# Chapter 22
# Emotion, Interventions, and Immunity

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## 22.1   Introduction

Psychological stress can alter one's immune function and increase susceptibility to physical disease [1–3]. It can be assumed that negative life events (stressors) lead to negative affective states (distress), producing alterations in human immunity [4]. For example, an individual's emotional states, such as anxiety or depression, can be key factors in triggering immune alterations [4, 5].

Anxiety and depression are associated with disease recurrence in patients with genital and oral herpes [6]. Emotional factors are also thought to play roles in numerous diseases, including Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, asthma, and diabetes [7]. Immunosuppression has been reported in human subjects who experience symptoms of anxiety and depression in response to situations such as examinations, bereavement, separation, and divorce [8–14]. In animals, immunosuppression has also been demonstrated in response to a variety of stressors [8, 15, 16].

Stress-reducing interventions such as relaxation may enhance immune function [17]. However, little is known about the effects on immune function of different coping styles or interventions in healthy individuals or in patients with emotional disorders. Herein, the author is going to review the effects of coping methods and interventions such as relaxation, meditation, cognitive behavioral therapy, psychotherapy, and pharmacotherapy on immune function, as well as the relationship between stress or emotion and immunity.

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## 22.2   Stress and Immunity

Academic stress, such as an examination period for medical students, has long been used as a model for investigating the interaction between stress and immunity. A number of studies using this model have indicated that examination stress down-regulates immune functions such as lymphocyte proliferation, natural killer (NK) cell activity, salivary immunoglobulin A (IgA), latency of herpes virus and Epstein-Barr virus, production of interferon-γ (IFN-γ), interleukin-2 (IL-2) receptor gene expression, and mucosal wound healing [18–27]. In contrast, immune activation has been reported in response to examination stress in other studies. For example, salivary immunoglobulin A (IgA) levels were reported to be enhanced in students during an acute stress of an imminent examination [28]. The levels of phytohemagglutinin (PHA)-stimulated IL-2 production and lymphocyte proliferative responses to PHA were also shown to be significantly higher during an examination period than during a non-examination period [29–31]. Similarly, in another study, students with reactions to examination stress had significantly higher numbers of leukocytes, neutrophils, and monocytes during the examination period than those without stress reactions [32]. Such activated immune response may be associated with the intensity and/or duration of stress [15]. Mild, brief, and controllable states of challenged homeostasis may actually be perceived as pleasant or exciting, which could be positive stimuli for emotional and intellectual growth and development. Immune response may also be enhanced when the stressful condition is mild to moderate in intensity [15]. In contrast, more severe, protracted, and uncontrollable situations of psychological and physical distress are likely to lead to overt disease states [33], apparently resulting from immunosuppression. Therefore, immune activation can be considered to be a transient phenomenon that occurs prior to the downregulation of the immune function, which reflects the body's defensive response to stress [34]. It is also possible that arousal/hypervigilance associated with examinations play a role in activating immunity. From these perspectives, immune activation may be a biological signal warning an impending danger to health, as well as the body's physiological defense against stress.

Stress also modulates inflammatory responses [35, 36]. Previous research has suggested that psychological stressors or perceived stress levels are associated with increased production of proinflammatory cytokines, such as IL-1, IL-6, tumor necrosis factor-α (TNF-α), and IFN-γ [37–40]. In addition, a meta-analytic study found that brief stressors such as academic examinations changed the profile of cytokine production via a decrease in levels of IFN-γ and increases in levels of IL-6 and IL-10 [41]. However, one previous study reported reduced lipopolysaccharide (LPS)-stimulated expression of proinflammatory cytokines, such as IL-6 and TNF-α [42]. This is in line with the finding of Koh et al.'s study [43] in which only PHA was used to stimulate lymphocytes and reduced IL-6 production levels were found during an academic stress period. These differences might depend on cognitive stress appraisals such as the perceived levels of challenge or threat, control expectancy [42], and the intensity and duration of stressors or coping ability [31, 44]. Koh et al. [43] also reported that

vacation associated with low stress is more likely to have a counterstress effect on proinflammatory cytokines (e.g., IL-6 and TNF-α production) than on an anti-inflammatory cytokine (e.g., IL-10 production) and that a stressor may affect changes in immune function independently of self-reported stress.

