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Understanding Self-Compassion:
A Social Neuroscience Approach

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Psychology

by

Michael Parrish

2022

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ABSTRACT OF THE DISSERTATION

Understanding Self-Compassion:
A Social Neuroscience Approach

by

Michael Parrish
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2022
Professor Naomi I. Eisenberger, Chair

Self-compassion, being kind, understanding, and mindful toward the self, is an effective regulatory strategy which is protective against threats to emotion well-being and physical health. Despite rapidly growing research interest on the topic within the social, behavioral, and health sciences, very little is known about the underlying neurocognitive mechanisms of self-compassion. Therefore, the goal of this dissertation research was to begin to fill in this critical gap in knowledge, leveraging the methods and approaches of social neuroscience. Across three functional magnetic resonance imaging (fMRI) studies, it was found that self-compassion and its subcomponents relate to: 1) the functioning of negative emotion regulation related circuitry in response to social evaluative feedback, 2) change in the functional integration of large-scale intrinsic networks implicated in cognitive control and self-referential processing, and 3) change in the functioning of mesocortical circuitry during reward-processing.

The dissertation of Michael Parrish is approved.

Julienne E. Bower

Matthew D. Lieberman

Carolyn M. Parkinson

Naomi I. Eisenberger, Committee Chair

University of California, Los Angeles

2022

To my mother Wanda Parrish

In honor of her fierce love, strength, and resilience

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Acknowledgments

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Next, and probably most importantly, I would like to acknowledge my mother Wanda Parrish, who has been my biggest supporter and most dedicated cheerleader since I was a young kid. She generously gave me the gift of loving to learn during my childhood, and no amount of words is adequate to express my gratitude for that. It's likely the primary reason for many of my successes and why I've been able to become a scientist and researcher today. Despite her facing academic difficulties in school, she was determined to make sure I did not struggle in the same way. She is the most loving, wise, and dedicated mother that I have ever encountered (and I say this thinking as a scientist with as little bias as possible). She taught me the value of compassion, and I don't have any doubts that this shaped by research interests, as seen in this dissertation. Thank you, Mom. I could not have done this without you.

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Vita

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Academic Honors and Awards

NSF Social, Behavioral, and Economic Sciences Postdoctoral Fellowship	**2022**
Society for Affective Science Poster Spotlight	**2018**

Society for Personality and Social Psychology Diversity Fund Graduate Travel Award	**2017**
University of Michigan fMRI Course Trainee	**2017**
Social and Affective Neuroscience Society Conference Poster Award	**2017**
UCLA Graduate Summer Research Mentorship Award	**2016**
National Science Foundation Graduate Research Fellowship	**2016**
UCLA University Distinguished Fellowship	**2015**
UNC Psychology Departmental Highest Honors	**2015**
Graduated from UNC with Distinction	**2015**
Sigma Xi Associate Membership	**2014**
UNC Celebration of Undergraduate Research Poster Award	**2014**
Order of the Grail-Valkyries (UNC’s academic honorary society)	**2014**
David Bray Peele Memorial Research Award	**2013**
Howard Hughes Medical Institute Future Scientists and Clinician Fellowship	**2013**
Carolina Covenant Scholarship for First Generation College Students	**2011**

“Caring for myself is not self-indulgence,

it is self-preservation”

-Audre Lorde

Background

When we think about the feeling of compassion, we usually imagine being kind and caring toward others, such as our partners, friends, or family members. This type of compassion is beneficial because it helps maintain interpersonal relationships and ensures the emotional health of our social groups and communities. However, less often realized is the vital importance of another form of compassion - self-compassion, defined as being kind, understanding, and mindful to the self (Neff, 2003). While thoughts about close others can often engender feelings of compassion, we regularly fail to treat ourselves with the same type of respect or kind concern. Indeed, we can habitually direct intense criticism at ourselves in ways in which we would simply not for other individuals. In light of this, multiple questions about the underlying mechanisms of self-compassion naturally arise, including "what is the biological basis of self-compassion and how can it be effectively (or ineffectively) developed in the human mind and brain?" Unfortunately, not very much is known concerning answers to these questions, yet solid evidence exists that shows self-compassion can contribute to a happy and healthy life. Over the past two decades, research accumulated from several academic fields within the social, behavioral and health sciences has consistently shown self-compassion to be an effective regulatory strategy and psychological trait which promotes emotion well-being, mental and physical health, and positive interpersonal functioning (Diedrich et al., 2014; Hughes et al., 2021; Kılıç et al., 2021; Leary et al., 2007; MacBeth & Gumley, 2012; Neff et al., 2007; Neff & Beretvas, 2013; Neff & Germer, 2013; Neff & Pommier, 2013; Neff & Germer, 2017; Wang et al., 2017). Given the current gaps in scientific knowledge and these health and interpersonal benefits, the research presented within this dissertation was motivated by a goal of understanding the mechanistic basis of self-compassion, specifically from a social and affective neuroscience perspective. In this introductory section, I will give an overview of the dissertation research and contextualize the motivation to do such research.

Self-compassion as an academic topic should first be properly situated in its unique cultural and historical context. Outside the academic setting, self-compassion has likely grown in popularity in part due to cultural, social, and generational reasons. Since roughly the year 2015, there has been a resurgence in interest in not only the academic topic of self-compassion but also in the cultural phenomenon that is the self-care social movement (Google Trends, 2022). This can be seen playing out in popular culture in several different ways. In music trends, there has been a rise in fame of artists such as Lizzo, Solange, Alessia Cara, and Logic, who profess the importance of self-care and self-love. In technology trends, there has been growth in popularity of mental health apps, such as BetterHelp and Talkspace. In economic trends, the self-care industry has experienced a recent boom - growing to be worth a staggering ten billion dollars. These trends will likely continue during the 2020s given the shifts in social attitudes and the deleterious effects of the COVID-19 pandemic.

The interest in self-care during the last half of the 2010s can most likely be specifically attributed to social, political, and economic changes that have occurred within the past decade. First, millennials, the largest generation since the "baby boomers" have started to enter the workforce and climb the social status hierarchy. As a result of this, a group of individuals who have grown up understanding how to use internet technologies has slowly been exposed to the emotions and pains that come along with professional life. Responding to this, they have chosen to invest in themselves and their well-being and communicate the importance of these new values to the world through social media. Second, the cultural and economic turmoil following 9/11, the wars in Iraq and Afghanistan, and the Great Recession also introduced a great degree of stress and uncertainty for all adults. These events served as the backdrop to a decade in the 2010s characterized by a high degree of social discontent. Third, intensifying political polarization in America and elsewhere reached a "tipping point" when Donald Trump was elected as the U.S. President in 2016. Since that time, political discord has continued to accelerate, and this has resulted in likely unprecedented levels of societal stress and personal unease for countless individuals. These social and cultural factors have combined to create an environment in which one's own emotional well-being needed to be prioritized not only for long-term happiness and life satisfaction, but also for self-preservation. These patterns have been mirrored by similar trends in academic research.

Within the academic context, the accelerating interest in self-care and self-compassion has been coupled with a stronger focus on the general area of compassion in psychology and neuroscience in particular. The science of compassion has built steadily over the past decade, and much more is known about underlying mechanisms than ever before (Seppälä et al., 2017). Methods such as functional and structural neuroimaging in addition to peripheral physiological and hormonal measurement tools have helped ground compassion in its underlying biology. Compassion is now known to be associated with a distinct set of brain regions when compared to closely related psychological constructs such as empathy or sympathy (Kim, Cunnington, et al., 2020). In particular, based on functional magnetic resonance imaging (fMRI) meta-analytic evidence, compassion-related processes have been tied to several regions within frontal, limbic, and subcortical areas, but not parietal or occipital areas. A meta-analysis of peripheral physiological results has also recently linked compassion to vagus nerve-mediated heart-rate variability (HRV; (Di Bello et al., 2020; Kim, Parker, et al., 2020). Multiple studies have also linked compassion to the hormone and neurotransmitter oxytocin (Bellosta-Batalla et al., 2020;

Palgi et al., 2015; Rockliff et al., 2011). Even though compassion science is still in its infancy, this research shows the great promise in understanding compassion towards other and the self from a biological perspective.

Discussion of self-compassion should also be situated within the cumulative base of knowledge on its benefits from the health and behavioral sciences. Self-compassion has been shown to be related to reduced levels of depression and anxiety (MacBeth & Gumley, 2012; Wilson et al., 2019) and reduced suicidal ideation and non-suicidal self-injury (Suh & Jeong, 2021). The negative associations with anxiety and depression have been specifically confirmed by meta-analysis within the context of chronic physical illness populations (in which most of the studies involved cancer patients; Hughes et al., 2021). Self-compassion related interventions reliably increase self-compassion and decrease depression in chronic physical illness patients (Kılıç et al., 2021; c.f., Mistretta & Davis, 2021). Interventions targeting self-compassion reduce self-criticism (Ferrari et al., 2019; Wakelin et al., 2022), suggesting that reduced self-criticism may be a consistent mediator in the negative relationships between self-compassion and depression or anxiety. In terms of other psychosocial outcomes, self-compassion reliably relates to increased self-efficacy (Liao et al., 2021), decreased stress and rumination (Ferrari et al., 2019), improved moral judgments (Wang et al., 2017), healthier eating behaviors (Ferrari et al., 2019), enhanced self-improvement motivations (Breines & Chen, 2012), bolstered hope and life satisfaction (Yang et al., 2016), and meaning in life (Yela et al., 2020). Taken together, the current state of the research on self-compassion shows that it is critically beneficial for emotional and physical well-being.

Despite the long list of salutary and psychological benefits of self-compassion, relatively little work has been conducted to examine its neurocognitive mechanisms. To date, only approximately five studies have been conducted using neuroimaging to unpack the multifaceted construct of self-compassion (Berry et al., 2020; Guan et al., 2021; Liu et al., 2022; Lutz et al., 2020; Parrish et al., 2018). This is not only surprising, but also concerning because many people have serious doubts about the underlying basis of self-compassion and its benefits (Breines & Chen, 2012; Neff & Germer, 2017). Besides giving insight into its cognitive mechanisms, neuroscience studies may also help reduce this doubt in the long-term and help reify self-compassion as a legitimate scientific construct and intervention target. Previous research has shown that brain imaging results lead cognitive science findings to be found more credible, persuasive, and also more interesting (McCabe & Castel, 2008). Therefore, fMRI studies unveiling the mechanisms and predictors of self-compassion may help dissuade skeptics of this science. In sum, neuroscientific research on the topic is needed to understand mechanisms linking self-compassion to its benefits and to help provide a biological grounding for this important socially and culturally relevant construct.

The goal of this dissertation is to describe a set of studies aimed at understanding the neurocognitive mechanisms of self-compassion. Here, two main approaches are taken to understanding self-compassion. In the first paper, an individual differences approach is taken to understanding the neural mechanisms underlying how trait self-compassion naturally varies from person to person. In the second and third papers, a longitudinal approach is taken to assess the mechanisms underlying how a specific subcomponent of self-compassion, self-kindness, increases in response to a health intervention. These sets of studies relate to analyses of both healthy young adults and a clinical sample of cancer survivors. Moreover, self-compassion is shown to relate to multiple types of psychological task contexts, specifically a social evaluation task and social/non-social reward task, in addition to the context of the resting state mind and brain. Specific objectives include demonstrating how neural functioning, as assessed by both activation and connectivity analyses, concurrently and prospectively relates to self-compassion or self-kindness. The findings reported herein will ideally serve as one of the starting foundations for future research on the topic of self-compassion in basic, translational, and clinical neuroscience.

Self-Compassion and Responses to Negative Social Feedback:
The Role of Fronto-Amygdala Circuit Connectivity

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Self-compassion has been shown to have significant relationships with psychological health and well-being. Despite the increasing growth of research on the topic, no studies to date have investigated how self-compassion relates to neural responses to threats to the self. To investigate whether self-compassion relates to threat-regulatory mechanisms at the neural level of analysis, we conducted a functional MRI study in a sample of college-aged students. We hypothesized that self-compassion would relate to greater negative connectivity between the ventromedial prefrontal cortex (VMPFC) and amygdala during a social feedback task. Interestingly, we found a negative correlation between self-compassion and VMPFC-amygdala functional connectivity as predicted; however, this seemed to be due to low levels of self-compassion relating to greater positive connectivity in this circuit (rather than high levels of self-compassion relating to more negative connectivity). We also found significant relationships with multiple subcomponents of self-compassion (Common Humanity, Self-Judgment). These results shed light on how self-compassion might affect neural responses to threat and informs our understanding of the basic psychological regulatory mechanisms linking a lack of self-compassion with poor mental health.

Self-compassion is defined as the tendency to be kind, warm, and understanding toward oneself in the midst of our pain and failures rather than being self-critical and over-identifying with negative emotions (Neff, 2003). Research on self-compassion has attracted increasing attention since it was first introduced in psychological science 15 years ago (Neff, 2003). While the importance of compassion directed toward the self has been recognized historically (Brach, 2004; Gunaratana, 2010; Kabat-Zinn, 1982; Salzberg, 1998), only recently have researchers sought to systematically understand its unique contributions for mental health and well-being (MacBeth & Gumley, 2012). Moreover, research in this area is beginning to establish connections between self-compassion and interpersonal functioning (e.g., Yarnell & Neff, 2013). Despite many correlational studies establishing broad associations between self-compassion and its health and interpersonal benefits, the mechanisms underlying these advantages remain poorly understood. Thus, the goal of the current study was to begin to explore the neural regulatory mechanisms that may underlie the benefits of self-compassion.

Extensive research has highlighted the benefits of self-compassion. Self-compassion has been linked to decreased risk for psychopathology and related maladaptive cognitive and behavioral patterns. For instance, self-compassion has been linked to decreased risk for depression (Krieger et al., 2013; MacBeth & Gumley, 2012; Raes, 2010), and depressed patients, compared to healthy controls, report less self-compassion, even when statistically controlling for differences in depressive symptoms (Krieger et al., 2013). In addition, the benefits of self-compassion extend into interpersonal domains of psychological functioning. For example, self-compassion is associated with greater relationship satisfaction, perspective-taking, and forgiveness, as well as less self-defensive relationship behaviors, such as being detached, domineering, and verbally aggressive (Neff & Pommier, 2012; Neff & Betertvas, 2013) (Neff &

Beretvas, 2013; Neff & Pommier, 2013). Taken together, these results suggest that self-compassion allows individuals to cope with negative affect and threats to the self in a way that preserves a healthy, confident sense of self while not being reactive. Therefore, when individuals are self-compassionate, threats to the self are met with neither self-defensiveness and anger nor avoidance and fear (e.g., Leary et al., 2007; Neff et al., 2007).

Research in social and personality psychology has recently begun to explore the mechanisms underlying self-compassion and has suggested that self-compassion may act as an emotion regulatory or coping mechanism useful for reducing feelings of threat, stress, or anxiety (A. B. Allen & Leary, 2010). For example, in an investigation of how self-compassion may be protective against threat, research has shown that trait self-compassion is linked to less avoidance coping and more positive emotional restructuring (A. B. Allen & Leary, 2010). These findings have been supported by experimental work showing that self-compassion uniquely buffers against self-evaluative anxiety in potentially threatening social settings like mock job interviews (Neff et al., 2007). Relatedly, self-compassion relates to less public self-consciousness as well as greater emotional stability, such that self-compassionate individuals' emotional states are less contingent on external circumstances (Neff & Vonk, 2009). In sum, self-compassion may lead to less ego-defensiveness, fear, and anger in response to negative social evaluation (Leary et al., 2007; Neff & Vonk, 2009).

