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Links between inflammation, amygdala reactivity, and social support in breast cancer survivors

Keely A. Muscatell [a,b,*], Naomi I. Eisenberger [c], Janine M. Dutcher [c], Steven W. Cole [d,e,f], Julienne E. Bower [c,d,e,*]

[a] Robert Wood Johnson Foundation Health and Society Scholars Program, University of California, San Francisco/University of California, Berkeley, United States
[b] Department of Psychology, UC Berkeley, United States
[c] Department of Psychology, University of California, Los Angeles, United States
[d] Department of Psychiatry and Biobehavioral Sciences, UCLA, United States
[e] Cousins Center for Psychoneuroimmunology, UCLA, United States
[f] Division of Hematology-Oncology, Department of Medicine, UCLA School of Medicine, United States

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ABSTRACT

Psychosocial stress can affect inflammatory processes that have important consequences for cancer outcomes and the behavioral side effects of cancer treatment. To date, however, little is known about the upstream neural processes that may link psychosocial stressors and inflammation in cancer patients and survivors. To address this issue, 15 women who had been diagnosed with early-stage breast cancer and completed cancer treatment and 15 age- and ethnicity-matched women with no cancer history were recruited for a neuroimaging study. Participants provided a blood sample for levels of circulating inflammatory markers (CRP and IL-6), underwent an fMRI scan in which they completed a threat reactivity task designed to elicit activity in the amygdala, and reported their levels of perceived social attachment/support. There were no significant differences between cancer survivors and controls in levels of CRP or IL-6, in amygdala reactivity to the socially threatening images, or in levels of perceived social support. However, results showed a strong, positive correlation between CRP concentration and left amygdala reactivity in the survivor group that was not apparent in controls. Higher levels of social support in the survivor group were also associated with reduced amygdala reactivity and CRP. These data suggest the possibility of a stronger "neural-immune pipeline" among breast cancer survivors, such that peripheral inflammation is more strongly associated with neural activity in threat-related brain regions.
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1. Introduction

Psychosocial stress can activate the innate immune system, leading to mobilization of pro-inflammatory cells and release of inflammatory mediators (Irwin and Cole, 2011). Inflammation, in turn, has important consequences for cancer outcomes: inflammation is known to facilitate many hallmark characteristics of cancer (e.g., proliferation, angiogenesis, resistance to cell death, invasion, metastasis; Hanahan and Weinberg (2011)) and among breast cancer survivors, is associated with increased risk for breast cancer recurrence and mortality (Villasenor et al., 2014). Inflammation is also associated with behavioral side effects of cancer and its treatment (e.g., fatigue, cognitive disturbance; Bower and Lamkin (2013)). Investigators have begun to examine the neuroendocrine mechanisms linking stress and inflammation in the context of cancer, with studies highlighting the role of the sympathetic nervous system as a key mediating pathway (Cole and Lutgendorf, 2015). However, there has been minimal examination of the upstream neural processes that may link psychosocial stressors with peripheral inflammatory processes in cancer patients. The paucity of work that has been done in this area has focused on links between inflammation and neural activity related to cognitive complaints following cancer treatment (i.e., "chemobrain"; Pomykala et al. (2013)), but no known studies have examined the association between inflammation and activation in brain structures relevant for psychosocial stress, including threat-related brain regions.

Research in healthy participants has identified the amygdala as a key neural region underlying bidirectional links between peripheral inflammation and psychosocial/behavioral symptoms. Greater amygdala activation during social evaluation has been

* Corresponding authors at: UC Berkeley Department of Psychology, 4143 Tolman Hall MC 5050, Berkeley, CA 94720-5050, United States (K.A. Muscatell). UCLA Department of Psychology, 1285 Franz Hall Box 951563, Los Angeles, CA 90095-1563, United States (J.E. Bower).
E-mail addresses: kmuscatell@berkeley.edu (K.A. Muscatell), jbower@ucla.edu (J.E. Bower).

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linked with heightened inflammatory responses to social stress (Muscatell et al., 2015), possibly due to the fact that the amygdala has dense projection to brainstem areas that can generate sympathetic nervous system responses (LeDoux and Cicchetti, 1988) and in turn activate pro-inflammatory transcription factors (Bierhaus et al., 2003). At the same time, animal (Frenois et al., 2007) and human (Inagaki et al., 2012) research has shown that increases in peripheral inflammation lead to heightened amygdala activation to threatening information. Thus, threat-related amygdala activation may serve as both a potential cause and consequence of peripheral inflammation. As such, the amygdala may play a key role in establishing a "neuro-immune pipeline" (Miller et al., 2011; Miller and Cole, 2012) or "neuro-immune network" (Nusslock and Miller, in press) linking neural activity and peripheral inflammation in breast cancer survivors. The present study was designed to assess relationships between amygdala reactivity and inflammatory markers in breast cancer survivors, and a comparison group of healthy controls. Given that greater social support has been linked to lower inflammation and greater survival in cancer populations (e.g., Costanzo et al., 2005; Kroenke et al., 2006; Lutgendorf et al., 2012), analyses also examined the relationship of social support/attachment to inflammation and amygdala activity.

