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# Psychoneuroimmunology—developments in stress research

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**Summary** Links between the central nervous stress system and peripheral immune cells in lymphoid organs have been detailed through 50 years of intensive research. The brain can interfere with the immune system, where chronic psychological stress inhibits many functions of the immune system. On the other hand, chronic peripheral inflammation—whether mild (during aging and psychological stress) or severe (chronic inflammatory diseases)—clearly interferes with brain function, leading to disease sequelae like fatigue but also to overt psychiatric illness. In recent years, it has been observed that psychological stress can be disease permissive, as in chronic inflammatory diseases, cancer, cardiovascular diseases, acute and chronic viral infections, sepsis, asthma, and others. We recognized that stress reactivity is programmed for a lifetime during a critical period between fetal life and early childhood, which then influences stress behavior and stress responses in adulthood. First phase II clinical studies, e.g., on cognitive behavioral therapy and mind–body therapies (e. g., mindfulness-based stress reduction), are available that show some benefits in stressful human diseases such as breast cancer and others. The field of psychoneuroimmunology has reached a firm ground and invites therapeutic approaches based on Good Clinical Practice phase III multicenter randomized controlled trials to influence stress responses and outcome in chronic illness.

**Keywords** Stress research · Brain · Immune system · Rheumatic disease · Psychoneuroimmunology

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## Introduction

For centuries, stressful life experiences and an individual's psychological state have been known to influence manifestation and course of diseases. In the 1960s, studies were initiated to discover links between psychological stress (brain) and the immune system (periphery) [2, 4, 66, 68, 69]. At the time, it remained obscure how the brain can exert influence on peripheral immune function. While many studies started as black box experiments, where the connecting pathways remained unknown, more than 50 years of intensive investigation uncovered important physiological pathways that connect the brain and the immune system.

The important role of the hypothalamic–pituitary–adrenal axis (HPA axis) was stressed very early after discovery of the anti-inflammatory role of cortisol (and, later, adrenal androgens) [7, 34, 66, 76]. This was supported by studies showing that defects of the HPA axis can even induce chronic inflammatory diseases in animal models [63, 71]. Soon it became clear that the HPA axis played a role in human chronic rheumatic diseases such as rheumatoid arthritis [21, 23].

A second pathway was related to the sympathetic nervous system (SNS), with the two branches of the adrenal medullary system (adrenaline) and sympathetic nerve fibers (noradrenaline), which reach nearly every site in the body [9, 32, 36, 40]. Sympathetic, anti- and proinflammatory effects were observed.

During the 1980s and 1990s, the roles of many more non-adrenal stress hormones, such as growth



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hormone, thyroid gland hormones, hormones of the renin–angiotensin–aldosterone system, and others have been added to the concept of stress-induced immunomodulation [6, 26, 43]. Finally, the parasympathetic nervous system (PSNS) with its major neurotransmitter acetylcholine was observed to play an anti-inflammatory and immunosuppressive role via alpha7 subunit nicotinergic receptors [11, 62]. While the SNS is up-regulated during the stress response, the PSNS is downregulated, so that the anti-inflammatory response of the PSNS is probably missing. Similarly, the hypothalamic–pituitary–gonadal axis is downregulated during stress, which similarly removes anti-inflammatory influences of androgens on immune responses.

While psychological stress mainly starts in the brain to influence these four major downstream hormonal and neuronal pathways and, thereby, the immune system, the immune system can itself influence the brain and the four downstream operators. These *reciprocal influences* were described as immune-neuro-endocrine feedback circuits with short (local in the organ or tissue) and long loops (between organs) [8]. These cybernetic concepts were mainly derived from physiological considerations of a normally functioning body challenged for a short period of time (such as during infection or wounding). However, peripheral inflammatory influence directed towards the central nervous system can be highly unfavorable when it is long standing (chronic). Repeated cytokine injections into humans over weeks induced marked changes of stress responses and behavior [52, 60]. The last 20 years have linked peripheral inflammation with development of major depression and other neurological diseases such as Alzheimer dementia, diseases which are experienced as chronically stressful [25, 59].

