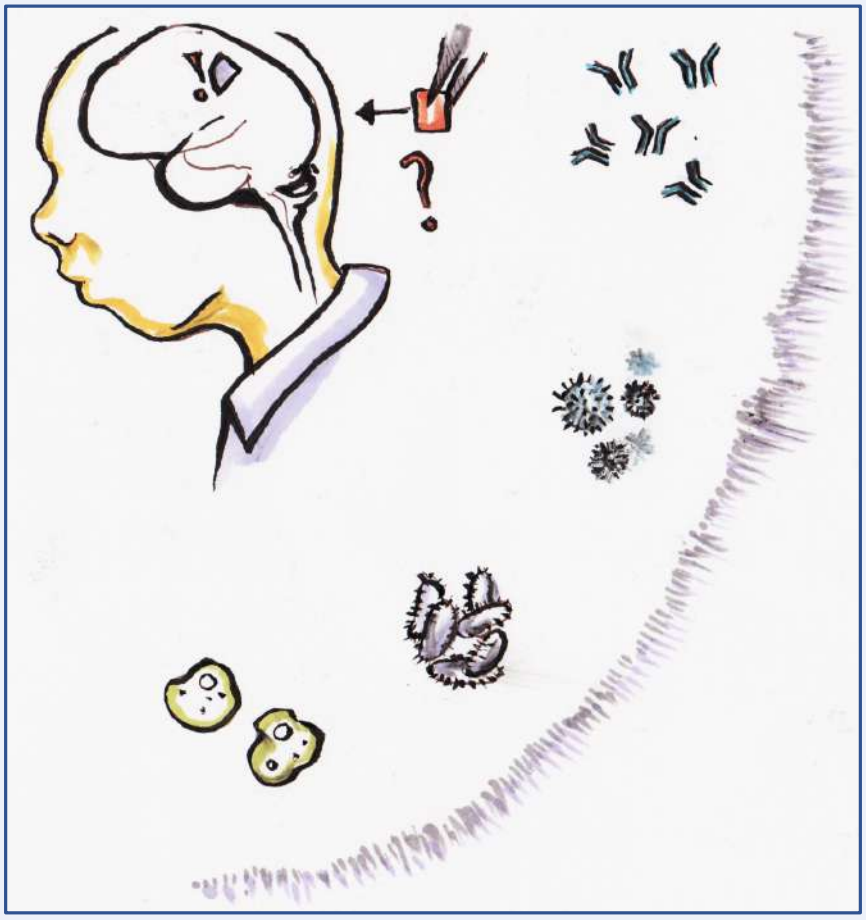
Mind, Brain, Immunity



Ann Fink, Ph.D.
Fri 11/15/2019

Bioscience in the 21st Century

Immunity and the Nervous System: A Mystery in 5 Acts

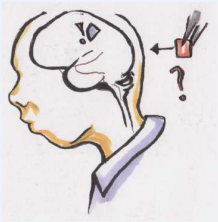
1. Immunity: a review
2. Central nervous system (CNS) structure
3. Cellular, molecular and structural features of CNS and Immune function
4. The lymphatic system and glymphatic system
5. Health relevance of mind-brain-immunity connections

What happens when foreign tissue is grafted into the body?

Into a leg?

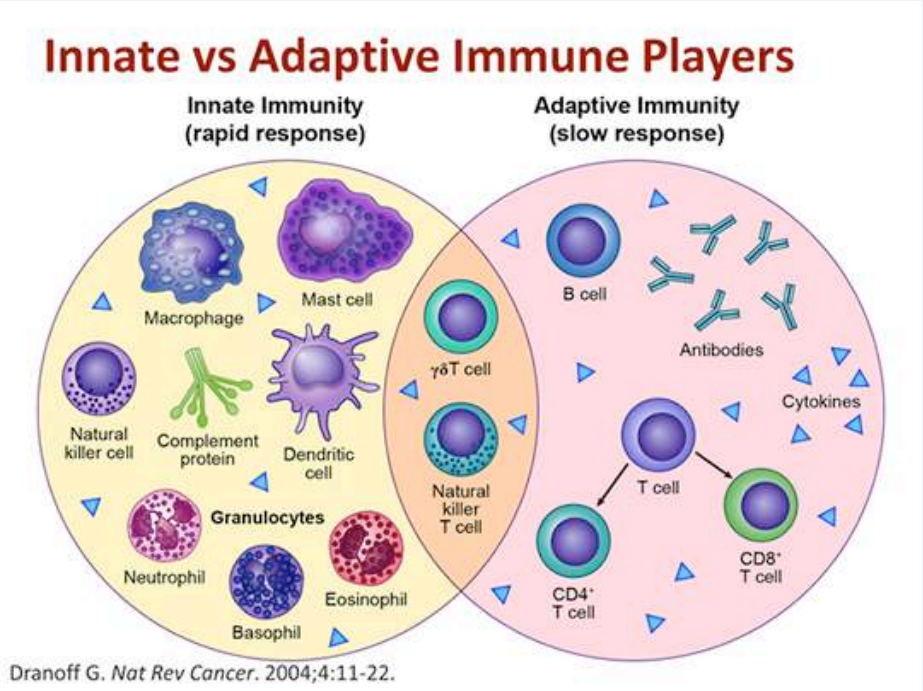
Into the brain?

Into the leg and then into the brain?