2. Materials and methods

2.1. Participants

Breast cancer survivors were identified from a larger study focusing on stress and tumor biology. Participants for the parent study were recruited from the UCLA Tumor Registry if they had been diagnosed with early stage breast cancer (stages I–III) within the past 5 years, had undergone surgical removal of their tumor, and were able to speak, read, and understand English. Individuals with metastatic or recurrent disease were excluded. To be eligible for the present study, survivors had to have completed any adjuvant cancer therapy with radiation or chemotherapy at least 6 months previously, have no evidence of recurrence or residual disease, ages 30–70 years old, no current medical conditions or medications that would impact inflammation, no metallic implants that would jeopardize safety in the MRI scanner, right-handed, and not claustrophobic. Control participants were recruited via word-of-mouth from participants in the survivor group, as well as via advertisement in a local newspaper. Eligibility criteria for the control group included all the inclusion criteria for the survivor group, with the addition of no history of any type of cancer diagnosis. Participants in the control group were age and ethnicity matched to those in the survivor group.

2.2. Procedure

Recruitment letters were sent to 84 potential participants identified from the parent study of breast cancer survivors; 49 women responded, and 15 were eligible, interested, and ultimately enrolled in the study. For the control group, 93 potential participants responded to a newspaper advertisement, 12 were eligible and interested, and 9 were ultimately enrolled. The remaining 6 participants in the control group were recruited via word-of-mouth from the survivor group. The UCLA IRB approved all study procedures, and all participants provided written informed consent.

Study sessions were scheduled between 8:00 AM and 10:00 AM. Upon arriving at UCLA, participants provided a blood sample for circulating inflammatory markers, which were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80 °C for subsequent batch testing. Next, participants underwent an fMRI scan while they completed a threat reactivity task designed to elicit amygdala activation. Following the scan, participants completed questionnaire measures, and were debriefed and dismissed.

2.3. Measures

2.3.1. fMRI task and image acquisition

To examine amygdala reactivity, participants underwent a functional MRI scan while they completed a standard threat-reactivity task that is widely used in the affective neuroscience literature to elicit amygdala activation. Specifically, participants viewed blocks of threatening facial expressions from a standardized stimulus set (Tottenham et al., 2009), and completed blocks of a shape-matching task, which served as the comparison condition (Lieberman et al., 2007). Each block lasted 30 s, followed by 12 s of fixation crosshair. During the threat-processing blocks, participants were instructed to passively view 6 threatening facial expressions (3 angry, 3 fearful) for 5 s each. During the shape-matching blocks, participants were asked to indicate (via button press) which of a pair of shapes presented at the bottom of the screen matched the shape at the top of the screen. Each set of three shapes was presented for 5 s each, and six different sets of shapes were presented during each block. Participants completed three blocks of each condition, in randomized order.

Imaging data were acquired using a Siemens Trio 3.0 Tesla MRI scanner at the UCLA Staglin Center for Cognitive Neuroscience. First, we acquired a T1-weighted MPRAGE anatomical image for functional image registration and normalization (slice thickness = 1 mm, 176 slices, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, matrix = 256 × 256, FOV = 256 mm). Then, we acquired 276 functional T2-weighted EPI volumes (slice thickness = 3 mm, gap = 1 mm, TR = 2000 ms, TE = 25 ms, flip angle = 90°, matrix = 64 × 64, FOV = 200 mm).

2.3.2. Inflammatory assessments

Plasma levels of IL-6 were determined by high sensitivity ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols, with a lower limit of detection of 0.2 pg/ml. CRP levels were determined by a high sensitivity ELISA (Immundiagnostik, ALPCO Immunoassays, Salem, NH) according to the manufacturer's protocol, but with an extended standard curve to a lower limit of detection of 0.2 mg/L. For each analyte, all samples were run in duplicate on a single immunoassay plate. Mean intra-assay coefficients of variation across all study samples were 4.1% and 4.5% for CRP and IL-6, respectively. Inflammatory data were positively skewed, so raw values were log transformed to normalize the distribution prior to statistical testing. For ease of interpretation, untransformed values are listed in the text and table.

2.3.3. Social support/attachment

Perceptions of social integration and support were assessed using the Social Provisions Scale (Cutrona and Russell, 1987). This 24-item scale asks participants to indicate the extent to which they receive (or do not receive) different types of support from their social network, including perceptions of attachment, integration, and alliance. The Social Provisions Scale was of interest here because it has been associated with reduced inflammation and enhanced survival in cancer patients (Costanzo et al., 2005; Lutgendorf et al., 2005, 2012).

2.4. Data analysis

Neuroimaging data were pre-processed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK). Pre-processing was conducted