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Invited minireview

Psychoneuroimmunology and health psychology: An integrative model

Susan K. Lutgendorf * and Erin S. Costanzo

Department of Psychology, University of Iowa, E11 Seashore Hall, Iowa City, Iowa 52242, USA

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Abstract

The biopsychosocial model describes interactions between psychosocial and biological factors in the etiology and progression of disease. How an individual interprets and responds to the environment determines responses to stress, influences health behaviors, contributes to the neuroendocrine and immune response, and may ultimately affect health outcomes. Health psychology interventions are designed to modulate the stress response and improve health behaviors by teaching individuals more adaptive methods of interpreting life challenges and more effective coping responses. These interactions are discussed in the context of aging.

1. Introduction

In 1977 George Engel published a landmark article in *Science* in which he argued that biological factors such as genetics do not account for all health outcomes; rather, a proper understanding of the etiology and progression of disease must take into account the interactions of psychological and social factors along with biological processes (Engel, 1977). Health psychology is the domain of psychology predicated on Engel's ''biopsychosocial model'' and encompasses domains such as effects of psychological and social factors on disease risk, prevention, treatment compliance, morbidity, quality of life, and survival. Psychoneuroimmunology provides an understanding of some of the fundamental mechanisms involved in the biopsychosocial model.

Psychological and social factors are thought to influence disease processes via two main mechanisms, *psychosocial processes* and *health behaviors*. Psychosocial processes include factors that affect interpretation of and response to life events and stressors, such as mental health and mood factors, personality characteristics, and resources such as social relationships. Health behaviors such as exercise, nutrition, and smoking serve as indirect pathways by which psychosocial processes can influence health, as they may be strongly influenced by factors such as mood (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). Fig. 1 provides a model illustrating the interaction of psychosocial and biological factors as conceptualized in the biopsychosocial model.

Within the domains of psychosocial processes (A) and health behaviors (C), there are factors that are thought to serve as resources, by enhancing resistance (e.g., social support, exercise) and factors that are thought to increase vulnerability (e.g., depression, cigarette smoking). These factors can be acute (e.g., temporary lack of sleep before writing a grant) or chronic (e.g., caregiving for a chronically ill spouse). According to the biopsychosocial model, these psychosocial factors interact with a person's biological characteristics (B: e.g., genetics, constitution) to create a vulnerability to disease processes (G) (Engel, 1977). Moreover, according to this model, the genetic predisposition to develop a disease (B; also called a diathesis) may remain latent unless a

* Corresponding author. Fax: 1-319-335-0191.
E-mail address: susan-lutgendorf@uiowa.edu (S.K. Lutgendorf).

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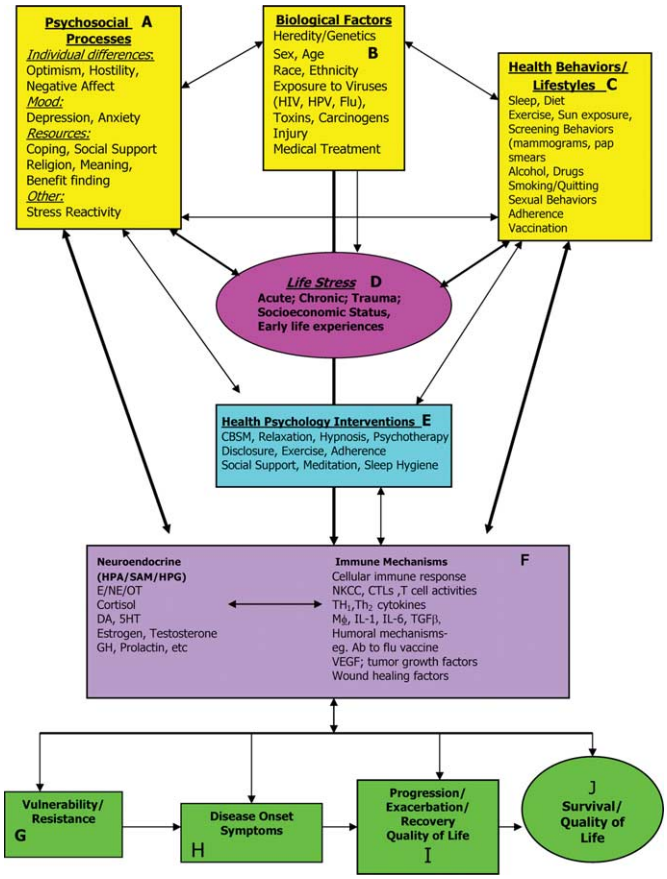

