthy adults has found a relationship between higher performance on perceptual tasks and increased functional connectivity between visual and prefrontal regions (Baldassarre et al., 2012). A study in healthy adults using noninvasive high-frequency repetitive transcranial magnetic stimulation showed improved memory was accompanied by strengthened hippocampal-cortical functional connectivity (Wang et al., 2014). In a study by Seeley and colleagues, stronger functional connectivity within the executive-control network was related to higher executive task performance in younger healthy adults (Seeley et al., 2007). Studies in aging populations have found increased connectivity in the default mode network in healthy older adults compared with MCI subjects (Dong et al., 2012). In the current study, we compared hippocampal functional connectivity during the covert spatial memory task (Ryals et al., 2015a) between survivors and healthy controls, and hypothesized that compensatory differences in task-based functional connectivity would be observed in survivors and they would be related to measures of objective and subject tests of cognition. Additionally, research has found an association between cytokine concentration and cognitive performance in breast cancer patients (Cheung et al., 2015). For example, increased sTNFRI and sTNFRII concentrations have been associated with poorer visual memory performance (Williams et al., 2018). To explore relationships of connectivity imaging markers with systemic inflammatory markers as a potential mechanism for CRCI, several pro-inflammatory cytokine markers including interleukin-1 (IL-1), IL-6, and IL-10 as well as c-reactive protein (CRP) and tumor necrosis factor (TNF α) were collected and analyzed in the survivors. Relationships between elevated cytokines and measures of imaging, cognition and self-report were also explored.

2. Participants and methods

2.1. Participants

The Institutional Review Board at Northwestern University approved this study in accordance with the Declaration of Helsinki. As described in our previous paper (Apple et al., 2017), 16 pre-menopausal breast cancer survivors and 18 healthy controls gave written informed consent and were enrolled into the study. Breast cancer survivors had invasive ductal carcinoma, metastatic lobular carcinoma or inflammatory breast cancer without brain metastases, confirmed with histology. All survivors had completed systemic chemotherapy interventions within 18 months of the study, and were undergoing estrogen blockade therapy (Tamoxifen) at the time of the study. Only breast cancer survivors who scored a 0 or 1 on the physician-rated Eastern Cooperative Oncology Group (ECOG) were included in the study (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). As an exploratory analysis, inflammatory markers were collected in a subset of the participants. Serum was harvested and assayed in duplicate by custom multiplex immunoassay (MesoScale Discovery V-Plex) on a SECTOR Imager 2400A (MesoScale Discovery) and IL-10 and IL-10 M450 from 11 cancer survivors and 12 controls, and IL1 β , IL1 β M450, IL6, IL6 M450, TNF α , TNF α M450, CRP and CRP M450 were collected from 12 participants per group.

Participants were right handed 18–45 years old, had normal or corrected vision, reported no history of current or past neurological or psychiatric disorders or psychoactive drugs at the time of the study. Of the 18 controls, one was unable to complete fMRI, and one did not complete the cognitive testing. Of the 16 survivors, one did not complete self-report questionnaires and cognitive testing. Objective cognitive performance data included 15 survivors and 17 controls, self-report data included 15 survivors and 18 controls, and fMRI data included 16 survivors and 17 controls.

2.2. Cognitive assessment

The NIH Toolbox Cognition Battery (www.nihtoolbox.org) (Weintraub et al., 2013) was administered to participants on site, consisting of seven subtests including picture Sequence Memory Test (measure of episodic memory thought to be related to hippocampal functioning (Bauer et al., 2013)), List Sorting Working Memory Test (for working memory), Flanker Inhibitory Control and Attention Test (for executive function, attention and inhibitory control), Pattern Comparison Processing Speed Test (for processing speed), and Dimensional Change Card Sort Test (for executive function and set shifting), Picture Vocabulary Test, and Oral Reading Recognition Test (for language). Raw scores on each subtest were standardized to a standardized T-scores with a normative mean of 50 and a standard Deviation of 10.

