

Neuroinflammation in CNS disorders

New entry points for biomarkers?

NeuroInflammation

Heat

Swelling

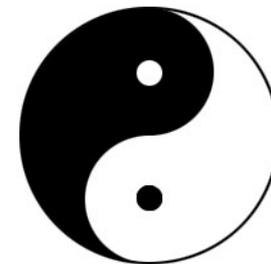
Redness

Pain



“A protective attempt by an organism to remove an injurious stimulus and initiate the healing process for the tissue.”

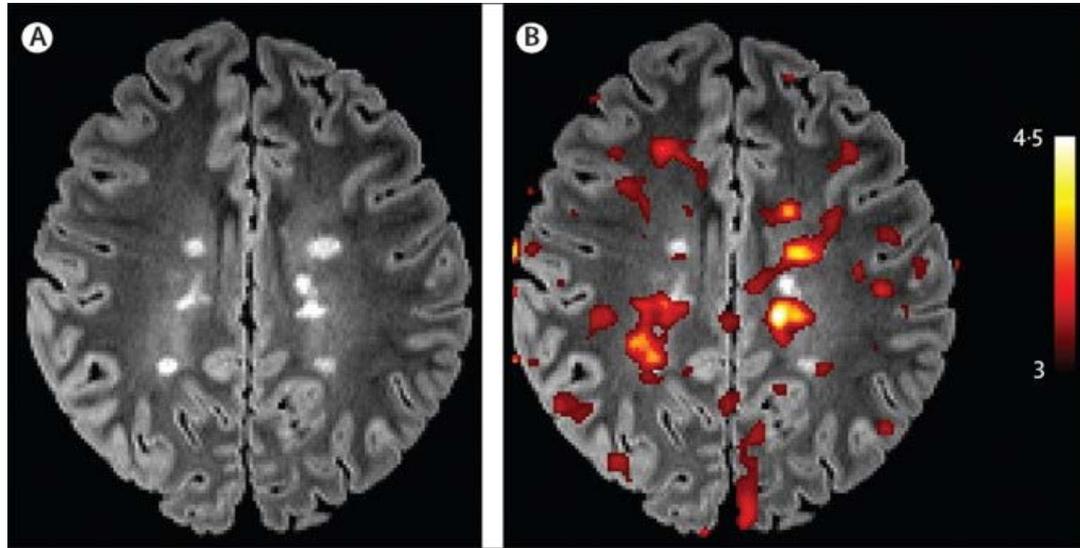
- Increased blood vessel permeability
- Invasion of circulating immune cells
- Release of inflammatory mediators
- Loss of trophic support



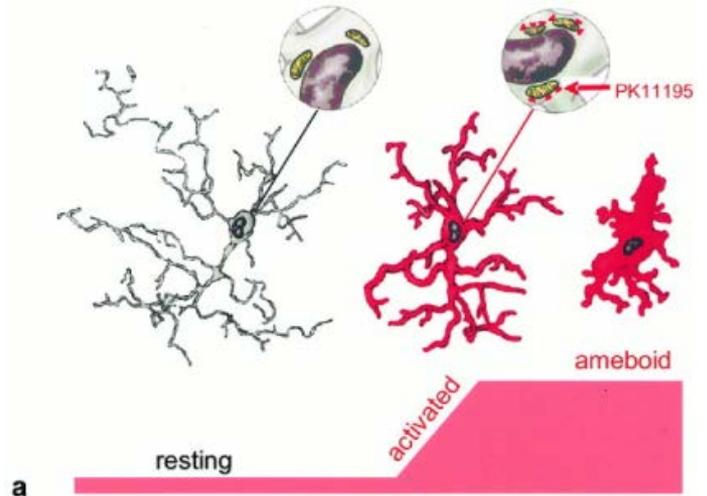
Chronic neuroinflammation is detrimental