Fig. 1. The figure illustrates the Biopsychosocial Model. The interaction between psychosocial processes (Box A), biological factors (Box B), and health behaviors (Box C) leads to a vulnerability (or resistance) to illness (Box G), disease onset and symptoms (Box H), progression, exacerbation, recovery, with concomitant quality of life (Box I), and survival with concomitant quality of life (Box J) via processes involving neuroendocrine and immune mechanisms (Box F). Effects of life stress (Box D) are filtered through psychosocial processes (Box A) and health behaviors (Box C) in their resultant effects on downstream mechanisms. Health psychology interventions (Box E) can modulate effects of psychosocial processes and health behaviors on neuroendocrine and immune mechanisms and on resultant health outcomes. There are also pathways between biobehavioral factors and disease outcomes not involving neuroendocrine or immune mechanisms, but other pathways are not included in this figure. Psychosocial processes (A) encompass psychological and social factors, particularly those that involve interpretation of and response to life stressors. These include personality variables (e.g., optimism, hostility, and negative affect), mental health and mood variables (e.g., depression and anxiety), coping, social support, spirituality, and sense of meaning. Health behaviors (C) include drug and alcohol use, smoking, sleep, nutrition, exercise, adherence to medical regimens, physical examinations, risk screenings, and risky sexual behaviors, among others. Health psychology interventions (E) can be used to alter psychosocial processes (A: e.g., decrease depression, increase coping) or improve health behaviors (C: e.g., smoking cessation) to provide a more positive influence on neuroendocrine and immune factors and perhaps slow disease progression/exacerbation. Interventions include cognitive behavioral stress management (CBSM), relaxation, hypnosis, meditation, emotional disclosure, adherence-based interventions, sleep hygiene, exercise, social support groups, psychotherapy, imagery, distraction, behavioral pain management, yoga, massage, biofeedback, drug/alcohol prevention/rehabilitation, psychotherapy, and behavioral conditioning. These interventions can be used at all points of the trajectory of the disease or condition. Box F shows selected mechanisms involved in the bi-directional interactions between neuroendocrine and immune axes that mediate the relationships between biobehavioral factors (A–D) and disease outcomes (G–J). This by no means is an all-inclusive list of mechanisms, but it represents some of the commonly studied factors in this literature. Once vulnerability (G) has been established, continued interaction with positive or negative psychosocial factors (A: e.g., depression/social support), disease factors (B), adaptive/maladaptive health behaviors (C) and stress (D) will contribute to expression (or lack thereof) of disease symptoms (H), disease free intervals/progression/exacerbation, and quality of life (e.g., functional, physical, emotional, and social well-being) (I), and survival (J). HPA: Hypothalamic pituitary adrenocortical axis, SAM: sympathoadrenomedullary axis, HPG: hypophyseal pituitary gonadal axis, OT: oxytocin, DA: Dopamine; 5HT: seratonin; GH: growth hormone; NKCC: Natural killer cell cytotoxicity; CTLs: cytotoxic lymphocytes; M_ϕ: macrophage; IL-1: interleukin 1, IL-6: interleukin 6; TGFβ: transforming growth factor beta; Ab: antibody; and VEGF: vascular endothelial growth factor.

certain level of life stress is present, in which case the disease may become manifest. Effects of stress (D) are mediated through psychological processes (A) such as one's perception of the severity of the stress and one's ability to respond to the stressor (Lazarus & Folkman, 1984). Furthermore, the perception of social support may contribute to experiencing a stressor as less overwhelming, and thus may inhibit neuroendocrine reactivity (F) (Seeman & McEwen, 1996). Neuroendocrine and immune responses to stress (F) will have downstream effects on health, depending on the chronicity of the stress and the underlying biological makeup of the individual (B) (Chrousos, 1992). There may be a limited range within which psychosocial factors are able to influence biological processes; the extent of this influence is still unclear (Cohen & Rabin, 1998).

Interactions between psychosocial and immunologic factors are relevant to a variety of diseases including inflammatory diseases, cardiovascular disease, infectious diseases, cancer, diabetes, osteoporosis, muscle wasting, and multiple sclerosis, and processes such as wound healing, surgical recovery, and efficacy of vaccination (Chrousos, 1992; Kiecolt-Glaser et al., 2002). There are many non-immune interactive pathways as well; however, we will limit this review to pathways mediated by immune and neuroendocrine processes.