## 22.3   Emotion and Immunity

### 22.3.1   *Depression and Immunity*

Many studies have suggested that depressed patients exhibit decreased immune functions in a variety of immune measures when compared to nondepressed controls [45–48]. Examinations of the impact of depression on T cell responses in humans found that, in the context of bereavement or severe major depressive disorder, proliferation of peripheral blood mononuclear cells in response to the T cell mitogens, PHA and concanavalin A (Con A), was significantly reduced [8, 45, 49–51]. The degree of immunosuppression may be related to the severity of the depression in depressive disorders [48]. Lymphocyte responses to PHA and pokeweed mitogen (PWM) in patients with melancholic and psychotic depression were significantly lower than those with minor depression [52]. Compared to patients with non-melancholic depression, patients with melancholia demonstrated reduced in vivo cell-mediated immunity as assessed by delayed-type hypersensitivity skin responses [53].

Although there have been both successful and unsuccessful replication attempts, meta-analyses in this area have reached a consensus that reliable decreases in T cell responses are observed in depressed individuals [54, 55]. In addition, in vivo measures of cell-mediated immune function including skin responses to commonly encountered antigens have suggested decreased T cell activity in depressed patients [53].

The mechanisms of T cell alterations in depression in humans have yet to be established. However, a number of possibilities have been identified. Interestingly, flow cytometric assessments revealed that CD4+ T cells from depressed patients exhibit evidence of accelerated spontaneous apoptosis as well as increased expression of the receptor for Fas (CD95), which mediates apoptotic signaling by Fas ligand [56–58]. One possibility that might explain increased T cell apoptosis in depression, especially in the context of increased immune activation, is tryptophan depletion. A number of cytokines and cytokine signaling pathways have been known to activate the enzyme, indoleamine 2,3-dioxygenase (IDO), which breaks down tryptophan into kynurenine, thus depleting serotonin [59, 60]. Activations of both IDO and kynurenine have in turn been associated with the development of depression [59, 61, 62]. Relevant to T cell apoptosis, tryptophan is an essential proliferative stimulus for effector T cells, and in a tryptophan-deprived environment, T cells undergo apoptosis [63, 64].

Another mechanism that has been considered regarding T cell responses in major depressive disorder is inhibition of T cell function by glucocorticoids. Glucocorticoids have multiple effects on immune responses including inhibition of inflammation, mediation of cell trafficking, and induction of apoptosis in multiple immune cell types including T cells [65]. In addition, increased peripheral blood concentrations of the glucocorticoids (cortisol) are a hallmark of major depressive disorder [66]. Nevertheless, no relationships have been found between increased cortisol secretion and decreased in vitro proliferative responses to T cell mitogens in depressed patients [67]. Moreover, several studies demonstrated that peripheral blood lymphocytes from depressed patients exhibit decreased responsiveness to the in vitro inhibitory effects of glucocorticoids on T cell proliferation [66, 68, 69]. Such decreased responsiveness of peripheral blood lymphocytes, including T cells, to glucocorticoids in depressed patients may be related to decreased expression of glucocorticoid receptors [66, 69].

An additional potential mechanism whereby T cell function may be impaired in patients with depression is the disruption of T cell function by inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), which is elevated in depressed patients [70]. For example, both in vitro and in vivo studies demonstrated that chronic exposure of T cells to TNF-α decreases T cell proliferation and cytokine production [71, 72]. In addition, depression enhances the production of proinflammatory cytokines, including IL-6 [73–75]. There is growing evidence that the production of proinflammatory cytokines stimulated by depression can influence a spectrum of conditions associated with aging, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, periodontal disease, frailty, and functional decline [76]. Therefore, depression can downregulate the cellular immune response; as a consequence, processes such as prolonged infection and delayed wound healing that fuel sustained proinflammatory cytokine production may be promoted by depression [76].

Several genes that play roles in T cell function are associated with major depressive disorder and responses to antidepressants [77]. Single nucleotide polymorphisms (SNPs) in the genes PSMB4 (proteasome beta4 subunit, which is important for antigen processing) and TBX21 (T bet, which is important in T cell differentiation) are associated in a dose-dependent fashion with the likelihood of being diagnosed with depression [77].

