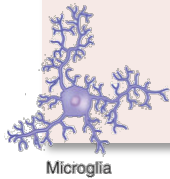


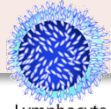
Key Concepts in Neuroimmunology, a dialogue between Philosophers and Scientists



**Which cells are the immune
cells of the brain?**



Microglia



Lymphocyte



Neutrophil



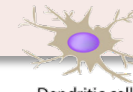
Eosinophil



Basophil



Monocyte

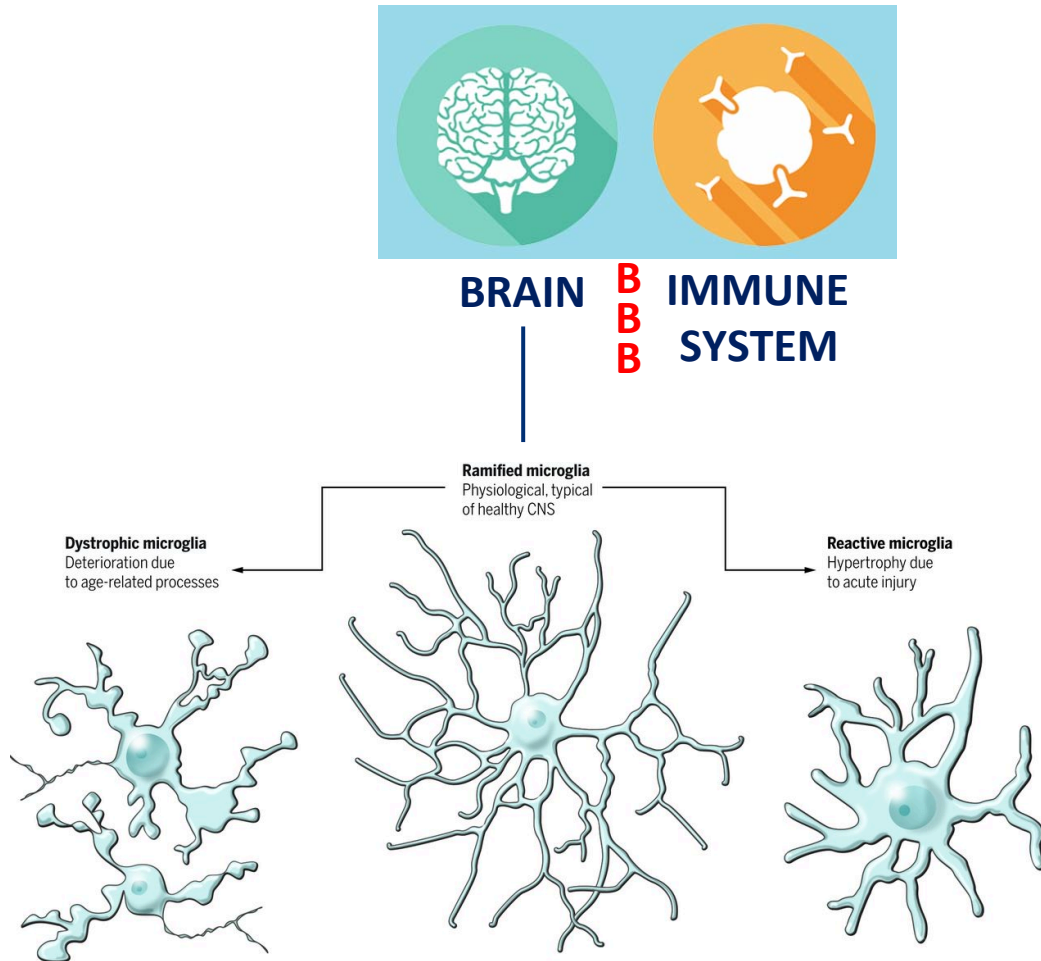


Dendritic cell

Agnès Nadjar
NutriNeuro, UMR INRA 1286
University of Bordeaux, France

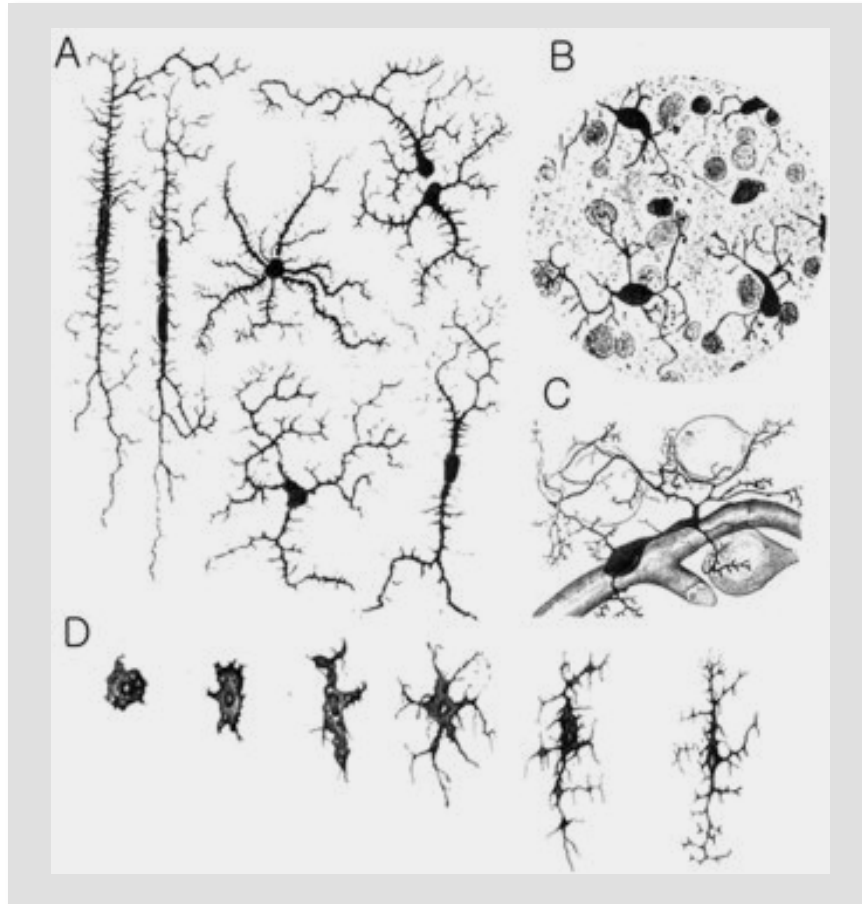
MICROGLIA: THE BRAIN INNATE IMMUNE SYSTEM

