



# Neuroimmunology: The brain as a cognitive antigen

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**Sheba Medical Center, Tel-Hashomer**  
**ISRAEL**



**NEW HORIZONS IN  
CLINICAL NEUROSCIENCE**  
In cooperation with Human Brain Project



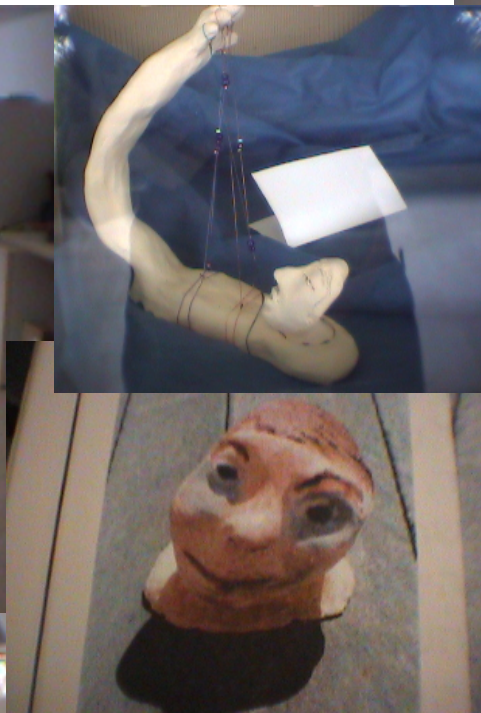
# Itinerary

- Self-recognition
- Basic brain immunology
- The brain as an antigen
- BBB
- PML
- Myelin
- Autoimmunity
- Multiple sclerosis
- Brain plasticity
- The brain as a cognitive antigen





# Sheba Multiple Sclerosis Center





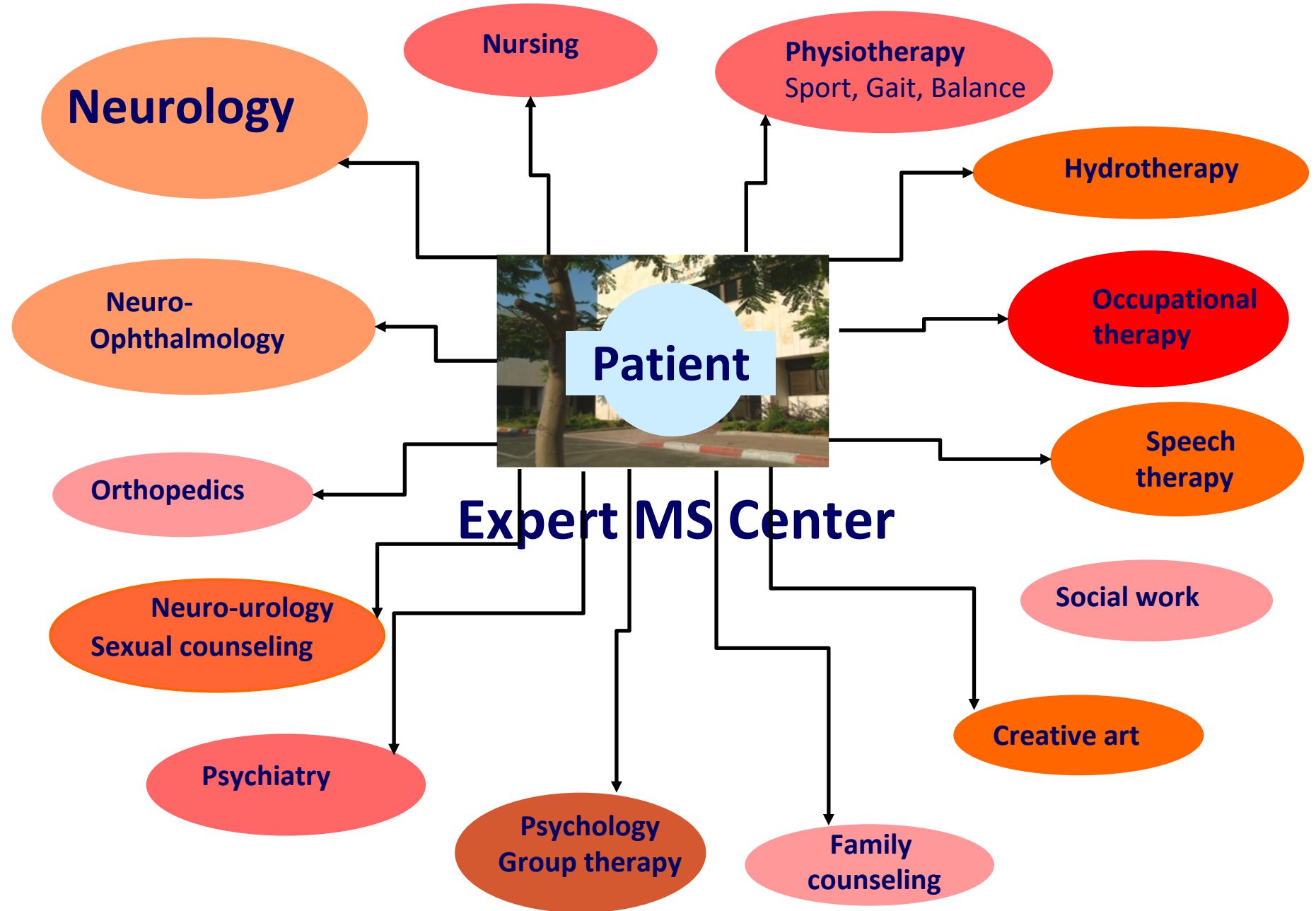
# Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, ISRAEL



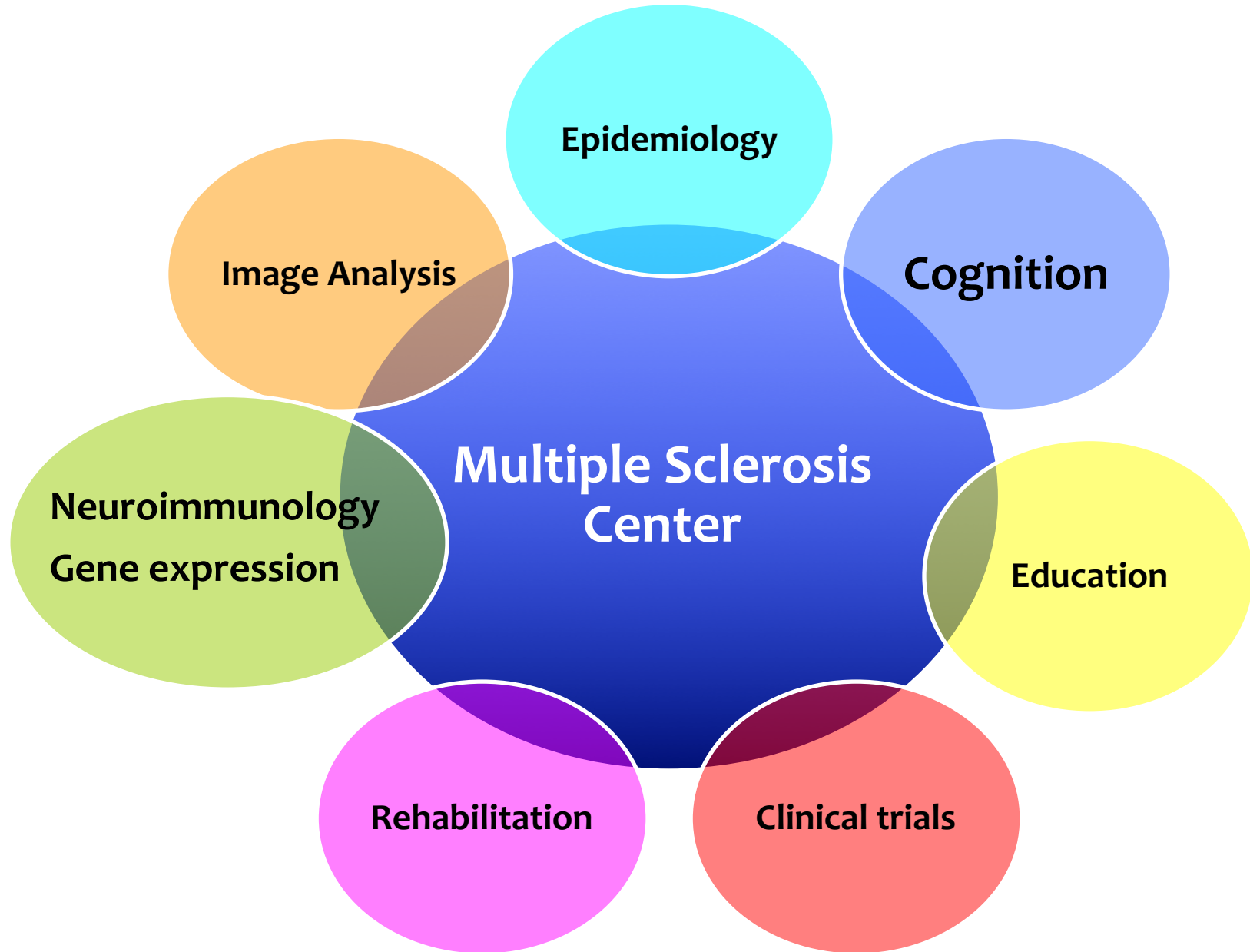
**1995 – 2016....**

**No of MS patients = 4071**

# Sheba Comprehensive Multiple Sclerosis Center



# Sheba Comprehensive Multiple Sclerosis Center





# Immune system– Basic definitions

- **Innate immune system** aimed at acute rapid immune response.
- Detects pathogens or **PAMPs (pathogen-associated molecular patterns)** which are characteristic structures present in microorganisms by receptors belonging to two diverse receptor families: the Toll-like receptor family and the Nod protein (or NBD-LRR protein) family.
- In vertebrates, the **innate immune system** activates the more evolved **adaptive immune system**, which is composed of T and B lymphocytes.

# Immune system – detection & response

## **Innate immune response:**

- 1) Antigen-presenting cells (APCs) are activated through recognition of pathogens (or PAMPs) by receptors such as TLRs or NBD-LRR proteins.
- 2) This activation leads to the production of inflammatory cytokines and the expression of co-stimulatory molecules on the cell surface.