On the other hand, activated T cells may play an important neuroprotective role in the context of stress and inflammation [78–80]. For example, generation of autoreactive T cells through immunization with central nervous system (CNS)–specific antigens reverses stress-induced decreases in hippocampal neurogenesis as well as depressive-like behavior in rodents. T regulatory cells may also play a role in depression through the downregulation of chronic inflammatory responses. Based on the hypothesis that T cells may subserve neuroprotective and anti-inflammatory functions during stress and inflammation, impaired T cell function may directly contribute to the development of depression. Further elucidation of T cell pathology may lead to new insights into immune system contributions to depression. Moreover, enhancement of T cell function may represent an alternative strategy to treat depression [81].

## 22.3.2  Anxiety and Immunity

It was observed that a group of subjects with generalized anxiety disorder, panic disorder, or both had a higher frequency of upper respiratory infection compared with controls [82]. Recurrent lesions of genital herpes were preceded by higher levels of anxiety and concomitant blunting of T cell blastogenesis [24]. In another study, lymphocyte response was negatively correlated with anxiety among hospitalized patients [83]. A 72-h stimulation with anti-CD3+ induced significantly lower expression of CD25+ in generalized anxiety disorder patients compared to controls [84]. In addition, patients with panic disorder had significantly lower levels of CD4+ than healthy controls and depressive disorder patients [85]. Koh et al.'s study [86] found a reduced cell-mediated immune function (e.g., lymphocyte proliferative response to PHA and IL-2 production) in patients with anxiety disorders compared to normal controls. However, lymphocyte proliferative response to mitogens varies within a wide range; decreased, normal, and increased responses have been observed in panic disorder patients compared with normal controls [87–91]. IgA levels are increased in panic disorder patients compared to normal controls [92].

Patients with obsessive-compulsive disorder do not differ from normal controls in plasma concentration of IL-1β, IL-6, soluble IL-6 receptor, sIL-2R, or transferrin receptor [93]. Subjects suffering from posttraumatic stress disorder (PTSD) after a hurricane had lower NK cell activity when compared to normal controls [94]. In another study, however, combat veterans with PTSD had enhanced cell-mediated immunity compared with healthy civilians and servicemen in a test of cell-mediated immunity [95]. Such unexpected findings suggest that the arousal/hypervigilance associated with PTSD may be more influential on immune functioning than the anxiety symptoms which often accompany PTSD.

Anxiety disorders such as panic disorder are accompanied by activation of the hypothalamic-pituitary-adrenal (HPA) axis, which seems to be correlated with the degree of anxiety experienced by patients. On the other hand, decrease of anxiety after alprazolam therapy occurs in concert with normalization of the HPA axis function [89]. In panic disorder, however, there may be dissociations between the HPA axis and immune systems. This hypothesis is supported by the observation that administration of corticotrophin-releasing hormone (CRH) with the ensuing adrenocorticotropic hormone (ACTH)-cortisol hypersecretion failed to modify the lymphocyte proliferative response to PHA [89].

As opposed to a clinical level of anxiety, subclinical anxiety seen in people suffering from familial traumatic injury [96] or medical students during examination stress [97] may be associated with increased immune function (e.g., mitogen-induced lymphocyte proliferation, NK cell activity). Such immune enhancement in subclinical anxiety may be considered a transient phenomenon occurring prior to the downregulation of immune function, reflecting the body's defense against a stressor. Thus, immune alteration depends on clinical or subclinical levels of anxiety and the levels of hypervigilance [34]. In addition, it was reported that subclinical anxiety during an examination period was associated with reduction in proinflammatory cytokines such as TNF-α production [98].

## 22.4    Coping Strategies and Immunity

Coping responses or strategies represent specific actions that people take in order to deal with a given problem or stressor [99]. An individual's coping strategies are known to affect the stress responses [100] such as endocrine and immune functions. A significant negative correlation was reported between an individual's coping style of "comforting cognition" and cortisol response during mental stress [101]. Coping by accepting the reality of stressful situations proved protective for patients with hepatitis B, whereas coping by substance use increased the risk of having an inadequate count of hepatitis B antibody [102]. In the context of personal relationships and immune function, lonelier medical students had lower NK cell activity than students who were not as lonely [103]. Medical students who reported greater social support showed stronger immune response to hepatitis B vaccine than those with less support [104]. In an experimental study, expressing emotionally traumatic events that had not previously been disclosed to others was associated with increased proliferative response to PHA [24].

