

## Rassegne

# Links between immunity and conditions leading to psychotherapy

## *Legami tra immunità e condizioni che conducono alla psicoterapia*

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**SUMMARY. Introduction.** People seeking for psychotherapeutic help present with a variety of conditions including stress, depression, anxiety, and maladaptive individual difference factors. This paper reviews the studies investigating the link between these conditions and immunity. **Findings.** The relationship between stress-related conditions and immunity varies depending on the nature of the stressor. Acute time-limited stressors are associated with an upregulation of natural immunity, brief naturalistic stressors with a shift from cellular to humoral immunity, while long-term and chronic stressors with a decrease in most functional immune measures. Depression is associated with changes in both enumerative and functional immune measures. The most consistent association is with decreased cellular immunity. There is considerable heterogeneity in study findings that may be accounted for by clinical and demographic factors. Only limited evidence has been presented for an association between anxiety and changes in immune function. The results are somewhat inconsistent and no firm conclusions can be drawn from these studies. Relatively few studies investigated the relationship between maladaptive individual difference factors and immunity. Replicated findings include an association between alexithymia and impaired cellular immunity and altered cytokine balance with a shift towards proinflammatory mediators, and a link between Type C and Type C-related coping and HIV progression and impaired immunity. **Conclusions.** Several conditions leading people to psychotherapy are associated with changes in immune function. However, several findings are preliminary and demand replication. Also, most of the evidence is correlational and further studies allowing for causal inferences are needed. Future psychoimmunology studies should better clarify the clinical relevance of the findings.

**KEY WORDS:** psychotherapy, immunity, stress, depression, anxiety, individual difference factors.

**RIASSUNTO. Introduzione.** Le persone che richiedono un trattamento psicoterapeutico presentano una molteplicità di condizioni che comprendono stress, depressione, ansia e tratti di personalità maladattativi. In questo articolo vengono passati in rassegna gli studi che hanno indagato i rapporti tra tali condizioni e le funzioni immunitarie. **Risultati.** La relazione tra condizioni correlate allo stress e immunità varia in base alla natura dello stressor. Gli stressor acuti di durata limitata nel tempo sono associati a un aumento dell'immunità naturale, gli stressor naturalistici brevi a uno spostamento dall'immunità cellulare a quella umorale, mentre gli stressor cronici e di lunga durata nel tempo sono associati a una diminuzione della maggior parte dei parametri funzionali del sistema immunitario. La depressione è associata a cambiamenti nei parametri immunitari sia numerici sia funzionali. L'associazione più costantemente osservata è quella con una riduzione dell'immunità cellulare. È presente una notevole eterogeneità nei risultati degli studi, probabilmente ascrivibile a fattori clinici e demografici. Sono state fornite soltanto evidenze limitate di un'associazione tra ansia e alterazioni del sistema immunitario. I risultati osservati sono variabili e non è possibile trarre conclusioni definitive da tali studi. Relativamente pochi studi hanno indagato la relazione tra funzioni immunitarie e tratti di personalità maladattativi. Tra i risultati che sono stati replicati vi sono un'associazione tra alessitimia e diminuzione dell'immunità cellulare, un'associazione tra alessitimia e alterazione dell'equilibrio delle citochine con sbilanciamento verso i mediatori proinfiammatori, e un'associazione tra stile di coping di Tipo C o correlato al Tipo C, progressione dell'infezione da HIV, e diminuzione della funzionalità immunitaria. **Conclusioni.** Varie condizioni che possono portare le persone a richiedere una psicoterapia si associano a modificazioni della funzionalità del sistema immunitario. Diversi risultati sono tuttavia preliminari e necessitano di essere replicati. Inoltre, la maggior parte delle evidenze proviene da studi non sperimentali, e sono pertanto necessari ulteriori studi che permettano inferenze causali. I futuri studi in ambito psicoimmunologico dovrebbero infine chiarire meglio la rilevanza clinica delle alterazioni osservate.

**PAROLE CHIAVE:** psicoterapia, immunità, stress, depressione, ansia, tratti di personalità maladattativi.

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## INTRODUCTION

People suffering from psychiatric disorders and emotional difficulties may turn to various providers to look for help, especially mental health specialists (1). In mental health settings, psychotherapy is one of the main therapeutic options available for patients suffering from a variety of psychiatric disorders, particularly depressive and anxiety disorders. Also, psychotherapy is often offered to persons seeking help for emotional distress correlated with stressful events and situations or with the presence of maladaptive personality traits and individual differences factors.

The literature contains many hints of an association between altered immune function and several conditions that may lead people to seek for psychotherapeutic help, such as stress-related emotional difficulties, depressive and anxiety states, neuroticism, introversion, trait hostility, propensity to negative affect, attachment insecurity, alexithymia, emotional repression, social inhibition, and maladaptive coping style. This paper aims at presenting an overview of these findings.

## STRESS-RELATED EMOTIONAL DIFFICULTIES

Already in 1936, Selye reported that laboratory animals presented a common response to noxious stimuli such as heat, cold, epinephrine, strenuous muscular exercise, and X-rays, and used the term “stress” to indicate it (2). Stress was defined as “the nonspecific response of the body to any demand”. He termed “stressors” all stimuli able to induce it. Selye first reported alterations to immune organs and cells after stress, such as lymphocytopenia and atrophy of the thymus and other lymphatic structures, with increased morbidity, mortality, and susceptibility to infection.

