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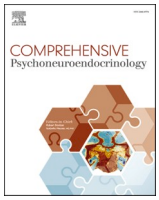

Moving toward affective immunology: Legacy and future directions

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ABSTRACT

The term "affective immunology" has recently been used to denote a field focused on the interplay between affective processes (including mood states, specific emotions, and regulatory processes) and various aspects of immune function. The overarching goals of this commentary are **a)** to provide historical underpinnings of this field with a focus on the profound impact of the work of Janice Kiecolt-Glaser, who is further honored in this special issue, **b)** to review important off-shoots of her legacy work in this domain, and **c)** to highlight important future directions for the field. Kiecolt-Glaser's work laid much of the foundation for affective immunology, with groundbreaking research related to depression, hostility and dyadic interactions, loneliness, and other affective patterns, often in the context of holistic models, novel experimental designs, and interventions. Her former mentees (and many of their mentees) have carried on her legacy in these domains, in ways that continue to advance appreciation of how affective processes relate to immune function. There are numerous remaining questions for the field to pursue, including better understanding of the role of emotion regulation, emotional reactivity and recovery, restorative processes, affective variability, and developmental and dynamic social processes. Such work will require greater use of longitudinal and within-person approaches and/or examination of processes in daily life, as well as models that account for interactive and reciprocal processes and which integrate behavior, social context, sociocultural factors, individual differences, and other aspects of health. As more work in these domains continues, building on Kiecolt-Glaser's rich legacy, we move toward the emergence of affective immunology as an important subfield in the domain of psychoneuroimmunology, one which will offer more nuanced understanding of the role of affective processes in immune health.

1. Introduction

In the past few years, the term "affective immunology" has been used to denote a new field [e.g., [1,2]] – one in which the interplay between affective processes (involving mood states, specific emotions, regulatory processes, etc.) and various aspects of immune function is recognized and described. There have been indeed great advances in understanding the nuances in how such processes influence (and are influenced by and interwoven with) factors related to immune function, from inflammation to viral response and disease susceptibility. It is important, however, to recognize that the field is not brand new in many ways, and in fact has a rich legacy. The term "affective immunology" itself is justified and useful, and the goal of moving toward greater understanding of how affective processes specifically are linked with immunity is highly worthwhile. Better understanding the underpinnings of this field will help inform understanding of extant literature as well as future directions. The goal of this commentary is to **a)** briefly review early work in this domain, with a focus on the profound impact of the work of Janice Kiecolt-Glaser, who is further honored in this special issue, **b)** to review important off-shoots of the legacy work in this domain, **c)** and to highlight important future directions for the field.

2. Review of legacy work

2.1. Early perspectives

Long before the term psychoneuroimmunology was popularized by Robert Ader in the early 1980s, there has been recognition of connections between disease risk and phenomena linked with affect. Ancient medical practices – such as ancient Greek medicine and Ayurvedic medicine in India – acknowledged that trait-like tendencies linked with personality or depression were associated with risk or resilience to disease, and later philosophers as early as the Middle Ages started to acknowledge likely bi-directional connections between mental and

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physical well-being [for reviews, [3,4]]. Driven by a wide variety of mechanistic work that later emerged, including research illuminating physiological stress responses in the 1940s [5] and other pivotal animal research, George Solomon led what was perhaps the first article to focus on emotion with a modern psychoneuroimmunology (PNI) perspective: In 1964, the piece "Emotion, Immunity, and Disease …" [6] posited deep connections between autoimmune disease and patterns of emotional awareness and expression, depression, and anxiety (as well as other factors). Although ground-breaking, this work was rather before its time. It would take further developments in mechanistic PNI research [7] and development and acceptance of the biopsychosocial model (first truly promoted in 1977 [8], with substantial ongoing calls for action [9]) before there was widespread modern scientific acknowledgement of a meaningful link between affect and immune function.

2.2. Kiecolt-Glaser's legacy in affect and PNI

Even in her earliest work, Kiecolt-Glaser included an emphasis on not just psychological stress but on affective phenomena positioned as relevant to stress. Although a key goal of this early work was to provide more robust evidence that stressors could alter immune parameters, she included measures of mental health and psychosocial functioning in even these first PNI studies. For example, an early line of inquiry on which Kiecolt-Glaser and Ron Glaser collaborated was to examine the role of school testing (examinations) among medical students. Using this paradigm, they established that stress related to taking medical examinations (a relatively mild and acute stressor compared to major life events or caregiving, which were other early topics of study) was associated with decreased immune performance as evidenced by multiple observations, including decreased lymphocyte proliferative responses and natural killer cell activity as well as Epstein-Barr virus (EBV) antibody titers [10]. These findings had a profound impact in the emerging field of PNI. Importantly, Kiecolt-Glaser went further than just reporting linkages with stress even in these early studies, recognizing that the impact of stress (such as examination stress) likely included negative emotionality and that effects might hinge on or be exacerbated by negative emotion. She and colleagues thus also reported on multiple affect-related parameters in these early studies, including depressed mood, trait anxiety, hostility, and interpersonal sensitivity [11,12]. For example, early work showed that immune parameters were more disrupted during periods where students were taking examinations, relative to a non-examination period, among participants who were higher than other participants on perceived loneliness (with a scale tapping feelings of disconnection from others); specifically, natural killer cell activity was the lowest during examinations relative to baseline among those who were more lonely [12] and EBV titers were higher [11]. In a line of work involving anxiety, Kiecolt-Glaser (along with former mentee Kathi Heffner) observed that feelings of anxiety enhanced the effects of psychological stress on allergen-induced skin responses and inflammatory responses [13]. Reflecting on some of their and others' early work, which encompassed numerous populations, Kiecolt-Glaser and Glaser wrote, *"it now appears that distressing psychological responses are one common denominator through which psychosocial events or psychological variables might have an impact on immunity"* (p. 679 [7]).

