

## Mini Review

# The Merging of Mental and Physical Health Mechanisms

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**Abstract**

This brief review discusses the ties between the endocrine, immune and nervous systems, which support the merging of mental and physical health concepts and health care. Mental and physical health's are dependent on multidirectional interactions of the neuroendocrine immune network. Communications among neuronal connections within the central nervous system (CNS) regulate our behaviors, cognitive ability and numerous peripheral activities, including endocrine and immune responses. Conversely, immune cells, microglia, within the CNS, and hormones influence the development of the neuronal circuits as well as neuro-degeneration. Peripheral immune cells and factors entering the brain also affect behaviors and cognition. Cells of the immune and nervous systems also share a number of receptors, modulatory ligands, and transcription factors. Although CNS and immune associations have been reported for more than a century, only recently have the elusive mechanistic interactions been more thoroughly researched. Current studies are implicating endocrine, immune and nervous system interactions in behavior pathophysiology.

**INTRODUCTION**

Societies, including public and private organizations, often think of mental health and physical health as separate entities. As biomedical scientists gain more appreciation for and understanding of the biochemical and physiological mechanisms of each organ system, there is more evidence that connects mental and physical processes. In fact, mental processes are physical processes. An understanding of mental health has long lagged behind that for physical health, in part, because of the mysteries of the mind and the incorporeal concept of mind and soul with their religious and philosophical connections. The long and circuitous path to achieve a better understanding of mental health and to have it merged with that of physical health is nearing a more enlightened roadway. The incidences of behavioral diseases and disorders, such as Alzheimer's disease, autism spectrum disorder (ASD), attention deficit and hyperactive disorder (ADHD), posttraumatic stress disorder (PTSD), and schizophrenia are being related with biochemical and physiological changes to organ systems. Due to exogenous stress and endogenous changes, organ systems, especially the endocrine, immune and nervous systems, are posited to synergize to induce these pathophysiological outcomes [1-3]. Understanding neuro developmental and neuro-degeneration disorders/diseases will require a systematic analysis of physiological networks as recently reviewed [4]. The associations of networks acknowledge and define the clinical and biophysical connections between mental and physical health. Awareness of the interdependencies among the organ systems has increased interest in systems biology approaches toward illnesses. A systems biology approach takes into consideration

the complexity of multidirectional influences of inter-organ communications. There is now a wealth of knowledge connecting biophysical and biochemical pathways that influence behaviors, and these pathways intimately connect with the endocrine, immune and nervous systems. Depression and pain are major public health disorders of the nervous system with increasing prevalence, and they are associated with immune activities [5,6].

**Neurodevelopment and immunity**

An early in life stress (perinatal stress) can affect behaviors, immunity, and overall health for a lifetime [7-9]. A peripheral infection stimulates the immune system, which produces cytokines in the periphery. Unlike hormones, immune cytokines, such as interleukins (ILs), interferons (IFNs), and tumor necrosis factors (TNFs), are usually produced for local (paracrine and autocrine) reactions. However, low levels of cytokines can diffuse systemically and act in an endocrine fashion. The pro-inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  enter the brain to stimulate the hypothalamic-pituitary-adrenal (HPA) axis. Although the blood brain barrier (BBB) is organized to minimize peripheral factors from entering the brain, low levels of cytokines and antibodies can transigrate. During the perinatal period, the BBB has not completely formed so greater levels of factors have access to the developing brain. The activation of the HPA axis of adults induces "sickness behavior", which can include sleepiness, loss of appetite, lethargy, depression, anxiety, hyperalgesia, and fever. With these known potential outcomes of infections, which are commonly experienced to varying degrees, it is surprising that studies of mental and physical health have remained apart

for so long. Maternal infections (maternal immune activation, MIA) elevates fetal brain pro-inflammatory cytokine levels in different brain regions, which can lead to neuropathology and aberrant behaviors in the offspring [10]. In addition to infections, perinatal inflammation in the brain can be affected by exogenous stressors such as alcohol [11] and high fat diet [12], and these stressors can induce aberrant behaviors in offspring. Human fetal brain programming has been suggested to affect behaviors [13] as well as neurodegenerative diseases including Parkinson's disease and Alzheimer's disease [14]. Hypertension, which is known to perturb numerous organ systems including the brain, is mediated, in part, by immune cytokines, which are regulated by CNS activities [15].

### Sex and brain laterality

It is especially important to note the convergence of behaviors with multidirectional connections among the endocrine, immune and nervous systems. The sex hormones estrogen and testosterone affect neurons and immune cells, and testosterone has been reported to affect early brain development and the establishment of brain laterality; i.e. differential functions and regulatory interactions between the right and left hemispheres. This sexual dimorphism of the neuroendocrine immune network and HPA axis activation is suggested to be responsible for the immune and longevity differences between males and females, which relate to greater incidence of cardiovascular diseases in males due to elevated stress responses [16]. The Geschwind and Galaburda hypothesis [17] has been contested ever since it proposed that testosterone induces developmental brain lateralization, which creates sex differences in cognitive function and immune parameters. Although still debated testosterone is believed to slow fetal left hemisphere development or accelerate growth of the right hemisphere [18]. Sex differences affecting brain development and neuropathology have been suggested to relate to microglia activities [19].