A few studies reported relationships between coping and immunity in different stress situations and at different perceived stress levels. Law students who were optimistic showed higher numbers of CD4+ cells in less conflictual situations and lower numbers of CD4+ cells in more conflictual situations [105]. However, in another study, higher levels of active coping were significantly related to greater increases in proliferative response to PHA and Con A at high stress levels. In contrast, at low stress levels, active coping was not significantly related to proliferative responses, whereas avoidance was associated with greater proliferative response to Con A [106]. Positive reappraisal and seeking social support were associated with alteration of immune function during chronic stress periods in another previous study; in particular, positive reappraisal was found to reverse stress-induced immune responses [31].

## 22.5    Interventions and Immunity

### 22.5.1    Stress Reduction Interventions and Immunity

Stress management techniques such as relaxation and meditation may affect immune function. It was reported that biofeedback-assisted relaxation training was associated with reductions in tension and anxiety and improvement in phagocytic abilities, such as enhanced neutrophil activation [107]. In another study, a single 20-min session of relaxation training resulted in significant increases in salivary IgA concentrations from the prerelaxation period to the postrelaxation period, in contrast to a non-relaxation control group [108]. Stress reduction has also been shown to diminish inflammatory responses [109, 110]. Koh et al. [111] reported that significant reductions in the change (stress period value minus baseline period value) in
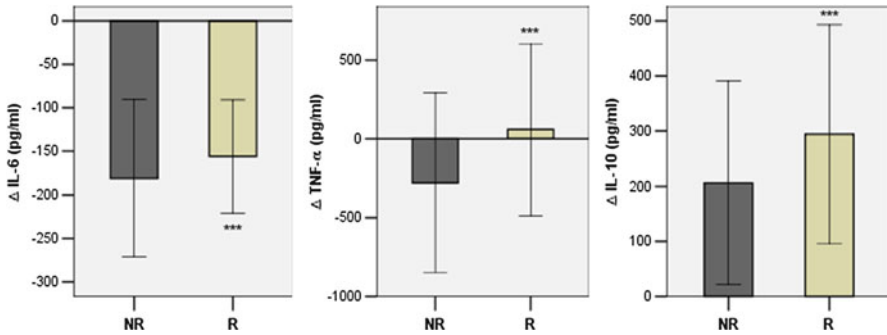
**Fig. 22.1** Effects of relaxation on the changes in proinflammatory and anti-inflammatory cytokine production. *R* relaxation group, *NR* non-relaxation group. ***Significant reductions in the change (stress period value minus baseline period value) in the levels of IL-6 and TNF-α production, but significant enhancement in the change in the level of the IL-10 production in a relaxation group compared with a non-relaxation group (From Koh et al. [111])

the total Global Assessment of Recent Stress score, systolic and diastolic blood pressure, levels of IL-6, and TNF-α production and significant enhancement in the change in the level of the IL-10 production were found in a relaxation group of medical students compared with a non-relaxation group (Fig. 22.1). These results suggest that relaxation is associated with reduction in stress-induced psychological or physiological responses and proinflammatory cytokine alterations but with enhancement in stress-induced anti-inflammatory cytokine alteration. Therefore, relaxation is more likely to have counterstress effect on proinflammatory cytokines than on anti-inflammatory cytokine.

Healthy individuals experiencing job-related stress who participated in mindfulness meditation showed greater antibody responses to the influenza vaccine when compared to a control group [112]. Within the meditation group, increased meditation practice was correlated with decreased stress-induced IL-6. These data suggest that engagement in compassion meditation may reduce stress-induced immune responses [113]. However, one study found that stress reduction techniques such as relaxation did not affect IL-6 levels in healthy individuals [114].

Telomerase activity is a predictor of long-term cellular viability, which decreases with chronic psychological distress [115]. In a study investigating the effects of a 3-month meditation retreat on mononuclear cell telomerase activity, telomerase activity was significantly greater in retreat participants than in controls at the end of the retreat [116].

