Psychoneuroimmunology: Stress Reduction To Prevent Cancer Recurrence

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After the surgical removal of a malignant tumor, the chance that cancer will re-appear in a different location of the body remains high. But new research from Tel Aviv University, in a bold new field called Psychoneuroimmunology, may prevent those cancer cells from taking root again - and the key to the treatment is stress reduction.
Psychoneuroimmunology

A new study led by Prof. Shamgar Ben-Eliyahu, from Tel Aviv University's Department of Psychology, has shown scientifically that psychological and physiological stress prior to, during and after surgery has a biological impact that impairs immune system functioning. This impairment bears down on disease progression, he says, especially at the critical point during oncological surgery when a primary tumor is being removed.

The study was published in the journal Brain, Behaviour, and Immunity (2007). The results are expected to influence cancer intervention programs in the future.

Effects of Fear

"The psychological stressors of surgery deal a blow to the immune system, but this is hardly discussed in the medical community," says Prof. Ben-Eliyahu. "Ours is among the first studies to show that psychological fear may be no less important than real physiological tissue damage in suppressing immune competence."

The surprising part of Prof. Ben-Eliyahu's studies is that stress hormones such as adrenaline, which are released before and during surgery, "underlie much of the devastating effects of surgery on immune competence," says Prof. Ben-Eliyahu.

Until now, doctors assumed that the immune system was weakened due to tissue damage and the body's responses to it. A weak immune system is one of the major factors that promotes cancer metastases after an operation, explains Prof. Ben-Eliyahu.

"Timing is everything after cancer surgery," says Prof. Ben-Eliyahu. "There is a short window of opportunity, about a week after surgery, when the immune system needs to be functioning maximally in order kill the tiny remaining bits of tumor tissue that are scattered around the body."

An Early Boost

The main stress hormones that appear to have an impact on immune competence are released before and during surgery, Prof. Ben-Eliyahu has found. He is currently developing a novel intervention program, based on existing generic drugs, to block the influence of these hormones.

Pre-clinical studies in a 2005 study also published in Brain, Behaviour, and Immunity reveal that by blocking these stress hormones, cancer metastases in animal models could be reduced. In a recent study (in progress), Prof. Ben-Eliyahu also found that by blocking these hormones, he could increase long-term post-operative survival rates from cancer in animal models, by as much as 200-300 percent.

Prof. Ben-Eliyahu and his students are now also trying to integrate stimulation of the immune system just before surgery and prevent its suppression. This may provide the immune system
with an opportunity to eradicate cancer residuals after the surgical removal of the primary tumor, and before these residuals are re-established and become resistant to immunity, he says.

Prof. Ben-Eliyahu concludes, "By boosting the immune system and blocking its suppression by psychological and physiological stress, starting a day or two before surgery, during surgery and after surgery, we may be able to provide an intervention program that can extend people's lives and potentially increase their chances for long-term survival."

He plans on starting clinical trials within the next year or two.

Prof. Ben-Eliyahu is one of about 200 other scientists working in the novel and emerging field of Psychoneuroimmunology. It is an interdisciplinary study of the interaction between the psychological processes of the brain, and the nervous and immune systems of the human body. In this field, Prof. Ben-Eliyahu collaborates regularly with Prof. Gayle Page from the Johns Hopkins School of Nursing and other scientists from the United States and Israel. His work is supported by the U.S. National Institute of Health. In May, he plans on attending the Psychoneuroimmunology Research Society conference in Madison, Wisconsin.

Psychoneuroimmunology

Psychoneuroimmunology (PNI), also referred to as psychoendoneuroimmunology (PENI) or psychoneuroendocrinoimmunology (PNEI), is the study of the interaction between psychological processes and the nervous and immune systems of the human body. PNI takes an interdisciplinary approach, incorporating psychology, neuroscience, immunology, physiology, genetics, pharmacology, molecular biology, psychiatry, behavioral medicine, infectious diseases, endocrinology, and rheumatology.

The main interests of PNI are the interactions between the nervous and immune systems and the relationships between mental processes and health. PNI studies, among other things, the physiological functioning of the neuro-immune system in health and disease; disorders of the neuroimmune system (autoimmune diseases; hypersensitivities; immune deficiency); and the physical, chemical and physiological characteristics of the components of the neuroimmune system in vitro, in situ, and in vivo.

