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CONCISE REVIEW

# Stress and the psyche–brain–immune network in psychiatric diseases based on psychoneuroendocrineimmunology: a concise review

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In the last decades, psychoneuroendocrineimmunology research has made relevant contributions to the fields of neuroscience, psychobiology, epigenetics, molecular biology, and clinical research by studying the effect of stress on human health and highlighting the close interrelations between psyche, brain, and bodily systems. It is now well recognized that chronic stress can alter the physiological cross-talk between brain and biological systems, leading to long-lasting maladaptive effects (allostatic overload) on the nervous, immune, endocrine, and metabolic systems, which compromises stress resiliency and health. Stressful conditions in early life have been associated with profound alterations in cortical and subcortical brain regions involved in emotion regulation and the salience network, showing relevant overlap with different psychiatric conditions. This paper provides a summary of the available literature concerning the notable effects of stress on the brain and immune system. We highlight the role of epigenetics as a mechanistic pathway mediating the influences of the social and physical environment on brain structure and connectivity, the immune system, and psycho-physical health in psychiatric diseases. We also summarize the evidence regarding the effects of stress management techniques (mainly psychotherapy and meditation practice) on clinical outcomes, brain neurocircuitry, and immune-inflammatory network in major psychiatric diseases.

**Keywords:** psychoneuroendocrineimmunology; stress; allostasis; epigenetics; mind-body therapies; NF- $\kappa$ B

## Introduction

The immune system is under neuroendocrine control; conversely, products of immune cells can affect central and peripheral nervous activity.<sup>1</sup> Brain-immune cross-talk is deeply influenced by mental states and psychosocial factors. The study of the complex interrelations between psyche, brain, and biological systems is the specific aim of psychoneuroendocrineimmunology (PNEI), a

paradigm that proposes a systemic multidimensional approach to human health, by integrating scientific knowledge derived from both psychological and biological sciences.<sup>2,3</sup> More than 40 years ago, Ader and Cohen reproduced an experimental behavior-conditioned immunosuppression in rats,<sup>4</sup> providing the first *in vivo* indirect evidence of communication between the central nervous system (CNS) and the immune system. In the early 1980s, Besedovsky *et al.* detected changes in the activity of two main neuroendocrine axes, namely, the hypothalamic–pituitary–adrenal gland (HPA) and hypothalamic–pituitary–thyroid gland, triggered by interleukin-1 (IL-1)-mediated immune response,<sup>5,6</sup>

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This demonstrated that the activity of HPA neuroendocrine branch of the stress response can be enhanced by inflammatory signals produced by immune cells. In 1989, Blalock discovered the production of peptide hormones by peripheral leukocytes and different types of neuroendocrine-derived cytokines and chemokines, establishing the “molecular basis for bidirectional communication between the immune and neuroendocrine systems.”<sup>7</sup> Since 1990, subsequent experimental studies found cytokine expression in CNS both in physiological and pathological conditions and provided the evidence that peripheral immune system can affect the cytokine balance in the brain, thereby altering mood and behavior, as observed in clinical studies conducted on patients exposed to cytokine therapies for cancer or chronic viral hepatitis.<sup>8</sup>

A major factor that can profoundly affect the psycho-neuro-endocrine-immune network is stress (see below). Stress is the physiological response of the body to any demand: biological, emotional, and cognitive.<sup>9</sup> Whereas acute stress may induce dynamic adaptation to different demands, chronic stress can have long-lasting maladaptive effects, with pathologic consequences on nervous, immune, endocrine, and metabolic systems.<sup>10</sup> Many psychosocial conditions entailing high levels of chronic stress, that is, poor socioeconomic state, adverse life events, loneliness, experiences of trauma and/or abuse, have been associated with network dysregulation and are thought to be relevant clinical risk factors. Just to mention a few pertinent examples, healthy individuals with a history of childhood trauma showed signs of enhanced inflammation assessed through serum C-reactive protein (CRP), leukocytes count, and fibrinogen; higher levels of inflammation markers were found among subjects with current depression in addition to a history of trauma.<sup>11</sup> Moreover, recent studies have detected increased levels of inflammation in schizophrenia and other mental disorders.<sup>12,13</sup>

In this brief review, we have recognized the role of stress on the brain and immune system, highlighting the importance of epigenetics as a mechanistic pathway mediating the deep influences of the social and physical environment on brain structure and functions, the immune system, and mental and physical health.