Another important concept builds on acute stress versus chronic stress, which changed the understanding of stress-induced immunomodulation by the brain [27]. While long-term stress is generally harmful and immunosuppressive, short-term stress can be protective and immunsupportive, as it prepares the organism to deal with challenges [27]. This interpretation is based on the threats posed to animals and humans during evolutionary history, where short—not long or chronic—psychological stress was a normal factor in daily life.

Based on research performed in the past decades, it seems that *psychological stress can influence pathogenesis and exacerbation of chronic autoimmune-inflammatory rheumatic diseases* such as rheumatoid arthritis, systemic lupus erythematosus, juvenile idiopathic arthritis, and many others [22, 39, 47, 75, 79]. This influence can occur many years before outbreak, shortly before, and during the disease. Most stressful events stimulate the inflammatory process in these chronic inflammatory diseases. One or two concomitant factors can aggravate stress-induced disease flares. The parallel appearance of psychological stress and another proinflammatory factor was called the “two hit model” of stress-induced inflammation in chronic inflammatory diseases [73]. Additionally, recent studies demonstrate that the four major downstream hormonal and neuronal pathways described above show signs of dysfunction in these patients, leading to incomplete stress responses and, consequently, proinflammatory sequelae [74].

It was demonstrated that *stress influences the development and progression of cancer*, which was first confirmed in defined experimental models, where the immunosuppressive influence of stress was strong [5]. The major immune cells suppressed were natural killer cells, cytotoxic T cells, T helper type 1 cells, and macrophages [54]. In the last 10–20 years, researchers tried to carry out studies in humans to reveal an influence of stress on cancer and immune response. Epidemiological and clinical studies have now provided evidence for links between chronic stress, depression, and social isolation on one side and cancer progression on the other [44, 49].

The influence of *stress on the cardiovascular system* is another important aspect of psychoneuroimmunology, because stress-induced inflammation is linked to cardiovascular disease. Furthermore, many other inflammation-related diseases such as obesity, type 2 diabetes mellitus, hypertension, the metabolic syndrome, pain, and others have been linked to chronic stress and are accompanied by an increase in inflammatory factors [18, 45].

Another important concept came from *stressful events in fetal, perinatal, postnatal, and childhood life*, which can have long-term detrimental effects on stress responsivity and disease in later life [67]. In humans, maternal deprivation was linked to later development of cardiovascular disease [51], fetal stressful constraints were linked to the metabolic syndrome and obesity [37], and childhood trauma was positively linked to later appearance of autoimmune diseases [28, 55, 70]. Traumatic events can even lead to transgenerational transmission of physiological, behavioral, and cognitive problems, as well as psychopathology based on changes of the neuroendocrine crosstalk, epigenetic signatures in relevant pathways, alterations in neuroanatomical development, and set-point changes of the immune system [13].

Finally, *stress theories* were presented to explain the influence of acute or chronic stress on health in animals and humans (homeostasis as the basis; [15]). The first theory of Hans Selye mentions the acute stressor that leads to an acute stress response (alarm reaction), which is usually adaptive (stage of resistance) but may, over time, lead to a maladaptive response and breakdown of the HPA axis (stage of exhaustion) [65]. Similarly, the “stress response–allostasis response–allostatic load theory” says that allostatic load can accumulate, and the overexposure to mediators of neural, endocrine, and immune stress can

have adverse effects on various organs leading to disease. Allostatic load over a lifetime may cause the allostatic systems to wear out or become exhausted, which then leads to chronic disease [48].

The cognitive activation theory of stress is based on coping concepts, where chronic activation in the absence of coping can lead to stress-related diseases (summarized in [77]). This theory also links recurring subjective health complaints and repetitive extensive activation of cognitive networks related to illness and pain, called psychobiological sensitization (similar to sensitization of pain pathways as an aggravating process) [77]. A similar approach was demonstrated as perseverative cognition hypothesis manifested in worry, rumination, and anticipatory stress that are linked to illness [14, 64]. Worry, rumination, and anticipatory stress are associated with enhanced cardiovascular, endocrinological, immunological, and neurovisceral activity [14].