History

Interest in the relationship between psychiatric syndromes or symptoms and immune function has been a consistent theme since the beginning of modern medicine.
Claude Bernard, a French physiologist of the Muséum national d'Histoire naturelle, formulated the concept of the milieu interieur in the mid-1800s. In 1865, Bernard described the perturbation of this internal state: “...there are protective functions of organic elements holding living materials in reserve and maintaining without interruption humidity, heat and other conditions indispensable to vital activity. Sickness and death are only a dislocation or perturbation of that mechanism” (Bernard, 1865). Walter Cannon, a professor of physiology at Harvard University coined the commonly used term, homeostasis, in his book The Wisdom of the Body, 1932, from the Greek word homoios, meaning similar, and stasis, meaning position. In his work with animals, Cannon observed that any change of emotional state in the beast, such as anxiety, distress, or rage, was accompanied by total cessation of movements of the stomach (Bodily Changes in Pain, Hunger, Fear and Rage, 1915). These studies into the relationship between the effects of emotions and perceptions on the autonomic nervous system, namely the sympathetic and parasympathetic responses that initiated the recognition of the freeze, fight or flight response. His findings were published from time to time in professional journals, then summed up in book form in The Mechanical Factors of Digestion, published in 1911.

Hans Selye, a student of Johns Hopkins University and McGill University, and a researcher at Université de Montréal, experimented with animals by putting them under different physical and mental adverse conditions and noted that under these difficult conditions the body consistently adapted to heal and recover. Several years of experimentation that formed the empiric foundation of Selye’s concept of the General Adaptation Syndrome. This syndrome consists of an enlargement of the adrenal gland, atrophy of the thymus, spleen, and other lymphoid tissue, and gastric ulcerations.

Selye describes three stages of adaptation, including an initial brief alarm reaction, followed by a prolonged period of resistance, and a terminal stage of exhaustion and death. This foundational work led to a rich line of research on the biological functioning of glucocorticoids.

Mid-20th century studies of psychiatric patients reported immune alterations in psychotic individuals, including lower numbers of lymphocytes and poorer antibody response to pertussis vaccination, compared with nonpsychiatric control subjects. In 1964, George F. Solomon, from the University of California in Los Angeles, and his research team coined the term "psychoimmunology" and
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published a landmark paper: "Emotions, immunity, and disease: a speculative theoretical integration."

Birth of psychoneuroimmunology

In 1975, Robert Ader and Nicholas Cohen, at the University of Rochester, advanced PNI with their demonstration of classic conditioning of immune function, and they subsequently coined the term "psychoneuroimmunology". Ader was investigating how long conditioned responses (in the sense of Pavlov's conditioning of dogs to drool when they heard a bell ring) might last in laboratory rats. To condition the rats, he used a combination of saccharin-laced water (the conditioned stimulus) and the drug Cytoxan, which unconditionally induces nausea and taste aversion and suppression of immune function. Ader was surprised to discover that after conditioning, just feeding the rats saccharin-laced water was associated with the death of some animals and he proposed that they had been immunosuppressed after receiving the conditioned stimulus. Ader (a psychologist) and Cohen (an immunologist) directly tested this hypothesis by deliberately immunizing conditioned and unconditioned animals, exposing these and other control groups to the conditioned taste stimulus, and then measuring the amount of antibody produced. The highly reproducible results revealed that conditioned rats exposed to the conditioned stimulus were indeed immunosuppressed. In other words, a signal via the nervous system (taste) was affecting immune function. This was one of the first scientific experiments that demonstrated that the nervous system can affect the immune system.

In 1981, David L. Felten, then working at the Indiana University School of Medicine, discovered a network of nerves leading to blood vessels as well as cells of the immune system. The researcher, along with his team, also found nerves in the thymus and spleen terminating near clusters of lymphocytes, macrophages, and mast cells, all of which help control immune function. This discovery provided one of the first indications of how neuro-immune interaction occurs.

Ader, Cohen, and Felten went on to edit the groundbreaking book Psychoneuroimmunology in 1981, which laid out the underlying premise that the brain and immune system represent a single, integrated system of defense.

