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Neural responses to threat and reward and changes in inflammation following a mindfulness intervention

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ABSTRACT

Objective: Mindfulness meditation has been shown to reduce distress and increase well-being among individuals with chronic disease, including breast cancer survivors. However, the neural correlates of these changes and their links with inflammatory biology are not yet known. The present study examined whether a mindfulness meditation intervention was associated with changes in neural responses to threat and reward from pre- to post-intervention, and whether those neural changes were associated with changes in markers of inflammation in breast cancer survivors.

Methods: This was a single-arm trial of a standardized, validated 6-week mindfulness meditation intervention. Participants were 20 women who had been diagnosed and treated for early-stage breast cancer. Participants provided peripheral blood samples and underwent a 90-minute neuroimaging scan before and after the intervention, with a focus on tasks known to elicit activity in threat- and reward-related neural regions.

Results: There were significant changes in neural responses to the two tasks of interest from pre to post-intervention ($ps < 0.042$). Participants showed significant reductions in amygdala activity in response to threatening images and significant increases in ventral striatum activity to rewarding images from pre- to post-intervention. Although changes in amygdala activity were not correlated with inflammatory markers, increases in ventral striatum activity were correlated with decreases in circulating concentrations of the proinflammatory cytokine IL-6 and the inflammatory marker CRP.

Conclusions: These results, while preliminary, suggest that while a mindfulness meditation intervention can alter neural responses to both threat and nonsocial reward-related stimuli, changes in neural reward activity may be more closely linked to changes in circulating levels of inflammation.

1. Introduction

A large body of literature has documented benefits of mindfulness meditation for mental health, including reductions in stress and distress and increases in positive affect and other positive psychological states (Brewer et al., 2009; Chin et al., 2019; Creswell et al., 2014; Garland et al., 2015; Geschwind et al., 2011; Kober et al., 2017; Lindsay et al., 2018a, 2018b). Mindfulness meditation has also been shown to modulate inflammatory biology, leading to decreases in markers of inflammation in a number of randomized controlled trials (Creswell et al., 2012; Jedel et al., 2014; Malarkey et al., 2013). However, the neurobiological mechanisms for these effects have not been determined. The current study investigated whether mindfulness training was associated with changes in activity of threat- and reward-related neural regions, and whether these changes were linked to changes in circulating markers of inflammation in breast cancer survivors. Elevated inflammation is particularly relevant for this group given links with cancer-related symptoms and long-term survival (Bower, 2019; Pierce

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et al., 2009).

One of the most widely-studied neural regions implicated in responding to threat—the amygdala—has been of particular interest to researchers studying how mindfulness training reduces stress. Dispositional mindfulness has been linked with lower levels of amygdala reactivity to threatening or emotional stimuli (Creswell et al., 2007; Way et al., 2010). Similarly, mindfulness meditation training has been shown to reduce amygdala reactivity to negative, emotional images (Desbordes et al., 2012; Kober et al., 2017; Leung et al., 2018), particularly among individuals who engage in more meditation practice (Kral et al., 2018). Mindfulness training has also been linked with reduced amygdala activity during a breath-focused attention task in a single-arm trial (Goldin and Gross, 2010), highlighting the amygdala's potential as a neural region of interest in mindfulness meditation training studies.

Mindfulness training has also been linked to reward-related neural regions, including the ventral striatum (VS). In particular, mindfulness meditation training leads to reduced cue reactivity in the VS in smokers or patients addicted to opioids (Froeliger et al., 2017; Garland et al., 2014). Furthermore, experienced meditators showed reduced VS reactivity to monetary incentives compared to non-meditators (Kirk et al., 2015). Reduced reward system activity to drug cues and monetary incentives might be adaptive, particularly among individuals struggling with addiction. However, mindfulness interventions also promote cultivating and savoring positive experiences, and might be expected to increase neural activity in response to other types of reward. To date, effects of mindfulness training on neural responses to positive stimuli, such as viewing positive non-monetary images that are known to evoke increases in VS activity, have not been examined.

Both the threat and reward systems in the brain have outputs to physiological stress response systems that enable the organism to respond to the environment, including effects on the immune system and inflammation (Eisenberger and Cole, 2012). Indeed, stress- and emotion-related activity in regions in the threat system in the brain (amygdala, dorsal anterior cingulate cortex) have been associated with increased inflammatory activity (Gianaros et al., 2014; Kraynak et al., 2018; Muscatell et al., 2015, 2016; Swartz et al., 2017). An emerging body of evidence suggests that activity in reward-related neural regions might also be linked with immunity (Dutcher and Creswell, 2018). For example, activating the neural reward system in preclinical models is related to improved innate immunity (Ben-Shaanan et al., 2016) and enhanced anti-tumor immunity (Ben-Shaanan et al., 2018). In humans, positive affect, pro-social behaviors and eudaimonic well-being are associated with lower levels of inflammation (Fredrickson et al., 2013, 2015; Moieni et al., 2019; Moreno et al., 2016; Pressman et al., 2019; Seeman et al., 2020), though links between increases in activity in reward-related neural regions and downstream inflammatory processes have not yet been examined.