Is the brain **immune privileged?**

Innate and adaptive immunity

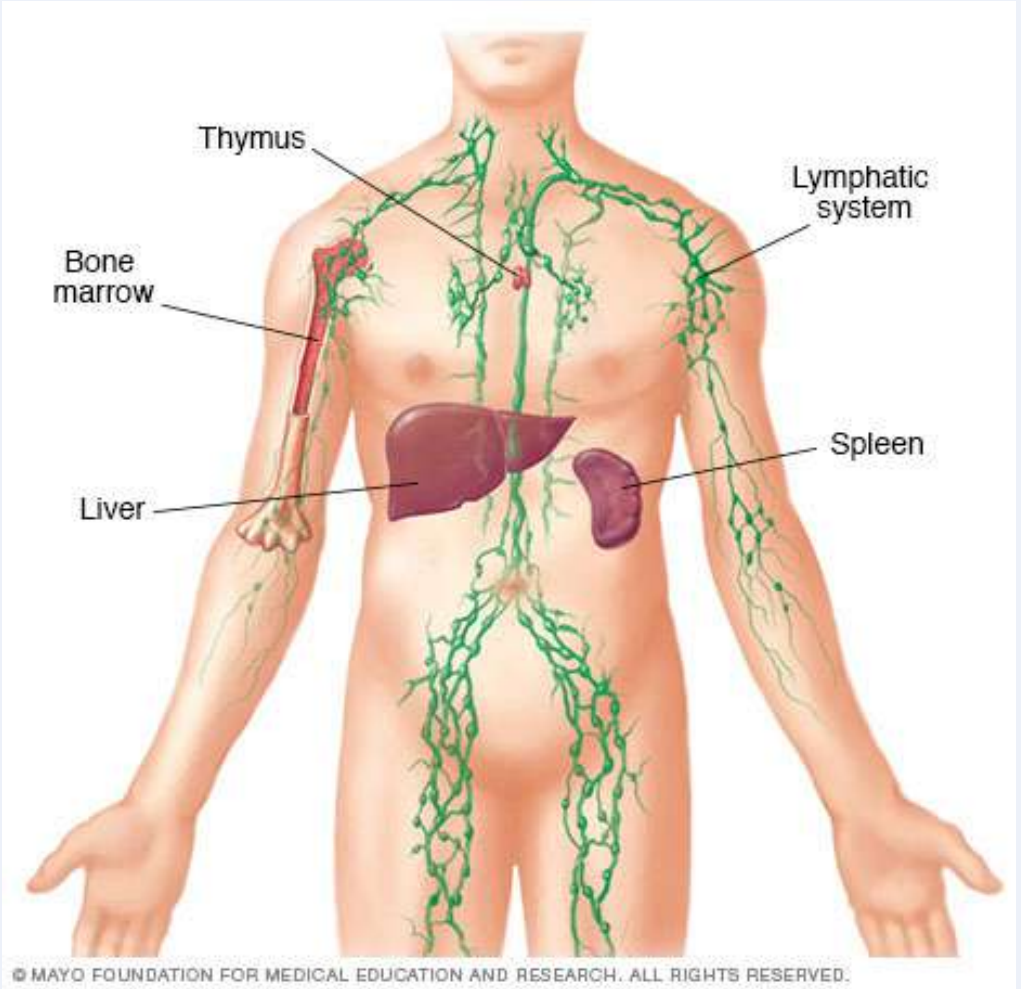


Dranoff G. *Nat Rev Cancer*. 2004;4:11-22.

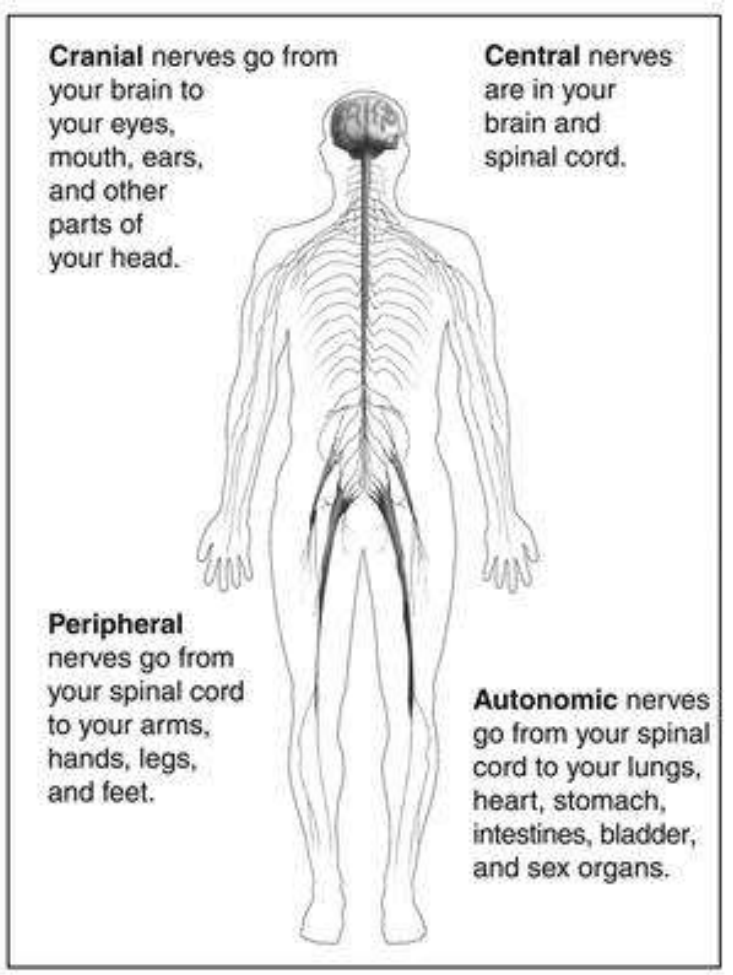
Less specific but faster: mediates *inflammation*, can be "called" by adaptive immune system.

More specific immunity: "learns" about pathogens (bacteria, viruses, etc.) through *antibodies*.

Lymph nodes: a structural network mediating immunity and fluid / molecular exchange in tissues



