Study Title: Effects of a Wellbeing Intervention on Inflammation Through Reward and Threat Processes

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## Specific Aims

Aim 1. Investigate whether a novel savoring intervention is associated with changes in positive affect. We hypothesize that the savoring intervention will increase positive affect measured via questionnaire.

Aim 2. Examine changes in daily experiences of reward and threat from pre- to post-intervention. We hypothesize that the savoring intervention will be associated with enhanced reward reactivity to daily social and nonsocial positive experiences and decreased threat reactivity to daily stressful experiences. More specifically, we expect greater increases in positive affect in response to social and nonsocial rewarding experiences and smaller increases in negative affect in response to stressful experiences.

Aim 3. Examine changes in neural measures of reward and threat from pre- to post-intervention. We hypothesize that the savoring intervention will be associated with increased activity in neural regions related to reward (e.g., ventral striatum) and decreased activity in neural regions related to threat (e.g., amygdala) during specialized tasks designed to activate these regions.

## Background and Significance

According to the World Health Organization, wellbeing is a positive state that encompasses quality of life, sense of meaning, and capacity to overcome health challenges (World Health Organization, 2021). Philosophers like Aristotle have traditionally split wellbeing into two components: eudaimonic and hedonic. Eudaimonic wellbeing concerns living a meaningful life with purpose, while hedonic wellbeing involves pleasant and happy emotional states (Asano et al., 2020). While these two components may have separable impacts on health, Centers for Disease Control and Prevention (2018) has concluded that in general, enhanced wellbeing is associated with "decreased risk of disease, illness and injury; better immune functioning; speedier recovery; and increased longevity".

Ryff and Singer hypothesize that one fundamental way wellbeing enhances human health is by optimizing physiological processes, like immune function (Ryff & Singer, 1998). In the past decade, studies have found increasing support for this hypothesis (Bower et al., 2019). Positive affect is associated with lower levels of circulating inflammatory markers, like IL-6, TNF-α, and CRP (Brouwers et al., 2013; Ironson et al., 2018). A longitudinal study of older adults found that hedonic wellbeing was associated with lower white blood cells, and eudaimonic wellbeing was associated with lower CRP, fibrinogen, and white blood cells (Fancourt & Steptoe, 2020). Eudaimonic wellbeing is also associated with down-regulation of the conserved transcriptional response to adversity (CTRA), which includes decreased pro-inflammatory gene expression and increased antiviral and antibody related gene expression (Fredrickson et al., 2013; Cole et al., 2015). Overall, these studies suggest that wellbeing is effective at modulating immune function (Huppert et al., 2004).

Though many types of interventions have the potential to enhance wellbeing, we focus on a positive psychology intervention that targets affect through the mindfulness technique of savoring. A daily diary study found that savoring mediates the impact of daily positive events on

happy mood (Jose et al., 2012). Greater improvements in mood are also associated with greater reward-related activation in the brain during savoring (Speer et al., 2014). Indeed, a recent clinical trial confirmed that the Positive Affect Treatment intervention, which relies heavily on savoring, increases reward anticipation motivation and response to reward attainment, improvements that were correlated with positive affect (Craske et al., under review). These findings suggest that savoring-related increases in wellbeing may drive greater affective reactivity to reward; it may also decrease affective reactivity to threatening or stressful experiences. Multiple savoring-focused interventions have proved effective in reducing negative affect and depressive symptoms in undergraduate students (Hurley & Kwon, 2012; Craske et al., 2019). One savoring intervention successfully reduced both negative mood and cortisol levels after an acute stress exposure, though it remains unclear exactly how these benefits occur (Speer & Delgado, 2017).

The field of psychoneuroimmunology has only recently begun to investigate potential neural pathways translating wellbeing into reductions in inflammation, but reward and threat circuitry are a primary suspects. The ventral striatum is a central structure involved in reward processing (Satterthwaite et al., 2011). Sustained ventral striatum activity in response to positive stimuli is associated with greater wellbeing and lower cortisol output (Heller et al., 2013). Animal studies have found that increased activity in the reward system boosts innate and adaptive immunity (Ben-Shaanan et al., 2016). While there are fewer studies investigating reward-related inflammatory changes in humans, Chat et al. found that young adults with both elevated threat sensitivity and reduced reward sensitivity displayed the highest levels of peripheral inflammation (Chat et al., 2017). While reward processing is a more recent therapeutic target (Craske et al., 2016), it may prove to be an important neural mechanism through which wellbeing impacts inflammation.

