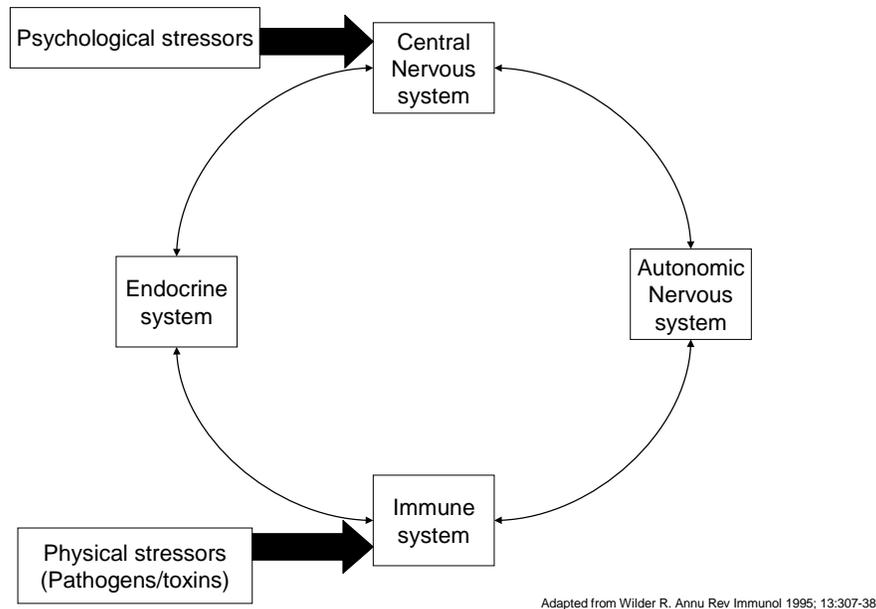


CHAPTER 34

PSYCHONEUROIMMUNOLOGY – IMMUNOPSYCHIATRY

“There is increasing evidence of a strong interconnectivity between genetic disposition, epigenetic processes, stress-related hormonal systems and immune parameters in all forms of (mal)-adjustment to adverse living conditions”
(Ehlert, 2013).



The label of this branch of study/medicine has varied over time.

The label “**Psychoneuroimmunology**” (PNI) was first used in the 1970s.

And looks at interactions between

- 1) Psychology/mind
- 2) Neurological system, and
- 3) Immunological system.

The label “Psychoneuroendocrineimmunology” and other variants have been used to indicate an additional link, that is, to 4) Endocrine system.

The label “**Immunopsychiatry**” has appeared in the last couple of years. As has, the term “neuroimmune system”.

From the current author’s perspective, most of these labels which deal with the interaction of one or two systems can be used interchangeably. The label “Immunopsychiatry”, while it leaves out explicit reference to the neurological and endocrine systems (these are well known to be linked), is likely to survive.

AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis (AIE) is dealt with separately (Chapter 36). The role of AIE in some cases of psychosis shot to prominence in the last few years. It involves “neuronal surface antibodies” (NSAbs) – which often attack NMDA receptors.

However, Pape et al (2019) observe the pathological role of NSAbs came into question recently when they were found in 10% of healthy controls as well as patients with the classic picture of psychosis.

The reader is referred to Chapter 36 for details of this specialized topic.

SOME BASIC CONCEPTS/FACTS

“Stress” is a central issue and is defined as a general body response to initially threatening external or internal demands. Longer definitions mention disturbance of homeostasis. Much of this chapter deals with mechanism which work to restore homeostasis.

“Cytokines” are a category of “signaling molecules” which enable cellular communication. The distinction between cytokines and hormones is becoming less clear/important. Cytokines are produced by immune cells, particularly, monocytes and macrophages, (but also by brain neurons and glial elements; Breder et al, 1988).

“Circumventricular organs” (CVOs) are structures bordering the 3rd and 4th ventricles, regions of the brain in which the capillary bed does not form a blood brain barrier (BBB), but instead the vessels are leaky. They allow penetration of the barrier by hormones, neurotransmitters and cytokines.

