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Psychoneuroimmunology or Immunopsychiatry?

Carmine M. Pariante, MD, FRCPsych, PhD

Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London UK

Studying the communication between the brain and the immune system, a discipline generally known as *psychoneuroimmunology*, is a hot area in psychiatry and neuroscience research, and has led to the introduction of a new term to define the field: *immunopsychiatry*.¹ The review by Khandaker and colleagues in this issue of *The Lancet Psychiatry*² specifically “considers whether we are entering a new era of immunopsychiatry that will change our understanding of the brain’s maladies”. Why a new name? To paraphrase Shakespeare’s Juliet, that which we call psychoneuroimmunology by any other name would smell as sweet. I would like to propose that these two names – psychoneuroimmunology and immunopsychiatry – represent two different conceptualisation of the brain-immune communication. While advocates of both terms acknowledge bidirectional communication between these two systems, I would argue that the recent use of the term *immunopsychiatry* represents a hierarchical shift: it suggests that our brain no longer governs the immune system, but, on the contrary, that our behaviours and emotions are governed by peripheral immune mechanisms. You cannot cure yourself of a fever by meditation, but fever can make you sad and grumpy.

Psychoneuroimmunology originally implied a bidirectional communication between the brain and the immune system on “equal terms”, with an emphasis on the notion that psychological and neural phenomena can influence the immune system.³ In their 1982 seminal paper, Bovbjerg and his colleagues⁴ demonstrated that the administration of saccharin together with the immunosuppressant, cyclophosphamide, led to a conditioned response, so that eventually saccharin alone was able to suppress the immune system. The hierarchical model was very clear: a nerve impulse due to a taste stimulus had profound effects on the immune system. Dozens of studies in the 1980s then examined the relationship between major depression and the immune system, based on the model that depression as a mental state was able to influence the immune system.⁵ More controversial studies reported that psychosocial interventions could prolong survival in cancer patients by improving immune function,⁶ and attempts to modify the immune system through hypnosis and relaxation.⁷

In the 1990s, two factors drove a conceptual shift in the field that led to the reversal of the hierarchy between the brain and the immune system. First, studies using animal models showed clear molecular mechanisms by which immune activation leads to behavioural

changes, especially changes resembling depressive symptoms;⁸ and, second, clinical studies showed that patients exposed to cytokine therapies for cancers or chronic viral hepatitis develop depressive symptoms and other psychiatric adverse effects.⁹ Later, increased inflammation was described in otherwise healthy individuals with a history of childhood trauma, one of the more powerful risk factors for depression,¹⁰ implying a potentially “causal” role of the increased inflammation in the future onset of depression. The time was ripe for affirming that the immune system can “subjugate the brain” in inducing behavioural changes and psychiatric symptoms.¹¹ Finally, the most recent studies have shown that increased inflammation is present not only in depression but also in psychosis and other psychiatric disorders, as discussed in the review by Khandaker and colleagues.²

It is important to consider two more points for discussion. First, as raised by Khandaker and colleagues,² the initial evidence linking immune activation to psychiatric disorders comes from studies in patients with infections, some conducted more than one century ago, and again implying that the infections (most likely through immune activation) can induce behavioural changes and psychiatric symptoms. Second, this theoretical shift in the brain-body hierarchy does not minimise the importance of psychosocial factors for immune regulation, as shown by recent evidence that disruption of immune function by psychological stress impairs wound-healing.¹²

The introduction of the term *immunopsychiatry* has created the opportunity of managing psychiatric disorders through novel treatment approaches targeting the immune system. Randomised controlled studies using anti-inflammatories for depression have shown therapeutic effects,¹³ and extended the use of these drugs to other psychiatric disorders¹³ and to prophylactic interventions.¹⁴ More importantly, this new theoretical approach facilitates the identification of biological mechanisms and therapeutic interventions with well-defined, hypothesis-based immune mechanisms and pharmacological targets. This, together with the introduction of the notion of psychiatric disorders as disorders with biological changes that are outside the brain and measureable in the blood, could close the gap between psychiatry and the rest of medicine, potentially reducing the stigma associated with mental health problems.

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