The central, peripheral, and autonomic nervous system

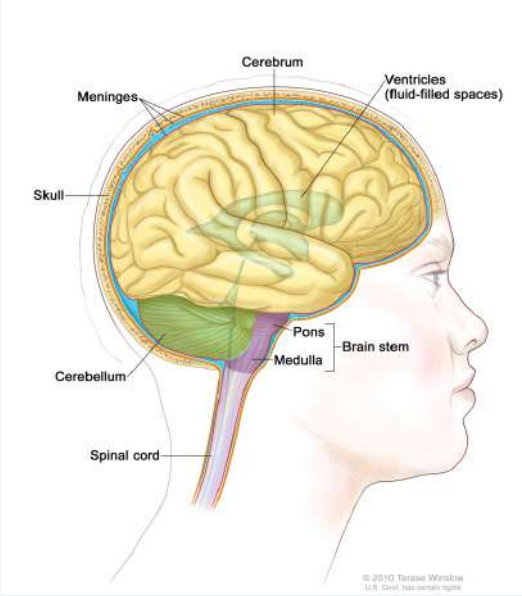


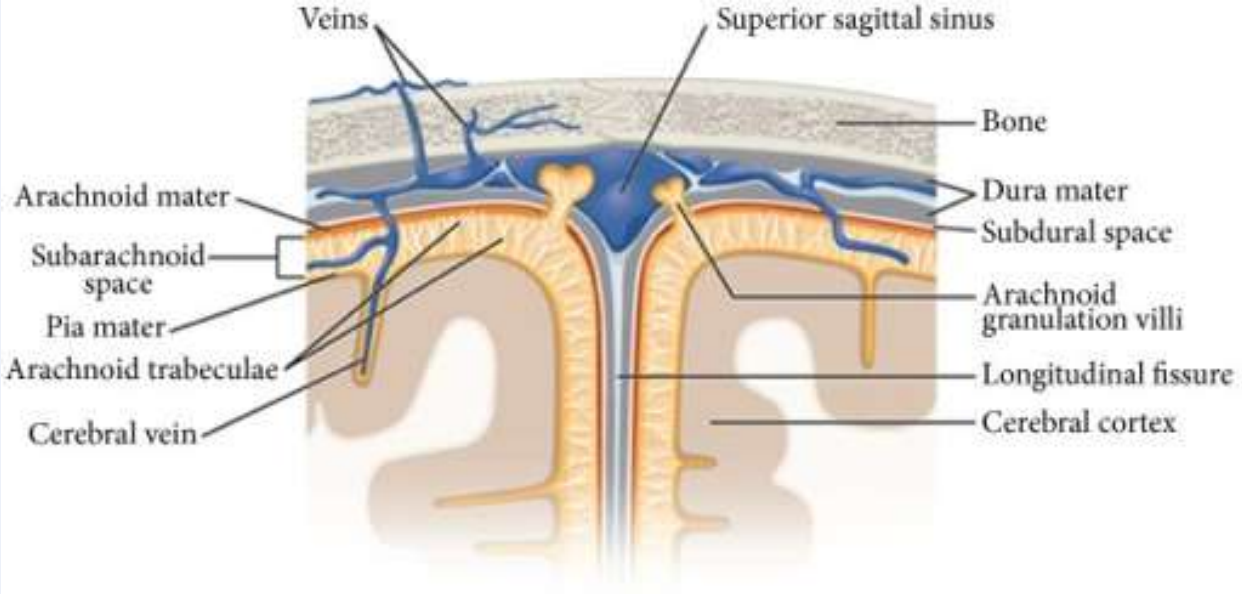
https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0024762/

Meninges cover the central nervous system

3 Layers:

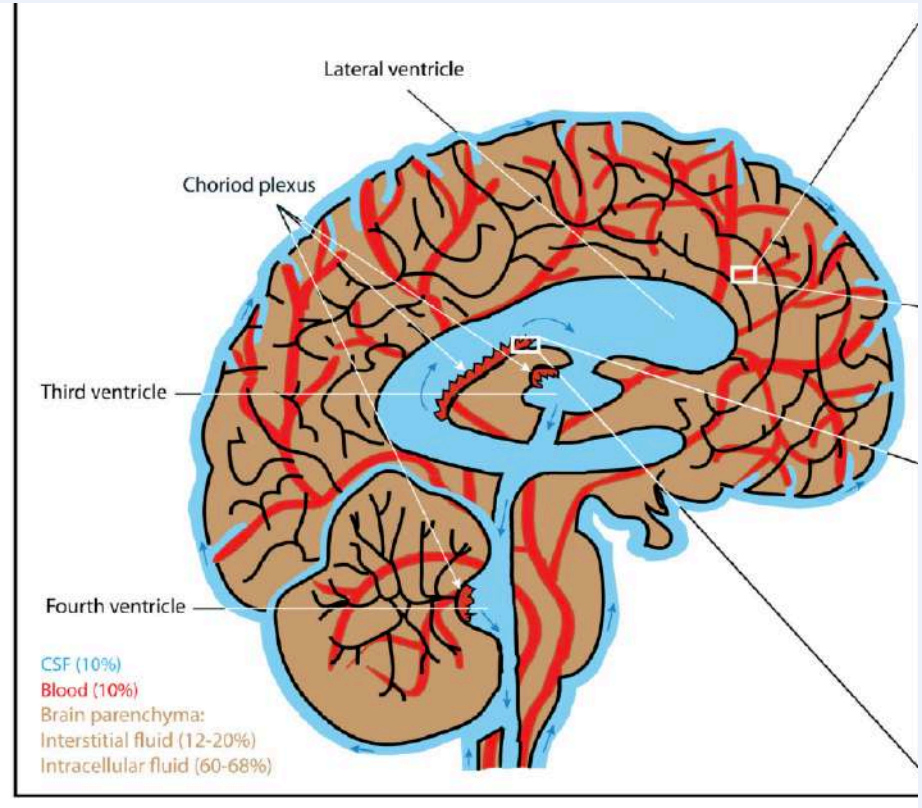
1. **Dura mater (outer)**
2. **Arachnoid: (middle)**
3. **Pia mater (inner)**





Saboori & Sadegh (2015). *Anatomy research international*, *2015*, 279814.

And cerebrospinal fluid bathes the brain.

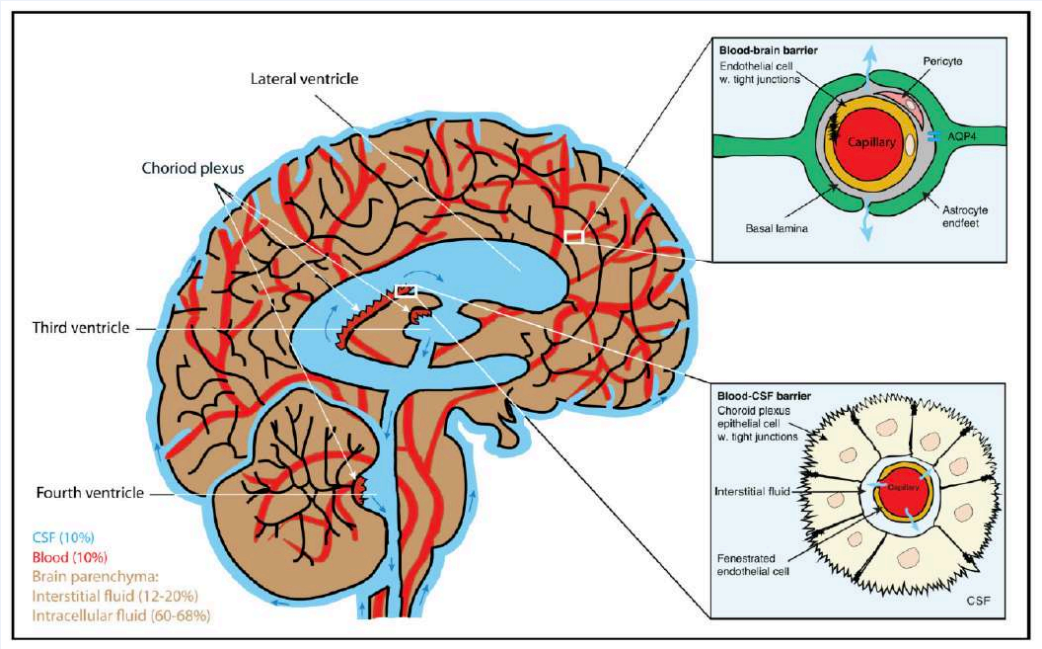


Jessen et al. *Neurochem Res*. 2015, 40(12): 2583–2599.

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.