THE CNS: A SITE OF LIMITED IMMUNE SURVEILLANCE



MICROGLIA: THE RESIDENT IMMUNE CELLS OF THE BRAIN

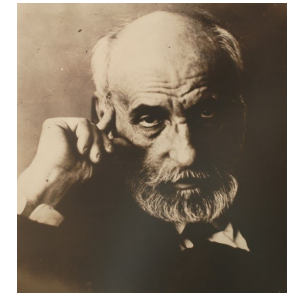
THE DISCOVERY OF MICROGLIAL CELLS



- ✓ FIRST CALLED “MICROGLIA” AROUND 1920
- ✓ BASED ON NISSL STAINING



**PIO DEL RIO HORTEGA
(1882-1945)**



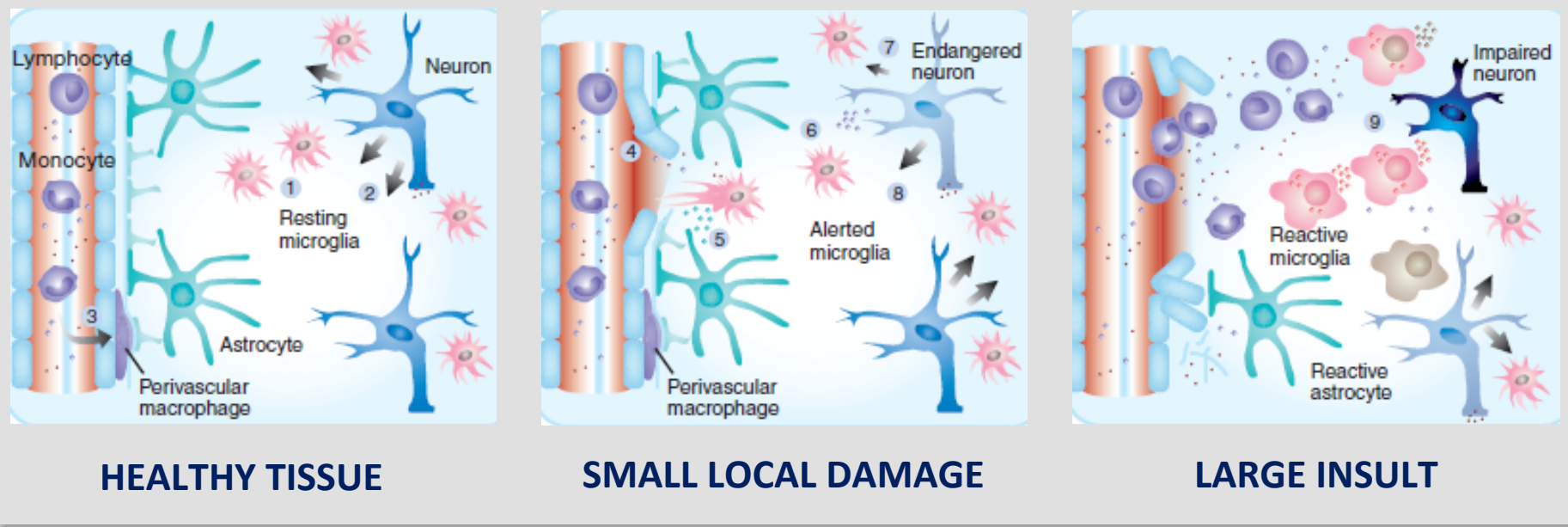
**SANTIAGO RAMON
Y CAJAL (1852-1934)**

ORIGINAL STATEMENTS FROM HORTEGA

1. Microglia enter the brain during **early development**.
2. These invading cells have amoeboid morphology and are of mesodermal origin.
3. They use vessels and white matter tracts as guiding structures for migration and enter all brain regions.
4. They transform into a **branched, ramified morphological** phenotype in the more mature brain (known today as the resting microglia).
5. In the mature brain, they are found almost **evenly dispersed** throughout the central nervous system and display little variation.
6. Each cell seems to occupy a **defined territory**.
7. After a **pathological event**, these cells undergo a transformation.
8. Transformed cells acquire amoeboid morphology similar to the one observed early in development.
9. These cells have the capacity to **migrate, proliferate and phagocytose**.

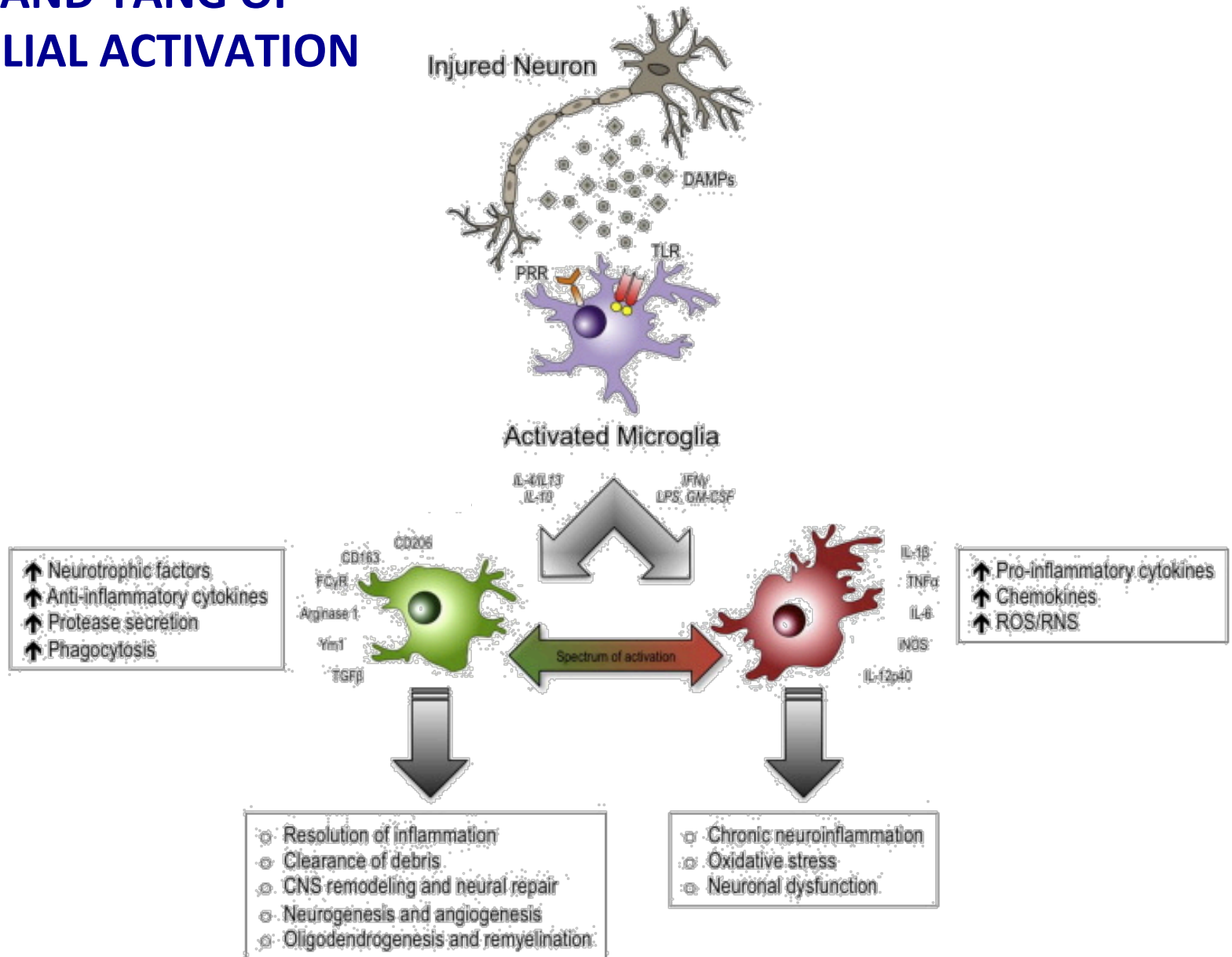
Still valid today

CNS IMMUNE REGULATION: THE CLASSICAL VIEW



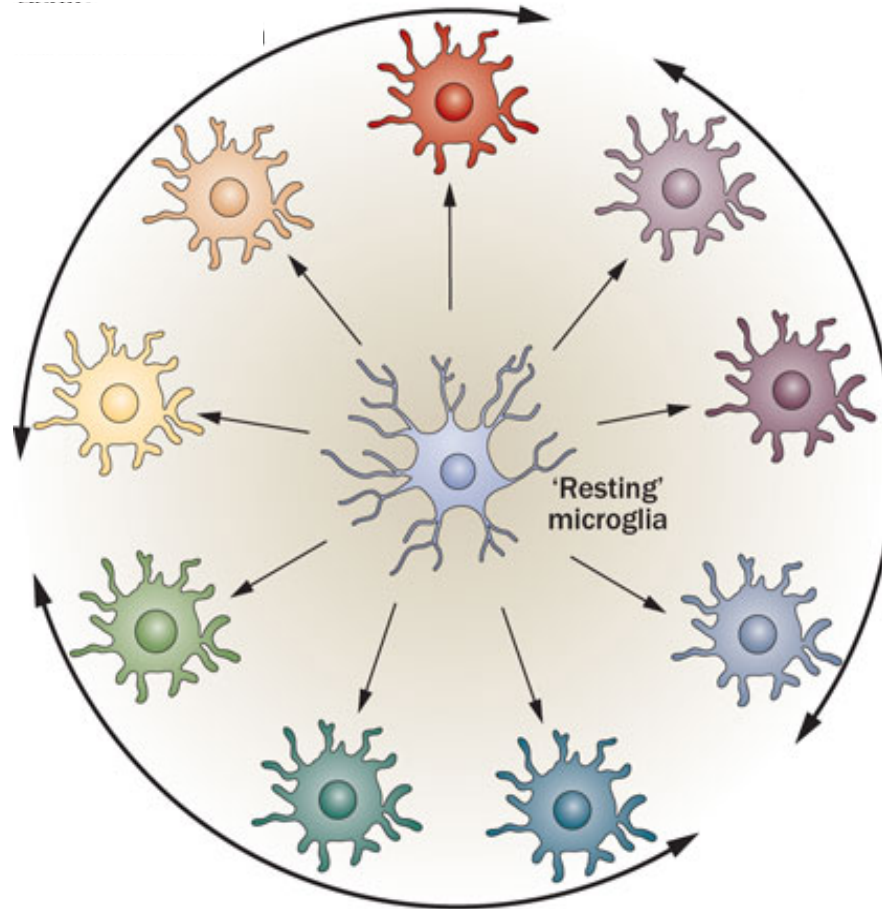
(Hanisch and Kettenmann, Nature Neuroscience, 2007)

THE YIN AND YANG OF MICROGLIAL ACTIVATION



(Gentleman, Neuropathology and Applied Neurology, 2013; Patel et al., Int J Physiol Patho Pharm, 2013; Aguzzi et al., Science, 2013)

