How and why NeuroImmunology & PsychoNeuroImmunology came to be and gave rise to neuroinflammation & immunopsychiatry
History of science ... why and what?

• Why apply a historical approach to science?
  – Master the literature and honor the first investigators on a theme
  – Acquire the history of development of a technique or instrument
  – Identify origins of disciplines and approaches
  – Describe history of ideas and concepts

• What is at stake when doing history of science?
  – Technology: between poor-parent and exclusive prism
  – Education: between immersion and past of the present
  – Ideology: between conditions of possibilities and scientism
  – Epistemology: between normative and empirical
You ought to know ... important new things are happening and have been learned


- Neurological Disease as a Failure of Brain-Immune Crosstalk: The Multiple Faces of Neuroinflammation, Schwartz & Deczkowska, Trends Immunol., 2016

What’s in a name?

Some historical (yet retrospective) affiliations

- Immunology or/and Neurology? → NeuroImmunology → Neuroinflammation

- Psychosomatic medicine → PsychoNeuroImmunology → ImmunoPsychiatry
What’s in a name?

NeuroImmunology avant la lettre

- Spread bugs & antibodies to CNS
- Brain as immune-priviliged organ
- Microglia as phagocytes
- Experimental Allergic Encephalomyelitis
Neuroimmunology avant la lettre
Spread bugs & antibodies to CNS (1)

- Penetration of the virus of poliomyelitis from the blood into cerebrospinal fluid, Flexner & Amoss, J. Exp. Med., 1914

- The relation of the meninges and choroid plexus to poliomyelitic infection, Flexner & Amoss, J. Exp. Med., 1917

- The passage of neutralizing substances from the blood into the cerebrospinal fluid in poliomyelitis, Flexner & Amoss, J. Exp. Med., 1917

- The passage of neutralizing substances from the blood into the cerebrospinal fluid in actively immunized monkeys, Flexner & Amoss, J. Exp. Med., 1917

- Survival of poliomyelitic virus in the rabbit brain, Amoss, J. Exp. Med., 1918

- Experiments on the nasal route of infection in poliomyelitis, Flexner & Amoss, J. Exp. Med., 1920
- Les rapports entre augmentation de la perméabilité de la barrière hématoencéphalique et les alteration de son substratum biologique, Stern & Rapoport, C. R. Soc. Biol., 1928

- The blood-brain barrier in infectious diseases: its permeability to toxins in relation to their electrical charges, Friedeman & Elkeles, Lancet, 1934


Modified from Allen, J. Pathol. Bacteriol., 1965
Neuroimmunology avant la lettre
Brain as immune-priviliged organ

- Conditions determining the transplantability of tissues in the brain, Murphy & Sturm, J. Exp. Med., 1923

- Immunity to Homologous Grafted Skin. III. The Fate of Skin Homographs Transplanted to the Brain, to Subcutaneous Tissue, and to the Anterior Chamber of the Eye, Medawar, Brit. J. Exp. Pathol., 1948


Modified from Murphy & Sturm, J. Exp. Med., 1923
Neuroimmunology avant la lettre

Microglia as phagocytes

- Studies on the Relation between Microglia, Histiocytes and Monocytes, Dunning & Furth, Am. J. Pathol., 1935
- The microglia, Rio-Hortega, Lancet, 1939

Dunning & Furth, Am. J. Pathol., 1935
van Furth et al., Bull. World Health Organ, 1972
Allergic encephalomyelitis in monkeys in response to injection of normal monkey cord, Morgan, J. Bacteriol., 1946

The role of antibody in "allergic" encephalomyelitis, Thomas et al., J. Clin. Med., 1950

Demyelination in the guinea pig in chronic allergic encephalomyelitis produced by injecting guinea pig brain in oil emulsion containing a variant of mycobacterium butyricum, Freund et al., Arch. Pathol. (Chic.), 1950

Allergic encephalomyelitis as an experimental model for multiple sclerosis, Calif. Med., 1959

The passive transfer of experimental allergic encephalomyelitis and neuritis with living lymphoid cells, Astrom & Waksman, J. Bacteriol. Pathol., 1962
More than fifty years ago it was realized that certain neurological disorders were related to allergic reactions and thus attention was drawn to the role of immunological factors. Since then, it has been shown that immunological mechanisms are involved not only in a growing number of disease processes of the nervous system, but also in the development of nervous tissue. ... Thus, with the continuing and intensive application of immunological techniques to the neurological sciences, the specialty of neuroimmunology has evolved. (Raine & Behan, J. Neuroimmunol., 1981)