2.3. Self-report measures

Participants completed two computerized adaptive tests to assess their subjective daily function, Neuro-QoL and PROMIS pain interference. Neuro-QoL (www.neuroqol.org) reports cognitive, emotional, and functional concerns in the past week. PROMIS pain interference (www.nihpromis.org) assesses the extent to which pain affects their functioning (Cella et al., 2012). In Neuro-QoL, the Applied cognition-General Concerns subtest assesses cognitive functioning including perceived difficulties in memory, attention and decision making (e.g. “I had to read something several times to understand it,” “I had difficulty doing more than one thing at a time,” “I had trouble thinking clearly,” “My thinking was slow,” “I had trouble remembering new information, like phone numbers or simple instructions,” “I had to work really hard

to pay attention or I would make a mistake,” and “I had trouble concentrating”) on a scale from one to five. The Neuro-QoL Applied cognition-Executive Function subtest assesses applications of mental function related to planning, organizing, calculating, working with memory and learning (e.g. “How much difficulty currently having checking the accuracy of financial documents? counting the correct amount of money when making purchases? reading and following complex instructions? planning for and keeping appointments that are not part of your weekly routine? managing your time to do most of your daily activities? taking care of complicated tasks like managing a checking account or getting appliances fixed? keeping important personal papers such as bills, insurance documents and tax forms organized? learning new tasks or instructions?”). Neuro-QoL also contains self-reported anxiety, depression, fatigue, and sleep subtests (Cella et al., 2012). PROMIS pain interference scale (www.nihpromis.org) was to assess the extent to which pain affects functioning on a 5-point Likert scale (e.g. “How difficult was it for you to take in new information because of pain?” “How much did pain interfere with your enjoyment of life?”) (Cella et al., 2012). Neuro-QoL and PROMIS pain interference yielded T-scores for each participant (standardized with a mean = 50, sd = 10).

2.4. MRI data acquisition and processing

Participants were scanned on a 3T TIM Trio scanner (Siemens Medical Systems) with a 32-channel head coil. Anatomical MRI was acquired using a high-resolution 3D T1-weighted MPRAGE sequence (TR = 2400 ms, TE = 3.16 ms, voxel size = 1 mm³, FOV = 25.6 cm, flip angle = 8°, 176 sagittal slices, slice thickness = 1 mm, matrix = 256 × 256, sagittal, time = 8:09 min). Three fMRI runs were acquired during a configural covert spatial memory task (Ryals et al., 2015a). Each of the three runs consisted of a study and test block. During the study block, participants viewed 12 scenes for 8 s each. During the test phase, participants viewed 24 novel scenes in which half of the scenes were similar in configuration to the 12 study scenes and the other half were configurally different or “new.” After each scene, participants rated how familiar the scene was on a 4-point scale. See Supplemental Fig. 1 (Ryals et al., 2013, 2015b) for more details. All images were acquired axially, parallel to the anterior-posterior commissure plane using a T2* echo-planar sequence (TR = 2000 ms, TE = 20 ms, voxel size = 1.7 × 1.7 × 3 mm³, FOV = 220 × 220 mm, flip angle = 80°, time = 16 min each run). The first 3 images of each run were excluded to account for nuclear magnetic resonance and eddy-current equilibrium leaving a total of 1464 images for analysis.

Functional data preprocessing and analyses were conducted using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Preprocessing included slice-timing and motion correction, registration, spatial smoothing to 8-mm FWHM, and alignment to Talairach-Tournoux template. Images were censored if their translational or rotational change was > 0.7 mm or radians. The median percentage of images that were censored for the survivors and controls were 0.51% and 1.51% respectively (survivors mean = 1.69%, interquartile range = 1.57%; control mean = 2.22%, interquartile range = 2.08%). No participants had > 15% of their images censored, therefore all subjects were included in subsequent analysis.

Multiple linear regression was used to model motion parameters with a hemodynamic response function and its temporal derivative to yield least squares estimates of the linear regression coefficients as well as the residual time series used in all subsequent analyses. Average signals from the whole brain, cerebrospinal fluid, and white matter were regressed from the residual time series followed by temporal filtering (0.009–0.08 Hz). For task-based functional connectivity, bilateral hippocampal segmentation extracted from the Talairach atlas was used to extract the time series for each participant. The mean time series across the seed was cross-correlated to every other gray matter voxel and then z-transformed. These task-based hippocampal functional

connectivity maps were used in subsequent statistical analyses.

