Mind, immunity and health – the science and clinical application of psychoneuroimmunology

Psychoneuroimmunology is a multidisciplinary field spanning immunology, psychology and neuro-endocrinology.

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Developing an understanding of the relationship between psychosocial factors, behaviour, immunity and health is a central focus in psychoneuroimmunology (PNI). A broader point of focus in behavioural medicine (mind-body medicine) is the wellness and ongoing development of the individual on all levels – physical, emotional, mental and spiritual.

The science of PNI

Every part of the immune system is connected to the brain in some way, be it via a direct nervous tissue connection, or by the common chemical language of peptides. Branches of the autonomic nervous system densely innervate lymphoid tissues. The sympathetic nervous system directly influences the immune system as nerve fibres go directly to zones where T cells and macrophages are in high concentrations. Nerve endings have been observed to make small indentations on the surface of individual lymphocytes, which have B-adrenergic receptors, and as a result the sympathetic nervous system is able to mediate the brain's influence on immunity.[1]

Peptide macromolecules including hormones, neurotransmitters, neuropeptides, releasing factors, cytokines and endorphins are able to occupy specific surface receptors on all leucocytes and as a result influence the growth, activity and protein synthesis of these cells. Leucocytes themselves produce peptides once only thought to be manufactured and secreted by tissues in the brain and endocrine system. T cells, for example, are able to synthesise their own adrenalin and noradrenalin.

Not only do various neuropeptides, hormones and nervous system mediators influence immunity, the immunological hormones (the interleukins, interferons and tumour necrosis factors – also known collectively as cytokines) have significant effects on the body and central nervous system (affecting mood, cognitive abilities and neuroendocrine functions as well as playing a role in depression).[1] Cytokine receptors have been found on cells of the endocrine system and these cells under normal or stress conditions manufacture various cytokines themselves.

This complex communication between systems reflects a network connecting the brain, endocrine and immune systems into one functioning 'psychosomatic network', with systematic communication taking place.[2] Specific areas of the brain that modulate emotion (the amygdala and hypothalamus particularly) have been found to be rich in peptides (up to 40× more than other areas of the brain). Peptides secreted from the brain (in relation to stress or a particular mental and emotional state), via the psychosomatic network, can affect the behaviour, metabolism and migration of an immune system cell, and its ability to produce antibodies or related cytotoxic chemicals.

This communication is also bi-directional: in immune activation macrophages secrete the pre-inflammatory cytokines Interleukin-1, 6 and alpha TNF. This results in a fever and the activation of the body's energy-conserving responses such as withdrawal, decreased social interaction, reduced aggression, reduced sexual behaviour, need to sleep and loss of appetite. All of these responses, which we call 'sickness', are initiated by the immune system. The cytokines induce a stress response by the release of corticotrophin-releasing factor (CRF) and the activation of the hypothalamic-pituitary-adrenocortical (HPAC) system with a sustained increase in cortisol, which can result in behaviour that mimics depression.[3]

The concept of 'a mind-body connection' seems to downplay the degree of integration of the various systems and many favour the idea of a BODYMIND – an organised whole with two-way communication with no hierarchy of mind over body, but rather a complex system.

Stress and immunity

Stress begins with an actual or perceived threat activating sensory or higher centres in the cerebral cortex. Cortical fibres to the amygdala are activated, and the messages reach this area of the brain, which is the primary mediator of the stress response. Other signals, sometimes preconscious, also result in activity in the amygdala.

Once activated, the cells of the central nucleus of the amygdala release CRF which stimulates the brainstem to activate the sympathetic nervous system, eventually resulting in adrenalin being released from the adrenal glands. The CRF also triggers the release of glucocorticoids. This is the typical 'fight or fright' response, usually short lived. If the stress becomes chronic, the

glucocorticoids begin to induce the locus coeruleus to release its own noradrenalin that acts on the amygdala, resulting in more production of CRF, which in turn results in further activation of the stress pathway.

