Mind, Brain, Immunity
Today’s Plan

1. Immunity: a review
2. Central nervous system (CNS) structure
3. Cellular, molecular and structural features of CNS and Immune function
4. The lymphatic system and beyond
5. Health relevance of mind-brain-immunity connections
What happens when foreign tissue is grafted into the body?

Into a leg?
Into the brain?
Into the leg and then into the brain?

Is the brain **immune privileged**?
Innate and adaptive immunity

Innate vs Adaptive Immune Players

Innate Immunity (rapid response) vs Adaptive Immunity (slow response)

- **Innate Immunity**
  - Mediates inflammation
  - Can be "called" by adaptive immune system
  - Less specific but faster

- **Adaptive Immunity**
  - "Learns" about pathogens (bacteria, viruses, etc.) through antibodies
  - More specific immunity

Lymph nodes: an structural network mediating immunity and fluid / molecular exchange in tissues
The central, peripheral, and autonomic nervous system

Meninges cover the central nervous system

3 Layers:

1. Dura mater (outer)
2. Arachnoid: (middle)
3. Pia mater (inner)

And cerebrospinal fluid bathes the brain.


By © Nevit Dilmen, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=9388427
The blood-brain barrier

Astrocytes form a gateway between the bloodstream and the brain.

Based on this information, how could the immune system and central nervous system interact?

Your answers here:
Immune – CNS interactions

Areas of overlap?


Phalloidin-labeled microglia (green) after phagocytizing [neurons]
Immunity, inflammation and the brain: *glial cells* are key.

Molecular overlap between immune system and CNS

- The example of **Major Histocompatibility Complex (MHC) Class 1** molecules:
  - A surprising find in the CNS
- Immune signaling and neuronal signaling were thought to be independent
  - **except for microglial cells**

**Immune function of MHC Class 1:**
Antigen presentation in adaptive immunity

**Neuronal function:**
- Activity-dependent expression?
- Plasticity and development?


http://bio1152.nicerweb.com/Locked/media/ch43/mhc.html
Anatomical overlap between immune system and CNS?

Systems for immune molecule and fluid transport?

The glymphatic system

Drainage of interstitial fluid (between brain cells), solutes, other macromolecules but too small for immune cells to pass.

The molecule **Aquaporin 4 (AQP4)** gates the flow of water and solutes.


Lymphatic drainage / immune molecule interaction in the meningeal space

Drainage to the broader lymphatic network documented in 2015 papers


Inflammation, fluid clearance and the CNS: Connection to Multiple Sclerosis and Alzheimers

**MS - hypothesized mechanisms:**
1. Injury / infection releases CNS antigens into meningeal lymphatic system

**Alzheimers:** Are you as young as your glymphatic system? Importance of fluid and debris clearance, especially the $\beta$ peptide.


Infection and inflammation during pregnancy might affect the brain of the offspring

Potential effects of infection and inflammation
** note that these effects don’t happen most of the time, and evidence is unclear for some of them.

Fig. 2: Knuesel et al., 2014, *Nat Rev Neurology*
Stress and immunity: links to health

- Stress signaling pathways can activate or suppress the immune system.
- The **sympathetic nervous system** can increase *innate* immunity
  - Immune cells have receptors for norepinephrine and epinephrine!
- Stress signaling through **glucocorticoids** can suppress *adaptive* immunity
  - Higher susceptibility to infections
Infection, Inflammation and Mental Health

• The depression connection
• “Sickness behavior”
• An evolutionary tug-of-war between “sickness” behavior and sociability?

Dantzer, 2018
Visceral nervous system interacts with the gut.

There is an enteric nervous system.

STRONG interdependence with microbiota: nutrients, neurotransmitters, and immunity

Enterochromaffin and enteroendocrine cells PRODUCE neurotransmitters and hormones
  - 95% of the body’s serotonin is stored in the gut: enterochromaffin cells and enteric neurons!

Link between gut microbiome, brain function and mental health

e.g. some evidence that probiotics transiently improve depressive symptoms.

Open questions

• What are those T cells doing around the meninges?? How do they get in and out of the CNS?
• Why does autoimmunity develop for some people, but not others?
• When are immune molecules part of healthy brain functioning, and when are they pathological?
• How can immune-CNS connections be used to treat disease and to promote health?

Thank you, and take care of your brain, your body, and your microbiome!