After this seminal observation, a huge number of subsequent investigations provided detailed knowledge of the mechanisms of the stress response and of possible consequences that result in adaptation of the whole organism to stressors or different disease conditions (3). A major theoretical advance has been the recognition of the role of individual cognitive appraisal of potentially stressful psychosocial stimuli (4,5) and of the role of emotional arousal (6) in respectively moderating and mediating the stress response in humans.

In the past 20 years, compelling evidence that immune function is stress-sensitive has been collected, which suggests that acute or chronic stressful life events may contribute to the pathogenesis of immune-

related diseases (7). Indeed, stressful psychological stimuli can induce modifications in the central nervous system (CNS) (8,9), the autonomic nervous system (ANS) (10), and the neuroendocrine system (11). The neurobiology of psychological stress at all these levels is a key step to the understanding of stress-induced changes in immune function (12).

Clinical and experimental evidence indicates that stress duration and course are the pivotal factors in determining the nature of stress-induced immune changes (13).

Elliot and Eisdorfer (14) characterized various types of stressor according to their duration and course (e.g., discrete vs. continuous). The taxonomy they proposed includes five categories of stressors: acute time-limited stressors, brief naturalistic stressors, stressful events sequences, chronic stressors, and distant stressors. Many independent studies evaluated the correlations between stress arising from each of these different stressors and immune changes. In 2004, this literature has been thoroughly reviewed by Segerstrom and Miller, in a comprehensive meta-analysis (15). **Table 1** summarizes the main findings of this meta-analysis and of the studies published in subsequent years.

### *Acute time-limited stressors*

Studies regarding acute time-limited stressors involved laboratory challenges such as public speaking or mental arithmetics. Similar patterns of immune change across a wide spectrum of durations ranging from 5 though 100 min were found, irrespectively of whether they involved social, cognitive, or experiential stressors.

The most robust finding on cellular populations elicited by acute time-limited stressors was an increase in the number of natural killer (NK) cells and large granular lymphocytes in peripheral blood. Also, a less pronounced increase in the number of T-cytotoxic lymphocytes and neutrophils in peripheral blood was found.

The most notable effect on immunoglobulins was a significant increase in secretory IgA in saliva. This finding is supposed to be due to a relocation of already-synthesized antibody from plasma cells and increased translocation of antibody across the epithelium and into saliva (16), as the time frame of acute stressors evaluated in laboratory studies is too short for the synthesis of a significant amount of new antibody.

In a large number of studies, NK cell cytotoxicity (NKCC) was found to be significantly increased after

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**Table 1. Significant (p<.05) findings from Segerstrom and Miller (15) meta-analysis of stress-associated immune changes with comments based on the results of recent studies**

	<b>Acute stress</b>	<b>Brief naturalistic stress</b>	<b>Stressful event sequences</b>	<b>Chronic stress</b>	<b>Distant stress</b>
Cellular populations	<ul style="list-style-type: none"> <li>↑ leukocytes (r=.17)</li> <li>↑ neutrophils (r=.30)</li> <li>↑ NK cells (r=.43)</li> <li>↑ lymphocytes (r=.18)</li> <li>↑ large granular lymphocytes (r=.53)</li> <li>↑ T-cytotoxic lymphocytes (r=.20)</li> </ul>	<ul style="list-style-type: none"> <li>↑ leukocytes (r=.20)</li> </ul>	<ul style="list-style-type: none"> <li>↑ NK cells (r=.17)</li> </ul>		
Immunoglobulin	<ul style="list-style-type: none"> <li>↑ secretory IgA in saliva (r=.22)</li> </ul>	<ul style="list-style-type: none"> <li>↑ AB to EBV (r=.20)</li> </ul>	<ul style="list-style-type: none"> <li>↑ AB to EBV (r=.21)</li> </ul>	<ul style="list-style-type: none"> <li>↓ AB to influenza after vaccination (r=-.22)</li> </ul>	
Functional effect	<ul style="list-style-type: none"> <li>↑ NK cytotoxicity (r=.30)</li> <li>↓ mitogen-stimulated proliferative response</li> </ul>	<ul style="list-style-type: none"> <li>↓ lymphocyte proliferation to ConA (r=-.32)</li> <li>↓ lymphocyte proliferation to PHA (r=-.19)</li> <li>↓ NK cytotoxicity (r=-.11)</li> </ul>		<ul style="list-style-type: none"> <li>↓ NK cytotoxicity (r=-.12)</li> <li>↓ lymphocyte proliferation to ConA (r=-.13)</li> <li>↓ lymphocyte proliferation to PHA (r=-.16)</li> </ul>	
Cytokine	<ul style="list-style-type: none"> <li>↑ IL-6 (r=.28)</li> <li>↑ IFN<math>\gamma</math> (r=.21)</li> </ul>	<ul style="list-style-type: none"> <li>↓ IFN<math>\gamma</math> (r=-.30)</li> <li>↑ IL-6 (r=.26)</li> <li>↑ IL-10 (r=.41)</li> </ul>		<ul style="list-style-type: none"> <li>↓ IL-2 (r=-.21)</li> </ul>	
Comments	<ul style="list-style-type: none"> <li>upregulation of natural immunity;</li> <li>downregulation of specific immunity</li> <li>retention of less mature T cells within lymphoid tissue or skin and mobilization of effector-type T cells into the blood (20)</li> <li>inconsistent findings from recent studies (21,22)</li> </ul>	<ul style="list-style-type: none"> <li>shift from cellular (Th1) to humoral (Th2) immunity; effect more pronounced in older ages</li> </ul>	<ul style="list-style-type: none"> <li>no robust pattern of immune changes when considered as a whole; according to stressor's nature:                             <ul style="list-style-type: none"> <li>loss of a spouse: ↓ NK cytotoxicity</li> <li>natural disaster victims:                                     <ul style="list-style-type: none"> <li>- ↓ T-helper lymphocytes</li> <li>- ↓ T-cytotoxic lymphocytes</li> <li>- ↑ NK cytotoxicity</li> </ul> </li> <li>↑ lymphocyte proliferation to PHA</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>negative effects on almost all functional measures of the immune system</li> <li>consistent findings from recent studies (i.e. ↓ IgA salivary secretion in caregivers (24); ↓ NK cytotoxicity impairment in unemployed healthy men and women (25))</li> </ul>	<ul style="list-style-type: none"> <li>only NKCC was evaluated and it was found not to be reliably reduced</li> </ul>

