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Publication Date

2019-05-01

DOI

10.1016/j.psyneuen.2019.01.024

Peer reviewed

Psychoneuroendocrinology 103 (2019) 173–179

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Changes in eudaimonic well-being and the conserved transcriptional response to adversity in younger breast cancer survivors

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ARTICLE INFO

Keywords:
Eudaimonia
Psychoneuroimmunology
Cancer
Mindfulness meditation
Gene expression
Immune system

ABSTRACT

Background: The conserved transcriptional response to adversity (CTRA), characterized by increased expression of proinflammatory genes and decreased expression of antiviral and antibody-related genes, is upregulated in the context of chronic adversity and distress and has been linked to cancer progression. Several studies suggest that the CTRA may also be down-regulated in association with some positive psychological states, particularly eudaimonic well-being. However, it is not clear if the link between inter-individual differences in the CTRA and eudaimonic well-being can be extended to intra-individual change. Using a standardized mindfulness-based intervention, the current study tested whether mindfulness-related increases in eudaimonic well-being related to intra-individual reduction in the CTRA in a sample of younger breast cancer survivors.

Methods: Participants were 22 women who had been diagnosed and treated for early-stage breast cancer at or before age 50 (M_{age} = 46.6 years) and had no evidence of active disease. Women completed self-report questionnaires and provided peripheral blood samples before and after a 6-week mindfulness meditation intervention. Regression analyses were used to quantify associations between the magnitude of change in eudaimonic well-being and the magnitude of change in the global CTRA score.

Results: Women reported significant increases in eudaimonic well–being and showed decreased expression of the pro-inflammatory subcomponent of the CTRA from pre- to post-intervention. The magnitude of increase in eudaimonic well-being was associated with the magnitude of decrease in the composite CTRA score, and this relationship was driven primarily by increased expression of the antiviral/antibody-related CTRA subcomponent. While the intervention was also associated with reduced depressive symptoms, there was no association between change in depressive symptoms and change in the overall CTRA composite score or either of its subcomponents.

Conclusions: Results are consistent with the hypothesis that eudaimonic well-being may be an important mechanism in interventions aimed at enhancing health in vulnerable groups, and contribute to our understanding of how psychological well-being may influence physical health in cancer patients.

1. Introduction

Chronic adversity and distress are associated with higher risk of morbidity and early mortality (Holt-Lunstad et al., 2015; Penninx et al., 2013). There is increasing evidence that this relationship is mediated at least in part by stress-induced modulation of immunological processes, including alterations in inflammatory and anti-viral responses (Miller et al., 2011; Rohleder, 2016). Individuals exposed to trauma (Kohrt et al., 2016), chronic loneliness (Cole et al., 2015), caregiving stress (Miller et al., 2014) and low socioeconomic status (Levine et al., 2017; Powell et al., 2013) all exhibit a gene expression pattern that is conducive to the development of chronic disease. This conserved transcriptional response to adversity (CTRA) is characterized by the up-regulation of proinflammatory genes and down-regulation of genes

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https://doi.org/10.1016/j.psyneuen.2019.01.024
Received 9 September 2018; Received in revised form 10 November 2018; Accepted 21 January 2019

involved in antiviral response and antibody synthesis in circulating immune cells (Cole, 2009). Elegant work in animal models has shown that early life and social stress induce CTRA upregulation (Chun et al., 2017; Cole et al., 2012; Heidt et al., 2014; Korytář et al., 2016; Powell et al., 2013; Snyder-Mackler et al., 2016; Tung et al., 2012), and there is evidence in humans that acute stress can increase related signaling of the pro-inflammatory transcription factor NF-κB (Bierhaus et al., 2003). Less work has focused on whether positive psychological states, such as eudaimonic well-being, can be similarly leveraged to alter these transcriptome dynamics. Here, we use a clinical intervention to interrogate the relationship between changes in eudaimonic well-being and down-regulation of the CTRA in a sample of younger breast cancer survivors.