In 1985, research by neuropharmacologist Candace Pert, of the National Institutes of Health at Georgetown University, revealed that neuropeptide-specific receptors are present on the cell walls of both the brain and the immune system. The discovery that neuropeptides and neurotransmitters act directly upon the immune system shows their close association with emotions and suggests mechanisms through which emotions, from the limbic system, and immunology are deeply interdependent. Showing that the immune and endocrine systems are modulated not only by the brain but also by the central nervous system itself had an impact on the understanding of emotions, as well as disease.

Contemporary advances in psychiatry, immunology, neurology, and other integrated disciplines of medicine have fostered enormous growth for PNI. The mechanisms underlying behaviorally induced alterations of immune function, and immune alterations inducing behavioral changes, are likely to have clinical and therapeutic implications that will not be fully appreciated until more is known about the extent of these interrelationships in normal and pathophysiological states.
The immune-brain loop

Further information: Cell signaling networks and Signal transduction

PNI research is looking for the exact mechanisms by which specific brain-immunity effects are achieved. Evidence for nervous system–immune system interactions exists at several biological levels.

The immune system and the brain talk to each other through signaling pathways. The brain and the immune system are the two major adaptive systems of the body. Two major pathways are involved in this cross-talk: the Hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system (SNS). The activation of SNS during an immune response might be aimed to localize the inflammatory response.

The body’s primary stress management system is the HPA axis. The HPA axis responds to physical and mental challenge to maintain homeostasis in part by controlling the body’s cortisol level. Dysregulation of the HPA axis is implicated in numerous stress-related diseases, with evidence from meta-analyses indicating that different types/duration of stressors and unique personal variables can shape the HPA response. HPA axis activity and cytokines are intrinsically intertwined: inflammatory cytokines stimulate adrenocorticotropic hormone (ACTH) and cortisol secretion, while, in turn, glucocorticoids suppress the synthesis of proinflammatory cytokines.

Molecules called pro-inflammatory cytokines, which include interleukin-1 (IL-1), Interleukin-2 (IL-2), interleukin-6 (IL-6), Interleukin-12 (IL-12), Interferon-gamma (IFN-Gamma) and tumor necrosis factor alpha (TNF-alpha) can affect brain growth as well as neuronal function. Circulating immune cells such as macrophages, as well as glial cells (microglia and astrocytes) secrete these molecules. Cytokine regulation of hypothalamic function is an active area of research for the treatment of anxiety-related disorders. 
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Cytokines mediate and control immune and inflammatory responses. Complex interactions exist between cytokines, inflammation and the adaptive responses in maintaining homeostasis. Like the stress response, the inflammatory reaction is crucial for survival. Systemic inflammatory reaction results in stimulation of four major programs:  

- the acute-phase reaction
- sickness behavior
- the pain program
- the stress response

These are mediated by the HPA axis and the SNS. Common human diseases such as allergy, autoimmunity, chronic infections and sepsis are characterized by a dysregulation of the pro-inflammatory versus anti-inflammatory and T helper (Th1) versus (Th2) cytokine balance.

Recent studies show pro-inflammatory cytokine processes take place during depression, mania and bipolar disease, in addition to autoimmune hypersensitivity and chronic infections.

Chronic secretion of stress hormones, glucocorticoids (GCs) and catecholamines (CAs), as a result of disease, may reduce the effect of neurotransmitters, including serotonin, norepinephrine and dopamine, or other receptors in the brain, thereby leading to the dysregulation of neurohormones. Under stimulation, norepinephrine is released from the sympathetic nerve terminals in organs, and the target immune cells express adrenoreceptors. Through stimulation of these receptors, locally released norepinephrine, or circulating catecholamines such as epinephrine, affect lymphocyte traffic, circulation, and proliferation, and modulate cytokine production and the functional activity of different lymphoid cells.

Glucocorticoids also inhibit the further secretion of corticotropin-releasing hormone from the hypothalamus and ACTH from the pituitary (negative feedback). Under certain conditions stress hormones may facilitate inflammation through induction of signaling pathways and through activation of the Corticotropin-releasing hormone.

These abnormalities and the failure of the adaptive systems to resolve inflammation affect the well-being of the individual, including behavioral parameters, quality of life and sleep, as well as indices of metabolic and cardiovascular health, developing into a "systemic anti-inflammatory feedback" and/or "hyperactivity" of the local pro-inflammatory factors which may contribute to the pathogenesis of disease.