Despite evidence that mindfulness meditation leads to changes in neural processes, and the well-documented links between the CNS and the immune system, surprisingly few studies have examined the association between changes in neural and immune activity following mindfulness training. Indeed, to our knowledge, only one previous study has linked changes in brain activity and changes in inflammation following mindfulness training, showing an association between changes in resting state functional connectivity and reductions in levels of the proinflammatory cytokine IL-6 (Creswell et al., 2016). Thus, the primary goal of this study was to evaluate changes in neural reactivity and their association with immune processes following a standardized mindfulness intervention. We have previously shown that a 6-week mindfulness meditation intervention decreased inflammatory signaling, reduced stress and depressive symptoms, and increased positive affect and meaning relative to wait list control in younger breast cancer survivors (Bower et al., 2015). We recently replicated these effects in a single-arm trial with younger breast cancer survivors (Boyle et al., 2019). The current study was designed to identify neural mechanisms underlying these effects, and specifically to probe links with systemic inflammation. We hypothesized that following mindfulness training participants would show decreases in amygdala reactivity to threatening stimuli and increases in VS reactivity to rewarding stimuli. Further, we hypothesized that these changes would be linked to changes in circulating markers of inflammation. We focused on the proinflammatory cytokine IL-6 and on CRP, as elevated levels of IL-6 and CRP have been linked to cancer-related behavioral symptoms (Bower, 2019; Low et al., 2014) and predict survival in breast cancer survivors (Pierce et al., 2009). Because the primary goal of this study was to examine links *between* neural and immune processes (rather than documenting intervention effects on these outcomes), the single-arm trial design was determined to be appropriate (Goldin and Gross, 2010).

2. Methods

2.1. Participants

Participants were women diagnosed with early stage breast cancer (Stage 0-III) at or before the age of 50. All participants had completed primary treatment (surgery, chemotherapy, radiation) at least three months before study enrollment and had no evidence of active disease. All participants were scanner eligible (i.e., right-handed, not claustrophobic, free of ferrous metal implants, not pregnant). Participants were excluded if they had mindfulness meditation experience or medical conditions that involved the immune system (e.g., autoimmune or inflammatory disease).

Potential participants were identified through the UCLA Tumor Registry or physician referral. Letters describing the study were mailed to 512 women and 197 responses were received. Of these, 49 women did not meet inclusion criteria, primarily due to claustrophobia (n = 16), left-handedness (n = 13), or prior mindfulness meditation experience (n = 8). 126 women declined to participate, primarily because they were too busy or lived too far away (n = 89). This left a sample of 22 women who were eligible and able to participate. Two participants did not have complete fMRI data (one did not have a baseline scan session, another did not have a post-intervention scan session), resulting in a sample of 20 women who completed all procedures. The UCLA IRB approved all study procedures, and participants were compensated $100 in total for their participation.

2.2. Procedures

2.2.1. In-person assessment sessions

After providing informed consent, eligible participants completed an in-person assessment at UCLA within two weeks of the start and end dates of the intervention. In-person assessment sessions were scheduled between 8:00 a.m. and 11:00 a.m. to control for potential diurnal variation in inflammatory markers. After signing informed consent, 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 during which they completed a threat reactivity task and a reward reactivity task. Participants also completed a resting state scan, a compassion task, an emotion regulation task, and a values affirmation task, results of which will be reported elsewhere. During the scan, participants viewed trials through scanner-compatible goggles and were asked to make responses (when appropriate) using a 4-button box. Following the scan, participants completed questionnaire measures.

2.2.2. Mindfulness meditation intervention

Participants completed a standardized 6-week mindfulness meditation-based intervention called Mindful Awareness Practices (MAPs), which was developed by Diana Winston and colleagues at the Mindfulness Awareness Research Center at UCLA. Participants met once per week for a 2-hour group session and were instructed to practice

mindfulness exercises at home (starting at 5 and progressing up to 20 min daily). Three cohorts of women completed the study between May and November of 2015, with group size ranging from 6 to 10.

MAPs is a manualized intervention that has been used in several previous studies (Black et al., 2015; Bower et al., 2015). Class sessions included presentation of theoretical materials on mindfulness, relaxation, and the mind-body connection and experiential practice of meditation (e.g., mindful breathing) and gentle movement exercises (e.g., mindful walking). The MAPs program also teaches mindful approaches to working with difficult emotions and techniques for cultivating positive emotions.

2.3. Measures

2.3.1. Participant characteristics

As previously reported (Boyle et al., 2019), participants completed self-report measures for assessment of demographic, medical, and treatment-related characteristics at the initial in-person session. Participants also completed psychological measures, including symptoms of depression in the past week using the 20-item Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977). Internal consistency for the CES-D was high ($\alpha > 0.84$).