Note: AB = antibody; ConA = concanavalin A; EBV = Epstein-Barr virus; IgA = immunoglobulin A; IFN = interferon; IL = interleukin; NK = natural killer cells; NKCC = natural killer cell cytotoxicity; PHA = phytohemagglutinin; r = effect size (Pearson's r; values of .10, .30, and .50 corresponding to small, medium, and large effects)

administration of acute stressors, whereas a decreased lymphocyte proliferation to the mitogens concanavalin A (ConA) and phytohemagglutinin (PHA) was found.

The production of two cytokines, interleukin (IL)-6 and interferon (IFN)- $\gamma$ , was found to be increased significantly following acute stress. This finding may suggest an upregulation of natural immunity as IFN- $\gamma$  stimulates macrophages and NK cells as well as T cells.

Globally, the immune response to acute stress seems to be characterized by an increase in the nonspecific, natural immunity. The only exception is the increased secretion of salivary IgA, a product of the specific immune response. As suggested by some authors, this may be part of a larger nonspecific protein release in the oral cavity in response to acute stress (16). These findings suggest that acute stressors may lead immune cells to redistribute into the compartments in which they will be most effective against invaders (17). These results are also suggestive of an upregulation of natural immunity, which seems to be better suited to managing the potential complications of life-threatening situations than specific immune responses, because it is faster, it is subject to fewer inhibitory constraints, and it requires less energy to be diverted from other bodily systems that support the fight-or-flight response (18,19). Acute psychological stress also seems to promote the retention of less mature T cells within lymphoid tissue or skin and the mobilization of effector-type T cells into the blood in order to be able to rapidly migrate into peripheral tissues (20). Some subsequent studies showed inconsistent findings, with non-significant changes in the lymphocyte subsets (21), in phagocytic activity of neutrophils and monocytes, serum immunoglobulins, or C3 and C4 complement (22).

#### *Brief naturalistic stressors*

Brief naturalistic stressors, such as academic examinations, involve a person confronting a real-life short-term challenge.

Stress due to brief naturalistic stressors seems not to affect the number or percentage of cells in peripheral blood. The most significant findings regarding immunity were an increased antibody production to latent virus, particularly Epstein-Barr virus (EBV), and a decrease in NKCC and in lymphocyte proliferative response to ConA and PHA.

In many studies exposition to brief stressors was also associated to a change in the profile of cytokine production via a decrease in a IFN $\gamma$  levels (a Th1-type cytokine) and an increase in the Th2-type cytokines IL-6 and IL-10, both indicating a global shift from cellular (Th1) to humoral (Th2) immunity.

Seegerstrom and Miller (15) noted that age contributed to vulnerability to stress-related immune change during brief naturalistic stressors, with a more pronounced effect in older subjects.

#### *Stressful event sequences*

In stressful event sequences, a focal event gives rise to a series of related challenges. The studies on stressful event sequences can be divided into two groups: bereavement and trauma. A large number of studies evaluated immune changes in widows and widowers after the death of their spouse, while a smaller number of studies investigated immune function in natural disasters victims.

Interestingly, no robust pattern of immune changes was found other than an increase of NK cell number in peripheral blood, when groups were considered as a whole. With regards to the first group alone, the most consistent finding was a decline in NKCC, whereas no alterations were found in lymphocyte proliferative response to ConA, PHA, and Pokeweed Mitogen (PWM) or in the number of T-helper or T-cytotoxic lymphocytes in peripheral blood. Studies evaluating natural disaster victims found an increase in NKCC and PHA-stimulated lymphocyte proliferation, as well as a decrease in the number of T-helper lymphocytes and T-cytotoxic lymphocytes (15).

The different results regarding loss and trauma seem to mirror the neuroendocrine effects of these two types of adverse events. While bereavement is commonly associated with increased cortisol production (10), trauma and post-traumatic stress disorder are commonly associated with decreased cortisol production (23). As cortisol suppresses immune processes such as NKCC, the different neuroendocrine correlates of loss and trauma event sequences may explain their dissimilar effects on immunity (15). Also, the differences in the immune response to acute and chronic stressors suggest that another possible explanation for the dissimilar effects of trauma and loss on immunity may rest on the different time frame of these stressors and of the studies investigating their immune correlates. Traumatic events are acute, time-limited stressors, while bereavement is both an acute and a long-term stressor as the pain of grief renews itself everyday for a long time. Also, most psychoimmunological studies of disaster victims have been carried out within a short time period after the event, whereas studies of bereaved individuals have often been carried out several months after loss.