“Sickness behavior” refers to the symptoms associated with inflammation (low mood, reduced appetite, increased fatigue and social withdrawal; Irwin and Cole, 2011). This follows penetration of the BBB and access to the hypothalamus by cytokines released from activated immune cells (and toxic products from bacterium cell walls).

Interestingly, many of these symptoms are shared with depressive disorder. Studies report 16-45% of patients treated with interferon (IFN)-alpha develop depressive symptoms during the course of therapy (Hauser et al, 2002). This is not to suggest that all depressive disorder is an immune response (although the case has been made that a sub-set of depression is of immunological origin (Howren et al, 2009)), but it alerts us to the difficulties which may be encountered when making psychiatric assessments of physically unwell patients.

THE NEUROENDOCRINE SYSTEM

Hans Selye (1937) pioneered the concept of “biological stress”. He demonstrated that a noxious stimulus (called a stressor) induces the release of adrenal cortical steroids. From early stress response investigations, neural and endocrine system interactions were noted, leading to the concept of the “neuroendocrine system”.

When stress impacts on the brain, there are two outflow pathways to the periphery. One is the hypothalamic-pituitary-adrenal (HPA) axis – traditionally conceptualized as part of the endocrine system – here termed neuroendocrine because of the input from hypothalamic nuclei (particularly the paraventricular nucleus). Neuroendocrine cells receive neuronal input (neurotransmitter stimuli) and release hormones. Ultimately, glucocorticoids from the adrenal cortex.

The other outflow pathway involves the sympathetic nervous system (commencing with corticotropin releasing hormone (CRH) stimulation of the locus coeruleus (LC) in the brain stem. It is conceptualized as having three parts. First, neural communication leading to release of epinephrine and norepinephrine from the adrenal medulla (Nicolaidis et al, 2015). Second, neural communication with cells and tissues with an immune function (liver, spleen, bone marrow, thymus, lymph nodes, skin and gastrointestinal system). And third, neural communication which directly prepares the body for action (dilating blood vessels to the muscles, constricting blood vessels to the skin, etc).