While behavioral research has begun to dissect the mechanisms of self-compassion, neuroimaging approaches may also prove to be useful in examining the underlying basis of this trait. Unfortunately, no research to date has investigated the neural mechanisms by which self-compassion may protect against threats to the self. Even though social neuroscience research on the closely related topic of self-esteem has emerged over the past decade (Chavez & Heatherton, 2015; Eisenberger et al., 2011; Somerville et al., 2010), the brain basis of self-compassion and specifically its relationship with social threats remains unknown.

Given behavioral research on self-compassion's threat-reducing effects, the effects of self-compassion as an emotion regulation mechanism may be apparent at the neural level of analysis. Neural systems that support successful emotional regulation and the regulation of threat-related processes have been well-characterized in human neuroscience research as well as in research on non-human animals. Specifically, threat-related activity in the amygdala is tightly controlled by direct projections from the ventromedial prefrontal cortex (VMPFC; (Milad et al., 2004).

In some cases, the VMPFC is thought to have a direct causal effect in reducing amygdala activity and the associated patterns of fearful behavioral responding (Adhikari et al., 2015; Vidal-Gonzalez et al., 2006). Along these lines, research has shown negative functional connectivity between these two regions in response to several different types of emotion regulatory processes, including fear extinction (Hare et al., 2008; Milad et al., 2014; Phelps et al., 2004; Yarnell & Neff, 2013) as well as cognitive reappraisal (Lee et al., 2012). Thus, greater negative functional connectivity is indicative of greater emotion regulatory processes.

In other cases, though, the VMPFC is thought to play a role in upregulating the amygdala's responses to threat (Johnstone et al., 2007). Thus, positive functional connectivity between VMPFC and the amygdala has been shown to increase in response to both short-term exposure to unpredictable threat (Gold et al., 2015) and longer-term responses to social threat (Veer et al., 2011). Along these same lines, neuroimaging research has shown that greater positive connectivity between ventral PFC and amygdala positively correlated with self-reported pain to a cold-pressor task (Clewett et al., 2013). In addition, greater positive connectivity within this circuit has been found to associate with higher levels of endogenous cortisol, a stress-related hormone (Veer et al., 2012). Along these same lines, another plausible way to understand positive connectivity is in terms of the use of bottom-up salience attribution from the amygdala to the frontal cortex (Cunningham & Brosch, 2012). This circuitry is thought to be necessary for effective emotional and motivational responding to personally relevant stimuli in the social environment. Taken together, these lines of research suggest that the VMPFC-amygdala circuit is broadly involved in emotion and motivation, but in particular with threat-related processes.

Based on this work, human neuroimaging research can attempt to better understand the brain bases of self-compassion by examining the interplay between self-reported levels of self-compassion and VMPFC-amygdala functional connectivity in response to negative interpersonal feedback. To examine whether self-compassion is associated with VMPFC-amygdala circuit functioning, we conducted secondary data analyses on an fMRI study utilizing a social evaluative feedback paradigm (Eisenberger et al., 2011). The data were gathered from a study that explored the neural correlates of changes in state self-esteem as a function of social feedback. For the present paper, we explored whether self-compassion was linked to differences in functional connectivity between VMPFC and amygdala in response to negative (relative to neutral) social feedback. We hypothesized that self-compassion would correlate negatively with connectivity in the VMPFC-amygdala circuit, such that greater self-compassion would be associated with relatively greater negative connectivity in this circuit and less self-compassion would be associated with relatively greater positive connectivity between the VMPFC and amygdala.

Methods

Participants

Nineteen college-aged participants (12 female; M= 20.316 years, range= 18-27 years) took part in the present study. Participants were recruited from UCLA and the surrounding community. The study was representative of standard UCLA demographics: 47% Asian, 16% White, 16% Filipino, 11% Latino/Chicano, 5% Black/African American, and 5% Other.

Procedure

Potential participants were excluded during phone screening due to contraindications for the MRI environment (e.g. metallic implants, left-handedness, claustrophobia) and history of neurological or psychiatric disorders. During the study session, participants met with a confederate and the experimenter in the laboratory. The participant and confederate were informed that they were taking part in an fMRI study on impression formation. They were told that, during the first part of the study, they would each fill out some questionnaires and then engage in an audio-recorded interview that would later be listened to by the other participant. During the second part of the study, they would each complete the fMRI scan while the other participant listened to their interview and gave feedback about how the person was coming across in the interview while sitting outside of the scanner. The person being scanned would simultaneously view this feedback and rate their emotional responses.

Following the explanation of the procedure, the participant and confederate were placed into different testing rooms and given questionnaire packets. The experimenter then started the interview with the participant. The interview involved asking about the participant's personal characteristics and attitudes such as "What makes you happy?" and "What is your greatest shortcoming?" Following approximately 10 min of questions, the interview was finished, and the participant was reminded of what would happen during the scanning session. The experimenter then instructed the participant to finish the questionnaires while the confederate was ostensibly interviewed for the next 10 minutes. Before leaving the laboratory, the experimenter requested the participant and confederate draw slips of paper to determine who would be scanned first. The drawing of the slips of paper was rigged such that the participant's name was always picked so they would be scanned first (the confederate was never scanned). After the participant and confederate picked slips of paper, the experimenter guided the participant and the confederate to the UCLA Brain Mapping Center to complete the imaging session.

Once at the neuroimaging facility, the confederate was instructed to wait in the lobby as the participant was set up in the scanner. After the participant was situated in the scanner, the experimenter brought the confederate into the scanner control room and reminded the participant and confederate of the task procedure. The confederate then asked the experimenter some additional questions about the protocol (to increase believability that the confederate was a real subject). These questions could be heard by the participant via the intercom in the scanner. The participant heard the confederate being instructed to click on a descriptive feedback button once every 10 seconds while listening to the participant's interview, and to give their honest impressions of the participant in their interview. Participants were reminded to rate how they felt after seeing each feedback word using the button box in the scanner.

fMRI Social Feedback Task

While in the scanner, participants viewed the computer screen displaying an array of adjective "buttons" (i.e., "interesting," "modest," "boring") and watched a pre-recorded video of a cursor moving around the screen, which they were led to believe was the real-time display of the confederate's feedback on their interview. The number of feedback adjectives were equally divided into a positive category (e.g. 'intelligent'), a neutral category (e.g. 'practical') and a negative category (e.g. 'annoying'). Participants watched a new adjective button selected every

10–12 s. During the entirety of the scan session, participants received fifteen each of positive, neutral and negative feedback selections. After seeing an adjective button selected, participants were told to respond to the question ‘How do you feel?' by responding on a 4-point Likert scale (from 1 (really bad) to 4 (really good)) with a button box. This was done during the 10-12 s period in which they were shown the adjective. Overall neural responses to this task, as well as how they relate to self-reported feelings, have been reported previously (Eisenberger et al., 2011); in this paper, we focus specifically on how self-compassion modulates functional connectivity during the task. Following the experimental session, participants were promptly debriefed in a funneled manner and informed of the true purpose of the study. No participants reported suspicion prior to debriefing about the true purpose of the study.

Self-compassion Measure

To measure self-compassion, we used the self-compassion scale (SCS; Neff 2003). This scale was administered prior to the MRI scan. The scale consists of six subscales divided into three pairs of two opposite factors: Self-Kindness (e.g., “"When I'm going through a very hard time, I give myself the caring and tenderness I deserve") vs. Self-Judgment (e.g., "When times are really difficult, I tend to be tough on myself"), Common Humanity (e.g., "When I feel inadequate in some way, I try to remind myself that feelings of inadequacy are shared by most people") vs. Isolation (e.g., "When I think about my inadequacies, it tends to make me feel more separate and cut off from the rest of the world"), and Mindfulness (e.g., "When something upsets me I try to keep my emotions in balance") vs. Over-identification (e.g., “When I'm feeling down, I tend to obsess and fixate on everything that's wrong"). Participants were asked to indicate how they typically act toward themselves in difficult situations. Each statement was scored on Likert scales from 1 (almost never) to 5 (almost always). Item scores from the negative subscales representing uncompassionate responding (e.g., self-judgment, isolation, over-identification) were reverse-coded. The positive and negative subscale items were then combined and averaged to create an overall self-compassion mean score.

Trait self-compassion as measured by the SCS has been shown to be best summarized by a single general factor, including both the positive and negative items of the scale (Neff et al., 2019). Research using bifactor exploratory structural equation modeling has shown that 94% of SCS item variance can be explained by this general factor.

The 26-item SCS measure was found to be highly reliable (α = .913). Moreover, the six subscales were shown to have good reliability: the five-item SCS-Self-Kindness subscale (α = .729), the five-item SCS-Self-Judgment subscale (α = .759), the four-item SCS-Common Humanity subscale (α = .724), the four-item SCS-Isolation subscale (α = .669), the four-item SCS-Mindfulness subscale (α = .818), and the four-item SCS-Overidentification subscale (α = .792).

MRI data acquisition

MRI data were acquired using a Siemens Trio 3-Tesla MRI scanner at the UCLA Brain Mapping Center. A high-resolution structural scan (echoplanar T2-weighted spin-echo, repetition time (TR) = 4000 msec, echo time (TE) = 54 msec, matrix size = 128 × 128, field of view (FOV) = 20 cm, 36 slices, 1.56-mm in-plane resolution, 3-mm thick) coplanar with the functional scans was obtained for coregistration with functional images during data preprocessing. Following the structural scan, the social feedback task was completed during a functional scan, which lasted 498 seconds (echoplanar T2*-weighted gradient-echo, TR = 3000 msec, TE = 25 msec, flip angle = 90°, matrix size = 64 × 64, 36 axial slices, FOV = 20 cm, 3-mm thick, 3-mm cubic voxel size, skip = 1 mm).

MRI Pre-processing

MRI data were pre-processed with the Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK). The pre-processing pipeline incorporated image realignment to correct for head movement, co-registration of the functional to the structural images, and spatial normalization to Montreal Neurologic Institute (MNI) space (resampled at 3 mm isotropic), and spatial smoothing using an 8mm Gaussian kernel, full width at half maximum, to increase signal-to-noise ratio.

Functional Connectivity Analyses

To examine potential interactions between targeted neural regions of interest (ROIs), functional connectivity analyses were conducted with the CONN toolbox (nitrc.org/projects/conn) implemented through MATLAB and SPM8 software. The pre-processed functional and structural data were entered into the toolbox. Confounding variables that distort functional connectivity values were removed through the CONN CompCor algorithm for physiological noise as well as temporal filtering ($f > .008$Hz). Realignment parameters (representing head movement) produced during pre-processing were also entered in the toolbox as nuisance covariates to be removed from statistical analyses. For the functional data collected during the social feedback task, condition onsets and duration were specified in the toolbox, so that BOLD time series could be appropriately divided into task-specific blocks.

For the main statistical tests of interest, we conducted ROI-to-ROI analyses to determine functional connectivity (i.e., temporal correlations) between the VMPFC and both the left and right amygdala. For these analyses, we chose ROIs based on previous studies of emotion regulation (e.g., Diekhof et al., 2011). The VMPFC ROI was generated from the Harvard-Oxford probabilistic cortical atlas (Desikan et al., 2006), and the right and left amygdala ROIs were generated from the Automated Anatomical Labeling (AAL) Atlas (Tzourio-Mazoyer et al., 2002). Within the ROIs, the BOLD activation time series was averaged across all voxels. Functional connectivity values were computed on each individual's feedback condition time series from these ROIs at the single-subject level. These connectivity values provide a measure of the statistical dependence of the ROIs' BOLD activation time series. Connectivity values underwent Fisher's *r*-to-*Z* transformation to ensure assumptions of normality. This procedure was completed to generate task-evoked connectivity measures for each of the three social feedback conditions. We then explored whether self-compassion correlated with connectivity during negative (relative to neutral) feedback as well as during positive (relative to neutral) feedback. These relative connectivity measures were generated by taking the difference between connectivity values produced by the original, absolute, condition-specific (negative, positive, neutral) analyses. In other words, they should be interpreted as the difference in the functional coupling between these neural regions (i.e., VMPFC and amygdala) between these conditions (i.e., during negative feedback compared to during neutral feedback). These absolute and relative connectivity values were imported into SPSS v23 for further statistical analyses.

To examine correlations between self-compassion and VMPFC-amygdala connectivity during negative feedback specifically, we computed Pearson's correlations between self-compassion and VMPFC-amygdala connectivity during negative relative to neutral feedback (to allow for a baseline comparison). Any significant effects were followed up by additional analyses exploring whether the effects were being driven by the negative feedback condition or by the neutral feedback condition. To do this, we examined correlations between self-compassion and VMPFC-amygdala connectivity during the negative feedback condition and during the neutral feedback condition separately. These same procedures were repeated to examine correlations between self-compassion and VMPFC-amygdala connectivity during the positive vs. neutral feedback conditions. Finally, any significant correlations between self-compassion and connectivity were followed up by subscale analyses, which examined which specific subscales correlated with connectivity.

Results

Self-compassion and VMPFC-amygdala connectivity

As predicted, statistical analyses revealed that self-compassion (averaged across subscales) was negatively correlated with VMPFC- right amygdala connectivity during negative vs. neutral feedback ($r(18) = -.402$; Table 1.1.). As displayed in Figure 1.1., higher self-compassion was associated with more negative functional connectivity between VMPFC and right amygdala during negative relative to neutral feedback, whereas lower self-compassion was associated with greater positive connectivity between VMPFC and right amygdala. There was no significant correlation between self-compassion and VMPFC-left amygdala connectivity in response to negative vs. neutral feedback ($r(18) = -.263$, $p = 0.165$), though the relationship was in the same direction as found with the right amygdala.

To further explore whether the relationship between self-compassion and VMPFC-right amygdala connectivity was being driven by negative feedback (as expected) or by neutral feedback, we analyzed correlations between self-compassion and connectivity during negative and neutral feedback separately. Here, we found that the relationship between self-compassion and VMPFC-right amygdala connectivity reported above appeared to be driven by connectivity in the negative feedback condition (Fig. 1.2.). Specifically, there was a negative correlation between self-compassion and connectivity in response to negative feedback ($r(18) = -.458$, $p = 0.024$), whereas, self-compassion was not associated with connectivity in response to neutral feedback (*r*(18) = .044, *p* > .05) . Somewhat surprisingly, the negative correlation between self-compassion and connectivity in response to negative feedback appeared to be explained by those lower in self-compassion showing higher positive VMPFC-amygdala connectivity, rather than those high in self-compassion showing greater negative connectivity.

We also explored whether self-compassion correlated with connectivity during positive vs. neutral feedback and found no significant effects for VMPFC-right amygdala connectivity (*r*(18) = -.262, *p* = .140) nor VMPFC-left amygdala connectivity (*r*(18) = -.366, *p* = .062). In light of these non-significant findings for the positive feedback condition, further analyses of the positive feedback condition were not explored.