Long-term chronic increases in adrenalin secretion suppress immunity: both noradrenalin and adrenalin decrease cell-mediated immune responses (noradrenalin via alpha- and beta-adrenergic receptors, and adrenalin via an increase in interleukin 6 (IL-6)).[4]

Chronically elevated adrenalin secretion results in a shift away from cell-mediated defences (with decreased cytotoxicity and a shift in CD4/CD8 ratio) as well as a decrease in natural killer (NK) cell activity. If a fight-or-flight situation (or the perception that one exists) becomes chronic, there can be long-term effects, such as a decreased T-cell proliferation and suppressed immunity.

The glucocorticoids have been found to have significant roles to play in both autoimmune processes, and in immune deficiency. Cortisol has potent anti-inflammatory and immuno-suppressive affects and is an important part of the negative feedback loop during an immune response. The HPAC system is responsible for cortisol release from the adrenal gland. Cortisol plays its biggest role in the stress response when active control-based coping has broken down, and the perception of control has been lost (the stress is now overwhelming, unpredictable and unrelenting).

In chronic long-term stress lymphocyte proliferation is reduced, NK cells are unable to destroy cancerous and virally-infected cells, lymph gland structure deteriorates, and cognitive damage may occur, resulting in memory deficits, anxiety and depression.

There is consistent evidence that depression and anxiety enhance the production of the inflammatory cytokines, including interleukin-6, and higher levels of IL-6 were associated with greater distress.[5]

Stress and disease

Stress is not universally immunosuppressive, and there are different PNI responses to acute and chronic stress. Acute stress (defined as episodic events measured in minutes or hours) is often associated with a short-term 'up-regulation' of cell-mediated immunity and no long-term dysfunction. Chronic stress results in a decrease in circulating lymphocytes, particularly T helper cells, less efficient proliferation in response to a challenge, fewer circulating NK cells and less cytotoxicity, antibody titres to specific viruses are raised and there is decreased secretion of nonspecific secretory IgA.

When considering stress in an individual it is wise to bear in mind not only psychological and behavioural stressors, but physiological stressors as well. Abnormalities in the immune system and pain result in a secondary stress response in the central nervous system. The immune system acts like a sensory organ for the brain and the response of the brain to inflammation or infection is identical to its response to a stressful stimulus.

Stress itself is neither good nor bad, and while various psychosocial factors have been shown to impact on immunity and resistance (Table I) their impact depends on the resilience of the individual who encounters these factors. If these factors present themselves in a patient's life they need to be addressed and suitable interventions facilitated to counteract their effect, as they could interact negatively with pre-existing conditions.

Table I. Psychosocial factors impacting on immunity

- Absence of social support
- Significant loss
- Unemployment
- Loneliness
- Bereavement
- Homelessness
- Retirement
- Suppressed anger
- Suppressed emotions
- Denial coping
- Time urgency
- Living in a hazardous location
- Taking care of someone with a serious disease
- Low marriage quality
- Divorce and separation
- Insomnia
- Miscarriage
- Stroke
- Surgery
- Exam-related distress

Bear in mind that health and potential for wellness depend on an interaction between psychosocial factors, availability of coping response, genetic factors, age, social conditions and previous medical/stress history.

Clinical challenges

An ongoing challenge in PNI research is to deepen our knowledge of how thought, perception and emotion result in changes in immunity and ultimately health.

It is widely accepted that chronic stress and depression cause immune dysfunction in a susceptible individual; this may result in disease progression and increased disease susceptibility. Removing the source of stress is an obvious strategy, but this is often impossible. An alternative strategy is to focus on the factors that make an individual stress or disease resistant. Alleviating the damaging effects of stress and depression by facilitating resilience and stress resistance should lead to an enhancement of immunity, resulting in the prevention of disease or possibly remission.

The research to date is as compelling concerning immuno-enhancement and recovery as it is concerning immuno-suppression and stress. Various factors have been linked to disease resistance and speedy recovery and hold much promise in the clinical application of the field.