2.5. Statistical analysis

Group differences on demographic, cognitive, self-report and inflammatory variables were tested with *t*-tests, chi-square tests and *F* tests where appropriate. Group differences on hippocampal functional connectivity were tested with analysis of variance (ANOVA) using AFNI's *3dttest++*. Pearson correlations were used in the exploratory analysis examining the relationship between inflammatory markers and imaging, cognitive and self-report measures in the survivor group. AFNI's *3dClustSim* (Forman et al., 1995) was used to determine a minimum cluster size of ≥ 131 contiguous voxels at uncorrected voxel threshold of *p* = .005 for a corrected *p* = .05. Clusters showing significant difference between the groups were reported and used to further examine relationships with objective or subjective measures that differed between groups using multiple linear regression models. In addition, the average functional connectivity measures across all significant clusters was related to objective and subjective measures using linear regression models. Since age differed between groups (see results), we controlled for the effect of age in the following two ways: 1) Within the NIH Toolbox Cognition Battery (e.g. Picture Sequence Memory test), age was controlled for by using Standard Scores, typically used to reflect performance independent of age. 2) For measures that did not have standardized scores available, i.e. self-report measures and fMRI measures, age was included as a statistical covariate.

3. Results

3.1. Demographic, cognitive, self-report and inflammatory measures

Demographic, cognitive and self-report data can be found in Table 1. Survivors were 10 years older than controls [*t*(31) = 6.69, *p* = .001], therefore, all subsequent analyses were performed while accounting for age. Survivors reported greater cognitive concern than controls [*F*(1,30) = 4.71, *p* = .038], but not in perceived executive function, anxiety, depression, fatigue, sleep disturbance or pain. Episodic memory performance (i.e., the Picture Sequence Memory Test from the NIH Toolbox Cognition Battery) was significantly poorer in survivors [*t*(30) = 2.13, *p* = .041]. No group differences were observed for the rest of the NIH Toolbox Cognition Battery. Exploratory analysis looking at pro-inflammatory markers found higher levels of IL6 concentration in the survivors (*t* = 2.54, *p* = .019). No other group differences in inflammatory markers were observed.

3.2. Hippocampal connectivity: group comparison

Hippocampal functional connectivity maps for survivors and controls (Fig. 1) revealed expected patterns in both groups based on previous literature (i.e. strong intra-hippocampal connectivity) (Ranganath et al., 2005; Stein et al., 2000). Whole-brain group-level comparisons identified four clusters with significantly different hippocampal connectivity (Table 2). After controlling for differences in age, cancer survivors showed higher hippocampal connectivity in the left cuneus, left lingual, left precuneus, and right middle frontal gyrus compared to controls (Figs. 2 and 3).

3.3. Hippocampal connectivity: correlations

To analyze relationships between hippocampal connectivity and the significant objective and subjective group differences (NeuroQoL general cognition measure and NIH Toolbox episodic memory subtest), age-corrected residuals for both the connectivity in the significant clusters as well as the general cognition self-report measures were used in linear regression models. Linear regression predicting self-reported cognitive concerns found a significant group by connectivity interaction

Table 1
Patient demographics, self-report and cognition.

	Oncology group (n = 16 ^a)	Control group (n = 18)	t-test (df)	p value	Cohen's D
Demographics mean (SD) [Range]					
Age	38.31 (5.25)	27.42 (4.06)	6.69 (32)	0.001 ^b	2.321
Years of education	16.73 (1.62)	16.22 (1.86)	0.831 (31)	0.413	0.292
Handedness (R/L)	100% R	100% R		–	–
Self-report mean T-score (SD)					
Neuro-QoL					
Applied cognition - general concerns ^a	36.96 (5.42)	42.08 (4.18)	4.71 (1,30)	0.038 ^b	1.058
Applied cognition - executive function ^a	40.55 (5.96)	43.56 (5.58)	0.76 (1,30)	0.389	0.521
Anxiety	53.95 (4.78)	51.37 (4.66)	2.58 (1,30)	0.119	0.547
Depression	48.24 (6.08)	44.77 (4.51)	0.38 (1,30)	0.543	0.648
Fatigue	47.86 (7.76)	46.30 (6.01)	0.72 (1,30)	0.402	0.225
Sleep disturbance	50.37 (9.72)	46.50 (6.10)	0.002 (1,30)	0.965	0.477
PROMIS					
Pain interference	47.91 (10.22)	42.71 (5.81)	1.43 (1,30)	0.241	0.626
NIH toolbox mean standard score (SD)					
(n = 15)					
Picture Sequence Memory Test (EM)	96.96 (13.73)	107.05 (13.01)	2.13 (30)	0.041 ^b	0.754
Flanker Inhibitory Control and Attention Test (Att., EF)	95.61 (7.68)	95.29 (12.02)	0.09 (30)	0.930	0.032
Pattern Comparison Processing Speed Test (PS)	88.51 (12.21)	82.65 (10.03)	1.49 (30)	0.147	0.524
Dimensional Change Card Sort (EF)	95.92 (8.57)	98.72 (11.84)	0.76 (30)	0.455	0.271
List Sorting Working Memory Test (WM)	101.84 (13.29)	107.03 (13.43)	1.10 (30)	0.282	0.388
Picture Vocabulary Test (lang.)	134.54 (20.24)	136.03 (17.49)	0.22 (30)	0.824	0.079
Oral Reading Recognition Test (lang.)	111.61 (10.93)	118.77 (15.11)	1.52 (30)	0.140	0.543

% = years of education were only recorded for 15 survivors; 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, lower scores signify fewer symptoms (i.e. less anxiety); NIH toolbox measures are adjusted for age, ethnicity, gender and level of education.