Subscales of Self-compassion and VMPFC-amygdala connectivity

Based on the significant relationship between self-compassion and VMPFC-amygdala connectivity during negative vs. neutral feedback, we then further examined how the subscales of the self-compassion scale correlated with these connectivity scores. In our analyses of subscales of the SCS, we found significant correlations with two of the subscales: Self-Judgment and Common Humanity (Fig. 1.3.). Specifically, there was a significant positive correlation between SCS-Self-Judgment and VMPFC- right amygdala connectivity (*r*(18) = .417; Table 1.1.). This effect did not seem to be specific to either the negative or neutral feedback, as VMPFC-right amygdala connectivity did not significantly correlate with SCS-Self-Judgment during negative (*r*(18) = .205, *p* = .200) or neutral (*r*(18) = -.226, *p* = .176) feedback conditions when they were examined separately. There was also a significant negative correlation between SCS-Common Humanity and VMPFC-right amygdala connectivity in response to negative vs. neutral feedback (*r*(18) = -.518; Table 1.1.). This effect was likely driven by the significant negative correlation with absolute VMPFC-right amygdala connectivity during negative feedback (*r*(18) = -.442, *p* = .029), as we did not find a significant association between SCS-Common Humanity and connectivity during neutral feedback (*r*(18) = .156, *p* = .262). Thus, it appeared that having low levels of Common Humanity was associated with greater positive connectivity between VMPFC and right amygdala during negative feedback. In addition to these subscale results, we found a marginally significant negative correlation between SCS-Mindfulness and VMPFC-right amygdala connectivity in response to negative vs. neutral feedback (*r*(18) = -.321; Table 1.1.). We also found a marginally significant positive correlation between SCS-Over-Identification and VMPFC-right amygdala connectivity in response to negative vs. neutral feedback (*r*(18) = .317; Table 1.1.). The other subscales were not significantly correlated with connectivity (Table 1.1.).

Discussion

To our knowledge, this is the first study to examine the neural processes by which self-compassion relates to neural responses to social feedback. As predicted, we found a negative association between self-compassion and VMPFC-amygdala connectivity during negative (relative to neutral) feedback. Thus, those higher in self-compassion showed relatively greater negative VMPFC-amygdala connectivity in response to negative (vs. neutral) feedback, whereas those lower in self-compassion showed relatively greater positive connectivity to negative feedback. Upon further parsing of the data, these responses seemed to be driven by patterns of connectivity to negative rather than neutral feedback, as expected. However, somewhat surprisingly, rather than high levels of self-compassion being related to greater negative connectivity, we instead found that lower levels of self-compassion were related to greater positive connectivity between VMPFC and amygdala. We interpret these unexpected findings as indicating that a lack of self-compassion may lead to heightened sensitivity to negative emotional experiences. We also show that Self-Judgment and Common Humanity components of self-compassion show particularly strong associations with functioning of this circuit. Taken together, these results shed light on the emotion processing functions related to individual differences in self-compassion and the role of the VMPFC-amygdala circuit in contributing to the effects of self-compassion on responding to threats to the self. These findings may help address the underlying mechanisms that link low levels of self-compassion with poor mental health and interpersonal problems.

From a psychological perspective, the findings of this fMRI study contribute to our understanding of the functioning of emotion/affective processing mechanisms associated with self-compassion. While multiple lines of neuroimaging research link the functioning of VMPFC-amygdala circuitry to emotion regulation processes, there is also substantial evidence to suggest that this circuitry is involved in emotion generation processes as well (Gold et al., 2015; Johnstone et al., 2007; Veer et al., 2012). More specifically, based on this research, one possible interpretation of our results is that individuals lacking self-compassion elicit an over-exaggerated response to negative information in their social environments. VMPFC-amygdala circuitry has been implicated in top-down signaling mechanisms for ascribing affective salience to stimuli in the environment (Cunningham & Brosch, 2012). The function of the top-down connections from the VMPFC to the amygdala can be thought of as facilitating switching attention to, and preparing behavioral responses to, emotionally or motivationally relevant stimuli (Cardinal et al., 2002; Ochsner et al., 2009).

This heightened detection of salient negative social stimuli may directly lead to negative emotions in daily life. The emotional consequences associated with low levels of self-compassion have been described in the multiple behavioral studies primarily aimed at determining the special benefits of self-compassion for psychological well-being. For example, individuals lacking self-compassion were more likely to ruminate and experience negative affect after being exposed to critical social evaluations (Leary et al., 2007). Similar findings have shown that low levels of self-compassion lead to relatively greater anxious feelings when experiencing social-evaluative threat after being judged in a mock job interview (Neff et al., 2007). Many of these and other similar behavioral studies originally highlighted the unique advantages associated with high levels of self-compassion, but our neuroimaging results also point to the potential importance of determining the unique disadvantages associated with low levels of self-compassion (i.e., a tendency to up-regulate threat and negative affect). However, this is not to suggest that correlations with low levels of self-compassion were better explained by the negative subscales, given that both certain positive and negative subscales related significantly to VMPFC-right amygdala functional connectivity during negative vs. neutral feedback, as discussed below. Additionally, these neuroimaging analyses help potentially clarify the source of these experimental effects by specifically showing that low levels of self-compassion may be a key contributor to differences in emotional consequences. Given the behavioral findings alone, it is not clear which group of participants (low vs. high self-compassion individuals) may be the driver of these associations. Moreover, it is unclear whether distinct psychological processes may be involved in these different groups. These imaging approaches can be leveraged to begin to effectively resolve some of these inferential issues.

From a neuroscience perspective, the findings also inform our understanding of the emotional processing functions subserved by VMPFC-amygdala circuitry. While a great deal of research shows that the VMPFC can modulate amygdala activity in the context of learning about threat-related cues associated with nonsocial dangers (Diekhof et al., 2011), less is known about the role of VMPFC-amygdala functional interactions in the context of socially threatening/evaluative situations. While previous neuroimaging research has shown that ventral PFC activation correlates with self-reassurance in reaction to negative events (Longe et al., 2010), no research has shown an association between the functional connectivity of this region and trait-level self-compassion, as it is traditionally measured. Moreover, the social stimuli used in previous research on the emotion processing functions of this circuit (e.g., Gee et al., 2013; Urry et al., 2006) were static pictures presented in the MRI scanner. The current results extend other findings by showing that VMPFC-amygdala functional connectivity is also relevant in the context of a more dynamic social feedback task, during which participants believed they were being evaluated in real time.

Importantly, these findings reinforce multiple lines of evidence which suggest that heightened positive VMPFC-amygdala connectivity is associated with negative outcomes. While many initial studies examining this circuit focused on negative connectivity between these two regions during emotional inhibition, multiple studies have also now shown that positive connectivity is associated with negative affect and individual differences suggesting greater propensity to experience negative affect. For example, positive VMPFC-amygdala connectivity has been associated with the experience of social stress (Veer et al., 2011), the stress-related hormone cortisol (Veer et al., 2012) as well as depression and anxiety (Johnstone et al., 2007; Satterthwaite et al., 2016). Interestingly, while not as often explicitly discussed, positive VMPFC-amygdala connectivity has also been associated with poorer negative emotion regulation abilities as measured by fMRI (Morawetz et al., 2017) and objective psychophysiological measures, such as corrugator electromyography (Lee et al., 2012). Taken together, our current results are in line with research showing the involvement of VMPFC-amygdala circuitry in several different forms of negative emotional processing.

Considering the results of our analysis of the subscales of the SCS, we should point out the potential importance of the Self-Judgment and Common Humanity components of self-compassion. We found that individuals who scored higher in Self-Judgment were more likely to recruit greater positive VMPFC-amygdala connectivity in response to social threat. This may be due to the fact that these individuals are harshly criticizing themselves following social evaluation, and thus up-regulating their negative affect. We also found that individuals who scored lower in Common Humanity were more likely to elicit positive connectivity in this circuit. This might be because these individuals are less likely to take a more globally oriented approach to their social evaluative feedback and are thus more prone to up-regulating unpleasant feelings occurring due to negative affect. Because they underestimate how much others suffer in a similar manner to themselves, they may be more likely to perseverate on these negative emotional experiences, blaming themselves for their suffering and external circumstances. We also found *marginally* significant relationships between VMPFC-amygdala connectivity and Mindfulness as well as Over-Identification subscales. We may have been able to detect significant relationships with a larger sample size, however. These findings seem plausible given that people low in Mindfulness or high in Over-Identification are likely more prone to feeling overly attached to their negative feelings. Specific hypotheses about how these emotional tendencies associated with the Self-Judgment, Common Humanity, Mindfulness, and Over-Identification subcomponents may relate to VMPFC-amygdala functioning should be followed up in future neuroimaging studies investigating the brain basis of self-compassion.

Given the results of the subscales analyses, our results reinforce current thinking that the positive and negative items of the SCS should be considered together as a whole (Neff et al., 2018, 2019). Moreover, it is notable that both positive (e.g., Common Humanity) and negative (e.g., Self-Judgment) subscales significantly correlated with VMPFC-right amygdala functional connectivity during negative vs. neutral feedback conditions, suggesting that it is not the case that the negative and positive subscales can be easily dissociated.

Lastly, given that positive VMPFC-amygdala connectivity was found in less self-compassionate individuals, the results are also potentially relevant to our understanding of this circuit's functioning in mediating negative affect associated with depression and related disorders (Johnstone et al., 2007; Satterthwaite et al., 2016). For example, Johnstone and colleagues (2007) showed that depression related to a similar pattern of VMPFC upregulating amygdala activity (i.e., positive connectivity) in response to negative emotional images; this same pattern of VMPFC-amygdala connectivity was seen in individuals who showed less self-compassion in the present study. Since we know that self-compassion is negatively correlated with depression (Neff, 2003; MacBeth & Gumley, 2012), an interesting direction for future studies would be to determine whether the functional interactions within this common neural circuit underlie both of these psychological factors. More specifically, future studies could test whether low levels of trait self-compassion could influence risk for increasing levels of depression though changes in VMPFC-amygdala connectivity.

The current study's findings should be contextualized by noting potential limitations regarding the research approach and methods. First, it should be noted that given the correlational nature of these results, interpretation of these findings should be treated with caution. In addition, we should note that the current study was likely underpowered due to our relatively small sample size. This lack of power could influence the detection of meaningful relationships between VMPFC-amygdala connectivity and the SCS subscales. It could also have influenced our ability to find a significant relationship between VMPFC-left amygdala connectivity and self-compassion. Importantly, because small sample sizes produce less stable estimates of effect sizes (Schönbrodt & Perugini, 2013), over-interpretation of the results should be cautioned against.

In terms of future directions for investigating the neural mechanisms underlying self-compassion, we suggest multiple potential approaches. First, it will be critically important for future researchers to understand how this neural circuitry may relate to low levels of self-compassion and risk for clinical disorders, such as for depression and anxiety. Given that this circuit's functioning has been shown to be potentially disrupted in these populations (e.g., Johnstone et al., 2007), future research may shed light on this issue. Future research could also examine whether the VMPFC-amygdala circuit is behaviorally relevant when individuals are actively engaging in self-compassion as opposed to simply exploring the correlates of self-reported compassion as was done here. Hence, researchers could implement an experimental task aimed at eliciting a short-term self-compassionate attitude in the MRI scanner. In addition, a comparison of neural responses to threat before and after a self-compassion-based psychological intervention, such as the Mindful Self-Compassion program (Neff & Germer, 2013), may elucidate how self-compassion training alters the neural correlates of self-compassion. Lastly, it will also be important for future research to investigate the overlapping and dissociable regulatory-related neural mechanisms associated with the distinct subcomponents (e.g., self-kindness vs. common humanity vs. mindfulness) of self-compassion.

In summary, the present study found an association between individual differences in self-compassion and VMPFC-amygdala task-evoked functional connectivity during negative social feedback. The results contribute to a growing body of research relating self-compassion to emotion regulation and coping mechanisms. Moreover, they may help explain the important links between lack of self-compassion and poor psychological well-being and interpersonal difficulties.

Mindfulness Training Increases Intrinsic Connectivity Between the Default Mode and Frontoparietal Control Networks: Positive Consequences for Self-Kindness in Breast Cancer Survivors

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Mindfulness training is suggested to be an effective strategy for reducing depression risk in breast cancer survivors. A recent study proposes that the beneficial effects of mindfulness training on health may be mediated, in part, by self-kindness, or a compassionate attitude towards the self in the face of suffering. While mindfulness and self-kindness have been repeatedly shown to be positive predictors of psychological health, the neural mechanisms underlying these factors are not well understood. Here, we use functional MRI to examine neural correlates of self-kindness following a standardized mindfulness meditation intervention for young breast cancer survivors (n = 20). Participants completed resting-state fMRI and questionnaires before and after the 6-week intervention and completed questionnaires at a 3-month follow-up. We found that the mindfulness intervention resulted in increased functional connectivity between two large-scale intrinsic neural networks, the Frontoparietal Control Network (FPCN) and Default Mode Network (DMN). The DMN is consistently implicated in self-processing, and the FPCN is implicated in executive control; thus, results potentially indicate increased top-down executive control of self-referential processes at rest. We also found that positive changes in connectivity between FPCN and the MPFC node of the DMN related to increased self-kindness at the 3-month follow-up compared to baseline. Overall, these results suggest that mindfulness training in younger breast cancers survivors may result in increased inter-network functional interactions and that these network-level changes are associated with positive consequences for thoughts and feelings about the self.

Multiple lines of clinical research have shown mindfulness meditation training to be an effective strategy for decreasing depression, anxiety, and stress, while also increasing protective factors, such as positive affect, meaning, and a sense of life purpose. Specifically, mindfulness interventions training can reduce risk for depression disorder relapse and reduce depression and anxiety symptoms, even in treatment-resistant patients (Creswell, 2017; Piet et al., 2012). On the other hand, mindfulness meditation has been shown to increase positive cognitions and rewarding experiences; bolster an accepting, non-judgmental attitude; and reduce stress levels (Chin et al., 2019; Garland et al., 2015; Geschwind et al., 2011). In addition to these behavioral and self-report findings, mindfulness has been shown to modulate nervous, immune (inflammatory biology; Black & Slavich, 2016; Carlson et al., 2007; Dunn & Dimolareva, 2022), and endocrine system (hypothalamic-pituitary-adrenal (HPA) axis; Creswell, 2017; Creswell & Lindsay, 2014) functioning in multiple clinical populations. Some of our recent research has proposed that some of these connections between mindfulness and mental and physical health benefits may be mediated by a change in attitudes towards the self, specifically increases in self-kindness (being kind to oneself; (Boyle et al., 2017; Neff, 2003). However, the neural mechanisms underlying mindfulness' self-kindness related benefits are not well-understood. Moreover, whether these neural mechanisms relate to changes in immunological functioning and inflammation is not yet known, but highly important for specific disease contexts such as cancer and cancer survivorship (Carlson et al., 2007). Therefore, the aims of the current study were to examine the neural network mechanisms of self-kindness change following a six-week mindfulness intervention for breast cancer survivors and examine possible relationships between self-kindness related neural mechanisms and peripheral inflammation.

Mindfulness training has been consistently linked to a more accepting, supportive attitude toward the self, specifically in the form of self-compassion (being kind, understanding, and mindful to the self; Neff et al., 2003). Research on individual differences has found moderate to strong positive correlations between trait mindfulness and self-compassion (Beshai et al., 2018; Keng & Liew, 2017; Makadi & Koszycki, 2020). In the context of mental health disorders, such as anxiety disorders (specifically social anxiety), trait mindfulness and self-compassion are highly significantly positively correlated (Hsieh et al., 2021; Makadi & Koszycki, 2020). In addition to research on these trait characteristics, clinical trials and behavioral interventions show that mindfulness can have a positive causal effect on self-compassion. In particular, previous research shows that a brief mindfulness training increases levels of self-kindness in cancer survivors and that importantly these beneficial effects can last up to three months later (Boyle et al., 2017). Mindfulness has been shown to not only work across patient population, but also for health care workers and teachers (Beshai et al., 2016; Raab et al., 2015) as well as across both adolescents and adults (Bluth et al., 2015). Taking nearly 30 studies together, meta-analysis reveals a moderate to large effect size for mindfulness interventions' benefits on self-compassion (Wasson et al., 2020).