Another stress theory explains homeostatic effect (y-axis) as a U-shaped function over stress system activity (x-axis), where healthy homeostasis (or eustasis) is achieved in the middle, optimal range of the curve, with a maximum beneficial homeostatic effect [18]. Suboptimal effects left and right of the optimum range may occur as cacostasis or distress (either excessive/prolonged or deficient/shortish activity) [18].

Based on the different models, several *therapeutic approaches* were suggested to balance or cope with stressful events. For example, cognitive behavioral therapy, mind–body therapies (including Tai Chi, Qigong, yoga, meditation, mindfulness meditation, mindfulness-based stress reduction), physical exercise, healing touch, music therapy, therapeutic massage, and health education among others can, to some extent, deal with distress and, importantly, they also beneficially affect readout parameters of the immune system (summarized in [12]).

The research field is highly active, adding innumerable publications to the body of information. A recent named series of publications with the title "Twenty Years of Brain, Behavior, and Immunity (1987–2007)" summarized some of these ideas in the abovementioned different fields of psychoneuroimmunology research [3, 10, 19, 24, 35, 41–43, 50, 53, 72]. Comprehensive textbooks presented further details which became available up until approximately 2007 [1]. Since this time, many aspects have been absorbed by the various clinical fields by demonstrating the multiplex influence of stress on immune-mediated disease. This review is written to highlight specific aspects of clinical psychoneuroimmunology since the year 2007.

## Reciprocal influence of inflammation on the brain

The reciprocal influence of inflammation on the brain has been shortly mentioned in the Introduction (in the context of depression and dementia). However, it remained unclear whether a proinflammatory situation prior to a psychological stress can influence, for example, the risk of developing posttraumatic stress disorder (PTSD). In cross-sectional studies, PTSD and inflammation were associated, but it is not known whether this observed association is the result of PTSD predisposing to inflammation or to inflammation predisposing to PTSD [30]. In the Marine Resiliency Study, 2600 war zone-deployed Marines were investigated for symptoms of PTSD, psychological parameters, and laboratory parameters (C-reactive protein, CRP) before deployment and at 3 and 6 months following a 7-month deployment. The main outcome parameter was the Clinician-Administered PTSD Scale (CAPS). Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, baseline plasma CRP concentration was a highly significant overall predictor of post-deployment PTSD [30]. This demonstrates that an existing inflammatory condition, albeit mild, can predispose to PTSD. Since inflammation can trigger depressive symptoms or even major depression [25], these findings once more demonstrate the crosstalk directed from the periphery (immune system and inflammatory condition) to the central nervous system (brain).

## Stress induces inflammation and is disease permissive

The examples of how psychological stress influences chronic inflammatory diseases, cancer, and cardiovascular disease were reported in the Introduction. Here are some new studies that confirm the permissive effect of psychological stress on chronic diseases.

People with a high body mass index (BMI) demonstrate an increased inflammatory state and somewhat increased plasma glucocorticoid levels. However, it is not known whether higher glucocorticoids in people with a high BMI elicit anti-inflammatory effects due to immunosuppressive effects of glucocorticoids. In addition, it is not known whether short-term stress that stimulates glucocorticoid release has a stronger immunosuppressive effect in people with a high BMI. In a study on 42 healthy men with a BMI of 21–34 $kg/m^2$, glucocorticoid sensitivity of monocytes were tested in vitro using increasing doses of dexamethasone as an immunosuppressant and lipopolysaccharide-stimulated tumor necrosis factor (TNF) as readout parameter [80]. A higher BMI was associated with a lower glucocorticoid sensitivity of monocyte TNF production after stress (main effect of BMI: $p < 0.001$) and with more pronounced decreases of glucocorticoid sensitivity following stress (interaction of stress-by-BMI: $p = 0.002$). The data suggest that with increasing BMI, glucocorticoids are less able to inhibit TNF production following stress. This might suggest a new mechanism linking BMI with an elevated risk for adverse cardiovascular, metabolic, and central nervous outcomes following stress [80].

