HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Brain Behav Immun. 2017 November ; 66: 85–88. doi:10.1016/j.bbi.2017.05.016.

Inflammation and Attentional Bias in Breast Cancer Survivors

Chloe C. Boyle[1], **Patricia A. Ganz**[2,3], **Kathleen M. Van Dyk**[2], and **Julienne E. Bower**[1,2,4]

[1]Department of Psychology, University of California-Los Angeles, Los Angeles, California

[2]Jonsson Comprehensive Cancer Center, University of California-Los Angeles, Los Angeles, California

[3]Schools of Medicine and Public Health, University of California-Los Angeles, Los Angeles, California

[4]Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California-Los Angeles, Los Angeles, California

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.

Keywords

inflammation; C-reactive protein; depression; attentional bias

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[1], and longitudinal studies have shown that elevations in inflammatory biomarkers predict the onset of depressive symptoms[2]. In experimental paradigms, inducing an inflammatory response through interferon-alpha treatment[3], typhoid vaccine[4], and endotoxin[5] elicits sickness behavior, a constellation of symptoms that overlap with depression[3]. 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[6]. Some studies suggest that depressive symptoms predict inflammation or fail to find any association[7].

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[8]. 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[9]. Indeed, individuals with depression or elevated depressive symptoms demonstrate biases towards negative emotional information[10]. These biases predict increases in depressive symptom severity and are evident in individuals at high-risk for depression[9]. Training individuals to reduce negative attentional bias alleviates depressive symptoms[9], 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[11]. Chronic inflammation (particularly CRP and IL-6[12]) contributes to the initiation and progression of cancer, and cancer treatment may further increase inflammation[13]. Behavioral comorbidities that arise in cancer patients have been partly attributed to inflammatory activity and described as sickness behaviors[14]; however, inflammation has been inconsistently linked with general measures of depressive symptoms in cancer survivors[11,15].

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[5] and neurocognitive performance and complaints[16–18], 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-March 2011[19]. 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[18,19]. In March 2013-July 2014, participants were invited to complete a final in-person assessment, which occurred between 3–7 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-minute 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[9,20]. 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[21] 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 500ms, followed by pairs of faces for 1000ms. A single red dot (2cm 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[10]. 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 200ms (.1% of data) and above 2000ms (.98% of data). The task was programmed using DirectRT. Stimuli were presented on an 11.6” screen; each photograph was 12cm × 10cm.

2.5. Inflammation

Inflammation was assessed by measuring circulating levels of the pro-inflammatory cytokine IL-6 and the systemic inflammatory marker CRP[1,12,13]. 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[18,21]. Participants are instructed to draw lines as quickly as possible sequentially connecting arrayed numbered items 1–25. Completion times were transformed into T-scores based on published age and education stratified normative data. The TMT-A was used to control for the influence of basic attentional function on the relationship between inflammation and attentional bias.

2.7. Questionnaires

Depressive symptoms were assessed with the Beck Depression Inventory-II[23], a 21-item measure that assesses severity of depressive symptoms over the past 2 weeks. The BDI-II was used to control for the influence of current emotional state on the relationship between inflammation and bias.

2.8. Data Analysis

Multiple regression analyses were used to examine associations between CRP, IL-6, and attentional bias. Covariates included chemotherapy, radiation, use of anti-depressant/anti-inflammatory medications (yes/no), time since last treatment, age, and BMI, which may influence inflammation and/or attentional bias[6,13,16]. CRP and IL-6 were log-transformed prior to all analyses. Analyses were performed in Stata 13.1 (StataCorp, College Station, TX). Statistical significance was set at $p < .05$.

