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2nd European Psychoneuroimmunology Network Autumn School: The Skin-Brain Axis and the Breaking of Barriers

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Multidisciplinary research in the field of psychoneuroimmunology (PNI) continues to grow and brings together basic scientists, clinicians, epidemiologists, and statisticians, uniting historically separated fields such as neuroscience, immunology, physiology, psychosocial disciplines, and organ-centered medicine. This year's EPN Autumn School is taking the skin as an exemplary organ to dissect and understand the link between the many functional psychobiological layers that contribute to health and fail in disease [1–7]. The manifold contributions to the school are giving yet another impressive example of the diversity of concepts and approaches in the exciting innovative PNI research field. Topics addressing the skin and beyond are presented and cover: (a) stress-, disease-, and treatment paradigms that allow the study of basic PNI interactions and players; (b) epithelial organs that form a constantly stress-challenged border with their environment and treatments that allow them to cope with stress; (c) disorders that disrupt the function of a prime epithelial task: sensory perception and how this affects health and disease; (d) PNI of psychiatric and neurodegenerative disorders and how mental health and organ functioning interact under these conditions; (e) PNI of exemplary metabolic disorders and infectious diseases that depend on the function of epithelial organs. Overall, the abstracts of the 2nd EPN autumn school address a diversity of topics with a common theme: the focus lies on health deregulation states, which demonstrate that it is a constant challenge to sense change and adapt to it by means of neuroendocrine-immune responses. More and more elaborate statistical approaches are employed to allow the analysis of the growing PNI complexity. The diversity demonstrates the to-date relevance of Solomon's initial conceptualization of psychoimmunology in the past century: stress and emotional strain affect the immune system, and through this, environmental and psychosocial factors can cause and alter infection, autoimmune disease, healing, and cancer. Studies along the skin-brain axis demonstrate that basic research in animal models and randomized controlled clinical studies remain pillars in the in-depth study of biological pathways [8–18].

Animal experiments allow us to understand neuroendocrine-immune interactions embedded in their structural and biochemical context beyond nerves,

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epithelial cells, and cells of the immune system. For example, in mice the serotonin synthesis pathway proves to be relevant for wound healing, demonstrating the role of depression associated neuro-immune signaling in epithelial organ homeostasis. The capacity of the brain to modulate peripheral inflammation can be studied in an elegant targeted recombination in active populations mouse model, used to genetically express designer receptors exclusively activated by designer drugs (DREADD; Gq) in active neurons within the insular cortex during peripheral inflammation. In this model, the results suggest that brain activity can elicit T-helper cell immune responses in the skin. In a mouse model of maternal immune activation by influenza A virus, which trespass epithelial barriers, fetal cortical architecture displays structural abnormalities. Even *C. elegans*, an only 1 mm long transparent nematode that is free-living in temperate soil environments, can be used to study neuroendocrine functioning. Aging can be studied in this model species in only 9 days, and it associates with excessive dendritic branching of sensory neurons and altered proprioception capacities, a process that can be alleviated by overexpression of collagens.

Human skin provides an easy access to microbiome material, cells, and even functional organ subunits for the ex vivo study of neuroendocrine-immune interactions. Skin swaps, for example, can be used to sample the skin's virome and study its richness under conditions of stress and inflammatory skin disease. Organotypic models of the human epidermis can be used to study epithelial organ interaction with sensory neurons. When sensing environmental interruptions, for example, in the context of pruritus-associated challenges, keratinocyte RNases such as Reg1 contribute to itch and the differential expressions of genes implicated in pruritus and skin inflammation. This translates into altered proliferation and differentiation capacities within the skin. Also, skin explants can be used to study the interference of different environmental stressors such as ultraviolet radiation with urban particulate matter as a major component of air pollution and demonstrate that cell regeneration and senescence status are targets. These examples demonstrate the relevance of skin as a model organ for the investigation of brain-organ interactions in humans.

Skin-related models are also instructive to understand the influence of lifestyle, behavior, and perception on organ functions. In infectious inflammatory diseases affecting the organism via mucosal skin such as influenza and SARS-CoV-2, it is possible to demonstrate the relevance of neuroendocrine-immune stress responses for the control of infections. Within the same subject, mucosal immune competence, for example, interacts both with emotions and the capacity to produce salivary IgA. Higher intraindividual variability to stress around the time of vaccination predicts more lasting antibody responses to influenza vaccination in older adults. With regard to lifestyle factors, it has been shown that regular physical activity has an immunoregulatory effect, improves cardiovascular and muscular fitness, and, at the same time, has a positive effect on depressive symptoms and mood. In addition to the anti-inflammatory effects, the release of endogenous opioid peptides, neurotransmitters like dopamine and neurotrophic factors such as BDNF appear to be important and have an effect on neuroplasticity. And last but not least, multimodal exercise training also works in aging adults (65–75 years old) by activation and strengthening of cognitively important brain systems involving BDNF and IL-6. Besides physical exercise, sleep is important for efficient adaptive immune responses. Sleep promotes, for example, T-cell migration toward the lymph-node homing chemokine CCL19, which is relevant in T-cell circulation in epithelial tissues in a neuroendocrine-mediator-dependent manner. Moreover, some evidence of PNI harmonizing effects of psychosocial interventions can also be demonstrated. As such, mindfulness meditation results in improved regulation of emotion, mental health as well as larger volumes of target brain regions and lower inflammation indicators. In addition, mindfulness-based stress reduction effectively improves mental health and IL-17 in patients with long COVID.