Another study demonstrated a similar stress-induced deficient glucocorticoid effect, which was coined glucocorticoid receptor resistance (GCR) [20]. The authors determined stressful life events, GCR, and control variables in 276 otherwise healthy adult subjects. These people were then quarantined, exposed to one of two rhinoviruses, and followed for 5 days with nasal washes for viral isolation and assessment of signs/symptoms of a common cold. Those subjects with recent exposure to a long-term threatening stressful experience demonstrated GCR—and those with GCR were at a higher risk of subsequently developing a cold [20].

In a second study, the authors studied 79 subjects who were subsequently exposed to a rhinovirus and monitored at baseline and for 5 days after viral challenge for the production of proinflammatory cytokines (interleukin [IL]-1β, TNF, and IL-6) locally in nasal secretions [20]. Now, greater GCR predicted the production of more local proinflammatory cytokines among infected subjects. They concluded that these data provide support for a model suggesting that prolonged stressors result in GCR, which, in turn, interferes with appropriate regulation of inflammation. Since inflammation plays an important role in the onset and progression of a wide range of diseases, this model may have broad implications for understanding the role of stress under normal healthy conditions [20].

Another investigation turned to the recurrence of *herpes simplex virus* disease upon psychosocial stress [17]. The authors performed a meta-analysis on 11 eligible studies on herpes simplex virus recurrence. They confirmed a robust positive association between psychosocial stress and symptomatic herpes simplex virus recurrence. Sensitivity analyses demonstrated that psychological distress was more strongly associated with symptomatic herpes simplex virus recurrence than stress stimuli per se, and that psychosocial stress tended to be more strongly associated with oral than genital herpes recurrence. Similar to the rhinovirus study, the herpes simplex virus study shows a clear relationship between psychological stress and a viral stimulus of inflammation. Repetitive or continuous psychological stress perceived as distress can, thus, lead to a more proinflammatory situation over longer time [17].

Psychological stress might be a forerunner of overt sepsis. In a cohort of 30,183 subjects within the Reasons for Geographic and Racial Differences in Stroke Study, the investigators determined the level of perceived stress and followed these people for 1–10 years [56]. In 2003 to 2012, 1500 participants experienced an episode of sepsis. Increased stress was associated with a higher 1-year adjusted incidence of sepsis, even after accounting for depressive symptoms. The association between stress and the 10-year adjusted incidence of sepsis was also significant, but this association was reduced when adjusting for depressive symptoms [56]. This study is another indication of a detectable link between psychological stress and inflammation/dysregulation of the immune response.

For a long time now, the link between psychological stress and asthma has been intensively discussed. Psychological stress can affect airway inflammatory responses to irritants and allergens [61], but the importance of stress in the etiology of adult-onset respiratory and dermatologic allergic disorders remains unclear. A total of 9785 subjects from the Copenhagen City Heart Study, Denmark, were included. At baseline (1981–1983), these subjects were free of atopic disorders and they were asked for stress intensity and frequency. The subjects were followed until 2010. Perceived stress was associated with atopic disorders in a dose-dependent manner: High versus low stress was associated with a higher risk of self-reported asthma incidence (odds ratio, OR = 2.32; 95% confidence interval, CI: 1.47–3.65), daily intake of asthma/bronchitis medication (OR = 2.26; 1.42–3.58), first-time asthma hospitalization (OR = 2.01; 1.41–2.86), allergic rhinitis (OR = 1.64; 0.99–2.72), and atopic dermatitis (OR = 1.75; 1.11–2.77), which was independent of smoking status [61]. This study shows another pathway by which chronic distress can influence systemic inflammation.

Intestinal permeability for bacteria is increased due to psychological stress, as studied in animals. In a recent investigation in human subjects, the authors quantified small intestinal permeability by a 2-hour lactulose-mannitol urinary excretion test [78]. Public speech—a paradigmatic test of acute psychological stress—increased intestinal permeability. This effect was only present in those subjects with an elevated saliva cortisol. Additional corticotropin releasing hormone stimulation even increased permeability, which was blocked by administration of a mast cell stabilizer [78]. Although psychological stress clearly increased intestinal permeability, the authors have not investigated a possible increase of lipopolysaccharide in the circulating blood, which would support animal studies. Nevertheless, this study can be seen as a forerunner for similar studies with a focus on inflammation and bacterial translocation.

