



## A review and novel theoretical model of how negative emotions influence inflammation: The critical role of emotion regulation



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### ABSTRACT

Psychological distress is an inevitable part of life. Research drawing on theories from clinical psychology, health psychology, and psychoneuroimmunology (PNI) has identified relationships between negative emotions such as anxiety and sadness with inflammation. When not regulated properly, negative emotions can create biological wear and tear on the body that can increase risk for morbidity and mortality. This review discusses previously available research on relationships between negative emotions and emotion regulation with inflammation among both physically healthy adults and those with chronic illnesses. I then present a novel comprehensive biobehavioral model of negative emotionality. This model emphasizes the influence of negative emotions and their contribution to heightened inflammation. Further, I also discuss how emotion regulation (including perseverative processes such as worry and rumination) mediates this association. The relationships between negative emotionality and emotion regulation may be bidirectional, and empirical investigation of this model should specifically seek to disentangle these relationships. The proposed model offers the opportunity to advance PNI research through understanding how emotional factors alter inflammation and contribute to accelerated biological aging and disease risk.

### 1. Introduction

Psychological distress is an inevitable part of modern life. Although many people are resilient in the face of stressors, a notable subgroup experienced prolonged negative emotions that reduce physical health and quality of life. These emotional experiences heighten physiological dysregulation and enhance disease risk. Further, this relationship is bidirectional, creating a vicious cycle between psychological distress and immune system dysfunction. Researchers from several fields including clinical and health psychology, psychiatry, and psychoneuroimmunology (PNI) have uncovered pathways through which psychological distress influences physical health via inflammation. However, the specific emotional processes that implicate biological functioning remain unclear. To address this question, this review discusses prior research on the relationship between negative emotionality (including negative emotions such as anxiety and sadness) and emotion regulation (such as worry, rumination, reappraisal, suppression) with altered immune functioning. Then, I present a novel biobehavioral model of negative emotionality. Specifically, this model highlights how negative emotions such as sadness or anxiety enhance immune system dysregulation and contribute to long-term health problems. Further, this model emphasizes

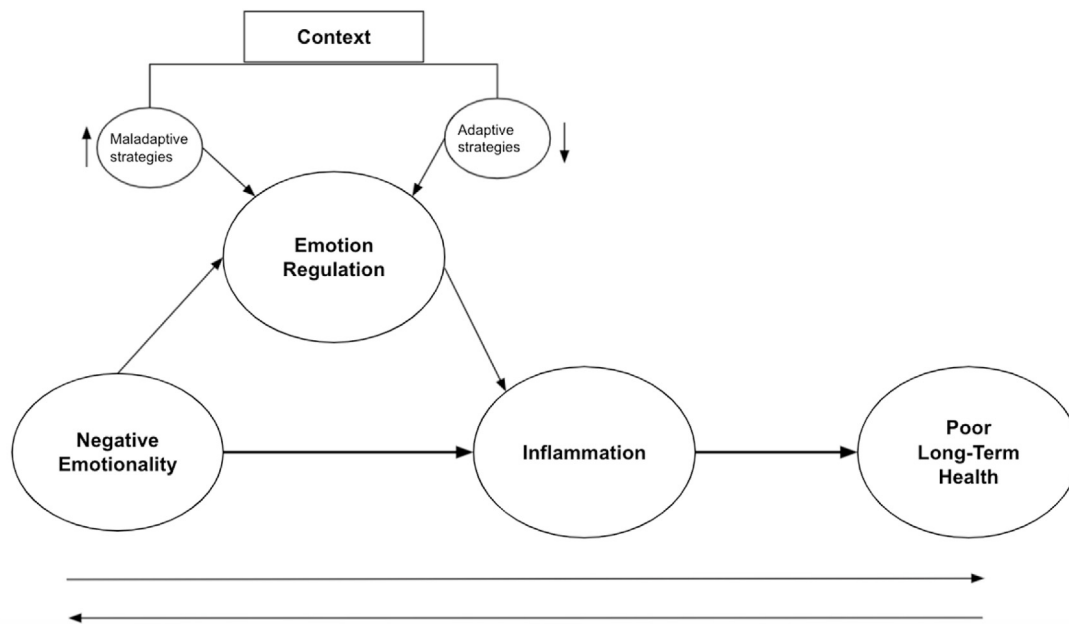
how emotion regulation skills can mediate negative emotionality's health impact, providing a viable intervention point and highlighting key areas for future research in PNI to target. Lastly, I discuss future directions and methods for testing the proposed model (see Fig. 1).