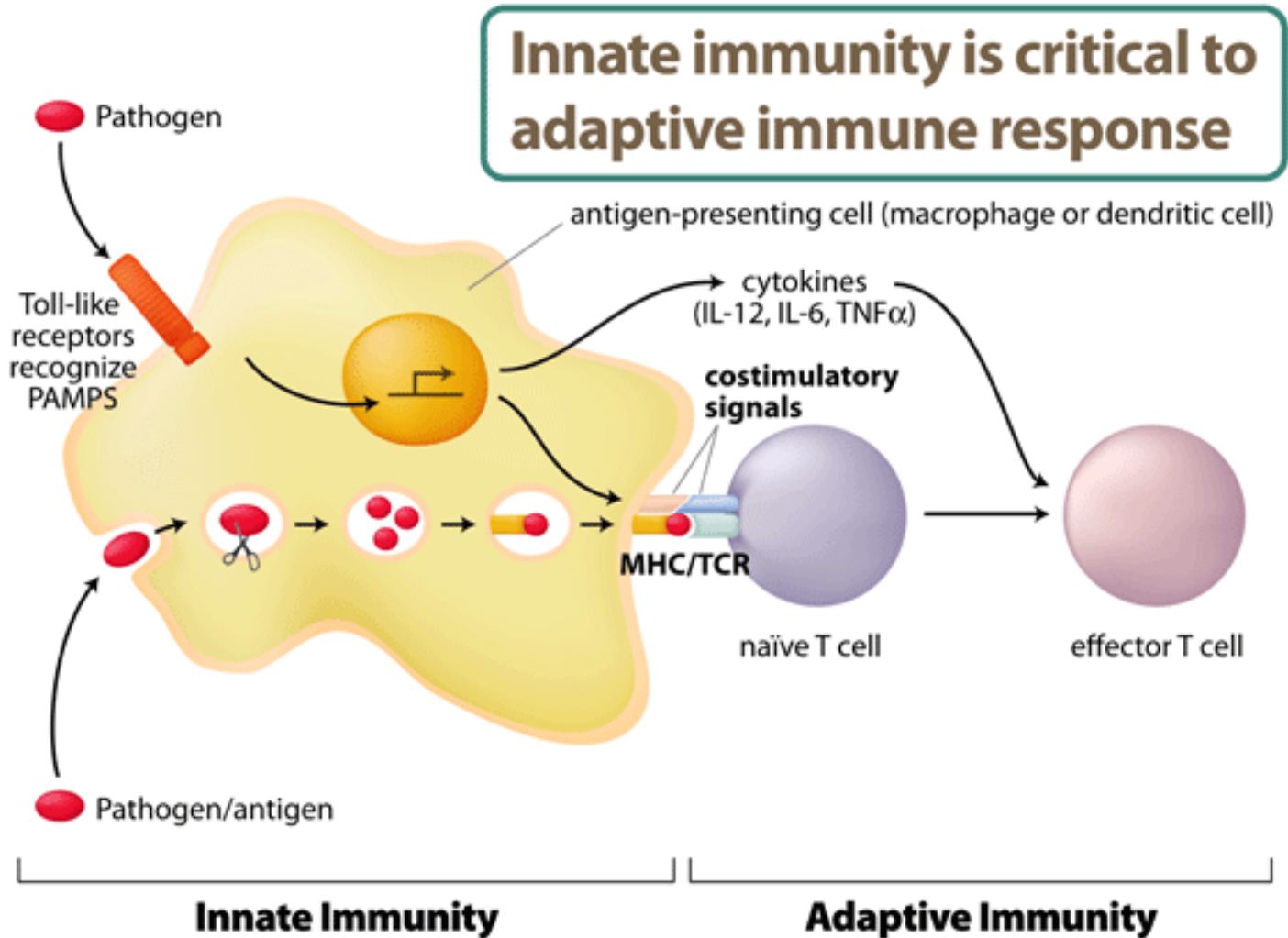
## **Adaptive immune response:**

- 3) Antigens will be presented by MHC molecules on APCs to T lymphocytes (Signal 1).

This is not sufficient to activate T lymphocytes and they need an additional signal from co-stimulatory molecules (Signal 2), of which expression on APCs is induced by TLR (or NBD-LRR) stimulation.

- 4) Activated T lymphocytes become further differentiated to effector T lymphocytes by stimulation with cytokines such as IL-12.

# Immune response - Detection & Recognition

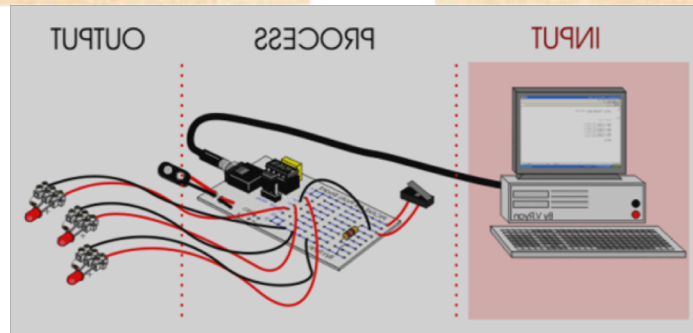
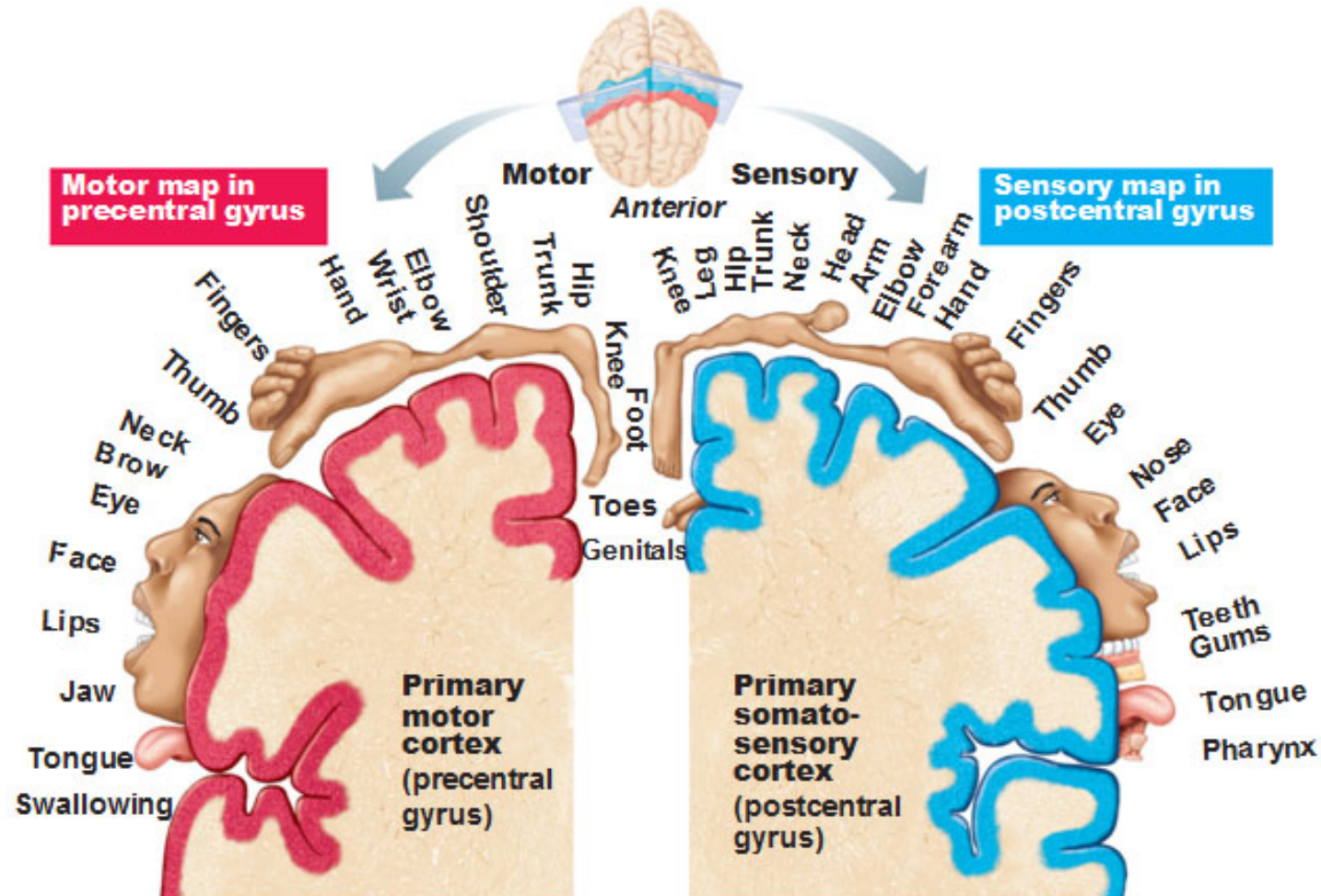


PAMPS= Pathogen-associated molecular patterns



Differences between innate and adaptive immunity		
	Innate Immunity	Adaptive Immunity
Action Time	Early (hours)	Late (Days)
Cell Types	Macrophages, Dendritic cells, Neutrophils	B, T Lymphocytes
Receptors	Fixed in genome e.g., Toll-like receptor	Gene rearrangement necessary e.g., B cell receptor, T cell receptor
Recognition	Conserved molecular patterns e.g., LPS	Wide variety of molecular structure (proteins, peptides) ~1,000,000,000,000,000,000
Evolution	Evolutionarily conserved (plants, animals)	Only vertebrates (jawed fish-human)

# The brain as an immunologic antigen







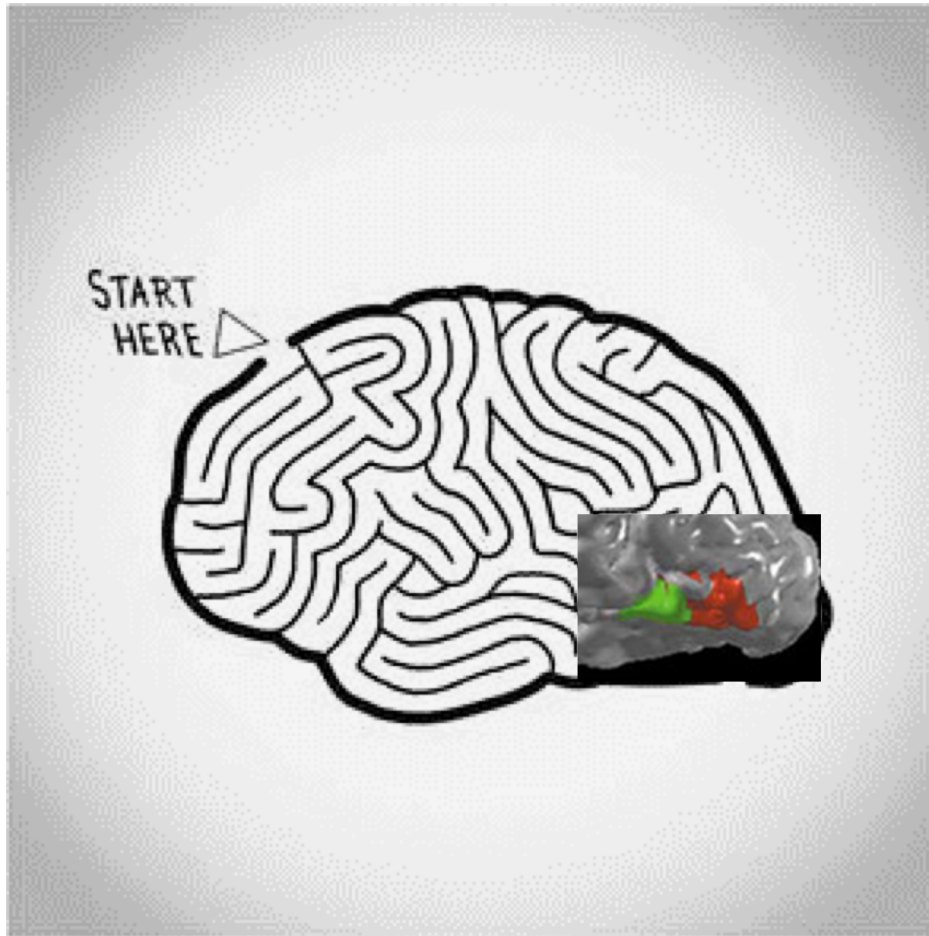
**Mass non-specific antigenic recognition**





Target antigen recognition

# Brain visual-facial antigen recognition



The Fusiform Gyrus is the area in the brain responsible for facial recognition.