In a study in mice, it was demonstrated that chronic psychological stress activates hematopoietic stem cell activity leading to stress-induced monocytosis and neutrophilia. This depended on noradrenaline-induced increase of hematopoietic stem cell proliferation [38]. The authors also examined atherosclerosis-prone Apoe$^{(-/-)}$ mice, where accelerated hematopoiesis promoted dangerous plaque formation associated with vulnerable lesions that cause myocardial infarction and stroke in humans [38]. Such a stress-induced pathway may additionally lead to cardiovascular sequelae and a higher inflammatory load.

In another study in mice, the authors investigated the link between chronic stress and cancer progres-

sion [46]. Chronic stress restructured lymphatic networks within and around tumors to provide pathways for tumor cell escape. Pharmacological inhibition of the sympathetic nervous system blocks the effect of chronic stress on lymphatic remodeling in vivo and reduces lymphatic metastasis in preclinical cancer models and in patients with breast cancer [46]. This can be a novel route for how the activation of the sympathetic nervous system can stimulate cancer outcomes.

In conclusion, this section clearly shows the permissive effects of psychological stress on chronic disease and inflammation.

## Stressful events in fetal, perinatal, postnatal, and childhood life

In the Introduction, we already linked early life stress and later disease outcomes. Two important studies—one in humans and one in mice—support the enormous impact of early life events and later disease.

Disasters provide natural experiments that can simulate prenatal stress. Five months after the 1998 Quebec ice storm, women were recruited who had been pregnant during the disaster [16]. The authors assessed the degrees of objective hardship and subjective distress. Thirteen years later, they investigated DNA methylation profiling in T cells obtained from 36 of the children [16]. Prenatal maternal objective hardship was correlated with DNA methylation levels at 1675 CpG (cytosine-p-guanine) sites affiliated with 957 genes predominantly related to immune function [16]. Changes in DNA methylation in the genes of secretogranin V and lymphotoxin alpha both highly correlated with maternal objective stress, and were comparable in T cells and peripheral blood mononuclear cells (PBMCs). These data provide first evidence in humans supporting the conclusion that prenatal maternal stress results in a lasting, broad, and functionally organized DNA methylation signature in several tissues in offspring [16].

Prenatal infection and exposure to traumatizing experiences during peripuberty have each been associated with an increased risk for neuropsychiatric disorders [33]. Evidence is lacking for the cumulative impact of such prenatal and postnatal environmental challenges on brain functions and vulnerability to psychiatric disease. In a translational mouse model that combined exposure to prenatal immune challenge and peripubertal stress, the authors demonstrated synergistic pathological effects on adult behavioral functions and neurochemistry [33]. The prenatal insult markedly increases the vulnerability of the pubescent offspring to brain immune changes in response to stress [33]. The findings reveal interactions between two adverse environmental factors that have individually been associated with neuropsychiatric disease (another “two hit model of stress”). This supports theories that mental illnesses with delayed onsets involve multiple environmental hits.

## Therapeutic approaches to balance or cope with stressful events

With all the information gathered through more than 30 years of intensive research, the first therapeutic approaches were expected to treat subjects with exaggerated stress responses. The different theories provided a platform to tackle stress behavior.