Self-kindness may emerge from mindfulness meditation training through multiple mechanistic pathways. Multiple lines of evidence provide strong support for the conclusion that mindfulness enhances executive function, and this may have direct implications for cognitive control over self-related thinking. Moreover, mindfulness training enhances the ability to control thoughts and emotions generally and beneficially influences self-views more specifically. Related to this, mindfulness interventions have been repeatedly shown to increase executive functioning and cognitive control skills. Specifically, mindfulness meditation training can lead to enhanced executive functioning, attentional abilities, inhibitory processing, and conflict monitoring (Basso et al., 2019; Gallant, 2016; Im et al., 2021; Millett et al., 2021; Slagter et al., 2011). The neurobiological mechanisms of these connections between mindfulness and executive functioning have been intensively investigated as well (Guendelman et al., 2017; Malinowski, 2013; Posner et al., 2015; Tang et al., 2015). Compared to an active control condition, mindfulness training participants showed improved affective Stroop task performance and modulated activity within the frontoparietal control network (Allen et al., 2012). These neuroplastic changes emerged within executive function related neural regions such as the DLPFC after a brief 6-week mindfulness intervention (Allen et al., 2012).

In addition to executive control, mindfulness leads to more positive self-related thinking and decreases maladaptive forms of self-focus. Overall, intensive mindfulness training has been shown to profoundly increase levels of positive self-evaluation for meditators and improve personal, social, familial, and physical conceptions of self (Emavardhana & Tori, 1997; Hölzel et al., 2011). Mindfulness meditation also leads to decreased self-focus and increased decentering, the process through which individuals generate a greater sense of subjective detachment between themselves and their cognitions (Logie & Frewen, 2015). In the context of clinical treatment, this decreased self-focus translates to reduced habitual rumination and use of ego-defensive cognitive strategies (Emavardhana & Tori, 1997; Goldin et al., 2009). At the neural level, mindfulness experience is associated with alterations in within- and between-network default mode network (DMN) connectivity (Brewer et al., 2011; Garrison et al., 2015; Goldin et al., 2009). Specifically, mindfulness practice is associated with greater functional connectivity between the DMN and frontoparietal control network (FPCN; Brewer et al., 2011). Moreover, a history of meditative experience is associated with reduction in DMN regional activation compared to both resting baseline and active tasks (Garrison et al., 2015). Reduced DMN activation is believed to be related to decreased self-related thinking (Garrison et al., 2015). This is specifically true for the MPFC, a region which has been consistently implicated in self-referential cognition (Lieberman et al., 2019). In sum, neuroplastic changes within DMN and interconnected networks may underlie long-term improvements in self-referential cognition, which may be related to increased self-kindness.

In addition to these behavioral and self-report findings, mindfulness has been shown to modulate immune and endocrine system functioning in multiple clinical populations (Bellosta-Batalla et al., 2018; Black & Slavich, 2016; Chin et al., 2019; Creswell & Lindsay, 2014). Evidence from over twenty randomized clinical trials suggest that mindfulness meditation reduces cortisol levels and signs of inflammation processes, such as NF-kB transcription activity, and proinflammatory markers (IL-6, CRP; Black & Slavich, 2016; Carlson et al., 2007; Dunn & Dimolareva, 2022). Benefits for immune and endocrine system functioning such as these may be especially important in disease contexts, such as cancer and cancer survivorship (Carlson et al., 2007). Some of our recent research has proposed that some of these connections between mindfulness and mental and physical health benefits for cancer survivors may be mediated by a change in attitudes towards the self, specifically increased self-kindness (Boyle et al., 2017).

Even though mindfulness training has been shown to be beneficial for self-kindness and immune system functioning, no studies to date have investigated the neural mechanisms underlying these changes. While there is some evidence that mindfulness-related improvements in regulatory control over self-related thinking and inflammatory profiles arise from similar patterns of increased functional integration between DMN and FPCN (Brewer et al., 2011; Creswell et al., 2016), no research investigations have so far explored this possibility. Therefore, the primary aims of the current investigation were to examine changes in self-kindness due to a mindfulness intervention, examine the network-level neural correlates of this change, and assess whether these neural mechanisms relate to changes in systemic inflammation. Moreover, given the consistent role of the MPFC in self-referential cognition (Lieberman et al., 2019), we aimed to explore whether changes in FPCN-MPFC connectivity would specifically relate to changes in self-kindness, stress, and depression, and proinflammatory markers. In two previous studies, we have shown that six-weeks of mindfulness meditation training can result in decreased stress, depression, and inflammation and increased positive affect, emotion regulation, and self-kindness for younger breast cancer survivors (Bower et al., 2015; Boyle et al., 2019; Dutcher et al., 2021). The current study aims to extend this line of research by characterizing the neurocognitive mechanisms underlying these intervention-specific benefits for cancer survivors. We hypothesized that mindfulness training would result in increased self-kindness, decreased stress, and depression in the long-term, increased resting-state FPCN-DMN/FPCN-MPFC functional connectivity, and that these improvements would relate to decreased levels of proinflammatory markers (IL-6, CRP).

Methods

2.1. Participants, recruitment, and procedure

Participants (*N* = 20) were women previously diagnosed with early-stage breast cancer (Stage 0-III) at or prior to age 50 years, who had undergone primary treatment (i.e., surgery, radiation, and/or chemotherapy) at least 3 months beforehand, and who had no signs of active disease. Exclusion criteria included presence of inflammatory disease, previous mindfulness meditation experience, and conditions concerning MRI scanning safety (e.g., claustrophobia).

Potential participants were recruited based on the UCLA Tumor Registry as well as through physician referral. Following initial recruitment, 197 responses were collected. 49 women failed to meet inclusion criteria, primarily because of prior mindfulness experience ($n = 8$), claustrophobia ($n = 16$), and left-handedness ($n = 13$). 126 women declined to participate, principally due to scheduling or travel-related issues. 20 women were unable to be reached after initial contact. A remaining sample of 22 women was eligible for participation.

Following informed consent procedures, eligible participants underwent two in-person assessments. Assessments occurred during the two weeks immediately before and after a UCLA-based standardized mindfulness training program. At assessment, participants completed questionnaires, blood sample collection, and a 90-minute MRI scanning session. UCLA IRB approved all study procedures. There were no adverse events during the intervention period. Participants were compensated $100 for their participation.

2.2. MAPs intervention

Participants completed the Mindful Awareness Practices (MAPs) training program, created by the UCLA Mindfulness Awareness Research Center. Participants attended 6 weekly, 2-hour group sessions. In addition, they were asked to practice and log formal mindfulness exercises which they completed at home. Participants were instructed to start with 5 min of meditation and eventually increase to 20 min daily. Three cohorts of participants, ranging in size from 6 to 10 people, completed the program between May and November 2015.

The MAPs program is a manualized intervention which has been repeatedly used in prior research (e.g., Black et al., 2015; Bower et al., 2015). Class sessions involved education on theoretical principles of mindfulness, relaxation, and mind-body connections. Specifically, this included experiential practice of meditation along with gentle movement exercises, such as mindful walking. The mindfulness training program focuses on important aspects of psychological well-being, including self-acceptance, interpersonal connections, and personal growth and life purpose. Building self-acceptance was targeted throughout the training period with instructor reminders to treat oneself kindly and return attention to the present moment during meditative exercises without self-judgment. The third and fourth weeks involved loving kindness meditation practice, during which they were instructed to generate positive and warm feelings toward others and themselves. The fifth and sixth weeks focused on dealing with negative emotions through mindfulness, specifically learning to recognize their difficult emotions, accepting them as a common human experience, and creating a sense of space around them in order to "disidentify" from them. Disidentifying is a practice demonstrated to increase positive emotional reappraisals, meaning making, and personal growth (Garland et al., 2015).

2.3. Measures

2.3.1. Participant characteristics

Participants completed self-report measures, including demographic and medical characteristics during the pre-intervention assessment (as previously reported in Boyle et al., 2019), the post-intervention assessment, and three month follow-up assessment. Psychological assessments, including self-kindness, depression, and stress measures, were collected at the initial and final assessments. Self-kindness was measured with the self-kindness sub-scale of the Self-Compassion Scale (Neff, 2003). The self-kindness scale demonstrated good internal consistency (baseline: $\alpha > 0.91$). One participant did not provide response for self-kindness at baseline and, therefore, were excluded from analyses involving the baseline timepoint, leaving a sample of n=19. Depression symptoms were measured with the Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977). CES-D internal consistency was high (baseline: $\alpha > 0.84$). Stress was measured with the Perceived Stress Scale (Cohen, 1988). PSS internal consistency was also high (baseline: $\alpha > 0.91$).

2.3.2. MR image acquisition

MRI data were collected with a Siemens Prisma 3.0 Tesla scanner housed at the UCLA Ahmanson-Lovelace Brain Mapping Center. A T1-weighted MPRAGE anatomical image was first acquired 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). Functional T2-weighted EPI volumes for each task (data reported separately) and a 5-minute resting-state run was then acquired (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). During the resting state fMRI scan, subjects were given the follow instructions: “You will not be doing a task in this part, but we’d like you to just lie still and look at the cross on the screen. Just let your thoughts and mind wander and we’ll check in with you when this scan is done. It will be about 5 minutes long”.

2.3.3. Inflammatory assessments

High sensitivity enzyme-linked immunosorbent assays (ELISA) were used to quantify IL-6 and CRP plasma levels (R&D Systems, Minneapolis, Minn, for IL-6; ImmunDiagnostik, American Laboratory Products Company [ALPCO], Salem, NH, for CRP). Samples were run in duplicate and, for an individual, the sample was run in parallel to decrease interassay variability. Intra- and inter-assay coefficients of variation (CVs) of the IL-6 and CRP assays were calculated to be less than 5%. The lower limits of detection were calculated for both assays: IL-6: 0.2 pg/mL; CRP: 0.2 mg/L. A single IL-6 value was imputed as 50% of the lower limit of detection for that assay.

2.4. Data Processing and Analysis

2.4.1. MRI data processing

Imaging data were analyzed using Statistical Parametric Mapping (SPM) software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England) and the CONN Functional Connectivity toolbox (CONN; Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessing of the MRI data involved the following steps: reorientation, realignment, coregistration, MPRAGE segmentation, artifact detection ("scrubbing"), spatial smoothing with 8mm Guassian kernel full width at half maximum, and normalization. Artifact detection settings were set to "intermediate" thresholds in the CONN toolbox (ART: Global z-signal threshold = 5, Subject-motion mm threshold = 0.9 mm).

2.4.2. Resting state functional connectivity analyses

Preprocessed functional and structural MRI data were first entered into the CONN toolbox. Confounding variables were removed through the CONN CompCor algorithm for physiological noise and band-pass temporal filtering was applied (0.008 - 0.09 Hz). Realignment parameters (rotational and translational head movement) and artifact detection outliers were included as nuisance covariates from preprocessing were also entered in the toolbox as nuisance covariates to be removed from first-level statistical analyses.

For this study, we focused on region-of-interest (ROI-to-ROI) bivariate correlation analyses of the BOLD time-series. ROIs were chosen based on their relevance to mindfulness and self-kindness: 1) Default mode network (DMN) mask from a cortical parcellation based on data-driven clustering of resting-state functional connectivity (Yeo et al., 2011); 2) Frontoparietal control network (FPCN) mask from the same cortical parcellation (Yeo et al., 2011); and 3) MPFC based on manually construction in FSLview in a voxelwise manner, informed by meta-analyses and reviews on MPFC function (Morelli et al., 2018; Rameson et al., 2012). This MPFC ROI was bounded within the following MNI coordinates: $-20 < x < 20$, $46 < y < 76$, $-10 < z < 24$.

2.4.3. Inflammation data processing

IL-6 and CRP data raw values were natural log transformed due to normality concerns. Change scores were calculated by subtracting the natural log corrected values from the baseline log corrected values at post-intervention. IL-6 and CRP means and standard deviations are for untransformed raw values.

2.4.4. Data analysis approach

Initial analyses targeted changes in self-reported self-kindness and resting state neural connectivity from pre- to post-intervention using paired samples t-tests. For correlational analyses, change scores (T2-T1, Follow-up-T1) were calculated for self-kindness, stress, depression, IL-6, and CRP. Primary analyses focused on associations between neural connectivity and the other measures (self-report, inflammation). Both Pearson's and Spearman's rank bivariate correlation analyses were conducted due to concerns about normality of the neural connectivity and inflammation measures. Given the exploratory nature of the current study and specific directional hypotheses, significance was set at $p < .05$ (one-tailed) for all analyses.

Results

3.1. Participant characteristics

The sample (*N* = 20) consisted of early-stage breast cancer survivors who were diagnosed between 2010 and 2014. Mean age of participants was 46.6 years old (*SD* = 4.1, range = 38-52 years; see Table 2.1. for additional demographic, psychosocial, and medical-related characteristics). For key self-report measures at baseline, mean perceived stress was 15.1 (*SD* = 7.8, range = 4-30), mean self-kindness was 3.3 (*SD* = 0.8, range = 1.6-4.6), and mean depression was 14.0 (*SD* = 9.5, range = 1-29). Pre-intervention depression levels were moderately elevated from normal levels in healthy populations but were standard for samples of young breast cancer survivors (Ganz et al., 2012). Notably, 55% of the sample endorsed clinically significant levels of depressive symptoms (scores at or above 16). Peripheral measures of inflammation (IL-6) were at or below standard levels (Kim et al., 2011; Woloshin and Schwartz, 2005) (Kim et al., 2011; Woloshin & Schwartz, 2005). Adherence to the intervention was high (mean session attendance = 5.7) and 17 participants attended all six sessions.

3.2. Self-Report Measure Changes

3.2.1. Self-Report Measure Changes from Pre- to Post-Mindfulness Training

As discussed in previous reports, we found there were significant decreases in depression levels from pre- to post-intervention ($t(19) = 2.55$, $p = 0.020$, $d = 0.57$) (Dutcher et al., 2021; Boyle et al., 2019) (Table 2.1.). There was also a marginally significant decrease in perceived stress (*t*(19) = 1.50, *p* = .075, d = .34). In addition, we found no significant increase in self-kindness from pre- to immediately post-training (*t*(18) = 0.29, *p* = .39, *d* = .07).

3.2.2. Self-Report Measure Changes from Pre-Mindfulness Training to 3-Month Follow-Up

Considering changes after the intervention, we found there was a highly significant decrease in depression levels (*t*(19) = 3.68, *p* < .001, *d* = 0.82) from pre-training to 3-month follow-up assessment and a non-significant decrease in depression levels (*t*(19) = 0.17, *p* = .44, *d* = 0.04) from post-training to 3-month follow-up assessment (Table 2.1.). Although not significant, there was a trend towards decreased stress from pre-intervention to 3-month follow-up (*t*(19) = 1.12, *p* = 0.14, *d* = 0.25) and a non-significant decrease in stress from post-intervention to 3-month follow-up (*t*(19) = 0.51, *p* = 0.31, *d* = 0.11).. Finally, self-kindness significantly increased from pre-training to follow-up (*t*(18) = 2.33, *p* = 0.02, *d* = 0.54) and significantly increased from post-training to follow-up (*t*(19) = 2.26, *p* = 0.02, *d* = 0.51) (Fig. 2.1.) (Table 2.1.).

