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Short Communication

Inflammation and attentional bias in breast cancer survivors

Chloe C. Boyle [a,*], Patricia A. Ganz [b,c], Kathleen M. Van Dyk [b], Julienne E. Bower [a,b,d]

[a] Department of Psychology, University of California-Los Angeles, Los Angeles, CA, United States
[b] Jonsson Comprehensive Cancer Center, University of California-Los Angeles, Los Angeles, CA, United States
[c] Schools of Medicine and Public Health, University of California-Los Angeles, Los Angeles, CA, United States
[d] Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California-Los Angeles, Los Angeles, CA, United States

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ABSTRACT

Evidence suggests an association between inflammation and depression, although findings are mixed. Focusing on core processes in depression may clarify associated biological underpinnings. Negative cognitive bias is a key component of depression, but has not been examined in relation to inflammation. Thus, we tested the hypothesis that elevated inflammatory markers would be associated with negative attentional bias in a sample of 91 breast cancer survivors. Participants were drawn from a larger study and provided blood samples for assessment of peripheral markers of inflammation and completed questionnaires and neuropsychological testing. Attentional bias towards emotional stimuli was assessed with a dot-probe computer task using emotional (sad, happy, angry) and neutral faces. Circulating concentrations of C-reactive protein (CRP) were positively correlated with negative attentional bias ($p = .03$), such that women with higher CRP allocated greater attention towards sad faces. This association held when controlling for attention function and current depressive symptoms. While cross-sectional, results are consistent with research showing that inflammation heightens the salience of negative emotional stimuli, and identify a novel pathway through which inflammation may lead to depression.

1. Introduction

A growing literature implicates inflammation in the pathogenesis of depression. Meta-analysis demonstrates that individuals with depression have elevated levels of inflammatory biomarkers (Howren et al., 2009), and longitudinal studies have shown that elevations in inflammatory biomarkers predict the onset of depressive symptoms (Gimeno et al., 2009). In experimental paradigms, inducing an inflammatory response through interferon-alpha treatment (Raison et al., 2006), typhoid vaccine (Harrison et al., 2009), and endotoxin (Eisenberger et al., 2010) elicits sickness behavior, a constellation of symptoms that overlap with depression (Raison et al., 2006). However, a number of inconsistencies have also been noted. Inflammation is neither a necessary component nor a sufficient cause of depression, and there is notable variability in whether an inflammatory stimulus elicits depressive symptoms (Slavich and Irwin, 2014). Some studies suggest that depressive symptoms predict inflammation or fail to find any association (Steptoe et al., 2003).

Such inconsistencies may arise from the heterogeneous nature of depression, which is characterized by a constellation of cognitive, affective, and somatic symptoms. As recently articulated by the NIMH Research Domain Criteria initiative, focusing on core processes in depression may help clarify its associated biological underpinnings (Cuthbert and Insel, 2013). One such process is attentional bias, which plays a critical role in cognitive theories of depression. Selective attention towards and difficulty disengaging from negative, and especially sad, stimuli is theorized to reinforce negative mood and contribute to the development and maintenance of depression (Gibb et al., 2015). Indeed, individuals with depression or elevated depressive symptoms demonstrate biases towards negative emotional information (Peckham et al., 2010). These biases predict increases in depressive symptom severity and are evident in individuals at high-risk for depression (Gibb et al., 2015). Training individuals to reduce negative attentional bias alleviates depressive symptoms (Gibb et al., 2015), suggesting attentional bias is not merely a symptom of depression but serves to initiate and sustain this disorder.

To date, no studies have examined whether inflammation is associated with attentional bias towards negative emotional stimuli. The current report focuses on breast cancer survivors, a population in which the inflammation-depression link is of particular importance. Depression is elevated in cancer survivors and associated with increased mortality, poorer adherence to medical treatment regimens, and impaired quality of life (Irwin et al., 2013).

* Corresponding author.
E-mail address: ccboyle@ucla.edu (C.C. Boyle).

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Chronic inflammation (particularly CRP and IL-6 (Sotelo et al., 2014) contributes to the initiation and progression of cancer, and cancer treatment may further increase inflammation (Aggarwal et al., 2009). Behavioral comorbidities that arise in cancer patients have been partly attributed to inflammatory activity and described as sickness behaviors (Dantzer et al., 2012); however, inflammation has been inconsistently linked with general measures of depressive symptoms in cancer survivors (Irwin et al., 2013; Bower et al., 2011).

The current study tested the hypothesis that elevated inflammation would be associated with attentional bias towards sad faces in breast cancer survivors using a dot probe task. This task is commonly used in the literature on depression, and assesses the relative allocation of attention towards emotional versus neutral stimuli. Because inflammation has been linked to both alterations in affect (Eisenberger et al., 2010) and neurocognitive performance and complaints (Ganz et al., 2013a,b; Cheung et al., 2015), we conducted analyses controlling for current mood and simple attention to identify whether any association between inflammation and attentional bias was driven by alterations in mood or in attention. In exploratory analyses, we examined links between inflammation and attentional bias for other emotional faces (happy and angry).