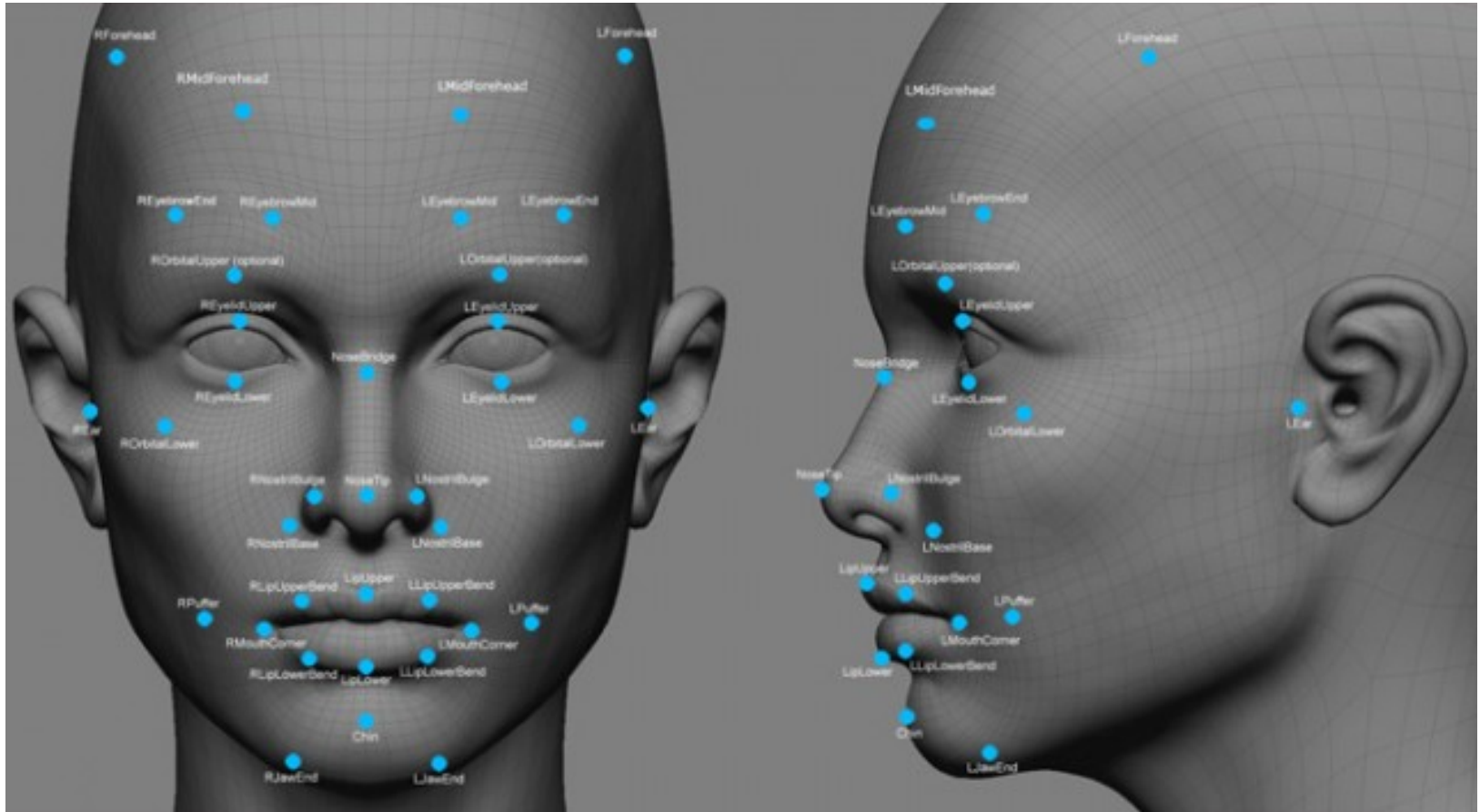
# Brain recognition without identification