### 2. Negative emotionality and inflammation

The fight or flight system has aided living beings for decades in response to danger. Adaptively, humans activate this system to help them flee from danger within the environment and return to a state of homeostasis following the dissipation of the threat. Unfortunately, this physiological process activates at times of real *or* perceived threat, and therefore, people experiencing high rates of negative emotions may have an over-activation of the fight or flight system. In other words, the fight or flight system in individuals experiencing prolonged and/or pervasive negative emotions may not shut off in the same way that it would for someone else without this heightened emotional intensity (Curtis and O'Keefe, 2002). This over-activation puts them at an increased likelihood for physiological dysregulation over time, as the activation of this system creates a physiological cascade that is difficult to reverse once it has begun. Both the experience and regulation of negative emotions relate to

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**Fig. 1.** The biobehavioral model of negative emotionality. This highlights how negative emotions promote immune system activation/dysfunction and ultimately increases risks for morbidity and mortality. This model also highlights the role that emotion regulation plays in mediating the relationship between negative emotionality and immune system activation. Within this framework, the process of regulating one's negative emotions serves an essential function in understanding negative emotionality's health impact. Within this model, emotion regulation serves as a moderator in the link between negative emotionality and inflammation. This model also accounts for contextual differences in whether an emotion regulation strategy is adaptive or maladaptive, and that contextually adaptive strategies suppress the adverse impact of negative emotionality (represented by the upwards facing arrow) while maladaptive strategies heighten inflammation (represented by the downward facing arrow). This increased inflammation resulting from negative emotionality and accompanying maladaptive emotion regulation heightens risk for poor long-term health outcomes. However, the arrows at the bottom of the model highlight the bidirectionality of the proposed relationships, indicating how poor long-term health and increased inflammation can promote negative emotionality.

inflammation. Overall, findings highlight a notable link between negative emotions and inflammation in both healthy individuals and those with chronic illnesses (Renna et al., 2018, 2020a; Duivis et al., 2011). Briefly, negative emotions such as anxiety and sadness promote a cascade of psychological and physiological processes which pose risks for long-term health (Michopoulos et al., 2017). To date, the relationship between increased inflammation and chronic health conditions is well established (Karajgi et al., 1990; Walker et al., 2008; Todaro et al., 2007). Throughout this review, I refer to negative emotions that are experienced frequently and/or intensely and psychological distress collectively as *negative emotionality*.

Several lines of research emphasize the relationship between negative emotionality and inflammation across both adults with psychopathology and those with chronic illnesses (Renna et al., 2018, 2020a; Kiecolt-Glaser et al., 2015; Osimo et al., 2019). Among the most widely studied populations relating negative emotionality to immune function in my work is breast cancer survivors (Renna et al., 2020a, 2021a). My work and that of others have highlighted an important potential psychological pathway to increased morbidity and mortality among these women (Renna et al., 2020a, 2021a; Padin et al., 2017). Understanding both how negative emotionality and immune function differ between survivors (e.g., between-person effects) offers insight into several notable findings (Padin et al., 2017; Jehn et al., 2006). Although the majority of available data on cancer-related distress focuses on differences between survivors, within-person changes (e.g., how a woman's distress varies compared to what is typical for her) may provide a new window into inflammatory changes among breast cancer patients (Thornton and Andersen, 2006). In a longitudinal study of breast cancer survivors before and after cancer treatment, my research showed that within-person, but not between-person, increases in cancer-related distress were linked to higher inflammation across three visits (Renna et al., 2020a). These findings highlighted that at visits when women had higher cancer-related distress than usual, they also had higher inflammation. In another

longitudinal study, I found that within-person increases in depressive and anxiety symptoms among obese breast cancer survivors across three visits also related to higher leptin production (Renna et al., 2021a). These findings are especially important because obesity promotes biological dysregulation among breast cancer survivors, thus increasing tumor initiation and growth and increasing risk for recurrence (Rose et al., 2002; Andò et al., 2019). Taken together, my earlier work highlights how negative emotionality in the form of increased psychological symptoms and distress is linked to heightened inflammation among breast cancer survivors, a group particularly at risk for prolonged health issues.