3.2.3. Correlations Between Self-Report Measure Changes

Considering changes in self-report measures from pre-intervention to post-intervention, we found depression change and stress changes to be significantly correlated (*r*(18) = .642, *p* = .001), depression change and self-kindness change to be significantly correlated (*r*(17) = -.568, *p* = .006), and stress change and self-kindness change to be marginally significantly correlated (*r*(17) = -.374, *p* = .058). Considering changes in self-report measures from pre-intervention to follow-up, we found depression change and stress changes to be significantly correlated (*r*(18) = .636, *p* = .001), depression change and self-kindness change to be significantly correlated (*r*(17)

= -.485, *p* = .006), and stress change and self-kindness change to be non-significantly correlated (*r*(17) = -.300, *p* = .106). Considering changes in self-report measures from post-intervention to follow-up, we found depression change and stress changes to be non-significantly correlated (*r*(18) = .203, *p* = .195), depression change and self-kindness change to be significantly correlated (*r*(17) = -.439, *p* = .026), and stress change and self-kindness change to be non-significantly correlated (*r*(17) = -.193, *p* = .208).

3.3. Neural Connectivity Changes from Pre- to Post-Mindfulness Training

We found significantly increased intrinsic functional connectivity between FPCN and DMN from pre- to post-mindfulness training (*t*(19) = 2.16, *p* = .02, *d* = 0.48) (Fig. 2..1.). In addition, there was marginally significant increased intrinsic functional connectivity between FPCN and MPFC from pre- to post-intervention (*t*(19) = 1.42, *p* = 0.09, *d* = 0.32).

3.4. Inflammation Analyses from Pre- to Post-Mindfulness Training

As reported previously (Bower et al., 2015; Boyle et al., 2019), we found 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. Additionally, we found no significant change in CRP from pre-training (M = 2.485 mg/mL, SD = 3.363) to post-training (*M* = 2.465 mg/mL, *SD* = 3.602), *F*(1, 17) = 0.982, *p* = 0.336. Despite this, we found 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 explore associations between changes in inflammation and changes in neural connectivity during resting state.

3.5. Associations Between Changes in Neural Connectivity and Self-Report Measures

3.5.1. Associations Between Changes in Neural Connectivity and Self-Report Measures Post-Mindfulness Training

Correlational analyses revealed a marginally significant negative association between pre- to post-training changes in FPCN-MPFC connectivity and changes in pre- to post-training in depression ($r(18) = -.309$, $p = .09$; $r_s(18) = -.367$, $p = 0.06$), a significant negative association between pre- to post-training changes in FPCN-MPFC connectivity with pre- to post-training changes in stress ($r(18) = -.382$, $p = .048$; $r_s(18) = -.424$, $p = 0.03$), and a marginally significant positive association between pre- to post-training changes in FPCN-MPFC connectivity with pre- to post-training changes in self-kindness ($r(17) = .329$, $p = .08$; $r_s(17) = .365$, $p = 0.06$). We found no significant relationships between FPCN-DMN connectivity change and the self-report measure changes from pre- to post training.

3.5.2. Associations Between Changes in Neural Connectivity and Self-Report Measures at 3-Month Follow-Up

Upon examination of longer term changes following the intervention period, analyses revealed a marginally significant negative association between pre-training to follow-up changes in FPCN-MPFC connectivity and changes in pre-training to follow-up in depression ($r(18) = -.290$, $p = .11$; $r_s(18) = -.368$, $p = 0.06$) (Fig. 2.2.)., a significant negative association between pre-training to follow-up changes in FPCN-MPFC connectivity with pre-training to follow-up changes in stress ($r(18) = -.436$, $p = .03$; $r_s(18) = -.423$, $p = 0.03$) (Fig. 2.2.)., and a significant positive association between pre-training to follow-up changes in FPCN-MPFC connectivity with pre-training to follow-up changes in self-kindness ($r(17) = .397$, $p = .046$; $r_s(17) = .559$, $p =$

0.006) (Fig. 2.2.). We found no significant relationships between FPCN-DMN connectivity change and the self-report measure changes from pre-training to follow-up. Analyses also revealed no significant or marginally significant correlations between connectivity measure changes (FPCN-MPFC, FPCN-DMN) and self-report measure changes from post-training to 3-month follow-up (all *p*'s > .18).

3.6. Associations Between Changes in Neural Connectivity and Changes in Inflammation

Correlational analyses between fMRI and immune measures revealed significant negative associations between pre- to post-training changes in FPCN-MPFC connectivity and pre- to post-changes in log-transformed IL-6 levels ($r(18) = -.538$, $p = .007$; $r_s(18) = -.414$, $p = 0.04$) (Fig. 2.2.).. There was also a marginally significant negative correlation between FPCN-DMN connectivity changes and changes in IL-6 levels ($r(18) = -.304$, $p = .096$; $r_s(18) = -.405$, $p = 0.04$). Generally, a similar pattern was observed for log-transformed CRP levels: we found a significant negative associations between pre- to post-training changes in FPCN-MPFC connectivity and pre- to post-training changes in log-transformed CRP levels ($r(18) = -.432$, $p = .03$; $r_s(18) = -.251$, $p = 0.14$) and a trend toward a significant association between pre- to post-training changes in FPCN-DMN connectivity and pre- to post-training changes in log-transformed CRP levels ($r(18) = -.196$, $p = .20$; $r_s(18) = -.247$, $p = 0.15$).

3.7. Associations Between Changes in Self-Report Measures and Inflammation

Lastly, we examined associations between changes in self-report measures and inflammation. No significant associations were found between pre- to post-intervention or pre-intervention to follow-up self-report measure changes and inflammation changes (*p'*s >.17).

Discussion

The present study's goal was to test whether inter-network (FPCN-DMN, FPCN-MPFC) neural connectivity changes relate to self-kindness, mental health, and inflammation changes following a brief six-week mindfulness intervention for young breast cancer survivors. Specifically, we investigated whether the mindfulness intervention would result in increased FPCN-DMN and FPCN-MPFC intrinsic (resting-state) connectivity and whether these pre- to post-intervention changes would relate to long-term (pre-intervention to three-month follow-up) changes in self-kindness. The current research build upon prior research by advancing knowledge about the underlying neurocognitive mechanisms underlying mindfulness meditation's beneficial, protective changes for self-related cognition and associated simultaneous improvements in negative mental health and immune related outcomes.

In line with our predictions, we found that the mindfulness meditation program improved self-kindness, specifically when considering the longer-term follow-up assessment. Importantly, it should be noted that self-kindness continued to improve, specifically at a significant level after the intervention. Results also indicated sustained significant decreases in depression levels and marginally significant decreases in perceived stress. At the neural level of analysis, we found significantly increased intrinsic functional connectivity between the FPCN and DMN and marginally significant increases between FPCN and the MPFC node of the DMN. Correlational analyses revealed that pre- to post-intervention changes in FPCN-MPFC connectivity significantly predicted longer term changes (pre-intervention to three-month follow-up) in self-kindness and stress.. Interestingly, while the meditation training program didn’t decrease levels of inflammation overall, we still found that these self-kindness-related neural connectivity changes (FPCN-MPFC, FPCN-DMN) were significantly associated with decreases in proinflammatory cytokine measures (IL-6 post-intervention). Together, these results suggest that FPCN-DMN functional integration from mindfulness training underlies improvements in self-kindness, mental health, and inflammation-related outcomes.

Despite progress on investigating the neurobiological changes associated with mindfulness interventions, relatively little is known about how these changes relate to changes in self-related cognition and social cognition more generally. Given the consistently reported increases in self-kindness following mindfulness training (Boyle et al., 2017; Hölzel et al., 2011) we hypothesized that the neuroplastic changes, particularly those involving functional networks implicated in self-referential cognition, would underlie and predict future changes in self-kindness. Our follow-up assessment findings are well-aligned with previous reports of beneficial psychosocial outcomes immediately following this program's mindfulness training (Boyle et al., 2017; Boyle et al., 2019; Dutcher et al., 2021; Bower et al., 2015). In addition to our own research, multiple other groups have confirmed increased self-compassion or self-kindness as a direct benefit of mindfulness training (Beshai et al., 2016; Birnie et al., 2010; Bluth et al., 2016; Gu et al., 2015; Kuyken et al., 2010; Szekeres & Wertheim, 2015). Our finding that benefits for self-kindness continue to increase after the post-intervention assessment is interesting and future research is needed to clarify the underlying mechanisms for this delay. Moreover, we found increased functional integration of the FPCN and DMN from pre- to post-training. This finding is in line with several other studies examining intervention effects and comparisons between long-term meditators and matched controls (Brewer et al., 2011; Creswell, 2017; Creswell et al., 2016; Hölzel et al., 2011; Tang et al., 2015). The finding that these changes in self-kindness and FPCN-DMN integration are related is novel, yet also reasonable in light of known self-related cognitive functions of the DMN in particular (Andrews-Hanna et al., 2014; Buckner & DiNicola, 2019; Raichle, 2015). These neural findings provide support for speculation that mindfulness may promote FPCN executive control over DMN activity and this enhanced control may result in better regulated self-related thoughts and emotions. Whether or not FPCN-DMN integration always leads to greater levels of self-kindness or if this relationship is specific and unique to effects of mindfulness interventions remains to be elucidated.

Examination of relationships between neural connectivity and negative mental health outcomes (depression, stress) also revealed significant associations. It is well-established that self-kindness (or the broader construct self-compassion, being kind, understanding, and mindful to the self) relates to decreased stress or threat related responding (Ewert et al., 2021; Ferrari et al., 2019; Leary et al., 2007; Wilson et al., 2019). This is likely one of several reasons why self-kindness is strongly negatively related to psychiatric disorders such as depression and anxiety (MacBeth & Gumley, 2012). Moreover, mindfulness training has also been shown to be preventative against these stress-related disorders (Goldberg et al., 2018). The underlying physiological mechanisms connecting self-kindness or mindfulness to their benefits for emotional health and well-being have not yet been fully determined (Chin et al., 2019; Lindsay et al., 2021; Parrish et al., 2018). The current results shed light on another possible mechanistic pathway though which self-kindness and mindfulness may exert their positive psychological effects (Hall et al., 2013). To date, mindfulness researchers focused on physical health have focused on stress-buffering accounts for the salutary effects of mediation and mindfulness practice (Creswell et al., 2019; Creswell & Lindsay, 2014; Lindsay et al., 2021; Taren et al., 2015). Less attention has been focused on the up-stream cognitive systems which may ultimately lead to improved stress buffering and coping. This study highlights that functional integration of FPCN and DMN systems may be an up-stream catalyst for later positive impacts on depression, stress, and stress-related HPA and SNS responses (Creswell & Lindsay, 2014). At the psychological level, our results are suggestive that the functional integration of executive control and self-referential cognitive systems are beneficial for not only self-kindness, but also depression, stress, and similar mental health outcomes.

In addition to significant correlations with mental health, we found that changes in self-kindness related connectivity measures were associated with reductions in inflammatory markers. Specifically, results indicated that FPCN-DMN and FPCN-MPFC connectivity increases were significantly positively associated with IL-6 decreases from pre- to post-intervention. We also found some evidence that FPCN-MPFC connectivity increases correlated with CRP decreases. The finding that the intervention-increased FPCN-DMN functional integration relates to inflammatory changes is consistent with multiple other research studies on mindfulness (Creswell, 2017). First, a solid body of evidence points to mindfulness interventions consistently reducing patterns of proinflammation (Black & Slavich, 2016). Mindfulness interventions reduce circulating markers of IL-6 (Creswell et al., 2016) and CRP (Malarkey et al., 2013), in addition to decreasing proinflammatory gene expression (Boyle et al., 2019; Creswell et al., 2012; Dutcher et al., 2022). Moreover, the associations with changes in FPCN-DMN intrinsic connectivity is reasonable given similar lines of evidence from mindfulness neuroimaging studies. Creswell and colleagues (2016) using an active-controlled study design found that the functional integration of nodes in the FPCN (DLPFC) and DMN (PCC) relate to changes in IL-6 at a four-month follow-up assessment; furthermore, the mindfulness training improvements in inflammatory measures were statistically mediated by increases in FPCN-DMN connectivity strength. Our current findings extend these sets of results by showing that FPCN-DMN connectivity change is relevant not only for immune system functioning (in cancer survivors specifically), but also has important implications for social cognitive changes, such as improvements in self-kindness. Future work is needed to clarify which FPCN-DMN functional connections are most important for both immune-related and social cognitive outcomes.

While the current study extends prior knowledge on the neural mechanisms of self-kindness and mindfulness, there are still multiple limitations worth noting. Critically, this intervention involved a single-arm design and no control group for comparison of intervention effects. Therefore, from this study alone, it is impossible to definitively determine whether changes in intrinsic connectivity are specifically due to mindfulness training or more general intervention, maturation, or testing effects. With this said, the study's findings converge with multiple other studies that report similar changes and differences in FPCN-DMN connectivity attributable to meditation training (Brewer et al., 2011; Creswell, 2017; Creswell et al., 2016). Prior studies from our group (Bower et al., 2015) have conducted RCTs using this mindfulness training program and shown that many of the psychosocial outcome improvements are specific, when considering control group results. In addition, our interpretation of FPCN-DMN coupling as representing a functional integration of executive control and self-referential cognitive systems is somewhat speculative and preliminary in nature. Even though these functional networks are implicated in these psychological processes, it's not entirely clear that their coupling represents a simple integration between them. Other researchers have reported FPCN-DMN connectivity positively correlated with diverse characteristics and functions, such as trait mind-wandering, autobiographical planning, and goal directed cognition for example (Gerlach et al., 2011; Godwin et al., 2017; Spreng et al., 2010; Spreng & Schacter, 2012). While these possible explanations of the functioning of this inter-network connectivity are not necessarily mutually exclusive, we nevertheless continue to assume our characterization of this connectivity change is accurate on the whole. This is because self-kindness change necessarily presupposes more effective regulation of self-directed cognition and emotion. It's highly plausible that FPCN-DMN coupling is a mechanistic underpinning of this improved regulation or control of self-processes. Lastly, our small sample size (n=20) limits some confidence in the generalizability of the study findings. Future researchers in this area should aim to replicate this study results with both larger ($n > 100$) clinical and non-clinical samples.

In conclusion, our study findings advance knowledge about the mechanisms underlying the beneficial effects of mindfulness interventions for cancer survivors, while also revealing the neural network interactions through which self-kindness may be improved over time. Using resting-state fMRI, we found that FPCN-DMN functional coupling in response to a six-week mindfulness meditation intervention significantly related to changes in self-kindness, mental health outcomes (depression, stress), and immune related outcomes (proinflammatory markers such as IL-6). Our study results reinforce lines of evidence suggesting the importance of inter-network functional integration for mindfulness intervention. Moreover, the study helps build and strengthen the nascent area of research on the neurocognitive mechanisms of self-kindness and self-compassion (Berry et al., 2020; Guan et al., 2021; Liu et al., 2022; Lutz et al., 2020; Parrish et al., 2018). Given the neural-inflammation associations, these findings may also have implications for the recently emerging subfield of health neuroscience (Erickson et al., 2014; Inagaki, 2020), which has been focused on understanding the neural substrates of physical health and its deterrents. Future neuroscience research will be needed to provide further mechanistic characterization of the beneficial effects of mindfulness intervention on self-kindness and related social cognitive outcomes.