Times Square, NY 4.2016

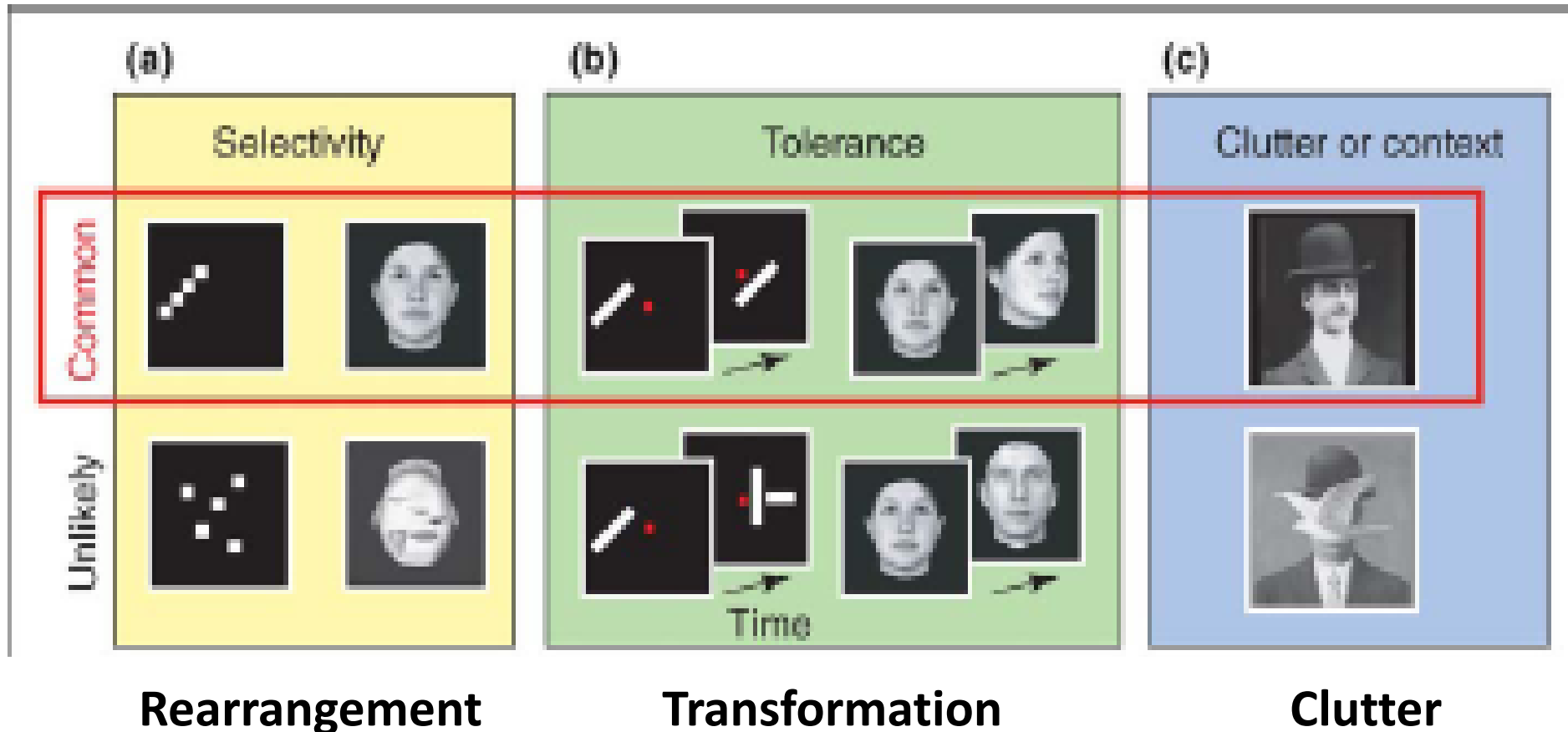


# Brain “HLA” pattern recognition



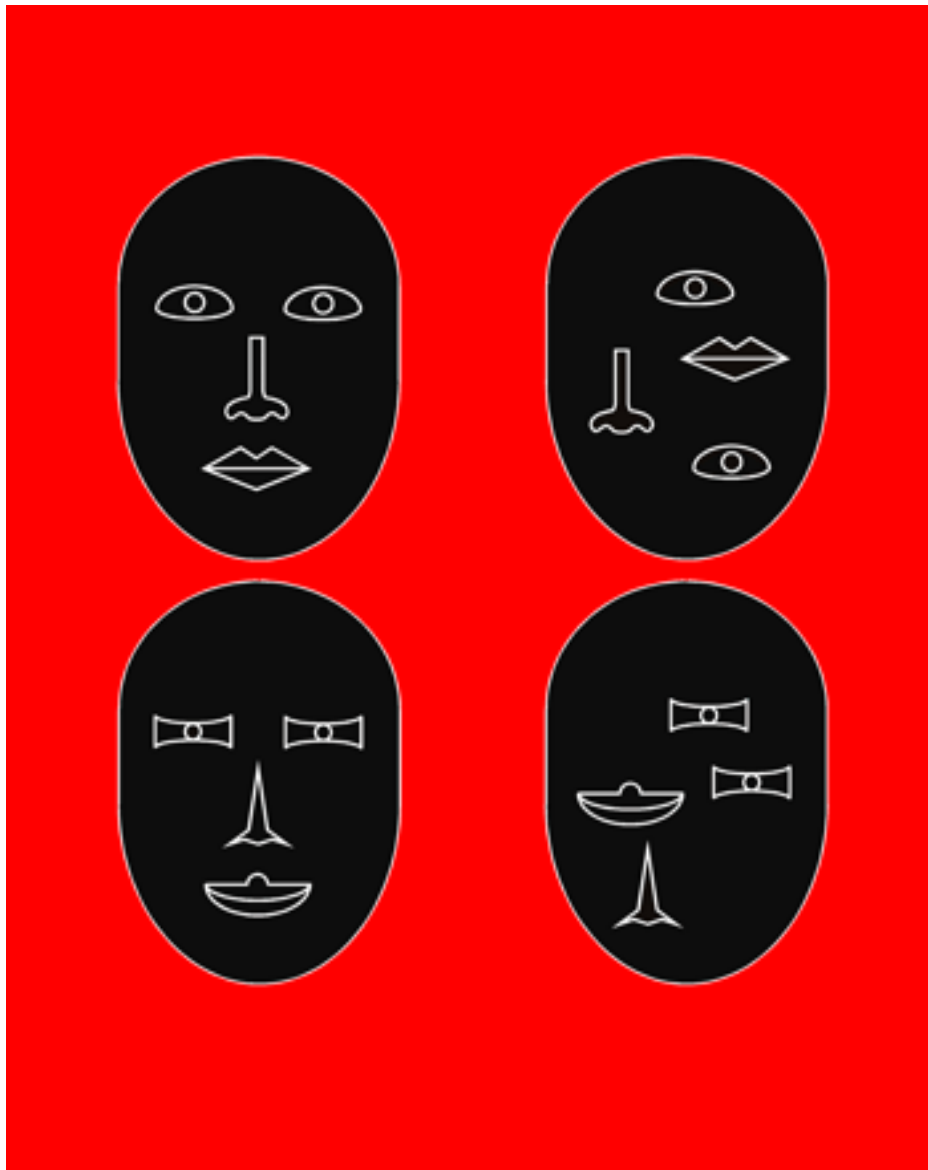
# Brain response to various antigents

Object recognition through **visual experience**



face-like objects

NFOs



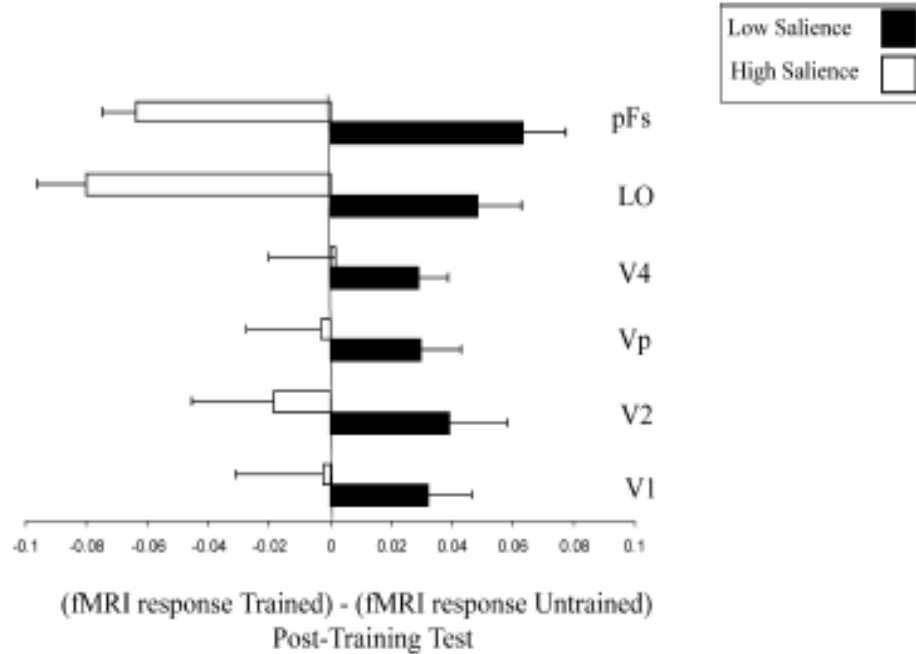
FOs, left) and their corresponding non-face-like objects (NFOs, right) composed of the same set of parts.

The **inferior temporal neurons** revealed spike correlation that depended on the feature configuration within a unique whole object.

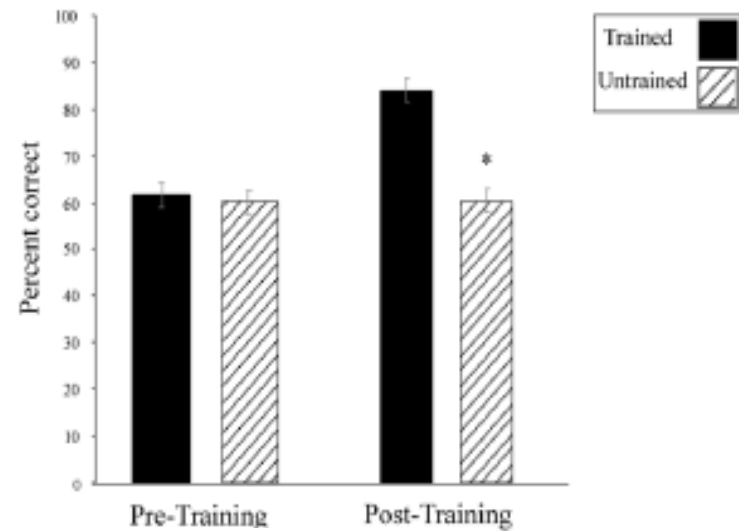
The configuration-dependent spike correlation emerged within **300 ms after stimulus onset**, which is rapid enough to mediate recognition of the stimulus.

Hirabayashi & Miyashita  
J Neuroscience 25:10299-307, 2005.

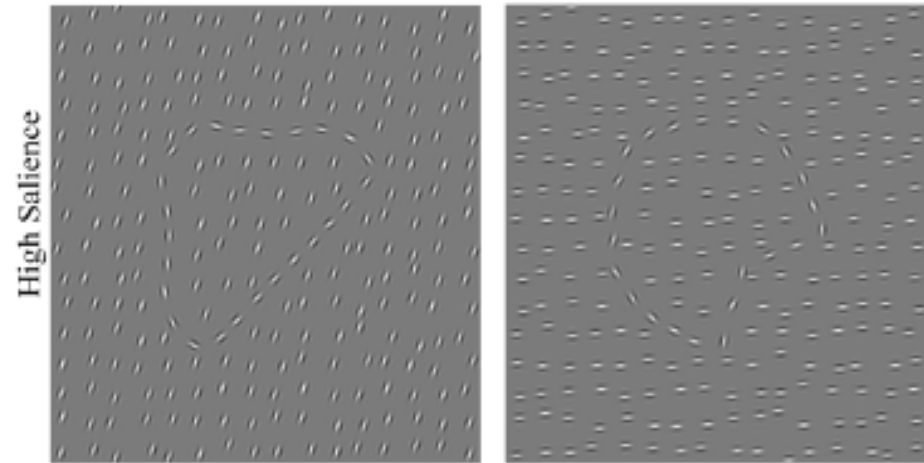
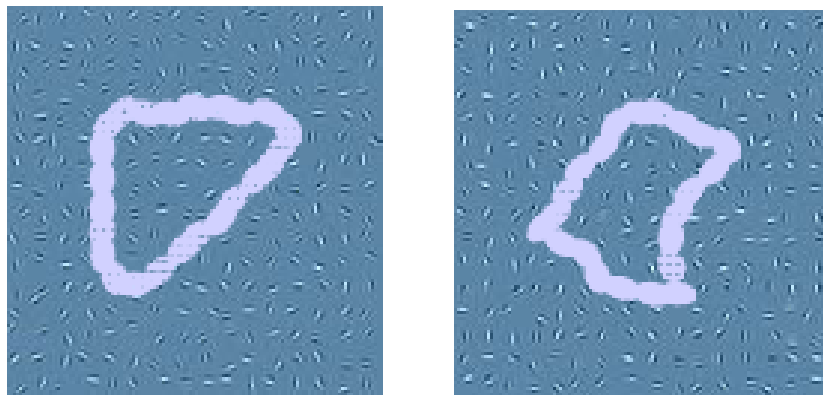