Unsurprisingly, a great deal of research from Kiecolt-Glaser and her team focused on depression and depressed mood. Although depression is a complex clinical construct with cognitive, behavioral, and physiological components, it includes a strong affective component [14] and Kiecolt-Glaser was at the forefront of research positing that connections between depressed mood and immune function could be a key contributor to morbidity and mortality [4,15]. Although others were also examining depression in connection with immune parameters in the early decades of Kiecolt-Glaser's work, a particularly striking feature of her work in the domain of depression from early on was that she did not just examine it as a mediator of stress effects on immune function. A lasting legacy of Kiecolt-Glaser's work with depression has been her recognition of the broad and powerful role of depressed mood and depression in multiple dimensions and directions: Her research features and shows the value of thinking about depressed mood as a precipitating factor, outcome, moderator, and a covariate, as well as mediator [16–21]. Further, she incorporated depressive history and symptomatology into many of her models as well, including experimental work, recognizing that participants do not start a study in a vacuum [e.g., [17,22]].

Some of Kiecolt-Glaser's most lasting contributions in the area of depression involved its connection to inflammation, a central mechanism underlying the link between psychological stress and health [23–27]. Between her broad conceptual and empirical work in this domain and contributing one of the more influential reviews at the time of the connection between depression and inflammation [16], she has contributed immensely to what has been one of the hottest topics in PNI for the past two decades [28–34]. However, Kiecolt-Glaser's contributions toward understanding depression-immune connections go beyond that of the role of inflammation. Always looking for the cutting edge new scientific discoveries, she continued to weave in new and complex behavioral and physiological issues into her research throughout her career. Key examples in the domain of depression and immune function included the role of social relationships [20,35] (a pivotal additional focus throughout her career), the role of mind-body practices [36], and the role of microbiome, gut health, obesity, and dietary factors [17,37,38], with an increasing body of work at the intersection of many of these areas (e.g. Refs. [38–40]).

In the domain of close relationships, Kiecolt-Glaser also incorporated other trait-like affective constructs, in particular anxiety and hostility (or trait-like tendencies toward anger and cynicism). Perhaps most notably, in her deep line of scientific inquiry involving couples Kiecolt-Glaser established that hostile interactions between couples had a particularly strong link (relative to other types of interactions) with multiple markers of immune function. Using an experimental paradigm in which couples are prompted to engage in multiple discussions – one focused on being supportive of each other and one focused on conflict-inducing topics – those who showed more hostility toward each other in the conflictive discussion showed greater inflammatory cytokine and endocrine responses during that discussion relative to the supportive discussion [41–44]. Effects of hostility in such studies were very large; for example, those who were higher in hostility showed a much greater difference between their circulating levels of the inflammatory cytokine interleukin (IL)-6 following conflict discussion compared to the supportive discussion (113 % vs. 45 %) compared to those who were lower in hostility (70 % vs. 65 %) [42]. Similar effects also extended into wound healing, a clinically relevant indicator of immune functioning [45,46]: Couples who exhibited more hostility during both a supportive and a conflictive discussion showed slower healing of an experimentally induced blister wound compared with others [42].

Much of Kiecolt-Glaser's early work that pointed to the potential impact of depression, hostility, and anxiety on immune function also suggested the potential value of psychosocial interventions to improve immunity [47] and she was involved in multiple clinical trials to reduce stress or improve coping and well-being in various ways. One of Kiecolt-Glaser's earliest such studies found that relaxation training led to favorable changes in natural killer cell activity and antibody titers among older adults recruited from independent living facilities [48]. Although that particular study included limited assessment of affective well-being and did not observe effects of loneliness [48], her later work tested and observed effects on mood. For example, randomization to a yoga intervention resulted in not only lower inflammatory markers among breast cancer survivors but also improved well-being on a scale that tapped both physical energy/vitality and positive mood [36]. Positive mood was also shown to be increased from experimental exposure to an ostensibly stimulating smell (via lemon oil), relative to exposure to either lavender or a no-odor control [49]. Another early study found that randomized assignment to disclose traumatic or troubling events had

some effects on positive feelings as well, in addition to reduced health care visits and some positive effects on immune-related parameters, 6 weeks later [50]; although this study did not explore the potential impact on emotion regulation, we know from substantial later work with similar paradigms that at least some of their benefits seem to be explained by emotional and cognitive processing subsequent to emotional disclosure, such as indexed by using words indicative of constructing a narrative about (or trying to find meaning in) past difficult experiences [51–53]. As will be reviewed below, it is unsurprising that this expanse of research led to multiple important off-shoots – in observational, mechanistic, and intervention work – that continue to inform current and future research.