Mindfulness Training Increases Self-Kindness in Cancer Survivors: A Role for Mesocortical Reward-Related Functioning

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Mindfulness training is a beneficial intervention for cancer survivors because it decreases depression risk while increasing protective factors, such as self-kindness and effective emotion regulation abilities. However, the neural predictors of these protective changes have yet to be clearly established. In particular, little is known about the predictive neural mechanisms underlying increases in self-kindness in both healthy and clinical contexts. We hypothesized that increases in reward-related processing, measured via changes in mesocorticolimbic circuitry activation (ventromedial prefrontal cortex (VMPFC), ventral striatum (VS), and ventral tegmental area (VTA)) while viewing positive social and non-social images, would positively relate to increases in self-kindness following mindfulness training. Here, we used functional MRI to test this hypothesis, focusing on a standardized mindfulness meditation intervention for young breast cancer survivors (n = 19). Participants completed an fMRI reward task and questionnaires before and after the 6-week mindfulness intervention and questionnaires at a 3-month follow-up. From pre-intervention to the 3-month follow-up, participants showed significant increases in self-kindness. Increases in VMPFC activation to positive images from pre- to post-intervention predicted increases in self-kindness at the 3-month follow-up, but not immediately after mindfulness training. Moreover, both VMPFC and VTA activation increases during presentation of non-social positive images also positively related to these sustained benefits. We found no such relationship for VS activation changes and no similar pattern for VMPFC and VTA activation changes during social reward processing. Overall, these results suggest that protective increases in self-kindness following a mindfulness intervention for cancer survivors are supported by increases in mesocortical functioning during specific types of reward processing.

Mindfulness interventions are beneficial for cancer patients and survivors, in part because they enhance protective psychological factors such as self-kindness, being kind to oneself, and effective emotion regulation abilities. Self-kindness is a specific subcomponent of the broader construct of self-compassion, which is more generally defined as being kind, understanding, and mindful to the self (Neff, 2003). However, little is known about the predictive neural mechanisms underlying increases in self-kindness specifically, in both healthy and clinical contexts. Compassion neuroimaging research suggests increased reward processing may act as a catalyst for such long-term beneficial changes. Although self-kindness has yet to be specifically connected to reward processing mechanisms, fMRI studies have shown that compassion behavioral interventions increase functioning within reward-related mesocorticolimbic circuitry. Thus, the goal of the present study was to test the hypothesis that increases in reward-related processing, measured via changes in mesocorticolimbic circuitry activation (ventromedial prefrontal cortex (VMPFC), ventral striatum (VS), and ventral tegmental area (VTA)) while viewing rewarding images, would positively predict increases in self-kindness following mindfulness training for breast cancer survivors.

Mindfulness training is thought to increase emotional well-being through multiple independent psychological and biological pathways (Hölzel et al., 2011). One such pathway is through improvements in self-kindness (Boyle et al., 2017); however, the underlying neurocognitive mechanisms of self-kindness (and generally self-compassion), are just beginning to be understood (Berry et al., 2020; Guan et al., 2021; Liu et al., 2022; Lutz et al., 2020; Parrish et al., 2018). Therefore, the mechanistic mediators connecting mindfulness interventions to improved self-kindness have remained elusive to date. Multiple lines of research have shown that mindfulness and self-kindness are related, in a wide range of populations and study contexts

(Beshai et al., 2016; Birnie et al., 2010; Bluth et al., 2016; Boyle et al., 2017; Gu et al., 2015; Kuyken et al., 2010; Szekeres & Wertheim, 2015). For example, a popular mindfulness therapeutic intervention, mindfulness-based stress reduction (MBSR) significantly increases levels of self-kindness (Birnie et al., 2010). Importantly for the present study, Boyle and colleagues (2017) found that a standardized mindfulness training program increased self-kindness and decreased depression in a sample of young breast cancer survivors. Interestingly, increases in self-kindness mediated the effect of mindfulness intervention on reduced depression levels. Similarly, self-compassion increases have been shown to mediate the positive effect of mindfulness-based cognitive therapy on depressive symptoms in recurrent major depressive disorder patients 15-month post-therapy (Kuyken et al., 2010). In sum, mindfulness training programs may be particularly effective forms of intervention and therapy because they bolster feelings of self-kindness.

Investigations of mindfulness interventions in the context of both affective science and neuroscience have become more numerous in recent years and these may provide clues about the mechanistic predictors of intervention-related benefits, such as increased self-kindness. One line of research has used experienced sampling methods (ESM) to provide evidence for links between mindfulness interventions and increases in reward processing and positive emotion (Garland, 2016; Geschwind et al., 2011). Specifically, a randomized controlled trial (RCT) investigating the effects of mindfulness in adults with a lifetime history of depression used ESM to show increased levels of momentary positive emotion and enhanced reward-related responsiveness (Geschwind et al., 2011). Importantly, relationships between intervention effects and improved positive emotion remained statistically significant even when considering reductions in negative emotion, rumination, and worry. Two other RCTs have provided replications of such findings, extending the research into effects of mindfulness on daily positive emotion in stressed community-based adults (Lindsay et al., 2018). Addiction-focused clinical and affective scientists have also shown that mindfulness-induced increases in VS activation during a positive emotion regulation task related to increases in positive affect and augmented natural reward processing (reward responsiveness to stimuli such as nature and social scenes, but not drug-related reward). Interestingly, a meta-analysis of morphometric MRI studies on meditation practitioners has found mindfulness to be related to structural increases in the VMPFC (Fox et al., 2014). Most relevant to the current study, our group has recently provided evidence of increased reward processing following a mindfulness practices training in young breast cancer survivors (Dutcher et al., 2021). Specifically, Dutcher et al. showed increased activation in the VS during nonsocial reward processing following mindfulness intervention.

The nascent area of compassion neuroscience points to possibility of similar reward-related neural systems as brain-based predictors of self-kindness changes. While more is known about the neural basis of the closely related construct of empathy, the neural circuitry underlying kindness and compassion for others and the self is much less well-studied (Novak et al., 2021; Preckel et al., 2018). On the one hand, empathy is believed to be underpinned by the functioning of neural regions, such as the anterior insula and anterior middle cingulate cortex (Lamm et al., 2011; Singer et al., 2004); on the other hand, compassion is thought to be supported by reward and affiliation related neural mechanisms centered on mesocorticolimbic regions, such as the VMPFC, VS, and VTA (Novak et al., 2021; Singer & Klimecki, 2014). This dissociation was targeted for intervention by Klimecki, Singer, and colleagues (2014) in a large-scale study investigating the effects of empathy and compassion training on functional neural plasticity during an emotion regulation task. The research revealed that compassion training not only specifically increased positive affect (in addition to decreasing negative affect), but it also increased activation in the VS and VMPFC during affective regulation (Klimecki et al., 2014). This set of findings and their conclusions have been recently supported by the first functional neuroimaging meta-analysis on compassion: it was found that VMPFC, basal ganglia, and midbrain regions were consistently involved in compassion related responding (Kim, Cunnington, et al., 2020).

Given the reported links between mindfulness, compassion, and reward-related processes, we aimed to conduct a study aimed at testing whether mindfulness intervention neural activation changes in mesocorticolimbic circuitry could predict long-term prospective self-kindness change in breast cancer survivors. To date, no research has been dedicated to developing neural predictors of long-term self-kindness (or self-compassion) change. Establishing these neural mechanisms as predictive could be informative for future translational and clinical neuroscience investigations aimed at increasing kindness and compassion toward the self. We hypothesized that changes in reward-related responses in VMPFC, VS, and VTA would be sufficient to predict long-term increases in self-kindness following a validated six-week mindfulness intervention (assessed at three-month follow-up). Moreover, given the similar functional roles for these regions in both nonsocial and social reward (Fareri & Delgado, 2014; Izuma et al., 2008; Lin et al., 2012), we aimed to explore whether mesocorticolimbic activation changes in response to either nonsocial or social positive images would be better predictors of self-kindness improvements.

Methods

2.1. Participants

Nineteen women who had been previously diagnosed early-stage breast cancer (Stage 0-III) participated in the study. Diagnosis must have occurred at or prior to age 50 years, and primary treatment (i.e., surgery, radiation, and/or chemotherapy) must have occurred at least 3 months beforehand. All participants had no current cancer symptoms (for full list of study eligibility criteria, see Boyle et al., 2019). After full study description, written informed consent was obtained.

2.2. Procedure

Participants underwent two in-person assessments: during the two weeks before and after a standardized mindfulness training program. The mindfulness program was developed by the UCLA Mindful Awareness Research Center and was hosted on the UCLA campus. During assessments, participants completed questionnaires, blood sample collection, and a 90-minute MRI scanning session. UCLA IRB approved study procedures. No adverse events were reported during the intervention or assessment periods. Participants were given $100 for their compensation.

2.2. Mindfulness intervention

Participants participated in Mindful Awareness Practices (MAPs) training, developed by the UCLA Mindfulness Awareness Research Center. The training course consisted of 6 weekly, 2-hour group sessions in addition to suggested daily meditation practice and formal mindfulness exercises completed at home. The suggested time period for daily practice began with five minutes and increased to 20 minutes by the end of the program. Three cohorts of participants (6-10 individuals) completed the training from May to November 2015.

MAPS training is a manualized intervention (Black et al., 2015; Bower et al., 2015) involving education on mindfulness theory and mind-body interactions in addition to guided mindfulness and relaxation sessions (for more specific details, see Boyle et al., 2019). Topics for the course included subjects such as building emotional well-being, self-acceptance, and interpersonal bonds, as well as finding life purpose. For a weekly topic outline, see Supplemental Information. In brief, the early weeks focused on basic mindfulness practice (e.g., breathing and attention control exercises) and theoretical principles, the subsequent weeks centered on loving-kindness and compassion, and the final weeks focused on using mindfulness to resolve emotional issues.

2.3. Measures

2.3.1. Participant characteristics

Self-report measures, including demographic and medical characteristics, were collected during baseline assessment (previously reported by Boyle et al., 2019), immediately post-intervention, and at three-month follow-up.. Self-kindness was measured via self-kindness sub-scale of the Neff Self-Compassion Scale (Neff, 2003). Self-kindness measures demonstrated good internal reliability (baseline: $\alpha > 0.91$). A single participant did not complete their questionnaire for self-kindness at baseline and, therefore, we excluded the from statistical analyses, giving us a sample of 19 participants. For a full list of self-report measures, see Supplemental Information.

2.3.2. MR image acquisition

Imaging data were collected from a Siemens Prisma 3.0 Tesla scanner within the UCLA Ahmanson-Lovelace Brain Mapping Center. T1-weighted MPRAGE anatomical images were first collected for the purpose of functional images co-registration and spatial 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). Functional T2-weighted echoplanar images for each behavioral task and a 5-minute resting-state run (data reported previously) was then collected (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. Reward Reactivity Task

We administered a reward reactivity passive viewing task involving presentation of blocks of images of three categories (social reward, non-social reward, neutral control). Stimuli were taken from two validated databases, the Geneva Affective Pictures Dataset (GAPED) (Dan-Glauser & Scherer, 2011) and the Nencki Affective Picture System (NAPS) (Marchewka et al., 2014). Social reward blocks involved images of individuals smiling and social interactions, non-social reward blocks involved images of nature and landscapes without humans, and neutral blocks involved images of household objects, office supplies, and furniture. Participants were instructed to view each 25 s block of images (five images, five seconds each) and pay attention to their thoughts and feelings in response. Participants also rated how happy and socially connected they felt after each block of images on a four-point Likert scale (1(not at all) – 4 (a lot)). Each passive viewing and rating period was followed by a 5 s of fixation crosshair period. The blocks for each condition were presented in randomized order.

2.4. Data Processing and Analysis

2.4.1. MRI data processing

MRI data were preprocessed and analyzed with Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). Preprocessing of the MRI data involved the following steps: manual reorientation, spatial realignment, spatial coregistration, artifact detection ("scrubbing"), spatial smoothing with 8mm Guassian kernel full width at half maximum, and DARTEL-based spatial normalization. Motion and outlier censoring was conducted with custom lab-based scripts (global signal z-threshold = 2.5; translational motion threshold = 1.5 mm, rotational motion threshold = 1.5 degrees).

2.4.2. fMRI data analyses

For first-level models, 25 s blocks of images of people were specified as the social reward condition, 25 s blocks of images of nature and landscapes were specified as the nonsocial reward condition, and 25 s blocks of images of common household objects was specified as a control condition. The resulting time series was convolved with the canonical hemodynamic response function. Six realignment motion parameters (representing translational and rotational movement) and a variable for each timepoint representing the artifact detection “scrubbing” output were included as nuisance regressors. A 128 Hz high-pass filter was applied and serial autocorrelation was specified as an AR(1) process.

Next, linear contrasts at each timepoint for each participant comparing BOLD signal for two main statistical contrasts were computed (social reward vs. control, non-social reward vs. control). Afterwards, individual contrast images were used in second-level group analyses to examine relationships with neural activation changes from pre- to post-intervention. Region-of-interest (ROI) analyses were used to examine activation of targeted neural regions (computing the mean across all voxels). Based on prior studies of reward processing, we focused on the VMPFC, left and right VS, and VTA. The VMPFC ROI was created by generating a spherical volume centered on peak coordinates from a previous paper on the neural mechanisms of social emotion regulation (Eisenberger et al., 2011). The VS ROI was based on structurally defined ROIs from the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Specifically, the caudate nucleus and putamen ROIs from the atlas were combined and modified. For the right VS, x was constrained between 0 and 10, y was constrained between 4 and 18, and z was constrained between 0 and –12. For the left VS, x was constrained between 0 and -10, y was constrained between 4 and 18, and z was constrained between 0 and –12. The VTA ROI was created by generating a spherical volume centered on coordinates informed by previous papers on the topic of reward processing (Krebs et al., 2009; Moll et al., 2006; Telzer et al., 2010; Zald et al., 2008). ROI parameter estimates were extracted for each participant using Marsbar and data were inputted into SPSS (Version 28) for correlational analyses.

2.4.3. Data analysis approach

Analyses targeted predicted changes in self-reported self-kindness (pre-intervention to follow-up) from neural activation from pre- to post-intervention. Change scores (post-intervention - pre-intervention, follow-up - pre-intervention) were computed for self-kindness for each participant. Primary analyses focused on Pearson's correlations between neural activation changes pre- to post-intervention and self-kindness changes. Given the exploratory nature of the current study and specific directional hypotheses, significance was set at $p < .05$ (one-tailed) for all analyses.

Results

3.1. Participant characteristics

The sample consisted of early-stage breast cancer survivors who were diagnosed between 2010 and 2014. Mean age of participants was 46.4 years old (*SD* = 4.4, range = 38-52 years; see Boyle et al., 2019 for additional demographic, psychosocial, and medical-related characteristics). For key self-report measures at baseline, mean self-kindness was 3.3 (*SD* = 0.8, range = 1.6-4.6) and mean depression was 13.4 (*SD* = 9.4, range = 1-29). Pre-intervention depression levels were moderately elevated from normal levels in healthy populations but were standard for samples of young breast cancer survivors (Howard-Anderson et al., 2012). Notably, 55% of the sample endorsed clinically significant levels of depressive symptoms (scores at or above 16). Adherence to the intervention was high (mean session attendance = 5.7) and 17 participants attended all six sessions.

3.2. Self-Report Measure Changes

As previously reported, for depression, we found significant decreases from pre- to post-training, significant decreases pre-training to 3-month follow-up, and a nonsignificant decrease from post-training to 3-month follow-up (Table 2.1.). For self-kindness, we found a nonsignificant increase from pre- to post-training, a significant increase from pre-training to 3-month follow-up, and a significant increase from post-training to 3-month follow-up (Table 2.1.).