### *Chronic stressors*

Chronic stressors are stable and tend to deeply affect a person's life. They are also usually scarcely controllable, and afford less hope for control in the future. Typical chronic stressors include suffering a traumatic injury that leads to physical disability, or providing care for a spouse with severe dementia. Chronic stressors are typically associated with changes in identity or social roles (e.g., acquiring the role of caregiver or refugee, or losing the working role). Chronic stressors have been the object of a large number of studies and were not found to have any systematic relationship with enumerative immune measures. On the other hand, they did have negative effects on almost all functional measures of the immune system, on both natural and specific immunity, as both Th1 (e.g., T cell proliferative responses) and Th2 (e.g., antibody to influenza vaccine) parameters were found to be negatively affected. Most chronic stressors were associated with global immunosuppression, with a shift from potentially adaptive to potentially detrimental changes, initially in cellular immunity and then in immune function more broadly (15). Recent studies corroborated these findings, with reduced IgA salivary secretion in caregivers (24), and persistent NK cytotoxicity impairment in unemployed healthy men and women (25).

### *Distant stressors*

Distant stressors, such as having been sexually assaulted as a child, or having been a prisoner of war, are traumatic experiences that occurred in the distant past yet have the potential to continue modifying immune function because of their long-lasting cognitive and emotional sequelae (26). The only immune correlate that has been examined regularly in the scientific literature is NKCC, which was found not to be reliably reduced in persons who report a distant traumatic experience.

On the whole, different kinds of stress seem to affect immune function differently. Acute time-limited stressors, which may have a minor role in determining seek for psychotherapeutic help, are associated with an upregulation of natural immunity and downregulation of specific immunity. Brief naturalistic stressors are associated with a shift from cellular (Th1) to humoral (Th2) immunity. Also, while stressful event sequences, when considered as a whole, seem to be associated with no robust pattern of immune changes, chronic stressors have negative effects on almost all functional measures of the immune system.

## **DEPRESSION**

In the last 20 years, an increasing body of evidence has shown that depressive disorders are associated with alterations in immune function (27), including both enumerative measures and functional parameters. Results seem to suggest a noteworthy heterogeneity in clinical findings that may be accounted for by moderating clinical and biological factors, such as age, gender, comorbidity and clinical features of depression (**Table 2**).

### *Depression and immune system parameters*

The impact of depression on immune function has been the object of a large number of studies. A relatively recent, comprehensive meta-analysis of over 180 studies described various immunological changes in individuals affected by major depressive disorder (28). With regard to cell populations, a fixed-effect analysis revealed an increase in the total number of white blood cells and in the number and percentage of neutrophils, as well as a decrease in the number and percentage of lymphocytes. Absolute NK and relative T-cell levels were found to be decreased, whereas relative B-cell levels, CD4 levels, CD4/CD8 ratio and levels of cells bearing activation markers, such as HLA-DR<sup>+</sup> and CD25<sup>+</sup>, were increased.

A significant association was also found between depression and lower proliferative responses of lymphocytes to the mitogens PHA, Con A and PWM (28). Also, neutrophil phagocytosis and NKCC were found to be reduced, with the second one now viewed as one of the most reliable immune alterations found in this disorder (28,29).

A general decrease in total serum protein levels was found in depression, accompanied by a decrease in the negative acute phase plasma protein albumin. In contrast, serum levels of the positive acute phase plasma proteins haptoglobin,  $\alpha$ 1-acid glycoprotein, and  $\alpha$ 1-antitrypsin were found to be increased. Circulating levels of IgM, PGF2, IL-6, and sIL-2r were also elevated (28).

Most studies have suggested that depression results in reduction of nonspecific cellular and natural immunity (27). However, Maes et al. (30) found an increase in levels of cells bearing activation markers (i.e., HLA DR<sup>+</sup> and CD25<sup>+</sup>) and in humoral factors of plasma proteins associated with the acute phase of the immune response, and an elevation of IL-6 blood levels; these findings, typically associated with inflammatory processes, may confirm the hypothesis that major depression is associated with an immune activation reminiscent of an acute phase response.

**Table 2. Immune changes found during depression**

	<b>Cellular populations</b>	<b>Immunoglobulin</b>	<b>Functional effect</b>	<b>Cytokine</b>	<b>Other</b>
Depression	<ul style="list-style-type: none"> <li>↑ leukocytes</li> <li>↑ neutrophils</li> <li>↓ NK</li> <li>↓ T-cells</li> <li>↑ B-cells</li> <li>↑ CD4</li> <li>↑ CD4/CD8 ratio</li> <li>↑ HLA DR<sup>+</sup></li> <li>↑ CD25<sup>+</sup></li> </ul>	<ul style="list-style-type: none"> <li>↑ IgM</li> </ul>	<ul style="list-style-type: none"> <li>↓ response to ConA</li> <li>↓ response to PHA</li> <li>↓ response to PWM</li> <li>↓ neutrophil phagocytosis</li> <li>↓ NK cytotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>↑ IL-2</li> <li>↑ IL-6</li> <li>↑ sIL-2r</li> </ul>	<ul style="list-style-type: none"> <li>↓ total serum protein levels</li> <li>↓ albumin</li> <li>↑ haptoglobin</li> <li>↑ α1-acid glycoprotein</li> <li>↑ α1-antitrypsin</li> </ul>
<i>Clinical moderating factors</i>					
Age	no age-related CD4 change in depressed patients vs. age-related increase in healthy subjects		no age-related mitogen response change in depressed patients vs. age-related increase in healthy subjects		more immune alterations in older compared with younger depressed subjects
Sex	depressed men: ↓ in NK & T-cells vs. women				
Panic comorbidity	↑ T cells in depressed subjects with panic		↑ response to PHA in depressed subjects with panic		
Alcohol dependence and abuse			↑ NK cytotoxicity in depressives with alcohol abuse or dependence		
Cigarette smoking	↑ leukocytes in depressed smokers compared with nonsmokers		↓ NK cytotoxicity in depressed smokers compared with nonsmokers		
<i>Depression clinical features</i>					
Hospitalization			↓ mitogen response in hospitalized patients		
Melancholia			↓ mitogen response and NK cytotoxicity in patients with melancholia	impaired DTH response in patients with melancholia	