2. Methods

2.1. Participants

Participants were breast cancer survivors from a longitudinal study of cognitive functioning after treatment for breast cancer at the University of California, Los Angeles (UCLA) which enrolled patients from May 2007 to March 2011 (Ganz et al., 2016). Criteria eligibility included: English language proficient, age 21–65 years, newly diagnosed with Stage 0-IIIA breast cancer, within 3 months of primary treatment (surgery, radiation, and/or chemotherapy), and not yet on endocrine therapy, if prescribed. Participants were ineligible if they had prior cancer diagnosis, current or past neurologic disorder, current major affective disorder, substance abuse/dependence, active autoimmune disorder or other disease involving the immune system. Details on participant screening, recruitment, and enrollment are reported in Ganz et al. (2013b). After approval by the UCLA IRB and with informed consent, data were collected in person at UCLA at study entry, 6 months, and 1 year (Ganz et al., 2013b, 2016). In March 2013–July 2014, participants were invited to complete a final in-person assessment, which occurred between 3 and 7 years after study entry. At each assessment, participants provided morning or early afternoon blood samples prior to undergoing neuropsychological testing and completing questionnaires.

The parent study enrolled 191 women; 103 came in for the final in-person assessment, and 91 provided blood samples for assessment of inflammatory biomarkers and completed a computerized task to assess attentional bias towards emotional stimuli. These 91 women did not differ significantly from the full sample in terms of race, marital status, income, age, depressive symptoms, cancer treatment or time since last treatment (all p's > .05).

2.2. Procedures

At the final in-person assessment, participants completed a 5-min dot probe computer task after providing blood samples and prior to undergoing neuropsychological testing.

2.3. Demographic and treatment-related variables

Demographic information was obtained from self-report. Treatment-related information was obtained from medical record abstraction.

2.4. Attentional bias

Attentional bias was assessed using a dot-probe task, which is widely used in clinical and non-clinical populations (Gibb et al., 2015; MacLeod et al., 1986). In this task, a dot is presented on either the right or left side of a computer screen, and participants indicate which side of the screen the dot is on as quickly and accurately as possible by pressing the "j" or "f" key. Prior to presentation of the dot, two faces are flashed side-by-side. Each pair of faces consists of an individual portraying one neutral and one emotional (i.e., sad, happy, angry) expression. A total of 30 different emotional faces (10 sad, 10 happy, 10 angry) were paired with 30 corresponding neutral faces. Faces were drawn from the NimStim set of facial expressions (Tottenham et al., 2009) and presented in color; half were male, half were female and each face pair was presented four times to accommodate all combinations of emotional face location and dot location, yielding 120 trials.

Each trial began with presentation of a centrally-positioned fixation cross for 500 ms, followed by pairs of faces for 1000 ms. A single red dot (2 cm diameter) was presented on either the right or left hand side of the screen until the participant made her choice. Attentional bias scores for each emotion were calculated by subtracting average response times for congruent dot probes (replaced emotional faces) from the average response times for incongruent dot probes (replaced neutral faces). A score of 0 indicates no attentional bias, positive values indicate greater attention towards an emotional versus neutral face, and negative values indicate greater attention towards a neutral versus emotional face (Peckham et al., 2010). In the current study, attentional bias scores more than four standard deviations from the mean were removed as outliers (.3% of data) as were response latencies below 200 ms (.1% of data) and above 2000 ms (.98% of data). The task was programmed using DirectRT. Stimuli were presented on an 11.6″ screen; each photograph was 12 cm × 10 cm.

2.5. Inflammation

Inflammation was assessed by measuring circulating levels of the pro-inflammatory cytokine IL-6 and the systemic inflammatory marker CRP (Howren et al., 2009; Sotelo et al., 2014; Aggarwal et al., 2009). Blood samples were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at 80 °C for batch testing. CRP levels were determined by a high-sensitivity ELISA (Immundiagnostik; ALPCO Immunoassays, Salem, NH) per the manufacturer's protocol but with an extended standard curve to a lower limit of detection of 0.2 mg/L. IL-6 levels were determined by high sensitivity ELISA (lower limit 0.2 pg/ml) (R&D Systems, Minneapolis, MN) per the manufacturer's protocols. Samples were assayed in duplicate. Intra- and inter-assay precision of all tests was less than or equal to 10%.

2.6. Visual attention

The Trail Making Test-A is a widely used, standardized measure of simple visual attention and psychomotor speed, used in several studies of breast cancer survivors and among the recommended tests in the cancer survivorship research community (Ganz et al., 2013b; Wefel et al., 2011). Participants are instructed to draw lines as quickly as possible sequentially connecting arrayed numbered items 1–25. Completion times were transformed into T-scores

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