2.3.2. fMRI image acquisition

Imaging data were acquired using a Siemens Prisma 3.0 Tesla MRI scanner at the UCLA Ahmanson-Lovelace Brain Mapping Center. First, we acquired a T1-weighted MPRAGE anatomical image for functional image registration and normalization (slice thickness = 0.90 mm, 192 slices, TR = 2300 ms, TE = 2.32 ms, flip angle=8 degrees, matrix = 256 × 256, FOV = 240 mm, bandwidth = 200 Hz/Px). Then, we acquired functional T2-weighted EPI volumes for each task (slice thickness = 3 mm, 3 mm *isovoxel,* 36 slices, TR = 2000 ms, TE = 24 ms, flip angle=90 degrees, matrix = 64 × 64, FOV = 200 mm, bandwidth = 2604 Hz/Px).

2.3.3. Threat reactivity task

To examine threat reactivity, participants 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., 2002), and completed blocks of a shape-matching task, which served as the comparison condition (Lieberman et al., 2007). Each block lasted 25 s, followed by 10 s of a fixation crosshair. During the threat processing blocks, participants were instructed to passively view 5 threatening facial expressions (angry or 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 5 different sets of shapes were presented during each block. Participants completed four blocks of each type, in randomized order, at both timepoints. Participants saw a different random order at each timepoint.

2.3.4. Reward reactivity task

To examine reward reactivity, participants completed a task in which they passively viewed blocks of images in three different categories from two validated databases, the Nencki Affective Picture System (NAPS) (Marchewka et al., 2014) and the Geneva Affective Pictures Dataset (GAPED) (Dan-Glauser and Scherer, 2011). Passive viewing of positive images has been used in prior studies to assess activity in the ventral striatum (Epstein et al., 2006; Heller et al., 2013; Inagaki et al., 2015a) and use of NAPS and GAPED in the current study ensured no repetition of images. The categories included: images of landscapes and sunsets without people (nonsocial reward images), images of people smiling and interacting (social reward images), and images of common household objects like cups and furniture (neutral images). For each 25 s block, participants were instructed to view 5 images for 5 s each, and to pay attention to and experience any feelings or thoughts that the pictures might bring up. Because this was not a previously validated task, we had participants rate how happy they were feeling on a 1 (not at all) to 4 (a lot) scale to ensure the task evoked positive feelings. This was then followed by 5 s of a fixation crosshair. Participants completed four blocks of each type (nonsocial, social, and neutral), in randomized order.

As a manipulation check at baseline, viewing social reward images led to significantly higher ratings of positive affect ($M = 3.58$, $SD = 0.469$) compared to the neutral images (M=2.684, SD =0.920), $t(18) = 3.302$, $p = 0.004$. Viewing nonsocial reward images led to a nonsignificant trend of higher ratings of positive affect ($M = 3.139$, $SD = 0.724$) compared to the neutral images ($M = 2.684$, $SD = 0.920$), $t(17) = 1.664$, $p = 0.114$.

2.3.5. Inflammatory assessments

Plasma levels of IL-6 and CRP were determined using a high sensitivity enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minn, for IL-6; ImmunDiagnostik, American Laboratory Products Company [ALPCO], Salem, NH, for CRP). All samples were run in duplicate, and samples for an individual participant were run in parallel to avoid interassay variability. The intra- and inter-assay coefficients of variation (CVs) for IL-6 and CRP assays were all less than 5%. Lower limits of detection were 0.2 pg/mL for IL-6 and 0.2 mg/L for CRP. One undetectable IL-6 value was imputed to 50% of the lower limit of detection.

2.4. Data analysis

2.4.1. Neuroimaging data

Imaging data were analyzed using Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). Prior to preprocessing, images were manually reoriented to maximize preprocessing alignment quality. For preprocessing, functional and anatomical images were realigned, co-registered to the structural scan, and normalized using the DARTEL procedure in SPM8. For the threat reactivity task, the 25 s threat blocks were modeled as the threat condition, and the 25 s shape matching blocks were modeled as the control condition. For the reward reactivity task, the 25 s blocks displaying images of landscapes and sunsets were modeled as the nonsocial reward condition, the 25 s blocks displaying images of people were modeled as the social reward condition, and the 25 s blocks displaying images of common household objects were modeled as the control condition. Implicit baseline consisted of the rest periods (viewing a fixation cross). Activation during each block was convolved with a canonical hemodynamic response function. Six motion parameters were included as nuisance predictors plus a predictor for each timepoint that the global signal change (GSC) exceeded 2.5 SDs of the mean GSC or where estimated motion exceed 1.5 mm of translation or 1.5° of rotation. No subjects showed excessive motion, so all available participants are included in analyses. We used a 128 Hz high-pass filter, and serial autocorrelation was modeled as an AR(1) process.