The hypothalamic pituitary adrenocortical (HPA) and sympathoadrenomedullary (SAM) axes are thought to be primary pathways by which psychosocial processes and health behaviors impact the immune mechanisms illustrated in Fig. 1. Both axes are responsive to stress and may become dysregulated under conditions of chronic stress (Chrousos, 1992). Modulation of these stress response systems by psychosocial resources (A) or interventions (E) may decrease the burden or allostatic load placed on the host by the stress response (Seeman & McEwen, 1996), allowing for normalization of neuroendocrine and immune function.

Health psychology has developed a number of behavioral interventions (E) that help participants improve health behaviors, increase social support, and alleviate depression and anxiety. Participants learn to adopt more adaptive methods of interpreting life challenges and more effective coping responses (see figure caption for enumeration of interventions). Interventions may be administered in individual or group settings; they vary from a single session to 10 or more weeks, and may require home practice. One commonly used intervention is cognitive behavioral stress management (CBSM), frequently administered in a 10-week group-based format. Participants learn to manage stress by (a) increasing awareness of stress and tension in their bodies, (b) learning how to appraise stress and cope with stress more adaptively, and (c) learning specific relaxation techniques. The group setting also provides participants with social support (Antoni, 2002).

Below, we will illustrate the relevance of PNI for health psychology in the context of aging. Because of the immune decrements characteristic of aging, interactions among the components of our model may be particularly relevant to the health and well-being of older adults.

2. Age-related alterations in immune and neuroendocrine functioning

Aging is typically associated with alterations in immunocompetence, including decreased signaling and regulatory abilities of T cells, decreased lymphocyte response to mitogens and cytokines, and dysregulation of B cells, resulting in elevated levels of auto-antibodies and diminished production of antibodies to exogenous antigen (Guidi et al., 1998). Decreased, unchanged, and increased natural killer (NK) cell cytotoxicity have all been reported in older adults (Guidi et al., 1998). In addition, production and utilization of cytokines is altered with aging. An age-related shift from a Th-1 type cytokine response to a Th-2 type response has been reported, with decreased Th-1 cytokines such as interleukin-2 (IL-2) and interferon gamma (IFNγ) along with increased levels of interleukin-4 (IL-4), a Th-2 cytokine (Han & Meydani, 2002). It has been suggested that the Th-1 to Th-2 shift may contribute to increased susceptibility to infectious illness among older adults (Ouyang et al., 2000).

In addition, higher levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and interleukin-1β (IL-1β), have been reported in older adults (Han & Meydani, 2002). IL-6 is of fundamental importance in the elderly as it contributes to the pathogenesis of a variety of age-related conditions including osteoporosis, cancer, cardiovascular disease, stroke, arthritis, and dementia (Kiecolt-Glaser et al., 2002). IL-6 becomes increasingly dysregulated with age and levels rise in the elderly; IL-6 dysregulation and associated chronic inflammation also contribute to muscle wasting, slower muscle repair, frailty, and disability in the elderly (Kiecolt-Glaser et al., 2002).

These immune alterations (F) may have relevance for susceptibility to disease (G) and survival (I). For example, deficits in cell-mediated immunity served as a robust prospective predictor of morbidity and mortality in 273 older adults over the subsequent 10 years with an age-adjusted hazard ratio of 1.89 (95% CI: 0.94, 3.79) for all cause mortality (Wayne, Rhyne, Garry, & Goodwin, 1990). In a large community sample of older adults, elevations in a single assessment of plasma IL-6 ($>$3.19 pg/mL) was related to a two-fold greater risk of all cause mortality over the subsequent 4–6 years (Harris et al., 1999).

Aging is also associated with changes in function and regulation of the hypothalamic–pituitary–adrenal (HPA) axis, including higher basal cortisol levels, a flattened diurnal slope of both ACTH and cortisol (Deuschle et al., 1997) reduced responsivity of the HPA axis to acute stress and to feedback, and slower neuroendocrine recovery from stress (Sapolsky, Krey, & McEwen, 1986). The net effect of these changes in older adults may be sustained presence of stress hormones long after a stressor has terminated, thus prolonging its potential immunomodulating effects. Individual differences in neuroendocrine response patterns are thought to influence overall patterns of health and aging (Seeman & McEwen, 1996).