Reward activity may impact inflammation by reducing threat reactivity. A meta-analysis found that wellbeing is associated with enhanced hemodynamic recovery after laboratory stressors, though it did not affect stress reactivity (DuPont et al., 2020). Evidence suggests that brain regions involved in reward processing dampen alarm signaling in the anterior insula and cingulate, which reduces activity in the amygdala (van Steenbergen et al., 2021). The amygdala is central to threat processing and has important implications for downstream inflammatory processes (Eisenberger & Cole, 2012). In particular, activation in the amygdala leads to up-regulation of the sympathetic nervous system and increases in pro-inflammatory cytokine activity (Muscatell et al., 2015; Ressler, 2010; Schiller et al., 2021). Thus, activation in reward-related neural regions likely blunts stress responses in order to alter downstream immune function and inflammation (Dutcher & Creswell, 2018). However, few studies have investigated the neural mechanisms involved, and to our knowledge, none have specifically examined how wellbeing alters reward and threat-related brain activity and downstream inflammation.

The Positive Affect Treatment intervention was created to target deficits in reward processing (Craske et al., 2016). The first module involves therapist-guided visualization and reimagining of enjoyable activities. This savoring part of the intervention aims to enhance mindful attention to positive aspects of experience in order to enhance reward processing. A randomized controlled trial confirmed that PAT lead to higher positive affect, lower negative affect, and fewer depressive symptoms at six months post intervention compared to cognitive behavioral therapy, which focused solely on reducing negative affect (Craske et al., 2019). A second randomized controlled trial replicated these results and additionally demonstrated increases in reward anticipation and reward attainment, which were associated with increases in

positive affect (Craske et al., under review).

In a small pilot study, we examined how a mindfulness intervention with savoring components altered neural processes and downstream inflammation in younger breast cancer survivors. We found significant reductions in amygdala activity in response to threatening images after the 6-week intervention, but this change was not correlated with inflammatory biomarkers (Dutcher et al., 2021). Additionally, we found increases in ventral striatum activity to nonsocial rewarding images, which was correlated with decreases in circulating IL-6 and CRP from pre to post-intervention. This study suggests that the intervention altered inflammation primarily via reward pathways. These mechanisms require further investigation, particularly with respect to their effects on daily experiences of social reward, non-social reward, and threat. Regulation of inflammation may be one of the primary pathways through which wellbeing improves mental and physical health.

We aim to examine if the savoring component of the Positive Affect Treatment intervention is driving increases in reward processing, which in turn leads to reductions in stress reactivity and downstream inflammation. Despite Dutcher et al.'s finding that increased ventral striatal activity was associated with positive nonsocial images, we expect positive social and nonsocial images to be associated with greater reward reactivity in our sample, since young adults are particularly sensitive to social stimuli (Foulkes & Blakemore, 2016). However, it is also possible that one type of positive experience may play a more privileged role in driving these effects.

**Eligibility Criteria**

**Inclusion criteria.** Moderate to moderately severe depression indicated by a PHQ-8 score between 9 and 20; low positive affect indicated by a PANAS score of less than 24; no to moderate anxiety indicated by a GAD-7 score of less than 15; 18 to 25 years old; English speaking; and willingness to refrain from starting other psychosocial/pharmacological treatments until study completion. Given the small sample size of this study and the lingual limitations of our study staff, we are recruiting only English speaking participants as the burden of translation exceeds the scope of this project.

**Exclusion criteria.** MRI contraindications (left-handedness, claustrophobia, colorblindness, pregnancy, metal implants, and BMI above 35); presence of disease that may influence inflammation (i.e. asthma requiring inhaler, autoimmune or inflammatory diseases, gum disease, sleep disorder, eating disorder); presence of serious medical conditions (i.e., anemia, cancer (current or history), diabetes, endocrine disorder, fibromyalgia, heart problems); presence of disease that may impact patterns of neural activity (i.e. Attention Deficit/Hyperactivity Disorder, bipolar disorder, schizophrenia, head trauma, epilepsy, problems with drugs or alcohol); use of medications that may influence inflammation in last 6 months; bupropion, dopaminergic or neuroleptic medications in last 6 months, consistent with other studies that investigate anhedonia (e.g., Hanuka et al., 2022), given their potential influence upon reward processing; current use of heterocyclics and SSRIs if not stabilized for at least 3 months; history of regular (5-7 times per week) drug use (marijuana, cocaine, stimulant use before age of 15); current nicotine use (more than 11 cigarettes a week or nicotine equivalent); prior or current behavioral activation psychotherapy; and concurrent psychotherapy. (PRN benzodiazepines and beta-blockers were permitted but discouraged on assessment visits.)