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*(continua)* **Table 2. Immune changes found during depression**

	<b>Cellular populations</b>	<b>Immunoglobulin</b>	<b>Functional effect</b>	<b>Cytokine</b>	<b>Other</b>
Sleep disturbances			<ul style="list-style-type: none"> <li>↓ NK cytotoxicity in depressed subjects with subjective insomnia</li> <li>↓ cellular &amp; natural immune function in depressed subjects with lesser sleep duration and efficiency</li> </ul>	<ul style="list-style-type: none"> <li>↑ IL-6 in depressed subjects with sleep disturbances</li> </ul>	
Severity (HDRS)			<ul style="list-style-type: none"> <li>↓ response to ConA and PHA in severe depression</li> </ul>		<ul style="list-style-type: none"> <li>NK activity was correlated with HDRS “retardation” and “sleep disturbance” symptom clusters</li> </ul>
Tricyclic antidepressant treatment	<ul style="list-style-type: none"> <li>↓ circulating lymphocytes</li> <li>↓ T cells</li> <li>↓ CD4</li> <li>↓ CD29</li> </ul>		<ul style="list-style-type: none"> <li>↑ NK activity</li> <li>↓ response to ConA</li> <li>↓ response to PHA</li> </ul>		
Other antidepressant treatment			<ul style="list-style-type: none"> <li>↑ NK activity in subjects treated with fluoxetine, nefazodone, paroxetine, venlafaxine and sertraline</li> </ul>		

Note: ConA = concanavalin A; DTH = delayed type hypersensitivity; HDRS = Hamilton Depression Rating Scale; IgM = immunoglobulin M; IFN = interferon; IL = interleukin; NK = natural killer cells; PHA = phytohemagglutinin; PWM = pokeweed; sIL-2r = plasma soluble interleukin-2 receptor

On the whole, depression seems to be associated with a decrease in NK responses in some patients, and an increase of inflammatory markers in other patients (31).

#### *Possible moderators of the relationship between depression and immunity*

In their meta-analysis, Zorrilla et al. (28) pointed out that a considerable heterogeneity in the results was observed for virtually all major immune cell class and functional measures. While no definite explanations of this heterogeneity are available (32), several clinical and biological factors may moderate the link between depression and immunity and account, at least in part, for the lack of consistency in results (27).

As regards demographic factors, age might be a moderator of the association between depression and immunity (31). Older depressed patients seem to have more immune alterations than younger depressed subjects (29,33). In one study, healthy subjects displayed an age-related increase in T4 cell number and in mitogen-induced lymphocyte proliferation, while depressed patients did not show any age-related change in these immune parameters (34).

With regard to gender, depressed men showed a major decline of T cell and NK cell response when compared to healthy men, while depressed women did not significantly differ from their healthy counterparts (35).

Health-related behaviors such as drinking and smoking may also play a role in modulating immune response in depressed subjects. Dual diagnosis of either alcohol abuse and secondary depression or depression with a history of alcohol abuse was associated with a further decrease in NK activity when compared with depressed patients or non-depressed alcoholics (36). Hence, alcohol and depression were found to show an additive effect on NK activity. However, a more recent study did not confirm these findings (37). Cigarette smoking is also supposed to have an influence on immunity in depressed subjects, with depressed smokers showing higher number of white blood cells than depressed nonsmokers and control nonsmokers and smokers, and lower values of NK activity compared with controls. The study authors stated that major depression and smoking interact and together contribute to an elevation of total WBC count and a decline of NK activity (38).

Further, several clinical variables seem to influence immune measures and moderate the association between depression and changes in enumerative and functional measures of immunity. For instance, de-

pressed subjects with comorbidity for panic disorder (PD) were found to have greater number of T cells and increased lymphocyte proliferative response to PHA than depressed patients without panic disorder (39).

Also, mitogen response seems to be decreased in hospitalized depressed patients when compared with outpatients (40). While some studies did not corroborate this finding (34), a meta-analysis confirmed the association between inpatient status and mitogen response in depressed patients (33).

Depressed patients with melancholia were found to have greater impairment in cellular immunity, such as decreased mitogen-induced lymphocyte proliferation and NK activity, when compared with nonmelancholic patients (30,41). Depressed patients with melancholic features showed also impaired delayed type hypersensitivity skin responses as compared with nonmelancholic patients (42).

