PSYCHONEUROIMMUNOLOGY
FALL, 2014

Instructor: Alexander Kusnecov, Ph.D.
Office Location: Psychology Bldg, Room 233a
Phone: 848 445 3473
Email: kusnecov@rci.rutgers.edu

Psychoneuroimmunology (PNI) is the study of functional interactions between the central nervous system (CNS) and the immune system. Any level of analysis is relevant. Research exists at the most basic, cellular level, and progresses to the whole animal, human and non-human, using the most appropriate research techniques for the particular question in mind. In this way it is not much different from any other biological field. However, what separates PNI from many other disciplines, is its *multidisciplinary* or interdisciplinary nature, bringing attention to the dynamic interactions between various behavioral and physiological domains of biology that affect any given aspect of organismic health and well-being. As such the area is not easy to study, and requires that training, or at least an understanding of the field, incorporate multidisciplinary skills. This means that the student approaching PNI keep in mind that they will be required to appreciate the workings of the immune system, the nervous system (and by virtue of this, behavior), and the endocrine system. Further, as the field matures, it has become relevant that metabolic and cardiovascular functions are affected by the interplay between the nervous and immune systems.

Textbooks and Reading: There is no textbook. Readings from various sources will be posted as appropriate for each particular section of the course. Since some people will not be familiar with the immune system, here is the website on PubMed which has free access (through a search function) to the 2001 edition of Immunobiology (http://www.ncbi.nlm.nih.gov/books/?term=Immunology). This may sound "outdated" but the cellular components, anatomy and principles of interaction in the immune system have not changed in millennia. So it's a good free source. There is also an additional book (by Frank) that you can actually browse, and will give an introduction to vertebrate immunology. Finally, the NIH has a brief overview of the immune system here http://www.niaid.nih.gov/topics/immunesystem/pages/default.aspx?wt.ac=bcNIAIDTopicsImmuneSystem

Overall, the rudimentary introduction to the immune system covered in class will be sufficient to allow you to understand the psychoneuroimmunological literature that you will be reading.

Assessment: There will be two take-home exams (50% of grade), plus a 2000-3000 word research paper (30% of grade) to complete on a topic of interest to you, and an in-class presentation (20% of grade) of your research paper effectively educating the rest of the class on the topic you chose. The length of the presentation will vary according to class size. The paper can be based on something we discuss in class (eg., clinical application of conditioned immunomodulation), or something you have been thinking about, and for which there is an immune literature relevant to PNI.

Alexander Kusnecov, Ph.D.
Psychoneuroimmunology
Fall, 2014

OUTLINE OF LECTURE TOPICS AND LEARNING GOALS

1. INTRODUCTION TO PNI AND OVERVIEW OF THE IMMUNE SYSTEM (3 lectures)

Class Dates: 9/2, 9/9, 9/16.

LEARNING GOALS: (i) Understand the composition and anatomical distribution of cells that make up the immune system; (ii) understand the principles by which different cell types in the immune system perform distinct functional roles; (iii) understand the soluble products (viz., cytokines, chemokines, antibodies) of the immune system that mediate and regulate immune responses, but that ultimately can affect neuronal function.

This set of lectures will provide an overview of the immune system and introduce terms and concepts. Detail at the level of an Immunology course is not necessary. The main intent is to allow you to understand the terms and methods used in research articles discussed in lecture, navigate the reading for your research paper, and understand the assigned reading.

Major features and terminology

a) immunological specificity, memory and self vs non-self discriminability;
b) the concept of *antigen*
c) anatomical and cellular components;
d) soluble mediators (*effector* molecules) – eg., cytokines, chemokines and antibody
e) distinction between innate ("natural") and acquired ("adaptive") immunity

Recognizing antigens

a) B lymphocytes (or B cells) and antibody molecules (immunoglobulin proteins);
b) the T cell receptor (TCR);
c) the major histocompatibility complex (MHC);
d) cognate interactions between immune cells (including antigen presenting cells), TCR, MHC and antigen in the development of an immune response

Regulation of the immune response:

a) Regulatory T lymphocytes (i.e. T cells)
b) Cytokines: cell-derived soluble mediators that regulate immune responses

Methods of assessing immune function

a) antigen and mitogen-induced proliferation;
b) cytotoxicity;
c) delayed type hypersensitivity;
d) cytokine and antibody production
e) phagocytosis, antigen presentation
f) mast cells and allergies
g) quantitative approaches: flow cytometry

Alexander Kusnecov, Ph.D.
Psychoneuroimmunology
Fall, 2014

2. BEHAVIORAL INFLUENCES ON IMMUNE FUNCTION (3 Lectures)

Class Dates: 9/23, 9/30, 10/7

LEARNING GOALS: (i) understand how basic behavioral studies involving learning paradigms demonstrated that responses to environmental stimuli linked to immune responses can serve to reenlist immune changes in a conditioned manner, (ii) understand the concept of stress, (iii) understand how acute and chronic exposure to stress can produce different changes in immune function, (iv) understand that stress effects on immune function are not always in the direction of suppression of function, but can augment immune responses

Classical (Pavolovian) Conditioning of the Immune System

1. Ader and Cohen (1975): Basic demonstration using taste aversion
2. Subsequent animal studies:
   (i) cellular immune parameters
   (ii) humoral immune measures
3. Controversies: Is conditioned immunomodulation a stress epiphenomenon?
4. Human studies of conditioning and immune function

Effect of Stress

i. Concept and definitions of stress
ii. Experimental paradigms of stress
iii. Animal Studies:
   (a) effects on *in vitro* vs *in vivo* measures of immune function
   (b) acute vs chronic stress
   (c) controllability