Eudaimonic well-being encompasses a sense of purpose and meaning in life, social embeddedness, and the potential for personal growth that may or may not be accompanied by hedonic well-being, or feelings of pleasure, happiness and positive affect (Keyes, 2002; Ryan and Deci, 2001; Ryff, 2018). Longitudinal prospective studies have linked eudaimonic well-being to better physical health, including reduced morbidity and all-cause mortality (Hill and Turiano, 2014; Steptoe et al., 2015). In several cross-sectional reports, eudaimonic well-being was associated with decreased activation of the CTRA (Cole et al., 2015; Fredrickson et al., 2013, 2015; Kitayama et al., 2016) with consistent evidence that this effect was independent of hedonic well-being and reduced distress (Fredrickson et al., 2013, 2015; Kitayama et al., 2016). Indeed, in a sample of older adults, eudaimonic well-being was a stronger correlate of CTRA gene expression than loneliness or depressive symptoms (Cole et al., 2015), which is particularly notable given well established relationships between loneliness, depression and physical health (Holt-Lunstad et al., 2015; Penninx et al., 2013).

Several randomized controlled studies have shown that components of the CTRA can be altered following psychological intervention, including cognitive behavioral stress management (CBSM) (Antoni et al., 2012, 2016) and mindfulness meditation (Black et al., 2015; Bower et al., 2015; Creswell et al., 2012). These interventions have demonstrated broad, beneficial effects on both psychological distress and eudaimonic well-being (Bower et al., 2015; Labelle et al., 2015; McGregor et al., 2004), but the extent to which these psychological processes are associated with changes in the CTRA has rarely been examined. One study found that baseline levels of distress were linked to changes in the CTRA following CBSM (Antoni et al., 2012), but eudaimonic well-being was not assessed. There is, however, preliminary evidence that an intervention with eudaimonic components decreased CTRA gene expression. Nelson-Coffey et al. (2017) found that participants who were assigned to enact acts of kindness to others, a behavior that promotes and is consistent with eudaimonia (Klein, 2016), exhibited decreases in CTRA gene expression over a 4–5 week period in comparison to participants randomized to a neutral activity control group. Together, this emerging body of evidence highlights a need for a comprehensive examination of both eudaimonic well-being and distress reduction as potential pathways to change in the CTRA.

Testing these pathways has particular relevance in the context of cancer. In a sample of breast cancer patients, reductions in the CTRA following CBSM were associated with longer disease-free survival over 8–15 years of follow-up (Antoni et al., 2016). Lower CTRA gene expression profiles were also associated with reduced risk of leukemia recurrence and mortality in patients receiving hematopoietic cell transplants (Knight et al., 2016). In breast cancer survivors, mindfulness meditation and yoga can reduce pro-inflammatory gene expression, concomitant with improvements in depressive symptoms and enhanced well-being (Bower et al., 2014, 2015). More broadly, inflammatory signaling is associated with cancer recurrence and tumor progression, as well as lingering post-treatment symptoms like fatigue, cognitive complaints, and depression (Hanahan et al., 2011; Irwin et al., 2013; Miller et al., 2008a).

Thus, the purpose of the current study was to use a psychological intervention to test for associations between increases in eudaimonic well-being and change in CTRA gene expression in a sample of younger breast cancer survivors. We also examined whether change in depressive symptoms, which are particularly elevated among younger survivors (Avis et al., 2013; Champion et al., 2014) and associated with higher mortality in cancer survivors (Pinquart and Duberstein, 2010), were associated with the CTRA. Research from our lab and others indicates that mindfulness has consistent effects on both well-being and depressive symptoms in this population (Bower et al., 2015; Schellekens et al., 2016); thus, mindfulness meditation was used as the treatment of interest here. We recruited younger breast cancer survivors naïve to mindfulness practice to participate in a single-arm longitudinal pre-post intervention trial. This design was appropriate given our aim to examine within-subject associations between psychological variables and the CTRA. We hypothesized that increases in eudaimonic well-being from pre- to post-intervention would correlate with reductions in CTRA gene expression. To examine whether changes in psychological processes more broadly were associated with the CTRA, we conducted secondary analyses to test whether increases in hedonic well-being or decreases in depressive symptoms were associated with alterations in the CTRA.