In depressed patients, subjective insomnia seems to be correlated with a decrease in NK activity (43); also, patients with more severe sleep disturbance appear to be at greater risk for elevated IL-6 levels and other proinflammatory markers (44). Likewise, in studies that evaluated sleep using polysomnography, the decreases in total sleep as well as sleep efficiency were found to be correlated with declines in natural and cellular immune function among depressed patients (32).

Severity of depression, as measured by the Hamilton Depression Rating Scale (HDRS) total score, was found to be associated with lower lymphocyte proliferative response to ConA and PHA, independently of gender, age, and inpatient status (34). However, other studies did not show a correlation between severity of depression and NK cell number or activity (36). Only retardation and sleep disturbances among depressive symptoms appeared to be correlated with NK activity (45).

Pharmacological treatment of depression seems also to affect immune response in depressed subjects. Two studies specifically investigated the effect on immune parameters of symptom reduction due to antidepressant treatment. Improvement with tricyclic antidepressant treatment was found to be associated with an increase in NK activity (46), a decrease in T cells, CD4, and CD29, decreased responses to PHA and ConA but not PWM (47). Also, treatment with the antidepressants fluoxetine (48), nefazodone, paroxetine, sertraline and venlafaxine (49) was associated with enhanced NK activity along with changes in depressive symptoms. Together, these data suggest that it is the resolution of depressive symptoms, rather than simply medication taking, that may result in improvements in lymphocyte proliferative response and NK activity (27).



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**ANXIETY**

There is only limited evidence regarding the effects of anxiety on the immune system, and the results are somehow contradictory. The main findings are summarized in **Table 3**.

In one study, anxiety was found to correlate negatively with lymphocyte proliferative response in hospitalized patients (50). In another study (51), untreated patients with anxiety disorders showed significantly reduced lymphocyte proliferative response to PHA, and reduced PHA-induced IL-2 production, when compared with normal controls. However, no significant difference was found in NK cytotoxicity between the two groups. Other authors found lowered salivary IgA levels in nurses who suffered from anxiety when compared with nurses without anxiety (52). Similar findings have also been reported in dental students (53). Also, subjects with higher anxiety levels were found to have a significantly lower lymphocyte proliferative response to mitogen ConA, as well as lower levels of circulating IL-1 $\beta$ , as compared with less anxious subjects (54). In a pilot study, patients with anxiety disorders showed higher ratio of CD4 versus CD8 lymphocytes compared to healthy controls, mainly attributed to a reduced count in CD8 (55).

On the other hand, a few studies suggest that anxiety may be associated with increased immune function. Scores on the Symptom Checklist-90-Revised (SCL-90-R) anxiety subscale, during an examination period in medical college students, showed a positive correlation with NK cell activity (56). In another study on medical college students two weeks before examination, a positive correlation was also observed between scores on the SCL-90-R anxiety subscale and IL-2 production (57). These findings seem to suggest

that subclinical anxiety may be associated with increased immune function (56), as opposed to a clinical level of anxiety. Such immune enhancement in subclinical anxiety may be explained as a transient phenomenon indicating the body's defense to a stressor.

When referring to specific anxiety disorders, no significant immunological changes were found in individuals suffering from Panic Disorder (PD). This applies both to enumerative (58) and functional measurements (58,59).

There are only sparse suggestions that immunity may be altered in PD (60). Such alterations may have been difficult to detect, as most studies measured immune parameters by using a single evaluation at a given time point during the course of the disorder (60). However, a recent study trying to evaluate cytokine and acute phase proteins in PD patients with 35% CO<sub>2</sub> inhalation-induced panic did not show significant differences between patients and healthy subjects (61).

Similarly, subjects with a diagnosis of Social Phobia (SP) showed similar immunological parameters when compared with normal subjects (62). Only in patients affected by Post-Traumatic Stress Disorder (PTSD) decreased white blood cell counts and increased NK cell activity were found (63).

Given these results, it is noteworthy that neither in PD nor in SP there is consistent evidence of hypothalamic-pituitary-adrenal (HPA) axis dysregulation (64,65). In contrast, decreased HPA-axis activity has been found in PTSD (23).

**INDIVIDUAL DIFFERENCE FACTORS**

It is commonly acknowledged that there are large differences in the nature of individuals' responses to similar stressful experiences. While some individuals

**Table 3. Significant findings regarding immune changes and anxiety**

Factor	Findings	No. of studies (sample different than healthy subjects)
Anxiety	↓ lymphocyte response	1 (hospitalized patients)
	↓ salivary IgA	2
	↓ lymphocyte proliferation to ConA	1
	↓ IL-1 $\beta$	1
	↑ NK cell activity	1
	↑ IL-2	1
Anxiety disorders	↓ lymphocyte proliferation to PHA	1 (untreated anxiety disorder patients)
	↓ PHA-induced IL-2	
PTSD	↓ WBC	1
	↑ NK cell activity	1

Note: PTSD = Post-traumatic stress disorder; IgA = immunoglobulin A; ConA = concanavalin A; PHA = phytohemagglutinin; WBC = white blood cells; IL = interleukin

respond with particular changes in affective state, others show no such change or a quite different affective response (66). Indeed, individual difference factors may exert an organizing influence on behavior and physiology, including the immune system (67).