3. Subsequent legacy-inspired and collaborative research

3.1. Legacy-inspired work with hostility, anger, and negative interpersonal interactions

Kiecolt-Glaser's work with hostility has inspired considerable work that has expanded understanding of the role of both anger and hostility in a PNI framework. Having started graduate school with an interest in the importance of acknowledging and expressing anger, some of my own first research linking affect-related processes with aspects of immune function involved secondary data analyses with some of Kiecolt-Glaser's samples with which I could explore phenomena around hostility. For example, among a sample of older adult caregivers and age- and gender-matched controls who were tracked over 6 years, we demonstrated that a self-reported tendency toward hostility was linked with higher levels of the inflammatory marker *C*-reactive protein (CRP) [54]. This line of inquiry later inspired Sunmi Song, who worked under my supervision as a graduate student, to demonstrate that individuals who reported more negative social interactions showed greater inflammatory responses to a laboratory stressor [55]).

Considerable other collaborative and legacy-inspired research with an emphasis on emotion has harnessed dyadic partner-focused protocols that Kiecolt-Glaser used to such good effect. In a separate secondary analysis of Kiecolt-Glaser and colleagues' wound healing study among married couples, colleagues and I found that individuals who used more words indicative of cognitive processing and meaning-making during the conflictive discussion showed smaller increases in two inflammatory cytokines (IL-6 and tumor necrosis factor-α [TNF-α]) relative to others, controlling for multiple factors including hostility and depressed mood [56]. I have continued to explore the effects of emotion (and anger-specific) expression in my later work [57–60]. Other former mentees of Kiecolt-Glaser have also moved in this direction in collaboration with her. For example, in a secondary analysis of Kiecolt-Glaser's blister wound protocol, work by Jean-Philippe Gouin found that those who reported a greater tendency to express their anger in calm, controlled ways showed faster healing of their experimentally induced wounds [61]. Former Kiecolt-Glaser mentees Stephanie Wilson and Rosie Shrout have also pushed forward understanding of dyadic processes related to negative emotionality. For example, they and others found that individuals whose spouse disclosed an upsetting memory with greater emotional intensity (or just greater negative emotion) showed larger increases in proinflammatory gene expression in the following hour and a half [62].

3.2. Legacy-inspired work with depression and depressed mood

Many of Kiecolt-Glaser's former mentees (and their mentees in turn) have also gone on to follow-up on her research in the domain of depression and PNI. For example, Sunmi Song from my group led work suggesting a longitudinal connection between depressive symptoms and CRP among midlife adults [63]. The depression-inflammation connection was also a particular emphasis of Marzieh Majd, whose primary mentor in graduate school was Christopher Engeland and who went on to do postdoctoral work with Christopher Fagundes (who himself worked with Kiecolt-Glaser as a postdoctoral scholar). Majd led a review linking inflammation and specific constructs within depression [29] and also led work showing distinct inflammatory response patterns among men and women in a midlife sample [64]. Kiecolt-Glaser's work with endotoxemia and gut health was instrumental to helping explain this and related observed patterns in follow-up research, including that led by Erik Knight [65,66] during the time he worked with me and Engeland as a postdoctoral scholar. My current group has been particularly involved lately in linking depression and depressed mood with both inflammation and cognitive brain health among older adults. For example, as a postdoctoral scholar with our group, Erin Harrington led work linking older adults' prospective memory lapses in daily life with inflammation and gender [67]. Other former Kiecolt-Glaser mentees, including Lisa Jaremka and Theodore Robles, have continued to move forward understanding of the links between stress, inflammation, and depressive symptoms [68–70].

3.3. Legacy-inspired work with loneliness

Multiple former mentees of Kiecolt-Glaser have gone on to follow up on her ground-breaking discoveries around loneliness in a PNI framework. Although loneliness can be triggered by objective social isolation, it is defined more broadly by the subjective and negative feeling of being lonely, or the feeling that one's social connections are deficient [71–73], which can occur even when surrounded by others [73,74]. Further, although loneliness is related strongly to broader constructs like depression and anxiety, it can be conceptualized as distinct and sometimes has unique predictive power in understanding health risk [73]. My own work included reviews of the importance of loneliness in PNI and collaboratively I have contributed to understanding connection between loneliness and multiple related phenomena, including depressed mood [75], daily social interactions [76], and daily stress [77]. Moreover, a graduate student working with me, Karina Van Bogart, has focused on the connection between loneliness and biobehavioral health. Building on past research linking loneliness with inflammation [e.g., [78–80]], which has primarily been conducted using retrospective measures of loneliness and in younger or midlife samples, Van Bogart spearheaded work in which she revealed a connection between aggregated momentary loneliness and CRP among older adults [81], who as a group are particularly vulnerable to both loneliness and inflammation-related sequalae [82,83].