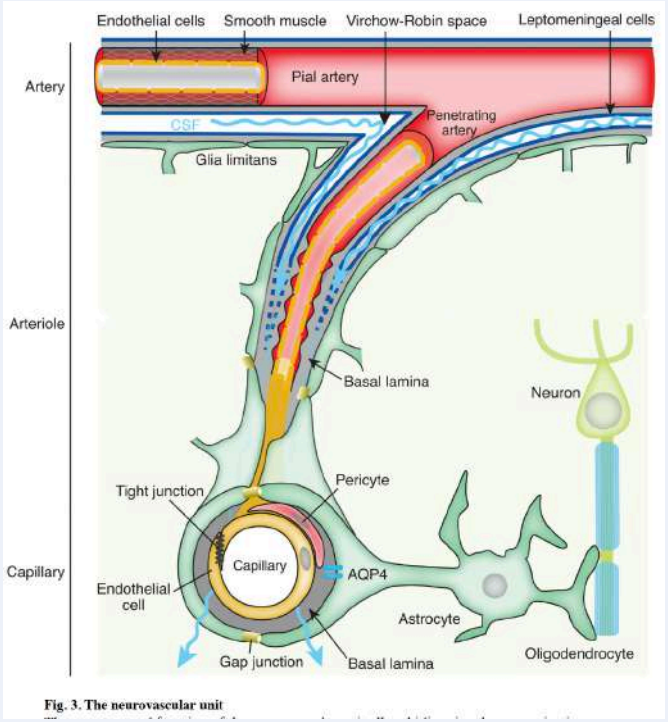


Fig. 3. The neurovascular unit

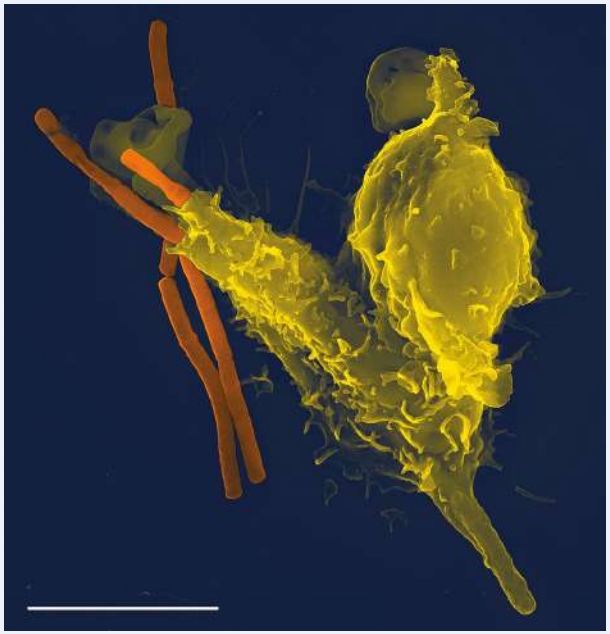
Jessen et al. *Neurochem Res*. 2015, 40(12): 2583–2599.

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

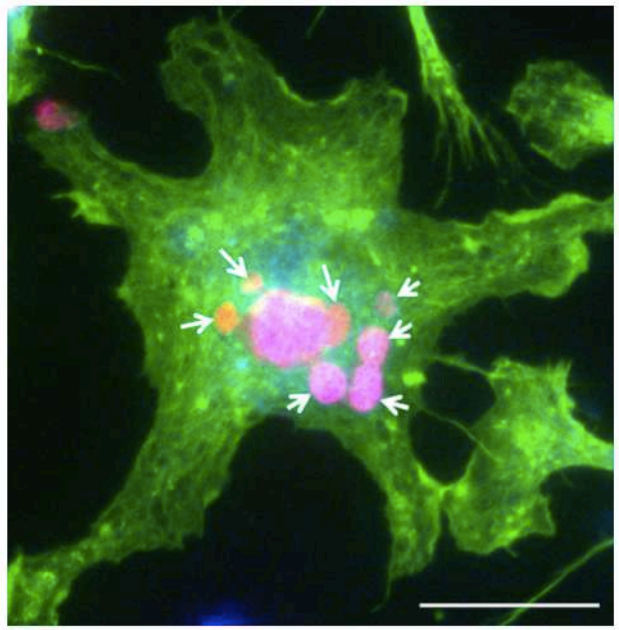
Your answers here:

Immune – CNS interactions

Areas of overlap?



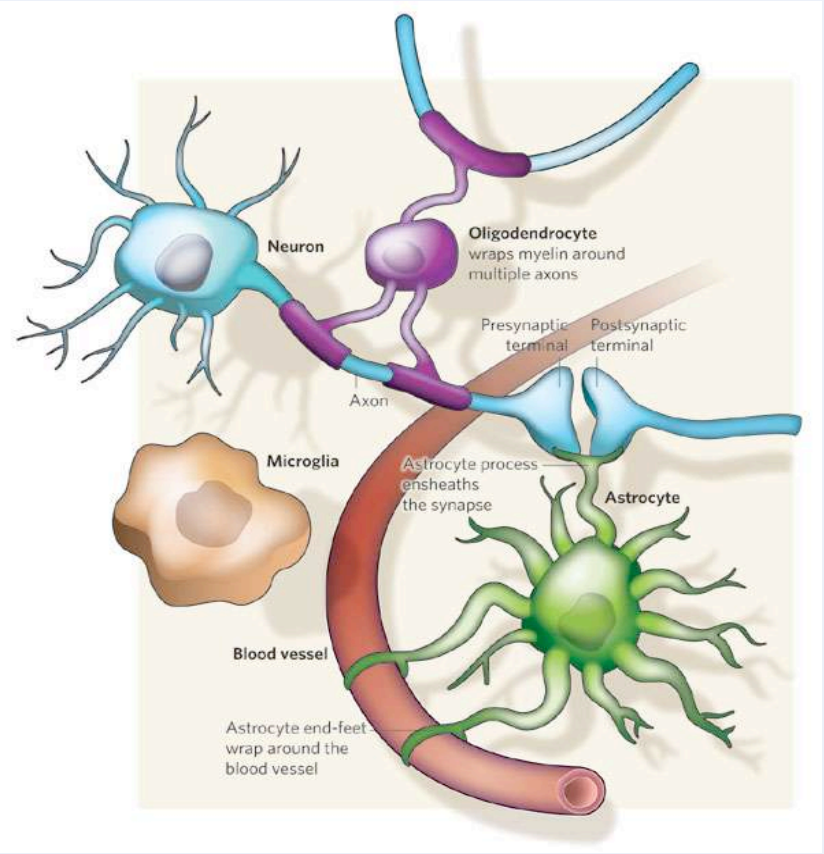
By Volker Brinkmann - (November 2005). **"Neutrophil engulfing Bacillus anthracis"**. PLoS Pathogens 1 (3): Cover page. DOI:10.1371. Retrieved on 2009-01-04., CC BY 2.5, https://commons.wikimedia.org/w/index.php?curid=2107792



Phalloidin-labeled microglia (green) after phagocytizing [neurons]
Zhao, X., et al. (2015). *J Neurosci* 35(32): 11281-11291.