This systemic or neuro-inflammation and neuroimmune activation have been shown to play a role in the etiology of a variety of neurodegenerative disorders such as Parkinson's and Alzheimer's disease, multiple sclerosis, pain, and AIDS-associated dementia. However, cytokines and chemokines also modulate central nervous system (CNS) function in the absence of overt immunological, physiological, or psychological challenges.
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Stress Effects and Health

• Everything that is psychological is also biological.

• **Psychoneuroimmunology** – a relatively new field that studies how psychological, neural, and endocrine processes combine to affect our immune system and health

• Immune response includes two types of **lymphocytes** (white blood cells), **macrophages**, and **natural killer** (NK) cells.

• Age, nutrition, genetics, body temperature, and stress all influence your immune response.

Psychoneuroimmunological effects

There is now sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes. Although changes related to infectious disease and wound healing have provided the strongest evidence to date, the clinical importance of immunological dysregulation is highlighted by increased risks across diverse conditions and diseases. For example, stressors can produce profound health consequences. In one epidemiological study, all-cause mortality increased in the month following a severe stressor – the death of a spouse.[15] Theorists propose that stressful events trigger cognitive and affective responses which, in turn, induce sympathetic nervous system and endocrine changes, and these ultimately impair immune function.[16][17] Potential health consequences are broad, but include rates of infection,[18][19] HIV progression,[20][21] cancer incidence and progression,[22][23] and high rates of infant mortality.[24][25]

Understanding stress and immune function

**Stress** is thought to affect immune function through emotional and/or behavioral manifestations such as anxiety, fear, tension, anger and sadness and physiological changes such as heart rate, blood pressure, and sweating. Researchers have suggested that these changes are beneficial if they are
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of limited duration, but when stress is chronic, the system is unable to maintain equilibrium or homeostasis.

In one of the earlier PNI studies, which was published in 1960, subjects were led to believe that they had accidentally caused serious injury to a companion through misuse of explosives. Since then decades of research resulted in two large meta-analyses, which showed consistent immune dysregulation in healthy people who are experiencing stress.

In the first meta-analysis by Herbert and Cohen in 1993, they examined 38 studies of stressful events and immune function in healthy adults. They included studies of acute laboratory stressors (e.g. a speech task), short-term naturalistic stressors (e.g. medical examinations), and long-term naturalistic stressors (e.g. divorce, bereavement, caregiving, unemployment). They found consistent stress-related increases in numbers of total white blood cells, as well as decreases in the numbers of helper T cells, suppressor T cells, and cytotoxic T cells, B cells, and Natural killer cells (NK). They also reported stress-related decreases in NK and T cell function, and T cell proliferative responses to phytohaemagglutinin [PHA] and concanavalin A [Con A]. These effects were consistent for short-term and long-term naturalistic stressors, but not laboratory stressors.

In the second meta-analysis by Zorrilla et al. in 2001, they replicated Herbert and Cohen’s meta-analysis. Using the same study selection procedures, they analyzed 75 studies of stressors and human immunity. Naturalistic stressors were associated with increases in number of circulating neutrophils, decreases in number and percentages of total T cells and helper T cells, and decreases in percentages of Natural killer cell (NK) cells and cytotoxic T cell lymphocytes. They also replicated Herbert and Cohen’s finding of stress-related decreases in NKCC and T cell mitogen proliferation to Phytohaemagglutinin (PHA) and Concanavalin A (Con A).

More recently, there has been increasing interest in the links between interpersonal stressors and immune function. For example, marital conflict, loneliness, caring for a person with a chronic medical condition, and other forms on interpersonal stress dysregulate immune function.

**Communication between the brain and immune system**
- Stimulation of brain sites alters immunity (stressed animals have altered immune systems).
- Damage to brain hemispheres alters immunity (hemispheric lateralization effects).
- Immune cells produce cytokines that act on the CNS.
- Immune cells respond to signals from the CNS.

**Communication between neuroendocrine and immune system**
- Glucocorticoids and catecholamines influence immune cells.
- Endorphins from pituitary & adrenal medulla act on immune system.
- Activity of the immune system is correlated with neurochemical/neuroendocrine activity of brain cells.