## Stress, allostasis, and the brain

Stress is well explained within the conceptual framework of allostasis, a brain-centered, predictive model of physiological and behavioral regulation.<sup>14</sup> Briefly stated, allostasis relates to the multiple systemic and neural processes that dynamically respond to novel and challenging situations, involving a complex network of nonlinearly and reciprocally interacting mediators (cortisol and catecholamines *in primis*, as well as the parasympathetic nervous system, cytokines, and metabolic hormones). The integrated action of these mediators is aimed at promoting fitness and adaptation to the ever-changing environment. In fact, physical and psychosocial threats trigger brain-driven, multisystemic stress responses that are apt to make the organism temporarily more fit to confront impending demands: An increase is seen in cortical arousal and sensory gating; cognitive and motivational resources are focused on the challenge; and mood shifts toward hypervigilance and anxiety in anticipation of danger. In parallel, endocrine and autonomic systems drive the emergency patterns of visceral activity and regulate inflammatory response. Adaptive in the short-run, excessive and/or protracted stress responses may have long-lasting maladaptive effects, with progressive and cumulative “wear and tear” effects on the physiological systems involved in allostasis (allostatic load and overload)<sup>15</sup> that adversely affect health trajectories over time. Moreover, to soothe stress-related anxiety and depressive symptoms, individuals may indulge in unhealthy behaviors (smoking, compulsive drinking and eating, taking drugs, and social withdrawal), further worsening social stigma, self-esteem, and allostatic load/overload.<sup>15</sup>

The cortico-limbic structures involved in cognition and emotional processing (prefrontal cortex (PFC), anterior cingulate, amygdala, insula, hippocampus, and striatum) attribute valence and personal salience to stimuli—under the influence of a variety of moderating factors, such as social support, life experiences and habits, psychological traits, and genetics—and orchestrate behavioral and physiological response to the stressors. In turn, the same brain structures are major target of stress hormones and mediators. Stress-induced neuronal remodeling (i.e., changes in dendritic extension and branching, spine density, and synapse turnover) is mainly due

to the action of norepinephrine and glucocorticoids (GCs), along with other mediators, that is, glutamate and its receptors, brain-derived neurotrophic factor (BDNF), corticotrophin-releasing factor, cell surface molecules, protease tissue plasminogen activator, and endocannabinoids. This results in dynamic structural and functional changes in multiple brain areas, depending on nature, magnitude, timing, and persistence of stress exposure.<sup>16,17</sup>

Prolonged stress leads to gray matter reduction and hypofunction of the PFC, a structure critical for working memory, context appraisal, executive, and self-regulatory functions.<sup>17,18</sup> Neurons of the hippocampus, which are crucial for memory and mood, are endangered by chronic stress through exposure to excess GCs;<sup>17</sup> in keeping with this, prospective reports of chronic life stress in humans have been shown to predict hippocampal volume.<sup>19</sup> Moreover, cumulative adverse life events correlate with gray matter reduction in many emotion-related brain areas (medial prefrontal, anterior cingulate, and insular cortices).<sup>20</sup> Opposite stress-related effects occur in the amygdala, including cellular hypertrophy and enlarged dendritic arborization,<sup>21</sup> with enhanced reactivity to adverse stimuli in humans reporting long-term exposure to a disadvantaged psychosocial environment.<sup>15,22</sup> Despite being generally adaptive in situations that require enhanced vigilance and rapid responses, these structural and functional changes may come, in vulnerable individuals, at the cost of anxiety, poor extinction of adverse memories, and reduced cognitive and behavioral flexibility. This enhances long-term risks for psychopathology, such as depression, post-traumatic stress disorder (PTSD), and addiction.<sup>23,24</sup> It is worth noting that structural remodeling of the hippocampus and PFC are common traits in psychiatric diseases and in conditions characterized by chronic stress accumulation (as in shift workers and caregivers) often associated with cognitive deficits, dysregulated cortisol secretion and metabolism, and immune disorders.<sup>15</sup>

Epigenetic mechanisms are regarded as potential mechanistic pathways mediating the transduction of environmental inputs into ever-changing patterns of gene expression. Stress has been associated with changes in DNA methylation and histone alterations in many stress-sensitive brain regions,<sup>25</sup> with gene expression changes showing relevant overlap with those found in psychiatric conditions, such as