3.3. Predicting Long-Term Self-Kindness Changes from Reward Processing Neural Activation

For the non-social reward processing condition (vs. control), VMPFC activation changes from pre- to post-intervention significantly predicted self-kindness changes from pre-intervention to 3-month follow-up (*r*(17) = .481, *p* = .037) (Fig. 3.1.). Similarly, VTA activation changes from pre- to post-intervention significantly predicted self-kindness changes from pre-intervention to 3-month follow-up (*r*(17) = .390, *p* =.0495) (Fig. 3.1.). Neither LVS nor RVS activation changes predicted long-term self-kindness changes (*p*'s > .1) (Fig. 3.1.).. For the social reward processing condition (vs. control), none of the VMPFC, VTA, LVS, and RVS activation changes from pre- to post-intervention significantly predicted self-kindness changes from pre-intervention to 3-month follow-up (*p*'s > .1).

3.4. Associations Between Concurrent Changes in Self-Kindness and Reward Processing Neural Activation

While the goal of primary analyses was to predict long-term prospective self-kindness changes from reward-related neural activation changes, we also sought to explore whether these regions with significant predictive relationships would show similar patterns for concurrent change in self-kindness (pre- to post-intervention). Here, we found that changes in VMPFC activation during non-social reward processing (vs. control) did not significantly correlate with simultaneous self-kindness change (*r*(17) = .082, *p* =.370). However, we found that changes in VTA activation during non-social reward processing (vs. control) marginally significantly correlated with simultaneous self-kindness change (*r*(17) = .378, *p* =.055).

Discussion

Over the past decade, there has been a growing interest in investigations seeking to understand the neurocognitive mechanisms underlying kindness and compassion towards others and the self. Despite this, one sizable gap in the literature remains: very little to no work has been dedicated toward developing neural predictors of longitudinal change in kindness, specifically self-kindness. Here, we report results from an intervention fMRI study with cancer survivors which: a) help establish a general mechanistic role of reward processing in self-kindness, and b) show that reward-related neural predictors can be leveraged to predict long-term change in self-kindness in response to a mindfulness training program. In particular, we have found that increases in activation within VMPFC and VTA during non-social (but not social) reward processing predict subsequent increases in self-kindness. This set of findings corroborate and extend results from compassion neuroscience which suggests that reward-related circuitry functioning may undergird dynamic changes in kindness toward the self and others (Kim, Cunnington, et al., 2020; Klimecki et al., 2014; Singer & Klimecki, 2014).

The finding that mindfulness-induced increases in mesocortical activation associate with prospective increases in self-kindness could be interpreted from multiple different, but complementary angles. First, generally speaking, these results are in line with longitudinal compassion intervention fMRI studies (Kim, Parker, et al., 2020; Klimecki et al., 2014) and a recently published meta-analysis of cross-sectional neuroimaging studies focused on reliable compassion-elicited neural activations (Kim, Cunnington, et al., 2020). For example, a large-scale study focused on contrasting the neuroplastic changes resulting from compassion and empathy intervention indeed found that regions such as the VMPFC and VS increased in activation during a kindness-focused emotion regulation task uniquely in response to compassion, but not empathy training (Klimecki et al., 2014). Another study investigating the effects of compassion training on neural activation during an altruistic decision-making task however did not find increases in VS activation (Weng et al., 2013). Meta-analytic evidence however has previously provided support for the involvement of all three regions (VMPFC, VS, midbrain) in compassionate functioning (albeit, through use of a diverse array of behavioral tasks). For the current study, the result that increases in VS activation during reward processing did not predict self-kindness increases should be investigated more thoroughly in the future. To date, no studies have been reported linking self-kindness to VS functioning specifically. With that said, it's especially interesting that VS activation changes did not relate to significant predictions, given that we have previously shown the VS activation during non-social (but not social) reward processing increases in response to this mindfulness program (Dutcher et al., 2021). Although functional neuroimaging studies investigating compassion would broadly suggest that all three regions targeted (VMPFC, VTA, and VS) would significantly relate to kindness-related increases, it's possible that self-kindness, compared to other-kindness, is somewhat unique in its neural associations. Importantly, to the best of our knowledge, no studies have yet related self-kindness or self-compassion to VS functioning. Functional connectivity analyses from the aforementioned compassion intervention fMRI study (Weng et al., 2013) revealed that PFC-VS connectivity during altruistic cognition did however increase; therefore, examining VMPFC-VS circuitry changes in relation to self-kindness change could be a promising future direction which help disambiguate the mechanistic role of this striatal region in self-kindness.

From the perspective of mindfulness neuroscience, significant predictions based on increases in VMPFC and VTA activation during reward processing are both reasonable and suggestive of multiple potential theoretical implications for self-kindness change. Mindfulness interventions have been postulated to alter value signals from rewards and modulate value-related learning and decision making (Froeliger et al., 2017; Garland, 2016; Kirk et al., 2014). While not definitive, the predictions based on VMPFC activation changes in particular are suggestive that alterations in value signals in the VMPFC act as a catalyst for increases in self-kindness. Expanding upon this, it's possible that mindfulness training enables a reorientation of valuation signaling away from being driven primarily by conceptual (and perhaps social) knowledge and promotes an enhanced role of interoception; moreover, this reorientation of valuation signaling may spur an increase in compassionate attitudes toward the self in the long-term. This line of thinking coheres well with the interpretation of findings of mindfulness studies in the context of addiction neuroscience. Garland et al. (2016) have shown that mindfulness-oriented recovery enchantment (MORE) treatment for substance use disorder (SUD) patients can be beneficial for emotional well-being because it helps to recalibrate the relative salience of natural rewards compared to drug rewards. This form of mindfulness treatment is thought to restructure bottom-up reward learning and the schema of stimuli-value associations through sustained training in selective attention to natural rewards. Given our observed pattern of condition-specific results and the types of rewarding stimuli involved in the nonsocial task condition (i.e., nature scenes and landscapes), it's possible that our reward reactivity task could be indexing the potential to restructure bottom-up reward-related learning. While indeed speculative, intervention-induced increases in mesocortical circuitry functioning during non-social reward processing may prime improvements in proregulatory functioning and ultimately shape a remapping of stimuli-value associations to be more conducive for self-kindness and effective emotion regulation.

One interesting aspect of our findings was that we did not find significant relationships between VMPFC/VTA activation changes and concurrent changes in self-kindness (as assessed immediately post-intervention). This finding should be interpreted in light of the fact that there was also a non-significant increase in self-kindness from pre- to post-intervention. Given that there was not a significant change in self-kindness during this period, there was likely not enough meaningful variability in the target measure of the neural prediction. Whatever mechanism causing the general increase in self-kindness in the group as a whole is also likely involved in driving individual differences in these change measures. We speculate that the mindfulness intervention provides cognitive resources and strategies for self-kindness, but that these tools must be learned and practiced over an extended period of time for significant beneficial effects. This group of cancer survivors was likely highly motivated and therefore likely persistently applied the mindfulness strategies in their daily life following the intervention. This cumulative effect over an extended period (approximately twice as long as the intervention period itself) was likely also driven by valuation and motivation related circuitry. Future neuroimaging research is needed to examine participants at multiple time points post mindfulness intervention to assess the point at which these benefit for self-kindness become significant (e.g., 1-month, 2-month, 3-month follow-ups). This could also be informative for understanding the role of reward-related functioning neural circuitry and the manner in which it is predictive of self-kindness change.

There are multiple critical limitations worth noting for the current study. First, importantly, this intervention utilized a single-arm design, which is a considerable drawback. Therefore, it is difficult to determine whether increases in VMPFC-VTA reward-related functioning are unique for the mindfulness training or are a result of other confounds, such as maturation or testing effects. With this said, previous studies from our group (Bower et al., 2015; Boyle et al., 2017) have conducted past clinical trial research using the MAPS program and have found many of the key psychosocial outcome improvements to be specific, in comparison to a control condition. Second, our behavioral task may have been inherently limiting, specifically as it relates to our result interpretations focused on reward processing. The reward reactivity task we used was a passive viewing task, which may not have effectively engaged targeted action-oriented reward motivational processes. Future work should utilize fMRI tasks, such as the monetary incentive delay (Knutson et al., 2000) and social incentive delay (Rademacher et al., 2010) tasks to target changes in such reward processes and their specific relationships with self-kindness change. Lastly, the current research used a relatively small sample size. While this was a small-scale initial study of a special population, young breast cancer survivors with no signs of recurrence, future research should aim to replicate these findings in both larger clinical and healthy populations ($N > 100$; Cremers et al., 2017; Turner et al., 2018).

The current research extends a line of research dedicated to understanding the neural mechanisms and predictors of self-kindness. Specifically, we provide evidence here that reward-related neurocognitive mechanisms may serve as effective predictors for increases in self-kindness in response to a validated mindfulness intervention for cancer survivors. To our knowledge, this is the first task-fMRI based predictor of long-term self-kindness change. This set of findings provides a proof-of-concept and lays a foundation for future intervention studies in social, clinical, and health neuroscience related to self-compassion.

General Discussion

The goal of this dissertation research was to investigate self-compassion and its underlying mechanisms using the methods and approaches of social and affective neuroscience. The primary focus was on establishing answers to the following questions: 1) does negative emotion regulation related circuitry function associate with individual differences in trait self-compassion, 2) does the functional integration of the FPCN and DMN relate to increased self-kindness in response to mindfulness training, and 3) can reward-related neural functioning be used to predict improvements in self-kindness following mindfulness intervention? In the preceding sections, the following results and interpretations were highlighted. First, results indicated that there was a negative relationship between VMPFC-amygdala functional connectivity during negative social evaluative feedback processing and overall trait self-compassion, as predicted (although, interestingly, results may have been at least partially driven by greater connectivity relating to less self-compassion). This was taken as evidence for the conclusion that individuals with high levels of self-compassion may be better able to regulate their negative emotions in social evaluative contexts; alternatively, self-compassionate individuals may be somewhat protected from overly negative emotional reactions in these situations. Second, results indicated that FPCN-DMN intrinsic connectivity was increased in response to mindfulness training, and that FPCN-MPFC connectivity related to increases in self-kindness in the long-term. This same circuit's connectivity related to stress, depression, and peripheral inflammatory markers. This was taken as evidence for the conclusion that increased self-kindness may arise from the functional integration of cognitive control and self-referential processing systems, and that this integration may be important for multiple other health-relevant intervention outcomes. Third, results indicated that changes in VMFPC and VTA activation during specific non-social reward processing conditions could be used to predict changes in self-kindness that were measured three months after the mindfulness intervention. This was taken as evidence that reward processing changes may act as a catalyst for long-term improvements in self-kindness. Overall, these findings help establish relationships between the functioning of multiple neurocognitive systems and self-compassion.

While the research shows the promise of self-compassion neuroscience research, multiple limitations for these set of studies should be explicitly stated. In general, the research studies were statistically underpowered, given our sample sizes (N= 19; N =20). As a result, the reliability, specificity, and positive predictive value of the findings could be reasonably called into question by critics (Button et al., 2013; Durnez et al., 2014). Studies targeting the neural mechanisms of self-compassion with larger sample sizes are currently underway in this laboratory, which should help mitigate this concern. Next, the studies used specific populations of participants, the results from which may not be able to be appropriately generalizable to other groups of individuals (healthy middle aged and older adults, adolescents, other clinical populations). This is especially true for findings from the second and third papers which focused only on middle aged women with a history of cancer. With that said, the focus on this clinical population may help establish an important precedent for examining self-compassion related neural mechanisms (and interventions targeting them) in physical illness patients and survivors. Lastly, and possibly most importantly, none of the task contexts from the studies were explicitly aimed at eliciting psychological states of self-compassion in the scanner environment. This is a critical caveat that needs to be addressed for the improvement of self-compassion science.

With these caveats duly noted, these findings still have meaningful implications for our understanding of self-compassion, at a mechanistic level, and as a psychological construct in general. The current research begins to situate self-compassion as a trait and cognitive capacity in the context of a brain which is actively making sense of its social world. No studies besides the ones reported in this dissertation have focused on the neural mechanisms of self-compassion as it relates to social functioning. Therefore, the positive results of this research highlight the importance of examining self-compassion from a social neuroscience perspective. In addition, the current research, particularly the results from the third paper, underscore the significance of attempting to understand the shared and distinct neural mechanisms underlying compassion for the self and others. Given the results showing that reward-related functioning relates to self-kindness, it would suggest that the reward-related aspects of compassion are actively involved regardless of the target of the compassion (Kim, Cunnington, et al., 2020). What degree these reward-related mechanisms are similar or distinct for self- or other-focused compassion remains an open question, however. Furthermore, considering results showing that self-compassion mediates the effects of psychological interventions on improved emotional well-being (e.g., Boyle et al., 2017), these findings are suggestive that some of the self-compassion related benefits of intervention may be influenced or undergirded by these health-relevant targets of neurocognitive functioning (e.g., activity or connectivity within neural circuitry and networks related to emotion regulation and reward processing). Lastly, the studies in this dissertation generally help continue a trend of newfound interest in self-compassion by neuroscientists and a growing effort to understanding compassion for self and others at a biological level of analysis (Berry et al., 2020; Guan et al., 2021; Liu et al., 2022; Lutz et al., 2020; Parrish et al., 2018). As stated previously, this is important to consider given the fact that so little is known about the cognitive mechanisms of self-compassion and that many well-informed skeptics have serious doubts about the basis of this construct and its usefulness for health interventions (Muris &

Petrocchi, 2017; Neff & Germer, 2017). This research, along with that of others, helps substantiate self-compassion as a worthwhile neuroscientific topic. Taken together, these studies suggests that this type of research is valuable because of its potential for broader implications. Overall, this research makes a meaningful contribution to this larger research area, which is now quickly expanding thanks to the hard work and curiosity of fellow scientists.

Continuations and extensions of this research should likely proceed in multiple potential future directions. First, future studies should be aimed at understanding the developmental mechanisms underpinning the growth of self-compassion. Such studies could be especially important for developmental populations, such as adolescents, given that this period of their life span is characterized by intense self-focus and self-criticism. Second, future researchers should focus on examining the computational underpinnings of self-compassion. For example, related open and interesting questions include “what type of learning and belief updating mechanisms support self-compassionate responding in the face of social evaluation”, and “how are parameters for decision-making tuned similarly for compassionate acts directed toward the self and others?” Lastly, it will be critically important to investigate self-compassion and its related neurocognitive and computational mechanisms in a wider variety of health intervention contexts for different clinical populations. If this research is effectively pursued, all these future lines of investigation could contribute to an enhanced understanding about the inner workings of self-compassion. More importantly however, this science will hopefully move researchers and clinicians from simply seeking to understand self-compassion's neural underpinnings to cultivating the growth of such mechanisms for the well-being and prosperity of many generations to come.

“If your compassion does not include yourself, it is incomplete.”