Despite psychoimmunology decades-long interest in stress-induced immune changes and the recognized influence of personality and individual difference factors on physiology as well as on anxious and depressive reactions to stressful stimuli (68), relatively few psychoimmunological studies primarily aimed at investigating the relationship between specific traits and the immune system. The immune correlates of individual difference factors that may lead people to psychotherapy and have been the object of psychoimmunology studies are summarized in **Table 4** and discussed below.

*Neuroticism, negative affectivity, hostility*

The terms “negative affectivity” and “positive affectivity” refer to stable individual differences in the degree to which people report negative and positive mood and emotions, respectively (69). Marsland et al. (70) found that trait negative affectivity was associated with lower antibody response to hepatitis B vaccination. However, it remains to be clarified whether this finding should be ascribed to the presence of distinct negative feelings or to the absence of positive affect. In this regard, it should be noted that Cohen et al. (71) found that positive, but not negative, emotional styles predicted the incidence of upper respiratory infections.

The personality dimension named “neuroticism”, characterized by predisposition to negative affect and impulsiveness (72), seems not to be significantly corre-

**Table 4. Significant findings from selected studies of stable individual difference factors and the immune system. Modified from Segerstrom, et al. (65)**

Factor	Findings	No. of studies (sample different than healthy subjects)
Positive affect	↓ susceptibility to upper respiratory infections	1
Trait positive affect	↑ antibody response to HBV vaccination	1
Trait negative affect	↓ antibody response to HBV vaccination	1
Extroversion	↓ NK cytotoxicity ↓ risk developing cold symptoms	1
Hostility	↑ NK during acute stressor ↑ CD57+ during acute stressor	1+1 (male subjects) 1
Attachment-related avoidance	↓ NK cytotoxicity	1
Repressive style	↑ AB to EBV 2 ↓ monocyte and eosinophil ↓ T cells	1 (clinic patients) 1
Alexythymia	↓ circulating lymphocytes ↓ IL-4 ↑ IL-4  ↓ IL-6 ↓ IL-2 receptor α ↓ HIV-inhibiting MIP-1α β-chemokine ↑ TNF-α	3 1 1 (somatoform disorders) + 1 (patients awaiting endoscopy) 1 (patients awaiting endoscopy) 1 (somatoform disorders) 1 1 (rheumatoid arthritis)
Social inhibition	↑ DTH ↑ risk to develop infectious diseases and cancer ↑ CD4 decline	1 (fibromyalgia, irritable bowel syndrome) 1 (HIV+ homosexual men) 1 (HIV+ homosexual men)
Type C coping	↑ HIV progression ↑ IL-6	2 (HIV+ patients) 1 (HIV+ patients)
Type C-related coping styles	↓ immune function ↑ HIV progression	3 (HIV+ patients)

Note: AB = antibody; DTH = delayed-type hypersensitivity response; HIV+ = Human Immunodeficiency Virus seropositive; NK = Natural Killer cells.

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lated with immune function (73,74), although state negative affect was associated with lower functional immune measures and reduced resistance to rhinovirus (75,76).

Trait hostility, as opposed to agreeableness, is characterized by suspiciousness, mistrust, and the tendency to show interpersonal behaviors such as criticism and disapproval. During exposure to acute stressors, hostility was found to be associated with increases in NK cell number (77) and CD57+ cell count (78). Another study reported significant correlations between hostility and increase in NK cell count in men, though not in women (74).

*Attachment style*

Attachment theory (79) postulates that human beings are born with a disposition to form and maintain some key social bonds that are crucial for survival and health from early infancy to old age. Each individual displays a distinct attachment style that reflects individual differences in emotion regulation and in perceptions of and beliefs about self and significant others. This style is an enduring trait which starts developing in childhood, based on the child's relationship with the primary caregiver, and then it influences and is shaped by committed romantic relationships during adolescence and adulthood. Two dimensions, called attachment-related anxiety and avoidance, underlie adult attachment style. Individuals with secure attachment display relatively low levels of these dimensions, and they tend to see themselves as valued and worthy of affection, and to see their partner as trustworthy, dependable, and available for support when needed. Insecure attachment is characterized by high attachment-related anxiety, avoidance, or both. The persons with high attachment-related anxiety tend to be preoccupied with their romantic relationships, to feel unappreciated, and to worry about insufficient love or abandonment. Individuals with high attachment-related avoidance have difficulties trusting or depending on others, feel uneasy with emotional closeness and intimacy, and are reluctant to ask their partner for support.

There is reason to believe that attachment insecurity is often present in individuals asking for psychotherapeutic help, as it is associated with several mental disorders (80), as well as with impaired emotion regulation, alexithymia (81), and altered autonomic and endocrine reactivity to stress (82,83).

A recent study on 61 female nurses found that attachment-related avoidance was associated with lower NKCC. This association was independent from per-

ceived stress and support, alexithymia, health-related behaviors possibly influencing immunity, and use of anti-inflammatory drugs, tobacco or alcohol. It was also independent from the number of circulating NK cells, which suggests a change in cell functionality (84).

*Repressive style, alexithymia*

Repressive style refers to the inhibition of the negative affective reactions to events (67). Individuals defined as "repressors" may exhibit low manifest levels of anxiety, while showing high autonomic reactivity (85). Repressors showed also higher antibody titers to EBV (86), and reduced monocyte and eosinophil counts (87); also, T-cell counts tended to be low in subjects classified as repressors of negative affect (88).