**Recruitment**

Participants were recruited via advertisements on the UCLA campus. Eligibility will be determined on a rolling basis per study recruitment needs. Participants will first complete a pre-screening questionnaire by scanning the QR code on the study flier. Those who may be eligible will then complete a phone screener with study staff. Eligibility will be determined by Robin Blades, Julienne Bower, and Michelle Craske. Robin Blades and Julie Bower will have primary responsibility for reviewing potential participant questionnaire and phone screener responses. Michelle Craske will be consulted to determine eligibility in more complicated cases.

Potential participants will complete a questionnaire online to assess:

- Undergraduate student status
- Depression (9<PHQ-8<20)
- Positive affect (PANAS-P<24)
- Anxiety (GAD-7<15)

All potential participants who fill out the pre-screening questionnaire will receive the following mental health resource information: "Please note that if you are in need of immediate mental health services, we would like to refer you to the Counseling and Psychological Services (CAPS) at UCLA. CAPS is a multidisciplinary student mental health center for the UCLA campus. They offer individual counseling and psychotherapy, psychiatric evaluations and treatment, as well as campus mental health and wellness support services. They are located at:

John Wooden Center West 221 Westwood Plaza
Box 951556
Los Angeles, CA 90095-1556
Phone: (310) 825-0768
www.counseling.ucla.edu"

All ineligible participants will also be given a more detailed mental health resource sheet for reference via email. The detailed resource sheet includes: emergency assistance contacts; 24-hour hotlines for suicidal thoughts; more UCLA mental health services; resources for sexual assault, intimate partner violence, and stalking; community mental heath organizations; a national self-help hotline; and national organizations for anxiety and depression.

For those who fit the pre-screener criteria, a phone screener will be scheduled to assess:

- MRI contraindications
- Presence of serious medical conditions
- Presence of disease that may influence inflammation
- Presence of disease that may impact patterns of neural activity
- History of drug use
- Current nicotine use
- Prior or current behavioral activation psychotherapy
- Concurrent psychotherapy
- Use of medications

Ineligible potential participants will again receive information about accessing CAPS, as well as a more detailed mental health resource sheet for reference via email. Eligible participants will be enrolled in the study.

**Research Design and Methods**

This single-arm pilot study examines how savoring alters psychological, neural, and immunological processes in a sample of 30 undergraduate students at UCLA. Participants complete baseline questionnaires, blood collection, behavioral task, and MRI, followed by seven weekly intervention sessions. Daily diaries are completed during the week before and week after the intervention. Post-intervention assessments repeat questionnaires, blood collection, behavioral task, and MRI.

**Questionnaires** will be completed at in-person assessments conducted pre-intervention and post-intervention. The primary outcome is positive affect assessed with the PANAS questionnaire. We will also collect other mental health outcomes, including depressive symptoms (PHQ-8), anxiety (GAD-7), stress (PSS-4), wellbeing (MHC-SF), rumination (RRS), and loneliness (UCLA Loneliness Scale). We will measure positive and negative affect with two emotion questionnaires (mDES and PANAS), as well as use of savoring techniques (WOSC) and reward activation (PVSS). In addition, we will collect several exploratory questionnaires assessing interoception (MAIA-2), posttraumatic stress (PDS), beliefs about emotions (EBQ), difficulties with emotion regulation (DERS), and social attachment (SPS attachment subscale). We will also collect information about health behaviors and sleep disturbance (ISI). We will assess background demographics, medical history, and intervention credibility (CEQ) only at the pre-intervention assessment.

**Blood samples** will be collected at in-person assessments conducted at pre-intervention and post-intervention to assess inflammatory biomarkers. Dried blood spots will be collected using Tasso OnDemand devices and used to examine circulating inflammatory markers (Bower & Irwin, 2016; Creswell et al., 2012). Plasma levels of Interleukin-6 and C-Reactive Protein will be determined using a high sensitivity enzyme-linked immunosorbent assay (ELISA). All samples will be run in duplicate, and samples for an individual participant were run in parallel to avoid inter-assay variability. We will also examine genomic markers of inflammation, which may be more sensitive to intervention effects than circulating inflammatory markers (Creswell et al., 2012).