The far-reaching relationships between negative emotionality and inflammation are notable among those with distress disorders such as major depressive disorder, generalized anxiety disorder, or post-traumatic stress disorder (Renna et al., 2018; Osimo et al., 2019). Several meta-analyses highlight links between mood disorders and inflammation, reliably demonstrating that people diagnosed with major depression are more likely than their psychologically healthy counterparts to have heightened inflammation both at baseline and in response to stress (Osimo et al., 2019). A meta-analysis that I conducted also showed that adults diagnosed with anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder had, on average, higher baseline inflammation compared to psychologically healthy controls (Renna et al., 2018; Passos et al., 2015). However, more broadly, heightened anxiety and depressive symptoms can also correspond to inflammation among physically healthy adults and those with chronic health conditions (Duivis et al., 2011; Kiecolt-Glaser et al., 2015; Pierce et al., 2017; O'Donovan et al., 2010; Whooley et al., 2007; Powell et al., 2013).

A growing and compelling body of literature suggest bidirectional relationships between inflammation and some aspects of negative emotionality, particularly in reference to depressive symptoms/low mood (Kiecolt-Glaser et al., 2015; Beurel et al., 2020). While the above-mentioned studies supply evidence for the pathway where

negative emotionality provides a pathway to higher inflammation – the opposite is very much true, at least in the depression literature (Dantzer et al., 2008; Raison et al., 2006; Miller et al., 2009). Specifically, heightened inflammation alerts the central nervous system to induce or intensify negative mood states and accompanying depressive symptoms (Dantzer et al., 2008; Raison et al., 2006). Cytokine-based therapies can also produce low mood and major depressive disorder, providing evidence for the inflammation-negative emotionality pathway (Kiecolt-Glaser et al., 2015; Raison et al., 2006). Despite this cogent body of literature on inflammation and depression, less is known how other aspects of negative emotionality are influenced by inflammation.

Taken together, this research presents an important and necessary perspective in understanding the relationship between negative emotionality on inflammation. Despite these advances in this research, further information is needed to determine how and why these emotional experiences and inflammation are linked. Specifically, *are there psychological factors that heighten or dampen this relationship?* Theoretical and experimental work over the past several decades have gleaned some insight into one notable pathway through which negative emotionality relates to immune dysregulation and chronic health conditions: emotion regulation (DeSteno et al., 2013; Brosschot et al., 2006).

### 3. Regulating emotional distress: emotion regulation as a proposed mediator of the negative emotionality-inflammation link

Although emotions such as anger, sadness, and anxiety are important in the context of health, it remains unclear how specific regulation processes mediate the relationship between negative emotionality and inflammation. Emotion regulation refers to “the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions” (Gross, 1998). Therefore, emotion regulation in this context represents a response-focused process where an individual responds to an emotion after it is generated. Emotion regulation strategies such as reappraisal, acceptance, and decentering are generally considered adaptive, while strategies such as worry, avoidance, and rumination might heighten inflammation (Brosschot et al., 2006; Ellis et al., 2019). However, recent work suggests that regulatory strategies are not inherently adaptive or maladaptive, but rather, they have different consequences in different contexts (Aldao, 2013; Bonanno and Burton, 2013; Gross, 2015; Sheppes, 2020). This conceptual view highlights the importance of understanding the context in which an emotion regulation strategy is used in understanding its influence.