2. Methods

2.1. Participants, recruitment, and procedure

The findings in the current report come from a study designed to examine neural processes linking stress reduction to inflammation reduction following mindfulness meditation. Participants were women diagnosed with early stage breast cancer (Stage 0-III) at or before age 50, who had completed primary treatment (i.e., surgery, chemotherapy, and/or radiation) at least 3 months previously and had no evidence of active disease. Exclusion criteria included previous mindfulness meditation experience, presence of inflammatory disease and conditions related to safety for neuroimaging (e.g., left-handed, presence of claustrophobia).

Potential participants were identified through the UCLA Tumor Registry and through physician referral. Letters describing the study were mailed to 512 women, 197 responses were received, and 49 women did not meet inclusion criteria, primarily due to claustrophobia ($n = 16$), left-handedness ($n = 13$), or prior mindfulness experience ($n = 8$); 126 declined to participate, primarily because they were too busy or lived too far away ($n = 89$) or were unable to be reached after expressing initial interest (passive refusal; $n = 20$). This left a sample of 22 women who were eligible and able to participate.

After providing informed consent, eligible participants completed an in-person assessment before and after a standardized mindfulness intervention at UCLA. At each assessment (within two weeks before and after the intervention), participants provided a morning blood sample, underwent a 90-minute fMRI scanning session (results reported separately), and completed questionnaires. Study procedures were approved by the UCLA IRB and no adverse events were reported during the intervention. Participants were compensated $100.

2.2. MAPs intervention

Participants completed a 6-week mindfulness meditation-based intervention, Mindful Awareness Practices (MAPs), developed by Diana Winston and colleagues at the Mindfulness Awareness Research Center at UCLA. Participants met for 6 weekly, 2-hour group sessions and were additionally instructed to practice and document minutes spent on formal mindfulness exercises at home, beginning with 5 min and increasing to 20 min daily. The current study included three cohorts of women, with group size ranging from 6 to 10, conducted between May and November of 2015.

MAPs is a manualized intervention that has been used in several previous studies (e.g., 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 and gentle movement exercises (e.g., mindful walking). The intervention addresses key aspects of eudaimonic well-being, including self-acceptance, positive relations with others, personal growth, and purpose in life. Specifically, cultivating an attitude of self-acceptance was addressed throughout the intervention through reminders by the instructor to be kind to oneself, or "gently" return attention to the present moment during meditative exercises. Weeks 3 and 4 included practice of loving kindness meditation, in which participants were asked to generate caring, warm, and positive feelings toward the self and others. Weeks 4 and 5 focused on practicing a mindful approach to working with difficult emotions, which involves recognizing emotions, accepting them as part of the human experience, and learning to shift one's relationship with difficult thoughts by "disidentifying," or creating a sense of space or relief from difficult thoughts. Disidentifying has been theorized to increase the ability to positively reappraise the environment and allow for personal growth and meaning making (Garland et al., 2015).

2.3. Materials

2.3.1. Demographic and health history variables

Information on participant age, ethnicity, income, marital status, and type of treatment received was collected via self-report questionnaire. Time since diagnosis and disease stage was collected via tumor registry records.