-Jack Kornfield

Figures

Paper 1 Figures

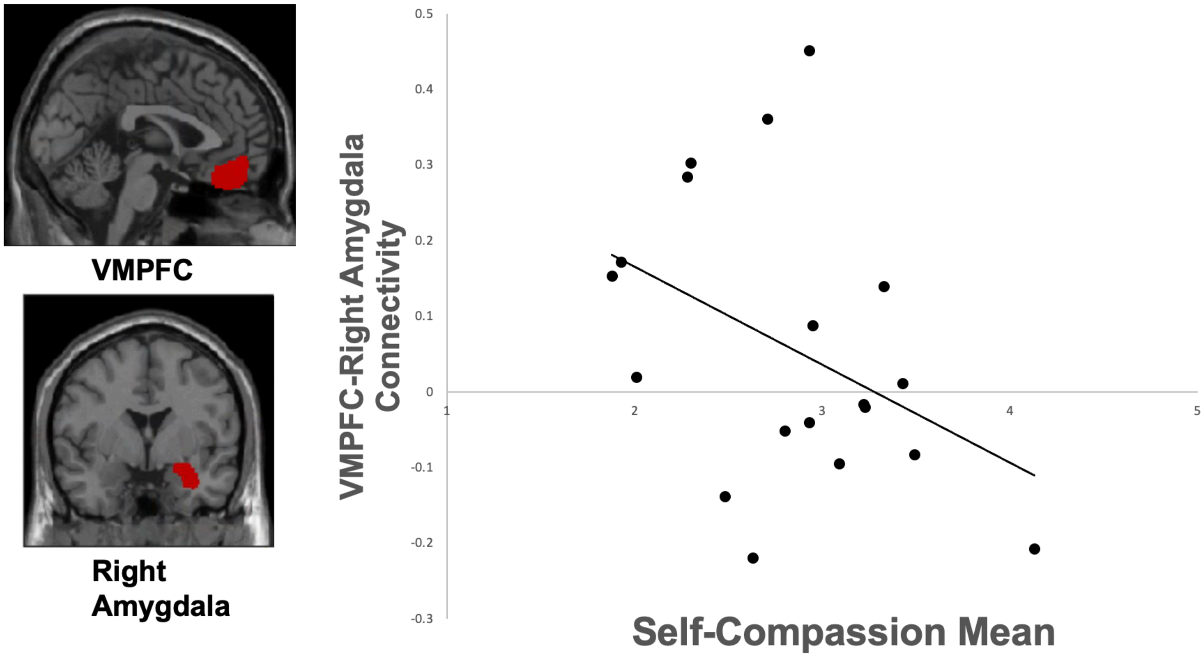

Figure 1.1. Scatterplot depicting the significant negative relationship between mean self-compassion generated from the average of the subscales and VMPFC-right amygdala functional connectivity during negative vs. neutral social feedback.

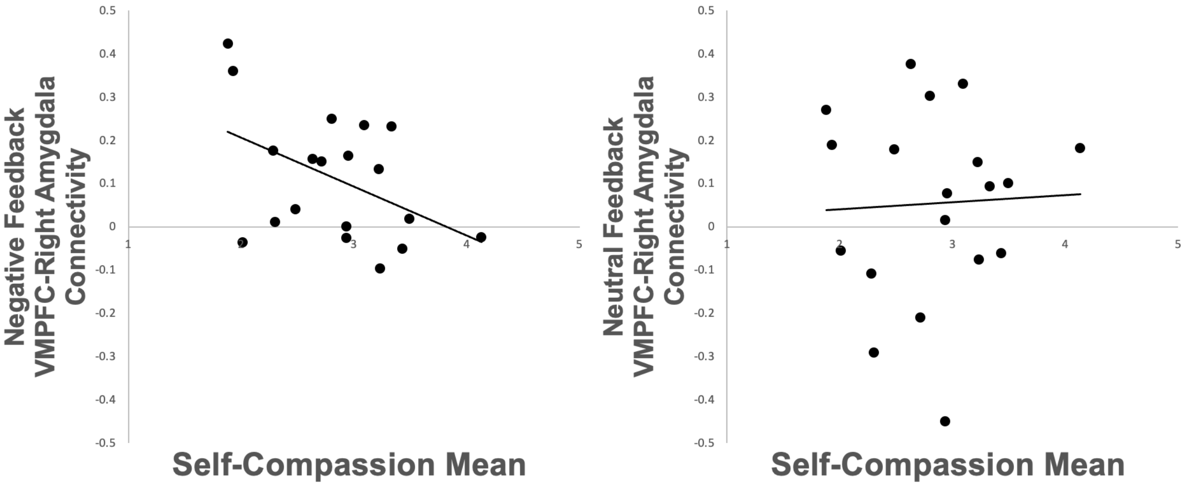

Figure 1.2. Scatterplot depicting the relationships between mean self-compassion and VMPFC-right amygdala functional connectivity separately during negative and neutral social feedback.

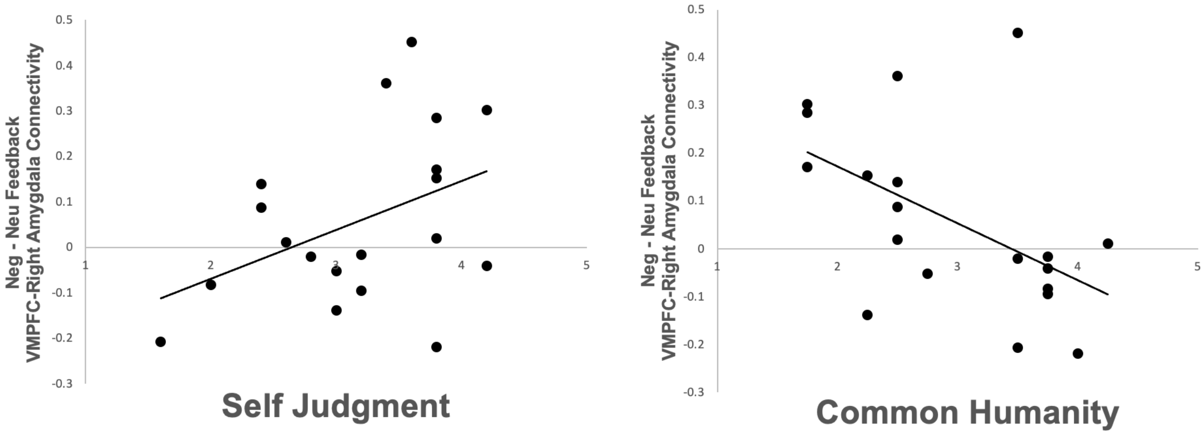

Figure 1.3. Scatterplots depicting the relationships between Common Humanity and Self-judgment subscales of the Self-Compassion Scale and VMPFC-right amygdala functional connectivity during negative vs. neutral social feedback.

Paper 2 Figures

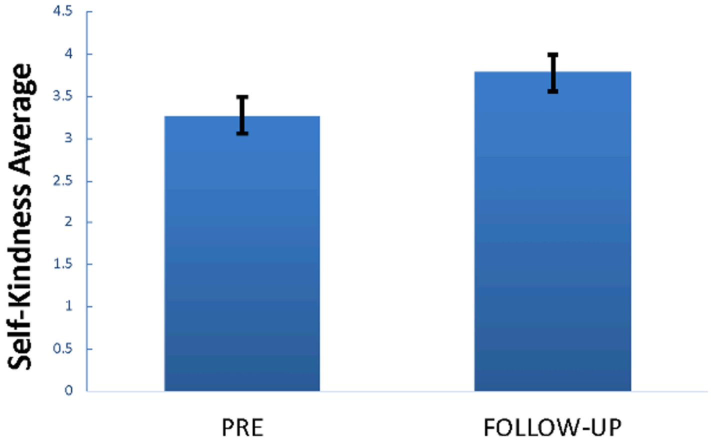

Figure 2.1. Bar graph depicting the significant difference between pre-intervention and follow-up levels of self-kindness.

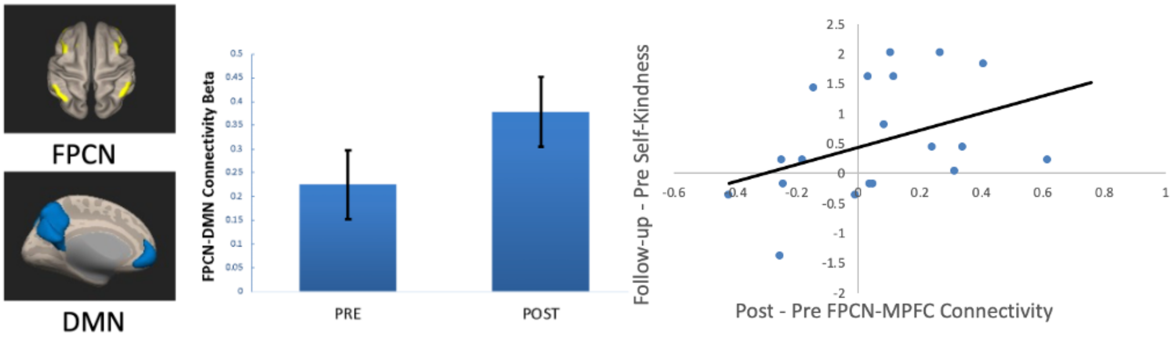

Figure 2.2. (Left) FPCN and DMN ROIs used in functional connectivity analyses. (Middle) Bar graph depicting the significant difference between pre-and post-intervention FPCN-DMN connectivity. (Right) Scatterplot depicting the significant positive relationship between increases in FPCN-MPFC connectivity and self-kindness increases.

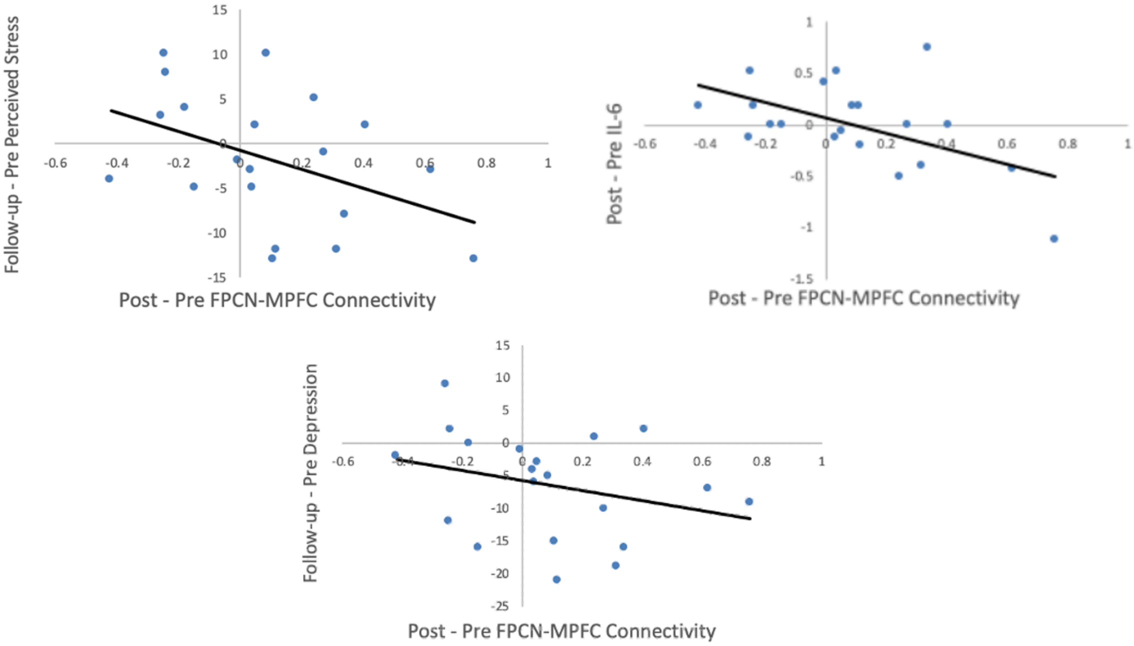

Figure 2.3. (Upper left) Scatterplot depicting the significant negative relationship between increases in FPCN-MPFC connectivity and stress decreases. (Upper right) Scatterplot depicting the marginally significant negative relationship between increases in FPCN-MPFC connectivity and depression decreases. (Lower) Scatterplot depicting the significant negative relationship between increases in FPCN-MPFC connectivity and inflammation decreases.

Paper 3 Figures

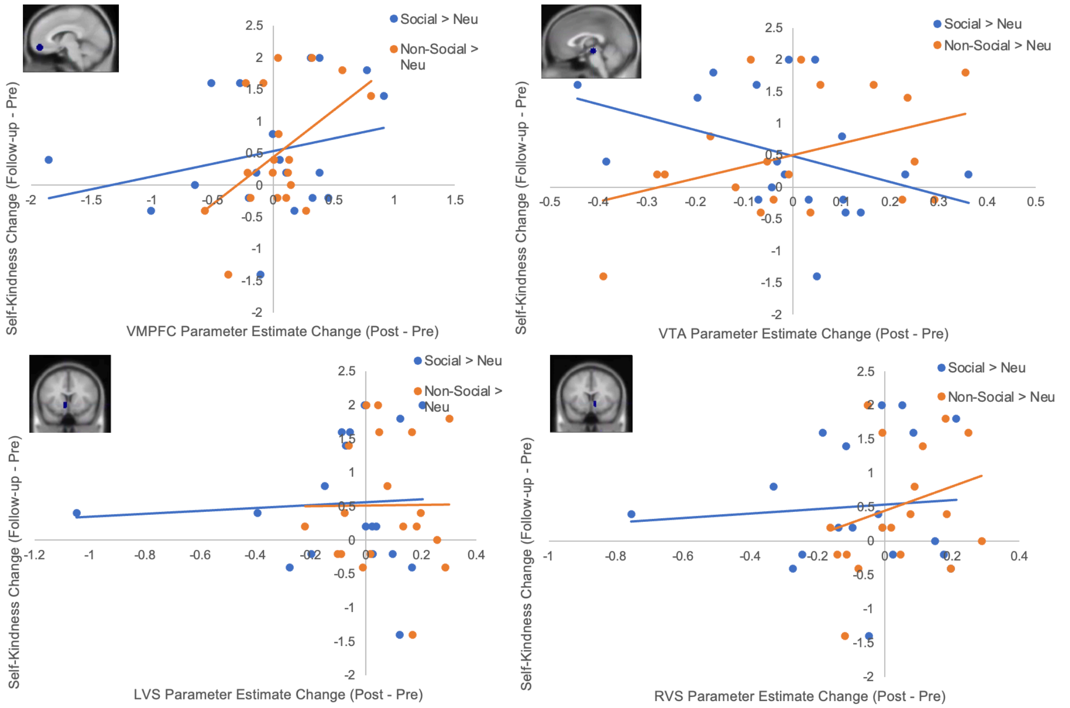

Figure 3.1. (Upper left) Scatterplot depicting the significant positive relationship between increases in VMPFC activation during non-social reward processing and self-kindness. (Upper right) Scatterplot depicting the significant positive relationship between increases in VTA activation during non-social reward processing and self-kindness. (Lower left) Scatterplot depicting the nonsignificant relationship between changes in LVS activation during reward processing and self-kindness. (Lower right) Scatterplot depicting the nonsignificant relationship between changes in RVS activation during reward processing and self-kindness.

Tables

SCS Score	Zero-Order Correlation	*p*-value
Self-Compassion Mean	-.402*	.044
Self-Kindness	-.182	.227
Self-Judgment	.417*	.038
Common Humanity	-.518*	.012
Isolation	.070	.387
Mindfulness	-.321†	.090
Over-Identification	.317†	.093

Note. Items from the negative subscales (Self-Judgment, Isolation, Over-identification) were reverse coded before the Self-Compassion Mean values were computed.
* $p<.05$
† $p<.1$

Table 1.1. Zero-order correlations between SCS total and subscale scores and Neg-Neu VMPFC-right amygdala connectivity.

	Pre-Intervention	Post-Intervention	3-Month Follow-Up
Depression	14.00 (9.52)	7.60 (8.11) *	7.40 (7.02) *
Stress	15.10 (7.78)	12.70 (6.34)	13.25 (5.73)
Self-Kindness	3.27 (0.79)	3.43 (0.95)	3.80 (0.85) *†

* *p*<.05 Paired samples *t*-test: significantly different from pre-intervention

† *p* <.05 Paired samples *t*-test: significantly different from pre-intervention (follow-up)

Table 2.1. Means (Standard deviations) for the three targeted self-report measures: depression, stress, and self-kindness. Paired samples *t*-test results for the differences between each timepoint.

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