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

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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

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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

using the DARTEL procedure, and included image realignment to correct for head motion, normalization into Montreal Neurologic Institute space (resampled at 3 × 3 × 3 mm), and spatial smoothing using an 8 mm Gaussian kernel, full width at half maximum, to increase signal-to-noise ratio. Following pre-processing, a general linear model was constructed for each participant, in which activation during each 30 s block of the task was convolved with a canonical hemodynamic response function. Our regressor-of-interest coded for the type of block (threat vs. shape match), and we included the six motion parameters as covariates. For each model, the time series was high-pass filtered using a 128 Hz function, and serial autocorrelation was modeled as an AR(1) process. Following estimation, we computed linear contrasts for each participant that compared BOLD signal during the threat reactivity trials to BOLD signal during shape matching. Contrast images for each participant were then entered into random effects analyses at the group level for statistical inference.

Given our *a priori* hypotheses regarding the associations between inflammation and neural activity in the amygdala, we conducted region-of-interest (ROI) analyses focusing on this region. Amygdala ROIs were defined anatomically based on the Automated Anatomical Labeling atlas (left amygdala: $-32 < x < -12$, $-12 < y < 4$, $-24 < z < -8$; right amygdala: $12 < x < 32$, $-21 < y < 4$, $-24 < z < -8$). Mean parameter estimates were extracted from the amygdala ROIs for each participant using Marsbar, and entered into SPSS for further analysis. All analyses involving the fMRI data were conducted as one-tailed tests, given convention in neuroimaging research.

3. Results

3.1. Participant characteristics

Participants in both groups were approximately 55 years old (range = 42–68), primarily white (79%), relatively well-educated (80% with a bachelor's degree or higher), married or in a committed relationship (67%), and employed full-or part time (77%). There were no significant differences between the survivor or control group on any of these demographic characteristics, nor in body mass index (all $p > .24$); thus, we present uncontrolled analyses below. Demographic characteristics for both groups are shown in Table 1. For the survivor group, the average time since breast cancer diagnosis was 3.83 years (range = 1.5–6 years). All women had been treated with surgery (either lumpectomy or mastectomy), and 11 participants had also received chemotherapy.

3.2. Comparing survivors and controls on levels of inflammation, amygdala reactivity, and social support

Independent-samples *t*-tests revealed no significant differences between survivors and controls in IL-6 ($t(28) = .06$, $p = .95$) or CRP levels ($t(28) = .40$, $p = .69$). There were also no significant differences between survivors and controls in left or right amygdala activation to threatening faces (vs. shape-matching control; $t(28) = .98$, $p = .33$ for left amygdala; $t(28) = 1.10$, $p = .28$ for right amygdala). Finally, survivors reported somewhat-higher levels of perceived social attachment/support than controls ($t(28) = 1.58$, $p = .13$), though this difference was not significant (see Table 1).

3.3. Survivors: relationships between inflammation, amygdala reactivity, and social support

Correlational analyses revealed a significant, positive correlation between left amygdala activity and CRP levels ($r = .49$, $p = .03$; see Fig. 1) and a marginally significant correlation between right amygdala activity and CRP ($r = .38$, $p = .08$) in the survivor group. Associations between IL-6 levels and amygdala activity showed a similar pattern, but did not reach statistical significance ($r = .33$, $p = .12$ for left; $r = .19$, $p = .25$ for right).

Based on previous research showing links between inflammation and neural processes only among chemotherapy-treated survivors (Pomykala et al., 2013), exploratory analyses examined inflammatory markers and neural activity in the subgroup of women treated with chemotherapy ($n = 11$). The correlation between amygdala activity and CRP was particularly strong in the subgroup of women who had been treated with chemotherapy ($r = .61$, $p = .008$ for left and $r = .45$, $p = .05$ for right). Of note, we

Table 1
Comparison of breast cancer survivors and controls on demographic characteristics, inflammatory markers, amygdala reactivity, and perceived social support.