Several theories support for the idea that emotion regulation can influence inflammation. The emotion dysregulation model of anxiety posits that sustained negative emotions such as anxiety and sadness can promote a cascade of maladaptive emotion regulation strategies, including worry, rumination, and self-criticism (e.g., negative self-referential processes, or NSRPs) (Mennin et al., 2005). Within this framework, a failure to regulate distress or using maladaptive emotion regulation strategies perpetuates negative emotions. NSRPs are used as a way of regulating negative emotional experiences (Mennin and Fresco, 2013; Northoff, 2007) and are characterized by thoughts that are repetitive, unwanted, and disruptive, ultimately prolonging negative emotionality (McEvoy et al., 2013; Sowislo and Orth, 2013). The perseverative cognition hypothesis (PCH) expands on the ideas from the emotion dysregulation model of anxiety and discusses how NSRP prolongs physiological activation, potentially putting individuals at risk for long term health problems (Brosschot et al., 2006). In short, worry and rumination serve as mediators when individuals experiences stress or negative emotions, prolonging physiological activation. Within the PCH framework, emotion regulation in the form of NSRP highlights a critical pathway to poor health – as negative emotionality increases, it also has the potential to become more intense, long lasting, and invasive through engaging in NSRP, subsequently prolonging physiological activation (Brosschot et al.,

2005, 2006; Brosschot, 2010).

Research testing the PCH has demonstrated relationships between NSRP and low heart rate variability (HRV), cortisol dysregulation, increased inflammation, and higher blood pressure across observational and experimental studies, providing information about both tonic and phasic biological functioning (Ottaviani et al., 2016; Verkuil et al., 2009, 2010; Brosschot et al., 2010). Meta-analytic investigations also highlighted that perseverative cognition also promotes engagement in negative health behaviors that increase risk for inflammatory dysregulation and chronic illness (Clancy et al., 2016). One of the major strengths of the PCH and its accompanying evidence is that it advanced our previously available understanding of how cognitive processes enhance disease risk through both alterations in both biology and health behaviors. NSRP, however, is often the result of negative emotions that come about through real or perceived threats or difficulties in our internal or external environments.

Several cross-sectional studies highlight relationships between other emotion regulation strategies outside of NSRP and inflammation. Among physically healthy adults, cognitive reappraisal, an adaptive emotion regulation strategy, has been associated with lower levels of baseline c-reactive protein (CRP), a protein produced by the liver in response to inflammation (Appleton et al., 2013). Although inflammatory markers are most typically derived from blood samples, salivary cytokines, or inflammatory markers derived from human saliva, can also provide insight into inflammatory responses in the context of emotion regulation. For example, in a laboratory-based study in healthy adults, distracting oneself from negative emotion was associated with an acute increase salivary cytokines (Newton et al., 2017). In contrast, suppressing emotions rather than expressing and experiencing them is associated with higher baseline CRP in an observational study of adult offspring in a national cohort of pregnant women (Appleton et al., 2013). My work and others have found that NSRPs are associated with increased inflammation in laboratory-based studies of physically healthy adults (Renna et al., 2020b; Zoccola et al., 2014). Specifically, when asked to ruminate rather than distract oneself following a laboratory-based stressor, physically healthy women were more likely to experience prolonged and heightened changes in CRP compared to a baseline measurement (Zoccola et al., 2014). Prior work by myself and colleagues demonstrated how experimentally-induced worry increases inflammation relative to a resting baseline collection in a community sample of physically healthy adults (Renna et al., 2020b). Further, among breast cancer patients, my work highlighted cross-sectional associations between NSRPs and increased pain and fatigue for patients who underwent surgery but were still awaiting adjuvant treatment. These findings were notable given that both pain and fatigue are associated with increased inflammation in this population (Renna et al., 2021b). Lastly, among breast cancer survivors, my work has highlighted that at visits where women had higher cognitive and emotional avoidance than what was typical for them, they also had increased chronic inflammation across three visits before and after adjuvant treatment (Renna et al., 2020a).

The above-mentioned findings highlight relationships between cognitive and emotional forms of emotion regulation with physical symptoms and inflammation. Emotion regulation can also be behaviorally focused and often takes the form of engagement in health behaviors that can suppress or enhance immune dysfunction. People who experience negative emotionality may be less likely to engage in a healthy lifestyle due to failures of their emotion regulation systems. Notably, these individuals may be more likely to experience poor sleep hygiene and may utilize alcohol, smoking, food, or drugs in an effort to regulate negative emotions (Clancy et al., 2016). Collectively, these behaviors subsequently put them at risk for experiencing increased inflammation and poor health outcomes (Duivis et al., 2011; Michopoulos et al., 2017; Loprinzi, 2016; Raposa et al., 2014).