The nervous system and the immune system interface at a variety of levels to create the discipline that has been termed neuroimmunology. Neuroimmunology I: Immunoregulation in Neurological Disease, (Weiner & Hauser, Ann. Neurol., 1982)
Inflammation in brain tissue takes a different form from that normally seen in other tissues. ... V. Hugh Perry (University of Oxford, UK) showed that lipopolysaccharide (LPS), a major inducer of the inflammatory response in most organs, causes a marked inflammatory response in the meninges and choroid plexus without recruitment of inflammatory cells to the parenchyma until several days after administration. (Rosenberg, Mol. Med. Today, 1997)

In the past two decades, our understanding of the CNS has been transformed from one of an immune-privileged site, to one where immune and inflammatory processes are pathognomic for some of the most prevalent and tragic neurological disorders and neurodegenerative diseases. (Emmerling & Barnum, Inflamm. Res., 1997)
In the name of ...
What may have been lost along the way (1)

- If neuroimmunology as a name seems to well accommodate the privileged status of the brain with respect to immune responses, this may be less the case for neuroinflammation as a term.

- Richness and complexity of a set of biological responses reduced to one or two cellular or molecular entities:
  o Alterations in immune cells and mediators in the brain: it's not always neuroinflammation! Estes & McAllister, Brain Pathol., 2014

- Diversity and heterogeneity of molecular profiles of "glia" in brain diseases:
  o Should We Stop Saying 'Glia' and 'Neuroinflammation'? Masgrau et al., Trends Mol. Med., 2017

→ How can neuroinflammation as a concept have grown from a descriptive entity specific to some conditions to something that is regularly invoked to be causal in so many different conditions?
What’s in a name?
Some historical (yet retrospective) affiliations

- Immunology or/and Neurology? → NeuroImmunology → Neuroinflammation

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What’s in a name? Psychosomatic

– I have tried to present in this section some of the historic antecedents as well as the core meaning of the connotation of the word "psychosomatic," which I propose to call "holistic."

– The second core connotation of the term "psychosomatic" may be referred to as equivalent to "psychogenic," in the sense that it implies an etiologic hypothesis about the role of psychologic factors in human disease.

– Indeed, the entire notion of psychogenesis, one incompatible with the currently prevailing doctrine of multicausality of disease, is no longer tenable, hence, the psychogenic connotation of the word "psychosomatic" should be explicitly discarded. As one writer put it succinctly, "To equate psychosomatic with psychogenetic is indeed pointless and obsolete" (62).
What’s in a name?
PsychoNeuroImmunology avant la lettre

- Conditioning of immune responses
- Immune alterations in mental disorders
- Effects psychological stress on immune system
Psychoneuroimmunology avant la lettre
Conditioning of immune responses

– Rôle des réflexes conditionnels dans la formation des anticorps, Metalnikov & Chorine, C. R. Soc. Biol., 1928

– Conditioning of allogeneic mice with crude and purified H-2 extracts, alone and combined with cyclophosphamide, for skin graft prolongation, Halle-Pannenko et al, Transplant. Proc., 1971


Psychoneuroimmunology avant la lettre
Immune alterations in mental disorders

- Pseudoallergic schizophrenia: a new clinical entity, Abrahamson, Ann. Allergy, 1959


- Secondary immune response to tetanus toxoid in psychiatric patients, Solomon et al., J. Psychiatr Res. 1970

- Cell-mediated immunity to human myelin basic protein in schizophrenic patients, Kuritzky et al., J. Neurol. Sci, 1976
Psychoneuroimmunology avant la lettre
Effects psychological stress on immune system


- Stress and susceptibility to viral infection. I. Response of adrenals, liver, thymus, spleen and peripheral leukocyte counts to sound stress, Jensen & Rasmusen, J. Immunol., 1963

- Immunity, emotions and stress with special reference to the mechanisms of stress effects on the immune system, Solomon et al., Psychother. Psychosom., 1974
Psychoneuroimmunology avant la lettre
Effects psychological stress on immune system

Jensen & Rasmusen, J. Immunol., 1963
What’s in a name?
PsychoNeuroImmunoology: psycho → immuno

– ..., “psychoneuroimmunology”\(^2\) has been used to refer to studies of the neuroendocrine mechanism mediating the effects of behavior on immune function – and vice versa.

– In an attempt to account for such phenomena, it is quite reasonable, then, to hypothesize that changes in immune function may mediate the effects of psychosocial factors on the development and/or progression of some pathophysiological states. Such a hypothesis is tenable, however, only if it can be shown that the CNS plays some role in the modulation of immunity.

What’s in a name?