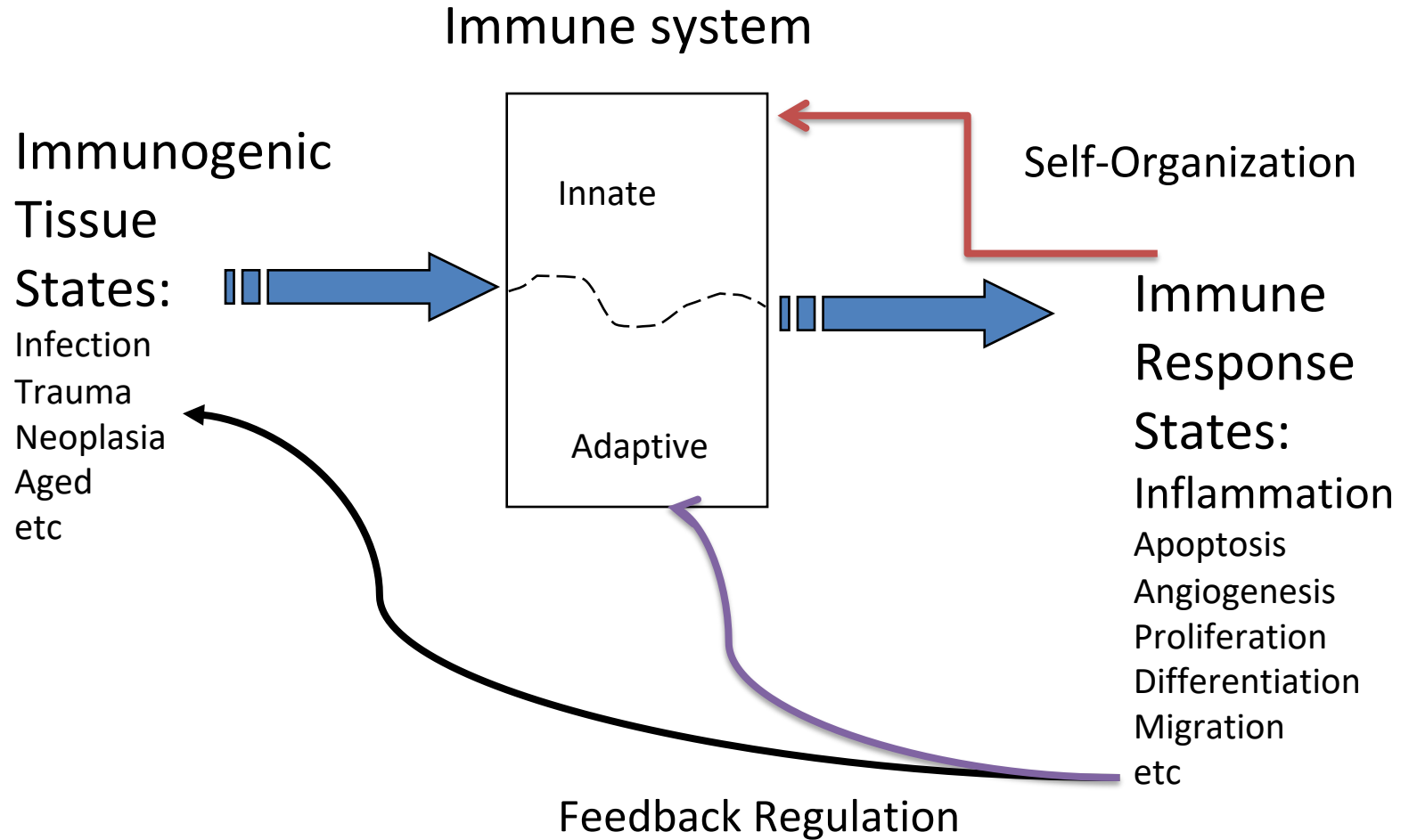
A. Experiment 1: Psychophysics



## Long-term plasticity: learning to see

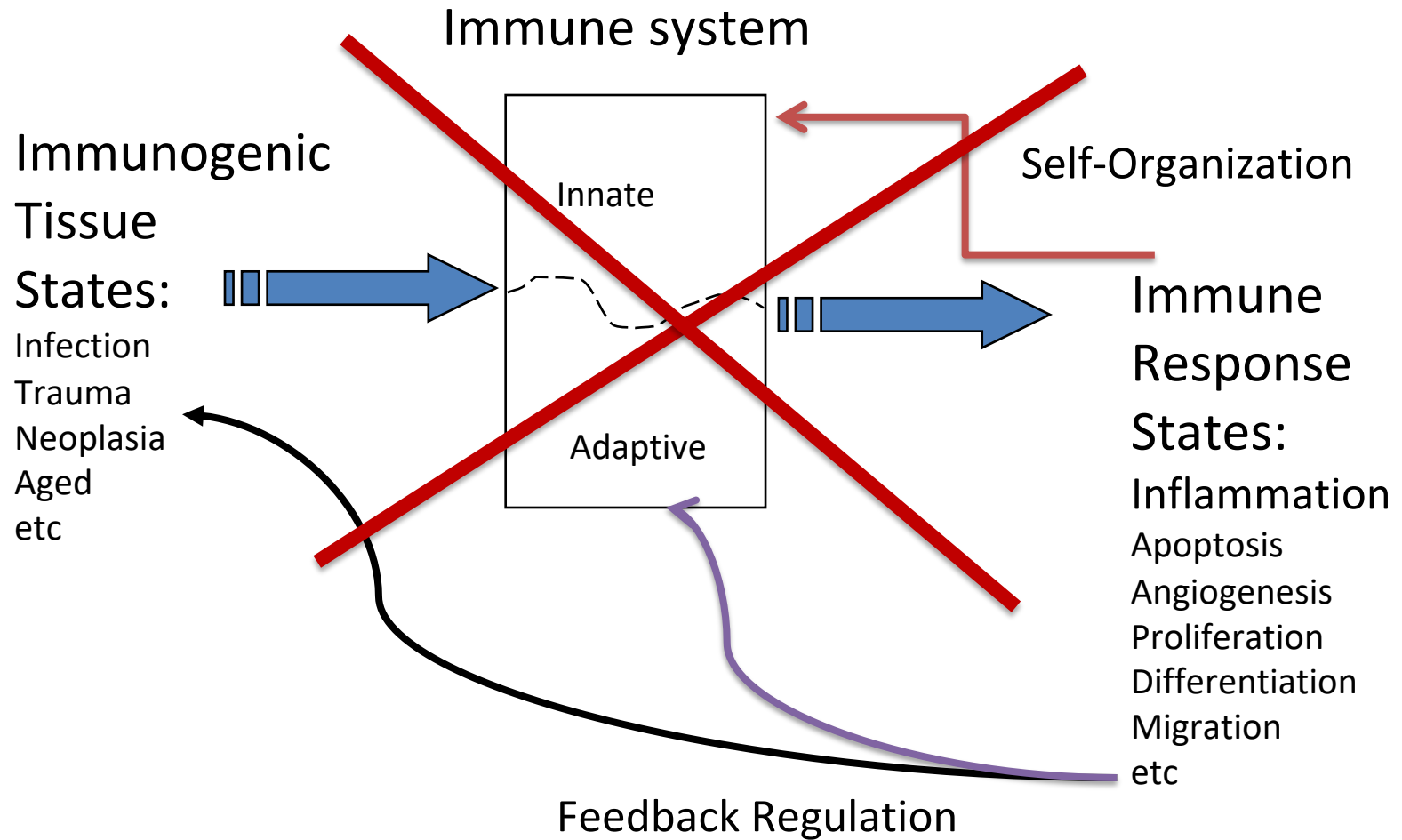


# Immune Computation

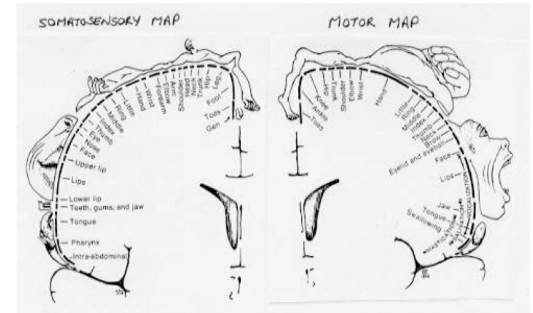


# Immune Computation:

## **Impaired recognition = Autoimmune disease**



# Autoimmune cognition ↕ CNS cognition

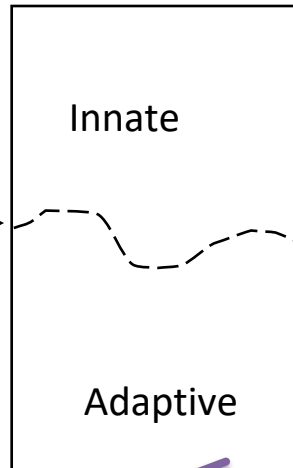


Immunogenic

Tissue

States:

Infection  
Trauma  
Neoplasia  
Aged  
etc

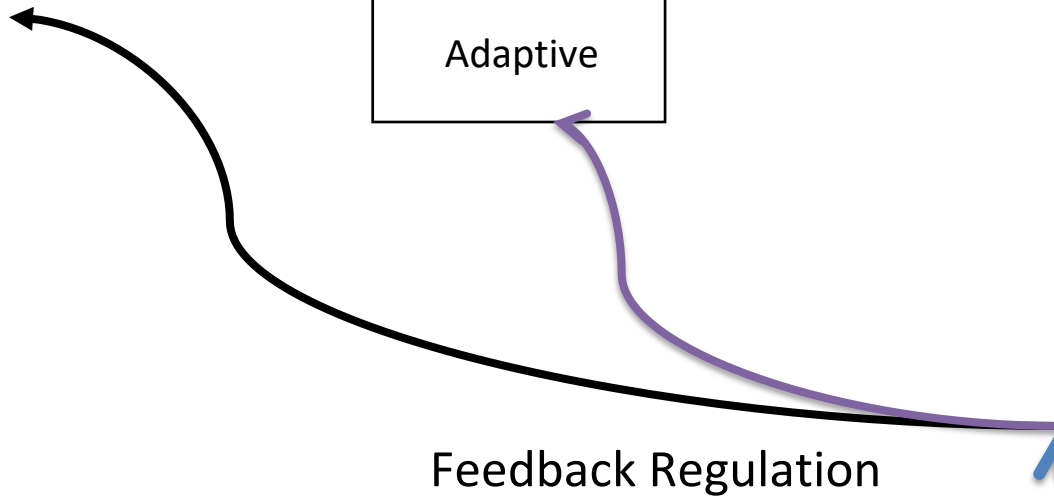


Self-Organization

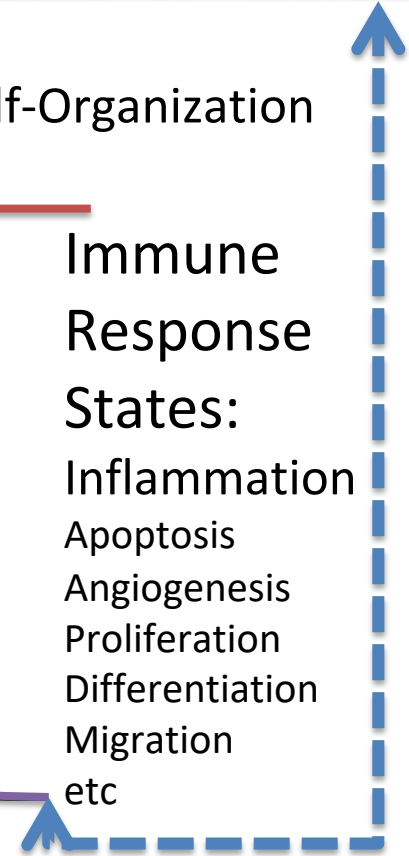
Immune  
Response

States:

Inflammation  
Apoptosis  
Angiogenesis  
Proliferation  
Differentiation  
Migration  
etc



Feedback Regulation







# Brain Protection



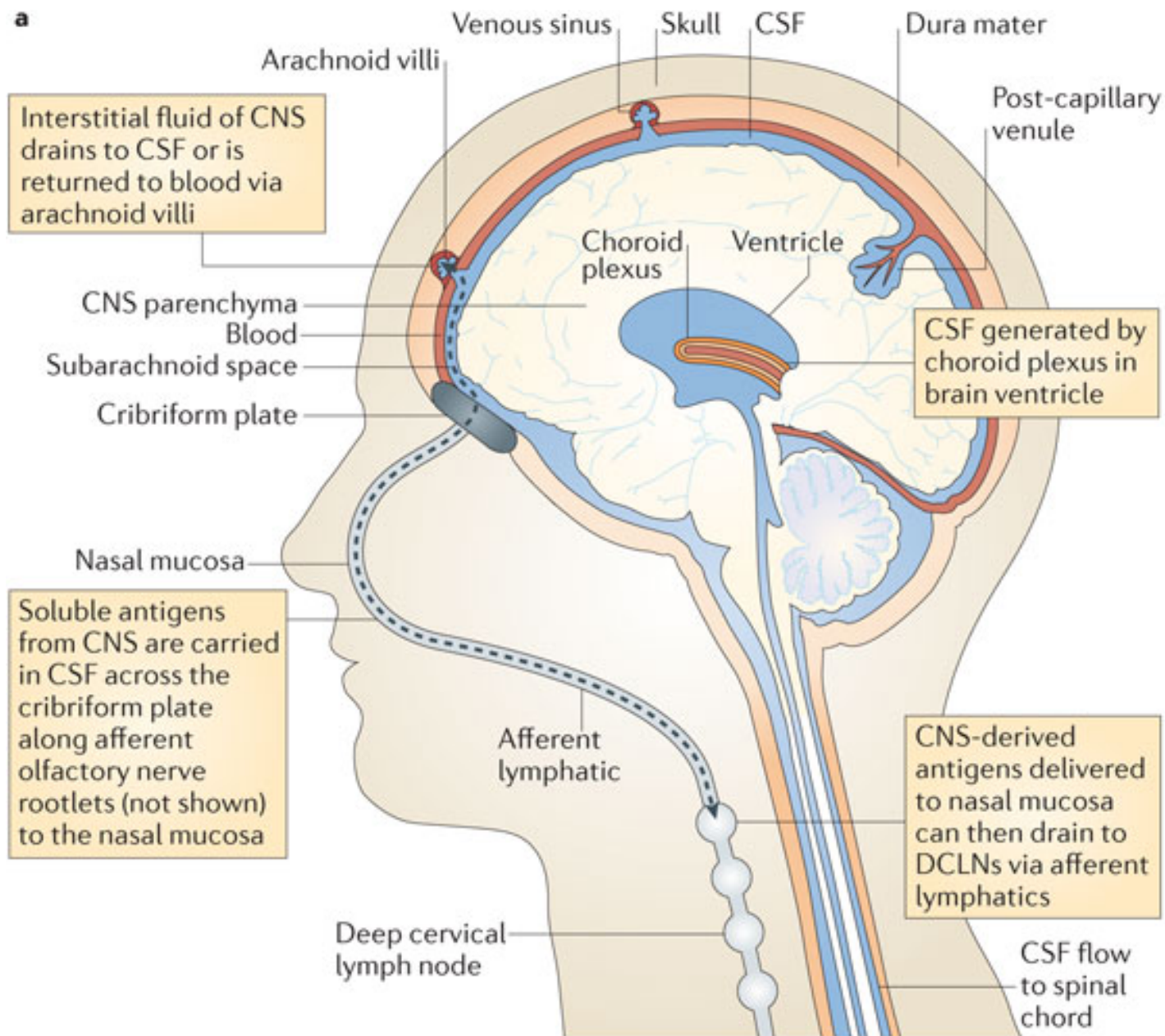
- The CNS is continuously monitored by resident microglia and blood-borne immune cells such as macrophages, dendritic cells and T cells aimed to detect damaging agents that would disrupt homeostasis and functioning.
- The CNS must balance between detection of potentially harmful factors and resolving immunological responses that in themselves can create damage if left unabated.