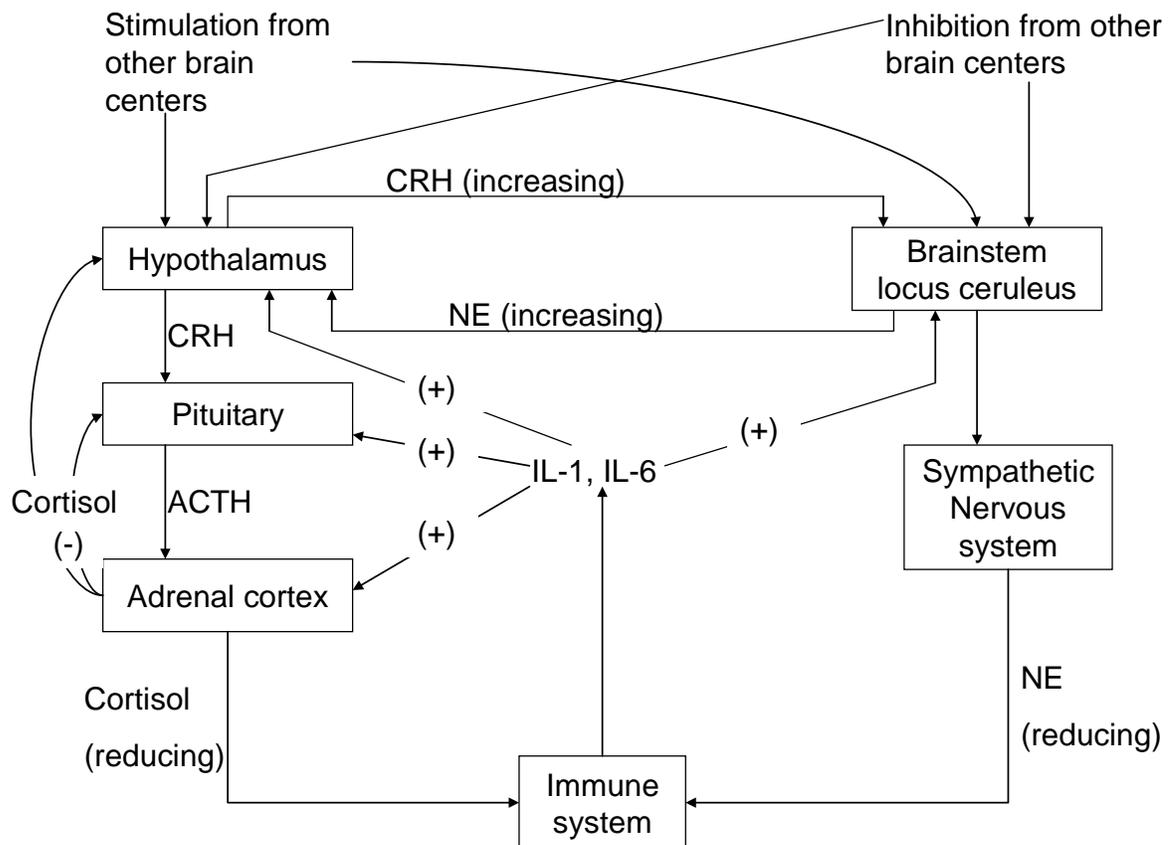
THE IMMUNE SYSTEM

The immune system responds to physical assault (in the form of pathogenic micro-organisms and tumor cells). [However, recently it has been claimed that social stressors can also trigger immune system activity (Lacy et al, 2013).]

Of particular interest in the current chapter (which attempts to integrate the immune and neuroendocrine systems) are chemicals (neurotransmitters, hormones and cytokines) which are released by the cells of one system and impact on the cells of the other. (The notion that there is more than one system (of course) simply reflects the history of scientific discovery.)

MODULATION

A thorough account of the bi-directional modulation of these systems is beyond the current author. Instead, some examples are offered, which support the notion that these systems are highly integrated. Future research will provide new therapeutic avenues.



Adapted from Wilder R. Annu Rev Immunol 1995; 13:307-38

The immune modulating the neuroendocrine system: examples

1. Cytokines, interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) pass through the circumventricular organs and impact on the hypothalamus, leading to fever and sickness behavior.
2. Cytokines impacting on the HPA lead to cortisol release from the adrenal cortex (Chowers et al, 1996; Dunn et al, 1999).
3. Immune cells synthesize IFN which passes the blood brain barrier, impacts on brain and may cause "depression" (Hauser et al, 2002).
4. Elevated levels of C-reactive protein (CRP) and IL-6 in children are associated with behavior problems (Slopen et al, 2013).
5. Lymphocytes synthesize hormones including ACTH, prolactin and growth hormone (Wilder, 1995).
6. Peripheral cytokines stimulate afferent pathways such as the vagus nerve which leads to the release of cytokine and stimulation of brain cells (McCusker and Kelley, 2013).

7. Cytokines reduce the efficiency of glucocorticoid receptors (resistance) which reduce the negative feedback (which may have a role in depression) (Pace and Miller, 2009).
8. Acetylcholine and adrenaline neurotransmitters, and hormones [recently, melatonin] are endogenously produced in the immune system (Blalock, 2005). For (simplified) details, see the following list:

<u>Source</u>	<u>Hormone/neurotransmitters</u>
Lymphocytes	Acetylcholine, melatonin
T Lymphocytes	ACTH, endorphins
B Lymphocytes	ACTH, endorphins
Macrophages	ACTH, endorphins
Splenocytes	Adrenalin, CRH,
Megakaryocytes	Neuropeptide Y