Van Bogart and multiple other individuals with whom I have been involved as a mentor – including Jee eun Kang, Karra Harrington, and Dakota Witzel – have led multiple other novel lines of inquiry related to loneliness, all involving midlife or older adults [77,84–86]. Research I am particularly excited to see move forward in this space (and in which my group is actively working) involves combining these multiple lines of inquiry to understand how biomarkers related to immune function and aging, psychosocial stress, and mental health parameters converge to help explain and predict brain health among older adults. For example, Jee eun Kang is examining how loneliness, stress, and cognitive performance relate across different time frames. It is also exciting to see other mentees of Kiecolt-Glaser working in the domain of loneliness and cognitive health as well, as it will take awareness of multiple converging physiological systems, behavior, and complex psychosocial forces to improve aging related outcomes. For instance, in secondary data analyses with Kiecolt-Glaser, Lisa Jaremka has shown that dietary supplementation with omega-3 fatty acids seems to attenuate declines in episodic memory among lonely adults over time [87]. Former Kiecolt-Glaser postdoctoral scholar Stephanie Wilson led work linking loneliness and telomere length, a marker of accelerated aging, among adults with lower heart rate variability [88]. Moreover, Kathi Heffner has carried forward Kiecolt-Glaser's behavioral intervention work in numerous domains, with particular emphasis on older adults, including via interventions to promote social connectedness in lonely and isolated

caregivers as well as with other interventions to improve immune related health and improve stress adaptation among older adults [e.g., [89]].

Yet other mentees of Kiecolt-Glaser are moving forward different but related science related to loneliness and PNI. For example, Lisa Jaremka (along with Christopher Fagundes, and others) has provided evidence to suggest that the greater pain, depression, and fatigue experienced by lonelier individuals may relate to them also having higher cytomegalovirus antibody titers [90]. She and Fagundes and other colleagues have also gone on to show that loneliness predicts cold symptoms after a viral challenge [91], in addition to having multiple other important lines of inquiry involving loneliness [92,93]. Kiecolt-Glaser's former mentees Annelise Madison and Rosie Shrout called for the importance of understanding the impact of loneliness when considering predictors of vaccine efficacy at the height of the COVID-19 pandemic [94]. Indeed, the pandemic highlighted for many individuals the importance of better understanding loneliness and loneliness-vulnerability [e.g., [95,96]].

3.4. Recent legacy-inspired expansion of affective processes and assessment

Along with greater awareness of individual and group-level vulnerabilities to impaired immune function has come greater awareness of measurement techniques that provide a better sense of how individuals are feeling in daily life and how affective processes relate to both acute and chronic health-related phenomena outside of (or sometimes in addition to) clinical levels of depression. Most of my own work relating affective phenomena with aspects of immune function has involved affective states (both positive affect and negative affect) captured in daily life, such as with daily or ecological momentary assessment (EMA) [e.g., [97,98]]. Such techniques provide novel and important information relative to more traditional retrospective reporting methods in many ways. First and foremost, although retrospective methods can tap important information about how a person views themselves and their past experiences, it is difficult (in many ways impossible) for individuals to self-report how they "tend" to feel; people have difficulty remembering how they felt even the day before (in part because mood states often vary across a day, sometimes dramatically), and their reports are often driven by both their global perspectives about themselves as well as by memory bias [99–101]. It is thus perhaps unsurprising that our group found that negative mood assessed with EMA was related to inflammatory cytokines in a midlife sample, whereas a retrospectively recalled measure of negative mood was not [97]; further, findings were suggestive of stronger trends of association when affective assessment and blood collection (from which the cytokine levels were derived) were closer together in time [97], a possibility that was replicated in later work by a different group [102].

In summary, multiple former "academic children" and "grandchildren" of Kiecolt-Glaser have worked with her and/or been inspired by her work to advance understanding of hostility, depressed mood, affective mood states, and loneliness within PNI frameworks. Importantly, they have carried on her legacy of doing so in complex, holistic models that take into account the role of behavior (e.g., sleep and diet), social context and relationships, sociocultural factors and individual differences, and other aspects of health. Some of this work has started to move beyond simply linking "bad stuff" with more "bad stuff" to help elucidate the role of emotion regulation and emotion-focused coping, as well as patterns that may emerge in daily life over time. Such dynamics remain important future directions for the field, as well as other important domains that are reviewed further below.

4. Future directions for the field

4.1. Longitudinal and/or intensive data collection in daily life

There is substantially more work needed to understand nuances in how affective processes relate to immune function, including the impact of emotional expression, emotional reactivity and recovery, emotional variability, positive mood, dynamic and developmental processes, the role of individual and environmental influences, and how such forces interact over time to influence health and well-being. All of these areas, reviewed in more depth below, will be enhanced and enabled by data collection techniques that are longitudinal (tracking individuals over time) and/or which include intense data capture in daily life using ecologically sensitive methods (i.e., those that enable understanding of people in lived environments) with repeated sampling of individuals over time (e.g., intensive within-person data capture). Research in PNI and related fields (such as immunopsychiatry) is already starting to move in this direction, with multiple other investigators calling for more longitudinal and intensive within-person designs to inform understanding of how emotional states, mental health, and other affective processes relate to immune function [103,104]. Doing so will require not only intensive capture of mood, affective states, and social and environmental context, but also multiple assessments of immune-related parameters on similar time scales [97,102].