**A Behavioral Task** will assess sustained attention to positive and negative stimuli. A dot probe attentional task was chosen, because depression and low positive affect are related to directing less attention toward positive information and more attention toward negative information (Joormann et al., 2007; Tamir & Robinson, 2007; Peckham et al., 2010; Winer & Salem, 2016). We Will use a modified version of the dot probe attentional task, in which participants view standardized male and female faces that are sad, happy, and neutral (Rudaizky et al., 2014; Biehl et al., 1997). Each person has an emotional face and neutral face in the set. Neutral trials establish baseline attention. Craske et al. found that the full Positive Affect Treatment does not change attention to positive stimuli, but decreases attention to negative

stimuli compared to an active control group (2023). Through this behavioral task, we will examine if the savoring module of the PAT intervention has the same effect.

**Neuroimaging** will be conducted at pre-intervention and post-intervention. During the 75-minute scanning session, participants will undergo a series of tasks that are known to activate the neural regions of interest.

I. *Consummatory reward activity* is operationalized as activity in the ventral striatum and related "neural reward" regions in response to a reward-related task, the Positive Pictures task (Dutcher et al., 2021). In this task, participants passively view three types of images from two databases (the Nencki Affective Picture System and the Geneva Affective Pictures Dataset): images of people smiling and interacting (social reward images), images of landscapes and sunsets without people (nonsocial reward images), and images of common household objects like cups and furniture (neutral images) (Dan-Glauser & Scherer, 2011; Marchewka et al., 2014). Passive viewing of positive images has reliably been used to measure activity in the ventral striatum (Epstein et al., 2006; Heller et al., 2013; Inagaki et al., 2015), and increases in striatal activity during this nonsocial reward images have been associated with decreases in inflammatory markers among breast cancer survivors (Dutcher et al., 2021). As a manipulation check, participants will be asked how pleasant they found the task to be on a scale from 1 (not at all) to 4 (a lot).
II. *Anticipatory reward activity* is operationalized as activity in the ventral striatum and related "neural reward" regions in response to the monetary incentive delay task during introduction of a cue informing participants about an upcoming potential reward (Knutson et al., 2000). In this task, participants press a button as quickly as they can in response to viewing a target shape in order to earn monetary rewards. The anticipation phase of this task reliably activates the ventral striatum, though there is a different pattern of activation in patients with depression (Knutson et al., 2001)(Knutson et al., 2008). Interestingly, Craske et al. found that participants in the PAT intervention had a marginally more stable cardiac responses, compared to a decline in cardiac acceleration in the active control group, indicated by lengthening cardiac inter-beat intervals during the monetary incentive delay task (2023).
III. *Threat reactivity* is operationalized as activity in the amygdala and related "neural alarm" regions in response to a threat-related task, the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005). The MIST reliably elicits activity in the amygdala and other threat-related neural regions, such as the anterior insula and anterior cingulate cortex (Goodman et al., 2020). As a manipulation check, participants will be asked how stressful they found the task to be on a scale from 1 (not at all) to 4 (a lot).

We will also include three non-task resting state scans during which the participants will view a fixation cross in order to establish baseline and sustained reactivity to tasks.

**Daily diaries** will be completed electronically using REDCap for one week before the intervention and one week after the intervention. We include daily diary measures because they are more accurate than retrospective reporting, provide more complete experiential feedback on the impact of an intervention, and may increase adherence to the intervention (Neale & Green, 2002; Okupa et al., 2013). We will collect event lists to assess number of positive and negative experiences (social and non-social) each day. We will also assess positive and negative emotions each day. Daily social reward reactivity is operationalized as positive affect in response to

positive social experiences; daily nonsocial reward reactivity is operationalized as positive affect in response to positive nonsocial experiences; and daily threat reactivity is operationalized as negative affect in response to negative experiences.