For the threat reactivity task, we computed linear contrasts for each participant at each timepoint that compared BOLD signal for one main contrast of interest: threat vs. control. For the reward reactivity task, we computed linear contrasts for each participant at each timepoint that compared BOLD signal for two main contrasts of interest: nonsocial reward vs. control and social reward vs. control. These individual contrast images were then used in group-level analyses testing whether there were changes in neural activity at post-intervention compared to baseline.

We conducted region-of-interest (ROI) analyses focusing on the hypothesized regions for each task and averaging across all voxels in the ROI. For the threat reactivity task, previous work has found this task to reliably activate the amygdala, thus we focused on amygdala ROIs. Amygdala ROIs were defined anatomically based on the Automated

Anatomical Labeling atlas (left amygdala: $-36 < x < -18$, $-8 < y < 6$, $-30 < z < -12$; right amygdala: $12 < x < 30$, $-8 < y < 4$, $-28 < z < -12$). Mean parameter estimates were extracted from the amygdala ROIs for each participant for each timepoint using Marsbar and entered into SPSS for further analysis. For the reward reactivity task, previous work has identified the ventral striatum as a key hub in the reward network (Izuma et al., 2008), so we focused on ventral striatum (VS) ROIs. The right VS ROI was structurally defined using the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002); caudate nucleus and putamen from the atlas were combined and constrained at x between 0 and 10, y between 4 and 18, and z between 0 and –12. The left VS ROI was defined the same way and constrained at x between 0 and −10, y between 4 and 18, and z between 0 and –12. Mean parameter estimates were extracted from the VS ROIs for each participant for each timepoint using Marsbar and entered into SPSS for further analysis.

2.4.2. Inflammatory data

Inflammatory data were positively skewed, so raw values were natural log transformed to normalize the distribution prior to statistical testing. Change scores thus reflect the difference between log corrected values at post-intervention minus the natural log corrected values at baseline. Reported means and standard deviations for IL-6 and CRP are of raw untransformed values.

2.4.3. Analytic approach

Preliminary analyses examined changes in neural reactivity from pre to post-intervention using paired samples *t*-tests, and changes in circulating markers of inflammation using repeated measures ANCOVA models with age and BMI—covariates known to be related to inflammation (O'Connor et al., 2009). Analyses indicating significant change in either left or right neural reactivity were followed up by regression models to directly test for evidence of asymmetry (i.e., a statistically significant difference between the left and right ROI response). We calculated left/right difference change scores (change in left amygdala minus change in right amygdala; change in left VS minus change in right VS) for use as outcome variables. A significant intercept would indicate that pre-to post intervention differences significantly differed for left and right ROI estimates.

The primary analyses focused on links between changes in neural reactivity and changes in inflammatory biology using multiple regression. Separate regression models were estimated to test the association between changes in the three neural contrasts of interest – threat vs. control, nonsocial reward vs. control, and social reward vs. control – and changes in the two inflammatory markers (IL-6, CRP). Baseline inflammation was included as a covariate to control for the confounding effects of baseline levels of inflammation (e.g., *higher* baseline levels of IL-6 were correlated with greater increases in amygdala activity, $r = 0.516$, $p = 0.020$; *see* Supplementary Material for additional analyses), and analyses controlled for age and BMI. Antidepressant use was examined but not included as an additional covariate because it was not a significant predictor and did not alter the results in any analysis.

Significant analyses were followed up by regression models to test for evidence of asymmetry in the relationship between neural changes and changes in inflammation. For these analyses, the predictor of interest was a left/right difference change score (evaluating amygdala response and VS response to non-social and social images in separate analyses; *See* Supplementary Materials for each condition compared to implicit baseline). Significance was set at $p < 0.05$ (two-tailed) for all analyses.

3. Results

3.1. Participant characteristics

Participants were, on average, 46.6 years old (range = 38–52 years), primarily non-Latina white (n = 12, 60%) and had been diagnosed with early stage breast cancer between 2010 and 2014. On average, depressive symptoms were elevated at baseline relative to population norms (Radloff, 1977), and were comparable to other studies of younger breast cancer survivors participating in mindfulness interventions (Bower et al., 2015). Nine women (40%) endorsed clinically significant depressive symptoms as indicated by scores greater than or equal to 16 on the CES-D, and five women reported taking anti-depressant medication at baseline. Circulating levels of IL-6 and CRP were comparable to or below population norms (Kim et al., 2011; Woloshin and Schwartz, 2005) (See Table 1 for demographic, medical, treatment-related, and psychosocial characteristics). Intervention adherence was high; on average, women attended 5.65 out of 6 sessions (range = 4–6 sessions) with fifteen women (75%) attending all six sessions (mean session attendance = 5.65, range 4–6). Additional minutes of home practice ranged from 115 to 651 ($M = 328.1$). As we have previously reported, there were significant reductions in depressive symptoms ($t(19) = -2.55$, $p = 0.020$, $d = 0.57$), and significant increases in eudaimonic well-being ($t(19) = -2.55$, $p = 0.020$, $d = 0.57$), from pre-to post--intervention (Boyle et al., 2019).