Glial cells play key functions in the nervous system:

- Regulating *electrophysiological* activity in neurons
- **Myelinating** axons / regulating physical structure and integrity
- Mediating immune and inflammatory responses!



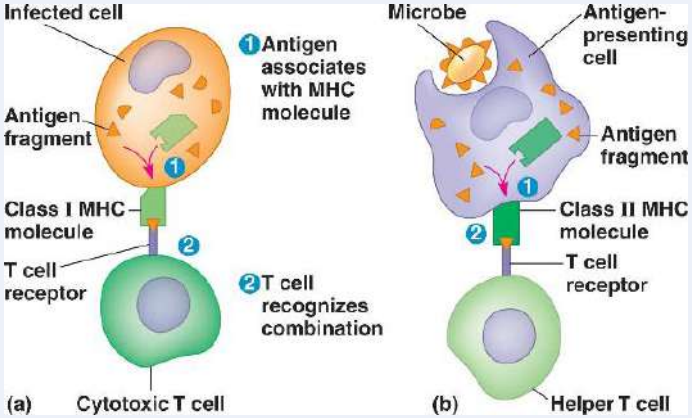
Allen and Barres, 2009, *Nature*

Molecular overlap between immune system and CNS

- Example: **Major Histocompatibility Complex (MHC) Class 1** molecules:
  A surprising find in the CNS! (1998)
- Immune signaling and neuronal signaling were thought to be independent (**except for ***microglia)***

Immune function of MHC Class 1:

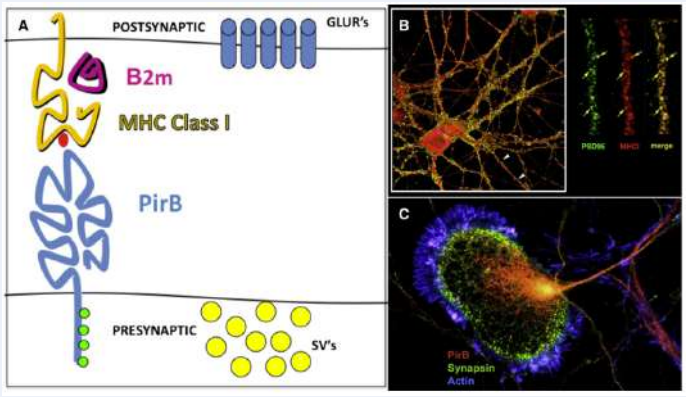
Antigen presentation in adaptive immunity



http://bio1152.nicerweb.com/Locked/media/ch43/mhc.html

Neuronal function:

- Activity-dependent expression?
- Role in plasticity and development?

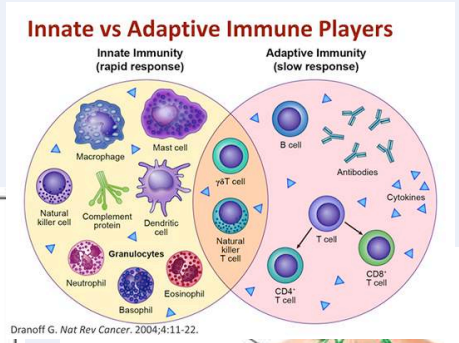


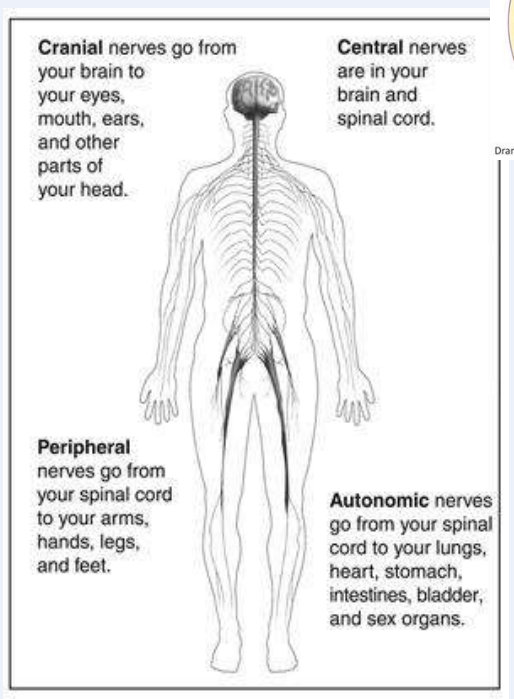
Shatz, 2009. *Neuron* 64: 40 – 45. DOI 10.1016/j.neuron.2009.09.044

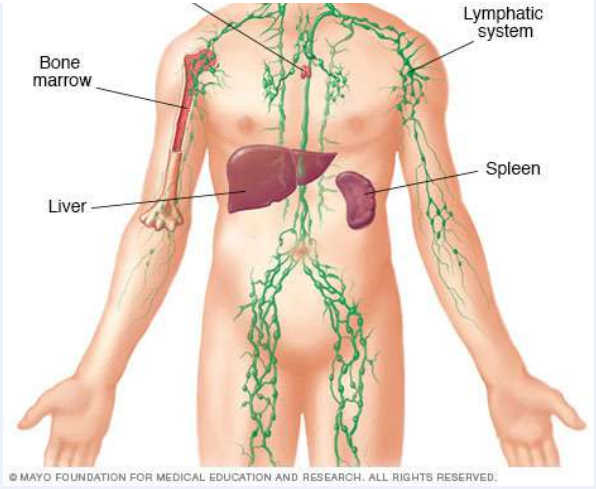
Is there anatomical overlap between immune system and CNS?

Overlap in systems for immune molecule and fluid transport?

Or are these entirely separate?







https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0024762/

1. 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.