Alexithymia is a personality construct related to repression and characterized by difficulty in identifying and describing emotions, difficulty in distinguishing between feelings and bodily sensations, poor imaginative processes, and an externally oriented cognitive style (89). A few studies suggested that immune function is impaired in alexithymia (90). Reduced rates of circulating lymphocyte subsets have been described in alexithymic women (91) and men (92). A positive correlation was also found between serum levels of IL-4 and alexithymia in healthy women (93). However, a study on patients with somatoform disorders reported the opposite finding (94). Higher TNF- $\alpha$  concentrations were found in alexithymic patients with rheumatoid arthritis (95). A recent study in 200 HIV-infected outpatients (96) showed a correlation between alexithymia and a decrease in stimulation of production of the HIV-inhibiting  $\beta$ -chemokine MIP-1 $\alpha$ .

Taken together, these findings suggest a link between alexithymia and impaired cellular immunity and altered pro/anti-inflammatory cytokine balance. However, two studies failed to find an association between alexithymia and IL-1 or IL-2 in patients with post-traumatic stress disorder (97) and in medical students in acute stress situations (98).

A recent, still unpublished study (99) investigated the association between alexithymia and circulating levels of cytokines in 68 subjects awaiting routine diagnostic upper endoscopy, controlling for anxiety, depression, and perceived stress. Significantly lower IL-4 and IL-6 concentrations in alexithymic patients were found. This finding further suggests that circulating cytokine profiles differ between alexithymic and non-alexithymic subjects, and it corroborates the notion that alexithymia may be associated with a shift towards pro-inflammatory mediators.

### *Social inhibition*

Social inhibition is a temperamental quality already evident in infancy. Inhibited children tend toward shyness, emotional restraint, and timidity when encountering novel people (100). An elevated activity of the HPA axis has also been observed in such children (101). In later stages of development, socially inhibited individuals seem to show elevated activity in the sympathetic division of the autonomic nervous system when facing social stimuli or stressful situations, as well as under resting conditions (102). It has been proposed that socially inhibited individuals' timidity and withdrawal may constitute a behavioral strategy for down-regulating high levels of autonomic activity by reducing exposure to provocative stimuli (103).

Cole et al. (104) examined the relationship between social inhibition and delayed-type hypersensitivity (DTH) responses to tetanus toxoid in 36 adults with inflammatory bowel disease and fibromyalgia. Under high engagement conditions, socially inhibited individuals showed increased induration in response to intradermal tetanus toxoid. Under low engagement conditions, these individuals showed less pronounced DTH responses that did not differ in magnitude from those of non-inhibited individuals. Cole et al. (105) also evaluated social inhibition in homosexual men, in whom concealment of sexual orientation was associated with an increased risk of infectious disease and cancer, particularly skin cancer. In HIV seropositive homosexual men, concealment was found to be associated with accelerated disease course, including CD4 T-cell decline (106).

### *Coping*

Coping is a psychological construct dealing with the adaptation to a stressor. Adaptation is likely best viewed as a dynamic process, as what is adaptive at one point in time may be less adaptive at another. Temoshok (103) theorized a specific coping pattern, called "Type C" ("cancer-prone") coping, which was first described in patients with malignant melanoma. This behavior pattern is characterized by a failure to recognize internal physical or emotional cues, a lack of emotional expression and communication of emotions and needs, an external focus on the needs and feelings of others, and a façade of normalcy and mental health. Similarly to alexithymia, to which Type C coping shares many features, this maladaptive coping pattern keeps the individual in a chronic state of unrecognized and unaddressed stress, with concomitant dysregulation of homeostatic responses, including inappropriate physiological responses to stressors (103). In a longitu-

dinal study, an association between disease progression in HIV seropositive patients and Type C coping was found (107). Also, a recent study on 200 HIV-infected outpatients reported a correlation between Type C coping and increased blood IL-6 levels (96).

It should be noted that coping styles that are conceptually related to Type C, such as reduced emotional expressiveness and repressive coping, were also found to be associated with decreased immune function and faster disease progression in patients with HIV (108,109).

## **CONCLUSIONS**

In the last decades, research has brought to light complex, reciprocal influences between the mind and the immune system. While the literature linking stress-related emotional difficulties and depression with impaired immune function is impressive, the immunological correlates of anxiety have been relatively unexplored, and only pioneer work has been performed about the relationship between immunity and individual difference factors.

Overall, the literature reviewed here corroborates the notion that our emotional life and the way it unfolds and is regulated is deeply linked to our physiology. While the findings on anxiety and immunity are not uniform, the studies investigating the immune correlates of emotional stress and depressed mood are relatively consistent in indicating an impairment in immune function, especially in cellular immunity. Also, the studies reviewed in this chapter suggest that personality and individual difference factors related to emotion regulation are correlated with immune function and may thus represent a promising avenue of research in psychoimmunology.

However, some words of caution are in order. First, many of the findings reviewed in this paper are preliminary and demand replication.

Second, a causal link between most of the conditions leading people to psychotherapy, impaired immunity, and poorer health is still to be proved. The design of most studies reviewed in this paper was adequate to detect associations between variables, but not to determine if such associations were causal in nature. To elucidate this issue, further studies with a design allowing for robust causal inferences are needed.

Third, the clinical relevance of the alterations in immune function that research has brought to light is still to be determined. Future studies should include not only immune measures but also measures of participants' health status in order to investigate whether the

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described impairments in immune function translate into increased disease susceptibility and poorer health.

We are confident that researchers in psychoimmunology will successfully meet these challenges in the future.

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