NeuroImage: Clinical 14 (2017) 685–691

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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

Alexandra C. Apple[a,b,*], Anthony J. Ryals[c], Kathryn I. Alpert[b], Lynne I. Wagner[f], Pei-An Shih[g], Mehmet Dokucu[b], David Cella[b,c,e], Frank J. Penedo[c], Joel L. Voss[b,c,e], Lei Wang[a,b,d]

[a]Division of Clinical Psychology, Northwestern University Feinberg School of Medicine, United States
[b]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, United States
[c]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, United States
[d]Department of Radiology, Northwestern University Feinberg School of Medicine, United States
[e]Ken and Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, United States
[f]Department of Social Sciences and Health Policy, Wake Forest School of Medicine, United States
[g]Department of Psychiatry, University of California, San Diego, United States

ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form 2 March 2017
Accepted 10 March 2017
Available online 16 March 2017

Keywords:
Hippocampus
Cancer-related cognitive impairment (CRCI)
Neurocognitive
NIH toolbox

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

* Corresponding author at: Northwestern University Feinberg School of Medicine, Abbott Hall Suite 1306, 710 N Lake Shore Drive, Chicago, IL 60611, United States.
E-mail address: Alexandra.Apple@northwestern.edu (A.C. Apple).

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

http://dx.doi.org/10.1016/j.nicl.2017.03.004

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