The neuroendocrine modulating the immune system: examples

1. Sympathetic/noradrenergic nerve fibers innervate important organs and systems related to the immune system, including the liver, spleen, thymus, bone marrow, lymph nodes, skin, and digestive tract and respiratory apparatus (Montoro et al, 2009; Irwin and Cole, 2011).
2. Adrenergic receptors are located on lymphocytes (Hadden et al, 1970).
3. Catecholamines and corticoids suppress the production of IL-12 by immune cells (Elenkov and Chrousos, 1999).
4. Increased cortisol suppresses immune function (McEwen et al, 1997).
5. Cortical steroids directly affect immune cells, increasing the production of IL-4, 10 and 13 (DeKruyff et al, 1998).
6. Neuropeptide, neurotransmitter and neuroendocrine hormone receptors are located on immune cells (Blalock, 2005).
7. Neurotransmitters (acetylcholine, noradrenaline, serotonin, histamine, glutamic acid, GABA), neuropeptides (ACTH, Prolactin, Vasopressin, Bradykinin, Somatostatin, VIP, SP, Neuropeptide Y, enkephalin, endorphin), neurological growth factors (NGF) and hormones (adrenalin and corticoids) modulate immune function (Montoro et al, 2009).
8. Neurons synthesize IL-1 and other cytokines (Breder, 1988).
9. Parental separation results in higher levels of C-reactive protein in the adult (Lacy et al, 2013).
10. Exogenous administration of CRH and ACTH produce a substantial increase in IL-6 in the adrenal glands (Hueston and Deak, 2014).
11. Marital distress has long-term immune consequences (Jaremka et al, 2013).

CLINICAL ISSUES

The clinician is interested in practical findings:

1. Some mental disorders are under-pinned by immune dysfunction

Proof is contained in the following:

- Evidence suggests cognitive decline and dementia may also be associated with “over-expressed cytokines” (McAfoose and Baume, 2009).
- Anxiety is associated with dysregulation of the immune system (Salim et al, 2012).
- A role for the immune system in the etiology of schizophrenia (Tomasik et al, 2014) and bipolar disorder (Barbosa et al, 2014) has been discussed.
- A stem cell transplantation from a brother with schizophrenia transmitted psychosis – “adoptive immune transfer had a role” (Sommer, 2015).
- The neuroimmune system plays a role in schizophrenia, depression and bipolar disorder - but this may not be a direct result of neuroinflammation, but as a result of non-inflammatory (homeostatic) functions (Mettei and Notter, 2019).
- Schizophrenia and PTSD – wide ranging dysregulation of mainly pro-inflammatory markers in particular IL-6, IL-2receptor, IL-1Beta, IL-17A, and C-reactive protein (CRP) (Pape et al, 2019).
- Increased levels of inflammatory markers in patients with psychosis (Jeppesen and Benros, 2019).

2. Psychosocial events can trigger mental disorders via immune dysregulation

Support is contained in the following:

- Healthy students under examination stress manifest a decrease in indicators of cellular immune response (Glaser et al, 1986).
- Stressful life events can play a part in the onset and exacerbation of autoimmune diseases (Homo-Delarche et al, 1991)
- PTSD has disturbed immune features (Pace & Heim, 2011).
- Complicated grief – similar in many ways to depression – appears to be associated with dysregulation of the immune system (O’Connor, 2012).
- Job stress is associated with immune dysregulation (Nakata, 2012).
- A history of childhood maltreatment is associated with a high level of CRP (Baumeister et al, 2016). The ‘Two hit hypothesis’ proposes that early stress increases microglial activity, such that the individual is primed and a further stress in later life leads to a psychiatric disorder.
- [**However** - A systematic review of the association between early life adversity and markers of inflammation (Kuhlman et al, 2019) found the evidence was limited by the number of studies and heterogeneous methodology.]

3. Immune based treatments may improve mental disorders

Support is contained in the following

- The effects of the antidepressants can be augmented with anti-inflammatory agents (aspirin, celecoxib) (Blume et al, 2011).
- Bone marrow transplantation could be effective or even curative for schizophrenia (Miyaoaka et al, 2017).
- In a meta-analysis, anti-inflammatory agents (including SSRIs and minocycline) were effective in the treatment of depression when used as either add-on or monotherapy (Kohler-Forsberg et al, 2019).

4. Limited evidence – psychological interventions can improve some physical disorders which have an immune component

Some support is contained in the following:

- Some studies involving education and psychological treatment have demonstrated increased cancer survival (Spiegel et al, 1989; Fawzy et al, 1993).
- Cognitive-behavioral interventions have been associated with improved physical symptoms of some autoimmune disorders (Radojevic, 1992).
- An important early review unexpectedly found that the immune system shows little response to psychological intervention (Miller and Cohen, 2001).
- Moraes et al (2018) found that yoga, meditation and related activities lowered many variables such as cortisone and epinephrine levels - however, only one study reported effects on disease progression

CONCLUSION

Close integration and bi-directional communication between the neuroendocrine and immune systems has been demonstrated.