**Connections between glucocorticoids and immune system**
- Anti-inflammatory hormones that enhance the organism's response to a stressor.
- Prevent the overreaction of the body's own defense system.
- Regulators of the immune system.
- Affect cell growth, proliferation & differentiation.
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- Cause immunosuppression.
- Suppress cell adhesion, antigen presentation, chemotaxis & cytotoxicity.
- Increase apoptosis.

Corticotropin-releasing hormone (CRH)

Release of corticotropin-releasing hormone (CRH) from the hypothalamus is influenced by stress.

- CRH is a major regulator of the HPA axis/stress axis.
- CRH Regulates secretion of Adrenocorticotropic hormone (ACTH).
- CRH is widely distributed in the brain and periphery
- CRH also regulates the actions of the Autonomic nervous system ANS and immune system.

Furthermore, stressors that enhance the release of CRH suppress the function of the immune system; conversely, stressors that depress CRH release potentiate immunity.

- Central mediated since peripheral administration of CRH antagonist does not affect immunosuppression.

Pharmaceutical advances

*Further information: Neuropsychopharmacology*

Glutamate agonists, cytokine inhibitors, vanilloid-receptor agonists, catecholamine modulators, ion-channel blockers, anticonvulsants, GABA agonists (including opioids and cannabinoids), COX inhibitors, acetylcholine modulators, melatonin analogs (such as Ramelton), adenosine receptor antagonists and several miscellaneous drugs (including biologics like Passiflora edulis) are being studied for their psychoneuroimmunological effects.

For example, SSRIs, SNRIs and tricyclic antidepressants acting on serotonin, norepinephrine and dopamine receptors have been shown to be immunomodulatory and anti-inflammatory against pro-inflammatory cytokine processes, specifically on the regulation of IFN-gamma and IL-10, as well as TNF-alpha and IL-6 through a psychoneuroimmunological process. Antidepressants have also been shown to suppress TH1 upregulation.

Tricyclic and dual serotonergic-noradrenergic reuptake inhibition by SNRIs (or SSRI-NRI combinations), have also shown analgesic properties additionally. According to recent evidences antidepressants also seem to exert beneficial effects in experimental autoimmune neuritis in rats by decreasing Interferon-beta (IFN-beta) release or augmenting NK activity in depressed patients.

These studies warrant investigation for antidepressants for use in both psychiatric and non-psychiatric illness and that a psychoneuroimmunological approach may be required for optimal pharmacotherapy in many diseases. Future antidepressants may be made to specifically target the immune system by either blocking the actions of pro-inflammatory cytokines or increasing the production of anti-inflammatory cytokines.

Extrapolating from the observations that positive emotional experiences boost the immune system, Roberts speculates that intensely positive emotional experiences — sometimes brought about during mystical experiences occasioned by psychedelic medicines — may boost the immune system powerfully. Research on salivary IgA supports this hypothesis, but experimental testing has not been done.
Psychoneuroimmunology (PNI) & Inflammation
Psychoneuroimmunology (say that three times fast, or just call it PNI) is the scientific study of your mind, body and overall health. Specifically it is the study of “the interaction between psychological processes and the nervous and immune systems of the human body.”

As a biohacker, if I wasn’t already happily unavailable, I’d want to date a psychoneuroimmunologist. That has to be the sexiest profession ever. One of the core tenets of the Bulletproof program is that if you get your “hardware” working right (your body), then your brain is capable of more than you’ve ever dreamed possible.

PNI is the research helping you upgrade your mind and body through food and stress control – the Bulletproof way. This supports the Bulletproof Diet because it is more than eating the right foods – it is a lifestyle that involves becoming more resilient and happier by increasing awareness of how your mind and body are affected by food and your environment. That’s the Bulletproof state of high performance I keep talking about.