3. Results

Participants were on average 57 years old (*SD*=7.85; range=36 to 69 years) and 4.8 years post-diagnosis (*SD*=.67; range 3.6–6.8 years). Most of the women had Stage I (n=44; 48%) and II (n=27; 30%) breast cancer. Fifty women (55%) had received chemotherapy and

67(74%) had received radiation treatment; 16(18%) were on anti-inflammatory and 19(21%) were on antidepressant medications. CRP levels ranged from .2 to 11.9 mg/L (M=2.43, SD=2.72), and IL-6 levels ranged from .3 to 5.1 pg/L (M=1.25, SD=.92); both markers were low relative to population norms[24,25]. Average scores for depressive symptoms were low on the BDI-II (M=7.7, SD=7.03) with 79% in the minimal range, 13% in the mild range, and 8% in the moderate range. Compared to published normative data, nearly all participants performed within normal limits or better on TMT-A; only one participant's performance fell in the impaired range. Response time on the dot probe task was comparable to that of individuals without cancer[26]. CRP was associated with depressive symptoms, (p=.03), but IL-6 was not (p=.15) (see Table 1).

3.1. Inflammation and Attentional Bias

As hypothesized, circulating concentrations of CRP were positively correlated with sad attentional bias (p=.03), such that higher levels of CRP were associated with greater attention towards sad faces. This association remained significant in analyses that additionally controlled for demographic and treatment-related covariates, b=6.92, t(85)=2.11, p=.04, for depressive symptoms and TMT-A, b=7.1, t(83)=2.08, p=.04, and for medications, b=6.81, t(82)=1.99, p=.05, but not for BMI, b=6.31, t(81)=1.59, p=.12.

Exploratory analyses suggested that CRP was also associated with attentional bias away from happy faces, though this effect was not significant (p=.13). Controlling for demographic, treatment-related and medication covariates yielded a significant association between CRP and attentional bias away from happy faces, b=-5.69, t(82)=-2.02, p=.046, but this association was not significant when additionally controlling for depressive symptoms and TMT-A, b=-5.56, t(80)=-1.89, p=.062, or BMI, b=-5.35, t(81)=-1.79, p=.077. We found no association between CRP and angry bias, and IL-6 did not predict attentional bias in any model. Of note, no covariates, including BMI, depressive symptoms, and TMT-A, predicted attentional bias in *any* of the regression models.

4. Discussion

This study examined whether inflammation was associated with negative attentional bias, a fundamental psychological process that underlies depressive symptomology, in a sample of women with a history of breast cancer (approximately 5 years post-diagnosis). As hypothesized, CRP was positively associated with sad attentional bias, indicating that women with higher CRP also attended more to sad than neutral faces. This association was not evident with IL-6, but as a downstream marker of inflammation[27], CRP may be a more stable indicator of chronic inflammation than IL-6.

Exploratory analyses revealed a trend for women with higher CRP to attend less to happy than neutral faces. This is consistent with the finding for sad faces, as avoidance of positive stimuli is also a feature of depressive symptomatology[28]. While there was no association between inflammation and angry faces, the stimuli in our study were presented for 1000ms, a relatively long exposure time that likely captures processes central to depression (like difficulty disengaging from negative stimuli or avoidance of positive stimuli[28]) rather than processes central to anxiety (like initial orientation towards threatening stimuli)[9].

Sad attentional bias remained significant when controlling for current depressive symptoms, suggesting that the effects may be independent of state dysphoria. This is consistent with past research showing that attentional bias is not only a symptom of depression, but may also represent a more general tendency that increases risk for depression[9]. The association between CRP and sad bias also remained when controlling for basic attentional functioning, suggesting that it is the emotional component of sad attentional bias that is related to inflammatory processes. Of note, while this association was rendered marginal when BMI was accounted for, BMI itself was not related to sad attentional bias. This suggests that BMI may contribute to post-treatment inflammation, which then influences attentional bias.