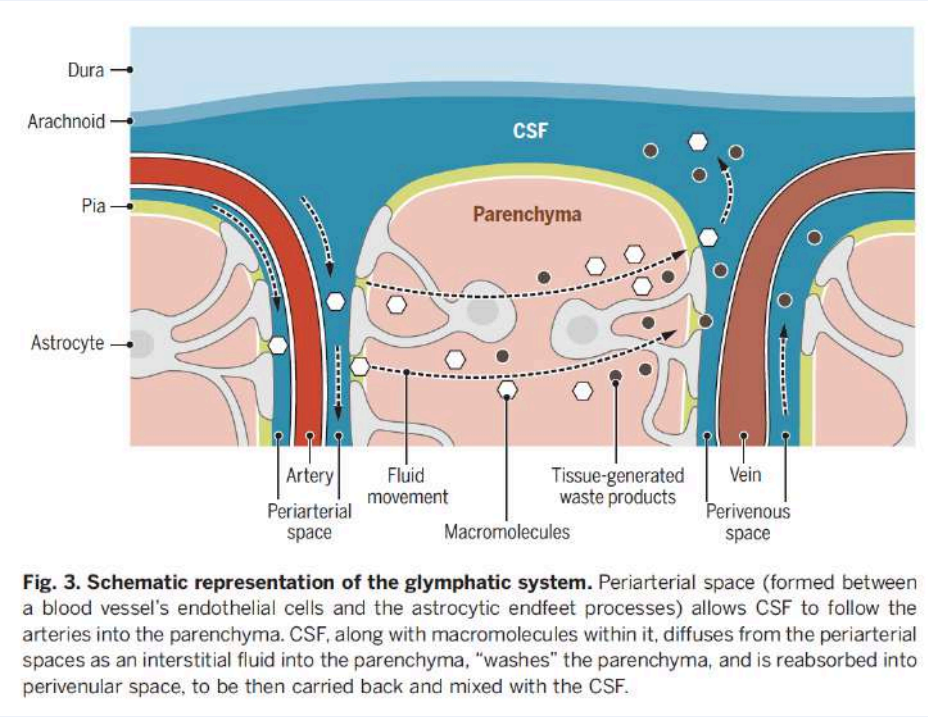
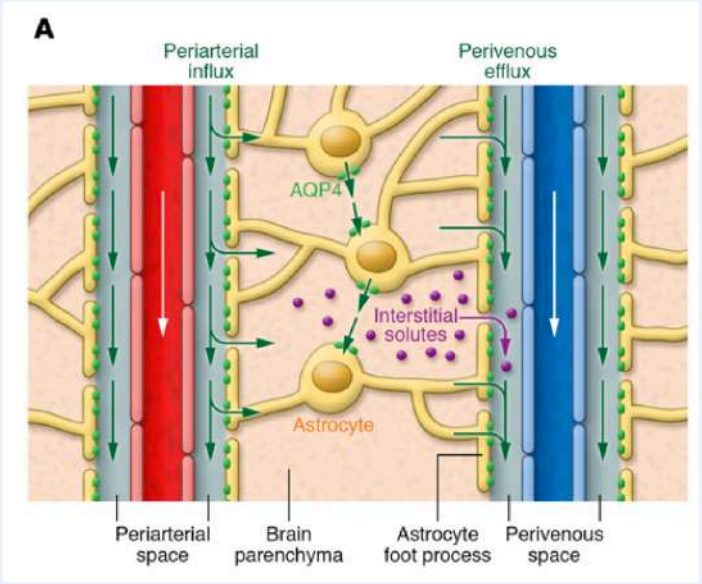


Fig. 3. Schematic representation of the glymphatic system. Periarterial space (formed between a blood vessel's endothelial cells and the astrocytic endfeet processes) allows CSF to follow the arteries into the parenchyma. CSF, along with macromolecules within it, diffuses from the periarterial spaces as an interstitial fluid into the parenchyma, "washes" the parenchyma, and is reabsorbed into perivenular space, to be then carried back and mixed with the CSF.

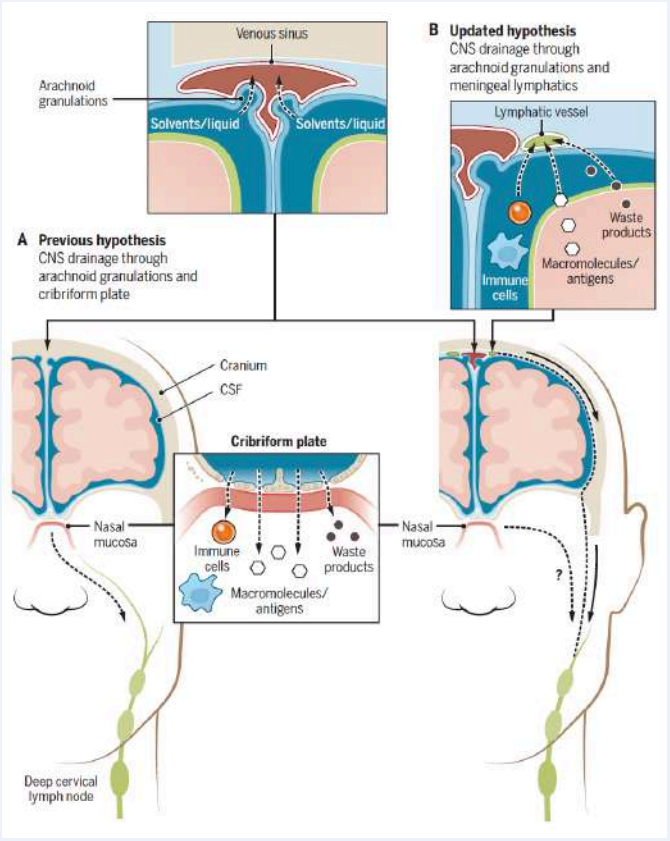
Kipnis (2016) Science 353 (6301), 766-771.



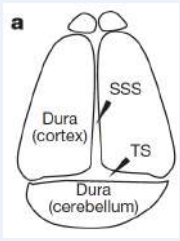
Louveau et al. J Clin Invest. 2017;127(9):3210–3219.

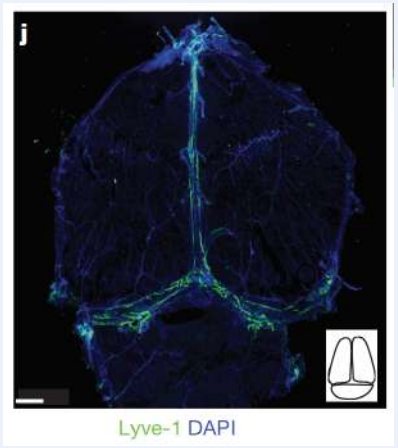
2. Drainage to the Lymphatic System -- immune molecule interaction in the meningeal (subarachnoid) space!

(Documented in 2015 papers)

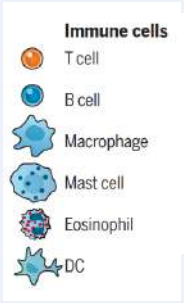


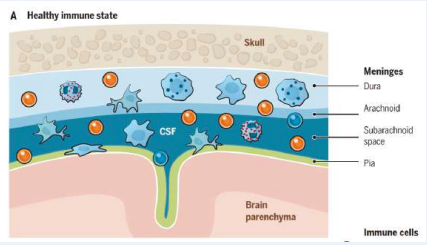
Kipnis (2016)
Science 353 (6301), 766-771.