^b Statistically differs between groups.

[F(1,31) = 4.58, $p = .041$]. However, linear regression predicting performance on the episodic memory subtest of the NIH toolbox was not significant for the interaction between group and connectivity. To explore this relationship further, linear regression models were run in each group separately. Two analyses per group were run between average connectivity of the four clusters and the general cognitive concerns (Fig. 4). Analyses revealed that higher connectivity averaged across all of the above four clusters (left cuneus, left lingual, left precuneus, and right middle frontal gyrus) was significantly associated

with lower general cognitive concerns score for the survivors [F(1,13) = 5.43, $p = .037$, $R^2 = 0.29$, standardized beta = -0.54]. Multiple linear regression revealed that only the hippocampal-precuneus connectivity was significantly associated with subjective cognitive concern scores ($p = .004$) out of the four clusters [overall model F(4,10) = 4.66, $p = .022$, $R^2 = 0.65$]. Analyses did not reveal a significant relationship between hippocampal connectivity and the Picture Sequence Memory cognitive test. No significant relationships were observed in the control group.

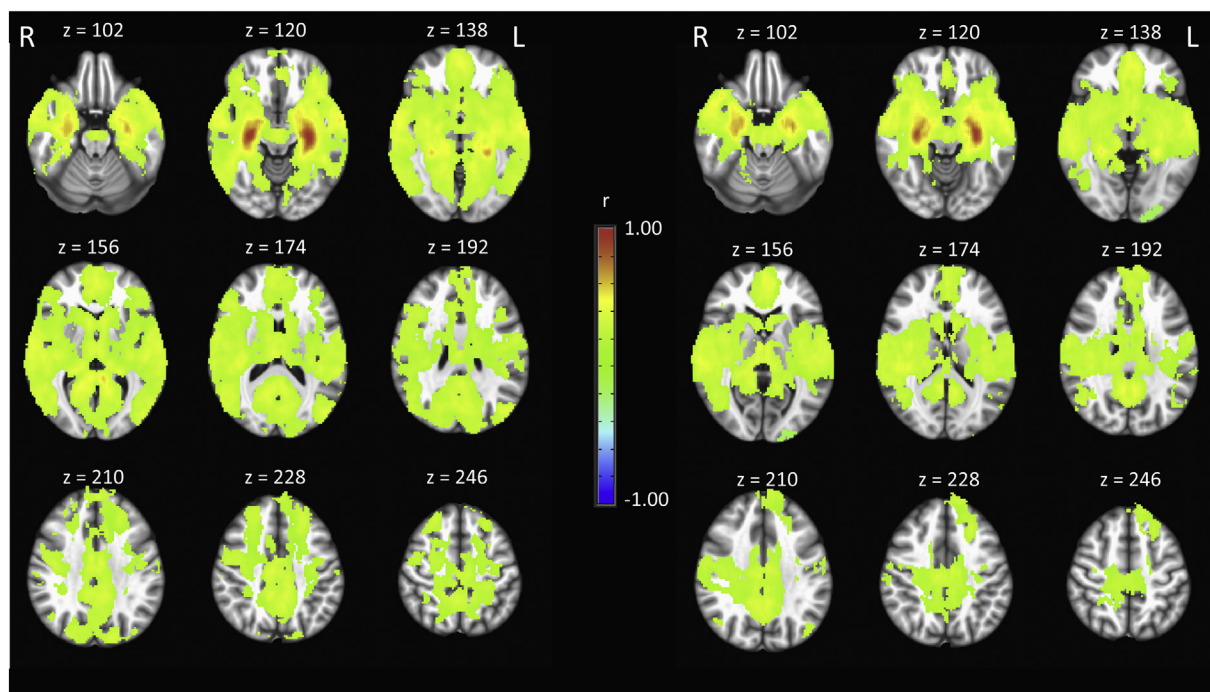


Fig. 1. Hippocampal functional connectivity map within groups of cancer survivors (left panel) and controls (right panel). All voxels represent positive hippocampal connectivity with warmer colors indicating higher correlations. The statistical threshold was set at $p = .005$ cluster size > 131 . View is radiological.