Researchers have called for examining emotion regulation more readily in the context of PNI and health more broadly, citing an affect science perspective (DeSteno et al., 2013). Despite a call to action across

disciplines to develop a better understanding of how emotion regulation influences physical health, few longitudinal and causal studies have been conducted (DeSteno et al., 2013). Overall, research on emotion regulation in PNI provides some cross-sectional findings on how use of cognitive, emotional, and behavioral strategies can heighten or dampen inflammation (Appleton et al., 2013; Newton et al., 2017; Renna et al., 2020b; Zoccola et al., 2014). These data supply some insight relationships between different regulation strategies and inflammation. However, emotion regulation strategies are used in response to negative emotionality. That is, emotion regulation often occurs within a specific emotional context that previous PNI research and theories have not accounted for. Next, I introduce a more comprehensive model of the unfolding of negative emotions and NSRPs and their immune consequences, in addition to the role that emotion regulation plays in this pathway.

#### 4. A novel model of understanding negative emotionality in the context of the immune system

To date, theories have highlighted how emotionality and perseveration heighten psychological and physical distress (Brosschot et al., 2006). However, no existing models incorporate the links among negative emotionality and emotion regulation in enhancing immune dysfunction and subsequent risk for chronic illness. Given the association between psychological distress and increased physiological activation, Fig. 1 presents the bibehavioral model of negative emotionality, a novel theoretical model guided by the emotion dysregulation model of anxiety and the perseverative cognition hypothesis (Brosschot et al., 2006; Mennin et al., 2005). The proposed integrated model highlights how negative emotions, such as anxiety and sadness, can lead to heightened inflammation. This heightened negative emotionality and corresponding increased inflammation ultimately worsens long-term health and promotes risk for chronic illness. Within this context, my past work and that of others have demonstrated how negative emotions, and the emotion regulation strategies that are typically used in response to them, link to inflammation. This model accounts for the temporal unfolding of emotional experiences and relates this process to inflammation and other common biological implications of this process.

Notably, this model emphasizes the central role of emotion regulation in heightening or dampening inflammation. The model distinguishes between two types of emotion regulation and their biological influences: adaptive and maladaptive. Adaptive strategies used in an effort to reduce negative emotions and their associated NSRPs are hypothesized to lower inflammation and related biological dysfunction. In contrast, maladaptive strategies, including engaging in poor health behaviors and emotional avoidance, can increase inflammation and heighten or prolong physical health risks over time. As noted earlier, the context in which one deploys different emotion regulation strategies is integral in determining a specific strategy's immune impact. Negative emotionality therefore promotes physiological activation *when* people use contextually maladaptive emotion regulation strategies, which can then ultimately impair long-term health. Within this framework, emotion regulation serves as a mediator between negative emotionality and inflammation.

#### 5. Future directions and model testing

The proposed model lends itself to experimental, observational, and ecological momentary assessment (EMA) studies and presents testable pathways to disentangle how negative emotions *and* emotion regulation deficits promote inflammation and subsequently puts individuals at risk for long-term physical health risks. Given the previously established utility of using a within-person approach to understand how psychological distress influences inflammation and other forms of biological dysfunction (Renna et al., 2020a, 2021a), EMA studies testing this model would allow for causal interpretations of how negative emotionality and emotion regulation influences immune function. Testing negative

emotionality using daily or momentary methods, and then subsequently assessing emotion regulation skills use and inflammation would provide valuable evidence supporting the directionality of the proposed model. However, this model would also lend itself to designing between-person studies and longitudinal research examining if these psychological and immune experiences resulted in poor physical health outcomes such as accelerated biological aging and disease development.

PNI has established bidirectional relationships between psychological distress and inflammation (Beurel et al., 2020). Within the proposed framework, heightened inflammation results from negative emotionality and accompanying maladaptive emotion regulation strategies. However, given extensive literature identifying that heightened inflammation can promote depression and increased negative emotionality (Raison et al., 2006; Miller et al., 2009), this model may be bidirectional. That is, chronic illness, along with increased inflammation, can promote negative emotions and NSRP, potentially creating a feedback loop across the factors accounted for in the proposed model. Future research testing the proposed model would benefit from exploring the directional and causal associations among the variables presented.