3. Psychosocial correlates of immune and endocrine functioning

3.1. Vulnerability factors

There is marked individual variation in age-related immune alterations. It has been proposed that individual differences in psychosocial factors (A) may account for some of the variability observed in the immune response among the elderly (Kiecolt-Glaser et al., 2002). The stress of caring for a spouse who has Alzheimer's disease has been frequently used as a model of chronic severe stress in the elderly, and has been linked to a host of immune impairments, including decreased NK response to IFNγ and IL-2, poorer lymphoproliferative response to mitogens, unpaired antibody response to influenza vaccine, poorer responses to delayed hypersensitivity skin testing, higher levels of the sympathetic neurotransmitter neuropeptide Y, slower wound healing (summarized in Glaser et al., 2001), and higher levels of IL-6 (Lutgendorf et al., 1999a) (F). Moreover, compared to non-caregivers, dementia caregivers exhibited higher percentages and increased numbers of CD4+ and CD8+ cells expressing the Th-2 cytokine IL-10, whereas no changes in expression of Th-1 cytokines IFNγ or IL-2 in these cells were noted, suggesting a stress-related Th-1 to Th-2 shift. Differences between caregivers and non-caregivers were most pronounced among younger participants, suggesting an interaction between stress and aging in these responses (Glaser et al., 2001). Dementia caregivers also reported more days of infectious illness than non-caregivers (Kiecolt-Glaser et al., 2002).

Vitaliano and colleagues studied the interactive effects of Alzheimer's caregiving stress and a history of cancer on immune function among older adults (Vitaliano et al., 1998). Although no one factor (caregiving, perceived stress, or cancer history) independently predicted NK cell activity, at study entry, caregivers with a cancer history had lower NK cell activity than non-caregivers with a cancer history and individuals (caregivers or non-caregivers) who had never had cancer. Furthermore, among caregivers with a cancer history, greater perceived stress prospectively predicted lower NK cell activity 15–18 months later. These findings indicate the importance of considering interactions between stress and aging in the context of the additional vulnerability that may be conferred by an individual's medical history.

Repetitive patterns of short-term negative emotions also are thought to constitute chronic stressors (Kiecolt-Glaser et al., 2002). Among older married women, but not among their husbands, escalation of negative behaviors during a 30-min martial conflict discussion was related to a greater rate of increase in neuroendocrine stress hormones. Both husbands and wives who showed more negative behavior during the conflict session, or reported that their usual marital agreements were more negative, demonstrated poorer responses to three functional immune assays. Although the laboratory-based conflict was a short-lived stressful event, there is strong consistency in negative behaviors of couples across a variety of situations. This suggests that behaviors seen in the laboratory may be indicative of longstanding marital difficulties and therefore better characterized as indicative of a chronic stress patterns (Kiecolt-Glaser et al., 2002).

Whereas many studies have now examined effects of severe chronic stress in older adults, there are few studies of moderate, controllable stress in this population. Healthy independent older adults anticipating voluntary relocation of their primary residence have been shown to have poorer NK cell activity one month before relocation compared to non-moving elders (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey, & Lubaroff, 1999b). Levels of IL-6 among women anticipating housing relocation were not significantly different than those of healthy non-moving controls; however both of these groups had significantly lower IL-6 than women who were dementia caregivers (Lutgendorf et al., 1999a). Furthermore, the mean IL-6 level of dementia caregivers in this study was almost double the 3.19 pg/mL previously associated with higher mortality risk (Harris et al., 1999). These findings suggest that that there may be a "dose–response" effect of stress on immune changes in older adults.

Little research has examined immune recovery from stress among the elderly. Kiecolt-Glaser and colleagues found little evidence of immune adaptation to the chronic stress of dementia caregiving, but rather found consistent decrements in several measures of functional immunity over time (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Moreover, several years following the death or placement of the dementia patient, former caregivers continue to exhibit poorer NK responses to stimulatory cytokines and do not differ from current caregivers in their humoral and cell-medi-

ated responses to influenza vaccine (Glaser et al., 2001). These findings suggest poor immune recovery among older adults who have experienced severe chronic stress.

Depression is a risk factor for myocardial infarction, osteoporosis, declines in physical functioning, and mortality, and has been associated with an impaired immune response in the elderly in several studies (Kiecolt-Glaser et al., 2002). These include declines in IL-2 stimulated NK cytotoxicity, poorer T cell response to the mitogen phytohemmaglutinin (PHA), and poorer stimulated production of IL-2, IL-4, and IFNγ among depressed older adults (Guidi et al., 1991). Even chronic, mild depressive symptoms in older adults have been associated with impaired immune function, including consistently poorer T cell responses to two mitogens during an 18-month period. The poorest immune responses were seen in older adults over 72 years of age who reported depressive symptoms (McGuire, Kiecolt-Glaser, & Glaser, 2002). These findings suggest that even mild mood alterations may be associated with immune impairments in the elderly, and that these effects appear to be stronger with increasing age.

