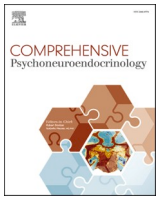
Comprehensive Psychoneuroendocrinology 19 (2024) 100247

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology



Interpersonal relationships, PNI, and health: Seeds in the 1980s, fruiting trees today

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ARTICLE INFO

Keywords:
Loneliness
Psychoneuroimmunology
Close relationships
Marriage
Gender
Health

ABSTRACT

In this contribution to the Special Issue, I highlight how Janice Kiecolt-Glaser's research in the 1980s planted the seeds for two areas of social relationships and health research: loneliness and intimate/marital relationships. I review the foundational "seed" studies from the mid-to late-1980s, the research "saplings" that sprouted and grew during the subsequent twenty years, and the "mature trees" that have gone on to fruit and grow their respective areas of inquiry over the past twenty years. In addition to highlighting the mature trees that have borne rich empirical fruit, my other goal for this contribution is to draw attention to ideas and concepts from Kiecolt-Glaser's work and writing that merit further conceptual and empirical examination in the next generation of research on social relationships, psychoneuroendocrinology, psychoneuroimmunology, and health.

1. Interpersonal relationships, PNI, and health: Seeds in the 1980s, orchards today

Consider the state of psychoneuroendocrinology (PNE) and psychoneuroimmunology (PNI) research at the time that Kiecolt-Glaser and Glaser began their collaborations in the 1980s [1,2]. In the late 1960s, preclinical animal studies established that experimental stress exposures could alter changes in immune function. In the mid-to-late 1970s, landmark studies demonstrated conditioned immunosuppression. By the early 1980s, researchers had discovered a potential basis for brain-to-immune communication: sympathetic nervous system (SNS) innervation of lymph nodes. Moreover, the development, use, and proliferation of monoclonal antibodies as a research tool allowed for much greater accessibility and precision in immune assays. Studies in humans almost exclusively focused on the effects of extreme stressors like spaceflight, extreme noise exposure and sleep deprivation, and adjusting to training at a military academy. The one exception was spousal bereavement, which is notable because it was far more prevalent than spaceflight or military training, and at the time, spousal bereavement was assigned the most "life change units" on a common checklist measure of stressful life events [3].

The research projects launched by Kiecolt-Glaser and Glaser in the 1980s planted the seeds that gave rise to two major trees of research on interpersonal relationships, biological mechanisms, and health: loneliness and marital/intimate relationships. After describing the initial seed studies, I briefly describe major developments in the growth and fruiting of both areas of inquiry. I then close by discussing several contributions from Kiecolt-Glaser and her research group that are important directions for continuing to grow and cultivate research on interpersonal relationships, PNE/PNI mechanisms, and health.

2. Loneliness

As recounted by her husband and collaborator Ronald Glaser twenty years later, for their very first collaboration together Kiecolt-Glaser and Glaser "decided that the best approach would be to start by studying healthy young adult individuals experiencing 'every day' types of stressors," [4] and specifically first-year medical students during final examination week. Three significant contributions of that approach were: 1) Introducing a new model of naturalistic stress exposure that would be adopted by other research teams, 2) Presciently measuring the inflammatory marker C-reactive protein, and 3) Publishing "the first article to provide biological health-relevant data for loneliness" [5], which turned out to be seed that sprouted future research on loneliness and physical health. Loneliness has been defined as the subjective distress associated with experiencing a discrepancy between one's desired and actual state of social relationships [6]. In their sample of 75 medical students, those reporting higher scores on the UCLA Loneliness scale [7] showed lower natural killer (NK) cell activity during a less stressful timepoint (1 month prior to exams) and during final examination week [8], as well as higher levels of antibodies against Epstein-Barr Virus in a subsample of 49 students (indicating poorer

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https://doi.org/10.1016/j.cpnec.2024.100247
Received 9 March 2024; Received in revised form 19 June 2024; Accepted 23 June 2024
Available online 24 June 2024

control of the latent herpesvirus, [9]). Similar results for loneliness and NK cell activity were observed in a sample of psychiatric inpatients [10]. Kiecolt-Glaser noted at the time that "Unlike social support, research on the medical consequences of loneliness has been very limited thus far" [8].

