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# Psychoimmuno-Dermatology: A Network Approach

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## Abstract

The present review explores several layers of the psychodermatological „network of networks" including neuroimmune mediators of dermatological neuroimmunomodulation, as parts of the so-called „neuroimmune-cutaneous system" and their mediator role between psychosocial, behavioral network changes and psychodermatological processes. The distress caused by psychosocial network disturbances such as serious life events, child traumas, bereavement, losses, dominance/submission, and shame might exert significant changes through dysregulated central and peripheral HPA activity caused by profound and enduring distress, with neuroimmunological consequences like rightward shift in frontal hemispherical lateralization and TH1/Th2 shift in the immune response. These changes are expressed by the transformation of network patterns of different layers of the social psychoimmun-dermatological network of networks. We explore the components of the neuroimmune-cutaneous network, with special regard to psoriasis and atopic dermatitis in a psychosomatic context. Psychosocial factors of psychodermatological diseases are taken as alterations of social-psychobehavioral networks exerting an impact on neuroimmune modulation of dermal inflammatory processes. In the final part of the paper, the therapeutic consequences of this complex, network medicine framework are discussed.

**Keywords:** Neuroimmune-cutaneous system; neuroimmune mediators of skin diseases; psycho-immune dermatology; Psoriasis; Atopic dermatitis; Hemispheric lateralization; Th1/Th2 shift, Network of networks"

## Introduction

Clinical and experimental studies support the brain's ability to influence skin processes. According to Locala [1], stressful life events have been associated with the emergence of immunological pathogenic dynamics in skin diseases. Emotional stressors, psychiatric illnesses, and dermatological pathologies such as acne, alopecia, atopic dermatitis, herpes simplex, psoriasis, urticaria, viral warts, and vitiligo were reported to have strong associations by Lugovic-Mihic et al. [2]. Nearly 30% of dermatology patients also suffer from depression, according to research by Filakovi and colleagues [3]. The so-called „Brain-Skin Connection" implies the network model and calls for interdisciplinary research including psychology, endocrinology, skin neurobiology, skin inflammation, immunology, and pharmacology, Chzuen, and Lyga offer a wide-scale comprehensive theoretical insight into the development of this research field [4]. Other papers deal with the brain-skin axis with special regard for a given psychosomatic skin disease, such as psychological, psychiatric, hormonal, and dermatological aspects of psoriasis [5]. Research regarding comorbidity of psoriasis and depression also proves network-like interrelationships including the HPA axis, and Maqbool et al found inflammatory markers TNF-α, IL-2, IL-6, IL-23, IL-1β, IL-10) and serotonin transporters (5-HTT) increased both in depression and psoriasis, showing the immune-inflammatory linkage between psoriasis and major depression [6]. The skin-brain interactions might show opposite dermo-psychological influence, too. Fregoso et al [7]. found that wounding in the periphery is associated with an altered expression of inflammatory mediators and PRR genes in the hippocampus, which may cause cognitive dysfunction, and depressed behavior in mice.

Bio-psycho-social modeling emphasizes the interconnected, hierarchical, multilayered network of these networks, which can sometimes play a symptom-creating or pathological role. Patients with chronic inflammatory skin diseases require complex care in the framework of the network approach, with psychosomatic or psychological treatment playing an important role in treating complex problems due to accumulated childhood trauma or abnormal coping patterns.

## The Neuroimmune-Cutaneous System

The skin has an ectodermal origin, so we can hardly be surprised by the rich network of nervous, endocrine, and immune components of this organ, which can be easily verified by light and electron microscopy. This system of relationships, which makes the skin a neuro-immunocutaneous system, is also manifested in the anatomical, physiological, and pathological characteristics manifested in diseases. The „external covering" of the internal body surface of the airways and the intestinal tract can be compared to this system, so in this sense, we can also speak of a neuroimmune-enteric or neuroimmune-bronchial system. The allergic symptoms in all three systems follow a similar pathology, in which, in addition to dendritic and other APC cells, TH1, TH2, TH17, and Treg cells, tachykinins and Substance P play a prominent role, but somatostatin and VIP also play an important role in influencing mast cells, lymphocytes, secretory, and muscle cells. Among the neurotransmitters and neurohormones of the skin, in addition to substance P, VIP, somatostatin, neuropeptide Y, neurotensin, CGRP (calcitonin gene-related peptide), and neurokinins all play a role. The prolactin, MSH, and ACTH hormones present in the skin, as well as the catecholamines, enkephalin, endorphin, and acetylcholine, can play an immunomodulatory role.

As a sensory organ and primary defense line, the skin has a rich sensory innervation, but it is also rich in post-ganglionic adrenergic and cholinergic fibers. The sources of the already mentioned substances P, VIP, and CRGP can be the sensory and vegetative nervous systems, but these mediators can also be released from the cells of the epidermis and other dermal cells. The targets of neuropeptides are the antigen-presenting dendritic cells and the migratory Langerhans cells, but the neuropeptides also affect the endothelial cells, and we have already mentioned the key cell under the influence of CRH, which is strongly influenced by stress mechanisms, the mast cell, which thus completes a special „brain-skin" circle. So, it means a reciprocal, immune-neural connection, where Merkel cells and Langerhans cells, keratinocytes, and melanocytes also play a role in the production of neurotransmitters in the skin. Merkel cells are located near nerve endings, and Langerhans cells also have dendrite-axon connections. Similarly, direct contact between mast cells and nerve fibers can be observed.