3.2. Neuroimaging analyses from pre-to post mindfulness training

3.2.1. Threat reactivity task

Consistent with our hypotheses, there was a significant decrease in right amygdala activity in response to threat (vs. control) stimuli from pre- to post-intervention ($t(19) = -2.177$, $p = 0.042$, Cohen's $d = 0.487$; See Fig. 1). The change in left amygdala activity from pre- to post-intervention to threat (vs. control) stimuli did not reach significance ($t(19) = -1.003$, $p = 0.329$, Cohen's $d = 0.224$), but there was no evidence that the change in right amygdala activity in response to threat was significantly different from the change in left amygdala activity in response to threat (intercept $b = 0.0439$, $p = 0.295$).

3.2.2. Reward reactivity task

Consistent with hypotheses, there was a significant increase in left VS activity in response to nonsocial reward vs. control from pre- to post-intervention ($t(19) = 2.419$, $p = 0.026$, Cohen's $d = 0.541$). The

Table 1
Demographic, medical and treatment-related characteristics of the sample.

	Total ($N = 20$)
Age, M (range)	46.55 (38–52)
Married or in a committed relationship, N (%)	16 (80%)
Race N (%)	
White	12 (60%)
Asian	5 (25%)
Other	3 (15%)
Family Yearly Income, N (%)	
$30,001-$60,000	3 (15%)
$60,001-$100,000	5 (25%)
Over $100,000	12 (60%)
Employment, N (%)	
Employed full or part-time	12 (60%)
Homemaker/volunteer	6 (30%)
Retired, on leave, unemployed	2 (10%)
Body Mass Index, M (range)	24.1 (18.5–36.6)
Years since diagnosis, M (range)	2.08 (1.4-0.5.1)
Cancer stage, N (%)	
0	4(20%)
1	4(20%)
2	11(55%)
3A	1 (5%)
Cancer treatments received, N (%)	
Chemotherapy	11 (55%)
Radiation therapy	12 (60%)
Current endocrine therapy	8 (40%)
Baseline CES-D, M (SD)	14 (9.75)
Baseline IL-6 (pg/mL), M (SD)	1.14 (1.07)
Baseline CRP (mg/mL), M (SD)	2.49 (3.36)

Note. M = mean; SD = standard deviation; CES-D = Center for Epidemiological Studies Depression Scale; IL-6 = Interleukin-6; CRP = C-reactive protein.

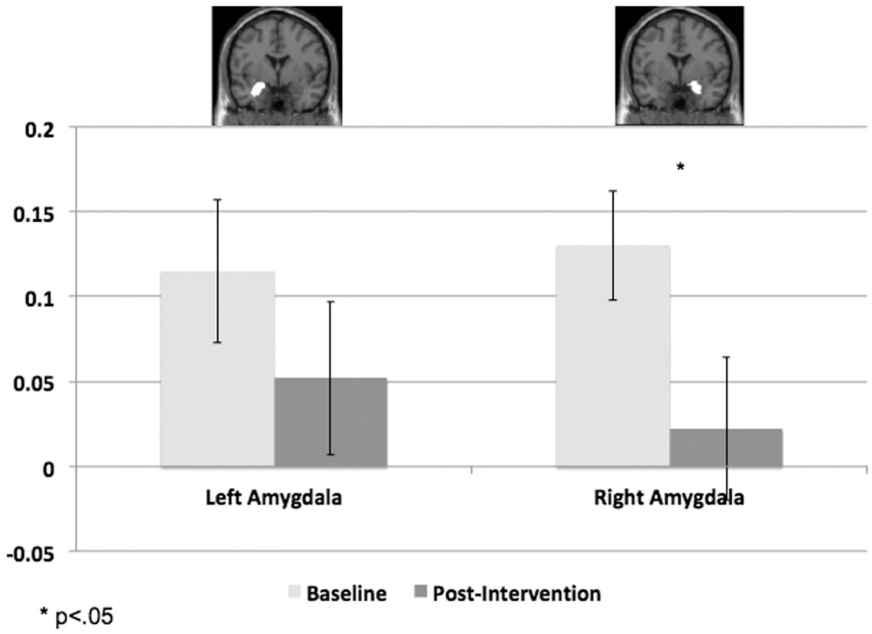

Fig. 1. Changes in amygdala activity to the threat reactivity task from baseline to post-intervention.

change in right VS activity did not reach significance ($t(19) = 1.504$, $p = 0.149$, Cohen's $d = 0.337$; See Fig. 2A), but there was no evidence that the change in left VS activity in response to nonsocial reward was significantly different from the change in right VS activity in response to nonsocial reward (intercept $b = 0.040$, $p = 0.203$). For social reward, there was no significant change in either the left VS ($t(19) = -1.293$, $p = 0.212$, Cohen's $d = 0.289$) or the right VS ($t(19) = -1.430$, $p = 0.169$, Cohen's $d = 0.320$, see Fig. 2B) from pre to post-intervention.