Table 2
Clusters showing group differences in hippocampal-cortical functional connectivity between cancer survivors and controls.

Region	BA	Cluster Size	Coordinates (Talairach RAI)
Left Cuneus/Middle Occipital Gyrus	18, 19	360	+10 +100 +16
Left Lingual Gyrus	17, 18	334	+6 +86 -14
Left Precuneus/Cuneus	7, 19, 18, 31	332	+20 +78 +34
Right middle frontal/ Superior frontal	10, 46	153	-40 -52 +22

Voxels size = 2 mm³; BA = Brodmann's area.

Although exploratory analysis found higher levels of IL6 concentration in the survivors ($t = 2.54, p = .019$), linear regression predicting IL6 concentration was not significant for the interaction between group and self-reported cognitive concern or episodic memory subtest of the NIH toolbox.

4. Discussion

In breast cancer survivors receiving adjuvant therapy, we previously reported localized hippocampal volume loss and reduced hippocampal activity in the absence of significant worsening performance in a covert spatial memory task, as compared with healthy controls (Apple et al., 2017; Ryals et al., 2015a). In the current study, we examined whether differences in hippocampal functional connectivity may be a marker of a compensatory mechanism for the structural and functional deficits in order to maintain task performance in the same group of breast cancer

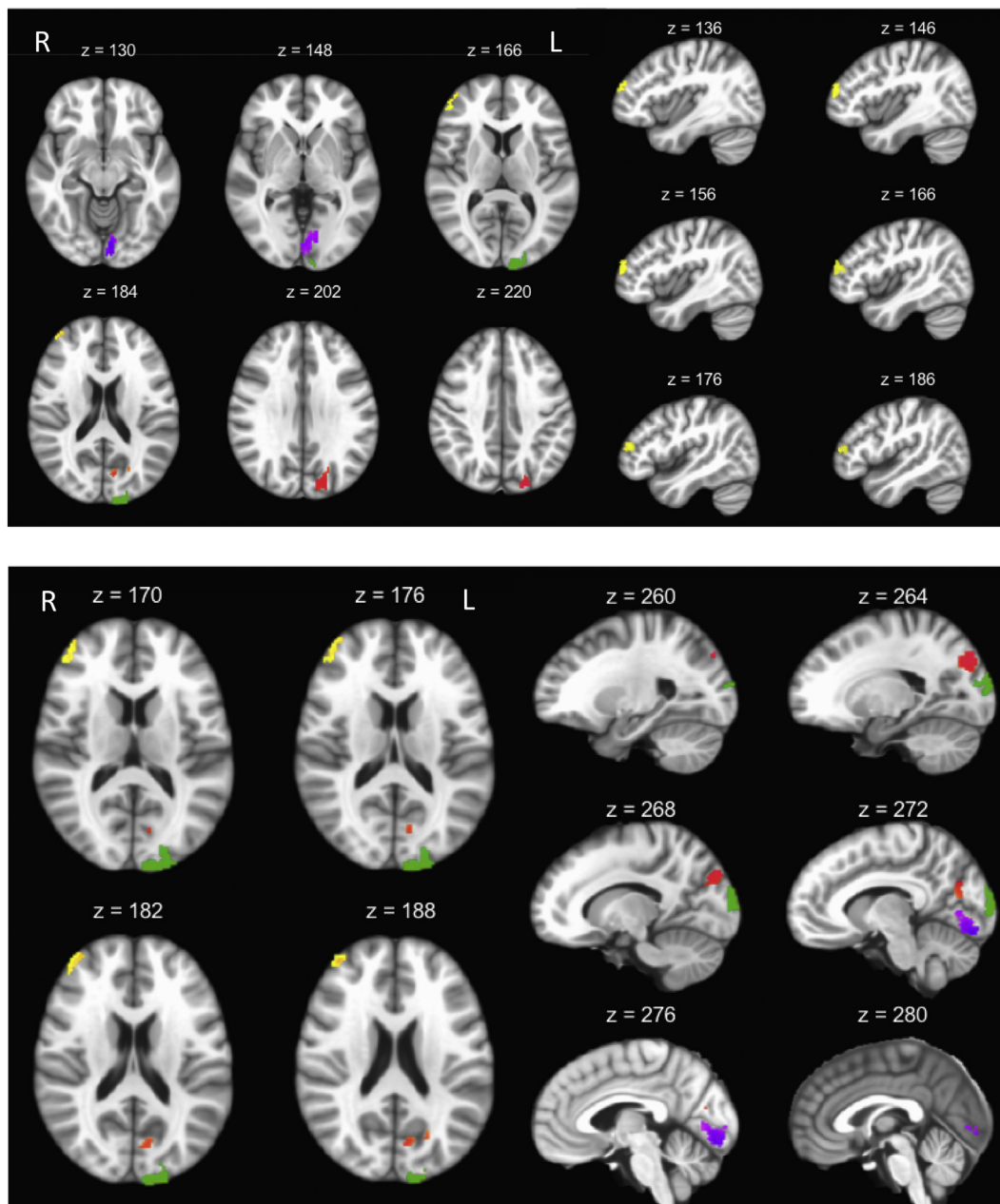


Fig. 2. The difference in task related hippocampal-whole brain connectivity between patients and controls. Clusters within the left cuneus (green), left lingual (purple), and left precuneus (red) in the top panel, and clusters in the right middle frontal gyrus (yellow) represent higher connectivity in the survivors when compared to the controls, after covarying for age. View is radiological.

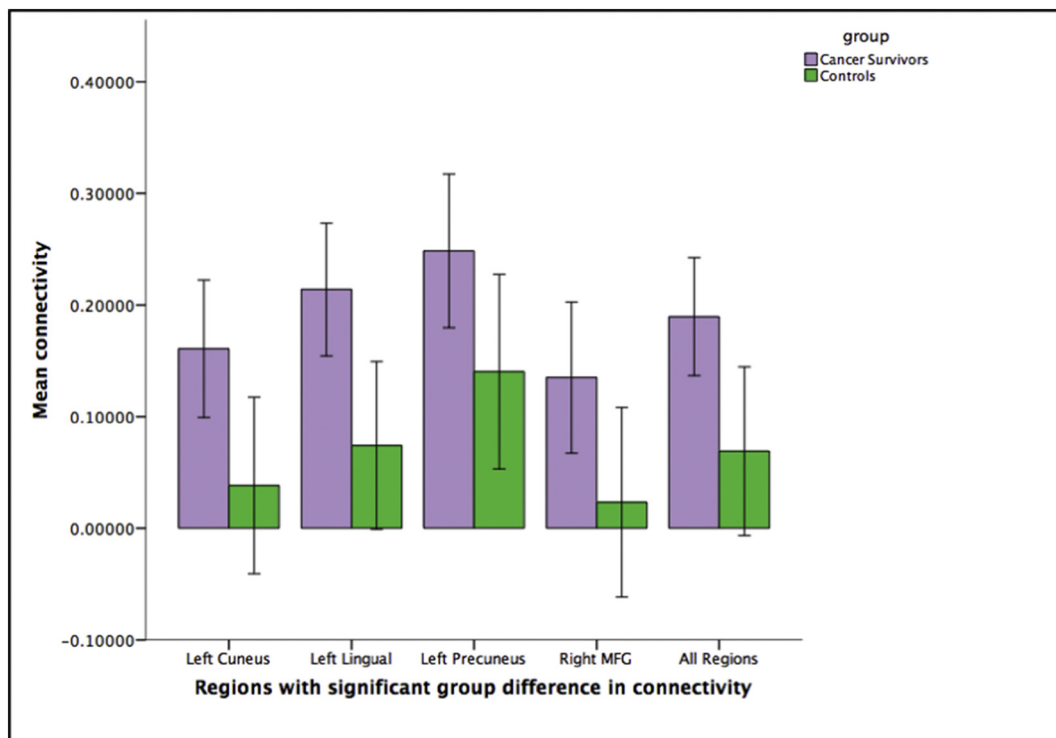


Fig. 3. Mean connectivity differences across the four clusters of significant group difference ($p < .005$ cluster size > 131). Error bars: 95% CI.