Mast cells are responsible for the symptoms of atopic dermatitis, which causes hives and local allergic edema. Thus, the increased IgE production, the dysfunctional TH1/TH2 shift, and eosinophilia all have a symptom-maintaining and aggravating role through the mast cell, and stress effects play a major role in this, according to Elenkov and Chrousos [8]. The TH1/TH2 shift increased as a result of stress creates a cytokine milieu favorable to the atopic response through increased IL-4, IL-10, and IL-6 levels and reduced IFN-alpha production due to stress, which increases skin symptoms. In atopic dermatitis, the role of the IL-23-TH17 axis can also be raised, similar to those already involved in asthma. A direct sensory nerve stimulus, axon reflex, which releases neuropeptides from the peripheral nerve endings, can also lead to the activation of mast cells. In addition to the mobilizing effect of antigen and IgE, cytokines, hormones, and neuropeptides such as somatostatin, neurotensin, CGRP, and especially substance P are capable of activating mast cells. NGF can also be considered a mast cell growth factor and can trigger mast cell degranulation. Other growth factors, such as SCF (stem cell factor), affect mast cell physiology and sensitize mast cells to PACAP (pituitary adenylate cyclase-activating polypeptide), which is considered important in the post-traumatic physiological response and has a similar effect to VIP.

The skin may be involved in the immuno-neural interactions observed during stress. This is indicated by an increase in the number of activated perifollicular macrophage cell groups and degranulated mast cells and a decrease in intraepithelial T cells as a result of stress.

Baldness and the inhibition of hair growth caused by stress are attributed to Substance P and NGF-dependent macrophage and mast cell activation. Mast cells also play a major role in immunosuppression caused by UVB radiation and sunburn. This phenomenon is indicated by the common form, or „neuro-cytokine" connection, because the immunosuppressive effect of mast cell-derived TNF triggers, among other things, the activation of the latent herpes virus after sunburn. TNF secretion by mast cells is facilitated by CGRP released from damaged nerve endings caused by UVB burns.

Stress exacerbates psoriasis and atopic dermatitis. All of this is a good example of the cross-talk phenomenon between mast cells, neurons, and keratinocytes, in which the increased production of CRH as a result of stress and the increased expression of the CRH receptor play a role. Mast cells themselves are capable of synthesizing and producing CRH in response to IgE and also have a CRH receptor. Rita Levi-Montecalcini recognized precisely this „neuroimmune" role of the mast cell. In addition to the neural activation of mast cells, mast cells are also an „interface" connecting station for mediators of peripheral nerves and local inflammation. The environment of the surrounding nerves is rich in mast cells, and the manipulation of sensory fibers affects the local density of mast cells. It is important to see how key elements of the local immune-neural network, including histamine, serotonin, and cytokines produced by it, all modulate NANC neurotransmission.

NANC fibers display both histamine (H1, H3) and serotonin (5-HT2a) receptors. These receptors are increased in inflammatory conditions, and the released TNF lowers the stimulus threshold of afferent C fibers and directly increases the secretion of Substance P, neurokinin A, and CGRP. As part of the stress response, neurotransmitters secreted by sensory fibers also influence barrier functions by inducing inflammatory processes. According to Raap and Kapp [9], a higher level of neuropeptides and a greater density of neuropeptide-positive nerve fibers are characteristic of lesions with atopic dermatitis.


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Dendritic cells, also known as Langerhans cells, are crucial components of psychodermatological phenomena in addition to mast cells and CGRP. Although Substance P is one of the key factors in inflammatory processes, in certain situations, Substance P and CGRP can inhibit antigen presentation. Since Langerhans cells are located near CGRP-containing fibers and CGRP can inhibit Ag-presenting cells (Langerhans cells, macrophages), local administration of CGRP may not result in a prolonged hypersensitivity reaction, which can be attributed to the inhibitory effects between the surrounding nervous system and the immune system.

## Psychoimmunology of psoriasis

Vitiligo, prurigo, psoriasis, and atopic dermatitis are only some of the dermatoses that can be affected by one's state of mind, and neuromediators play a role in all of them. Psoriasis can be triggered or worsened by emotional or mental strain. According to research by Mazzeti et al. [10], between 32 to 90 percent of psoriasis cases can be traced back to stress. Symptoms often appear between two and four weeks after the stressor has ended. Psychotherapy is known to improve psoriasis symptoms, and people with psoriasis are known to be more stress-sensitive than the general population. Two-thirds of patients show signs of psychiatric distress, typically in the absence of any obvious external stressors. Psoriatic lesions heal after trauma or surgery to the nerves that supply them, as reported by Pincelli et al. [11]. Psoriasis is characterized by an increase in the number of nerve fibers within the epidermis that are filled with Substance P. According to Abadia-Molina et al. [12], the increased nerve fiber density and SP, VIP, and CGRP in the nodular lesions of prurigo mean that they cannot be considered secondary lesions owing to scratching. Alterations in neurocutaneous function were also noted in atopic dermatitis by Cooper [13] Pincelli et al. [14] found that somatostatin-carrying fibers diminish while the number of fibers containing Substance P and CGRP increases and adrenergic innervation declines. All this refers to the weakening of the factors that inhibit the local inflammatory process.