Throughout the late 1990s and into the early 2000s, the seeds planted by Kiecolt-Glaser provided empirical foundations for work by other PNE and PNI research groups that spanned the lifecourse and helped usher in the focus on inflammatory mechanisms in the early 2000s. Regarding the lifecourse, foundational work in college students was conducted and published during this period by Cacioppo and Hawkley [6,11]. Steptoe and colleagues examined cardiovascular, hypothalamic-pituitary-adrenal (HPA) axis, and immune measures both at rest and in response to acute stress in a subset of middle-aged participants from Whitehall II [12]. That study is notable because it was also one of the first to identify inflammation (fibrinogen levels) as a plausible mechanistic pathway linking loneliness to health. Informed by those findings and other PNE research on loneliness, Cole and colleagues demonstrated links between chronic loneliness and the leukocyte transcriptome (i.e., mRNA expression) in older adults, including lower expression of genes bearing response elements for the anti-inflammatory glucocorticoid receptor and higher expression of genes bearing transcriptional response elements for the pro-inflammatory transcription factor nuclear factor-κB. That study also represented the first time that indicators of transcription factor activity derived from mRNA expression were linked to any psychosocial risk factor [13].

Those findings in the early 2000s provided the empirical basis for additional studies of loneliness and inflammatory pathways over the past 20 years. While work on loneliness and circulating inflammatory markers has been heterogeneous [14], more consistent are associations with mortality [15,16]. The past two decades also marked a return by Kiecolt-Glaser and her lab group to studying loneliness. Rather than a focus on main effect associations, such as "is greater loneliness related to greater inflammation?", her team focused on interactive effects, particularly loneliness as a moderator that may prime greater inflammatory responses to stress exposures [17,18], combine with lower parasympathetic activity related to predict greater latent cytomegalovirus activation and shorter leukocyte telomeres [19], and that the propensity for heightened inflammatory responses may increase risk for depressive symptoms in the face of social stressors [20]. Ultimately, loneliness both through and in concert with inflammatory processes may have clinical relevance for patient-reported outcomes including pain, depressive symptoms, and fatigue both cross-sectionally [21] and over time [22].

3. Marital relationships

Unlike loneliness and health, by the mid-1980s data were available linking marital quality as well as separation and/or divorce to health [23]. Marital quality has been defined as a person's global evaluation of their marriage along positive and negative dimensions including attitudes towards one's spouse, and reports of spouse's behaviors [24]. Strained or distressed marriages are characterized by low positive and high negative marital quality and are at greater risk for dissolution (separation or divorce, [25]). Noting that marital strain and disruption were also ubiquitous, everyday stress exposures, Kiecolt-Glaser examined neuroendocrine and immunological correlates of low marital quality and marital disruption in two studies of married and separated/divorced women [26] and men [27]. In this review, for brevity I primarily focus on functional immune measures from those studies, specifically *anti*-EBV antibodies, rather than enumerative measures (e.g., cell counts) and *in vitro* measures (e.g., lymphocyte proliferation to mitogens).

3.1. Marital quality

Higher marital quality measured by the Dyadic Adjustment Scale was related to lower EBV antibody titers, suggesting better control of the latent virus in women [26] and in men [27]. While results were reported for women and men separately, the observed effect sizes were larger for women compared to men. In a subsequent groundbreaking study conducted in a hospital research unit, Kiecolt-Glaser incorporated observational coding of behavior while couples discussed problems in the relationship along with repeated measures of neuroendocrine and immune function [28,29]. Importantly, the 90 newlywed couples were young and physically healthy, which helped increase internal validity by reducing the influence of health behavior and disease-related confounds [30]. While the findings may be less generalizable to couples where one or both spouses have existing physical illnesses, engage in health-compromising behaviors (sedentary activity, poor diet/nutrition, substance use, poor sleep health), or have highly distressed marriages, the findings most likely underestimate what might be observed in such marriages. For example, observed behavior in the laboratory is less negative and critical compared to when behavior is observed in the home [31].