2.3.2. Eudaimonic well-being, hedonic well-being, and depressive symptoms

Eudaimonic and hedonic well-being were assessed with the Mental Health Continuum-Short Form (MHC-SF; Keyes, 2002), which has high reliability and validity (Lamers et al., 2010). *Eudaimonic well-being* was assessed with two subscales capturing psychological and social well-being. The 6-item psychological well-being subscale addresses each of six theorized components of eudaimonic well-being as articulated by Ryff (2018): purpose in life, personal growth, positive relations, self-acceptance, autonomy and environmental mastery. The 5-item social well-being subscale assesses constructs like social integration, social acceptance, and social coherence (e.g., "that the way our society works makes sense to you"). *Hedonic well-being* was assessed with the 3-item hedonic well-being subscale, which consists of the following items: happy, interested, satisfied. For each scale item on the MHC-SF, participants indicate the frequency of feelings of well-being over the past month (0 = never; 1 = once or twice a month; 2 = about once a week; 3 = two or three times a week; 4 = almost every day; 5 = every day). In the current study, one participant did not complete the MHC-SF, leaving a final sample of 21 participants. Internal consistency was high at the pre- and post-intervention assessment (α's $>$ 0.80).

Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies-Depression scale (CES-D; Radloff, 1977). Participants rated how often they had experienced symptoms of depression during the past week (0 = none of the time or rarely; 3 = most of the time). Internal consistency was high at the pre- and post-intervention assessment ($\alpha > 0.84$).

2.3.3. Transcriptome profiling

At each time point morning blood samples (7:30-11:00AM) were collected by venipuncture, peripheral blood mononuclear cells (PBMC) were isolated by standard ficol gradient centrifugation, and CD14+ cells were isolated from PBMC by immunomagnetic positive selection (MACS, Miltenyi Biotec). CD14+ cells were selected because they are a primary source of pro-inflammatory cytokines and pro-inflammatory gene expression in the context of chronic stress (Miller et al., 2008b, 2014; Powell et al., 2013). RNA was extracted (Qiagen RNeasy), tested for suitable mass (Nanodrop ND1000) and integrity (Agilent TapeStation), converted to fluorescent cRNA (Ambion TotalPrep) and hybridized to Illumina Human HT-12 v4 BeadArrays following the manufacturer's standard protocol in the UCLA Neuroscience Genomics Core Laboratory. All samples were assayed in a single batch, quantile normalized, and $\log_2$-transformed for statistical analysis as described below. All but one sample yielded technically valid results according to study-specific probe signal distribution metrics (median intensity $>$ 100 units). The paired (baseline) sample for the single invalid observation was removed prior to analysis, as was the baseline sample from a second participant who provided no follow-up sample, leaving a final set of 20 paired baseline and follow-up samples available for analysis of change in gene expression.

2.3.4. Statistical analysis

We first verified that the intervention was associated with eudaimonic and hedonic well-being, depressive symptoms, and CTRA gene expression using paired samples t-tests to test the significance of pre-post intervention change. As in previous studies (e.g., Antoni et al., 2016), we assessed change in expression of the overall 53-gene CTRA contrast score, which includes a proinflammatory component as well as its inverse component involving 31 gene transcripts involved in Type I interferon response (e.g., *IFNB1*, *MX1*, *OAS1*, *IFIT1*) and 3 gene transcripts involved in antibody synthesis (e.g., *IGJ*). Pro-inflammatory genes were weighted + 1 and antiviral and antibody-related genes were weighted −1 as in previous research (Cole et al., 2015; Fredrickson et al., 2013, 2015; Kitayama et al., 2016). Standard errors for the change scores were derived from bootstrap resampling of linear model residual vectors (controlling for correlation among genes). Ancillary analyses also verified whether this sample showed changes in bioinformatically inferred activity of the pro-inflammatory transcription factor, NF-κB (using the TELiS system as previously described; Bower et al., 2015; Cole et al., 2005), and for preferential derivation of down-regulated gene transcripts from the pro-inflammatory CD16- "classical" subset of monocytes (using Transcript Origin Analysis as previously described; Bower et al., 2015; Cole et al., 2011). These ancillary transcriptome-wide analyses took as input all gene transcripts showing $>$ 1.15-fold change in expression from pre- to post-intervention; this threshold is consistent with our prior work (e.g., Bower et al., 2014; see supplement page 1–2 for additional detail on genomic analyses).