4.2. Emotion expression and emotion regulation

A key future direction for the field of PNI – indeed, one in which further growth seems needed for the emerging field of affective immunology to develop and thrive – is to better incorporate and understand the impact of emotion regulation at a mechanistic level. The term "emotion regulation" can be thought of as broadly encompassing the shaping of the experience and expression of emotion based on context, needs, and goals – such as via strategies related to changing situational context, attention, cognitions (e.g., cognitive reappraisal), and responses such as emotion expression or suppression [105–107]. Work in this area will be particularly valuable given that emotion regulation is a modifiable target [108–110]. Some excellent empirical research on neurological correlates of emotion-focused coping points to the value of examining emotion regulatory processes as key factors related to variation in inflammatory responses and immune function between individuals and across time [111,112]. Further, there are striking linkages between early life adversity and heightened inflammation and other indicators of immune dysregulation [113–115]; a review led by Ambika Mathur, a former graduate student in my group (along with current graduate student Sarah Lipitz), suggested that differences in emotion regulation may help explain the link between early life adversity and inflammation [116]. Recent findings are in support of this possibility. For example, childhood deprivation was shown to be linked with both emotional reappraisal and suppression, and that these emotion regulation strategies provided an indirect link to fibrinogen levels [117]. Other relevant work (although not testing mediation models) includes several recent papers (including one by Jean-Philippe Gouin, who worked with Kiecolt-Glaser as a postdoctoral scholar) indicating that trait-level emotion regulation strategies and related resources may moderate connections between early adversity and inflammatory profiles [118, 119]. Further, trait tendencies toward suppressing emotion, versus expressing it, have been linked with higher CRP levels among adults [120], and some work links unconstructive ruminative thought or rumination (which can be viewed as a typically maladaptive form of emotion regulation) with higher levels of inflammation, with particularly consistent findings observed in research using an experimental manipulation of rumination or acute stress [121]. There is also recent evidence that rumination and cognitive ability may interact to predict inflammatory biomarkers [122]. However, as has been named by former Kiecolt-Glaser mentee Megan Renna and others, longitudinal work conclusively linking emotion regulation behaviors in daily life with health parameters (and immune parameters specifically) remains scant [123,124].

A specific area related to emotion regulation that needs more attention is how awareness of negative emotion, appraisal of it (such as

whether or not it feels stressful in the context and how much it feels appropriate to feel or express it), and the expression of such emotion (be it sadness, anger, or worries, etc.) relates to immune function. Although it has long been a central tenant of clinical psychology that the ability to acknowledge and express negative emotion (in appropriate ways) is important for mental health [125], it has been challenging to link such processes with better physical health mechanisms. One reason for this difficulty is that the existence of negative emotion suggests that a stressor has occurred [53,126], a stressor which in turn can perturb various physiological systems; similarly, feeling intense negative emotion itself can be stressful, depending on multiple factors, including personality and situational context as well as the intensity of the emotion [53,127] (see Fig. 1). Although in certain situations there can be immediate value of expressing negative emotion (such as feeling understood and for self-protection), the value of expressing negative emotion typically plays out over time in terms of our health and well-being [for reviews, [53,57]]. Investigators do not often have data relevant to what downstream consequences would have looked like without such emotion-focused coping, at least not at a within-person level; as an example, we would ideally be able to contrast inflammatory parameters in a given person two days after an emotional outburst with parameters in the same person under the same circumstances but after they had suppressed their emotion. It is thus relatively difficult to demonstrate advantageous effects of the expression of negative emotion or emotion-focused coping compared to showing that reports of negative emotion are linked with seemingly adverse consequences. Fig. 1 provides a conceptual figure of what I have named the Context by Person model of emotion expression, by which mood states may interact with person-level and social-contextual factors to predict emotion expression and health-related trajectories.

This domain of inquiry also highlights the importance of assessing and examining both person-level factors and situational, environmental, and cultural factors and how these may interact to affect health over time. In the framework of the Context by Person model of emotion expression, for example, person-level factors might include a trait-like tendency to suppress anger or, alternatively, a tendency to be in situations (perhaps driven by sociocultural or environmental context) in which anger expression would feel inappropriate or dangerous [128]. At the within-person level, for example, a given person may suppress their anger at work one day, but then express it very actively with a family member when they get home. Although there is excellent theory and empirical work related to how person-level dynamics and situational context can interact [e.g., [129–131]], nuanced empirical work showing such interactions in daily life and how they inform health is relatively scant. A challenge for the field of affective immunology is to find ways to understand how such dynamics relate to immune function.