Characteristic	Survivors ($n = 15$)	Controls ($n = 15$)
Age (mean, SD, range)	55.27, 7.3 (42–68 yrs)	55.73, 6.9 (43–64 yrs)
Body mass index (mean, SD)	26.17, 6.20	23.75, 4.56
Ethnicity (n)		
White, non hispanic/latina	13	9
White, hispanic/latina	1	2
Non-white	1	2
Education level (n)		
Associates degree (AA)/some college	3	3
Bachelor's degree (BA/BS)	9	9
Post-graduate degree	3	3
Employment status (n)		
Employed full or part-time	11	12
Retired	3	0
Unemployed	1	3
Marital status (n)		
Married/committed relationship	12	8
Divorced/separated	2	3
Single/never married	1	4
Inflammatory markers (median, SD)		
CRP (mg/L)	.93, 3.5	.66, 5.8
IL-6 (pg/mL)	1.10, .89	.98, .59
Amygdala reactivity (mean, SD)		
Left amygdala (threat > shape)	.10, .27	.20, .30
Right amygdala (threat > shape)	.14, .28	.26, .29
Social support (SPS scores; mean, SD)	87.15, 7.7	79.8, 16.3

Note: Missing ethnicity data from one participant in the control-group. None of the mean differences between the groups are statistically significant (all $p > .13$).

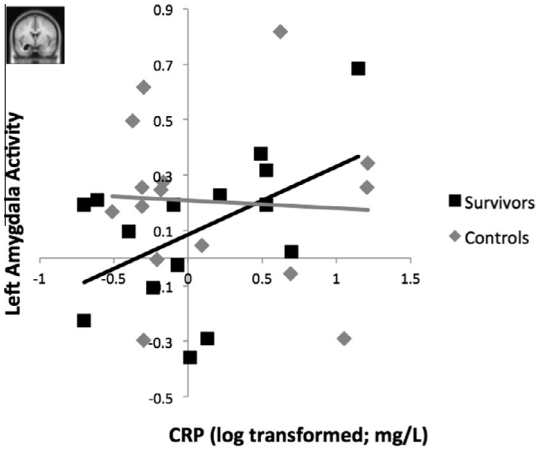

Fig. 1. Scatter plot showing the relationship between levels of CRP and left amygdala activation during threat processing for breast cancer survivors and controls.

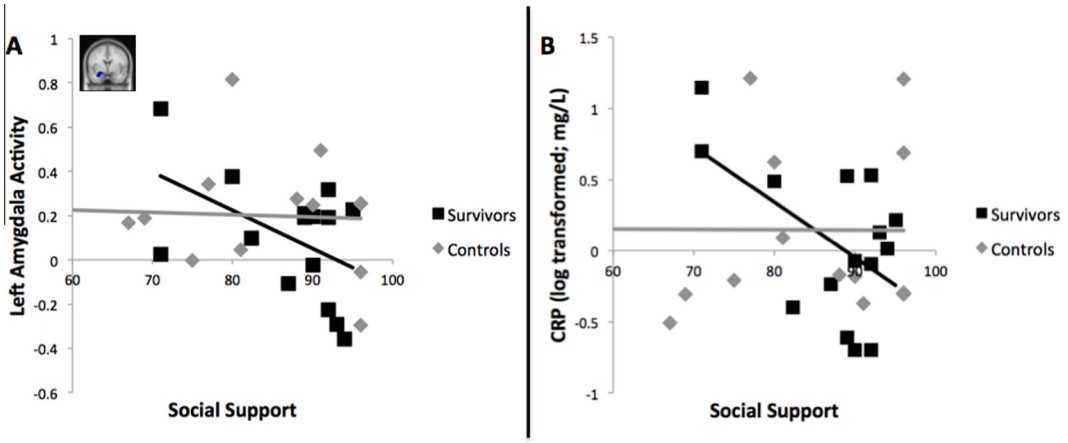

Fig. 2. Scatter plots showing the relationship between social support and left amygdala activation during threat processing (Panel A on left) and levels of CRP (Panel B on right) for breast cancer survivors and controls.

found no significant differences in overall levels of inflammation (IL-6: $t(28) = .36$, $p = .72$; CRP: $t(28) = .18$, $p = .86$) or amygdala reactivity (left: $t(28) = .56$, $p = .57$; right: $t(28) = 1.1$, $p = .28$) between the chemotherapy-treated survivors and controls, suggesting that the enhanced association observed in this subgroup was not driven by elevated neural or inflammatory activity.

Correlational analyses revealed a significant, negative correlation between social support/attachment and CRP levels ($r = -.55$, $p = .03$) in the survivor group (see Fig. 2). There was also a significant, negative correlation between social support/attachment and left amygdala activity ($r = -.49$, $p = .03$) in the cancer survivors (see Fig. 2). Patterns linking social support with IL-6 levels ($r = -.37$, $p = .18$) and right amygdala activity ($r = -29$, $p = .15$) were in the same direction, but did not reach statistical significance.