The high visibility of the skin and its underlying structures facilitate the observation of reciprocal interactions and allow the study of learned positive psychobiological effects often classified as placebo as well as learned negative expectations. In a mouse model for allergic contact dermatitis, conditioned taste avoidance can be used to modify the inflammatory response and the effects of immunosuppressive therapy. In a mammalian model of pain using a paradigm of toxin-induced paw edema, effects of nonsteroidal anti-inflammatory drugs on subcutaneous inflammation can be conditioned. How the periphery talks back to the brain can also be studied in mice subjected to operative procedures, resulting in neuropathic pain. Somatosensory processing of pain appears to be fractalkine receptor (CX3CR1)-dependent and involves microglia and astrocytes, as shown in a mouse model of chronic restraint stress-induced pain. In humans, the application of nonsteroidal anti-inflammatory drugs reduces both behavioral and immunological responses to LPS and also suppresses

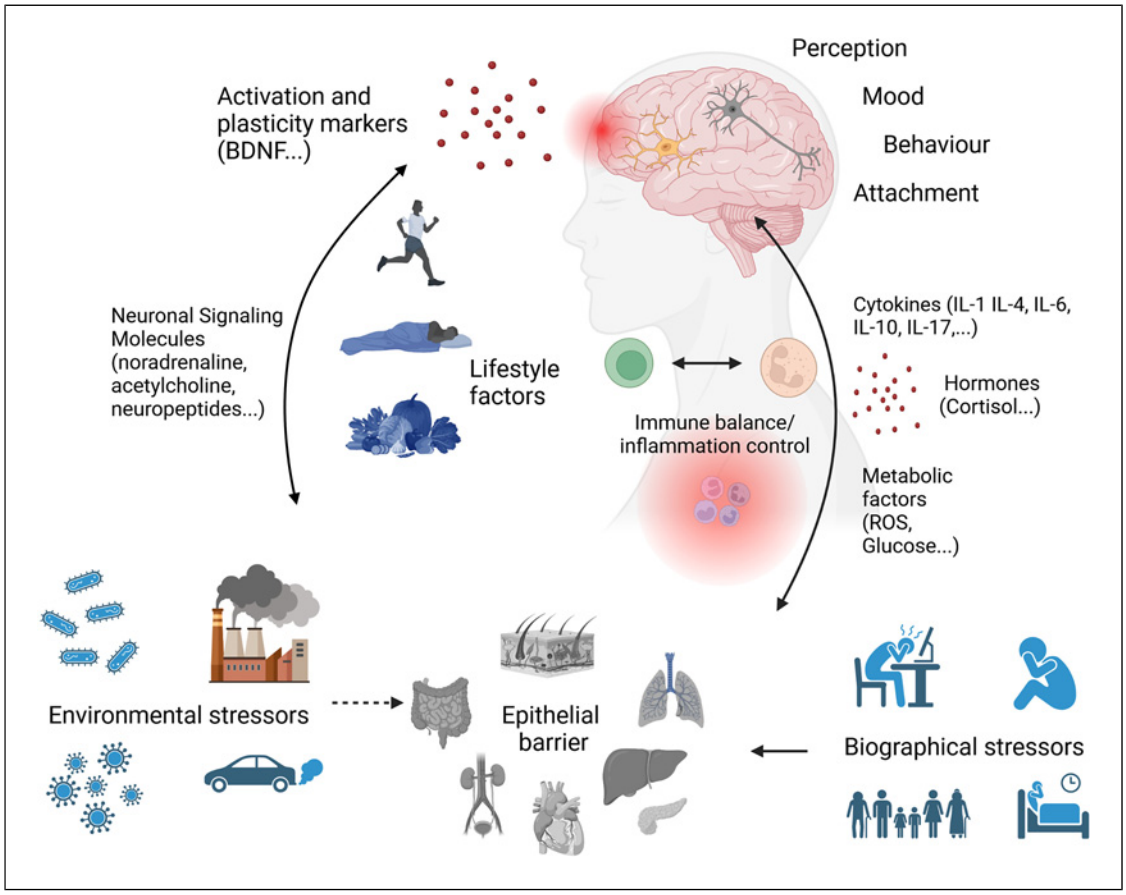

Fig. 1. Interactions between the skin and the brain are bidirectional and enable adaptation to environmental change and organ remodeling requirements. Skin inflammation mechanisms are analog to inflammation at other borders between the organism and the environment and always involve the brain by the release of mediators such as neuroendocrine signaling molecules, namely neurotransmitters, neuropeptides, neurotrophins, hormones, and cytokines. The brain and skin also communicate through immune cell trafficking. Communication generates oxidative and metabolic stress, and in proinflammatory conditions, this interacts with mental health in the dimension mood and behavior. Lifestyle factors act as moderators and potential therapeutic tools in the interaction. The figure was created with BioRender.com.

anxiety. On the other hand, pharmacological conditioned induction of taste avoidance to LPS associates with activation of the hypothalamus-pituitary axis.