Reactivity of the immune system to stress: Human Studies

a) Laboratory studies
b) Psychosocial studies
c) Stress and disease in humans
   (1) Cancer
   (2) Infectious Disease
   (3) Autoimmune Disease

Take Home Exam 1: 10/7 – submit exam via Sakai assignments link by 10/12

3. MECHANISMS BY WHICH THE NERVOUS SYSTEM AND STRESS INFLUENCE THE IMMUNE SYSTEM (2 LECTURES)

Class Dates: 10/14, 10/21

LEARNING GOALS: (i) Demonstrate knowledge of the CNS-activated pathways involved in affecting the immune system; (ii) understand the mechanisms by which neurotransmitters, neuropeptides and hormones can affect immune cells; (iii) understand the surgical and pharmacological approaches to showing how stress affects the immune system

a) Overview of the neuroanatomy of central and peripheral nervous systems
b) Hardwiring of the immune system: Innervation of lymphoid tissue by sympathetic and parasympathetic nerve fibers
    a. Neuropeptides
    b. Biogenic amines
        i. noradrenaline actions via adrenergic receptors on immune cells
        ii. Acetylcholine actions on immune function and survival
c) Hormonal Influences:
    a. The neuroendocrine system
    b. Focus: the hypothalamic-pituitary-adrenal (HPA) axis
        i. Glucocorticoid actions on immune cells via glucocorticoid receptors

d) Studies manipulating glucocorticoid, noradrenergic and cholinergic pathways during stress: Impact on stress-induced immune changes

4. IMMUNOLOGIC INFLUENCES ON THE CENTRAL NERVOUS SYSTEM (2 LECTURES)

Class Dates: 10/28, 11/4

LEARNING GOALS: (i) understand the various methodological approaches taken to confirm that the immune response results in detectable changes in CNS function; (ii) understand how cytokines produced by T cells and macrophages are capable of producing similar changes in CNS function as an ongoing immune response to antigen; (iii) demonstrate a knowledge of potential pathways by which immune products can influence the CNS; (iv) show an understanding of why immune-mediated activation of neuroendocrine and sympathetic pathways serves to regulate the immune response and limit morbidity and possible autoimmune reactivity

Changes in CNS function in response to peripheral immunological processes

a) Neurophysiological findings of increased neuronal activity in the brain during immune responses to antigen and products of activated immune cells (eg., cytokines)
b) Neurochemical alterations during the immune response and/or cytokine production/administration:
    (a) Changes in neurotransmitter and neuropeptide release and synthesis
    (b) immediate early gene responses in specific brain regions subserving emotional, cognitive and sensory processes
    (c) transcriptional changes in the neuron
c) Endocrine and autonomic nervous system responses to immunologic challenges
    (a) HPA axis response
    (b) Sympathetic nervous system response

d) Mechanisms by which the immune system affects the CNS:
    (a) Afferent neuronal processes: vagus nerve; glossopharyngeal nerve
    (b) Humoral mechanisms:
        (i) Active energy-dependent transfer of cytokines into the brain parenchyma
        (ii) Circumventricular regions containing weak blood-brain barrier

e) Feedback regulation of the immune system by HPA axis and sympathetic responses to immune activation
   i) Implications for control of toxic reactions
   ii) Implications for control of autoimmune reactivity

Behavioral effects of the Immune System in animals and humans

Administration of cytokines or bacterial toxins produces a range of motivational, emotional and cognitive changes. Historically, the constellation of observed behavioral changes has been called "sickness behavior."

a) The concept of "sickness behavior"
   a. Anorexia
   b. Anhedonia
   c. Lethargy and altered locomotion
   d. Relevance of sickness behavior to clinical symptom profile of depression
b) Cognition: learning and memory
   a. Behavioral tests of learning and memory
   b. Issues of attention
   c. Neurobiological and neurochemical basis for changes in cognition

c) Emotion: anxiety, depression
   a. Relationship to sickness behavioral profile
   b. Role of anxiogenic peptides – eg., corticotrophin releasing hormone (CRH; aka CRF)

d) Psychiatric conditions
   a. Immunological hypotheses for schizophrenia and depression
   b. Role of inflammatory cytokines

5. NEUROINFLAMMATION AND DISEASE (2 LECTURES)

Class Dates: 11/11, 11/18

LEARNING GOALS: (i) define neuroinflammation; (ii) differentiate between inflammatory responses originating in the CNS and those due to infiltrating immune cells; (iii) appreciate the conundrum and controversy surrounding the presence of "inflammatory" cells in the CNS as simultaneously beneficial, but potentially neurotoxic; (iv) appreciate evidence that neurodegenerative diseases involve neuroinflammation; (v) show an understanding of studies attempting to limit disease-based neuroinflammation through pharmacologic and vaccination procedures; (vi) appreciate why immunologic processes have been implicated in a range of adult and developmental disorders

a) Concept of neuroinflammation
b) Glial cells: oligodendrocytes, astrocytes and microglial cells
c) perivascular cells
d) CNS-infiltrating immune cells
   a. T cells
   b. macrophages
e) Neuroinflammation and disease: "double-edged" sword hypothesis

a. Reparative and neuroprotective function of microglial cells and cytokine production
b. Neurotoxic conditions

f) Neurodegenerative/Neurodevelopmental diseases: Alzheimer's disease; Parkinson's disease; Autism
g) Cardiovascular disorders – eg., stroke

6. STUDENT PRESENTATIONS

Class Dates: 12/2, 12/9

Take-Home Exam 2: 12/9; due on scheduled date of Final Exam