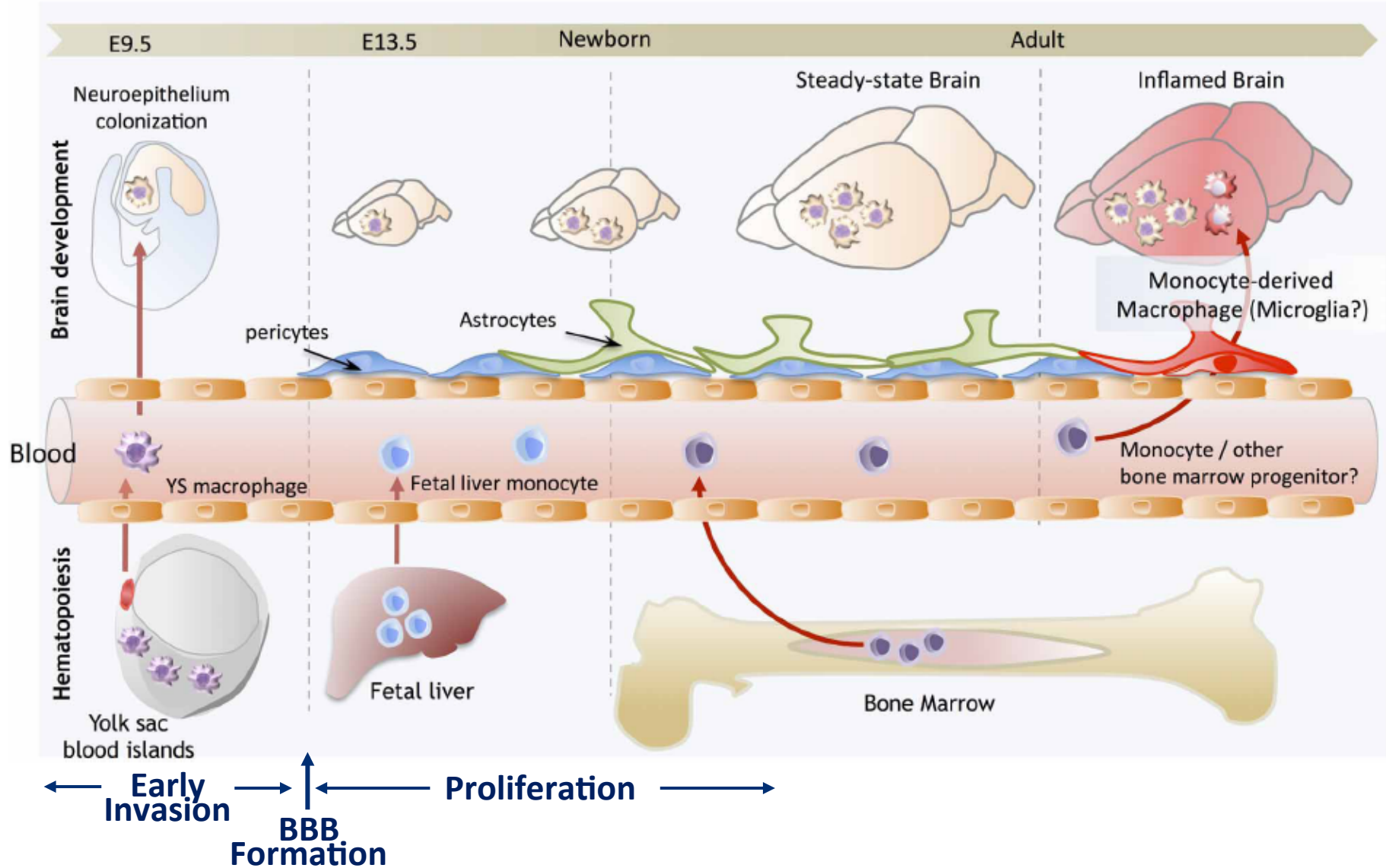
PHENOTYPIC PLASTICITY OF MICROGLIA



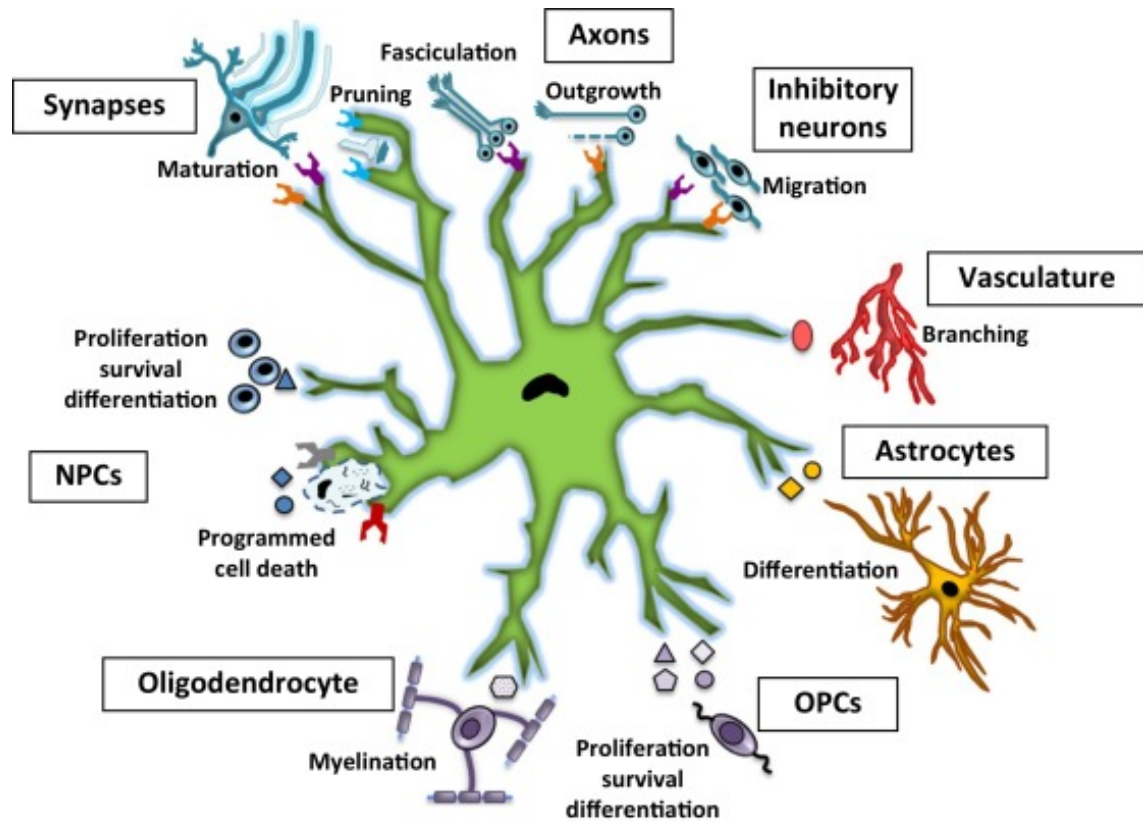
**EACH PATHOLOGICAL SITUATION IS ASSOCIATED TO A
UNIQUE PHENOTYPIC SHIFT**

**MICROGLIA IS NOT
JUST AN IMMUNE CELL**

MICROGLIA ENTERS THE BRAIN VERY EARLY DURING DEVELOPMENT



MICROGLIA IS INVOLVED IN CNS DEVELOPMENT



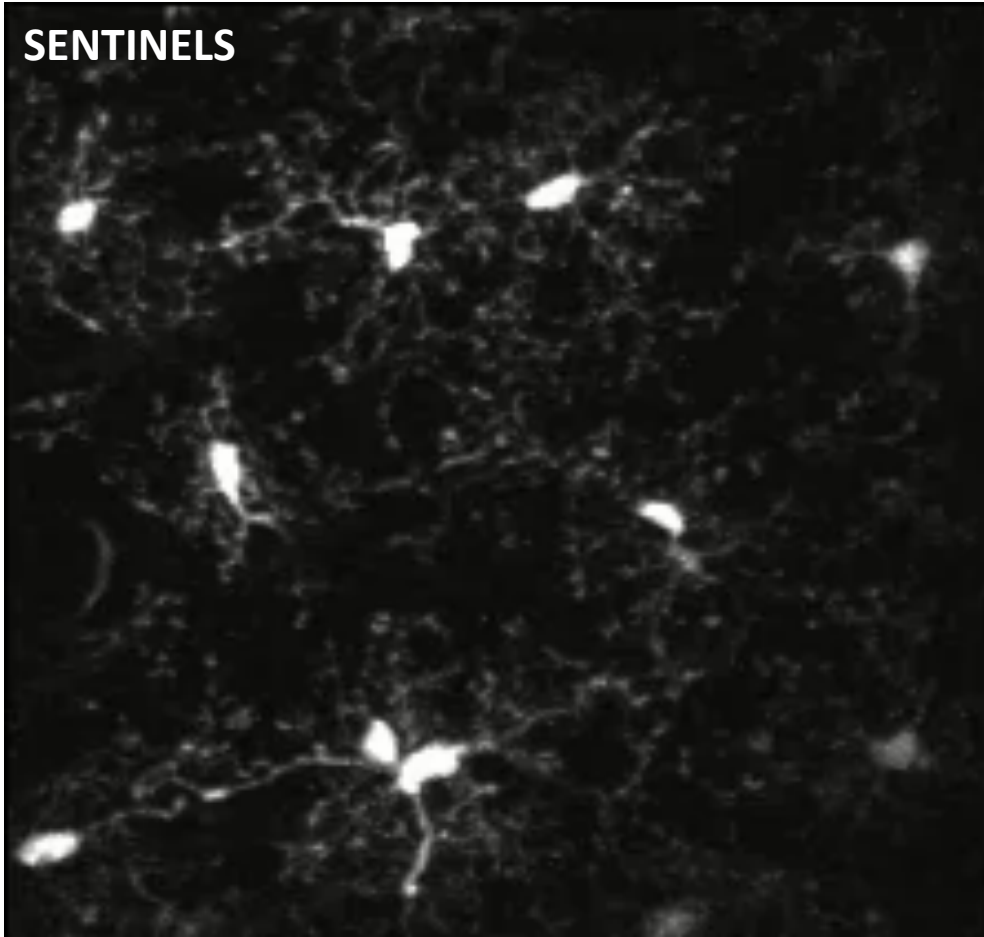
MICROGLIA: FAR FROM BEING « DORMANT SOLDIER »