Reciprocal brain-skin interactions are also relevant in autoimmune diseases such as lupus and urticaria. Shift work, a classical chronic stress paradigm, simulated in lupus-prone mice for 40 weeks, increases the number of neutrophils and basophils as well as regulatory T cells in the circulation. Suppression of inflammation by pharmacological neutralization of IgE in patients with chronic spontaneous urticaria reveals that the severity of the disease and quality of life are highly correlated.

Epithelial cancers appear to be highly sensitive to stress, and this is a challenge in the context of perioperative psychological stress. In classical models of cancer in mice, blockade of well-known stress mediators such as adrenaline or corticosterone were able to block stress effects. This is of high interest as, for example, the levels of cortisol, noradrenaline, and proinflammatory cytokines correlate with fatigue, a debilitating and prognostically negative symptom complex, in breast cancer patients.

Analog to the skin-brain axis, the gut-brain axis provides an excellent example for the investigation of the role of the microbiome for sex-specific behavioral phenotypes. If rats are injected with LPS during development, adult males show anxiety-like behaviors, but females show increased social interaction. Along the ear-brain axis, stress induces differential effects on the hypothalamus-pituitary-adrenal-immune axis accompanied by functional changes in hearing.

Metabolism plays a mediating role in interactions between neuroendocrine responses to stress and central as well as peripheral immune activation. Enhanced metabolism as evidenced by insulin-stimulated glucose uptake can be induced by peripheral injection of adrenocorticotrophic hormone, and this interacts with microglia cell density and peripheral IL-6 levels in an effort-related choice paradigm. Moreover, mammalian insulin-producing cells treated with a selective glucocorticoid receptor blocker may be protected from stress-induced damage. Last but not least, body pain in young adults with post mild-to-moderate SARS-CoV-2 infection associates with deregulated lipid metabolism and tissue-remodeling cytokines.

The study of skin diseases can further help understand the effect of peripheral inflammation on the brain and of neuroendocrine brain activation on peripheral inflammation. Neurodegenerative diseases and mental disorders offer insights into the role of metabolic intermediaries. Neutralization of oxidative stress, for example, can drive microglial polarization toward an anti-inflammatory phenotype. Peripheral inflammation talks back to the brain in depression, childhood trauma, and schizophrenia. Peripherally derived circulating dendritic cells and IFN-α, for example, are reduced, indicating compromised immune-sensory function in major depressive disorder and trauma. Interestingly, brains of humans with schizophrenia as well as of mice used as model of this disorder show inflammation-induced reduction in BDNF and associated players such as receptors, an effect that is not affected by neuroleptics. Conversely, another study confirms that childhood trauma exerts lasting effects on behavior, symptoms of depression, and the development of chronic diseases associated with inflammation, including dermatological diseases. Moreover, BDNF transcription in traumatized schizophrenics and in a model of schizophrenia in rats exposed to inescapable footshock during adolescence is associated with increased neutrophil extracellular traps and IL-6, suggesting a bias toward innate immune responses. Such increased innate immune activation may have long-lasting effects on mental health, as shown by the predictive capacity of baseline concentrations of IFN-α on mood 6 months after baseline, which is associated with proinflammatory cytokines and indicators of inflammatory damage (CRP) as well as EEG microstate abnormalities in patients with major depressive disorder.

Taken together, strong European connections and international cooperation laid the ground for PNI breakthrough discoveries in the past and provided a good understanding of the functioning of the brain in stress and disease. Focusing on upcoming but still largely understudied brain-organ interactions, namely, the lung-brain axis [19] and the skin-brain axis, in two Autumn Schools proves to be an instructive approach to deepen our understanding of PNI and confirms that the brain acts in concerted action with the immune system to shape organ health. Moreover, the maintenance of homeostasis also requires organs to talk to the brain. This reciprocity can bring PNI functioning to a more resilient level and prevent or reverse pathological changes during disease (Fig. 1). Studying exemplary organ-brain interactions allows the modeling and design of intensified studies of organs at the self-environment interface in general.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: C.R., E.P., K.K., and A.D.R.; writing – original draft preparation: E.P.; writing – review and editing: E.P., C.R., K.K., and A.D.R.; K.K.; and funding acquisition: C.R., E.P., and K.K. All authors have read and agreed to the published version of the manuscript.

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