Our primary analyses used linear regression to quantify associations between the magnitude of change in eudaimonic well-being and the magnitude of change in the global CTRA score. Significant bivariate associations were followed up with covariate-adjusted analyses controlling for age, BMI, time since cancer diagnosis, tumor stage, and use of endocrine therapy. To further interrogate the specificity of this association, we also tested whether this association held when simultaneously controlling for change in hedonic well-being. Secondary analyses were then conducted to examine whether increases in hedonic well-being alone were associated with the magnitude of change in the global CTRA score, and whether decreases in depressive symptoms alone were associated with the magnitude of change in the global CTRA score.

3. Results

3.1. Sample characteristics

Participants (n = 22) ranged in age from 38 to 52 (M = 46.6, SD = 4.1) and had been diagnosed with early stage breast cancer between 2010 and 2014 (see Table 1 for demographic, medical and treatment-related characteristics). Adherence in the intervention was high; the mean number of sessions attended was 5.8 (range = 4–6) and 17 women attended all six sessions. Additional minutes of home practice over the course of the intervention ranged from 113 to 651 (M = 327.9).

Women endorsed feelings of eudaimonic well-being two-to-three times a week over the past month (M = 3.11, SD = 1.01), with levels of

Table 1
Demographic, Medical and Treatment-Related Characteristics of the Sample.

	Total (N = 22)
Age, M (range)	46.55 (38–52)
Married or in a committed relationship, N (%)	17 (77%)
Children, N (%)	12 (55%)
Ethnicity, N (%)	
White	13 (59%)
Asian	5 (23%)
Other	4 (18%)
Family Yearly Income, N (%)	
$30,001-$60,000	3 (13.5%)
$60,001-$100,000	5 (23%)
Over $100,000	14 (63.5%)
Employment, N (%)	
Employed full or part-time	12 (54.5%)
Homemaker/volunteer	7 (32%)
Retired, on leave, unemployed	3 (13.5%)
Body Mass Index, M (range)	24.2 (18.5–36.6)
Years since diagnosis, M (range)	2.08 (1.4–5.1)
Cancer stage, N (%)	
0	5 (22.7%)
1	5 (22.7%)
2	11 (50%)
3A	1 (4.5%)
Cancer treatments received, N (%)	
Chemotherapy	11 (50%)
Radiation therapy	12 (55%)
Current endocrine therapy	9 (41%)

Note: M = mean; SD = standard deviation.

hedonic well-being in a similar range (M = 3.51, SD = 1.06). These levels of well-being are comparable to those observed in non-clinical samples (Lamers et al., 2010). Depressive symptoms were elevated at baseline; mean scores on the CES-D (M = 15.50; SD = 10.68; range 1–40) were comparable to other samples of younger breast cancer survivors (Ganz et al., 2012), including those in our previous intervention study (Bower et al., 2015). Of note, 55% endorsed clinically significant depressive symptoms, as indicated by CES-D scores greater than or equal to a 16.

3.2. Preliminary analyses: Intervention-associated changes in well-being, depressive symptoms, and gene expression

Paired samples t-tests demonstrated significant changes in well-being and depressive symptoms from pre to post-intervention (see Table 2). More specifically, there was a significant increase in eudaimonic well-being ($t(20) = 3.23$, $p = 0.004$, $d = 0.71$) and hedonic well-being ($t(20) = 2.16$, $p = .043$, $d = 0.47$). Depressive symptoms decreased significantly after the intervention, ($t(21) = -2.97$, $p = .007$, $d = 0.63$), with an effect size similar to that observed in our previous RCT (d = .54; Bower et al., 2015). See Table 3 for correlations among psychosocial measures.

In genome-wide transcriptional profiling of peripheral blood monocytes, there was no significant change from pre- to post-intervention in average expression of a 53-gene CTRA composite score

Table 2
Pre- and Post-Intervention Means and Standard Deviations for Eudaimonic Well-Being, Hedonic Well-Being, and Depressive Symptoms.