**The savoring intervention** is the first module of the Positive Affect Treatment (PAT) developed by Michelle Craske and colleagues to treat anhedonia, or loss of interest or pleasure in usual activities (Craske et al., 2016). Given research suggesting that anhedonia is caused by neural reward deficits, PAT aims to enhance reward sensitivity using a variety of approaches (e.g., behavioral activation, savoring, cognitive reappraisal, and loving kindness). We focus here on the behavioral activation and savoring components of the intervention, which are administered first and are considered the basis for other components. Of note, a variety of other positive psychology interventions include a savoring component (Bryant, 2021), but PAT is unique in its inclusion of six sessions devoted to savoring. These sessions involve pleasant events scheduling in which participants: 1) plan activities that generate anticipation of reward, 2) engage in activities that generate reward and 3) practice therapist-guided-in-the-moment recounting of positive emotions, sensations, and thoughts generated by these activities. We will additionally include an introductory psychoeducation session before the savoring module, as PAT does. An experienced therapist will implement the savoring protocol, and sessions will be held virtually via Zoom.

**Statistical Analyses**

Outcome measures are continuous and assessed at multiple time points. Thus, the data will be analyzed primarily using linear mixed effects models, with fixed effects for time and random effects for individuals. Analyses will be conducted under the intent-to-treat principle, accomplished by fitting models to all available data for each outcome measure, including data of participants with incomplete follow-up. Linear mixed models provide valid inference under a missing at random assumption (Laird & Ware, 1982). The outcomes of interest in this pilot study include wellbeing, reward reactivity, and threat reactivity. Prior to conducting analyses we will examine the distributions of scores on these outcomes and transform them to normality as needed for use as dependent variables in multiple linear regression. Variables to be considered as covariates include sociodemographic characteristics and biobehavioral factors. Each outcome variable will be analyzed separately. All tests will be at $\alpha$=.05 and two-sided. Appropriate scaling and transformation for variables will be assessed prior to analyses. For all outcome analyses, we will conduct diagnostics to examine the effects of outliers, and we will assess influential cases by re-analyzing the data with these cases omitted.

**Aim 1 Analysis**. We will examine changes in positive affect measured by questionnaires from pre to post-intervention using mixed models to confirm the effect of the savoring intervention.

**Aim 2 Analysis.** We will investigate intervention effects on daily diary outcomes of interest, specifically social and nonsocial reward reactivity and threat reactivity. Affective reactivity is commonly calculated as the difference in an individual's level of positive or negative affect in response to positive or negative experience (Almeida, 2005). This difference can be calculated using multilevel models where level 1 represents within-person variability and level 2 represents between-person variability. To examine daily social reward reactivity, we will calculate T1

within-person slopes indexing the change in positive affect from days without a reported positive social experience to days with a reported positive social experience for each individual. Participants' average level of positive affect on days with no positive social experience will be calculated and included as a covariate in all analyses, making it possible to distinguish between effects driven by how people react to daily positive social experiences (calculated by affective reactivity slopes) and effects driven by the daily positive affect they typically experience. We will perform the same analyses to calculate daily nonsocial reward reactivity and daily threat reactivity. We will winsorize to account for skewness if necessary to reduce the effect of spurious outliers. A similar method of measuring affective reactivity was used by Piazza et al. (2013) and is a common approach in the literature (Sin et al., 2015; Cohen et al., 2005). We will then use a mixed model to examine change in daily social reward reactivity, daily nonsocial reward reactivity, and daily threat reactivity slopes pre- to post-intervention. To confirm that wellbeing is driving effects, we will examine the correlation between change in wellbeing from pre to post-intervention and change in each type of daily reactivity.

**Aim 3 Analysis.** We will investigate intervention effects on neural outcomes of interest, specifically social and nonsocial consummatory reward reactivity, anticipatory reward reactivity, and threat reactivity. Neural social reward reactivity is operationalized as the difference in neural activation in reward-related regions (e.g. ventral striatum) between social positive images and neutral images during the Positive Pictures task; neural nonsocial reward reactivity is operationalized as the difference in neural activation in reward-related regions (e.g. ventral striatum) between nonsocial positive images and neutral images during the Positive Pictures task; anticipatory reward reactivity is operationalizes as the difference in neural activation in reward-related regions (e.g. ventral striatum) during anticipation of reward vs. no anticipation of a reward; and threat reactivity is operationalized as the difference in neural activation in threat-related regions (e.g. amygdala) between stressful tasks and easy tasks during the MIST task. We will use mixed models to examine change in neural social anticipatory reward reactivity, neural nonsocial anticipatory reward reactivity, neural consummatory reward reactivity, and neural threat reactivity pre- to post-intervention. To confirm that wellbeing is driving effects, we will examine the correlation between change in wellbeing from pre to post-intervention and change in each type of neural reactivity.