depression.<sup>17</sup> Prenatal and early-life stressful experiences (ELSs) affect the ontogenetic origin of individual diversities in vulnerability to stress throughout life, producing persistent neuroplastic changes.<sup>26</sup> Seminal studies conducted in rats revealed that low levels of maternal behavior when nurturing pups, that is, poor licking and grooming or arch-backed nursing, have permanent epigenetic consequences in offspring, such as hypermethylation of the promoter region of GC receptor (GR) gene, thereby reducing hippocampal GR expression and blunting inhibitory control on HPA response.<sup>27</sup> Similar epigenetic changes are reported in humans who have experienced childhood abuse.<sup>28,29</sup> Growing literature confirms that ELS results in neurobiological and cognitive alterations that reflect system-level adjustments to risky environments, generally promoting avoidance versus approach-oriented behaviors. Maltreated children display enhanced reactivity and stronger functional interconnectivity of brain areas (amygdala and insula) in the “salience network” involved in threat detection and pain anticipation.<sup>30</sup> Moreover, ELS is associated with disrupted emotional regulation, reduced top-down control over amygdala reactivity,<sup>31,32</sup> and reduced thickness in many cortical regions involved in emotional processing (medial and lateral PFC and orbitofrontal cortex).<sup>33</sup> Reward system development is also affected: adolescents exposed to emotional neglect show blunted activation of ventral striatum to positive stimuli, which predicts depressive symptoms in later life.<sup>34</sup>

Importantly, stress-related neuroplastic changes seem to be largely reversible. Weakened functional connectivity in a neural circuit including PFC and reduced cognitive flexibility were found in students tested during a stressful period of examinations; alterations disappeared after a vacation period.<sup>35</sup> However, rather than complete reversal, resilience means achieving a new state and new reaction capabilities.<sup>36</sup> In the rat brain, some of the gene expression changes induced by chronic stress fail to return to prestress levels of transcription after extended recovery, despite a normalization of anxiety-related behavior.<sup>37</sup> In addition, morphological studies show that after stress abates, dendrites re-expand and spines/synapses regrow. However, these are more often proximal dendrites than apical ones, thus changing the global morphology (and the connectivity) of neurons.<sup>38</sup>

## The mutual link between stress and inflammation

The bidirectional link between stress and the immune system has been well documented for decades, both in animal models and humans. Studies on murine models of repeated social defeat (RSD) reveal that chronic stress and social isolation trigger neuroendocrine and behavioral changes through the activation of HPA pathway together with behavioral adaptation (anxiety). This triggering produces microglial activation and CNS inflammation via GR-mediated pathways, with increased *in situ* neuro-inflammatory cytokine production.<sup>39</sup> At the same time, RSD-induced stimulation activates the autonomic nervous system (ANS) branch of stress response, which increases sympathetic firing and induces synthesis, activation, and trafficking of peripheral monocytes, irrespective of GR-mediated pattern.<sup>40</sup> In line with evidence from animal models, human studies have shown that chronically stressed individuals, as in the case of caregivers, display increased blood CRP levels and higher NF- $\kappa$ B-mediated transcription products in circulating monocytes.<sup>40</sup> In this regard, seminal studies by Irwin and Cole established that life's adversities and chronic psychosocial distress are typically associated with a concert of epigenetic modifications in the immune cells, including hyperactivation of several proinflammatory transcription factors (i.e., NF- $\kappa$ B/Rel and GATA-family), suppression of genes involved in innate immunity (interferon (IFN) response factors), and impairment of GR expression (thereby altering stress response).<sup>41,42</sup> This "conserved transcriptional response to adversity," which is characterized by increased expression of proinflammatory genes and decreased expression of antiviral and antibody-related genes, has been found across a diverse array of adverse life circumstances: low socioeconomic status,<sup>43</sup> social isolation,<sup>44</sup> diagnosis and treatment of chronic diseases with higher psycho-emotional load, breast cancer recurrence,<sup>45</sup> and PTSD.<sup>46</sup>

If psychosocial stress is a powerful regulator of central and peripheral inflammation, then systemic inflammatory factors, in turn, can retroact on the CNS and increase the reactivity of many stress- and reward-related cortical and subcortical structures. This reaction affects social cognition and behavior

by enhancing the sensitivity to (thus the saliency of) threatening social experiences, while promoting a behavioral approach toward supportive figures (for a recent review see Ref. 47). Stress and inflammation are thus inextricably linked and can influence each other. In otherwise healthy subjects, higher sensitivity to social disconnection (and thus to psychosocial stressful events) has been associated with larger increases in circulating cytokines and proinflammatory gene expression in response to endotoxin injection.<sup>48</sup>