The interactions among stress, age, and health outcomes are perhaps most readily tested in vaccine models. Whereas vaccination (C) prevents influenza in 70–90% of younger adults, less than 50% of healthy older adults develop an adequate antibody response following vaccination and only 30% of older adults demonstrate adequate specific cytotoxic lymphocyte activity to influenza vaccine (Bernstein et al., 1999). Poorer response to vaccination is associated with greater incidence of influenza and other illnesses (Kiecolt-Glaser et al., 2002). Chronic stress further impairs age-related decrements in the immune response to influenza vaccine. Two studies have now shown that Alzheimer's caregivers were less likely to mount an adequate fourfold antibody response to influenza virus following vaccination (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Vedhara et al., 1999) and also showed poorer in vitro cytokine responses to influenza virus than non-stressed older adults (Kiecolt-Glaser et al., 1996). Impaired antibody levels were accompanied by higher mean diurnal salivary cortisol concentrations in caregivers over a 6-month post-vaccination period, with higher cortisol levels related to poorer antibody response to one virus strain at 14 days post-immunization (Vedhara et al., 1999). Differences between caregivers and non-caregivers in antibody response to vaccine were greatest among individuals over age 70, suggesting greater vulnerability to stress with increasing age, even among the elderly (Kiecolt-Glaser et al., 1996).

Associations between stress and the immune response to influenza vaccine have also been noted among older adults with more moderate stress. In a community sample of older adults who had recently received influenza vaccination, perceived stress was related to decreased antibody titers to influenza vaccine and decreased IL-2 response to in vitro stimulation by influenza virus (Kohut, 2002). Among healthy, previously vaccinated older adults 1 month before vaccination, those who reported greater mood disturbance had poorer in vitro IFNγ responses to live influenza virus and vaccine stimulation, whereas those with greater optimism had greater stimulated IFNγ responses (Costanzo et al., under review). Taken together, these findings suggest that interactions between mood (A), age-related processes (B), health behaviors (e.g., vaccination) (C), and moderate or severe stress (D), may be associated with the robustness of the immune response to vaccination (F). The next step of this line of investigation is to examine whether such stress-related immune decrements contribute to greater vulnerability to influenza (G).

3.2. Protective psychosocial factors

There has been relatively little examination of immune and neuroendocrine correlates of health protective factors such as social support, optimism, and adaptive coping in the elderly. In epidemiological studies of mortality, high levels of social support have been consistently and robustly associated with diminished risk for morbidity and mortality, over and above standard medical risk factors (Seeman & McEwen, 1996). Among elderly Alzheimer's caregivers, higher levels of social support at the beginning of a longitudinal study were prospectively associated with less impairment across three measures of functional immunity 1 year later (Kiecolt-Glaser et al., 2002). Among both current and former Alzheimer's caregivers, those with higher levels of social support had a more robust stimulated NK cell response (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). In a MacArthur study of healthy older adults, older men with higher levels of emotional social support had lower levels of 12-h overnight urinary cortisol, norepinephrine, and epinephrine, adjusting for health-related covariates and age. Although these associations were not seen in women, married women had lower levels of epinephrine (Seeman & McEwen, 1996). As higher neuroendocrine levels have been associated with poorer cognitive and physical functioning among the elderly, these findings suggest the intriguing possibility that social support may have some protective effects on health and cognition, particularly among elderly men (Seeman & McEwen, 1996).

Other psychosocial resources (A) such active coping strategies and a sense of meaning appear to be important for older adults, particularly during times of stress. For example, use of active coping was associated with a greater lymphoproliferative response to PHA and Con A among older adults with high levels of perceived stress, but not among older adults with low

levels of stress (Stowell, Kiecolt-Glaser, & Glaser, 2001). Among older adults anticipating housing relocation, a greater sense of coherence, defined as seeing life situations as meaningful challenges that could be successfully mastered, was associated with higher NK cell activity. In contrast, among non-movers, who were not facing a stressful life event, sense of coherence was not related to NK cell activity (Lutgendorf et al., 1999b), suggesting that this factor may be most important for older adults when they are actively facing a stressor.