Repeated blood draws obtained while couples were discussing problems in the relationship ("problem discussions") allowed for examining associations between observed behavior and concurrent neuroendocrine hormone concentrations. Greater hostile behavior during problem discussions was related to larger increases in SNS hormones (norepinephrine and epinephrine) as well as adrenocorticotropic hormone [ACTH, 28], with a similar pattern of associations for older couples married for at least four decades on average [32]. Moreover, serum cortisol levels were persistently elevated throughout the day of the study for wives, and in particular, wives for whom husbands were more likely to respond to wives' demands during the problem discussion with avoidance and withdrawal [33]. In highly hostile problem discussions, wives' supportive behaviors during the discussion were related to steeper declines in wives' ACTH and cortisol, suggesting that positive and constructive behaviors during problem discussions could buffer against persistent HPA axis activation during problem discussions [34]. For functional immune measures, high levels of hostility during problem discussions were related to higher EBV antibody titers in newlyweds and in older couples [29,32].

During the first decade of the 2000s, PNE and PNI researchers began to emphasize that endocrine and immune changes associated with acute stressors needed relevance for clinical outcomes [35–37]. Kiecolt-Glaser's research on marital relationships began integrating clinical outcomes by incorporating blister wound healing as an observable health outcome with real-world implications for phenomena like surgical wound healing and chronic wounds [38,39]. In a within-couples design, couples visited the hospital research unit on two separate occasions [40]; during one visit couples discussed problems in their relationship similar to the previous studies, and during another visit couples discussed personal concerns (e.g., "I would like to exercise more"). The rate of blister wound healing following the relationship problem discussion was 73 % of the rate of healing following the personal concern discussion. The rate of blister healing in high hostility couples across both discussions was 60 % of the rate of healing in low hostility couples. In addition, couples characterized by the combination of low mutual discussion avoidance and high positive behavior showed the fastest wound healing [41].

Low quality relationships have implications for health in a variety of conditions [24], including cardiovascular disease risk and progression [42]. Influences on health behaviors and mental health are part of the mechanistic pathway [43,44]. At the same time, Kiecolt-Glaser uncovered how relationship functioning may impact how the brain and body respond to food, particularly high-fat meals. In another within-couples design, a sample of 43 married couples completed one hospital visit in which they consumed a high saturated fat breakfast meal, and another

visit in which they consumed a meal with the same number of calories, but with high oleic sunflower oil content (less saturated fat). During both visits couples discussed a problem in the relationship 2 h after meal consumption. Higher hostility across both discussions was related to higher post-meal insulin, larger peak triglyceride response in participants with a history of mood disorders, and most notably, lower post-meal energy expenditure. These influences on metabolism – particularly lower resting energy expenditure, when extrapolated over the long-term, highlight a mechanism whereby distressed marriages increase risk for cardiometabolic diseases [45]. Another pathway may involve elevated inflammation due to increased gut permeability to bacteria. In the same sample, greater hostile behaviors were related to higher levels of circulating lipopolysaccharide-binding protein in blood. Lipopolysaccharides are large molecules that are found on the cell membranes of Gram-negative bacteria like *E. coli* and *salmonella*; high levels of the binding protein indicate greater translocation of Gram-negative bacteria from the gut into circulation (a "leakier gut") and was also associated with elevated CRP [46].

3.2. Marital dissolution

In the initial marriage studies [26,27], separated/divorced participants showed higher EBV antibody titers compared to married participants. In the sample of women, a subset who had recently separated in the past year showed higher EBV antibody titers compared to married women, and greater self-reported attachment to one's ex-spouse was also related to higher EBV antibody titers. Men who initiated the divorce/separation showed lower EBV antibody titers compared to men who did not initiate the divorce/separation. This work provided the first evidence for biobehavioral mechanisms that could explain prior observations linking divorce to poor health [23]. However, except for a small study showing elevated salivary cortisol in the evening and higher cortisol during a dexamethasone suppression test in women undergoing divorce/separation compared to women in stable marriages, research on neuroendocrine and immune correlates of marital dissolution were non-existent in the late 1990's and during the 2000's. Instead, the directional arrow briefly turned towards testing associations between physiological responses to problem discussions early in marriage and separation/divorce later in the marriage.