ImmunoPsychiatry: immuno → psycho

– *Psychoneuroimmunology* originally ... an emphasis on the notion that psychological and neural phenomena can influence the immune system.³

– 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.
  o First, studies using animal models showed clear molecular mechanisms by which immune activation leads to behavioural changes, especially changes resembling depressive symptoms;⁸
  o 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

– The introduction of the term immunopsychiatry has created the opportunity of managing psychiatric disorders through novel treatment approaches targeting the immune system.

Pariante, Lancet Psychiatry, 2015
In the name of ... What may have been lost along the way (2)

– Normal physiology and behavior:
  o The physiological (fever) and behavioral changes (reduced food intake) induced by immune activation can above all be considered adaptive and regulated responses.

– Downward (top-down) causation:
  o Fever, once established through upward causation, can, as a system’s property, exert downward causation, for example on bacterial replication and certain immune responses.

→ Why have pathological conditions and upward (bottom-up) explanations been favored as of lately in psychoneuroimmunology up to a point to give rise to immunopsychiatry?
What’s in a name?

- History: Immunology or/and Neurology? → NeuroImmunology → Neuroinflammation

- History: Psychosomatic medicine → PsychoNeuroImmunology → ImmunoPsychiatry

→ Future: Neuroinflammation & ImmunoPsychiatry, a happy marriage of reason or a dangerous liaison?
The ambiguous relationship of science & medicine with philosophy and history of science & medicine

- Rather sloppy use of definitions and citations in science and medicine
- Scientists and clinicians self-declaring paradigm shifts or how Thomas Kuhn became the most cited historian of science
- Trading zones may better describe forces at work in interdisciplinary research fields
The ambiguous relationship of science & medicine with philosophy and history of science & medicine

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... it is argued that much can be learned by reflecting on the progression of models, or "paradigm-shifts," ....... It is argued, finally, that, with the emergence of behavioural medicine, and, more particularly, psychoneuroimmunology, ..., one can see a new conceptualization of the human body beginning to take shape. (Levin & Solomon, J. Med. & Phil., 1990).

This paradigm shift in the study of immunoregulatory processes and the elaboration of the mechanisms underlying behaviorally induced alterations of immune function promise a better understanding and a new appreciation of the multi-determined etiology of pathophysiological states. (Ader, Eur. J. Pharmacol., 2000)

Gaining a better understanding of the role of immune system could be paradigm changing for psychiatry. (Khandaker et al., Pscyhol. Med., 2017).
The ambiguous relationship of science & medicine with philosophy and history of science & medicine

- Rather sloppy use of definitions and citations in science and medicine

- Scientists and clinicians self-declaring paradigm shifts or how Thomas Kuhn became the most cited historian of science

- Trading zones/repertories may better describe forces at work in interdisciplinary/multidisciplinary research fields
What we have are quasi-stable scientific subcultures (roughly shared ways of handling practices with their attendant values, symbols, and meanings). Above all, we need to know how these scientific subcultures connect to each other, to the surrounding world, and to change.

The point of emphasizing the power of what goes on in the trading zone is that the trading zone is not “mere mortar” between the solidity of bricks. What is exchange work today may well become the disciplinary pillars of tomorrow: science is forever in flux, not just in its results but in the contours of its disciplines.

But the necessary condition for a trading zone is that practices (and their interpretations) tend to travel in packs rather than along arbitrarily combined trajectories. These “packs” might be a set of affiliated experimental procedures .... Here they are tactics, there they are strategies — but also regulative values.

Galison, 2010
Galison’s supposed resolution to the general problem was to posit the existence of in-between languages ... which developed to enable ‘trade’ to happen between communities with radically different languages.

His paradigm case was the invention of biochemistry which grew out of the invention of a new language which captured the appropriate parts of the language of chemistry and the language of biology.

Multi-disciplinarity is an extension of the specified deliverable model. It differs from interdisciplinarity because there is no attempt at common understanding by either home group or foreign group – indeed, it is not clear if there is a ‘home’ group.

Collins et al., 2017
The framework centers on the notion of a research repertoire, which encompasses well-aligned assemblages of the skills, behaviors, and material, social, and epistemic components that a group may use to practice certain kinds of science, and whose enactment affects the methods and results of research.

This account provides an alternative to the idea of Kuhnian paradigms for understanding scientific change in the following ways:

1) it does not frame change as primarily generated and shaped by theoretical developments, but rather takes account of administrative, material, technological, and institutional innovations …;

2) it thus allows for tracking of the organization, continuity, and coherence in research practices which Kuhn characterized as ‘normal science’ …; and

3) it requires particular attention be paid to the performative aspects of science, whose study Kuhn pioneered but which he did not extensively conceptualize.

Ankeny & Leonelli., 2017