The immune responses of left- and right-pawed mice differ due to brain asymmetry, and the differential behaviors and immunity of mice with right vs. left paw preference varies due to strain and sex [20]. Asymmetrical (right vs. left) brain lesions differentially modify immune functions; left lesions reduced certain immune responses [21]. Similarly, patients with left-sided brain injuries had greater incidence of hospital-acquired infections [22]. Female left-pawed C3H mice had more pronounced sickness behavior than right-pawed female C3H mice [23]. BALB/c male mice assessed for turning behavior were 1/3 preferential right-turning, 1/3 preferential left-turning and 1/3 had no preference. The right-turners had greater primary antibody responses, delayed type hypersensitivity and host defenses against *Listeria monocytogenes* infection than left-turners [24]. Right-handed monkeys also had better immune responses than left-handed monkeys [25]. A literature review indicated that human left hemisphere function mediates stronger immune activity [26]. Interestingly, the majority of humans ( $\geq 80\%$ ) are right-handed and the majority of monkeys (60%) are left-handed; however, for humans and monkeys, right-handedness or more prominent left hemisphere activity is associated with better immune responses. Generally, the brain asymmetry differences are believed to develop prenatally and most species assayed except humans

have near equivalent numbers of right and left-handedness [27], which suggests there may be a bias in this preference for humans. Cerebral asymmetry and immunity was implicated in patients with somatoform disorders [28] Although many of the posited suggestions associated with brain laterality remain theories, evidence supporting brain asymmetry, immune and behavior differences, and differential sensitivity to stresses have been accumulating [29]. Furthermore, altered anatomical brain asymmetry has been reported in individuals with schizophrenia, autism or dyslexia [30,31]. An immune imbalance has been implicated in schizophrenia [32] and ASD [33]. The dyslexia phenotype was an aspect of the original Geschwind-Galaburda hypothesis. Although the Geschwind-Galaburda hypothesis remains controversial, it is still being researched, and there is mounting evidence that cerebral asymmetry and immune involvement are implicated in behavioral pathophysiology [34]. Brain asymmetry affects differential behaviors and immunity and although neurotransmitters and immune cytokines are involved, the responsible cellular and molecular mechanisms are still being researched.

### Immune regulation, behavior, and the exposome

Females are more prone to develop many autoimmune diseases such as systemic lupus erythematosus (SLE) and multiple sclerosis (MS), and the Geschwind-Galaburda hypothesis suggests females would have more left hemisphere activity. Females also are more prone to depression, sleep disorders, and pain disorders [35]. Neuropsychiatric syndromes (NPSLE) are associated with SLE [36]. The immune and nervous system have common factors and receptors mediating functions, e.g., immune cells make neurotransmitters and neurons make cytokines. Patients with SLE have auto antibodies to the N-methyl-D-aspartate receptor (NMDA receptor, a glutamate receptor), which has been implicated in NPSLE; autoantibodies to brain antigens also have been implicated other disorders of the central nervous system, including ASD [37]. Auto antibodies to different brain antigens have been reported with some children with epilepsy [38]. In a mouse study, antibodies have been shown to play a role almost as important as genetics in development of behaviors resembling aspects of ASD [39].

Although progress is being made in our understanding of mental and physical health, there remain many unknowns. The mechanisms responsible for many brain controlling immune regulatory effects are still elusive. It has been over three decades since Robert Ader and colleagues demonstrated that behavior conditioning could affect a T-dependent antibody response [40]. Even longer ago brain control of immunity was shown with induction of an allergic response with an artificial rose [41]. Immune cytokines and antibodies can modify neuronal functions affecting behaviors [33] and central [42] and peripheral [43] neurons modulate immune responses. Many studies connecting psychology with the neuroendocrine immune network are reported in the volumes of Psychoneuroimmunology [44]. These sciences need to be further merged with genetics and toxicology, because it is a person's genetic susceptibility and lifetime of exposures to environmental biological, chemical, physical and psychological stressors that establish a person's exposome [45], which affects mental and physical health. Based

on the regulatory interactions among the endocrine, immune and nervous systems, it is not surprising that the microbiome affects this network [46] and that microbiota are suspect in immune effects in neuropsychiatric disorders [47]. It is also not surprising that endocrine, immune and nervous systems interactions are involved in the gut-brain axis [48]. This combination of genes (nature) and environment (nurture), an individual's exposome, affects the onset of a disease/disorder, its severity, and a person's behavior in response to the endogenous and exogenous modifications on all organ systems and their interactions. Nature and nurture bridge mental and physical health. The randomness of environmental exposures and the diversity of genes make interpretation of health disparities a challenge. However, disorders of mental and physical health are due to molecular and cellular interactions within the body, including those seemingly induced by ethereal events.

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