Resting Microglial Cells Are Highly Dynamic Surveillants of Brain Parenchyma in Vivo

Axel Nimmerjahn,¹ Frank Kirchhoff,² Fritjof Helmchen^{1*}

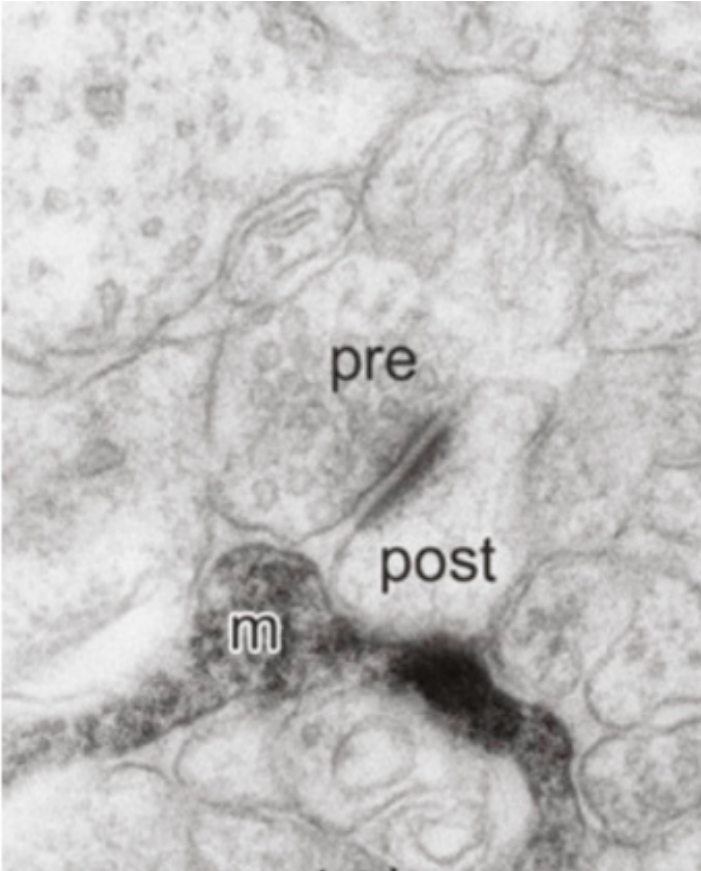
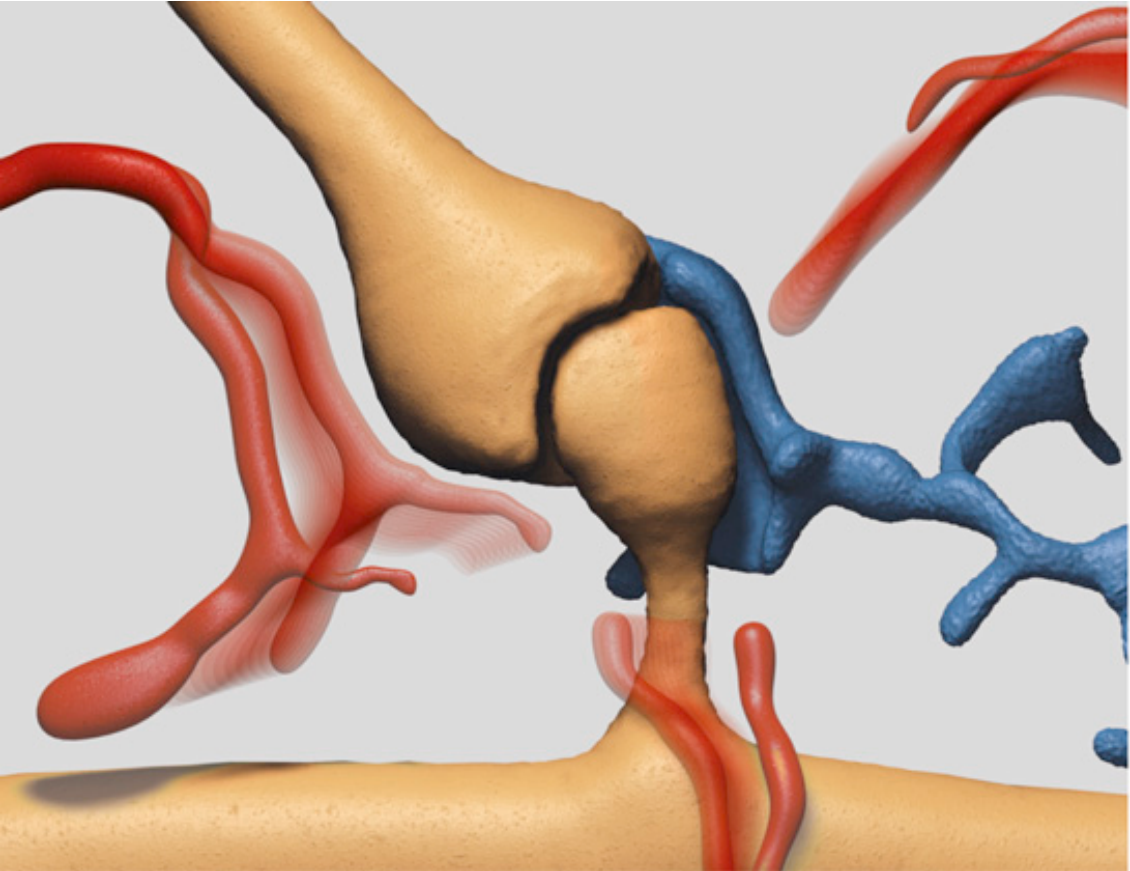
27 MAY 2005 VOL 308 SCIENCE

SENTINELS



(Nimmerjahn et al., Science, 2005)