	Pre-Intervention		Post-Intervention			
Outcome	Mean	SD	Mean	SD	*p value*	Cohen's *d*
Eudaimonic Well-Being	3.11	1.01	3.61	0.74	.004	.71
Hedonic Well-Being	3.51	1.06	3.83	0.80	. 043	.47
Depressive Symptoms	15.50	10.68	8.68	8.87	.007	.63

Note: SD = standard deviation. *p* value and Cohen's *d* are from paired samples t-tests.

Table 3
Correlations for Eudaimonic Well-Being, Hedonic Well-Being, and Depressive Symptoms.

		1	2	3	4	5
1	Eudaimonic_T1					
2	Hedonic_T1	.770*				
3	Depressive symptoms_T1	−.665*	−.754*			
4	Eudaimonic_T2	.673*	.667*	−.558*		
5	Hedonic_T2	.478*	.715*	−.679*	.700*	
6	Depressive symptoms_T2	−.271	−.355	.406	−.661*	−.674*

Note: T1 = Pre-intervention; T2 = Post-intervention.

($-0.046 \pm .042$, $p = .274$). However, analyses verified the previously observed effects of the MAPs intervention on reducing expression of the 19-gene pro-inflammatory subcomponent of the CTRA score (mean changen = $-.084$ $\log_2$ mRNA expression units $\pm$ 0.030 SE, $p = .013$; Bower et al., 2015). Consistent with the observed decrease in the a priori-specified pro-inflammatory composite score, ancillary analyses of all 78 genes that empirically showed 1.15-fold change in average expression from pre- to post-intervention (15 up-regulated and 63 down-regulated) indicated decreased activity in NF-κB/Rel family transcription factors (0.34-fold ratio of binding sites in up- vs. down-regulated genes: $\log_2$ ratio $= -1.56 \pm 0.60$, $p = .010$), consistent with our earlier trial (Bower et al., 2015). Further, Transcript Origin Analyses identified pro-inflammatory CD16- "classical monocytes" as the primary cellular origin of down-regulated gene transcripts (cell diagnosticity score: 0.66 $\pm$ 0.27, $p = .009$).

3.3. Primary analyses: Associations between changes in well-being, depressive symptoms and CTRA gene expression

Our primary interest was evaluating whether the magnitude of change in eudaimonic well-being was associated with the magnitude of change in CTRA gene expression. Although the 53-gene CTRA composite score did not show significant pre-post intervention change, there was sufficient variability in the magnitude of change to test for correlations with change in eudaimonic well-being. Results showed that women who reported greater increases in eudaimonic well-being over the 6-week intervention showed greater reduction in CTRA scores over the same period (change in $\log_2$ RNA abundance per SD change in eudaimonic well-being: $b = -0.140 \pm SE$ 0.040, $p = .0009$; see Fig. 1a), controlling for age, BMI, time since cancer diagnosis, tumor stage, and use of endocrine therapy. Similar results emerged in analyses that additionally controlled for changes in hedonic well-being ($b = -0.136 \pm SE$ 0.039, $p = .0009$) and analyses not controlling for any covariates ($b = -0.070 \pm .035$, $p = .0492$; see supplement page 2 for additional analysis of MHC-SF subscales). Exploratory analyses of specific components of the overall CTRA composite score indicated that increases in eudaimonic well-being were associated with an increase in the inversely weighted antiviral/antibody-related CTRA subcomponent in both unadjusted analyses ($b = .127 \pm .053$, $p = .0228$) and covariate-adjusted analyses ($b = .220 \pm .062$, $p = .0012$; Fig. 1b). However, changes in eudaimonic well-being were not significantly correlated with changes in the pro-inflammatory subcomponent (Fig. 1b; $p = .9215$).

In secondary analyses, regression analyses were also conducted to examine the association between changes in hedonic well-being alone and CTRA gene expression and between changes in depressive symptoms alone and CTRA gene expression. In these models, neither the magnitude of change in hedonic well-being nor depressive symptoms were associated with change in overall CTRA gene expression, in either unadjusted or covariate-adjusted analyses (all p's > 0.20; see Fig. 1a). Further, changes in hedonic well-being and depressive symptoms were not related to changes in either of the CTRA sub-components (all p's $> .05$).

