1st European Psychoneuroimmunology Network (EPN) Autumn School: Lung-Brain Axis in Health and Disease

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Introducing the 1st EPN Autumn School on “Lung-Brain Axis in Health and Disease” as an Emerging Field of Research

Psychoneuroimmunology (PNI) is a rapidly growing multidisciplinary research field that fosters interaction between historically separated fields and integrates neuroscience, immunology, physiology, psychosocial disciplines, and organ-centered medicine into a unifying concept of health and disease. Indeed, PNI research has lately gained much visibility. The field covers research at multiple levels, ranging from cellular aspects to whole organisms, from animals to humans, and from the molecular to the psycho-social level. Strong European connections have contributed to a number of breakthrough discoveries in the field, showing that the brain and the immune system are interconnected and shape health. It is long known that blood-borne humoral immune mediators, mainly of the cytokine family, signal to the central nervous system and that peripheral neuronal signals modulate immune function and convey immune-derived information to the brain (for review [1–3]), while novel insights into immune cell trafficking to the brain are recent pivotal additions to the understanding of immune-to-brain and brain-to-immune communication pathways [4–6] (see also Fig. 1). Notably, the gut-brain axis gained much attention when novel evidence suggested organ-specific characteristics of the respective signaling pathways [7]. Important new knowledge for understanding homeostasis and pathological changes during disease can be expected from an intensified study of other organs at the self-environment interface, such as the lung and skin.

We go this step further by focusing on these upcoming but by far less studied interactions between systems involving immune and inflammatory components, namely the lung-brain [8–11] and the skin-brain axis [12–15], in two Autumn Schools. Immune-brain communication
pathways and their relevance for organ health will be addressed at these Schools. These interactions will also be discussed in the context of lifestyle effects as preventive and therapeutic tools to regain homeostasis. A variety of methods that can be applied to address scientific questions in these new research topics, as well as applied statistics, will be offered to the trainees at the Autumn Schools. Moreover, they will be trained to propose defined research questions related to selected topics (module style and round tables). Teachers with a broad vision of science and a strong PNI background will be involved. The national and international speakers who have been recruited for the first autumn school cover numerous aspects of immune-brain communication, disease models, brain inflammation involving both the innate and adaptive immune system, and brain reaction patterns. In this first EPN Autumn School, the interdisciplinary character of the PNI field is fostered by including the new and emerging topic “the lung-brain axis and lifestyle interventions” to modulate brain-immune communication. This offers to the participants the unique opportunity to expand their knowledge on established excellent research and to integrate it into innovative avenues of interdisciplinary investigations.

The general concept of how organ specific signals that are altered by an unhealthy lifestyle, psychosocial stress, or lung injury/inflammation induce components of inflammation in the brain is introduced [16–18, 10, 11, 19]. The pivotal role that the innate immune system plays in this process, particularly during acute inflammatory responses, and the following adaptive immune activation and signaling will be remarked. Several studies have also
addressed humoral immune pathways to brain cell activation and its relation to pathology in the central nervous system [3]. Experimental studies have revealed several intriguing pathways that contribute to increased inflammation and vulnerability in peripheral organs like the lung after occurrence of brain pathologies, such as traumatic brain injury or ischemic stroke [20–22]. Conversely, compelling evidence has shown that peripheral inflammatory insults can alter brain functions or even exacerbate ongoing brain pathologies such as stroke [23, 24] or Alzheimer’s disease [25].

Since the COVID-19 crisis started, interest in lung-brain interactions and skin-brain interactions have evolved dramatically with a need to establish new curricula. We now have the unique opportunity to timely invest into the education of a new generation of young and uprisong scientists. The organizers know from their own experience the enormous impact that interdisciplinary and integrative training events can have upon a scientific career. Ranging from establishing new contacts to lighting up the fascination for novel research fields, the Autumn School facilitates an intense approach to leaders in these fields in an interactive atmosphere and at a personal level. The fostering of interdisciplinary discussion cannot be valued highly enough for career and concept progression.

Taken together, the “lung-brain-axis” describes bidirectional interactions between the lung and the brain [26, 8, 9]. As such, activation of the organ-specific immune system in the lung or the brain can alter the functioning of the respective other organ. Pathophysiological conditions that are accompanied by inflammatory and immune components are explored for organ-organ interaction between the lung and the nervous system.