These reciprocal interactions between stress-related brain circuitry and the immune system have been proposed as important contributors to the pathogenesis of a variety of medical and mental diseases. These conditions are frequently comorbid and variably associated with inflammatory system dysregulation; they include anxiety and depression, and cardiovascular and metabolic diseases. Increased inflammatory biomarkers, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , CRP, and ICAM-1, have been found in depression.<sup>49–51</sup> Moreover, inflammation can increase frequency and severity of depressive symptoms, as observed in patients suffering from several chronic pathologic conditions (i.e., inflammatory relapse in rheumatoid arthritis) or who underwent specific treatments, such as IFN therapy, which was initially used in the 1990s to treat patients affected by chronic viral hepatitis. Moreover, the higher prevalence of co-occurrence of depression and inflammatory diseases was clearly observed in several studies conducted in the last two decades. Patients with type 1 and type 2 diabetes are more likely to have depression, with prevalence more than three times and nearly twice higher, respectively, compared to nondiabetics.<sup>52</sup> In addition, a meta-analysis has recently shown that the prevalence of type 2 diabetes is consistently elevated among persons with severe psychiatric diseases (i.e., schizophrenia, bipolar, or major depressive disorders), including antipsychotic-naïve participants.<sup>53</sup>

Depression and anxiety are commonly diagnosed among patients with coronary heart failure (CHF). In CHF patients, depression worsens both primary and secondary outcomes: all-cause and cardiac mortality rates, cardiac symptoms, hospitalization, and quality of life. A recent Danish nationwide study, despite the use of strict inclusion criteria for the diagnosis of depression, has drawn the following conclusions: "A history of depression was

an adverse prognostic factor for all-cause mortality in heart failure patients with left ventricular ejection fraction  $\leq 35\%$  but not for other heart failure patients.<sup>54</sup> Mounting evidence indicates that patients diagnosed with depression exhibit autonomic and biochemical dysregulations comparable to those observed in patients with heart failure; these include decreased heart rate variability and increased elevated circulating levels of proinflammatory cytokines (i.e., TNF- $\alpha$  and IL-1), CRP, and platelet hyperactivity.<sup>55</sup> Interestingly, in response to a mental arithmetic task, patients with coronary artery disease have a greater increase of CRP and IL-6 compared to healthy controls, with an observed positive relationship between stress intensity and strength of inflammatory response.<sup>56</sup>

In sum, psychosocial stress can boost inflammation, and inflammation can, in turn, cause or aggravate depression and other cardiovascular and metabolic disorders. Taken together, these findings show that adverse life events and chronic stress are “getting under the skin” and can influence lifelong health trajectories through physical and mental consequences.

### **Focus on mental health and stress management: clinical effectiveness of psychotherapy and mind-body techniques**

Despite huge investments in the development of several new classes of antidepressants, depressive disorders remain the most diagnosed psychiatric diseases in the world with global estimates of prevalence of 322 million of people.<sup>57</sup> Average response rates to antidepressant drugs are approximately 40–60%, and remission rates range from 30% to 40%.<sup>58</sup>

Thanks to their synergistic effects, current therapeutic approaches tend to combine pharmacological and nonpharmacological interventions to improve symptoms and ameliorate quality of life in patients affected by psychiatric disturbances. Evidence-based psychotherapies<sup>59</sup> and mind-body therapies (MBTs) have proven effective in reducing symptoms of anxiety and depression in both patients with primary mental disorders and patients with chronic diseases (i.e., cancer<sup>60</sup> and chronic pain<sup>61</sup>).

One of the first applications of psychotherapy in psychiatric diseases was targeted to treat mood disorders. Cognitive behavioral therapy (CBT) exhibits a convincing cost/effectiveness profile in the man-

agement of a wide range of psychiatric diseases, including anxiety and depression,<sup>62</sup> both when used alone and in combination with antidepressants.<sup>63</sup> CBT is currently recommended as the first-line choice for ambulatory treatment of adult depressed patients<sup>64</sup> and as combined and/or sequential treatment to complement psychiatric drugs, in drug-resistant<sup>65</sup> and relapsed major depression,<sup>66</sup> panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder.<sup>64</sup>

A multispecialist approach is also recommended in therapeutic management of PTSD to mitigate symptoms (i.e., disturbing thoughts and feelings, recurrent dreams, and trauma-related distress) and reduce incidence of cognitive impairment, substance abuse, and suicidal behaviors. Despite limitations derived from the quality of the studies, Cochrane meta-analyses show positive results for all types of psychotherapies among children and adolescents.<sup>67</sup> In adults with PTSD, individual trauma-focused CBT, eye movement desensitization and reprocessing, and nontrauma-focused CBT are the psychotherapeutic approaches that have shown the highest efficacy; this approach is also successful among high-risk patients.<sup>68,69</sup>