Motivated by work that used couples' psychophysiological responses to viewing previous problem discussions to predict divorce six years later [47], Kiecolt-Glaser examined links between neuroendocrine responses in her sample of 90 newlywed couples and marital status outcomes 10 years later [48]. With 100 % retention of the newlywed sample after 10 years, out of 90 couples, 17 couples had divorced (11 within the first 4 years of marriage). Rather than using newlywed measures to predict later divorce, which would have been prohibitive given the sample size and base rate of divorce, Kiecolt-Glaser focused on identifying differences in measures during the first year of marriage between intact vs. eventually divorced couples.[1] Intact vs. divorced couples did not differ in baseline sociodemographic or relationship characteristics (dating or cohabitation before marriage), marital satisfaction, time talking during the problem discussion task, hostile personality, or mood during the baseline newlywed visit. Regarding behaviors, husbands who eventually divorced showed greater probability of responding to wives' hostile behavior with one's own hostile behavior compared to husbands in intact marriages (no differences for women); and no other differences were observed related to other negative or positive behaviors during the problem discussion.

Regarding physiology, in couples who eventually divorced, circulating epinephrine was 34 % higher during the problem discussion compared to those who stayed married. In addition, a group × gender interaction for ACTH showed that wives who eventually divorced had higher ACTH compared to wives who stayed married; no differences were observed between husbands that eventually divorced or those in intact marriages. No differences in circulating norepinephrine, cardiovascular reactivity, or cortisol were observed during the problem discussion. Most likely reflecting the experience of being in a hospital unit for 24 h together, differences in daytime and overnight epinephrine were 22 % and 16 % higher, respectively, for couples who eventually divorced compared to those that stayed married. No differences were observed for daytime norepinephrine (though overnight norepinephrine was 16 % higher in eventually divorced couples) and cortisol.

Since the initial studies in the 1980s, research on divorce and mortality showed the most growth over the decades, in part because marital status is regularly recorded in large epidemiological studies. Indeed, in the most recent meta-analysis of divorce and mortality involving 104 studies across 24 countries, and over 600 million respondents, divorce was related to a 30 % higher risk for mortality [49]. Theory and data continue to accumulate regarding mechanisms linking divorce to later poor health [50], and moderators that can help explain why some people are resilient in the face of this major life stressor, and why others are more vulnerable [51]. The challenges of long-term follow-up in samples of couples with behavioral and biological data early in marriage have limited the corpus of research predicting divorce from physiological responses. One notable example collected cardiovascular and cortisol responses to a problem discussion in a sample of 68 couples participating in randomized trial of relationship distress prevention program [52]. The researchers also collected a measure of f_0 (fundamental frequency), which corresponds to pitch in the human voice. A higher f_0, and a greater range of f_0 in recorded speech is related to higher emotional arousal, with small positive correlations with cardiovascular and cortisol reactivity during marital discussions [53]. Using statistical approaches specifically designed to prospectively test risk, Kliem et al. [52] predicted divorce status in the sample (22 couples divorced [32.5 %] after 11 years) and time to divorce. For wives, higher f_0 range during problem discussions predicted greater risk for divorce, and for husbands, higher baseline heart rate and larger increases in cortisol during discussion predicted greater risk for divorce (all were medium effect sizes, controlling for intervention condition). Coded behaviors did not predict divorce, and no measures predicted time to divorce. Thus, much like the intriguing Kiecolt-Glaser finding from the previous decade, objective physiological markers collected from couples during problem discussions were systematically related to divorce outcomes.

4. Suggested directions for "notching" inspired by Kiecolt-Glaser's work

Arborists can promote the growth of a new fruit tree branch by making a small cut in the bark just above a bud, known as "notching." In this final section I suggest specific directions for notching new branches based on Kiecolt-Glaser's work. Loneliness and social isolation are now recognized as a public health concern [54]. Main effect associations with depression [55] and mortality, and mixed findings with biological mechanisms like inflammation described earlier, suggest that the next branches in research on loneliness, biological mechanisms, and health should focus on "when" and "for whom" questions as well as moving from identifying biological mechanisms to intervention targets. Work by Kiecolt-Glaser's group provided insights into "when" [stress exposures combined with pathogen exposure, 17] and "for whom" [persons with lower resting parasympathetic activity, 19]. Additional "for whom" factors may also include individuals who experienced exposure to early social adversity (socioeconomic and/or interpersonal), and "where" factors - structural factors that may impact social, microbial, and chemical exposures [56–58]. Ultimately, if inflammation continues to be a mechanism that explains why the "when," "for whom," and "where" factors increase risk for poor health in persons reporting high loneliness,

[1] Kiecolt-Glaser et al. (2003) also reported differences between couples that were highly satisfied vs. less satisfied at 10-year follow-up, but for brevity those findings are not reviewed here.

future work should consider focusing on those specific populations when testing behavioral and pharmacological interventions that can reduce inflammation [59].