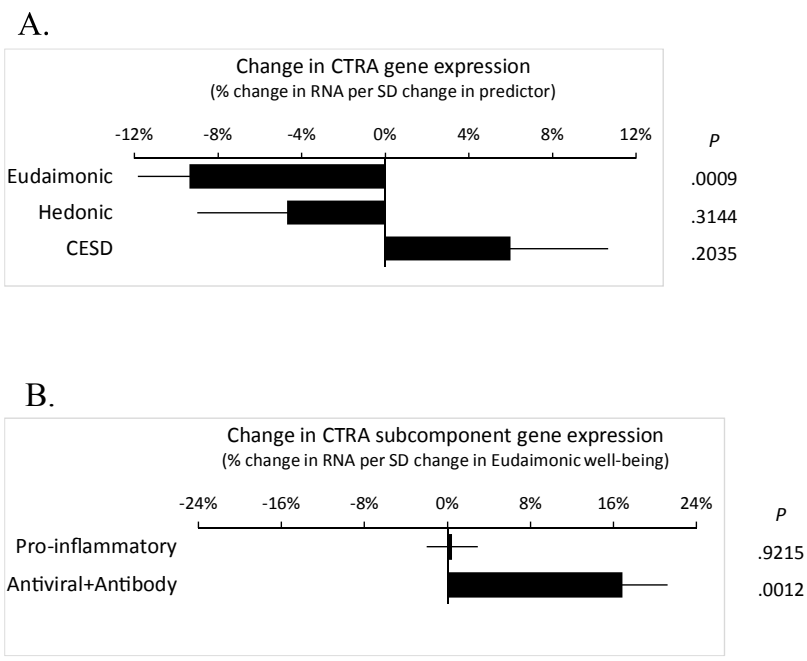

Fig. 1. Relationship of change in CTRA and change in well-being and depressive symptoms. Greater increases in eudaimonic well-being were associated with greater reduction in the 53-gene CTRA composite score from pre- to post-intervention (A). Increases in eudaimonic well-being were associated with an increase in the antiviral/antibody-related CTRA subcomponent, but not the pro-inflammatory subcomponent, from pre- to post-intervention (B). Data represent regression coefficients from linear regression models controlling for age, BMI, time since cancer diagnosis, tumor stage, and use of endocrine therapy.

4. Discussion

The present data are consistent with the hypothesis that the link between eudaimonic well-being and health may involve alterations in molecular signaling pathways that control immune function. In the present study, levels of eudaimonic well-being increased after participation in a 6-week mindfulness intervention, and those who showed the greatest increases in eudaimonic well-being showed the greatest decreases over time in expression of the CTRA transcriptome profile. The meditation intervention was also associated with decreases in depressive symptoms, but these changes were not significantly associated with changes in CTRA gene expression. These findings are consistent with previous cross-sectional studies reporting an association between individual differences in eudaimonic well-being and individual differences in CTRA gene expression under basal conditions, and these data show that such effects extend to intra-individual reductions in eudaimonic well-being as breast cancer survivors initiated a mindfulness meditation practice.

The association of increased eudaimonic well-being with decreased CTRA gene expression predominantly involved increased expression of antiviral and antibody-related genes from pre- to post-intervention, rather than reduced expression of pro-inflammatory genes over the intervention period. Some studies assessing eudaimonic well-being and the CTRA have not reported on the components of CTRA separately (Cole et al., 2015; Fredrickson et al., 2015), precluding direct comparisons. At least one study, however, has similarly shown that eudaimonic well-being was associated with the antiviral and antibody component of the CTRA (Fredrickson et al., 2013). Of note, Antoni et al. (2012) found that negative affect was associated with the pro-inflammatory, but not the antiviral component of the CTRA in a sample of breast cancer survivors. Further investigation of the components of the CTRA and its psychological correlates is an important topic for future research. However, it is important not to over-interpret the differential significance of inflammatory and antiviral gene associations with eudaimonic well-being in the current study, as these differences may also stem from sampling variability and the limited statistical power to detect true associations given this study's relatively small sample size.