Over the last decades, meditation practice has spread in Western countries as a safe and efficacious remedy to counteract distress. Evidence on the efficacy of mindfulness-based interventions (MBIs) for management of psychological health, both in medical and psychiatric patients, as well as in healthy subjects,<sup>70</sup> has been growing. Mindfulness-based cognitive therapy (MBCT), incorporating cognitive strategies into the theoretical and practical framework of mindfulness-based stress reduction (MBSR), is recommended as an adjunctive treatment for unipolar depression, since it has been found effective in reducing current episodes of depression<sup>71,72</sup> and relapse of the disease.<sup>73</sup>

As adjuvant therapy to standard medical treatment, MBIs reduced symptoms of depression and anxiety among elderly women<sup>74</sup> and in mothers who suffered from postpartum depression.<sup>75</sup>

In an RCT that included older adults with depression and neurocognitive decline, the mindfulness group, compared to controls, showed significant improvements in memory functions and mood outcomes.<sup>76</sup> Some results suggest that both MBSR and MBCT are safe and efficacious interventions for anxiety symptoms.<sup>77</sup> Moreover, MBI group therapy

was found to be noninferior to CBT when applied to patients with depressive, anxiety, or stress-related disorders in primary care.<sup>78</sup> In patients diagnosed with substance-use disorder, psychiatric disorder, and trauma exposures, MBIs have been associated with significant improvements in substance craving, relapse, and post-traumatic stress disturbances compared to CBT or usual treatment.<sup>79</sup> MBSR also resulted in effective improvement of symptoms and psychological quality of life in veterans with PTSD.<sup>80</sup>

Enhancements in cognitive functions and emotional regulation, including frequency of manic episodes, were observed in patients diagnosed with bipolar disorder (BD) following regular mindfulness meditation practice. Despite the limited number of studies, MBCT seems to represent a promising treatment in BD in conjunction with pharmacotherapy.<sup>81</sup> Promising but still embryonal results were found for symptom control in those with psychotic disorders.<sup>82</sup>

MBTs, which include tai-chi, qigong, yoga, and meditation, are commonly used to manage stress-related diseases. There is a growing body of evidence that supports the use of yoga practice in the treatment of psychiatric diseases. While meta-analyses of RCTs present some methodological drawbacks, yoga could be considered an effective add-on treatment option for depressive patients,<sup>83</sup> resulting in a significant reduction in depression severity scores,<sup>84</sup> ruminative thoughts, and depressive manifestations. These approaches have also been determined effective in pregnant women.<sup>85</sup>

The contribution of PNEI in the field of MBTs is represented, at least in Italy, by the PNEI-based meditation training (PNEIMED), a method that combines scientific, systemic vision of the mind-body relationship with philosophical principles and meditative practices of the Buddhist tradition, integrated with elements from Western traditions (psychosynthesis). In a first prospective, nonrandomized, cohort-controlled study, a brief PNEIMED training was able to reduce self-rating distress and salivary cortisol secretion in healthy middle-aged healthcare workers.<sup>86</sup>

### **Focus on mental health and stress management: biological effects on brain, inflammation, and the immune system**

Interestingly, the established efficacy of mind therapies on clinical outcomes (symptom control, relapse

frequency, and quality of life) in psychiatric diseases is paralleled by a mounting body of evidence that has demonstrated the benefits of psychotherapy and MBTs on biological systems and their influence on epigenetic expression, brain neurocircuits, and neuroendocrine patterns.

As mentioned above in this review, it is well established that chronic stress can activate both the ANS and the HPA axis; their final products, catecholamines and GCs, bind to specific receptors on immune cells and influence the production of proinflammatory cytokines, via enhancing NF- $\kappa$ B inflammatory cascade. It is also well accepted that, in turn, a chronic systemic inflammatory state may influence brain activities and peripheral systems, playing a role in symptoms of depression, fatigue, and pain that occur in patients suffering from chronic illnesses (cancer, cardiovascular, psychiatric, and neurodegenerative).