The onset of psoriasis is often preceded by a psychological stressor or a serious life event, which can also play a role in flare-ups of psoriasis symptoms. Richards et al. [15] found lower baseline cortisol levels and a low cortisol response in patients with stress-related psoriasis flares, similar to those found in atopic dermatitis. All this points to disturbed or exhausted hypothalamic HPA regulation, which may be a consequence of chronic stressors. At the same time, the catecholamine level was elevated (Buske-Kirschbaum et al. [16] and following the stressor, the circulating CD4+ and monocyte count increased and the CD3+/CD25+ T cell count decreased in psoriasis patients. Locally produced neuropeptides can also contribute to the maintenance of the disease. In the psoriatic plaques themselves, the density of nerve fibers increases, and local levels of calcitonin gene-related peptide (CGRP), Substance P (SP), vasoactive intestinal peptide (VIP), and NGF (Nerve Growth Factor) all increase. T cell and keratinocyte proliferation following NGF effect, mast cell migration, degranulation, and the chemotaxis of memory cells are also enhanced.

Psoriasis is the result of immunological events based on a complex genetic basis. For a long time, the histological characteristics of psoriasis were leukocyte infiltration of the epidermis and its deep layer, keratinocyte proliferation, and an autoimmune process mainly based on TH1, mediated by TH1 cytokines (gamma interferon and TNF alpha). However, the TH17 cytokine network also plays an equally important, central role in the development of lesions. TGF beta and IL-6, produced by Treg cells and keratinocytes also play a role in this process and help the transformation of naive T cells into TH17 cells. IL-23 produced by dendritic cells, Langerhans cells, and keratinocytes induces further TH17 expansion, and due to IL-22 produced by the increased number of TH17 cells, the number of keratinocytes increases. IL-22 stimulates the keratinocytes of the skin and activates the STAT3 pathway, and acanthosis occurs in addition to the proliferation of keratinocytes. IL-17 and IL-22 increase the infiltration of the skin, closing the psoriatic vicious circle. IL-36 produced by keratinocytes further deepens this, because it activates resident dendritic cells and increases the pathogenicity of TH17 cells through the release of IL-23. But IL-17 produced by activated TH17 cells also attracts neutrophil granulocytes to the affected tissue area. The levels of gamma IFN and TNF-α of TH1 and TH17 origin were also increased in these tissues.

Psoriasis is a real psychosocial immune disease since the skin changes aggravate the patient's state, who is also under stress for other reasons and has serious psychological problems. The quality of life deteriorates, social stigmatization, and difficulties at work can all lead to increased stress and even depression. 40% of patients report serious emotional and mood disorders, and depression and anxiety symptoms may also be present in more than half of patients.

The psychoneuroimmune nature of psoriasis is confirmed by the fact that therapeutic stress reduction has a good effect on the effectiveness of the treatment. However other psychotherapeutic methods have also proven to be effective, such as hypnosis. Cognitive behavioral therapy resulted in a reduction in the frequency and intensity of symptoms even six months after the treatment, and stress reduction and imagination techniques also had a good effect on the development of psoriasis.

## Psychoimmunology of Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, recurring, highly itchy skin disease provoked by allergens and infections, which can otherwise be considered a national disease in developed countries. Chronic inflammatory phenomena, damaged barrier function of the skin, and disruption of skin regeneration processes are characteristic of the disease. The early stage of atopic dermatitis is characterized


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by dryness of the skin, loss of water, and a reduced protective role against environmental pathogens. In the early phase, Th17-related cytokines: IL-6, IL-17A, and IL-23 play a role. Months later, TH2 cytokines, IL-4 and IL-13, predominate, with an unchanged gamma IFN level. TH2 cytokines, IL4, IL5, and IL13, produced by T cells attracted to the given area, have been detected in AD. IL-4 and IL-13 are responsible for the production of IgE by B cells, which is the result of increased activity of intracellular STAT-6. IL-5 is responsible for the development, activation, and survival of eosinophils, in atopic dermatitis, both the IgE level and peripheral eosinophilia can be observed, according to Leung [17]. IL-4, IL-5, IL-10, and IL-13 produced by allergen-specific T helper cells taken from the symptomatic skin area mainly reflect a TH2 cytokine profile, according to Brandt and Sivaprasad [18]. The disease can be characterized by both TH1 activity and a temporary predominance of TH2 activity. According to Thepen et al. [19], their dominance varies, and this appears in the context of the sequential cell activation of TH2 and TH1, whose dynamics depend on the chronicity of atopic dermatitis. The exhausted, hyporeactive HPA axis and the hyperactive LC adrenergic activity may play a role in this, which, in turn, may create an increased TH2 milieu for allergic hypersensitivity and the phenomenon of atopic dermatitis.