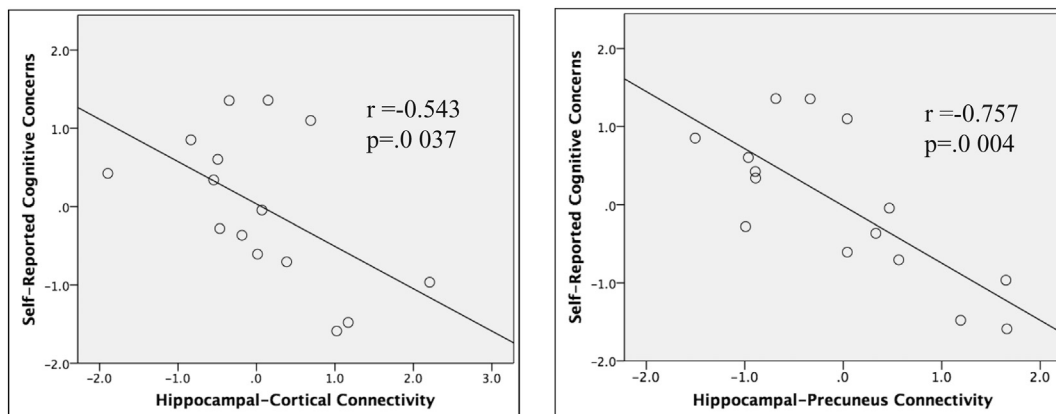


Fig. 4. Significant correlations between objective and subjective cognition in breast cancer survivors. Subjective cognitive concern was negatively correlated with hippocampus-precuneus/cortical connectivity in cancer survivors.

survivors. We observed higher functional connectivity between the hippocampus and left cuneus, left precuneus, left lingual gyrus, and right middle frontal cortex in cancer survivors compared to the controls. This higher connectivity was related to higher levels of self-reported general cognitive concerns in survivors, but not in controls. The survivors demonstrated elevated IL6 concentration compared with controls, which corroborates previous studies (Cheung et al., 2015; Dethlefsen et al., 2013; Williams et al., 2016). However, no show relationships between IL6 and imaging, cognition and self-report measures were found. To our knowledge, this is the first study to suggest that higher task-based hippocampal-cortical functional connectivity may reflect the brain's compensatory response to cancer or cancer-treatment related loss of hippocampal structure and function to maintain cognitive task performance.

In our study, the survivors reported significantly greater subjective concerns of general cognitive impairment as compared with healthy controls, and the degree of concern was significantly associated with the increases in task-based hippocampal-cortical functional

connectivity. I.e., survivors who were more similar to controls in terms of strength of functional connection between the hippocampus and the cortex reported less cognitive concerns. It is possible that this was due to the fact that they were not exerting as much “effort” or calling upon other regions of the brain to complete cognitive tasks. On the other hand, survivors with more general concerns with their own cognition may have compensated more (i.e., “worked harder”) during the task. Previous studies have observed aberrant activity and resting-state functional connectivity in breast cancer survivors (Bruno et al., 2012; Janelsins et al., 2014), and some suggest that increased activity and connectivity during task may help preserve cancer survivor's behaviors and bring them closer to their premorbid abilities that are comparable to that of controls (Ferguson et al., 2007a; Hosseini and Kesler, 2014; Janelsins et al., 2014). That breast cancer survivors may be working harder to restore to “normal” performance level may explain, in part, the difficulty of detecting these cognitive changes or deficits in cancer populations through subjective testing (Reuter-Lorenz and Cimprich, 2013). While cognitive neuroscience approaches are being leveraged to

improve assessment of CRCI (see National Cancer Institute 2016 FOA PAR-16-212), our hippocampal-cortical functional connectivity measure reported here may serve as an excellent neuroimaging biomarker for CRCI as it relates to the survivors self-reported cognitive concerns, therefore captures the subtle cognitive deficits at an earlier stage. Utilizing tools and techniques other than standard cognitive assessments to study complex disorders is important given the often subtle ways in which CRCI presents.

Research has shown that higher functional connectivity in both task negative and task-positive networks is associated with improved cognitive performance in young and older adults (Baldassarre et al., 2012; Dong et al., 2012; Meier et al., 2012; Seeley et al., 2007). Older adults who perform similarly behaviorally to younger adults on cognitive tasks recruit more brain regions comparatively (Berlinger et al., 2013; Cabeza et al., 2002). In breast cancer survivors, a study among twins found more activation in the twin cancer with in bilateral frontal and parietal regions during a working memory task compared to their non-affected twin (Ferguson et al., 2007b). Additionally, an EEG study of breast cancer survivors found higher EEG amplitude following motor and processing speed tasks and that the increases correlated with elevated self-reported physical and mental fatigue. This was thought to reflect increased effort to maintain performance during these physical and cognitive tasks (Moore et al., 2014). Perceived effort and/or a sense of mental fatigue may be greater when compensatory processes are needed compared to when they are not needed (Reuter-Lorenz and Cimprich, 2013). Although none of the survivors in the current study reported higher fatigue compared to controls, they reported worse perceived cognitive functioning; it is possible this higher effort is contributing to this notion of worse cognitive ability.