The importance of environmental input on the epigenetic signature has emerged in seminal studies (mentioned above), highlighting how early life adversities can switch-off, through methylation processes, key genes implied in neurogenesis and neural plasticity (i.e., BDNF), stress response (i.e., GR), mood regulation and adaptive processes (i.e., mono-amino-oxidase A, MAO-A), affecting emotional neural circuits and promoting the maladaptive cognitive processes seen in diverse psychiatric conditions. These observations constitute the starting point for subsequent experimental studies that have demonstrated the reversal of these epigenetic modifications, assessed through peripheral immune cells gene extraction, in patients treated with psychotherapy.<sup>87</sup>

In patients with eating disorders, behavioral therapy sessions led to a reduced methylation of BDNF gene (hence greater genetic expression) and correlated with symptomatic improvement.<sup>87</sup> Prolonged exposure therapy (PET) for patients with PTSD led to a significant reduction in methylation of the GR gene (NR3C1 exon 1F and the GR cochaperone FKBP5) that directly correlates with greater response to psychotherapy intervention, higher baseline levels of cortisol, and a decrease in cortisol reactivity, thus enhancing adaptive neurobiological responses.<sup>87</sup> After a CBT session to treat panic disorder, reduced methylation levels of MAO-A gene were observed (hence increased serotonin catabolism), with a parallel reduction

in symptom severity scores. Surprisingly, after 6 weeks of treatment, responders exhibited MAO-A hypermethylation, while nonresponders showed hypomethylation. The consequent increase of serotonin levels would serve to decrease central sympathetic hyperactivation, typical of panic attacks, and allow certain prefrontal areas (i.e., PFC) to be activated, thus facilitating adaptive responses.<sup>87</sup>

The therapeutic aim of psychotherapy (mainly cognitive-oriented approaches) focuses on reconfiguration of “default activation patterns” involved in emotion regulation and cognitive appraisal, through gradual restructuring of maladaptive models of behaviors, feelings, and thoughts which characterize, although with different clinical features, all psychiatric diseases.

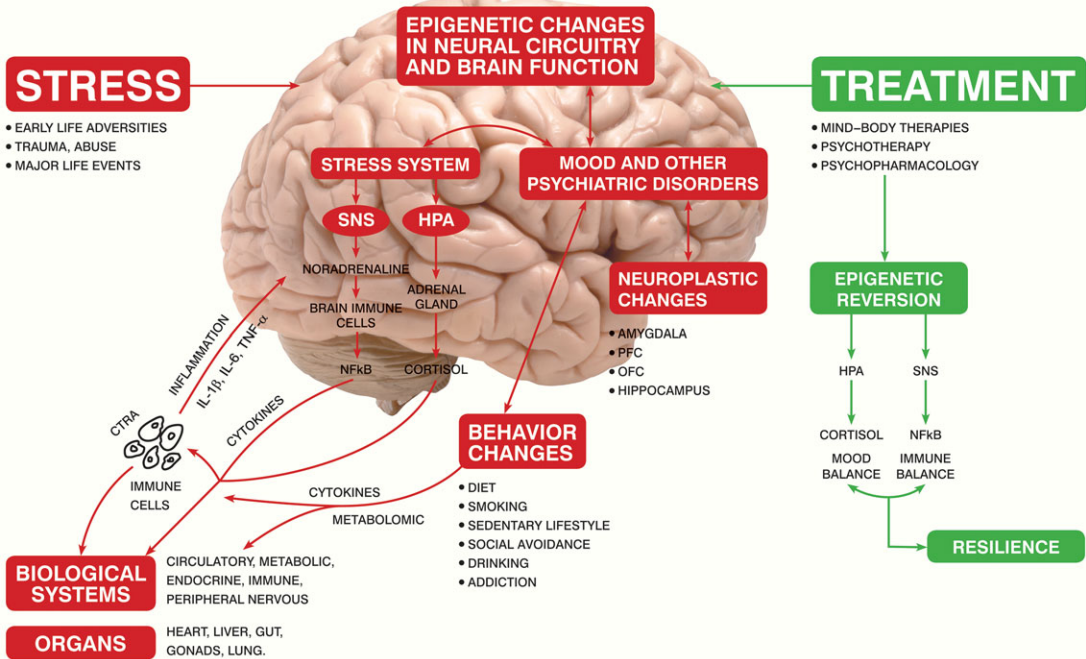
Neuroimaging findings, through the assessment of neural markers of treatment response, showed how psychotherapy acts on brain regions of interest and restores adaptive functional cerebral connectivity, as well as cognitive and emotional flexibility through the strengthening of top-down control circuits. For example, studies in CBT<sup>88</sup> and PET<sup>89</sup> post-treatment patients have revealed an increased recruitment of ventral cortical areas (ventro-lateral PFC and ventral striatum), the attenuation of dorsal cortical areas (dorso-medial and dorso-lateral PFC), and reduced activity of the amygdala, the anterior insula, the anterior cingulate cortex (dACC and sgACC), and dACC-amygdala-dmPFC connectivity, with concomitant increased hippocampal and parahippocampal activation.<sup>87</sup> Similar changes in the frontopolar cortex network have been demonstrated during cognitive reappraisal and fear response pattern extinction; consequent improvement was seen in negative emotions, hyperarousal, and reward pathway involved in anxiety, phobic behaviors, major depression, and PTSD.<sup>87</sup>