Louveau et al. (2015) Nature 523: 337 – 341.

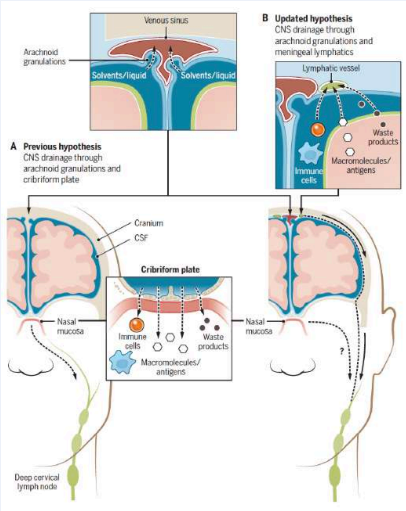




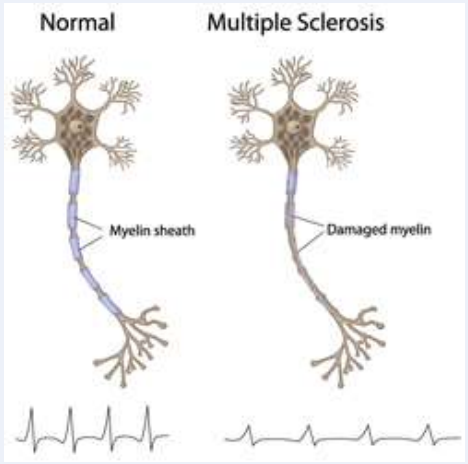
Inflammation, fluid clearance and the CNS: Two health connections of lymph and glymph

<u>Multiple Sclerosis (MS) -</u> hypothesized mechanisms:

1. Injury / infection releases CNS antigens into meningeal lymphatic system
2. A failure of self-recognition; the adaptive immune system attacks the body's healthy cells ***(autoimmune disease)***.



Kipnis (2016)
Science 353 (6301), 766-771.



https://mymsaa.org/ms-information/overview/process-symptoms/

<u>Alzheimer's Disease:</u> are you as young as your glymphatic system? Importance of fluid and debris clearance, especially the ***Aβ*** peptide.

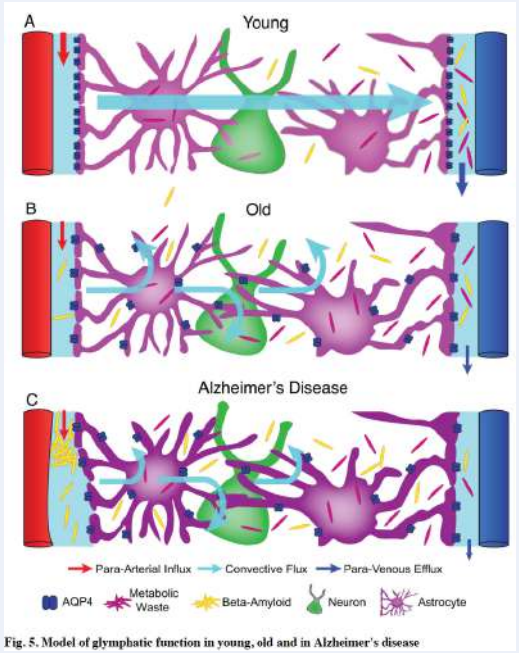
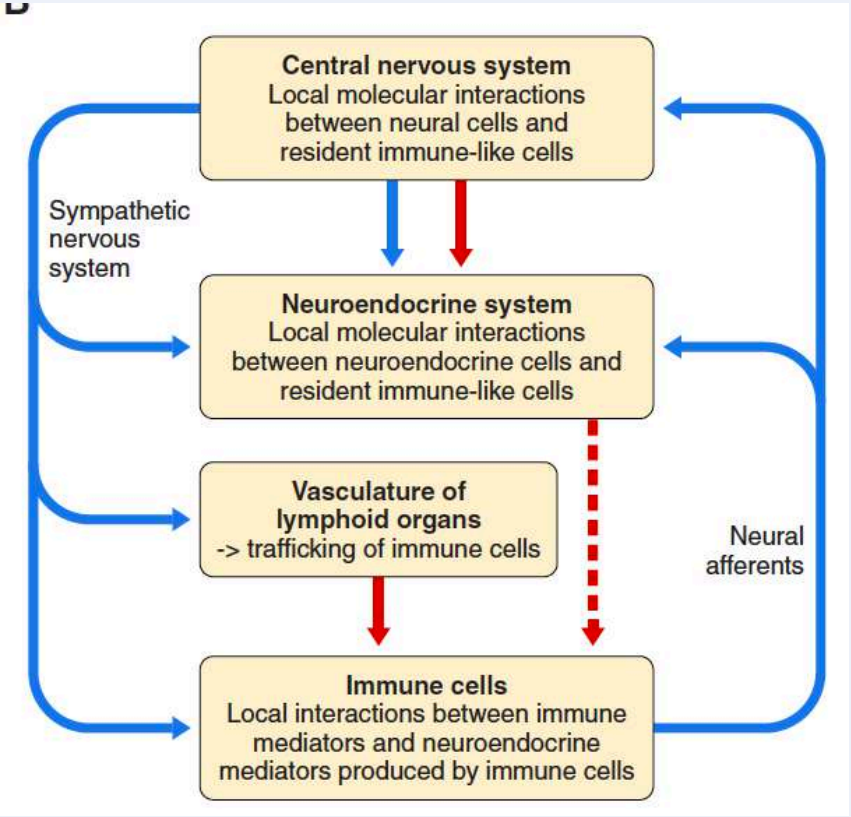


Fig. 5. Model of glymphatic function in young, old and in Alzheimer's disease

Jessen et al. *Neurochem Res*. 2015, 40(12): 2583-2599.