Indeed, long-standing epidemiological evidence has already shown that insults to the brain are accompanied by a higher incidence of lung inflammation and infection, which, in turn, is associated with higher mortality [20, 21]. Other studies have focused on the effects of lung inflammation on the brain, e.g. acute influenza infection [27], acute lung injury [11] or during chronic asthmatic inflammation [28]. For example, experimental S. pneumoniae lung infection revealed interactions between peripheral CCR2-positive inflammatory monocytes and microglia, mainly in the context of cognitive decline [29], or asthmatic lung inflammation modulates brain immune mechanisms and fear circuits [30]. In addition, it has been recently shown that COVID-19 disease induces acute respiratory distress (ARS) and the propagation of a cytokine storm to the brain known to induce cognitive dysfunction [31] associated with various neurologic manifestations that involve CNS, peripheral nervous system, and skeletal muscles in 36.4% of the patients [32]. Among the sequelae in survivors of SARS-CoV-2 infection are extreme fatigue and reduced motivation, resulting either from such cytokine storm or from neural effects of the virus itself. These and other observations have urged the study of lung-brain interactions.

In the First Autumn School, expertise on lung diseases such as acute inflammation induced by microbial agents, chronic airway inflammation caused, for example, by conventional aeroallergens, and brain diseases induced by bacterial/viral mimetic, alpha synuclein, ischemia, or virally induced inflammatory models will be brought together to provide an innovative view of organ interactions that interfere either with the reaction pattern of the brain or of the lung. After elucidating these interacting effects and selected underlying cellular and molecular signaling pathways in more detail, it will be possible to assess the impact of lung or brain disease on each other, which will also allow risk assessment and open the avenue for novel therapeutic strategies.

Organ-specific mechanisms of lung-derived signals to the brain have been studied using, for example, neuronal activation markers such as the immediate early gene c-Fos [33], and revealed region-specific changes in neuronal activity, confirming the tight connection of the lung-brain axis. Signals from the lung to the brain that contribute to alterations in brain functioning and activation patterns involve reactive oxygen species [34] or simply hypoxia [26], cytokines, and immune cells. However, the individual contribution of each of these three lung-to-brain signaling mechanisms, namely humoral, neuronal and immune cell trafficking, have not been investigated so far. Also, the relevance of various insults to the lung for brain health or ongoing brain pathologies remains largely unknown. Lung-dependent innate immune priming is expected to convey organ-specific alterations that are distinct from other systemic inflammatory insults like intra-peritoneal inflammation [35].

Moreover, it has been shown that lifestyle affects the development of systemic low-grade inflammation, which, among the general population, is known as an important modulator of risk factors for cardiovascular and metabolic diseases. In particular chronically elevated pro-inflammatory cytokines in blood, such as TNFα, and markers of inflammation, such as C-reactive protein (CRP), have been associated with lifestyle risk factors for “western” diseases like obesity [36], physical inactivity [37], cigarette smoking [17], malnutrition [38], stress [39], and...
sleep deprivation [40]. Recent studies provided evidence that lifestyle-induced systemic inflammation also contributes to brain injury, cerebral oxidative stress, and neuroinflammation, which negatively affects psychologic well-being and the onset, severity, and duration of neurodegenerative diseases [19].

Overall, it remains to each individual’s decision to maintain a healthy lifestyle. This includes an adequate level of physical activity, sufficient sleep, a balanced diet and good stress management. It has been shown that all these lifestyle factors have immune-regulating effects and, in parallel, exert neuroprotection. These positive effects are mediated by reduction of inflammatory stimuli in the brain, stimulation of the release of brain-derived neurotrophic factor (BDNF), followed by a balanced cerebral plasticity and function [41]. On the one hand, these lifestyle factors are complementary because they are interrelated. Selective interventions, such as exercise training, have been shown to have a therapeutic effect in moderate depression, provide a systemic immunoregulatory effect and positively address lung function [16, 42]. At the Autumn School, novel multimodal approaches to effectively implement combined lifestyle interventions for therapy and prevention of underlying low-grade inflammation and altered immune-to-brain communication will be addressed. Also, in this subject, separated research fields can only gain value when young scientists get immersed in the full and holistic approaches that are offered by PNI.

The abstracts in this issue cover key aspects of the reciprocal interaction between the brain and the immune system and, in particular, how this communication impacts on lung health, as the key organ addressed in the first of the two schools (shown in Fig. 1). They include the route from brain to organ by showing that neuroendocrine mediators such as noradrenaline, dopamine, and BDNF as well as mental, environmental and lifestyle factors affecting neuroendocrine signaling, such as depression, air pollution or smoking, can modulate the immune response with consequences for organ health. This is relevant for infectious agents such as HIV, tuberculosis, and Sars-Cov-2 as well as in non-transmissible disease models of chronic lung inflammation. Amazingly, a person appears to be actually able to say how well his/her immune defense is working before being exposed to an immune challenge, and IgA level correlates with disgust. Conversely, and as intriguing, is the report that a person is capable of recognizing that others are suffering a severe disease by looking at their gait. These findings indicate that it is possible to monitor immunological functioning by psychosocial indicators. However, correlational analysis does not always show the expected association between brain function/mental distress and inflammation status/lung health, which shows the complexity of the interaction.