It is plausible that this model would extend to both physically healthy individuals, individuals with psychiatric conditions, and those with chronic illnesses. Among physically healthy adults and those with psychiatric conditions, the proposed pathways may exacerbate immune system activation that may enhance risk for experiencing chronic illness throughout their lifespan. Among individuals with already existing chronic illnesses, the proposed model of psychological distress and accompanying inflammatory consequences can enhance symptoms associated with their illness, ultimately reducing quality of life. Thus, within physically healthy adults, the proposed model represents a risk pathway through which negative emotions influence inflammation. In contrast, among individuals diagnosed with a chronic illness, the proposed model presents how negative emotions maintain immune system dysfunction and its accompanying physical symptoms.

The proposed model names emotion regulation as a key pathway linking negative emotionality and inflammation. Specific emotion regulation strategies can have differential effects on the immune system depending on the context in which they are deployed. Therefore, future directions in model testing may benefit from examining emotion regulation strategy choice (e.g. how the emotion regulation strategy that someone chooses to use) in given contexts and how that corresponds to inflammation. Lastly, emotion regulation use as a mediator in the proposed model highlights an important potential intervention point to reduce negative emotionality's immune and long-term health impact. Interventions that emphasize enhancing adaptive emotion regulation skills including mindfulness-based interventions, emotion regulation therapy, and dialectical behavior therapy can offer insight into how to disrupt the pathway through which negative emotionality alters immune function and enhances risk for accelerated biological aging and disease risk (Renna et al., 2017; Linehan, 2014; Fresco and Mennin, 2019). Meta-analyses from my colleagues and I, as well as others, have shown how psychological interventions such as these exert a small, but significant, effects on inflammation (Shields et al., 2020; O'Toole et al., 2018). However, these interventions are comprised of multiple components, and future research should investigate whether skills acquisition and use in response to negative emotionality specifically heightens or dampens biological dysfunction. Further, earlier findings that show that inflammation reduces throughout psychological interventions do not necessarily test momentary skills acquisition and use *in response to* negative emotionality. The proposed model offers a more comprehensive and targeted approach for understanding and intervening on emotion regulation skills use as a means of altering inflammation.

Through synthesizing models from affect science, clinical psychology, and PNI, the proposed model allows for a more comprehensive understanding of how negative emotionality and its regulation influences inflammation. By examining both the emotions we experience and how we regulate them, future PNI research will be able to understand how our



psychological functioning influences the immune system and disease risk. Further, negative emotionality coupled with suboptimal emotion regulation skills ultimately may result in accelerated inflammatory aging – or inflammaging – contributing to heightened risk for morbidity and mortality (Franceschi et al., 2007). Without understanding and testing the relationship between each of the variables presented in this model, research can miss important links in the psychology-biology relationship along with emotional and behavioral factors that may be influencing this relationship.

## 6. Limitations

The literature to date and accompanying model are not without limitations. The goal of the proposed model is to present a framework for considering how psychological factors such as emotion regulation link emotionality and inflammation. It is relatively broad, as it does not identify the specific biological mechanisms that may underlie increases in inflammation. For example, cortisol dysregulation and lowered heart rate variability (HRV) both correspond to heightened inflammation and are associated with negative emotionality and/or emotion regulation (Renna et al., 2020b; Zoccola and Dickerson, 2012; Appelhans and Luecken, 2006; Chalmers et al., 2014, 2016). These specific potential mechanisms warrant important consideration in future work with the hopes of expanding the proposed model and enhancing biological specificity. Further, antecedents of negative emotionality, of which there are likely many, are not accounted for in this model.

## 7. Conclusion

Overall, currently available PNI research provides preliminary insight into negative emotionality and its regulation in influencing inflammation. However, theoretical and empirical conceptualizations of negative emotionality in PNI research has not yet fully accounted for how these psychological experiences then influence inflammatory dysfunction and subsequently enhance risk for chronic illness. Further, previously available research on how emotion regulation strategies *used in response to* negative emotions can influence inflammation. The proposed biobehavioral model of negative emotionality seeks to synthesize these factors to advance PNI research to incorporate emotion theory and research resulting in a more comprehensive understanding of how negative emotionality, and what one does to regulate those negative emotions, promotes immune system dysregulation.

## Declaration of competing interest

The author declares that they have no conflict of interest.

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