A recent systematic review<sup>90</sup> investigated the role of psychotherapy, in particular CBT, in reducing chronic inflammation among depressed patients. Despite the heterogeneity of the study design, population characteristics, study duration, and the presence of confounding factors such as drugs, the bulk of studies analyzed showed a clinically significant decrease in at least one inflammatory marker among a wide range of biomarkers assessed in the studies, such as serum cytokines (i.e., TNF- $\alpha$  and IL-6), nuclear factors expression (i.e., NF- $\kappa$ B), natural

and acquired immunity cells count and activity (i.e., natural killer and T lymphocyte cells). The analysis also concerned depressed patients comorbid with chronic diseases (cancer, chronic pain, cardiovascular disease, diabetes, rheumatoid arthritis, and irritable bowel disease), showing nonsignificant reduction of inflammatory signals following CBT. This was probably due to the higher levels of inflammation at baseline that characterize the population examined.

In this regard, it is worth noting that in pure psychiatric patients, the efficacy of both CBT and antidepressant medications can be influenced by higher pretreatment inflammation levels,<sup>91</sup> although evidence of specific prognostic inflammatory markers for poor response to psychotherapy is inconclusive and requires further research. The superiority of combined pharmacological and CBT therapy on clinical outcomes might be related to enhanced anti-inflammatory effect, and further investigation in this field is needed.

Based on ancient practices and traditions, MBTs have been recognized in the last two decades as effective techniques for counteracting the effects of stress on the immune system, yielding psychological and physical benefits. MBTs may have a neuro-immune regulatory effect. This is achieved by influencing the brain regions involved in neuro-vegetative and stress response pathways through downstream HPA axis regulation; this shifts the ANS balance toward an enhanced parasympathetic activity. These effects act directly on immune cell gene expression through the downregulation of NF- $\kappa$ B, thus reducing inflammation. A growing body of research has evaluated effects of MBTs on circulating, cellular, and genomic markers of inflammation. A recent qualitative review by Bower and Irwin<sup>92</sup> (including 26 trials) analyzed the effects of MBTs on circulating inflammatory markers, such as CRP, revealing that tai-chi, qigong, and yoga were more likely to reduce levels of CRP; half of the results were found in populations with specific medical conditions. For cytokines, the results are less straightforward. Although displaying a decreasing trend, IL-6 failed to show significant changes after MBT administration; attempts to draw firm conclusions on IL-18, TNF- $\alpha$ , and IL-1 receptor antagonist were hampered by data limitations. Intensive yoga practice has been shown to decrease LPS-stimulated production of TNF- $\alpha$ , IL-1, and IL-6 from peripheral



**Figure 1.** Chronic psychosocial stress, that is, early life adversities, trauma, abuse, and major life events, can induce neuroendocrine stress system activation and epigenetic changes in neural circuitry. Brain epigenetic changes drive mood and other mental and psychological changes, which, in turn, strengthen epigenetic signatures and feed neuroplastic changes in key brain areas for emotional and cognitive functions, such as the amygdala, prefrontal and orbitofrontal cortex, and hippocampus, thus increasing the risk of developing depression and other psychiatric disorders (i.e., anxiety and bipolar disorders). Mental disorders and associated behavioral changes (i.e., consumption of a high-fat diet, smoking, sedentary lifestyle, and social avoidance), by altering the production of proinflammatory cytokines and metabolic molecules (i.e., cholesterol, fatty acids, glucose, hormones as leptin and insulin), can affect the physiological function of organs and biological systems, including the immune system. The latter is shaped by the hormone cortisol, the final product of the hypothalamus-pituitary-adrenal (HPA) axis activity, and by proinflammatory cytokines released by immune cells of the central nervous system (CNS) that is, microglia, monocytes, and mastoid cells, through upregulation of the transcription factor NF- $\kappa$ B, mainly driven by sympathetic nervous system (SNS) and its neurotransmitter noradrenaline. Chronic activation of the stress system induces a “conserved transcriptional response to adversity” (CTRA) in peripheral immune cells. This is characterized by increased expression of proinflammatory genes (i.e., IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) and decreased expression of antiviral- and antibody-related genes. Systemic proinflammatory cytokines can reach the brain (via blood circulation and afferent branch of autonomic nervous system; not shown), thus increasing neuroinflammation, epigenetic brain changes, and mental disorders. Based on this interaction between psychic and biological systems, treatment for mental disorders could benefit not only from traditional psychiatric drugs but also from psychotherapy and body-mind therapies, including meditation, stress management, yoga, and tai chi. When the treatment works, epigenetic reversion of HPA axis activity and inflammatory transcriptional response (downregulation of NF- $\kappa$ B) seem to be the main mechanistic pathway that allows the recovery of balance of both mood and immunity, thus improving resilience, as the ability to respond effectively to stress. NF- $\kappa$ B, nuclear factor  $\kappa$ B; CTRA, conserved transcriptional response to adversity; PFC, prefrontal cortex; OFC, orbitofrontal cortex.