3.3. Inflammation analyses from pre-to post mindfulness training

Consistent with previous reports (Bower et al., 2015; Boyle et al., 2019), there was no significant change in circulating levels of IL-6 from pre-intervention ($M = 1.135$ pg/mL, $SD = 1.074$) to post-intervention ($M = 0.990$ pg/mL, $SD = 0.482$), $F(1, 17) = 0.222$, $p = 0.644$. Similarly, there was no significant change in CRP from pre-intervention ($M = 2.485$ mg/mL, $SD = 3.363$) to post-intervention (M = 2.465 mg/mL, SD = 3.602), $F(1, 17) = 0.982$, $p = 0.336$. However, there was sufficient variability in change scores (IL-6 range = −3.5 pg/mL to +1.0 pg/mL; CRP range = −7.8 to 9.8 mg/mL) to investigate the relationship between changes in inflammation and changes in neural activity to the two tasks.

3.4. Association between changes in neural activity and inflammation

Regression analyses were used to test the primary hypothesis that changes in neural activity would be associated with changes in inflammation following mindfulness training. Contrary to hypotheses, the relationship between decreases in right and left amygdala activity in response to threat (vs control) and decreases in IL-6 or CRP from pre- to post-intervention did not reach significance (all $ps > 0.075$). In contrast, increases in left VS activity to nonsocial reward images were associated with decreases in both IL-6 ($b = -1.648$, $SE = 0.358$, $p < 0.001$; see

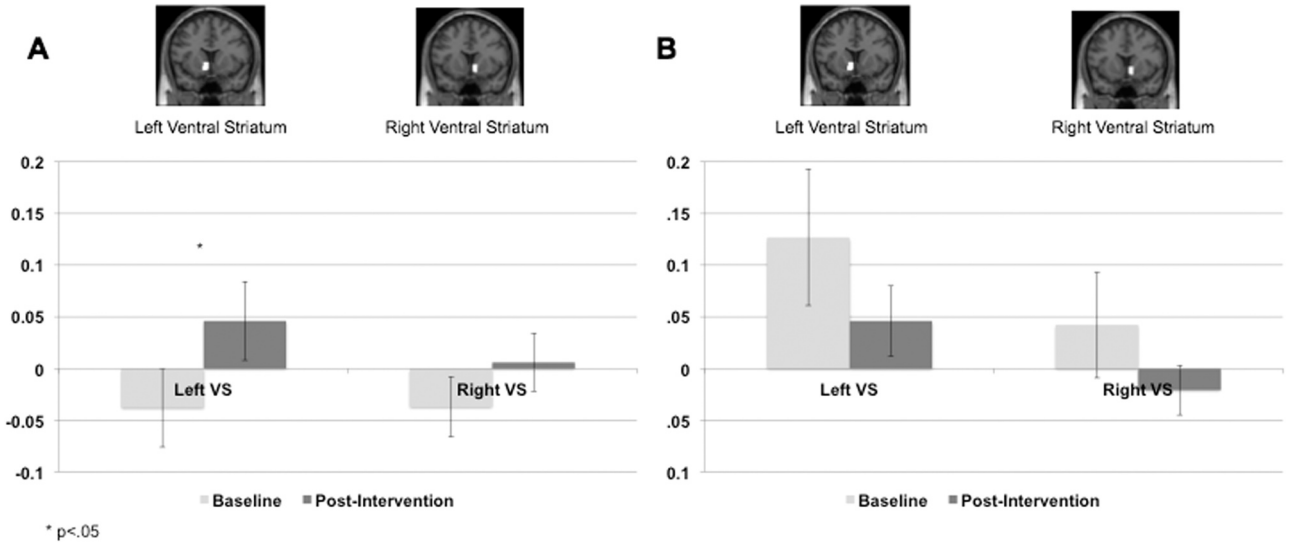

Fig. 2. Changes in ventral striatum activity to the reward reactivity task from baseline to post-intervention. Panel A shows neural activity to the nonsocial condition (vs. control), and Panel B shows neural activity to the social condition (vs. control).