Due to the development of TH2 dominance, we have to take into account the role of stress, inducing a TH1/TH2 shift, and the role of the pro-TH2 cytokines TSLP, IL-25, IL-33, which can polarize dendritic cells and contribute to the enhancement of the TH2 response, is also worth mentioning. TH2 cytokines (IL-4, IL-5, IL-13, IL-31, and IL-10) all play a role in the symptoms of atopic dermatitis. TH2 cytokines also play a major role in the maintenance and chronicization of atopic dermatitis, the synthesis of IL-4, IL-5, IL-6, IL-10, and IL-13 increases, as a result of which the IgE level rises, while circulating CD4 and IFN-gamma produced by CD8 lymphocytes decrease. This TH2 predominance is characteristic of the acute phase, which later shifts towards TH1 as the disease progresses. Changes in several immunological parameters have been described in atopic dermatitis, such as a decrease in the number of circulating T cells, reduced responsiveness to mitogens, reduced cytotoxic potential of monocytes and NK cells, reduced response to chemotactic mediators, and peripheral eosinophilia. In patients genetically sensitive to irritating environmental antigens, increased IgE production and increased histamine release from mast cells occur even without stress. But the skin, as a protective wall, can also become permeable to provocative antigens, which can lead to allergies.

IL-4 and IL-13 stimulate IgE synthesis and shift the B cell response from other Ig isotypes to IgE. However, their effect increases the expression of the adhesive molecule VCAM-1, which collects eosinophils at the site of inflammation. IL-4 and IL-10 are triggers of mast cell proliferation, and IL-5 has a role in further recruitment and stimulation of eosinophils. During the stimulation, cytotoxic proteins are released, such as the eosinophil cationic protein (ECP), which helps to extend the lifespan of the eosinophils and causes mast cell degranulation.

Antigen-presenting cells (Langerhans cells, macrophages) both have a surface IgE receptor. Chronic clinical consequences, chronic lichenification, and hyperkeratosis are associated with the proliferation of mast cells and eosinophils, and in atopic lesions, increased IL-12 expression and IFN alpha activity can be detected, which also indicates the involvement of TH1 processes. So, after the acute allergic response induced by IL-4 and IL-5, in the consolidation phase, IFN-alpha secretion is the determining factor in atopic dermatitis. IL-12 produced by activated eosinophils and macrophages causes this shift from TH2 to TH1 dominance, according to Boguniewicz [20].

TNF produced by macrophages, antigen-stimulated T cells, and mast cells all play an important role in the maintenance of chronic eczema. Various food allergens (cow's milk, eggs, peanuts, sea crabs, and fish) are capable of provoking atopic skin reactions and flaring up existing atopic dermatitis through IgE mediation.

Chronic eczematous skin diseases of non-allergenic origin form another subgroup. Questions arise regarding the reduced HPA activity observed in patients with atopic dermatitis, the background of which is the effect of persistent proinflammatory cytokines following chronic inflammatory processes of the skin, and the consequent reduction of HPA axis activity may also play a role, according to Turnbull and Rivier [21]. In addition to the persistent activity of proinflammatory cytokines, the negative feedback effect of persistently elevated cortisol levels can also lead to a decrease in the activity of the HPA axis. Tausk suggests a hereditary factor behind the reduced HPA activity observed in people with atopic dermatitis but draws attention to the fact that the compensatory element expressed in the increased number and increased sensitivity of the glucocorticoid receptors of the peripheral immune cells results in a response leading to an increased TH1/TH2 shift even to a minor rise in cortisol levels to stress.

Chronic stress or inappropriate, abusive, or negligent, maternal behavior also leads to disturbed responsiveness of the HPA axis. The catecholamine influence (noradrenergic, adrenergic innervation) shifts the TH1/TH2 shift in the latter direction, suppressing the IL-12 activity responsible for TH1 induction, while catecholamines promote the TH2 response by increasing IL-10 secretion. Ionescu and Kiehl [22] measured higher noradrenergic levels in adult patients with atopic dermatitis even at rest, which indicates internal anxiety. Among adults with atopic dermatitis, Buske-Kirschbaum et al. (2002) measured elevated basal levels of norepinephrine and adrenaline, and the activity of the LC-sympathetic IR-adrenal axis showed increased activity in response to stress. Endogenous cortisol also promotes the apoptosis of eosinophils and basophils, so stress mediators can act as brakes


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by increasing the apoptosis of eosinophils and basophils, however, with the depletion of the HPA axis, the chronic allergic response can also intensify, according to Meagher et al. [23].

The range of therapeutic interventions that act as a general stressor buffer or reduce the psychoimmunological response is wide, and many points of the involved networks offer opportunities for intervention. At the social-behavioral level, structural patient education programs, habit modification methods, and dermatological education programs can be applied. Cognitive-behavioral therapy and intensive short-term dynamic psychotherapy (ISTDP) are aimed at psychological-cognitive processes, while autogenic training can influence the patients' autonomous nervous system and moderate heightened activity. These therapeutic interventions can all affect the severity of eczema, itching, and scratching, i.e. the course of atopic dermatitis.

## Personality, Emotionality, and Psycho-Immune Dermatology

Alexander and French [24] suggested, as early as the 1940s, that the inhibition of the expression of anger and hostility causes increased stress in children suffering from atopic dermatitis. In Alexander's classification, atopic dermatitis – under the name neurodermatitis – was one of the seven psychosomatic clinical pictures. In the model, the authors attributed specific roles to different emotional conflicts in the elicitation and maintenance of the given medical condition. According to Alexander, the suppression of anger due to rejection by the mother plays a role in increased emotional stress, early mother and child relationships, and developmental psychology. In addition, personality problems caused by the distorted early relationships in the background of the conflict-specific pattern presumed by him can also explain psychoimmunological clinical features deeply affected by stress-biology processes.