One approach is mindfulness based stress reduction (MBSR), which was applied in a non-randomized controlled study in patients with early-stage breast cancer [81]. Early-stage breast cancer patients who did not receive chemotherapy self-selected into an 8-week MBSR program or an assessment only, control group. The first assessment was at least 10 days after surgery and prior to adjuvant therapy, as well as before the MBSR start-up. Further assessments were mid-MBSR, at completion of MBSR, and at 4 weeks post-MBSR completion [81]. At the first visit before MBSR start, reductions in peripheral blood mononuclear cell natural killer (NK) cell activity (NKCA) and interferon (IFN)-γ production and increases in IL-4, IL-6, and IL-10 production and plasma cortisol levels were observed for both groups of breast cancer patients. Over time, women in the MBSR group reestablished their NKCA and cytokine production levels. In contrast, breast cancer patients in the control group exhibited continued reductions in NKCA and IFN-γ production, with increased IL-4, IL-6, and IL-10 production [81]. MBSR women had reduced cortisol levels, improved quality of life, and increased coping effectiveness compared to controls [81]. These results provide preliminary evidence that MBSR can be favorable in breast cancer.

In another study with compassion meditation, the influence on physiological pathways was studied in more detail [57]. Much attention has been paid to meditation practices that emphasize calming the mind, improving focused attention, or developing mindfulness, but less is known about meditation practices that foster compassion. The presented study examined the effect of compassion meditation on innate immune, neuroendocrine, and behavioral responses to psychosocial stress and evaluated the degree to which engagement in meditation practice influenced stress reactivity [57]. Sixty-one healthy adults were randomized to 6 weeks of training in compassion meditation ($n$ = 33) or participation in a health discussion control group ($n$ = 28), followed by exposure to a standardized laboratory stressor (Trier social stress test [TSST]) [57]. Physiologic and behavioral responses to the TSST were determined by repeated assessments of plasma concentrations of IL-6 and cortisol, as well as total distress scores on the Profile of Mood States (POMS). No main effect of group assignment on TSST responses was found for IL-6, cortisol, or POMS scores [57]. However, within the meditation group, increased meditation practice was correlated with decreased TSST-induced

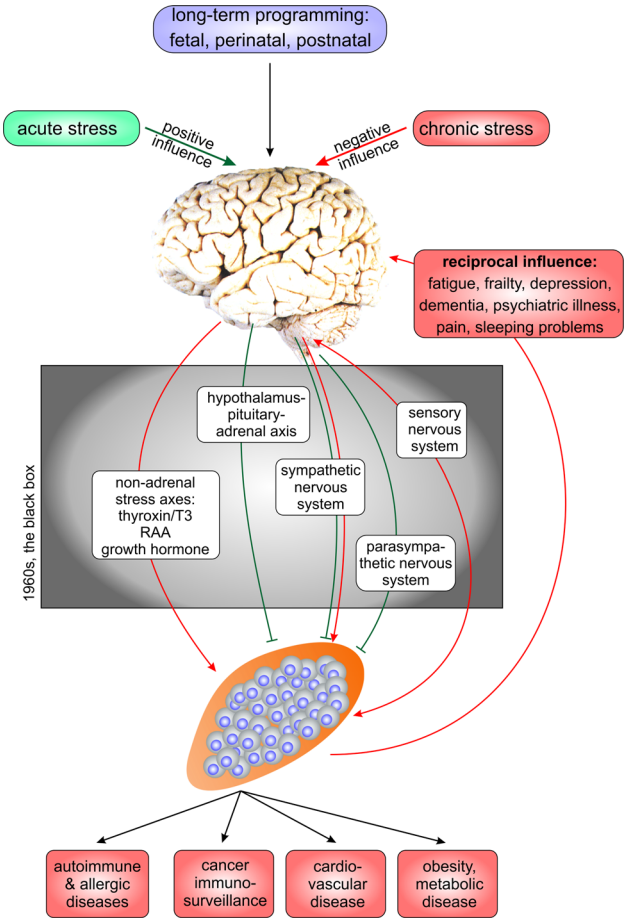


**Fig. 1** Psychoneuroimmunology crosstalk. The brain communicates with the immune system, thereby influencing immune function (*red lines:* stimulating; *green lines:* inhibiting). The immune system communicates with the brain by reciprocal pathways. Both directions are linked to the development of diseases. This is mainly relevant when either psychological stress lasts too long or immune system activation is chronic. In both situations, physical and mental activity are low, which can lead to illness. *RAA* renin–angiotensin–aldosterone system, *T3* triiodothyronine (active thyroid gland hormone)

IL-6 and POMS distress scores. Moreover, individuals with meditation practice times above the median exhibited lower TSST-induced IL-6 and POMS distress scores compared to individuals below the median, who did not differ from controls [57]. These data suggest that engagement in compassion meditation may reduce stress-induced immune and behavioral responses. Future studies are required to determine whether individuals who engage in compassion meditation techniques are more likely to exhibit reduced stress reactivity [57].