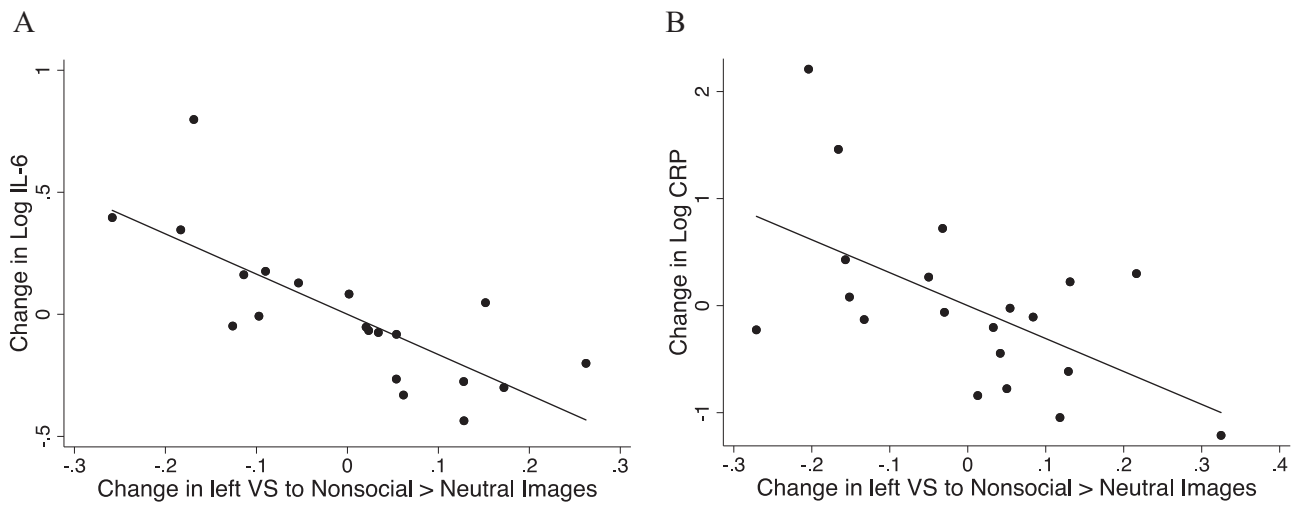

Fig. 3. Increases in left ventral striatum activity (to nonsocial vs. control) from baseline to post-intervention are associated with decreases in IL-6 (Panel A) and CRP (Panel B) from baseline to post-intervention.

Fig. 3A) and CRP ($b = -3.077$, $SE = 1.148$, $p = 0.017$; see Fig. 3B). Thus, as predicted, women who showed a greater increase in left VS activity to nonsocial vs. control images from pre- to post-intervention had greater decreases in two inflammatory markers. Changes in right VS activity to nonsocial images was not significantly associated with IL-6 or CRP (all *ps*>0.525), and the association between increases in VS activity to nonsocial reward images and decreases in IL-6 was significantly greater for the left compared to the right VS ($b = -1.468$, $SE = 0.441$, $p = 0.005$) with a similar pattern in association with decreases in CRP ($b = -3.194$, $SE = 1.420$, $p = 0.040$). There was no association between changes in VS activity to social images and inflammation (all *ps*>0.392).

4. Discussion

Mindfulness meditation interventions have been shown to reduce negative emotional states, increase positive emotional states, and modulate inflammatory signaling in younger breast cancer survivors and other groups (Bower et al., 2015; Boyle et al., 2019; Garland et al., 2015; Geschwind et al., 2011; Lindsay et al., 2018a, 2018b). The present study was designed to explore the neural mechanisms that might underlie these benefits and test for associations with markers of inflammation. Consistent with hypotheses, after a standardized 6-week mindfulness meditation intervention, younger breast cancer survivors showed lower right amygdala reactivity to threat stimuli and greater left VS reactivity to nonsocial rewarding images compared to baseline. Further, increases in left VS reactivity to nonsocial reward images were correlated with decreases in two key inflammatory markers: IL-6 and in CRP. However, changes in amygdala reactivity to threat and VS reactivity to social reward were not associated with changes in inflammation. Results suggest that mindfulness meditation may alter neural responses to both threat and reward stimuli, but that changes in neural reward reactivity may be more closely linked to circulating levels of inflammation than changes in neural threat reactivity.

Although changes in neural threat reactivity are proposed to underlie the effects of mindfulness training on health and stress, few studies have reported effects on activity in key neural threat regions including the amygdala. Here, we found reductions in amygdala reactivity from pre- to post-intervention using a standardized threat reactivity task. These amygdala reactivity results are consistent with conceptual models linking mindfulness to reduced threat reactivity (Creswell and Lindsay, 2014), and contribute to a small but growing literature showing mindfulness training and brief mindfulness induction reduce neural threat reactivity (Kober et al., 2017; Lutz et al., 2014). However, contrary to predictions, decreased amygdala reactivity to threatening images was not significantly correlated with changes in inflammatory markers in the current study. It is possible that more intensive or prolonged practice is needed for an attenuated neural response to threat to then buffer the biological cascade of the physiological stress response that leads to changes in circulating markers of inflammation (Marsland et al., 2017). Alternatively, changes in inflammation may be more closely tied to increased ability to regulate emotional responses, rather than decreased threat reactivity. Indeed, reductions in IL-6 following mindfulness training were previously associated with enhanced functional connectivity between the default mode network and the dorsolateral prefrontal cortex, an area implicated in executive control, suggesting more effective emotion regulation and stress resilience (Creswell et al., 2016). Moreover, in our previous study with younger breast cancer survivors, mindfulness training did not attenuate affective or autonomic reactivity to anxiety induction, but did facilitate more rapid recovery (Crosswell et al., 2017), indicative of improved emotion regulation during anxious experiences. These empirical findings have implications for theoretical models of mindfulness, which suggest that attending to present moment experience in a non-judgmental, accepting way may reduce threat reactivity (Brown and Ryan, 2003), or influence attentional deployment, appraisals and response modulation in ways that facilitate improved coping with threats (Slutsky et al., 2016).