# Brain protection



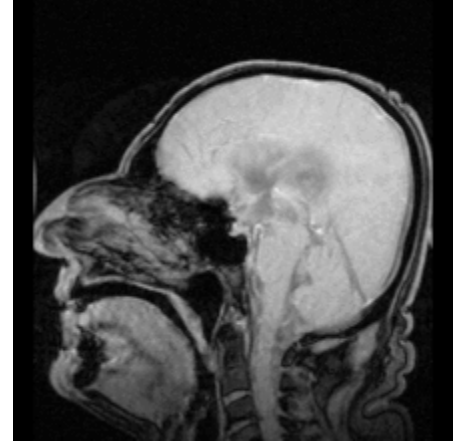
## No lymphatic vessels

- The interstitial fluid of the CNS drains via perivascular channels into the CSF, allowing meningeal macrophages and other APCs in the SAS to sample the full range of CNS antigens.
- CNS-derived soluble antigens are transported in the CSF to the nasal mucosa, and from there through afferent lymphatics to the deep cervical lymph nodes (DCLNs).
- CSF acts as a functional equivalent of lymph.



# CSF facts

- CSF volumes range 140 to 270 ml.
- Daily CSF production ~500 ml.
- CSF turns over between 3-5 times per day.
- Cellular composition of the CSF:
  - ~90% T cells, CD4+ to CD8+ = 3.5 to 1
  - ~5% B cells
  - 5% are monocytes
  - 1% DCs





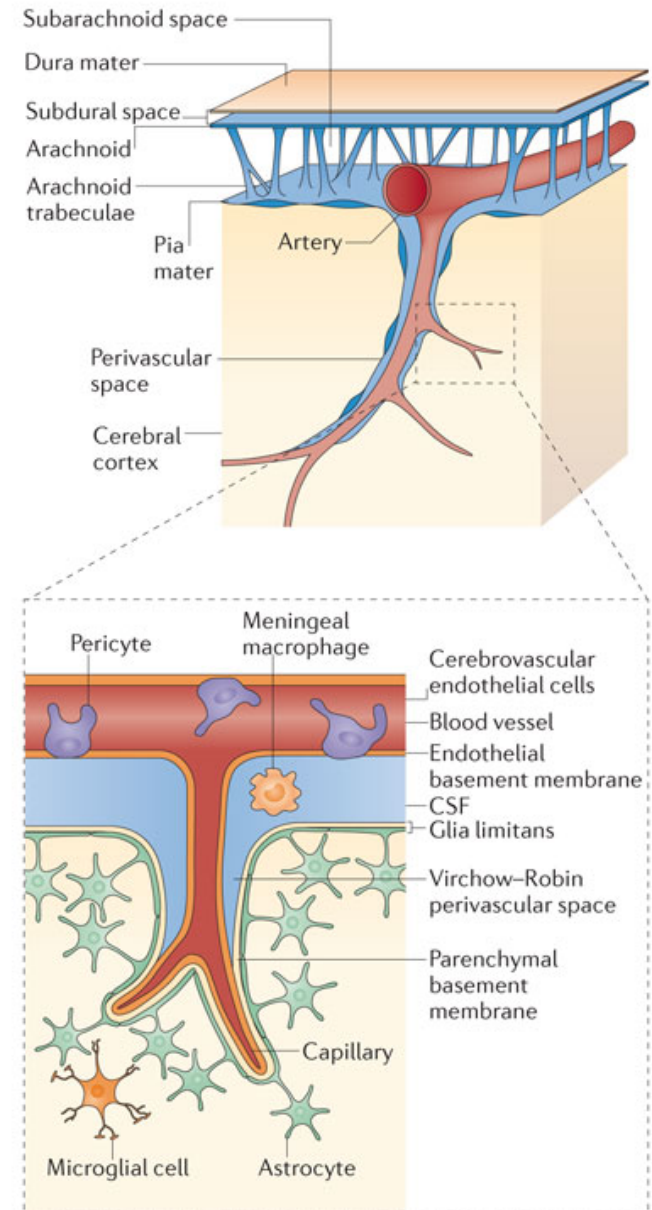
The CNS is immune privileged

## **Lack of a cell-mediated response to instilled antigens**

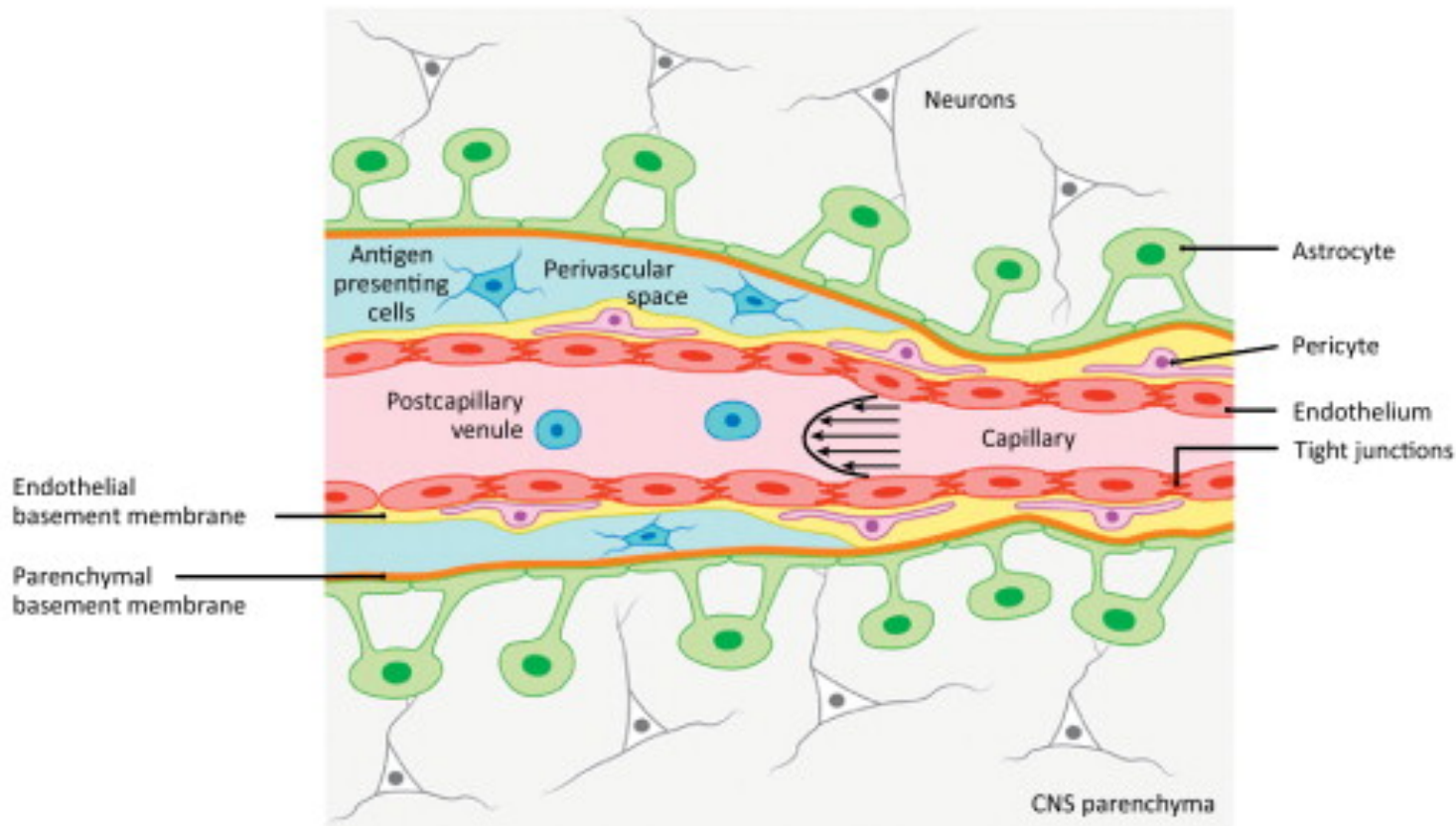
- CNS immune privilege is demonstrated by placing immunogenic material - tumor cells, viruses or bacteria - in the brain parenchyma, avoiding the ventricles and meninges and minimizing tissue disruption.
- Using this procedure, immunogenic materials escape immune recognition and fail to elicit adaptive immune response.

# BBB

- Endothelial cells lining CNS capillaries establish **the blood-brain barrier**: intercellular tight junctions, limited macropinocytosis and efficient efflux transporters, which strictly controls the movement of solutes across the CNS vasculature.
- **Neurovascular coupling**: The ability of the CNS microvessels to respond to increases in neuronal electrical activity by enhancing regional blood flow.
- **Neurovascular unit**: Brain microvascular endothelial cells embedded in the endothelial basement membrane that encloses numerous pericytes, astrocyte endfeet and neuronal processes.



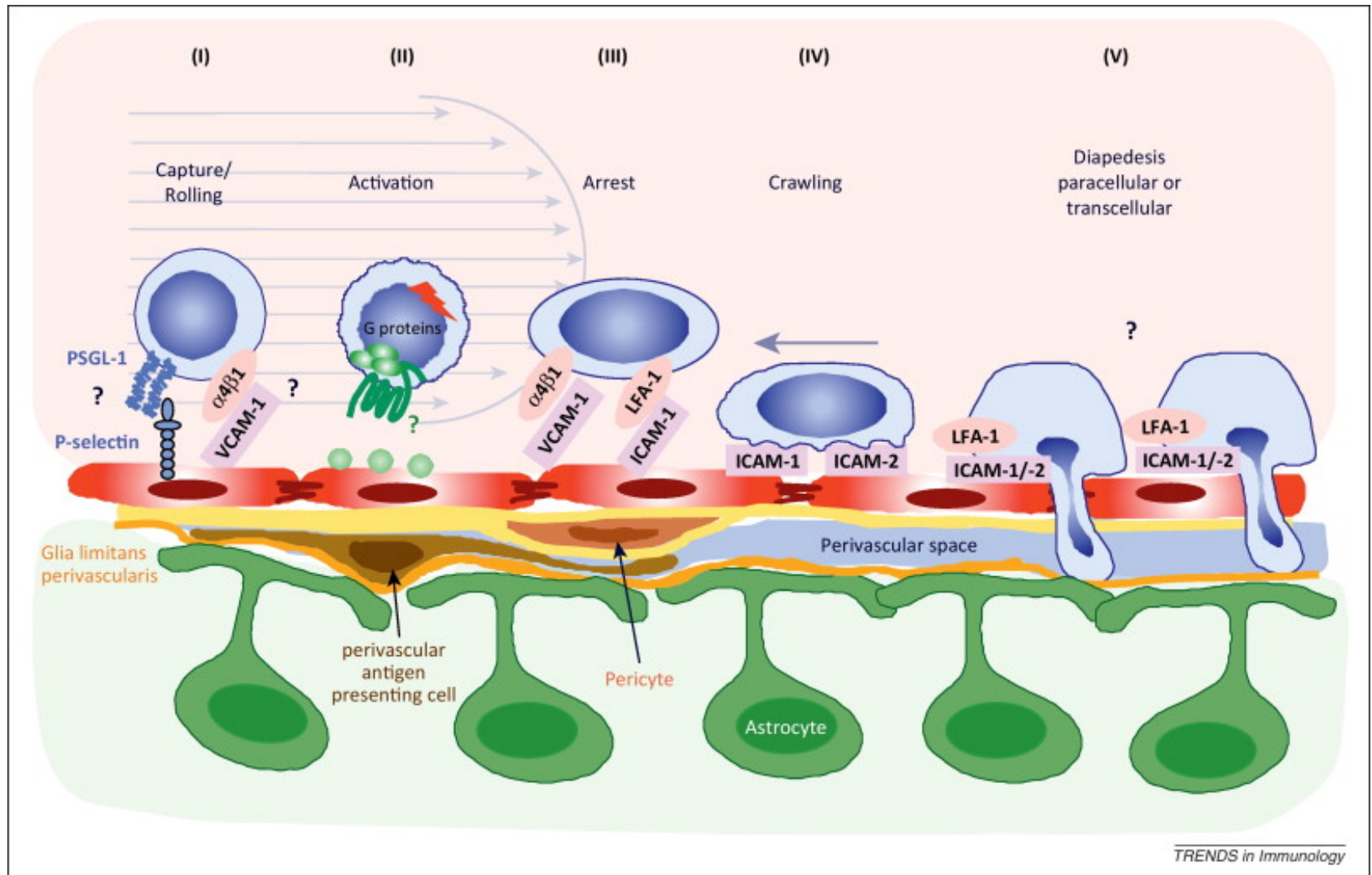
# Neuroanatomy of the vascular blood–brain barrier (BBB)



At the vascular segment of CNS capillaries, the endothelial and parenchymal basement membranes merge and cannot be ultrastructurally distinguished. However, at the post-capillary venules, these basement membranes separate to provide a cerebrospinal fluid (CSF)-drained perivascular space (blue), in which antigen-presenting cells can be found.