3.4. Controls: relationships between inflammation, amygdala reactivity, and social support

Among individuals with no cancer history, correlation analyses revealed no association between amygdala activity and IL-6 ($r = .05$ for left; $r = .13$ for right; both $p > .05$) or CRP ($r = -.05$ for left; $r = .13$ for right; both $p > .05$). Further, there were no significant associations between social support and amygdala activity ($r = .07$ for left; $r = .09$ for right; both $p > .05$) or social support and either inflammatory marker ($r = -.23$ for IL-6 and $r = -.01$ for CRP; both $p > .05$) among the healthy controls.

4. Discussion

The primary goal of the present study was to examine links between inflammation and amygdala reactivity to social threat in breast cancer survivors and healthy controls. Results indicated that while survivors and healthy controls did not differ significantly in levels of circulating inflammatory markers or amygdala reactivity to threat, only breast cancer survivors showed a significant, positive relation between CRP and amygdala activation. In addition, a higher level of social support among the cancer survivors was associated with reduced amygdala activity and lower levels of CRP.

Results from this study contribute to an emerging literature linking inflammation and neurocognitive function in the context of cancer (Pomykala et al., 2013), and suggest that inflammation may also be relevant for threat-related neural processes in cancer survivors. In particular, data from the present study add to a growing literature suggesting that the amygdala is a key neural structure supporting bidirectional links between inflammation and neurocognitive function (Frenois et al., 2007; Inagaki et al., 2012; Muscatell et al., 2015). The current study extends this prior work, which has primarily been conducted with healthy young adults, to breast cancer survivors, and further suggests that it is not just overall levels of inflammation or amygdala activation that may be affected following cancer, but rather the degree of cross-talk between these two systems.

Why would breast cancer survivors show a stronger relationship between inflammation and amygdala reactivity to threat? One possibility is that breast cancer and its treatment may activate microglia, which remain "primed" even after treatment has been completed and peripheral inflammation has resolved. Indeed, preclinical work in animal models has shown that cancer chemotherapy can induce increases in activated microglia (Christie et al., 2012), and stress has been shown to increase microglia activation in the amygdala (Wohleb et al., 2011). This priming may increase neural sensitivity to peripheral inflammation, as has also been shown in models of development (Schwarz and Bilbo, 2012) and aging (Henry and Wynne, 2009), with implications for neural function, cognition, and behavior. Consistent with this hypothesis, exploratory analyses revealed a particularly strong correlation between CRP and amygdala activity in women treated with chemotherapy. This mechanism is currently speculative, however, and future work is needed to examine it (and other potential mechanisms) more directly.

A secondary aim of this study was to examine links between inflammation, amygdala activity, and social support/attachment. Growing evidence indicates that social isolation is associated with activation of inflammatory processes (Cole and Lutgendorf, 2015), and greater social support has been shown to predict survival in women with breast (Kroenke et al., 2006) and ovarian cancer (Lutgendorf et al., 2005, 2012). Here, we found that breast cancer survivors with greater social support/attachment had lower levels of CRP as well as reduced amygdala reactivity to threat, suggesting a possible mechanistic pathway linking social support and cancer outcomes.

The current results should be interpreted in light of some important limitations. First, the sample size is small and may be underpowered to detect associations between inflammation and amygdala activation within the healthy control group, or in comparisons between controls and breast cancer survivors. Future studies attempting to replicate the present results in larger samples are necessary. Second, participants were relatively homogeneous in terms of ethnicity and socioeconomic status, thus limiting the generalizability of the findings. Third, the data are cross-sectional and as such it is unclear if the relation between

inflammation and amygdala activity was present prior to cancer diagnosis and treatment (for those in the breast cancer group) or resulted from this cancer experience. Along these same lines, we cannot be certain that participants' levels of perceived social support reported in the present study were similar to those that they experienced during cancer diagnosis and treatment. Finally, all analyses are correlational in nature, so we cannot determine if inflammation is causing increases in amygdala activity in the breast cancer survivors, or vice versa. It will be important for future research in this area to examine larger, more heterogeneous samples using longitudinal, experimental designs so we can further understand the links between breast cancer, different types of treatment, inflammation, amygdala activation, and social support.

In sum, data from the present study suggest that the cancer experience may strengthen or sensitize links between peripheral inflammation and activation in central neural circuits, and greater social support may attenuate amygdala activity and levels of inflammation in breast cancer survivors. These findings may have implications for breast cancer recurrence and survivorship.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2015.09.008.

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