Another "notch" involves findings from our meta-analysis on marital quality and health [24] that diverged from Kiecolt-Glaser's conclusions of larger effects for women compared to men in her 2001 review [60]. In studies with a larger proportion of women in the sample, the effect size for better marital quality and better health was larger (though this effect was $p = .051$). However, in studies that directly tested gender differences in the association between marital quality and health, gender differences were not statistically significant (34 studies, $p = .12$). Findings for cardiovascular reactivity and HPA axis responses were also equivocal. That being said, in seven out of the 34 health outcome studies that reported statistically significant gender differences, five studies found larger effects for women compared to men. Moreover, associations between marital quality and cardiovascular disease-related surrogate endpoints (e.g., blood pressure) were larger for women compared to men.

In addition to transparency and providing meta-analytic synthesis of the literature, my primary motivations for highlighting those findings in the 2014 review was to draw attention to two key points: 1) Having adequate power to test gender differences, in light of the observed effect sizes and the need to test a statistical interaction [61], requires very large sample sizes (>1500); and 2) Most importantly, that the field would benefit by moving from testing binary gender differences to focusing on gender-related moderators that exist along a continuum. Indeed, one of the major contributions of Kiecolt-Glaser and Newton [60] was drawing attention to gender-related self-representations, traits, and roles as moderators of links between marital functioning and health. Wanic and Kulik [62] highlighted power differentials in society and within relationships as an alternative moderator. My hope was that our 2014 review would encourage greater adoption of the constructs identified by Kiecolt-Glaser and Newton [60] and Wanic and Kulik [62] in future relationships and health research.

While that hope has not yet been fulfilled, I note that measuring gender-related moderators like self-representations, traits, roles, and power differentials in future intimate relationships and health research has multiple benefits that extend beyond increasing statistical power. First, androgen and estrogen hormones have been traditionally excluded from most human PNE/PNI research [63], due in part to logistical barriers (additional assay costs, the potential requirement of multiple samples to capture estradiol and progesterone fluctuations across the menstrual phase) and the exclusion of female animals in preclinical research [64,65]. Incorporating gender-related constructs alongside sex hormone measurements can help disentangle the contributions of culture, societal structure, and biology that are oversimplified and conflated when relying on the gender binary as an independent variable or covariate [66]. Second, moving beyond the gender binary allows for a more inclusive science of relationships and health – namely allowing sexual and gender diverse couples to contribute to the larger corpus of data generated almost exclusively from opposite-sex, heterosexual, White middle-class couples [67,68]. Finally, because the antecedents of gender-linked self-representations, traits, roles, and power dynamics are rooted in culture, incorporating these constructs can enable diversifying the cultures and identities that are included in the science of relationships and health.

5. Concluding comments

This contribution to the Festschrift issue celebrating Janice Kiecolt-Glaser's career focused on the "seed" studies planted in the 1980s that identified key PNE and PNI foundations for research on loneliness, close relationships, and health. In addition, Kiecolt-Glaser's work in these domains represented major conceptual and methodological advances in studying stress exposures (everyday, ubiquitous stress exposures like examination stress and relationship conflict), prescient methods that eventually became widespread decades later (inflammatory markers), fascinating findings on physiological responses to conflict discussions in the first year of marriage and associations with later divorce, and importantly demonstrated plausible health-relevant biological mechanisms in humans (inflammation and wound healing, metabolic responses to high-fat meals, intestinal permeability). Along the way, Kiecolt-Glaser and her research group made important conceptual contributions to how loneliness interacts with other "when" and "for whom" factors to influence health, and how gender-linked constructs may explain observed gender differences in the links between marital functioning, physiology, and health. Increased empirical attention to the latter has the potential to grow more diverse and inclusive orchards of research on social relationships, PNE, PNI, and health.

CRediT authorship contribution statement

Theodore F. Robles: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

None.

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