As has been previously observed (Cole et al., 2015; Fredrickson et al., 2015), the association between eudaimonic well-being and CTRA down-regulation was specific, with no association evident with depressive symptoms. This suggests that interventions targeting health in vulnerable populations, such as breast cancer survivors, should not exclusively focus on reducing distress. There was also no association between CTRA expression and hedonic well-being. While closely related and often co-occurring, eudaimonic and hedonic well-being are conceptually and empirically distinct (Ryff, 2018; Ryan and Deci, 2001) and may even have different neural substrates (Kringelbach and Berridge, 2009). Most notably, eudaimonic well-being, as defined in this and other studies, encompasses not only a subjective experience, but also a mode of being, or a striving towards optimal functioning (Ryan and Deci, 2001). The path to hedonic well-being, by contrast, can be heterogeneous and could involve permissive behaviors that undermine health (e.g., excessive drinking, smoking, sedentary behavior). Although not a consistent pattern, some studies have found that higher hedonic well-being is associated with greater CTRA gene expression, net of its correlation with eudaimonic well-being (Fredrickson et al., 2013; Kitayama et al., 2016).

The theoretical distinction between eudaimonic and hedonic well-being has significant implications for intervention design. Specifically, interventions that target eudaimonic well-being may lead to more lasting positive change than those that solely focus on hedonic well-being (Hernandez et al., 2017). Compared to hedonic behavior, eudaimonic behaviors induce a greater variety of positive emotions (e.g., gratitude, contentment, joy) and are comprised of complex behaviors that are more self-perpetuating, less likely to lead to boredom, and less subject to hedonic adaptation (Layous and Lyubomirsky, 2014). Positive activity interventions already incorporate eudaimonic activities (e.g., writing letters of gratitude, performing acts of kindness, engaging in self-affirmation exercises) and more traditional clinical psychological approaches, such as behavioral activation therapy, are also explicitly addressing constructs like meaning in life (Lejuez et al., 2011).

This study builds upon an emerging literature linking heightened eudaimonic well-being to gene expression alterations (Cole et al., 2015; Fredrickson et al., 2013, 2015; Kitayama et al., 2016), providing novel evidence that intervention-related change in well-being is associated with reduced CTRA gene expression over time. However, several important limitations should be noted. This was a small pilot study in a highly stressed and vulnerable group, and results require replication in other populations. The absence of a control group precludes causal claims, although work from our lab and others has shown that interventions such as mindfulness meditation increase eudaimonic well-being and decrease CTRA gene expression relative to a control group

(Antoni et al., 2016; Bower et al., 2015), supporting the hypothesis that the changes observed in this sample may be driven by the intervention. In addition, although we are interpreting results to support an effect of eudaimonic well-being on CTRA gene expression, it is also possible that changes in CTRA gene expression may drive changes in affect given the bidirectional links between the immune system and brain function (Dantzer et al., 2008). It is unclear whether the magnitude of molecular effects observed here, which were quantitatively modest, would have clinical significance, and future research will be required to assess the health impact of mindfulness meditation in the context of the highly stressful experience of cancer. Finally, while it is encouraging that our results held when controlling for important covariates (e.g., cancer treatment, BMI), these covariate-adjusted findings should be interpreted with caution given the small sample size. Despite these limitations, our results contribute to a growing literature delineating the central psychological processes relevant to mitigating CTRA gene expression, which represents a critical step in understanding how psychological well-being influences health.

Declarations of interest

None.

Funding

This work was supported by a Breast Cancer Research Foundation Grant # 20150695 and by the Cousins Center for Psychoneuroimmunology. CCB was supported as a postdoctoral fellow at the Cousins Center for Psychoneuroimmunology.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.01.024.

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