*TRENDS in Immunology*

# Molecular mechanisms involved in T cell migration across endothelial blood–brain barrier (BBB)



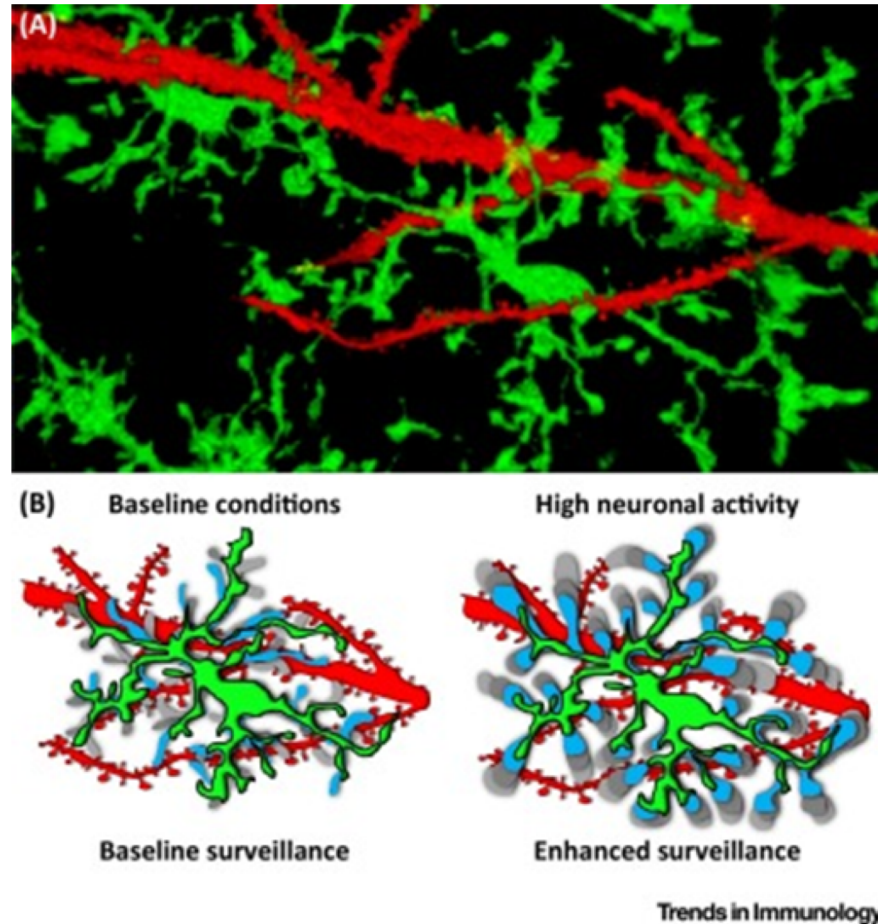


# Immune cells of the CNS

- **Parenchymal microglia:** arise from a yolk sac progenitor before definitive hematopoiesis. Maintained by local proliferation and possess abundant proliferative capacity so that microgliosis can occur without blood cell infiltration.
- **Choroid plexus macrophages, dendritic cells (DCs):** reside in the choroid plexus parenchyma (outside the CNS). They express DC-associated cell-surface markers such as CD11c and are increased in number during CNS inflammation.
- **Meningeal macrophages:** have a morphology and surface phenotype (CD11+ CD45hiF4/80+ ) typical of tissue macrophages. They have antigen-presenting cell functions during experimental autoimmune encephalomyelitis.
- **Perivascular macrophages:** found both in Virchow–Robin spaces and in the perivascular spaces of the parenchyma; express of MHC class II molecules and are responsible for re-stimulating lymphocytes with peptide–MHC complexes after extravasation and for licensing these lymphocytes to enter the CNS parenchyma.

# Microglia Surveillance

Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B. Microglia: Dynamic Mediators of Synapse Development and Plasticity. Trends Immunol 36:605-13, 2015.



- (A) Two-photon image of a microglia (green) and the dendrites of a single patch-filled CA1 pyramidal neuron (red) in a hippocampal brain slice from a CX3CR1–EGFP mouse.
- (B) Surveillance by microglial processes under baseline conditions. The blue and gray shaded regions represent the positions of microglial processes at different time points. High neuronal activity triggers enhanced surveillance, which is schematized by the movement from blue to light gray over time.

# Immune surveillance in the CNS

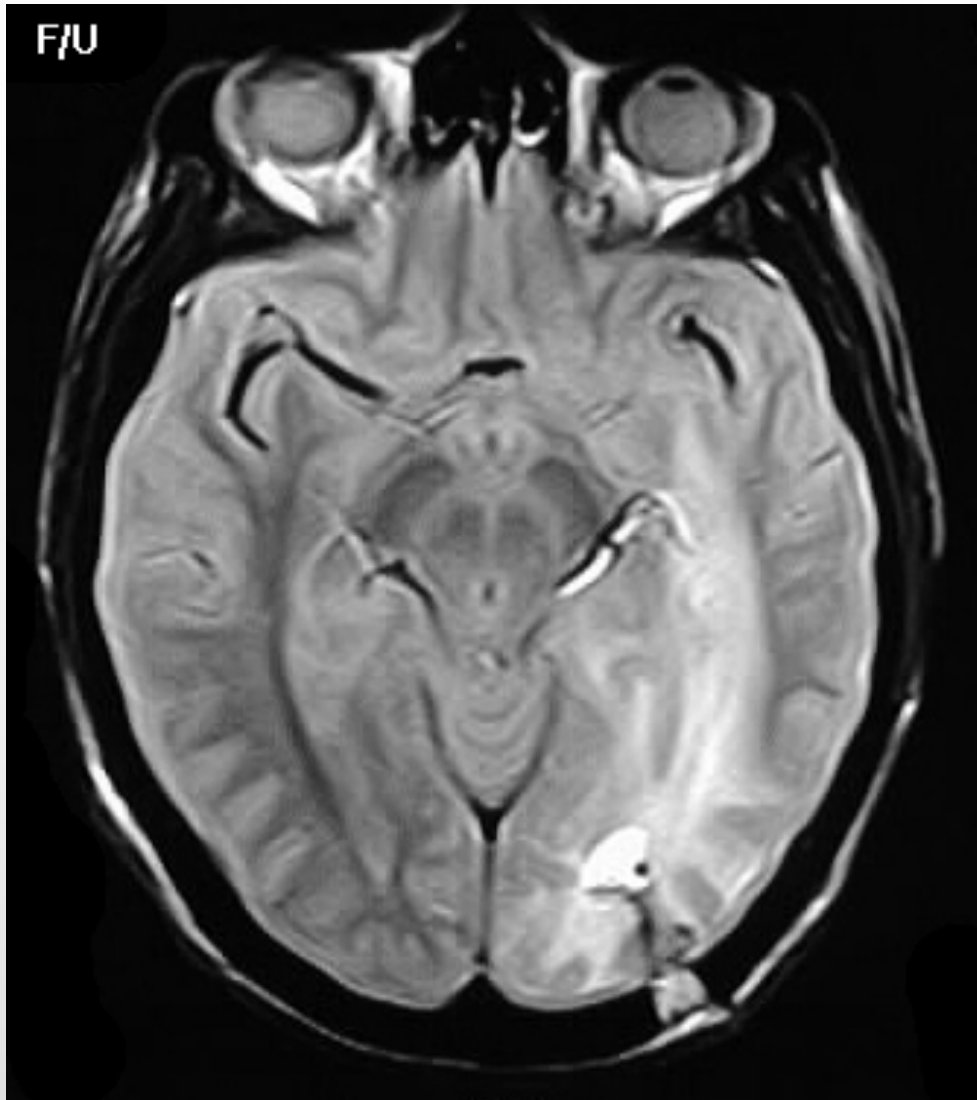
- Although the CNS lacks lymphatics, displays low levels of MHC molecules and is shielded from free diffusion of molecular and cellular components by the BBB and the blood–CSF barrier, the **immune response in the brain** can be impressive (meningitis).
- By contrast, **loss of immunity** is often highlighted by cerebral infections (JC polyoma virus (JCV), herpes simplex virus (HSV), West Nile virus (WNV) and HIV).

# Progressive multifocal leukoencephalopathy (PML)

- A usually fatal CNS infection caused by JCV.
- There are no treatments for PML, and most patients either die or are left with severe disability.
- Approximately 50% of humans harbor JCV that resides latently in bone marrow and renal tubular epithelial cells and B cells.



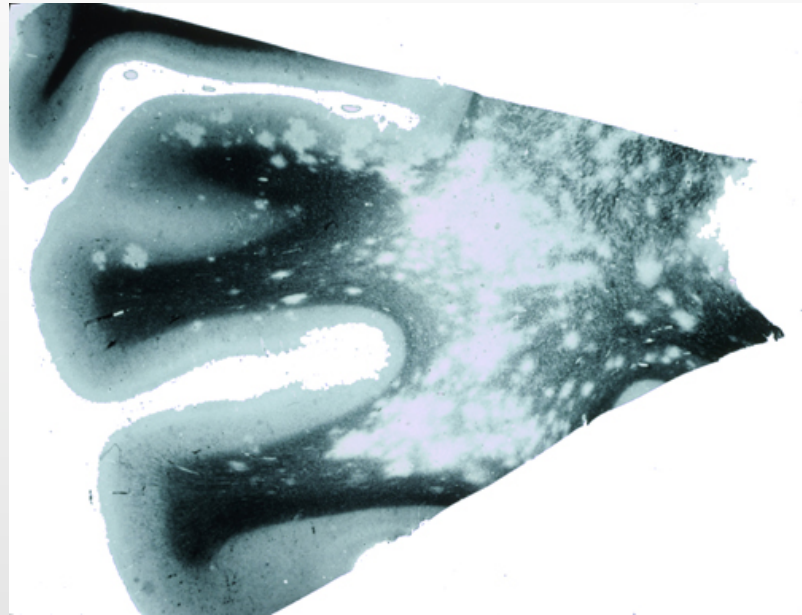
# Progressive Multifocal Leukoencephalopathy (PML)