4.3. Emotional reactivity and recovery

Emotion regulation processes relate to the intensity of an emotional reaction to a stressor and recovery to baseline, both in terms of emotional reactions as well as physiological reactions that often accompany them [132–134]. Although there is more research from a PNI framework in this domain than there is of emotion regulation behaviors per se, Kiecolt-Glaser and multiple mentees called for more research in the area of emotional reactivity and recovery in a 2020 review article [109]. Whereas blunted or insufficient acute stress responses are linked with problems, both exaggerated and prolonged responses to stress can serve as pathways to both depression and chronic illness [109]; thus, better understanding individual variability in these parameters may offer opportunities to intervene to improve health [135].

Past affect-focused PNI research in this area includes considerable experimental work in which either stress is manipulated (and both emotional and physiological responses assessed) [136–138] or emotion is manipulated and physiological responses assessed [e.g., [127,139,140]]. For example, individuals who were lonelier than others showed greater stimulated cytokine responses following an experimental stressor [78]. Similarly, multiple studies have shown that depressed individuals (sometimes only if they also have a history of early life adversity) show exaggerated inflammatory responses to lab induced acute stress relative to comparison participants [141,142]. As with emotion regulation, more work in this domain using daily life methodologies is needed. Existing work with daily methodologies is suggestive

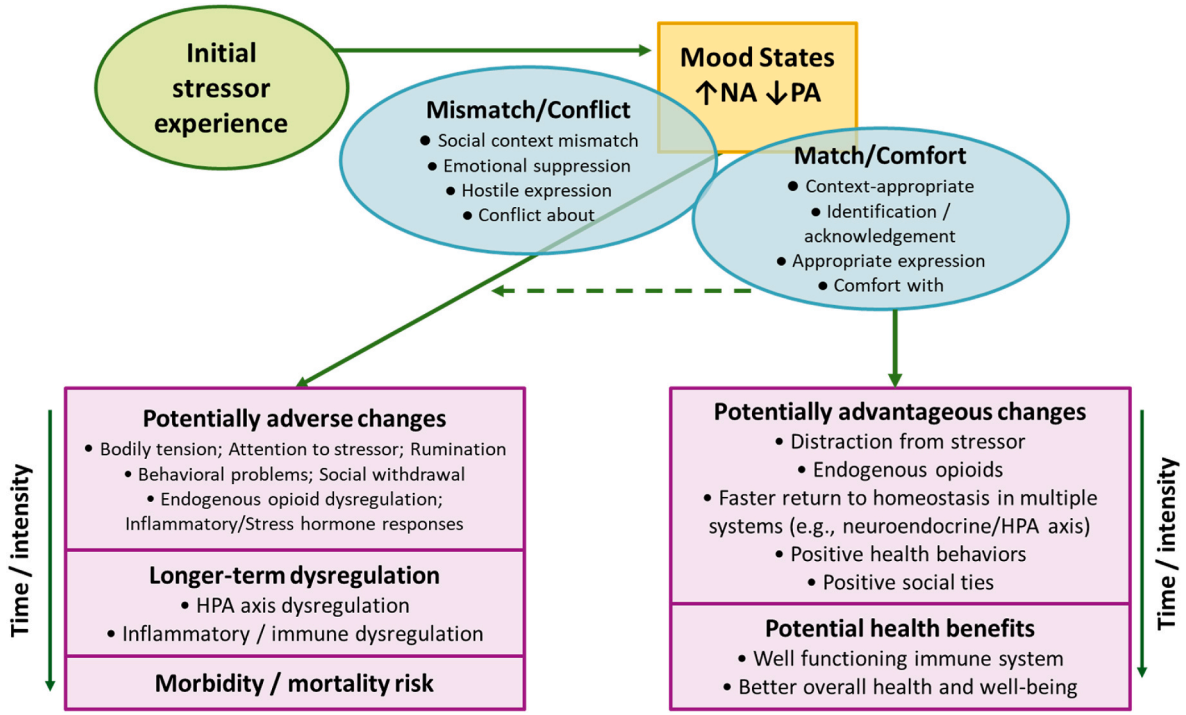

Fig. 1. Schematic of the context by person model of emotion expression.

of connections between affective reactivity and inflammation. For example, during the time she worked with my group as a postdoctoral scholar, Nancy Sin and colleagues found that individuals who evidenced greater decreases in positive affect on days when stressors were reported had elevated levels of IL-6 than those who maintained positive affect on such stressor days [143].

Existing research on daily or momentary capture of emotional reactions in daily life is often hampered by the difficulty inherent in establishing what is a "baseline" for someone when tracking them in daily life, with all of the ups and downs that come with moving through different social and environmental contexts [135]. A recent postdoctoral scholar with my group, Dakota Witzel, has proposed looking at "emotional residue" as a different way of examining emotional reactivity and recovery in everyday life and potential effects on health. Emotional residue, or the extent to which affective reactions to daily stressors are prolonged (i.e., continue into the next day) may be a key mechanism by which daily stress relates to long term health [126, 144–146]. It will be exciting to see this work applied in a PNI framework moving forward. It would also be illuminative to see intensive longitudinal assessment combined with event-contingent EMA techniques (where participants are prompted to report on certain events), which together might enable researchers following individuals over time to better characterize both reactivity and recovery processes to specific stressful events.