Stress management techniques may affect immune function in patients with physical diseases. One study of the effects of relaxation on immunity in males at high risk for human immunodeficiency virus (HIV)-1 infection found positive correlations between the frequency of relaxation practice and numbers of T helper cells, T inducer cells, the T helper/T suppressor ratio, and the number of NK cells during the high-stress week of serostatus determination [117]. A study of the effects of relaxation on immunity in HIV-positive men showed that lower stress levels

achieved after relaxation practice were associated with greater decreases in herpes simplex virus type 2 IgG [118]. A randomized study of relaxation, meditation, and hypnosis training in asymptomatic HIV-positive men found improved T cell counts in the treatment group which were maintained at a 1-month follow-up [119]. Geriatric patients who received relaxation training reported decreases in distress symptoms coupled with increased NK cell cytotoxicity and decreased antibody titers to latent herpes simplex virus [120]. In addition, psychological intervention, including relaxation, improved T cell blastogenesis in breast cancer patients [121]. However, it was reported that relaxation and visualization therapy did not affect lymphocyte proliferation in breast cancer patients undergoing radiotherapy [122].

A mindfulness-based stress reduction (MBSR) program that incorporated relaxation, meditation, gentle yoga, and daily home practice also increased NK cell activity in HIV-positive men [123] and buffered CD4+ T lymphocyte declines in HIV-1-infected adults [124]. Over time, women with breast cancer showed enhanced NK cell activity and reduced levels of IL-4 and IL-10 production in the MBSR group compared with the non-MBSR group [125]. In breast and prostate cancer patients, the post-MBSR intervention level of NK cell production of IL-10 and T cell production of IFN-λ were also reduced, whereas T cell production of IL-4 increased when compared to the pre-intervention level [126].

A combined program of light- to moderate-intensity aerobic and resistance exercise offsets the apparent decrement in NK cell activity with weight loss in obese women [127].

On the other hand, Koh and Lew [128] examined the effect of vitamin B complex on academic stress-induced immune alteration in medical students and found that vitamin B complex reduced anxiety levels, but did not affect cell-mediated immunity, such as lymphocyte proliferative response to PHA and PHA-stimulated IL-2 production.

### 22.5.2    Therapeutic Interventions and Immunity

There is consistent support for the efficacy of cognitive behavioral treatment (CBT) to aid the successful discontinuation of benzodiazepine medication in patients with panic disorder and to help maintain treatment gains while not taking medication [129]. However, there are very few studies on the effects of pharmacotherapy and CBT on immune function. One study reported that there was no significant effect of alprazolam therapy on lymphocyte proliferative response to PHA in patients with panic disorder [89]. Patients in the CBT plus paroxetine condition had significantly improved agoraphobic behavior and anxiety discomfort, whereas patients in the CBT plus placebo condition did not [130]. However, the differential efficacy of psychopharmacological treatment versus the combination of this drug with CBT on immunity remains unclear. One study examined the relationship between the reduced anxiety level by therapeutic interventions, such as CBT with an antianxiety agent, and cell-mediated immunity (CMI) in patients with panic disorder. This

study revealed that the reduced level of self-reported anxiety by the combined therapeutic intervention was associated with increased blastogenic response [91].

However, another study reported little effect of psychotherapy in patients with anxiety or depression on immunity. The CD4+/CD8+ ratio remained elevated in a small number of patients with anxiety disorders, but there were no significant changes in this parameter over the 8-week course of inpatient psychotherapy. In addition, no difference in the CD4+/CD8+ ratio was found between depressive patients and healthy controls nor in this parameter over the course of inpatient psychotherapy [131]

Symptom remission may abrogate reduced NK cell activity associated with major depressive disorder [132]. On the other hand, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) appear to promote a return of NK cell number to control levels. However, it is likely that effectiveness is related to the subtype of depressive disorder. It is particularly interesting that although both major depressive disorder and dysthymic disorder were successfully treated with these antidepressants, dysthymic patients required a more prolonged duration of treatment for NK cell numbers to return to control values than major depressive disorder patients. Thus, when assessing the relationship between depression and immune status, it is necessary to recognize not only the severity of illness but also the duration of illness and age of onset.

T cell proliferation in response to PHA and Con A remained stable or increased after psychological intervention (strategies to reduce stress, improve mood, alter health behaviors, and maintain adherence to cancer treatment and care) in patients with breast cancer [133]. In addition, breast cancer patients receiving cognitive behavioral stress management showed greater Th1 cytokine IL-2 and IFN-γ production than the control group [134]. Breast cancer patients who received experiential-existential group psychotherapy also showed lower percentages of NK cells, CD8+ cells, and CD4+ cells and lower proliferative response to PWM when compared to patients in the waiting list control group [135].