This inhibition can also be matched with the „shyness" characteristic of allergic patients and conjures up the problems of the suppression of aggression, so important in psycho-oncology. The issue of early mother-child relationships is cited by numerous related personality studies as well. According to Kagan [25], children suffering from allergic illnesses are characterized by shyness, withdrawal, and inhibition in addition to hypertonicity, higher levels of catecholamine derivatives in the urine, and higher cortisol levels in saliva. According to Jasnoski et al. [26] multi-directional links were detected between shyness, immediate oversensitivity, and anxiety traits. Hay fever, eczema, asthma, and urticaria are proportionate to excessive kindness, introversion, and fatigue, as described by Bell's [27] study. Immature, uncertain, anxious, dependent, rejecting, overprotective, and unconsciously aggressive mothers do not ensure skin contact to provide security. Due to a lack of caressing, tenderness, and warmth, a contradiction between the desire for symbiosis and the simultaneous fear of it can be typical. In atopic patients, situations causing infantile uncertainty are pathogenic. 60% of „Eczema" mothers do not calm down their babies, while this behavior occurs in 16% of the control group members.

According to epidemiological data, childhood atopic eczema increases the risk of ADHD, that is, attention deficit hyperactivity disorder, in later stages of life, as Buske-Kirschbaum et al. [28] stated. Inflammatory cytokines accompanied by higher psychic stress and allergic inflammatory processes can harm the development processes of the prefrontal cortex, and altered neurotransmitter activity can develop an ADHD clinical picture. On the other hand, higher stress levels detected in AHDH patients can exacerbate atopic eczema because of psychoimmunological background factors. Genetic factors and prenatal stress increase the morbidity of these diseases as common risk factors.

Divorce, mourning, and family conflicts are frequent before the recurrence of the illness. In 55%–86% of atopic dermatitis patients, emotional stress was among the triggering factors, according to Picardi and Abeni [29]. Kodama et al. [30] examined disaster stress after the Hanshin earthquake, involving 1457 patients diagnosed with atopic dermatitis. In seriously affected areas, the frequency of recurrence and aggravation of the illness was considerably higher one month after the disaster. Picardi and Abeni also emphasize that emotional stress associated with life events of great weight is accompanied by the recurrence/aggravation of atopic dermatitis. According to Scheich [31], increased everyday stress effects intensify atopic dermatitis symptoms, leading to deteriorating symptoms and increased pruritus. Consequential psychic difficulties, social stigmas, and cosmetic problems lead to further depression, social stress, and a vicious psychosocial circle, further complicated by inadequate coping characteristics.

Hashiro and Okumura [32] found patients suffering from atopic dermatitis to be more depressed and anxious than control subjects. NK cell activity was also significantly lower in patients with atopic dermatitis. In their research, anxiety measured by the STAI (State-Trait Anxiety Inventory) affected NK cell activity.

Emotional factors can both trigger and aggravate urticaria, according to Kaneko and Takaishi [33]. In their study of 27 patients receiving hypnotherapy, the authors found that symptoms had subsided in five cases, symptoms had nearly resolved in 9 cases, and considerable improvement occurred in 8 cases through hypnosis; the treatment proved to be ineffective only in 5 cases. In the course of the 7-month follow-up, there were only a few cases of relapse. The longer the illness prevailed, the less effective hypnosis was. Results showed similar correlations with hypnotic susceptibility. The results of relaxation suggestions lagged behind the results achieved in hypnosis targeted at eliminating symptoms.

In another study, the authors were able to trigger urticaria by


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the hypnotic suggestion of the conflict situation and the suggestion of hotness in patients, in these cases, urticaria was experienced to be triggered by physical warmth and emotional conflicts. In examining 53 patients suffering from urticaria, IgE values were high in several cases, even in the absence of the provoking antigen.

Mason [34] endeavored to treat ichthyotic erythroderma, known as incurable, by hypnosis and achieved a selective reduction of symptoms by selective hypnotic suggestion (first directed to the left hand), and a variable improvement of 50 to 95% by extending suggestion to the entire body. No relapse was experienced during a period of one-year patient follow-up. The remission of ichthyotic erythroderma was proportional to hypnotic susceptibility.

Teshima [35] explained the etiology of alopecia universalis by psycho-immune factors, and combined small doses of immunosuppressive medication with relaxation and stress relief, and five out of the six patients showed considerable improvement. It was only the control group treated with corticosteroids that did not show improvement. Background processes are indicated by the fact that in the case of patients involved in both autogenic training and imagery treatment, T helper/processor proportions significantly decreased, and the relative proportion of NK cells increased.

The psychoimmunological character of alopecia is supported by the fact that the clinical picture explained by autoimmune origin is frequently preceded in adults by states of subject loss and mourning, as shown by Misery et al. [36]. In the scope of their research, Colón et al. [37] also found depression and anxiety to be more frequent in their analyses. Liakopolou et al. [38] observed social inhibition and disorders of social relationships in children.