Mood, adaptive coping, continued life involvement, emotional processing, social support, doctor-patient relationship and spirituality, are all variables that influence healthy survival in the face of HIV infection and other life-limiting conditions.[6]

In linking personality traits and stress resistance, Kobasa identified three attitudes that collectively acted as a buffer against inner distress in the encounter with stressful life events – she called this hardiness.[7]

The attitudes of commitment, control and challenge lay a foundation for motivation based on a sense of meaning and a sense of self-efficacy, which has a positive effect on immunity in the face of stress.[8]

Linville described self-complexity as the capacity to understand oneself and the world in a complex, multifaceted way. It is the trait of having many traits and allows for flexibility in coping and provides an individual with a wide repertoire of emotional and cognitive responses to stress. Self-complex individuals are more subjectively and objectively resistant to stress, and show a decreased vulnerability to anxiety, depression and immune dysfunction.[9]

The suppression of emotions has been demonstrated to be one of the most significant psychological factors leading to immune system dysfunction.[10] Expressive writing has been shown to moderate the distress related to negative social interactions and lack of social support in cancer patients.[11] Strong associations have been found between repressive coping and the progression of cancer.[12]

Creating sustained and meaningful mental imagery has proven to be a powerful healing tool. The immune system is the ideal target for cellular imagery and its impact on immunity has been well documented.[13]

Davidson *et al.* have shown that a short programme in 'mindfulness meditation' produced lasting positive changes in

both the brain and the function of the immune system. The findings suggest that mindfulness, promoted as a technique to reduce anxiety and stress, might produce important biological effects that improve a person's resilience.[14]

It is important to emphasise that in the clinical application of PNI, causation is never implied. PNI explores the *interaction* between psychosocial events, stress, coping and immunity, simultaneously acknowledging the pre-existing biological conditions.[15]

A case has been made for an 'arthritis-prone' or 'cancer prone' *personality* – someone at risk for certain illnesses as a result of their attitude and coping. Immune dysfunction may result from stress and maladaptive coping strategies, but it must be acknowledged that other social, environmental and genetic factors influence the interaction. In short, how an individual thinks, or copes with life and stress does not necessarily cause disease.

PNI research has much to offer when we consider patients who are diagnosed with a life-threatening or life-limiting illness. Their mental and emotional well-being at the time of, and prior to, their diagnosis can have a significant effect on disease progression and prognosis. Assisting a patient in managing stress, as well as recognising and dealing with psychosocial factors that may interact negatively with existing conditions, is imperative. Broadening the individual's scope of attention, cognition and action, and building of physical, intellectual and social resources facilitates self-efficacy, optimism, resilience and health.[16]

Conclusion

The challenge in an emerging discipline has always been in its clinical application.

Working from a scientific basis in such a diverse field requires that guidelines for clinical practice be constructed and overriding principles established that can be kept in mind regardless of the therapeutic approach taken. It was suggested at the 1977 Yale Conference[17] that a therapeutic programme incorporating this new model of healing should meet four conditions:

- It should facilitate the awareness of behaviours and responses that are risk factors for disease.
- It should facilitate a change in behavioural and physiological response, thus enhancing well-being.
- It should improve compliance.
- It should facilitate a change in the way health care providers, at all levels, approach clients, and assist in supporting them in their efforts to improve health and alleviate suffering.

The clinical application of the field of PNI within behavioural medicine is eclectic and acknowledges the research, techniques and therapies suggested by contributors from various disciplines. PNI itself is simply a field of scientific exploration, providing scientific data that support the development of a more sensitive, integrative, multidisciplinary approach to patients.

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In a nutshell

- Psychoneuroimmunology (PNI) is a multidisciplinary field spanning immunology, psychology and neuro-endocrinology.
- The bi-directional communication occurs between the brain, endocrine and immune systems reflects a functional 'psychosomatic network'.
- Chronic stress influences all aspects of the psychosomatic network.
- Various psychosocial factors impact on immunity and resistance, their impact depends on the resilience of the individual who encounters these factors.
- Hardiness, self-complexity and balanced emotional expression are important buffers against stress and immune dysfunction.
- Mood, adaptive coping, continued life involvement, emotional processing, social support, doctor-patient relationship and spirituality, are all variables that can influence disease progression from a PNI perspective.
- Managing stress, identifying relevant psychosocial factors and promoting self-efficacy, optimism and resilience is an important facet of comprehensive health care.