## 22.6   Future Directions

Studies that have examined immune activity in somatoform disorder patients are sparse in comparison with those in depressive disorder and anxiety disorder patients. In Koh et al.'s study [136], patients with undifferentiated somatoform disorder as a group showed reduced cell-mediated immunity (e.g., blastogenic responses to PHA) when compared with healthy controls. Moreover, alteration of proinflammatory cytokines can be anticipated in patients with somatoform disorders who often show sickness behavior, because proinflammatory cytokines may trigger a brain-cytokine system that organizes the sickness response [137]. Therefore, further studies are needed to evaluate immunity in somatoform disorder patients.

In order to elucidate the relationship between stress or emotion and immunity, it is necessary to integrate the data related to immune, endocrine, autonomic nervous
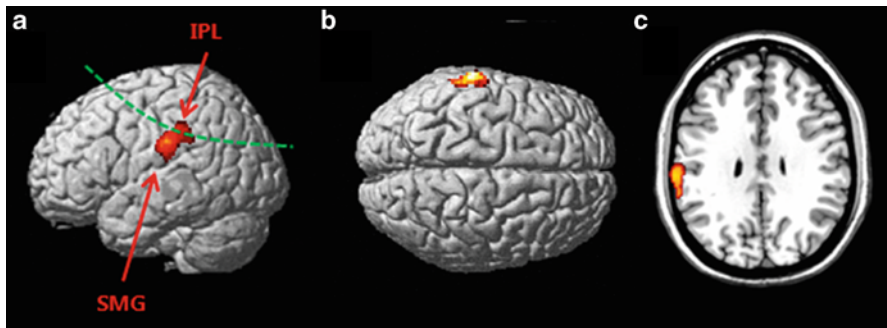
**Fig. 22.2** Hypoperfused brain areas in more immune-suppressed group compared with less immune-suppressed group in surface projection (**a**, **b**) and transaxial plane (**c**). Hypoperfusion was significant at the left inferior parietal lobule (*IPL*) and the left supramarginal gyrus (*SMG*) in more immune-suppressed group compared with less immune-suppressed group (FDR, $p < 0.05$). *FDR* false discovery rate (From Koh et al. [136])

system, and brain activity measured at the same time, because bodily homeostasis can be maintained by interaction between these variables [138]. In particular, these interactions should be examined in a clinical sample including somatoform disorder patients. In a previous study [139], changes in lymphocyte proliferation and NK activity have been associated with negative life events only among individuals with greater left frontal cortical activation. In a recent study on neural activity in patients with undifferentiated somatoform disorder, Koh et al. [136] reported that hypoperfusion was significant at the left inferior parietal lobule and the left supramarginal gyrus in the more immune-suppressed subgroup compared to the less immune-suppressed subgroup (Fig. 22.2). These results also suggest the role of cerebral asymmetry in altered immunity in the patients.

On the other hand, there have been few studies on the relationship between depression and cytokine-related genes, in contrast with a number of studies on the relationship between depression and inflammation-related cytokines or between depression and serotonin-related genes. Therefore, the interaction between depression, cytokines, and genes should be included in the future studies.

In addition, to confirm the interaction between emotion and immune function, the effectiveness of a variety of treatment modalities on immunity should be investigated in a clinical sample of mental disorder or physical disease patients.

## 22.7 Conclusions

Meta-analyses showed statistically reliable decreases in T cell responses in depressed individuals. Patients with anxiety disorders, especially panic disorder, are likely to show reduced immune function, although several studies showed contradictory findings. This literature review reveals evidence that relaxation,

mindfulness-based stress reduction, and cognitive behavioral therapy are effective interventions to counter the effects of stress on immunity. The ability of such interventions to improve immunity has been demonstrated for patients with panic disorder, for HIV-infected men, and for breast cancer patients, as well as for healthy individuals experiencing stress. These results provide a rationale for clinical applications to improve immunity in patients with immune-related disorders. Further studies are needed to examine the effects of a variety of therapeutic interventions on immunity in a larger variety of mental disorders or physical diseases, as well as the long-term effects of treatment on immune function. Research efforts in this area will also add to the body of literature regarding the interactions between emotion and immune function. In particular, the interaction between immune, endocrine, autonomic nervous system, and brain activity should be examined in a clinical sample including somatoform disorder patients. In addition, the interaction between depression, cytokines, and genes should be included in the future studies.

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