Shenefelt [39] found stress management techniques and relaxation treatments to be effective in treating atopic dermatitis. Ehlers et al. [40] found autogenic training, cognitive behavioral therapy, and a combination thereof to be effective in the improvement of symptoms, in the reduction of itching, and reduction of steroid medication. Ikemi and Nagakawa [41] had favorable therapeutic experiences using the combined treatment in the cases of allergic dermatitis and food allergy. According to Stangier et al. [42], the intensity of symptoms (strong itching) before treatment, low IgE, and coping development played a verified role in the effectiveness of psychological treatment. Stewart and Thomas [43] found hypnotherapy to be beneficial for atopic children and adults.

## Hemispherical lateralization and dermatological symptoms

Individuals with better paternal treatment had a relative left frontal dominance. In contrast, fearful attachment styles were significantly correlated with right hemispheric dominance. 60% of mothers with babies suffering „eczema" do not calm their baby when crying, compared to 16% in the control group, and immature, insecure, anxious-dependent, dismissive or overprotective, and unconsciously aggressive mothers do not provide secure skin-to-skin contact to their babies. Babies of depressed mothers show relative right prefrontal dominance, according to Jones et al. [44]. Right prefrontal hemispherical dominance is associated with an insecure attachment style, which in turn is associated with difficulties in emotion regulation and less adaptive coping strategies in adulthood as a result of adverse childhood experiences and inadequate parental treatment, especially in cases of high individual vulnerability.

These findings imply that early exposure to motherly love and care is linked to greater activity in the left hemisphere, while early exposure to trauma and fearful attachment causes the right hemisphere to become more dominant. Based on a comparison with the worldwide literature, we find that frontal dominance in the left hemisphere is more indicative of approaching behaviors, while frontal dominance in the right hemisphere is more indicative of avoiding behaviors. An increase in the degree to which an individual's right lateral frontal asymmetry (rLFA) is altered during times of stress is associated with an increase in the severity of adverse health consequences, as demonstrated by Lewis et al. [45]. During times of low academic stress, rLFA was higher among university students than during times of high academic stress, and vice versa. During times of high academic stress, rLFA was lower among university students than during times of low academic stress. According to the model of Mathersul et al. [46] adults with panic disorder have lower rLFA than healthy participants, suggesting that rLFA can be used as a predictor of anxiety. A state anxiety manipulation reduces rLFA in those with social anxiety, suggesting a link between acute anxiety and decreased rLFA [47].

According to research by Sackeim et al. [48], the right hemisphere of the brain handles negative emotions, while the left hemisphere cultivates positive ones. The right prefrontal cortex is involved in reserved, avoidance conduct, according to Davidson's [49] hypothesis, while the left prefrontal cortex is responsible for approaching behavior. Finally, there is a meaningful connection between hemispherical differences and stress-induced psychodermatological phenomena, as elevated stress can alter human hemispherical lateralization, causing a rightward shift in frontal dominance, according to Ocklenburg et al. [50].

In findings of Bozsányi et al. [55] group of atopic dermatitis patients showed right hemispheric shift (lower rLFA) and the results of the BIS/BAS questionnaire seem to support this model. The frontal EEG activity of the atopic dermatitis group was significantly more lateralized to the right compared to the control group. The observable neurophysiologic differences in psoriasis and atopic dermatitis raise the point that the two inflammatory skin diseases differ in both their pathogenesis and course and psychophysiological background mechanisms. Psoriasis is a Th1-predominant autoinflammatory skin disease, while AD is a typically Th2-dominant inflammatory skin disease. The marked


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differences in the degree of rLFA, SNS, and PNS features and BIS/BAS scale values prove the divergence of psychosomatic background mechanisms between the patient groups.

Bozsányi et al. also found a significant difference between controls and AD patients in the BIS scale, where AD patients have more avoidant and inhibited behavior, which suits the r_LFA dominance of AD patients well. The BIS is responsible for maintaining a continuous state of alertness and vigilance, and serves a control function, protecting individuals from negative and painful outcomes by increasing avoidance behavior. This is accompanied by a personality trait of a tendency to worry and increased brooding and rumination. All of this results in avoidant people constantly monitoring potential danger signals in the environment, which leads to generalized anxiety in the long term, according to Hargitai et al. [51]. It is important to take out left-handed patients, (predisposed to allergic and other immunologic diseases). There were not any remarkable changes in the significance of measured values, which suggests that the immunological and psychophysiological consequences of right frontal hemispherical dominance and right-handedness might have different background mechanisms.

## Behavioral network medicine and psychodermatology

When we examine psychodermatology from a behavioral, pathophysiological, and therapeutic perspective, we can see the validity of a systemic bio-psycho-social approach for diseases with significant public health impacts. If there is a shift in perspective, the large community of psychoimmunological specialists can include the diagnostic and treatment methods of psychosomatics, clinical psychology, and lifestyle medicine into an already robust biological care system [53]. Social hierarchy, imbalance of social status, dominance, submission, and social support are features and indexes of social network dynamics, which are deeply embedded in social cultural norms, perceptions, and expectations and mediated to the abyss of the body through psychophysiological processes shaped by psycho-developmental determinants. This way, social networks can influence psychophysiological networks, creating social-somatic continuity. The mental representations of social hierarchy, shame, loss of social support, control, and joy are transferred by neuroendocrine-immune informational pathways [52] and might influence the brain-neurocutaneous network included in psychodermatological diseases. The bio-psycho-social approach gives us a framework for network theory, which lets us understand how our neuroendocrine, immune, musculoskeletal, and adipose tissues „talk" to each other in the „network of networks" of social psychoimmunology.