Evidence indicates early life experiences, past infection, inherited genes and the microbiome (the collective genes of the gastro-intestinal microorganisms) are among the many factors which shape the immune status and the health (physical and mental) of the individual.

A current theory states the inheritability of schizophrenia involves an inheritance of vulnerability to infection which leads to activation the immune and endocrine systems.

Should “Immunopsychiatry” prove acceptable, the existing gap between psychiatry and general medicine will be largely closed.

There is evidence to substantiate:

1. Some mental disorders are under-pinned by immune dysfunction
2. Psychosocial events can trigger mental disorders via immune dysregulation
3. Immune based treatments may improve mental disorders
4. Limited evidence – psychological interventions can improve some physical disorders which have an immune component

To the delight of clinician, some depression, schizophrenia, bipolar disorder, anxiety, PTSD, dementia and other mental disorders may have unexpected roots, and new therapies appear to be quite close.

References

- Barbosa I, Bauet M, Machado-Vieira R, Teixeira A. Cytokines in bipolar disorder: paving the way for neuroprogression. *Neural Plast* 2014. doi: 10.1155/2014/360481.
- Baumeister D, et al. Childhood trauma and adult inflammation. *Mol Psychiatry* 2016; 21: 642-9.
- Blalock J. The immune system as the sixth sense. *Journal of Internal Medicine* 2005; 257:126-138.
- Blume J, Douglas S, Evans D. Immune suppression and immune activation in depression. *Brain, Behavior, and Immunity* 2011; 25:221-229.
- Breder C, Dinarello, C, Saper C. Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* 1988; 240, 4850, 321-324.
- Chowers I, Hammel H, Eisenman J, et al. A comparison of the effects of environmental and preoptic heating and pyrogen on plasma cortisol levels. *American Journal of Physiology* 1996; 210:606-610.
- Cohen S, Herbert T. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. *Annual Reviews Psychology* 1996; 47:113-142.
- DeKruyff R, Fang Y, Umetsu D. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4+ lymphocytes by inhibiting IL-12 production. *Journal of Immunology* 1998; 160:2231-2237.
- Dunn A, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv Exp Med Biol* 1999; 461:117-127.
- Ehlert U. Enduring psychobiological effects of childhood adversity. *Psychoneuroendocrinology* 2013; 38: 1850-1857.
- Elenkov I, Chrousos G. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology and Metabolism* 1999; 10:359-368.
- Fawzy F, Fawzy N Hyun C, et al. Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival six years later. *Archives of General Psychiatry* 1993; 50:681-689.

- Glaser R, Rice J, Speicher C, Stout J, Kiecolt-Glaser J. Stress depresses interferon production by leukocytes concomitant with a decrease in natural killer cell activity. *Behavioral Neuroscience* 1986; 100:675-678.
- Hadden J, Hadden E, Middleton E. Lymphocyte blast transformation. Demonstration of adrenergic receptors in human peripheral lymphocytes. *Cell Immunol* 1979; 1:583-595.
- Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of inferno-induced major depressive disorder in patients with hepatitis C. *Molecular Psychiatry* 2002; 7:942-7.
- Hueston C, Deak T. The inflamed axis: the interaction between stress, hormones, and the expression of inflammatory-related genes with key structures comprising the hypothalamic-pituitary-adrenal axis. *Physiol Behav* 2014; 124: 77-91.
- Homo-Delarche F, Fitzpatrick F, Christeff N, Nunez E, Bach J, Dardenne M. Sex steroids, glucocorticoids, stress and autoimmunity. *Journal of Steroid Biochemistry and Molecular Biology* 1991; 40:619-37.
- Howren M, Lamkin D, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine* 2009; 71:171-86.
- Irwin M, Cole S. Reciprocal regulation of the neural and innate immune systems. *Nature Rev Immunol* 2011; 11:625-32.
- Jaremka L, Glasser R, Malarkey W et al. Marital distress prospectively predicts poorer cellular immune function. *Psychoneuroendocrinology* 2013; 38: 2713-19.
- Jeppesen R, Benros E. Autoimmune diseases and psychotic disorders. *Front Psychiatry* 2019; 10:131.
- Kohler-Forsberg O, et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand* 2019; 139: 404-19.
- Kuhlman K, et al. Early life adversity exposure and circulating markers of inflammation in children and adolescents: a systematic review and meta-analysis. *Brain Behav Immun* 2019 April 15 [Epub ahead of print]
- Lacey R, Kumari M, McMunn A. Parental separation in childhood and adult inflammation. *Psychoneuroendocrinology* 2013; 38: 2476-84.
- McCusker R, Lelley K. Immune-neural connections: how the immune system's response to infectious agents influences behaviour. *J Exp Biol* 2013; 216: 84-98.
- McAfoose J, Baune B. Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews* 2009; 33:355-366.
- McEwen B, Biron C, Brunson K et al. The role of adrenocorticoids as modulators of immune function in health and disease. *Brain Res Brain Res Rev* 1997; 23(1-2):79-133.
- Mettei D, Notter T. Basic concept of microglia biology and neuroinflammation in relation to psychiatry. *Curr Top Behav Neurosci*. 2019. doi: 10.1007/7854_2018_83. [Epub ahead of print]
- Miller G, Cohen S. Psychological interventions and the immune system: a meta-analytic review and critique. *Health Psychology* 2001; 20:47-63.
- Miyaoka T, et al. Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: a case report. *Front Psychiatry* 2017; 8: 174.
- Montoro J, et al. Stress and allergy. *J Invest Allergol Clin Immunol* 2009; 19, Supple 1: 40-47.