4.4. Positive mood and restorative processes

In reflecting on the field of PNI, Kiecolt-Glaser, former mentees of hers, and others have reflected on the relative ease of demonstrating immune dysregulation linked to chronic stress compared to demonstrating the value of positive affective processes or resilience factors [147]. Theodore Robles, along with Judith Carroll, put out an inspiring call for more emphasis in this area [147], and pointed out that a key aspect of resilience in terms of immune function likely involves the ability – following perturbance in homeostasis – to return to baseline and to be able to engage with restorative processes, including coping resources and healthy behavior. Former Kiecolt-Glaser mentee Jeanette Bennett has contributed further to this perspective, pointing out that flexible emotion regulation as well as flexible and speedy physiological regulation (e.g., habituation of hypothalamus-pituitary-adrenal (HPA) axis response) are critical indicators of resilience to adversity [148]. Although work testing such processes empirically (particularly in daily life) is sparse, there is increasing interest in this domain and it remains an important area for future attention.

The role of positive mood is likely to play an important role in the maintenance of health and well-being in ways that involve the immune system and complex processes that are as yet not highly characterized [149]. For example, when she was working with me as a graduate student, Dusti Jones led a review of the literature linking positive affect and inflammation [150]. Although findings from past studies were found to be inconsistent, when there were significant linkages between positive affect and inflammatory markers, higher positive affect tended to be linked to lower inflammation; further, limited evidence suggested that positive affect might function as a buffer of stress [150]. For example, one study involving Jeanette Bennett observed that positive affect only appeared to be protective against higher CRP levels among those who also reported higher perceived stress [151]; and another study found that links between CRP and health conditions were weaker among those with greater recalled positive affect [152]. Further, aggregated momentary positive affect has been associated with lower fibrinogen reactivity after experimental stress tasks [153]. Positive affect has also been uniquely associated with downregulation of proinflammatory and antiviral gene expression [154]. It will be valuable to further explore mechanisms around positive affect and positive mood states, as well as the relevance of positive life experiences or events, which have also been linked to inflammatory biomarkers and other health parameters [155, 156].

4.5. Affect variability and other emotion dynamics

Along with emotion regulation and emotion expression, researchers have begun looking at affective variability, using various methods of computing the amount of variation in both positive and negative affect between assessment moment. Such research also tends to require EMA approaches to data collection. There are multiple theoretical perspectives by which affective variability may relate to physical health [for reviews, see [157,158]]. Emerging evidence in the PNI domain suggests that the story is not as simple as to suggest that stability in affect is adaptive or that only particularly high variability is maladaptive. For example, Jenkins and colleagues found that poorer antibody responses to influenza vaccine were observed among individuals who had both high overall (person-mean) positive affect but also greater variability in positive affect, compared with those who had high person-mean positive affect but less affect variability [159]; in this same study, those with less variability in negative affect overall had greater antibody responses [159]. When Dusti Jones led some of the first research to link affective variability with inflammation, we observed similar complexities: Among midlife adults we observed that person-mean affect (both positive and negative) moderated associations, such that for those with higher person-mean affect both high and low affect variability was associated with inflammatory markers [157]. Others' work with inflammation in different samples, as well as work with other health parameters, has also observed interactions between mean affect and variability [e.g., [158, 160]], which are in line with theoretical perspectives that both person-level phenomena (relatively stable individual differences) as well flexibility in responsiveness to context are likely critical to understanding the impact of affect variability and related dynamics. This line of inquiry (and investigation of other affect dynamics, including emotional diversity and flexibility [e.g., [161,162]]) thus represents another opportunity to better understand complex dynamics between person-level and within-person processes. Particularly given the speed with which affect can change in response to events, various time frames by which affective patterns likely relate to physiological health, and other complexities, advancing understanding in this domain will be another challenge for the field of affective immunology. Multiple investigators have pointed out the need for more research in this area and that it will likely require yet more intensive data capture, with new technologies (such as wearable devices) and new assessment techniques likely being critical [149,163].

4.6. Developmental and dynamic social processes

It will also be important to examine affective processes, including emotion regulation and emotional dynamics, in the context of dynamic social processes and also from a developmental lens. Stephanie Wilson, Rosie Shrout, and Annelise Madison, who all completed their postdoctoral work with Kiecolt-Glaser, have helped inform the field about the importance of the strong and interactive forces that couple-level dynamics can have on physiological functioning and health [164–167], and many other current and former mentees are doing inspiring work in this space as well. Interpersonal stressors influence affect, self-perceptions, and physiological functioning [e.g.,] [60,145]in ways that play out over time in complex ways that are poorly understood with regard to influences on immune function. Not just couple level dynamics but also family systems dynamics will also be important to incorporate. Illustrating the potential in this space, recent collaborative research involving my group has found that there were lower cholesterol levels and a trend toward lower CRP levels among parents who participated in a coparenting intervention [168]. Following up on this work and with the same sample, current postdoctoral scholar Alp Aytuglu is working on models showing significant linkages between parenting behavior and markers of inflammation among adolescents, as well as

children's HbA1c levels (a marker of diabetes risk). Incoming graduate student with my group, Caesar Liu, plans to push forward affective immunology from a developmental perspective, including to better understand the impact of early life experiences as well as aging-related factors in affect, inflammation, and their interactions [169]. It will be satisfying to see junior scholars continue to find novel ways to better integrate developmental, couple-level, and family systems approaches with health psychology, as doing so will not only advance the field of affective immunology but inform novel possibilities for intervention.