## Stress and telomere length

A new field of investigation links stress with a cellular aging marker, i. e., telomere length. The DNA replication machinery encounters problems at numerous genomic regions that are inherently difficult to replicate [31]. These genomic regions include telomeres, which contain repetitive DNA and telomere-binding proteins. If not properly regulated, replication of such genomic regions can result in DNA damage, leading to genomic instability [31]. Thus, the length of the telomere is a marker of genomic stability and it decreases with cellular aging. Telomerase activity plays an essential role in cell survival, by lengthening telomeres and promoting cell growth and longevity. It is now possible to quantify the low levels of telomerase activity in human leukocytes.

In a recent study, the authors tested whether leukocyte telomerase activity changes under acute psychological stress [29]. A total of 44 elderly women, including 22 high-stress dementia caregivers and 22 matched low-stress controls were subjected to a brief laboratory psychological stressor. At baseline, caregivers had lower telomerase activity levels than controls, but during stress, telomerase activity increased similarly in both groups [29]. Across the entire sample, subsequent telomerase activity increased by 18% 1 h after the end of the stressor [29]. The increase in telomerase activity was independent of changes in numbers or percentages of monocytes, lymphocytes, and specific T cell types. Telomerase activity increases were associated with greater cortisol increases in response to the stressor [29]. The authors conclude that telomerase activity is dynamic with exposure to an acute stressor.

In another study, global sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and diary-reported sleep duration were linked to telomere length in different immune cell subsets [58]. A sample of 87 obese men and women were investigated. Poorer PSQI global sleep quality was associated with statistically significantly shorter telomere length in lymphocytes but not granulocytes, and in particular in CD8+ T cells and CD4+ T cells [58]. Poorer global sleep quality predicted shorter telomere length in CD8+ T cells among those with high perceived stress but not in low-stress participants [58]. These findings provide preliminary evidence that poorer global sleep quality is related to telomere length in several immune cell types, which may serve as a pathway linking sleep and disease risk in obese individuals.

Since the cellular aging process can be proinflammatory per se, stress-induced changes in telomerase activity and telomere length might stimulate a more proinflammatory situation.

## Conclusions

Studies before 2007 defined the physical pathways between the brain and the immune system, i.e., the HPA axis, sympathetic nervous system, and non-adrenal stress hormones (e. g., angiotensin). With psychological stress, the parasympathetic nervous system and the hypothalamic–pituitary–gonadal axis are downregulated so that their anti-inflammatory influence is

missing (Fig. 1). We recognized that a chronically activated immune system can interfere with the brain, supporting psychiatric illness, dementia, and post-traumatic stress sequelae (Fig. 1).

With continuous support since 2007, we now recognize that chronic stress is disease permissive, which has been studied in patients with chronic inflammatory diseases, including rheumatic autoimmune diseases, cancer, cardiovascular diseases, acute and chronic viral infections, sepsis, asthma, and other diseases (Fig. 1). Stress typically activates proinflammatory pathways and, as detected only recently, telomere length and telomerase activity, markers of cellular aging.

The time between fetal and postnatal childhood life is highly critical for humans and experimental animals, because long-term programming of central nervous, neuroendocrine, and immune pathways appears in this vulnerable time. Stress exposure or infection during this time window can change important pathways and later reactivity of stress response systems (Fig. 1).

New therapeutic approaches show some benefit, but these studies have only started. It is important that these investigations are carried out as randomized control trials with adequate numbers of participants. The first phase II studies are available, but multicenter phase III trials using rules of good clinical practice are still missing.

**Conflict of interest** R.H. Straub and M. Cutolo declare that they have no competing interests.

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