MICROGLIA MAKES CONTACTS WITH NEURONS

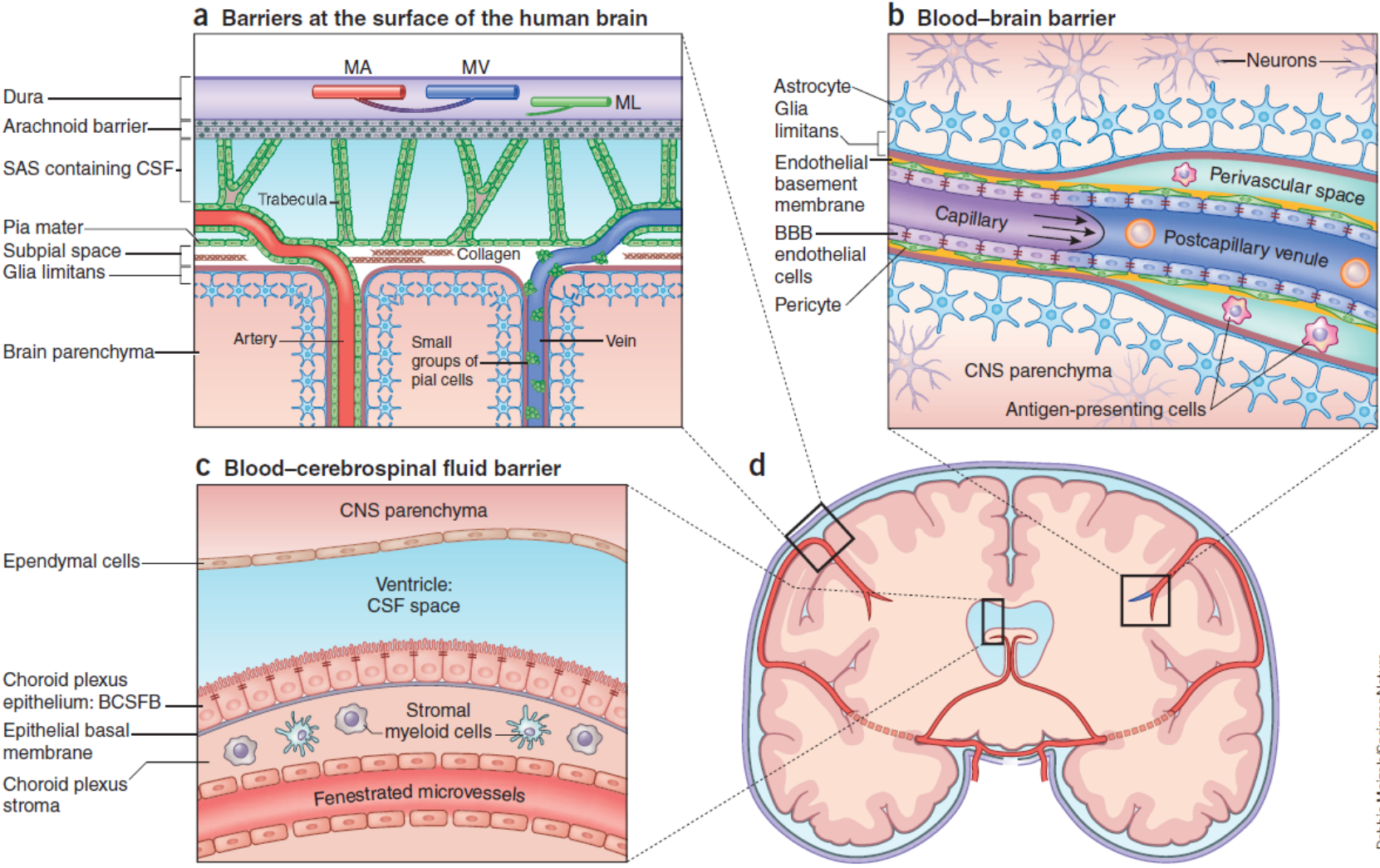


(Wake et al., Journal of Neuroscience, 2009; Kettenmann et al., 2012)

**MICROGLIA NEVER
WALKS ALONE**

THE BRAIN IMMUNE SYSTEM

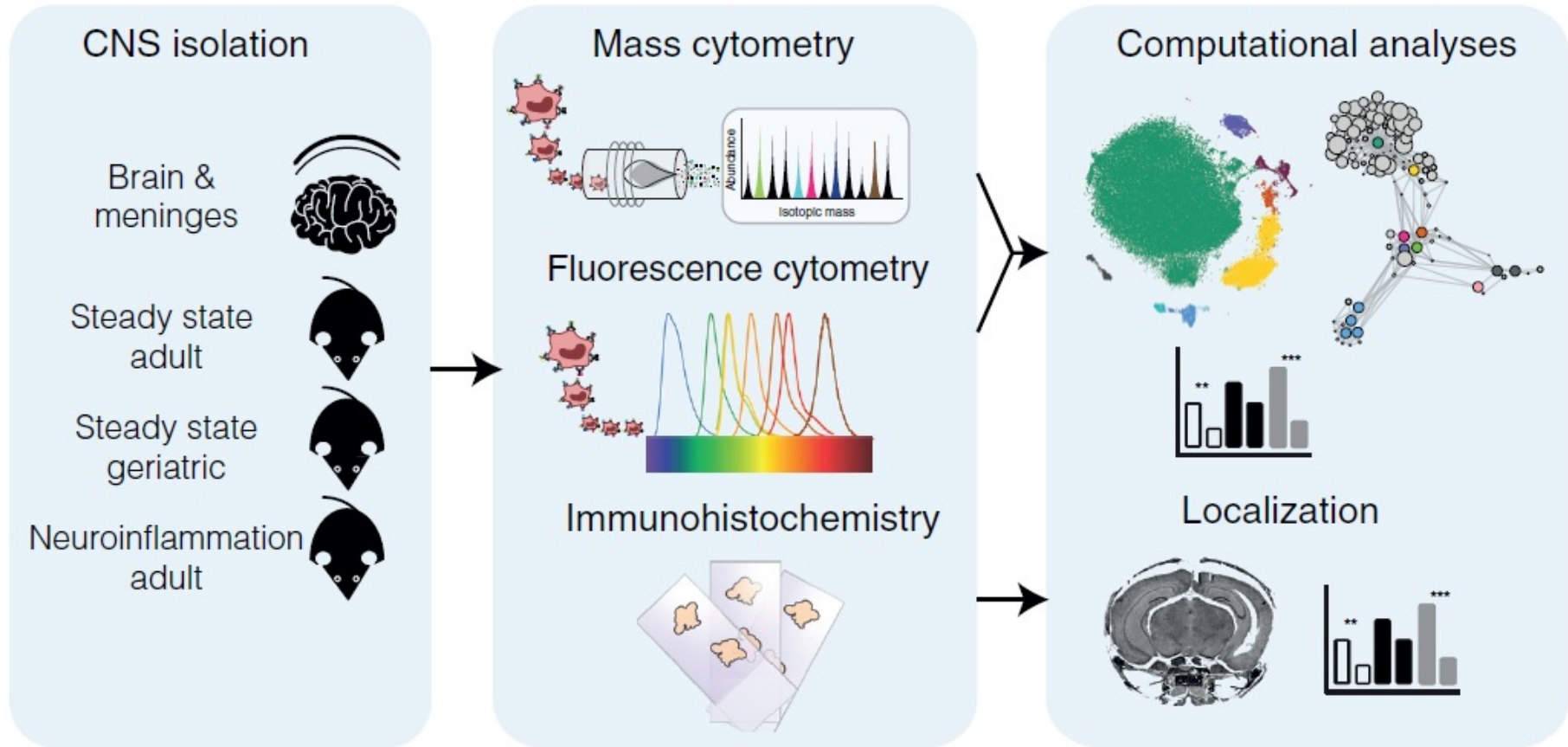
ANATOMY MATTERS



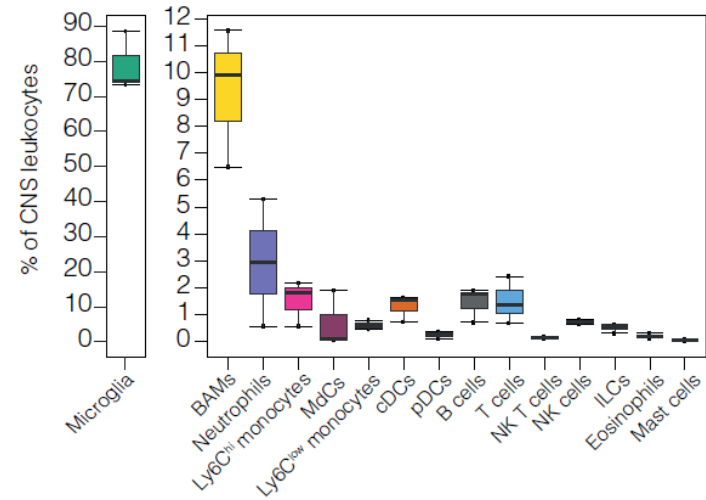
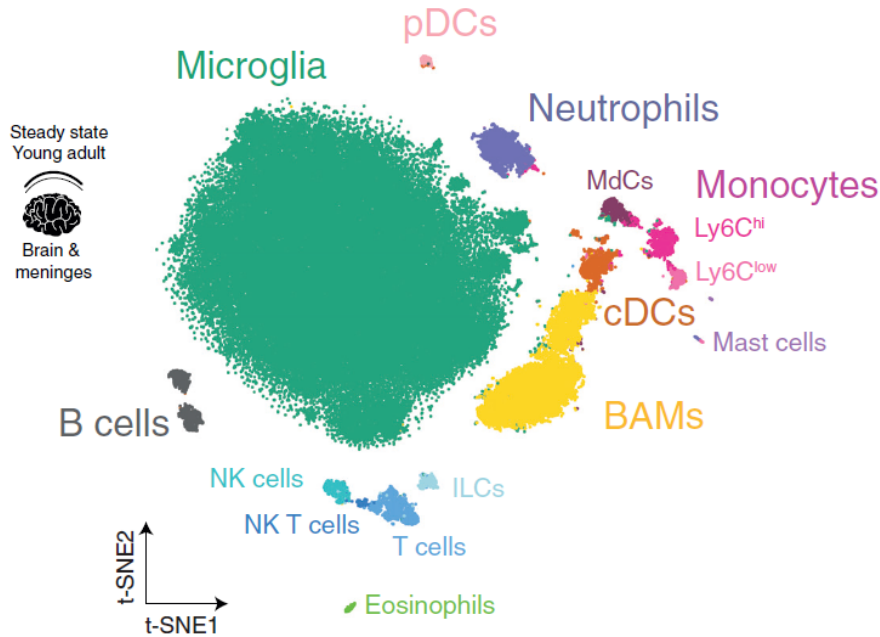
Debbie Matzels/Springer Nature

(Engelhardt et al., Nature Immunology, 2016)