monocytes among breast cancer survivors at 3-month follow-up. Practicing tai chi decreased monocyte expression of TNF- $\alpha$  and IL-6 in samples of insomnia patients, both immediately after training and in medium- and long-term follow-up.<sup>92</sup>

Genomic studies cited by Bower and Irwin yielded consistent findings about the ability of all MBTs to reverse the proinflammatory signaling pat-

terns, namely, the reduction of NF- $\kappa$ B activity. The authors have measured these effects in trials of yoga, tai-chi, and meditation (especially in MBSR) in different conditions (i.e., older adults suffering from loneliness, chronically stressed caregivers, and women diagnosed with breast cancer). Genetic modification in signaling pathways seemed to be more sensitive to MBTs in naive practitioners after a



few weeks of meditation, compared to effects on circulating proinflammatory markers, which required more prolonged meditation experience.<sup>92</sup>

A meta-analysis conducted by Buric and colleagues<sup>93</sup> highlighted the presence of a general pattern characterized by significant downregulation of proinflammatory genes and pathways, the key factor NF- $\kappa$ B, in meditation practitioners. Nonetheless, the authors pointed to a series of weakness and limitations of the currently available studies: few participants per study and small effect size, different characteristics of intervention groups (healthy versus diseased individuals), differences in control group (active versus wait list group), treatment duration and frequency of practice, diverse follow-up period, lack of correlation with psychological parameters, influence of lifestyle confounders (diet and exercise), and different methods of gene expression analysis. These findings support the merit of further studies based on a multidisciplinary approach regarding mind–body intervention effects on human health.

### Conclusions and perspectives

Distress can produce chronic “wear and tear” on all the physiological systems, leading to allostatic overload. Mutual communication between CNS and the immune system under acute and chronic stress and during chronic physical illnesses has been carefully studied (Fig. 1). Recent epigenetic research has shown the potential mechanistic pathways mediating the transduction of environmental inputs into patterns of gene expression. Stressful conditions, particular those in early life, have been associated with epigenetic alterations in specific cortical and subcortical brain regions, showing relevant overlap with different psychiatric conditions. Similarly, chronic social adversities activate a dysregulated response in circulating immune cells that is marked by increased expression of proinflammatory genes. Through findings in epigenetic research, we are coming to understand how human genome and biological systems are shaped by physical and social life events that occur during the lifespan. Indeed, the reversal of epigenetic marks, through transcriptional downregulation of NF- $\kappa$ B,<sup>92,93</sup> which has been demonstrated in many studies, can better explain the beneficial effects of stress management (psychotherapy, meditation, and other MBTs) on mental health. Furthermore, the bidirectional

relationship between mental disorders and lifestyle behaviors (i.e., a diet high in saturated fat, smoking, sedentary behavior, and lack of social support), via the release of proinflammatory cytokines, and changes in the metabolic profile (i.e., high serum cholesterol, free fatty acids and fasting glucose, increased hormones and signals as insulin and leptin) can alter the physiological functions of target organs and biological systems, thus affecting mental health.

The complexity of the human network invites the consideration and treatment of the psychiatric patient as a whole individual, particularly vulnerable to the effect of chronic stress. In the coming era of an integrated vision of human health and diseases, it is necessary to “put the patient back together,” going beyond biomedical reductionism.<sup>94</sup> The PNEI paradigm, which integrates scientific knowledge derived from both psychological and biological sciences, has moved in the last two decades from a “niche research area of psychosomatic and biological psychiatry to an established mainstream research and translational area.”<sup>51</sup> In the future, this paradigm could make a further fundamental contribution, not only in mental health management and neuroscience research but also in the general health area of prevention and therapy for major diseases.

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### Author contributions

All authors contributed equally to this work.

### Competing interests

The authors declare no competing interests.

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