# **Progressive Multifocal Leukoencephalopathy (PML)**

## **Cerebral cortex stained for myelin**

**Multifocal  
demyelination  
scattered throughout  
the subcortical white  
matter.**

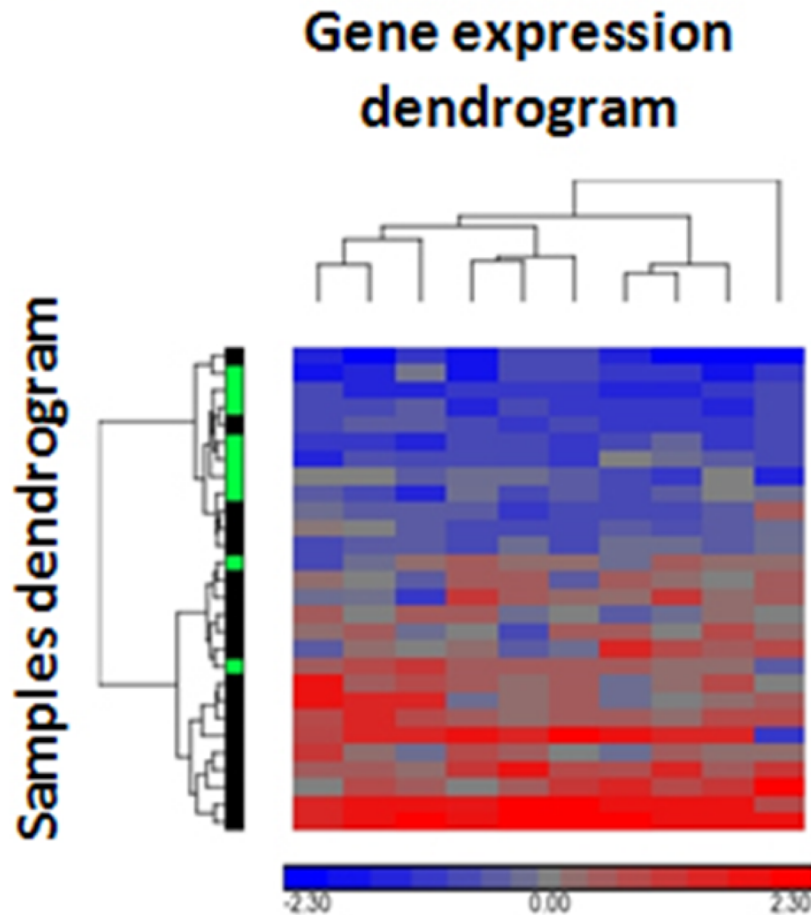


## Progressive multifocal leukoencephalopathy (PML): **Etiology**

- **Immune suppression:** Upon **suppression of CD4+ and CD8+ T cell migration** as occurs with **HIV infection, chemotherapy or immunosuppressive therapy**, the virus enters the brain, either within B cells or as cell-free virus, where it infects and kills oligodendrocytes leading to demyelination.
- **Tx-induced:** In order to prevent immune cells utilize cell adhesion molecules to infiltrate the CNS, monoclonal antibodies against B cells (rituximab), VLA-4 (natalizumab) and LFA-1 (efalizumab) had been developed to treat multiple sclerosis, non-Hodgkin lymphoma, rheumatoid arthritis, Crohn's disease and systemic lupus erythematosus.
- These medications inhibit migration of B and T cells into the CNS.

The lack of surveillance by the immune system allows unabated invasion of the JCV into the brain.

# Natalizumab induced JCV antibody switch in MS patients treated with Natalizumab

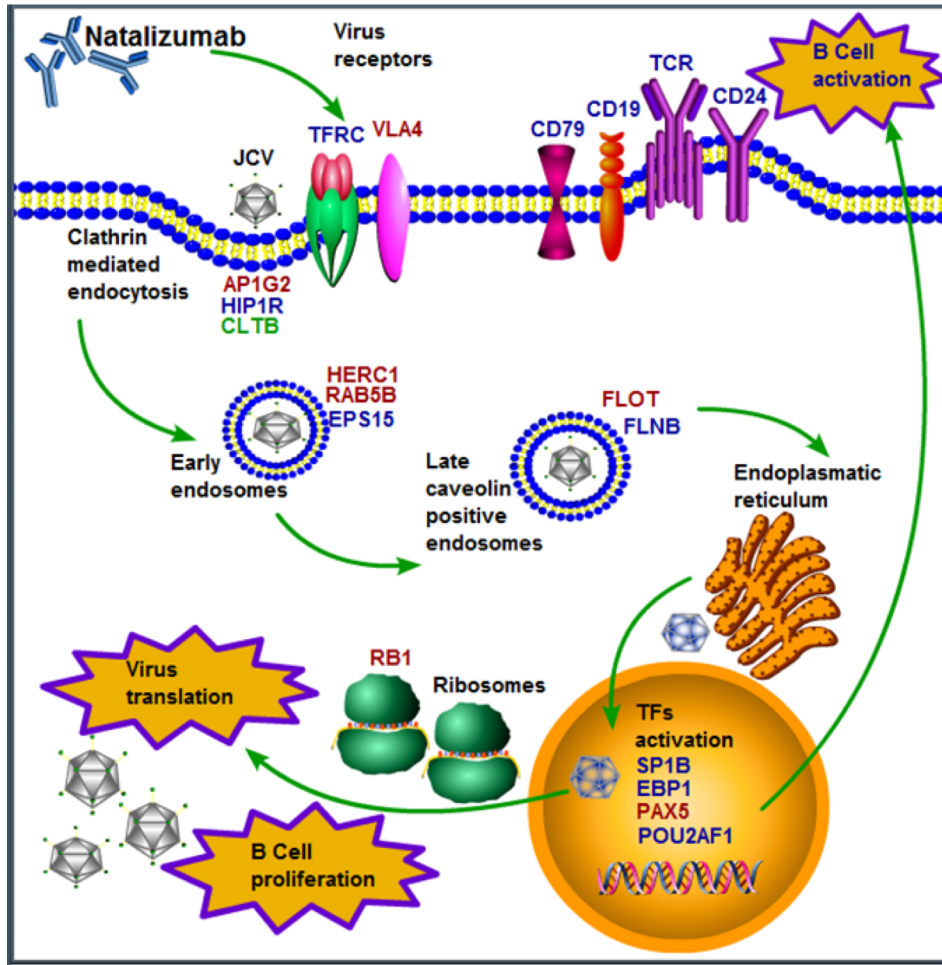


Within 3 years of natalizumab treatment, 24.6% of anti-JCV antibody-negative MS patients switched to become anti-JCV antibody positive - JCV-switchers.

Unsupervised hierarchical clustering of baseline MS samples demonstrate two clusters, one enriched by JCV switchers (**green color** in left dendrogram) and the other including mainly non-switching MS patients (**black color** in left dendrogram).



# Natalizumab induced JCV antibody switch in MS



In JCV-switchers, GE signature was enriched by overexpression of genes associated with the first stages of viral entry to host cells including:

- micropinocytosis
- virus entry via endocytosis
- clathrin-mediated endocytosis
- caveolar-mediated endocytosis.

# Progressive Multifocal Leukoencephalopathy

## PML - H&E staining



oligodendrocyte nucleus  
markedly enlarged with viral  
particles, giving it a magenta  
color.

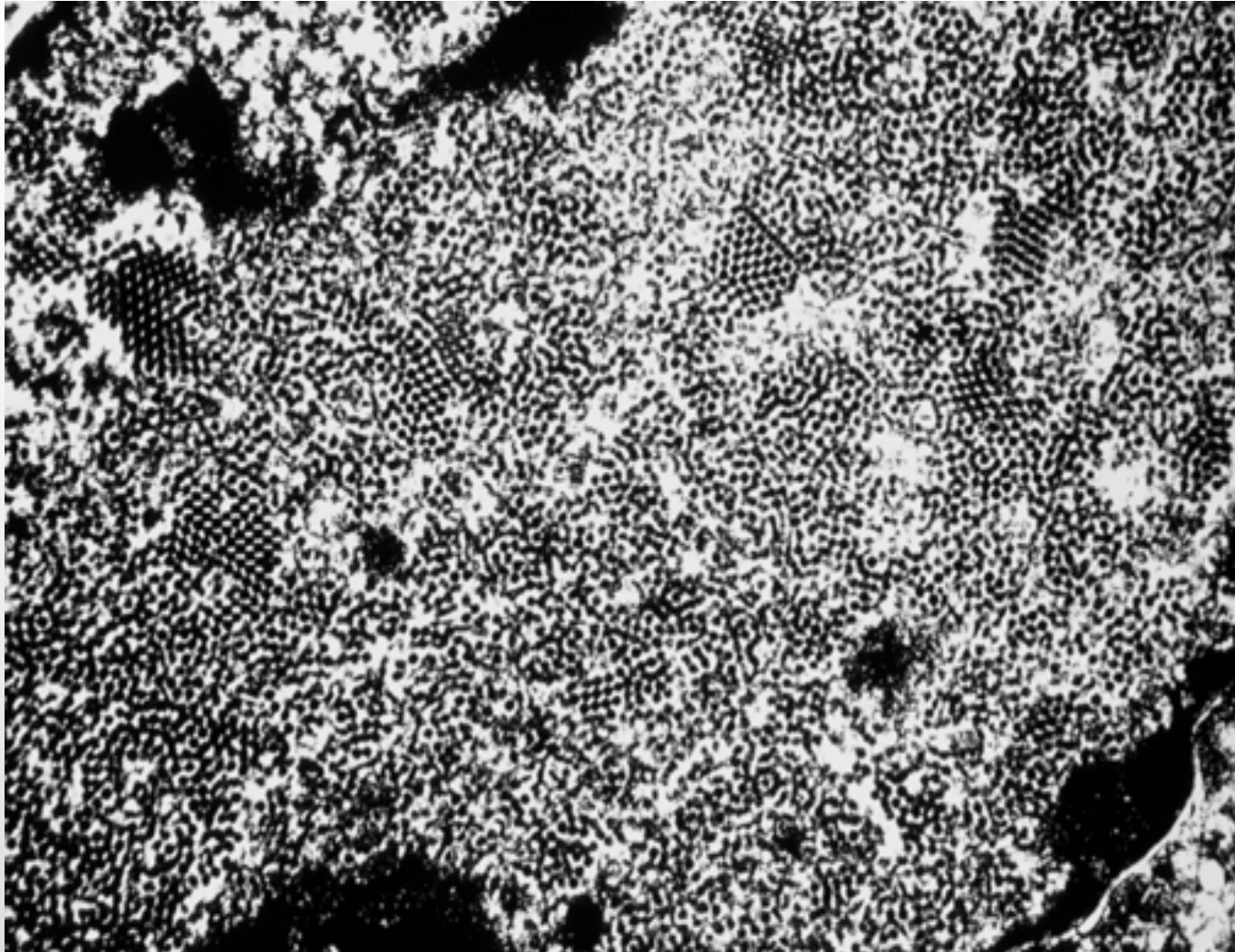
### Diagnostic Tirade:

- Demyelination
- Abnormal oligodendroglial nuclei
- Giant astrocytes



# Progressive Multifocal Leukoencephalopathy - PML

EM - JC virus particles in an oligodendrocyte nucleus



# MS: The brain as an auto-antigen

- Although neural-immune interactions can often serve to promote healing and recovery after insult, aberrant or unchecked inflammation can produce detrimental effects in the CNS.
- One such example is the autoimmune demyelinating disorder, multiple sclerosis.