CNS-ASSOCIATED LEUKOCYTE DIVERSITY IN THE STEADY-STATE

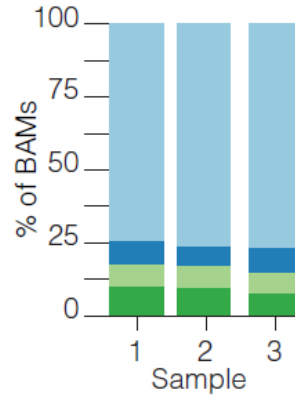
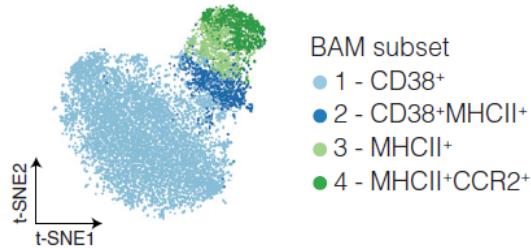


CNS-ASSOCIATED LEUKOCYTE DIVERSITY IN THE STEADY-STATE

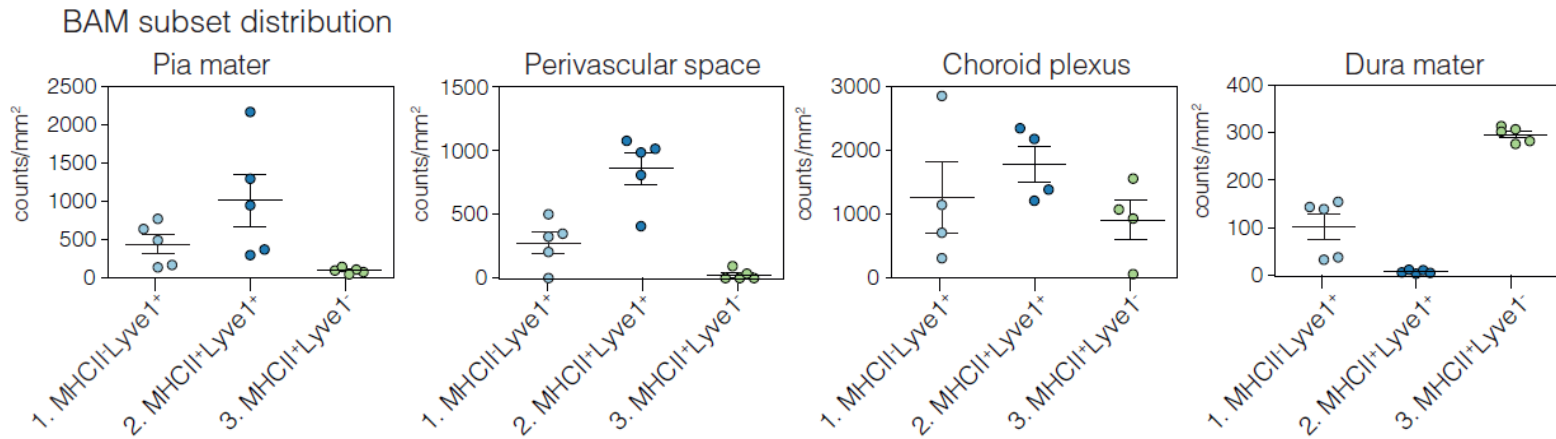


BORDER-ASSOCIATED MACROPHAGES (BAM)

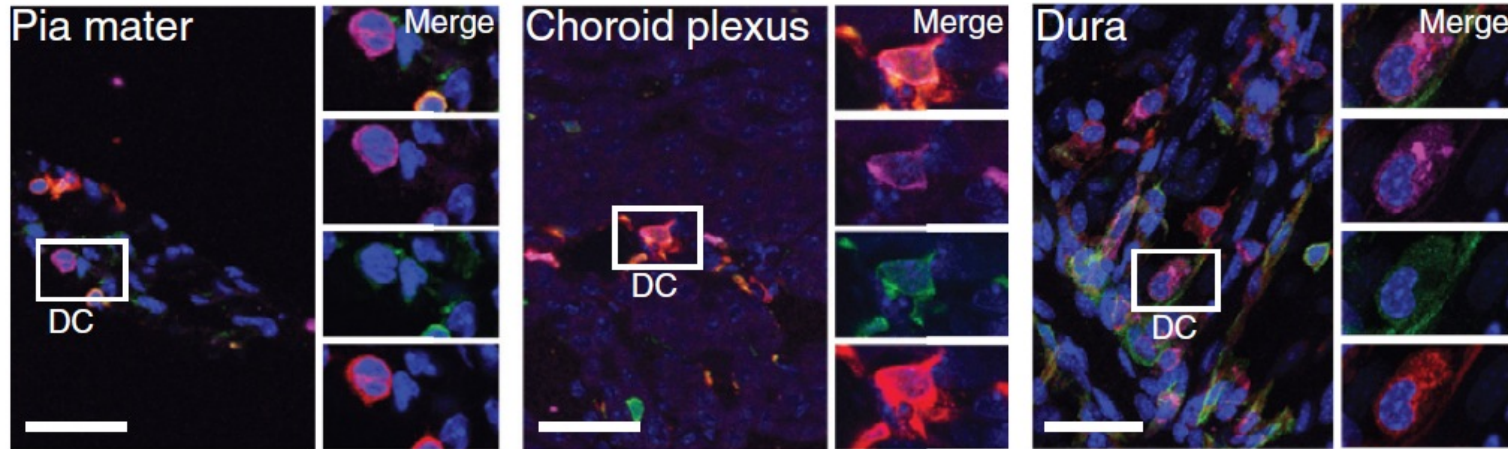
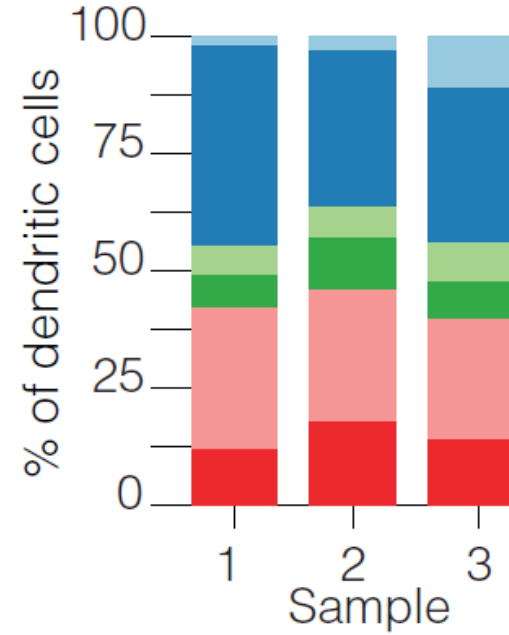
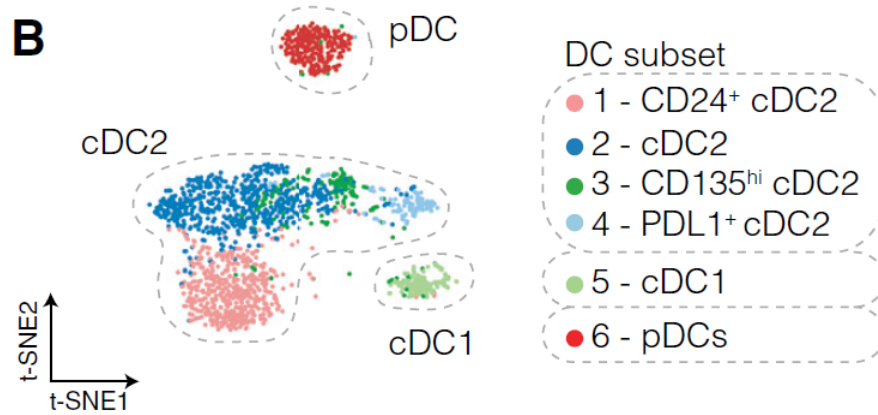
✓ 4 SUBSETS OF BAMS.