However, in the context of the socio-psychoimmunological approach, the limits of the graph's validity exceed the levels of the systems of molecules, organs, and organic systems and bypass the individual and personal as well. This approach includes the cultural and social spheres, the economy, politics, and the macro-social environment too. It includes partnerships, social support, control, power, the territorial principle, dominance and submission, and social ranking. They are all presented in a set of relationships that can be outlined by graphs, edges, and hubs. But connections over time are also aligned with the psychoimmunological interpretation of diseases as a graph and network, in the narrative framework of psychosomatics. Therefore, the particular 'metagraph network' of socio-psychoimmunology lies across several layers of graphs.

An overhauled definition necessitates a networked interpretation as the foundation for intervention in areas such as inter-organ communication networks, neuroendocrine adaptive and maladaptive interaction networks, neurocognitive networks organizing perception and behavior, and the interplaying social networks and patterns of socioeconomic and cultural factors.

For us, the most important thing in bio-psycho-social modeling is the interconnected, hierarchical, multilayered network of these networks. Nevertheless, sometimes these network patterns occur only temporarily, which can, however, play a symptom-creating or pathological role. Examples of this can be seen in the social transduction theory of depression, or in the consequences of early traumatization, which can result in the change of alleles or effects of epigenetic influence.

Thus, from the point of view of systems biology, the stressor transfers the dynamic biopsychosocial system, which is organized as a network of networks, from one attractor basin to another with a lower adaptation value and usefulness. The attractor basin as a phase space constitutes the state of dynamic systems—in this case, a complete biopsychosocial network ensemble, any element of which changes to the specific attractor. This can be called the basin of attraction, where the stressor moves the system to a different attractive „field", which causes the system to be placed in a boundary position, or the stressor slows the return to the optimal attractor basin. In this case, an attractor-borrowed by analogy from mathematics—is a specific subgroup of the phase space of the dynamic biopsychosocial (BPS) system, a specific event, and it limits the interval range of processes that ensures the functioning of the system in a homeostatic dynamic equilibrium or, inducing allostasis to meet the increased challenges while ensuring basic conditions. The dynamic system, which operates as a „network of networks", depends not only on environmental perturbations, which can be called stressors, but also on the person's perceptions, body type, memories, coping patterns, state of life, and genetic characteristics. Allostasis is reflected in allele change, gene transcription level change, epigenetic consequences, metabolic activity differences, receptor desensitization, or other changes in receptor sensitivity, as well as in changes in telomere length. Biopsychosocial resilience is denoted by the distance of the condition as an attractive pool from each other's narrowed, damaged, maladaptive, or preclinical „pool". But resilience is also characterized by the strength of the vector field in the given attractiveness basin, which helps to return quickly to the


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specific attractiveness, i.e., homeostatic physiological equilibrium, laboratory normal values, and ratios.

Patients with chronic inflammatory skin diseases such as atopic dermatitis or psoriasis, require complex care in the framework of a network approach, in which psychosomatic or psychological treatment can play an important role in treating a complex problem due to accumulated childhood trauma or abnormal coping patterns. Many therapies can potentially be used in these diseases. The treatment of psychodermatological diseases consists of standard psychotropic drugs, the placebo effect, and suggestion. It implies cognitive-behavioral methods, biofeedback, and hypnosis, all of which together offer several targets of the social-psychoimmunological „network of networks".-

## Conclusions

Stressful life experiences have been linked to the development of skin diseases with psychoimmunological pathogenic dynamics. The skin is a neuro-immunocutaneous system, a network of nervous, endocrine, and immune components, including networks of cells (dendritic, Langerhans cells, mast cells, TH1, TH2 and TH17 and Treg cells etc, neurons, etc. endocrine cells), networks of neuroendocrine mediators (histamin, tachykinins, Substance P, somatostatin, VIP, neuropeptide Y, neurotensin, CGRP, prolactin, MSH and ACTH catecholamines, enkephalin, endorphin, and acetylcholine) and cytokines (Th2 related IL-4, IL-5, IL-10, IL-13 cytokines, Th17-related IL-6, IL-17A, and IL-23 cytokines) and transcriptomal patterns, shifts in genetic alleles The stressful changes in psychosocial network patterns (traumatic early attachment, adverse childhood experiences, (dominance-submission, loss of spouse, SET-social evalutive threat, shameful experiences, harassment, and rumination of disturbing social anxiety) transform neural network patterns with neuroimmunological significance, leading to right frontal hemispheric dominance, or disturbed HPA axis feedback expressed by central and peripherial downregulation of GRs (suppressed DST, blunted glucocorticoid signaling). In this network model, glucocorticoids and the glucocorticoid receptor are hubs where psychosocial network changes, behavioral-neuroendocrine changes are transferred to several inflammatory pathways via TH1-Th2 shift, or diminished peripheral sensitivity to the immunosuppressive effect of glucocorticoids, leading to enhanced inflammation.