- Moraes L, et al. A systematic review of psychoneuroimmunology-based interventions. *Psycholo Health Med* 2018; 23: 635-52.
- Muller N. A brief history of immunological research into psychosis and pathways for immune influence of the brain. *Curr Top Behav Neurosci*. 2019 Feb 19. doi: 10.1007/7854_2018_82. [Epub ahead of print]
- Nakata A. Psychosocial job stress and immunity: a systematic review. *Methods Mol boil* 2012; 934:39-75.
- Nicolaides N, Kyratzi E, Lamprokostopoulou A, Chrousos G, Charmandari E. Stress, the stress system and the role of glucocorticoids. *Neuroimmunomodulation* 2015; 22: 6-19.
- O'Connor M. Immunological and neuroimaging biomarkers of complicated grief. *Dialogues in Clinical Neuroscience* 2012; 14:141-148.
- Pace T, Heim C. A short review on the Psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. *Brain, Behavior, and Immunity* 2011; 25:6-13.
- Pace T, Miller A. Cytokines and glucocorticoid receptor signalling. *Ann N Y Acad Sci* 2009; 1179: 86-102.
- Pape K, et al. Immunoneuropsychiatry – novel perspectives on brain disorders. *Nat Rev Neurol* 2019 Apr 15 [Epub ahead of print].
- Radojevic V, Nicassio P, Weisman M. Behavioral intervention with and without family support for rheumatoid arthritis. *Behavior Therapy* 1992; 23:13-30.
- Salim S, Chugh G, Asghar M. Inflammation in anxiety. *Adv Protein Chem Struct Biol* 2012; 88:1-25.
- Selye H. The significance of the adrenals for adaptation. *Science* 1937; 85:247-248.
- Sommer I, et al. Severe chronic psychosis after allogeneic SCT from a schizophrenic sibling. *Bone Marrow Transplant* 2015; 5-: 153-4.
- Slopen N, Nubzansky L, Koenen K. Internalizing and externalizing behaviors predict elevated inflammatory markers in childhood. *Psychoneuroendocrinology* 2013; 38: 2854-2862.
- Spiegel D, Bloom J, Kraemer H, Gotthel E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989; ii:901.
- Steinmann L. Elaborate interactions between the immune and nervous systems. *Nature Immunology*. 2004; 5:575-581.
- Tomasik J, Rahmoune H, Guest P, Bahn S. Neuroimmune biomarkers in schizophrenia. *Schiz Res* 2014. doi: 10.1016/j.schres.2014.07.025.
- Wilder R. Neuroendocrine-immune system interactions and auto-immunity. *Annual Review Immunology* 1995; 13:307-338.