There have been few studies of older adults examining psychosocial factors, neuroendocrine or immune mediators, and a health or survival outcome in the same investigation. These types of studies are extremely difficult and can be best done with prospective longitudinal research and relatively large samples. In one such investigation, religious attendance (A) in a sample of 557 older adults was prospectively related to improved survival (J) over the subsequent 12 years. Structural equation modeling indicated that levels of IL-6 assessed in year 6 of the study (F) mediated the prospective relationship between religious attendance and mortality, independent of covariates including age, sex, health behaviors, chronic illness, social support, and depression. These findings are consistent with the interpretation that among older adults (B), the psychosocial factor of religious attendance (A) may contribute to lower levels of IL-6 (or processes for which IL-6 is a proxy) (F), which subsequently affects survival (Lutgendorf, Russell, Ullrich, Harris, & Wallace, under review). This type of prospective model, including psychosocial factors, neuroendocrine or immune mediation, and disease or survival outcomes, is necessary for establishing the clinical significance of relationships observed between psychosocial variables and immunity in the elderly.

The findings that positive psychosocial factors may buffer stress-related immune decrements in the elderly have implications for the development of psychosocial interventions to enhance immunity in older adults. Few studies have examined effects of health psychology interventions on the immune response among older adults. In one such study, Kiecolt-Glaser and colleagues found that a 6-week relaxation intervention enhanced NK cell activity as compared to social contact or assessment only control groups. However, relaxation was only effective while it was being practiced, and 6 weeks following the intervention, the NK cell activity of the relaxers was commensurate with that of the other groups (Kiecolt-Glaser et al., 2002). This documentation of a post-intervention drop in NK cell activity highlights the importance of establishing ways for older adults to incorporate new behaviors in an ongoing fashion post-intervention for continued immune support. More recently, Irwin and colleagues found that older adults participating in a 16-week behavioral Tai Chi Chih intervention with components including exercise, breathing, and balance, produced increases in the memory T cell response to the varicella virus as compared to wait-list controls (Irwin, Pike, Cole, & Oxman, in press). In contrast, 6 months of moderate aerobic exercise training in the elderly produced only very modest immune changes, including slightly improved T-cell response to mitogens (Woods, Lowder, & Keylock, 2002). The authors proposed the possible importance of testing more prolonged exercise training in older adults.

4. Methodological considerations

It should be noted that many older adults have a variety of medical conditions and that medications frequently used in this age group (e.g., β-adrenergic blocking agents, hormone replacement therapy (HRT) may have some effects on the immune response (Kiecolt-Glaser et al., 2002). Based on practical considerations for obtaining a representative sample of patients, most studies have chosen to exclude only diseases and medications that would present the most severe confounds, with the possible limitation that all potential factors contributing to reported outcomes are not assessed. Practical issues such as this must be taken into account in addressing health psychology questions in older populations. It should also be noted that due to practical considerations to reduce patient burden, much of the aging research has been done with self-report measures, and thus findings may be limited by lack of objective verification of levels of affective distress, well-being, or illness. Third, investigations examining the complex interactions detailed in Fig. 1 may require advanced statistical models such as structural equation modeling or hierarchical linear modeling to capture the subtleties of the phenomena being examined.

5. Conclusions and future directions

Health psychology-PNI research among older adults is still in its early stages. This is an extremely promising area, as stress appears to compound age-related immune decrements. In contrast, resource factors appear to buffer stress-related decrements in the immune response and modulate neuroendocrine function. Behavioral interventions may be able to enhance aspects of the immune response in the elderly. Little is known concerning the extent to which older adults can recover immunologically from moderate and severe stressors, and little is known about possible mediating pathways such as effects of stress on sleep in the elderly, with potential downstream effects on immunity. Furthermore, most of this research has been correla-

tional. Future research would benefit from health psychology-PNI intervention studies with manipulation of variables such as social support, adaptive coping, or physical exercise to enable examination of direct effects on the immune response. In addition, understanding of which interventions are most acceptable to older adults and most likely to be incorporated into lifestyle changes appears fundamental for maintenance of any immune effects. It cannot be assumed that because there is an effect on the immune response there is also an effect on disease processes. To this end, it will be important for health psychology research to test the entire biopsychosocial model, including psychosocial factors, immune and endocrine mechanisms, and disease outcomes, in a longitudinal design in order to elucidate the complex interactions among these components and to understand their relevance for health outcomes.

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