According to PNI, upgrading your body begins with avoiding proinflammatory foods – the dominant principle in the Bulletproof Diet. A recent study done shows that insulin is a key pathway leading to stress and negative influences in the body.(1) Your diet modulates key pathways to inflammation through sympathetic activity, oxidative stress, and proinflammatory cytokine production.(5) Stress and depression are also correlated to higher insulin levels.(23)

Problems with Inflammation

High insulin levels in the body are at the center of many diseases. Together, cardiovascular disease, cancer, and diabetes account for almost 70% of all deaths in the United States –
inflammation is a common link between these diseases.(15,17) Inflammation is also linked to many autoimmune diseases and some mental health issues.(30) Diets that promote inflammation are high in refined starches, sugar, and trans-fats. Refined starches and sugars can alter blood glucose and insulin levels, and postprandial hyperglycemia can increase production of free radicals as well as proinflammatory cytokines.(15, 25) In order to avoid inflammation, and therefore many diseases, eating a diet with high ratios of omega-3 to omega 6 fatty acids and natural antioxidants is important. Omega-3 fatty acids found in fish oil, avocado, and grass-fed beef curb the production of AA-derived eicosanoids, which spike insulin.(27) American’s levels of omega-3 to omega-6 fatty acids are abysmal and contribute to many diseases of inflammation. These fatty acids compete for the same pathways, and thus their balance is important.(28) Think I’m kidding? On the Bulletproof Diet, my WellnessFX test showed my ratio of omega 6 to omega 3 was 1.28. Anti-aging doctors hope for 4:1, and the average American can be as high as 40:1. A study done in China found that lower n-6 to n-3 ratios (ie eating less omega 6) are associated with lower proinflammatory cytokine production and demonstrate significant inverse relationships between annual fish consumption and depression.(9) The more fish eaten, the lower the prevalence of serious clinical depression. Stress and depression were associated with less fruit and more snack consumption. You may want to try low-mercury fish like anchovies, tilapia, and trout to avoid harmful metals, or go with my favorite, krill oil.

**Stress and Your Gut**

The vagus nerve is involved in digestion, absorption, and metabolism of nutrients.(7) Unhealthy food, stress, and depression have negative effects on vagal activation. This shows that there is a direct correlation between your brain and gut because stress hinders your guts essential actions. Stress also influences your food choices, and increases insulin resistance. Stress increases maladaptive metabolic responses to unhealthy meals, which affects mood and proinflammatory responses to stressors.(1) Avoid or hack your stress at home and in the workplace in order to get the most from the nutrients in food.

Two ways I have successfully reduced stress are through learning to control my breathing and heart rate. For breathing, focus on using your whole diaphragm and slowly letting air in and out through your nose. It may help to place your hand on your belly and make sure your belly rises and falls while breathing in and out. Good practices for this are yoga (pranayama) and taking a class called “The Art of Living.” (If you have more share them!)
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Learn to control your heart rate with the help of technology. A device called the [emWave2](http://psycnet.apa.org/journals/gpr/10/3/229/) measures the space between heartbeats, and through feedback, can help you increase your heart-rate variability. Increased HRV is associated with being able to respond to situations in a healthy way [http://psycnet.apa.org/journals/gpr/10/3/229/]. There is a correlation between mental health and good heart rate variability.

As a biohacker, I am an advisor to the company that invented Heart Rate Variability training, and I insist that my executive performance coaching clients use the emWave2 because of the systemic effects it has on so many levels.

Combine the Bulletproof Diet with two of my biohacks – learning to breathe properly and improving your heart-rate variability – and your brain and gut will work better together. You will interpret this as feeling Bulletproof.

Psychoneuroimmunology is a relatively new field, and gives us an idea on how stress and food affect the body. Minimizing inflammatory foods and enhancing vital nutrients like omega-3 fatty acids and antioxidants, not only helps you avoid disease – you live more optimally. Add a life you enjoy into the equation and you can push your body and mind to new heights :). Hack on biohackers.

If you have questions about psychoneuroimmunology or have some cool insights about foods effect on your brain function share them below!

### Branches of Medicine

- Biological psychiatry
- Endocrinology
- Psychoneuroendocrinology
- Immunology
- Neuroanatomy
- Neurobiology
- Neurochemistry
- Neurology
- Neuropharmacology
- Psychiatry

### Neuroanatomy

- Locus ceruleus
- Pedunculopontine nucleus
- Raphe nucleus
- Reticular activating system
- Suprachiasmatic nucleus

### Related Topics

- Allostatic load
- Fight-or-flight response
- Healing environments
- Neural top down control of physiology
- Post-traumatic stress disorder
- Psychosomatic medicine
- Stress management

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