This neurocutaneous system is manifested in complex networked anatomical, physiological, and pathological characteristics manifested in diseases. Bio-psycho-social modeling extends its frame of understanding to the interconnected, hierarchical, multilayered network of these networks, which can sometimes play a symptom-creating or pathological role. At the onset of psoriasis, we often observe a preceding psychological stressor and a serious life event, that can also play a role in flare-ups of psoriasis symptoms. Lower baseline cortisol levels and a low cortisol response in patients with stress-related psoriasis flares indicate disturbed or exhausted hypothalamic HPA regulation, a chronic stress-induced change in the neuroendocrine network. Peripheral neuropeptide network changes also play a role, as locally produced neuropeptides contribute to the maintenance of the disease, with increased levels of calcitonin gene-related peptide, Substance P, vasoactive intestinal peptide, and NGF. Psoriasis is a psychosocial immune disease influencing psychosocial network patterns for cosmetic reasons, as the skin changes aggravate the patient's self-esteem, social competence, and communication. The psychoneuroimmune nature of psoriasis is confirmed by the effectiveness of therapeutic stress reduction, hypnosis, cognitive behavioral therapy, stress reduction, and imagination techniques.

Atopic dermatitis (AD) is also a convincing sample of a network view of a chronic skin disease, characterized by biased network patterns including both TH1 activity and a temporary predominance of TH2 activity. Th2 cytokines, such as IL-4, IL-5, IL-6, IL-10, and IL-13, play a major role in the maintenance and chronicization of AD. TH2 shift increases the synthesis of IL-4, IL-5, IL-6, IL-10, and IL-13, leading to increased IgE levels and peripheral eosinophilia. The recurring, highly itchy skin disease caused by allergens and infections influences the psychosocial network status of the patient, and the chronic inflammatory phenomena lead to morphological network transformations of the skin, damaged skin barrier function, and disruption of skin regeneration processes. The pathological cellular network dynamism is represented by chronic lichenification, and hyperkeratosis associated with the proliferation of mast cells and eosinophils. The importance of the pathological network dynamism of neuroimmune mediators is clear, seeing that mediators produced by macrophages, antigen-stimulated T cells, and mast cells all play an important role in the maintenance of chronic eczema. Antigenic challenges, like various food allergens, can also provoke atopic skin reactions, flaring up existing atopic dermatitis through IgE mediation. Chronic eczematous skin diseases lead to reduced HPA activity due to persistent proinflammatory cytokines and elevated cortisol levels. This may be due to hereditary factors or compensatory elements in peripheral immune cells. Chronic stress or inappropriate maternal behavior can also disrupt the HPA axis's responsiveness. Catecholamines can suppress IL-12 activity, promoting the TH2 response by increasing IL-10 secretion. Stress mediators can act as brakes by increasing the apoptosis of eosinophils and basophils, but with the depletion of the HPA axis, the chronic allergic response can intensify. These pathological processes prove the importance of a network approach in psychodermatological diseases.

The network approach creates a plausible framework for those developmental considerations, which find causal links between early life development, influenced by multiple genetic,


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neurological, and environmental factors, atopic dermatitis, and atypical neurodevelopment, [53].

The network approach offers hub-like foci to differentiate psychodermatological diseases, Bozsányi et al [54] found that atopic dermatitis patients showed right hemispherical shift (by lower rLFA), which supports the idea that inflammatory skin diseases have different pathogenesis and psychophysiological background mechanisms. Psoriasis is a Th1-predominant autoinflammatory skin disease, while atopic dermatitis (AD) is typically Th2-dominant. The BIS/BAS scale values also showed significant differences between controls and AD patients, with AD patients having more avoidant and inhibited behavior, which aligns with the r_LFA dominance of AD patients. This means that the hub-like role of frontal right hemispherical dominance of EEG and BIS tendencies of social behavior, and the immunological biases might have a diagnostic role. The other hub-like diagnostic point is the DST (dexamethasone suppression test) regarding the status of HPA feedback regulation. At the immunocellular level, the Th1/Th2 shift also serves as a hub-like center of network observation expressed by different cytokine levels.

The personality features, coping, developmental problems, life event burdens, emotional status, and cognitive-behavioral properties as psychosocial network features (shyness, C-type coping patterns, depression, behavioral inhibition tendencies) can be measured by psychological tests (ACE questionnaire, Beck depression scale, BIS-BAS questionnaire, Holmes-Rahe scale, etc,), which help to choose the proper psycho-behavioral intervention. Treatment interventions that act as a stressor buffer or reduce the psychoimmunological response are wide-ranging, and many points in the involved networks offer opportunities for intervention. Social-behavioral programs, habit modification methods, dermatological education programs, cognitive-behavioral therapy, intensive short-term dynamic psychotherapy (ISTDP), and autogenic training can all affect the severity of eczema, itching, and scratching.

Bio-psycho-social modeling emphasizes the interconnected, hierarchical, multilayered network of these networks, which can sometimes play a symptom-creating or pathological role. Patients with chronic inflammatory skin diseases require complex care in the framework of the network approach, with psychosomatic or psychological treatment playing an important role in treating complex problems due to accumulated childhood trauma or abnormal coping patterns. Understanding the intricate „communica-tion" between neuroendocrine, Immunological, musculoskeletal, and adipose tissues in the „network of networks" of social psychoimmunology is made possible by the network theory framework provided by the bio-psycho-social approach.

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