Stress and immunity: links to health

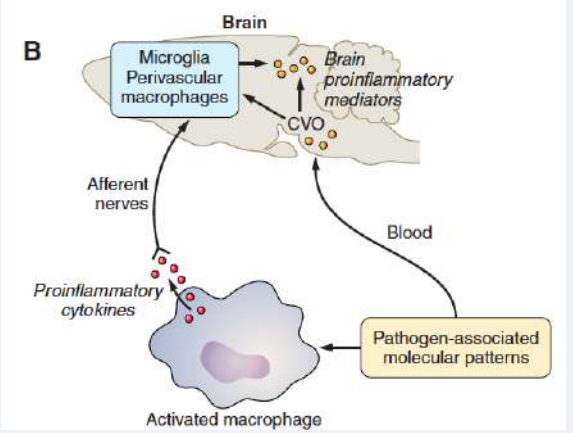
- Stress pathways can activate or suppress the immune system.
- The **sympathetic nervous system** can increase *innate* immunity
  - (Immune cells have receptors for the stress hormone / transmitters *norepinephrine* and *epinephrine*)
- Stress signaling through **glucocorticoids** can suppress *adaptive* immunity
  - Higher susceptibility to infections

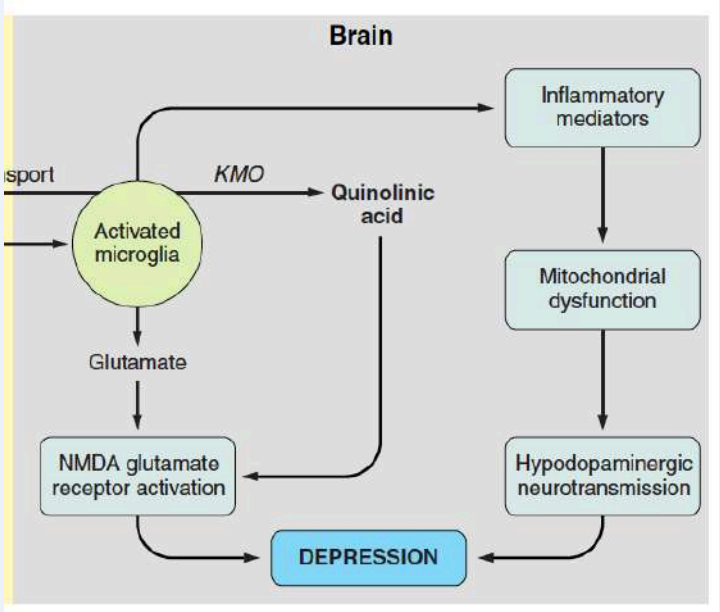


Dantzer, 2018

Infection, Inflammation and Mental Health

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

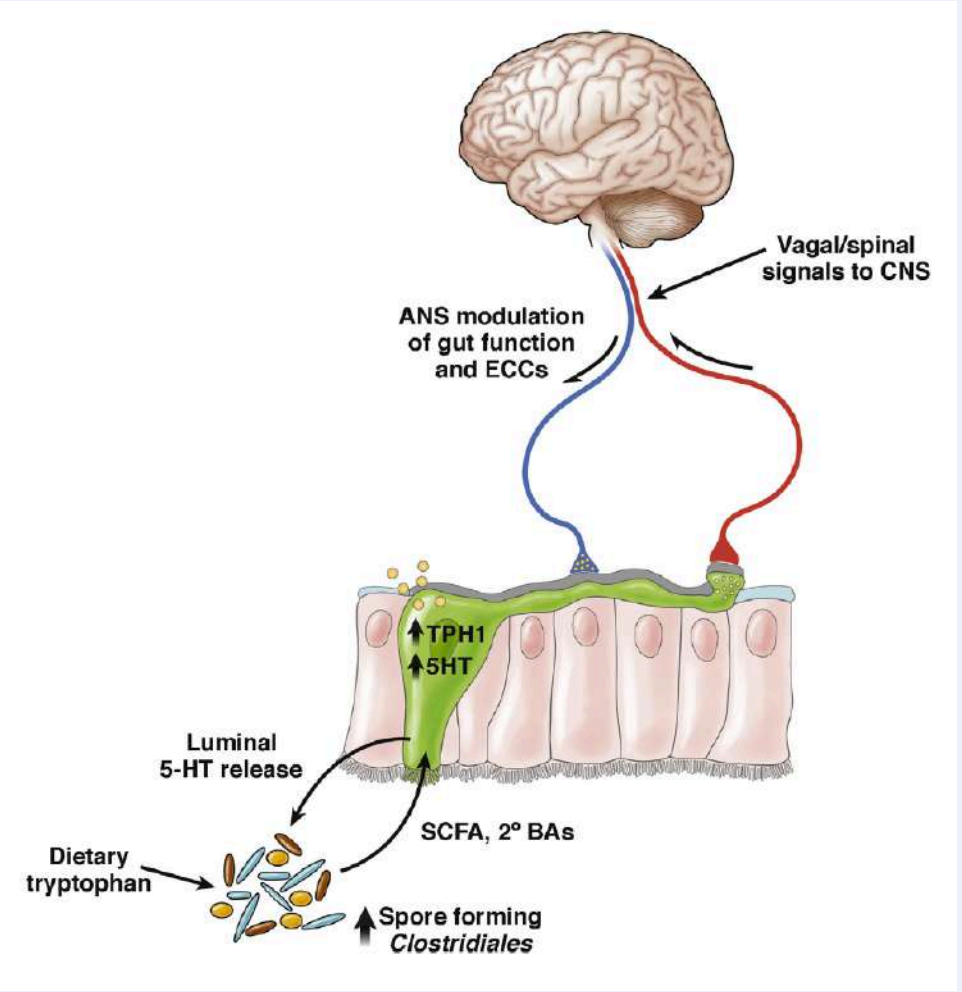




Dantzer, 2018

Gut-Brain-Immune Interactions and Mental Health

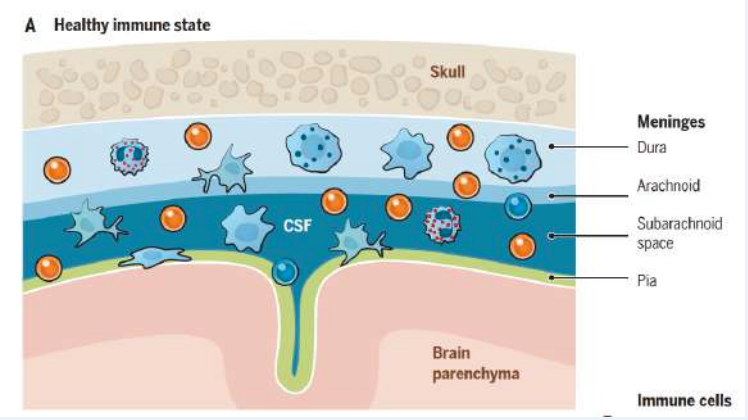
- There is an *enteric* nervous system.
- STRONG interdependence with **microbiome**: nutrients, neurotransmitters, and immune signaling
- **Enterochromaffin** and **enteroendocrine** cells in the lining of the gut PRODUCE neurotransmitters and hormones
  - 95% of the body's serotonin is stored in the gut!
- Link between gut microbiome, CNS function and mental health
- **e.g. Some evidence that probiotics *transiently* improve depressive symptoms.**



Martin et al. Cell Mol Gastroenterol Hepatol 2018;6:133–148.

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!