✓ DIFFERENT LOCATIONS WITHIN THE CNS

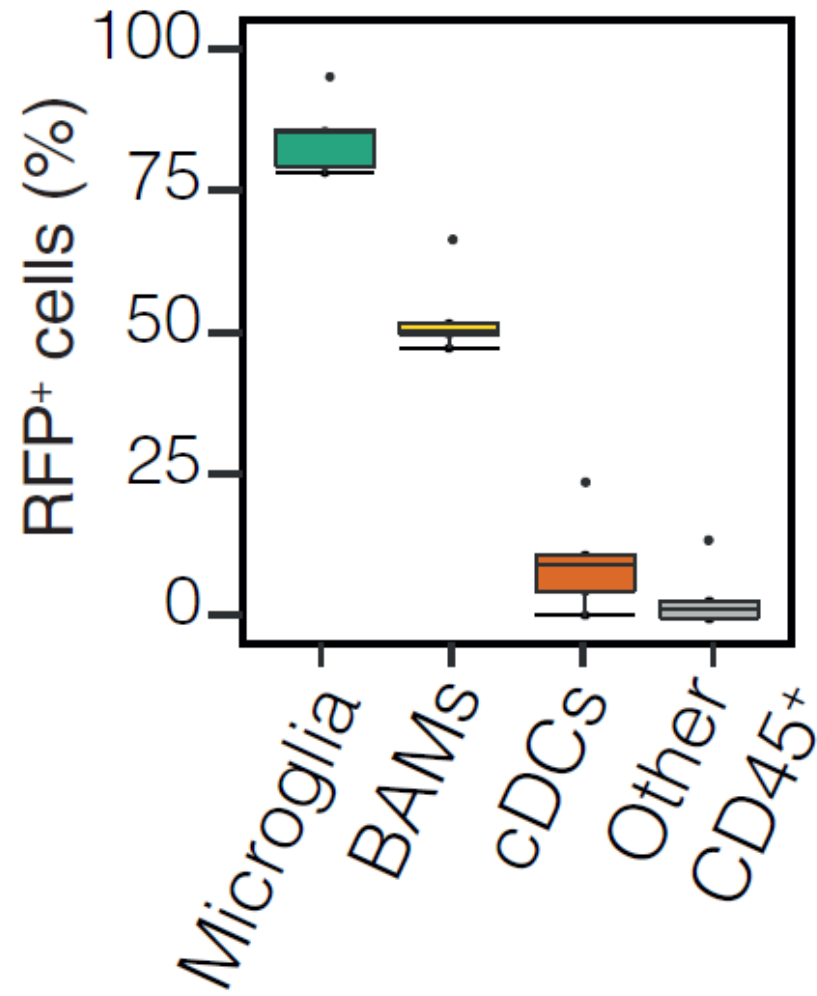


DENDRITIC CELLS

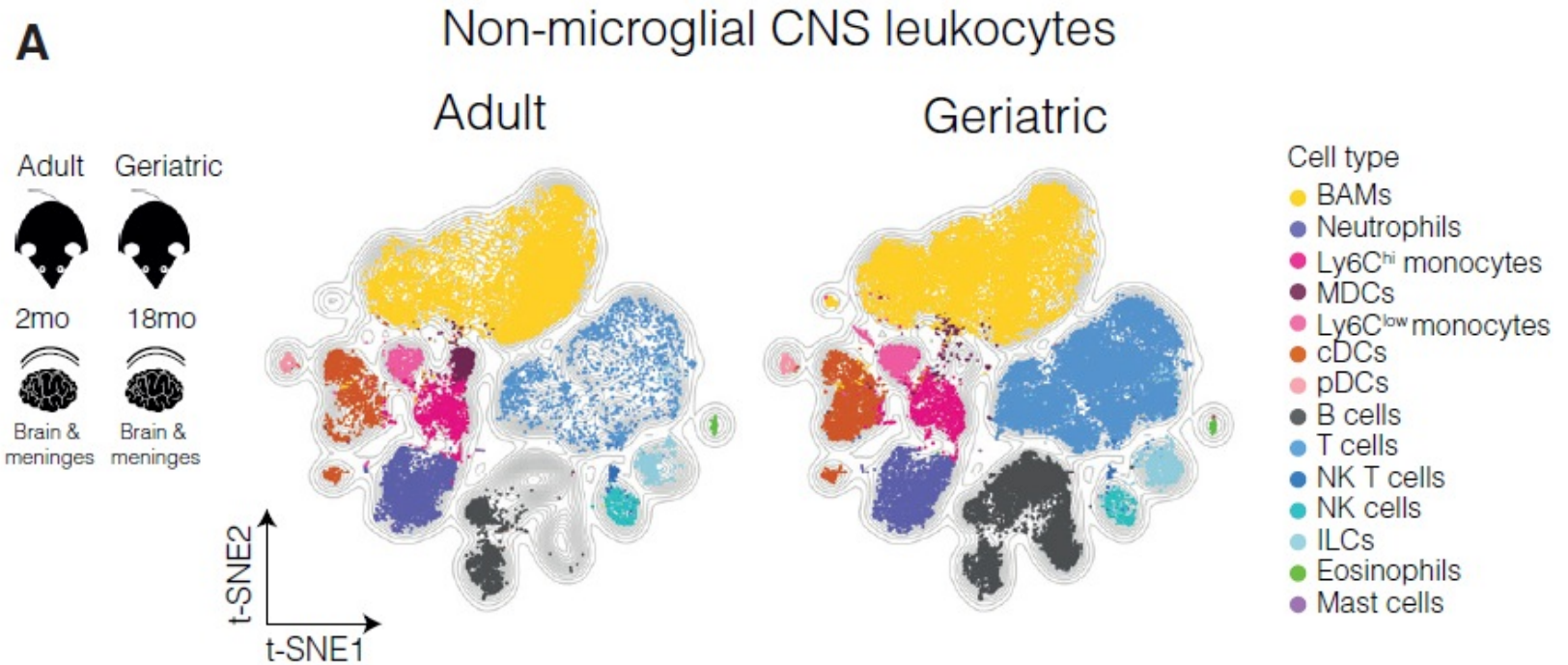


DAPI CD11c Iba1 MHCII

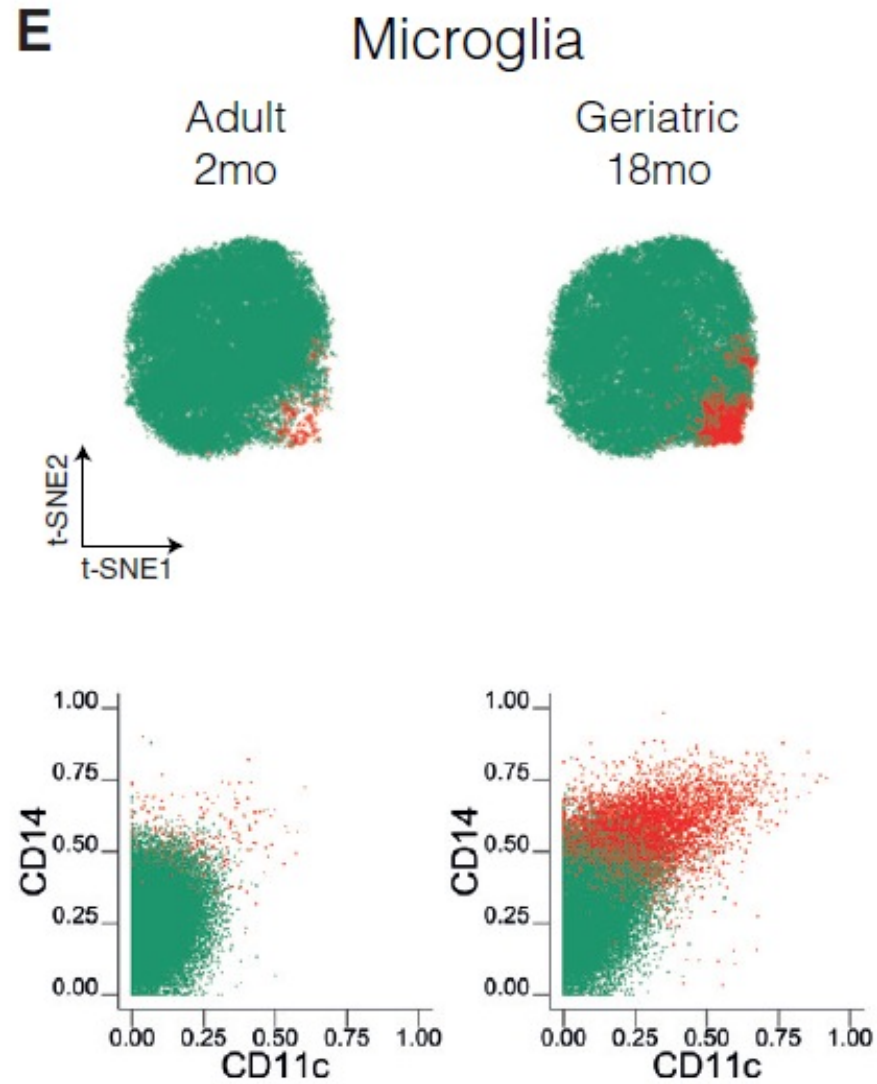
LEUKOCYTES TURNOVER



AGING CAUSES AN ALTERED CNS IMMUNE LANDSCAPE...