From lung to brain, the abstracts report that lung challenge with damages evoking inflammation (air pollution, hypoxia) as well as inflammatory agents such as chlamydia, mycobacterium tuberculosis, influenza, lipopolysaccharide, or allergens alter not only lung physiology and function but also brain physiology and connectivity as well as immune-mediated dysfunction in other organs, such as the gut, or the functioning of the peripheral nervous system. At organic level, this involves altered microglia activation in various brain regions, oligodendrocyte homeostasis, tissue cytokine levels and inflammatory status (e.g. hypothalamic and lung), brain macrophage and neutrophil-infiltration, and oxidative stress/HIF-pathway activation. At psychosocial level, it involves, for example, symptoms of depression or attention towards emotionally relevant cues along the so-called salience network.

Alterations of neuronal functioning by lung-derived immune changes can thereby involve afferent transmission, e.g. via the vagus cholinergic and sensory nerves, and interfere with diseases such as Alzheimer’s, multiple sclerosis, or Borna Virus disease, as well as inflammatory lung diseases such as influenza or asthma and their interaction (e.g. by enhanced TLR4 signaling). Accordingly, indicators of psychosocial distress such as fear and depression are shown to interact with both brain and immune functions. On one hand, they affect neural networks and microglia, and, on the other, the cytokine balance in inflammatory diseases of the lung, such as allergic airway inflammation in animal models and bronchial asthma in humans. Among other observations, this is shown, for example, by demonstrating that decreased lymphocyte and natural killer cell numbers associate with a chronic stress that results in increased noradrenaline levels.

These interactions are shown to drive the development of more severe inflammatory phenotypes in lung disease in animals and patients, partially depending on sex or the CACNA1C gene. In addition, rather recently acknowledged indicators of a compromised homeostasis in lung and brain are introduced, such as resolvins, GPR55, MSK1, dynamin-related protein 1 (Drp1) mediated mitochondrial fission, urinary creatinine secretion, or epigenetic clock deregulation. Analogue to the lung, other organs under constant inflammatory challenge such as the gut, joints, muscle or peripheral nervous system are also affected by brain-immune interactions. Examples il
Illustrated in the abstracts even show that organ and mental health in certain inflammatory diseases are further affected by simultaneous additional challenges to the immune system (e.g. dendritic cell glucocorticoid resistance induction when psychosocial stress, organ inflammatory disease and wounding occur simultaneously) and that, at the same time, challenges in the lung can alter neuro-immune homeostasis in other organs as well (e.g. cytoarchitecture and microbiome composition in the gut, demyelination in the peripheral nervous system).

In the light of such findings, therapy safety, e.g. during pregnancy, is of high importance. With respect to therapeutic options arising from the understanding of brain-immune interaction, specific nodes of interaction are suggested that deserve therapeutic attention, as they are capable of braking pathogenic effects in lung disease. At organic level, these include the microbiome, vitamin D, omega 3 (n-3) fatty acids and resolvin E1 (RvE1) or, at psychosocial level, avoidance behaviour, indicators of depressive and anxious mood and fatigue, which can be modified by aerobic training, environmental enrichment, or mindfulness.

To study brain-immune-lung interactions, a wide spectrum of methods is applied in the abstracts that cover the individual level, e.g. by cellular analysis or patient reported outcomes, and the global interplay, e.g. by various omics and machine learning approaches and large sample number analysis. In summary, these abstracts show that to learn the correlates of distress, brain-, immune- and organ function in disease models ranging from COVID-19 to asthma, from Alzheimer’s to depression will prove instructive for the development of future diagnostic and therapeutic tools addressing brain-immune interactions.

The second EPN Autumn School entitled “The skin-brain axis and the breaking of barriers” will implement the same conceptual educational scheme to train a future generation of scientists on this important topic. Indeed, neuropsychiatric/psychosomatic comorbidities are known to exacerbate inflammatory disease while knowledge on etiological mechanisms involved in escalation of organ-restricted disease is insufficient to prevent a vicious cycle of exacerbation between disease and the “stressed brain” [13–15]. The skin offers an excellent yet still understudied second exemplary organ to teach and learn state of the art brain-immune interactions and their role in health and disease.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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