4.7. Continued integration in complex models

Following Kiecolt-Glaser's lead, my hope is that research linking affective processes and immune function will continue to examine these connections in models that integrate individual differences, sociocultural and environmental influences, and behavior, as well as different physiological systems (e.g., microbiome, autonomic nervous system) and health conditions. Integration of research from the domain of affective neuroscience will also be valuable, as it is increasingly recognized that there are reciprocal interactions between social behavior, neural sensitivity, and immune-related parameters [e.g.,[170,171]].

In terms of individual-level factors, differences linked with age as well as with gender/sex have long been featured in my own research and that of mentees, as they are often related to both affective processes and aspects of immune function [82,172,173]. Research from our group has also examined differences linked with race or ethnicity to better understand individual variation as well as health disparities among those racialized as underrepresented minorities [e.g., [97]]; this is an important topic in which there is growing awareness in PNI [174–176] and which has been an area of emphasis for former Kiecolt-Glaser mentees, including Lisa Christian. As is already recognized by Christian's group, an important direction for such work is to move away from only examining sociodemographic factors as moderators of findings, but also to look within groups to better understand factors related to adverse as well as positive trajectories over time [66,177]. In a related vein, better understanding the impact of discrimination related to gender/sex, age, and racial or ethnic identity will also be important in the field of affective immunology. Discrimination, often embedded in deeply entrenched structural processes and environments, can serve as a unique stressor that influences affective and cognitive phenomena and physiological processes [60,178]. Once again, mentees inspired by the Kiecolt-Glaser legacy are leading novel research in this space. For example, Britney Wardecker, former postdoctoral scholar with my group, drew attention to the importance of looking at unique stressors among those identifying as LGBTQIA [179]. Incoming graduate student with my group, Destiny Gilliland plans to work at the intersection of understanding how socioeconomic status, experiences of discrimination, and affective processes relate to PNI and aging-related health. It is also exciting to see work relating to affect and health taking an intersectionality approach, recognizing that various aspects of identity can be interactive in their influences [180].

Individual differences, from personality to those relating to socioeconomic status and sociodemographics, are also intertwined with health behavior (such as diet, physical activity) and chronic health conditions in complex ways involving affective processes. Sleep (quality, duration, variability, and other sleep-related parameters) provides an excellent example in which there is substantial work from multiple scholars with links to Kiecolt-Glaser (including former mentees Matthew Cribbet and Kathi Heffner) as well as many others. Sleep is linked with many of the psychosocial and biobehavioral phenomena that are central in PNI, including affect and affect variability [181–184], depression [e.g., [63]], ability to engage in effective emotion regulation [185,186], relationship functioning [e.g., [187–189]], physical pain [190], and other health behavior [191], and has been linked with numerous immune related parameters. For example, a former graduate student with my group, Danica Slavish, led work linking insomnia symptoms with elevations in CRP among young adults [192] and has continued to expand awareness of how sleep relates to health. Inadequate or problematic sleep patterns are also a likely player in vicious cycles that can emerge between symptomatology, disease, and behavior. For example, chronic diseases are intertwined with poor sleep [193], while also increasing negative affect and psychosocial stress. Research by Nancy Sin and her mentee Jin Wen and colleagues suggests that, in turn, sleep patterns seem to influence affect, physical symptoms, and expectations as well as occurrences of stressors [194,195]. Research on reciprocal associations involving behavior as well as with disease and other various physiological systems are thus a key area for the field of affective immunology to incorporate.

5. Conclusion

In summary, the field of affective immunology can be seen as emerging from the rich history of research in psychoneuroimmunology (PNI), affective neuroscience, and immunopsychiatry that has involved affective processes. Kiecolt-Glaser's work laid much of the foundation for this field, with truly groundbreaking research related to depression and depressed mood, hostility and dyadic interactions, loneliness, and other affective patterns, often in the context of novel experimental designs and interventions. She took a holistic approach, examining both the correlates and consequences of affective processes in models that incorporated social, behavioral, and other physiological phenomena. In turn, her former mentees (and many of their mentees) have carried on her legacy in all of these domains, sometimes with new models and assessment techniques and in ways that continue to advance appreciation of how affective processes relate to immune function. There are numerous remaining questions for the field to pursue, including better understanding of the role of emotion regulation, emotional reactivity and recovery, restorative processes, affective variability, and developmental and dynamic social processes. All of these will be better enabled by longitudinal and within-person approaches and/or examination of processes in daily life, as well as complex, integrative models that account for interactive and reciprocal processes. As more work in these domains continues, building on Kiecolt-Glaser's rich legacy, we move toward the emergence of affective immunology as an important subfield in the domain of psychoneuroimmunology, one which will offer more nuanced understanding of the role of affective processes in immune health.

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Jennifer E. Graham-Engeland: Conceptualization, Writing – original draft.

Declaration of competing interest

None.

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