Overall, these results identify attentional bias as a novel pathway through which inflammation may influence depression. This finding is directly relevant for breast cancer survivors, who are at elevated risk for depression and may be particularly sensitive to neural effects of inflammation[29], and may also be evident outside of the cancer context. Indeed, our results are consistent with research showing that inflammation heightens the salience of negative emotional stimuli in healthy participants. For example, in comparison to placebo control, participants administered endotoxin demonstrate greater amygdala activation in response to negative feedback[30] and fearful, but not happy, faces[31]. Following typhoid vaccine, healthy participants exhibit decrements in mood that are associated with greater reactivity to emotional faces (sad, angry, happy) in the subgenual anterior cingulate, an area associated with depression[4]. Additional work is needed to interrogate the relationship between inflammation and attentional bias in healthy participants, and in individuals at risk for depression due to medical conditions such as cancer or other risk factors.

This study is limited by its cross-sectional design. While our conceptual framework suggests inflammation contributes to sad attentional bias, it is also possible that greater negative attentional bias fosters higher levels of negative mood and stress, which in turn promotes systemic inflammation. The causal direction of this association should be addressed in experimental studies, which may benefit from inclusion of measures of attentional bias. Advancing our understanding of basic processes that contribute to the onset or maintenance of depressive symptoms has the potential to inform detection of vulnerable individuals and development of targeted treatment and prevention.

Acknowledgments

This research was supported by funding from the National Cancer Institute R01 CA 109650 and the Breast Cancer Research Foundation (to PAG) and the NIH/NIMH Predoctoral Fellowship 5T32MH015750-35 (CCB)

References

1. Howren BM, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. (2009). Psychosom Med. 2009; 71(2):171–186. [PubMed: 19188531]
2. Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med. 2009; 39(3):413–423. [PubMed: 18533059]
3. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27(1):24–31. [PubMed: 16316783]

4. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009; 66(5):407–414. [PubMed: 19423079]
5. Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: An inflammatory challenge induces feelings of social disconnection in addition to depressed mood. Brain Behav Immun. 2010; 24(4):558–563. [PubMed: 20043983]
6. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol Bul. 2014; 140(3):774–815.
7. Steptoe A, Kunz-Ebrecht SR, Owen N. Lack of association between depressive symptoms and markers of immune and vascular inflammation in middle-aged men and women. Psychol Med. 2003; 33(4):667–674. [PubMed: 12785468]
8. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: The seven pillars of RDoC. BMC Medicine. 2013; 11(1):1–26. [PubMed: 23281898]
9. Gibb BE, McGeary JE, Beevers CG. Attentional biases to emotional stimuli: Key components of the RDoC constructs of sustained threat and loss. Am J Med Genet B Neuropsychiatr Genetics. 2015; 171(1):65–80.
10. Peckham AD, McHugh RK, Otto MW. A meta-analysis of the magnitude of biased attention in depression. Depress Anxiety. 2010; 27(12):1135–1142. [PubMed: 21049527]
11. Irwin MR, Olmstead R, Ganz PA, Haque R. Sleep disturbance, inflammation and depression risk in cancer survivors. Brain Behav Immun. 2013; 30:S58–S67. [PubMed: 22634367]
12. Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. Int Rev Psychiatr. 2014; 26(1):16–30.
13. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: Short-term friend, long-term foe. Clin Cancer Res. 2009; 15(2):425–30. [PubMed: 19147746]
14. Dantzer R, Meagher MW, Cleeland CS. Translational approaches to treatment-induced symptoms in cancer patients. Nat Rev Clin Oncol. 2012; 9(7):414–426. [PubMed: 22641361]
15. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: Do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol. 2011; 29(26):3517–3522. [PubMed: 21825266]
16. Ganz PA, Bower JE, Kwan L, Castellon SA, Silverman DHS, Geist C, Breen EC, Irwin MR, Cole SW. Does tumor necrosis factor-alpha (TNF-α) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun. 2013a; 30(Suppl):S99–108. [PubMed: 22884417]
17. Cheung YT, Ng T, Shwe M, Ho HK, Foo KM, Cham MT, Madhukumar P. Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: A multi-centered, prospective, cohort study. Ann Oncol. 2015; 26(8):1446–51. [PubMed: 25922060]
18. Ganz PA, Kwan L, Castellon SA, Oppenheim A, Bower JE, Silverman DHS, Cole SW, Irwin MR, Ancoli-Israel S, Belin TR. Cognitive complaints after breast cancer treatments: Examining the relationship with neuropsychological test performance. J Natl Cancer Inst. 2013b; 105(11):791–801. [PubMed: 23606729]
19. Ganz PA, Petersen L, Bower JE, Crespi CM. Impact of adjuvant endocrine therapy on quality of life and symptoms: Observational data over 12 months from the Mind-Body Study. J Clin Oncol. 2016; 34(8):816–824. [PubMed: 26786934]
20. MacLeod C, Mathews AM, Tata P. Attentional bias in emotional disorders. J Abnorm Psychol. 1986; 95:15–20. [PubMed: 3700842]
21. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, Marcus DJ, Westerlund A, Casey BJ, Nelson C. The NimStim set of facial expressions: Judgments from untrained research participants. Psychiat Res. 2009; 168(3):242–249.
22. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011; 12(7):703–708. [PubMed: 21354373]
23. Beck, AT., Steer, RA., Brown, GK. Beck depression inventory-II. San Antonio, TX: 1996. p. 78204-2498.

24. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. New Engl J Med. 2005; 352(15):1611–1613.

25. Kim HO, Kim HS, Youn JC, Shin EC, Park S. Serum cytokine profiles in healthy young and elderly population assessed using multiplexed bead-based immunoassays. J Transl Med. 2011; 9(1):113. [PubMed: 21774806]

26. Mather M, Carstensen LL. Aging and attentional biases for emotional faces. Psychol Sci. 2003; 14(5):409–415. [PubMed: 12930469]

27. Epstein FH, Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. New Engl J Med. 1999; 340(6):448–54. [PubMed: 9971870]

28. Winer ES, Salem T. Reward devaluation: Dot-probe meta-analytic evidence of avoidance of positive information in depressed persons. Psychol Bull. 2016; 142(1):18–78. [PubMed: 26619211]

29. Muscatell KA, Eisenberger NI, Dutcher JM, Cole SW, Bower JE. Links between inflammation, amygdala reactivity, and social support in breast cancer survivors. Brain Behav Immun. 2016; 53:34–38. [PubMed: 26384778]

30. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, Irwin MR, Eisenberger NI. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav Immun. 2016:1–9.

31. Inagaki TK, Muscatell KA, Irwin MR, Cole SW, Eisenberger NI. Inflammation selectively enhances amygdala activity to socially threatening images. NeuroImage. 2012; 59(4):3222–3226. [PubMed: 22079507]

Table 1

Correlations for Study Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Sad Bias													
2. Happy Bias	−.157												
3. Angry Bias	.097	−.132											
4. CRP	.224*	−.152	−.064										
5. IL6	.117	−.073	.011	.548***									
6. BDI-II	.047	−.077	.040	.227*	.151								
7. TMT-A	.060	.072	.091	.016	−.056	−.091							
8. Chemotherapy	.068	−.065	.082	−.031	.032	−.003	−.018						
9. Radiation	−.039	−.169	−.047	.028	.049	−.034	−.061	.112					
10. Time since last treatment	.167	−.143	.006	.054	−.014	.158	.103	−.171	−.120				
11. Age	−.062	−.117	−.068	.009	.148	.042	−.297**	−.266*	.130	−.013			
12. BMI	.132	−.081	−.138	.516***	.482***	.172	.094	−.006	.043	.024	.093		
13. Anti-inflammatory	−.100	.085	−.263*	−.035	−.034	−.126	−.085	−.042	.083	−.058	.154	.070	
14. Anti-depressant	.062	.129	−.112	.207	.184	.146	−.054	.091	−.058	.088	.166	.235*	.111

Note. CRP=C-reactive protein; IL-6=Interleukin-6; BDI-II=Beck Depression Inventory-II; TMT-A = Trail Making Test-A.

* p<.05,

** p<.01,

*** p<.001.