Mindfulness meditation is also posited to exert beneficial effects on mental and physical health by increasing positive affect and rewarding experiences (Garland et al., 2015; Geschwind et al., 2011; Lindsay et al., 2018a). Enhanced present-moment awareness may not only reduce threat reactivity (Brown and Ryan, 2003), but also help individuals see their environment in a different way and deepen their appreciation for daily events, such as viewing a sunset, that might otherwise be missed or dismissed as mundane. Our findings are consistent with this perspective, and build upon a past literature that has primarily focused on mindfulness and reduced neural reward reactivity in the context of addiction or monetary reward (Froeliger et al., 2017; Garland et al., 2014). In particular, we found that viewing pictures of landscapes was associated with increases in left VS activity, and that these changes were in turn associated with decreases in inflammation. Growing evidence suggests that positive psychological processes are closely tied with immunity, perhaps even more so than negative psychological states (Cole et al., 2015; Marsland et al., 2007). We have previously shown that while mindfulness training is associated with both increases in well-being and decreases in negative psychological states, only increases in well-being were associated with alterations in expression of genes related to antiviral/antibody and inflammatory immune function (Boyle et al., 2019). Indeed, this is consistent with emerging neurobiological work with

animals demonstrating strong relationships between the brain's reward system and innate immunity and anti-tumor immunity (Ben-Shaanan et al., 2016, 2018), associations between psychological well-being and lower inflammation (Fredrickson et al., 2013; Moreno et al., 2016; Pressman et al., 2019), and an emerging literature suggesting that the reward system plays a role in stress resilience (Dutcher and Creswell, 2018). This is particularly relevant for breast cancer survivors given that chronically elevated inflammation is associated with increased risk of recurrence (Pierce et al., 2009), and may therefore benefit from interventions that specifically target positive psychological processes. Although preliminary, our findings suggest a lateralized response to both rewards and threat, which has been previously noted (Martin--Soelch et al., 2011; Ohrmann et al., 2007). However, not all literature shows a lateralized response and thus further work is needed.

While mindfulness training in the current study was associated with an increase in left VS activity to nonsocial positive stimuli, there was no difference in VS activity for the social stimuli. This result was unexpected but may be attributable to the importance of social stimuli to humans, which might make it difficult to detect significant additional changes in VS activity following the intervention (i.e., a ceiling effect). Additionally, the stimuli were images of strangers, and it is possible we would have observed an increase in VS activity had the images included familiar and close others, consistent with work showing that neural responses to strangers and close others can differ under certain contexts (Acevedo et al., 2012; Inagaki et al., 2015a, 2015b). The portrayal of social connectedness may also have elicited complex emotional responses, including feelings of isolation or loss, particularly in women with elevated depressive symptoms (e.g., reward devaluation theory in the context of depression; Winer and Salem, 2016). The esthetic pleasure of non-social positive images, by contrast, is less emotionally complex and thus neural responses to them possibly more modifiable following intervention.

There are a few important limitations to this study worth noting. Most important, this was a single-arm trial, with no control group. Thus, a causal role of mindfulness training on neural reactivity or inflammation cannot be established. It is also possible that the observed decrease in right amygdala reactivity from pre- to post-intervention was due to habituation. However, previous work found no amygdala habituation to repeated presentation of emotional face stimuli in healthy adults (Spohrs et al., 2018), supporting the possibility that the observed decreases were related to the intervention. Moreover, the observed increases in left VS activity suggest that there is not a general habituation to viewing images at multiple assessments. This preliminary study also included a small sample, which may have precluded detection of associations between threat reactivity and changes in inflammation, or bilateral associations between reward reactivity and changes in CRP. Given the relatively small sample size, findings require replication in future randomized controlled trials of mindfulness meditation with breast cancer survivors (and other populations) that include both fMRI and inflammatory biology assessments.

5. Conclusion

A 6-week mindfulness meditation intervention with younger breast cancer survivors resulted in reductions in amygdala activity to threatening images, and increased VS activity to nonsocial, but not social, reward images. These increases in VS activity to nonsocial reward were associated with decreases in two markers of inflammation, IL-6 and CRP. This is the first study to explore the relationship between changes in neural responses to threat or reward and changes in circulating levels of inflammation following mindfulness training, and the first to do so in women with a history of breast cancer. These findings offer empirical support for the links between the brain and the immune system and how those relationships might be affected by a mindfulness intervention. The implication of these findings is that mind-body interventions could have value for altering neural responses to threat and reward in ways that influence inflammatory biology and possibly downstream physical health in vulnerable populations.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2020.105114.

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