Compensation by means of increased connectivity has been observed in other populations. In alcohol-dependent adults whose default mode network was disrupted (Dupuy and Chanraud, 2016), functional connectivity between the left posterior cingulate and left cerebellar regions was found to be increased in during a spatial working memory task, and alcohol-dependent adults performed as well as the control (Chanraud et al., 2011). Increased recruitment of cortical areas has been observed in survivors with hippocampal damage (due to medial temporal lobe resection for sclerosis or tumor). The survivors demonstrated intact memory performance but showed increased recruitment of cortical areas including the dorsolateral prefrontal cortex and the posterior parietal cortex (Finke et al., 2013). Additionally, survivors with mild Alzheimer's disease show higher functional connectivity in prefrontal areas during memory tasks compared to controls (Grady et al., 2003).

In the current study, the higher functional connectivity observed in breast cancer survivors may be suggestive of a compensatory recruitment of cortical regions to aid in successful cognitive performance (Cabeza and Dennis, 2013). Furthermore, the brain regions that demonstrated significantly higher functional connectivity during task with the hippocampus (i.e., precuneus/cuneus, middle frontal gyrus) are thought to play key roles in episodic memory (Euston et al., 2012; Fletcher et al., 1995). However, this difference in connectivity did not account for the observed degradation in the objective measures of episodic memory conducted outside of the scanner, suggesting the successful compensatory effort, marked by the higher functional connectivity, may be insufficient to meet the demands of the episodic memory tasks. Future research can examine if the overall hippocampal-cortical network can be further strengthened by noninvasive means such as repetitive transcranial magnetic stimulation to overcome cancer and treatment-related loss of hippocampal structure and function, thus improving memory performance (Wang et al., 2014).

Our study has limitations, including a cross-sectional design, differences in age between groups, and small sample size which may have contributed to the lack of relationships between inflammatory markers and other measures. Although we controlled for the difference in statistical analysis, future studies should recruit aged-matched controls

and collect pre-/post- treatment data to better track longitudinal change in network functioning and how it relates to subjective or objective measures. Additionally, inclusion of resting-state fMRI data can be beneficial for better understanding of the neural mechanisms underlying CRCI. Our study did not collect resting-state fMRI, nor did it contain enough fixation volumes to extract pseudo-resting state BOLD data (Fair et al., 2007). A caveat of this study is that the differences in connectivity between cancer survivors and controls are not necessarily selective, and survivors could demonstrate other aberrant connectivity patterns which may be related to other cognitive domains if tested with different paradigms. Finally, the observed differences in hippocampal-cortical connectivity may be due to the survivors' chemotherapy regimen, the effects of ongoing Tamoxifen treatment, or a combination of the two. Future studies should consider differences in stage (e.g. stages I-IV), type of treatment (e.g. different types of chemotherapy drugs including anthracyclines, taxanes, 5-fluorouracil, cyclophosphamide, carboplatin or a combination of the above), and therapy regimen (e.g. 3-month course vs a 6-month course, daily vs weekly etc.) of cancer to ascertain their effects on hippocampal-cortical connectivity.

5. Conclusions

The current study observed greater task related hippocampal functional connectivity in breast cancer survivors as compared with healthy controls. The higher connectivity was correlated with greater subjective feelings of cognitive concern in the survivors. These findings suggest that hippocampal-cortical task-based functional connectivity may be a biomarker for a compensatory mechanism in CRCI. As the field evolves, it may be important to utilize research to inform clinical practice as it is critical to develop strategies to palliate symptoms and improve patient quality of life. Along this same vein, self-reported cognition may be increasingly useful for identifying differences in brain behavior at an earlier time in order to implement a more effective intervention.

Conflicts of interest

Alexandra C. Apple, Anthony J. Ryals, Matthew P. Schroeder, Lynne I. Wagner, Pei-An Shih, David Cella, Frank J. Penedo, James Reilly, 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.

Acknowledgments and funding

This work was supported by award numbers 1F31CA210719-01 from the National Cancer Institute, T32-NS047987 from the National Institute of Neurological Disorders and Stroke, R01-NR014182 from the National Institute of Nursing Research, P30 CA060553 (L. Platania) from the Robert H. Lurie Comprehensive Cancer Center, and by a grant from the Lynn Sage Cancer Research Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.07.010>.

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