... AND A SUBSET OF REACTIVE MICROGLIA EMERGES



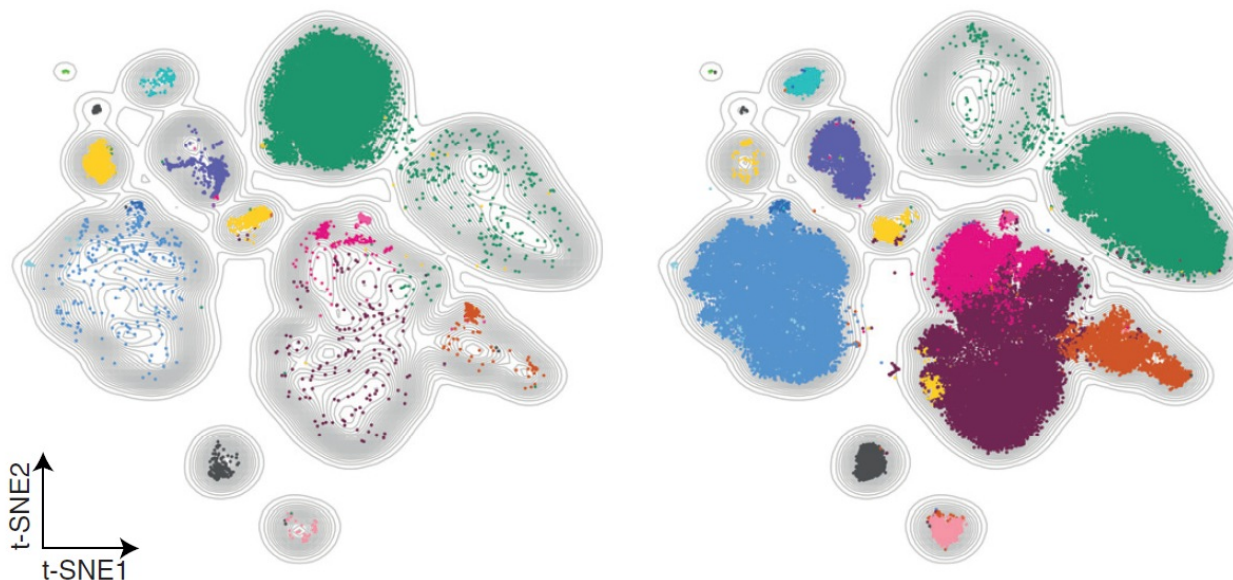
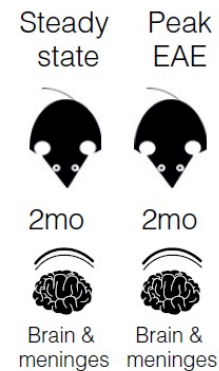
(Mrdjen et al., Immunity 2018)

AUTOIMMUNE NEUROINFLAMMATION EAE MODEL

A

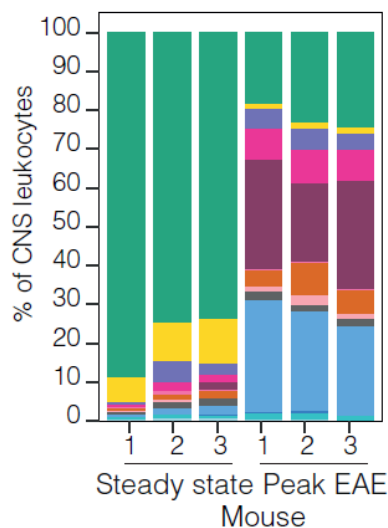
Steady state CNS leukocytes

Peak EAE CNS leukocytes



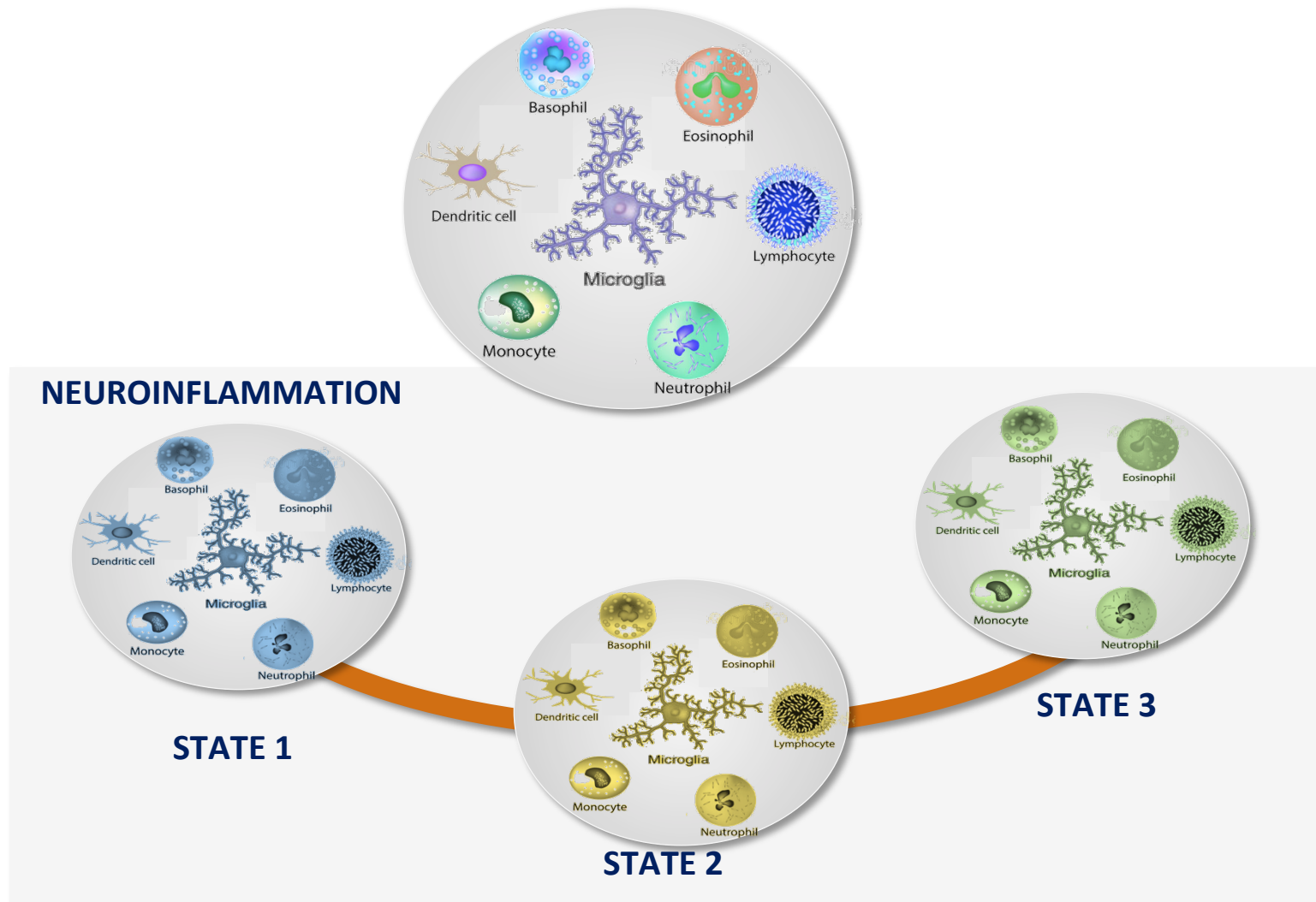
B

- Cell type
- 1. Microglia
 - 2. BAMs
 - 3. Neutrophils
 - 4. Ly6C^{hi} monocytes
 - 5. MDCs
 - 6. Ly6C^{low} monocytes
 - 7. cDCs
 - 8. pDCs
 - 9. B cells
 - 10. T cells
 - 11. NK T cells
 - 12. NK cells
 - 13. ILCs
 - 14. Eosinophils
 - 15. Mast cells



CONCLUSION

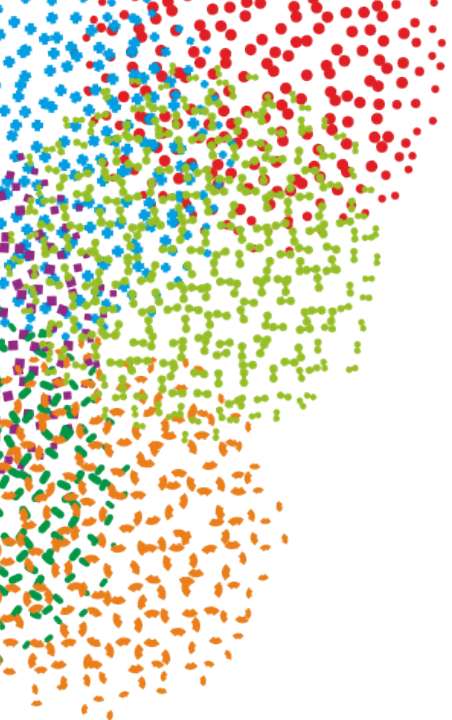
THE CNS IMMUNE SYSTEM: NEW CONCEPT



CONCLUSION

THE CNS IMMUNE SYSTEM: NEW CONCEPT

- ✓ WHAT IS THE BRAIN IMMUNE SYSTEM?
- ✓ WHAT IS ITS ROLE? STEADY-STATE, PATHOLOGY?
- ✓ HOW DO LEUKOCYTES COORDINATE THEIR RESPONSE IN THE CNS
- ✓ WHAT IS THE ROLE OF MICROGLIA UNDER IMMUNE ACTIVATION?
- ✓ INTERACTION WITH PERIPHERAL IMMUNE SYSTEM?
- ✓ IS THERE A FRONTIER BETWEEN PERIPHERAL AND CENTRAL IMMUNE SYSTEMS? ROLE OF THAT FRONTIER IN IMMUNE RESPONSE



BORDEAUX **NutriNeuro**
neurocampus

**Thank you for your
attention**