- The prototypical neuroinflammatory disease: Multiple sclerosis

TSPO ligands have been used to measure “neuroinflammation” in MS

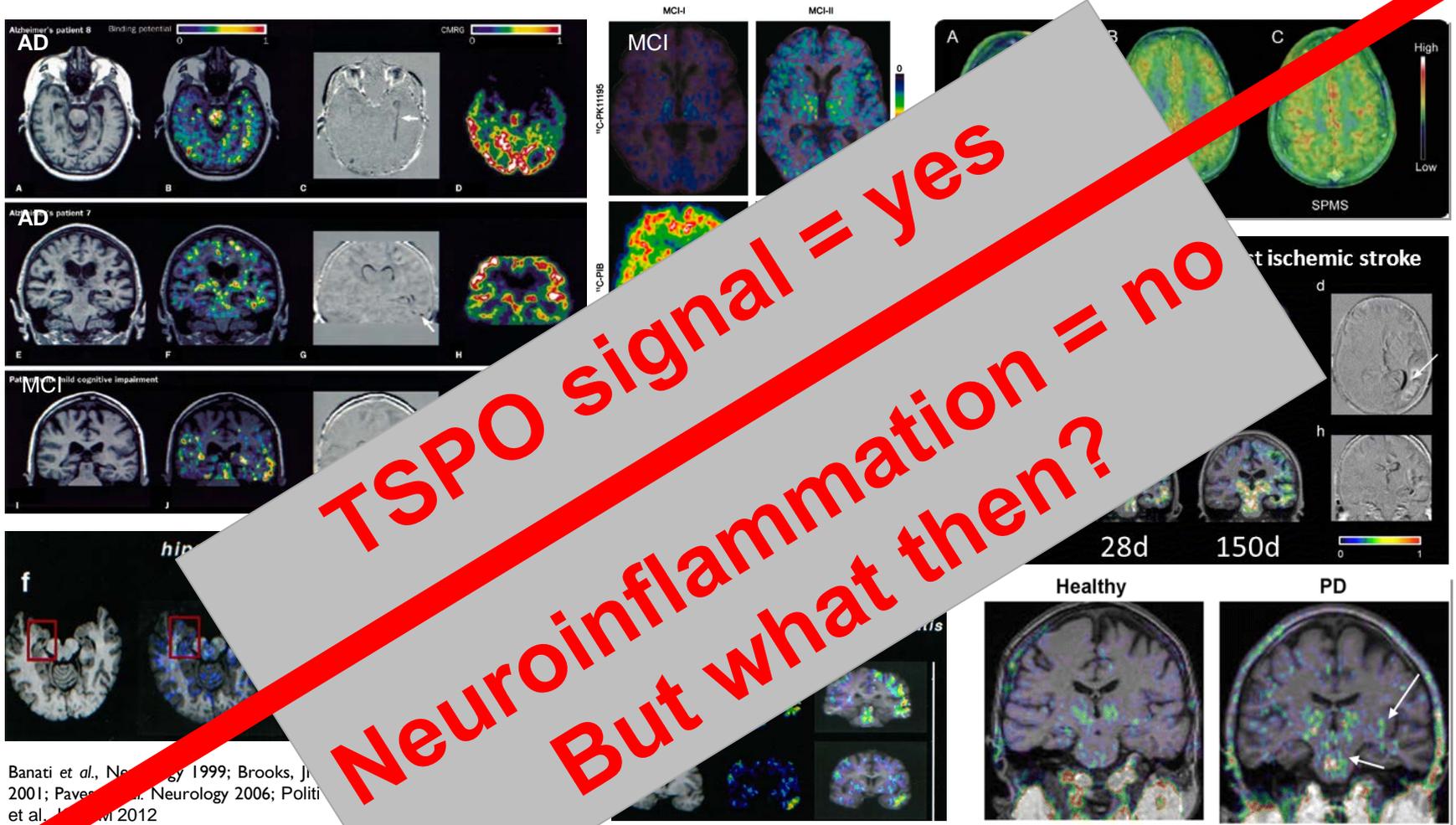


(A) FLAIR axial MRI (B) PBR111 PET TSPO image co-registered with the FLAIR image, in relapsing-remitting multiple sclerosis



- TSPO18 (translocator protein of 18 kDa), aka Peripheral Benzodiazepine Receptor (PBR)
 - located in outer mitochondrial membrane, cholesterol transport, Immunomodulation
- 150+ publications with PK11195 as “reactive microglia marker” = validated (?)
- **Are all diseases with TSPO signal “neuroinflammatory”?**

NI imaging of neurological diseases PK11195 PET



TSPO signal = yes

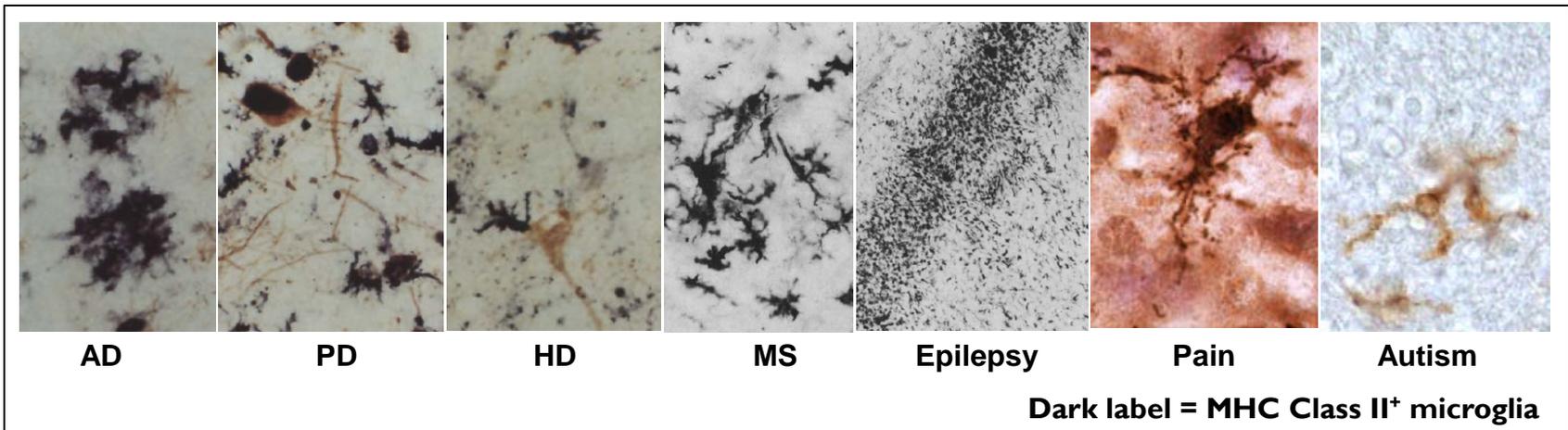
Neuroinflammation = no

But what then?

Banati et al., Neurology 1999; Brooks, Jr. et al., JAMA 2001; Pavese et al., Neurology 2006; Politis et al., JAMA 2012

Microglia – textbook view

- Main class of immune cells in the CNS (~10% of all cells)
 - Defend against damage or infection
 - Modulate neuronal signaling (e.g. prune synapses)
 - Mesodermal origin, derived from primitive macrophages (yolksack), PU.1⁺
- Chronic microglial “activation” found in almost all CNS disorders



- Pathological activation of microglia may contribute to etiology and progression of various neurological disorders
- Main mediators of “neuroinflammation”

Microglia activation – what is it?

- Pick and choose, free for all, rubber band term, mixed basket of misunderstandings

CD11b/OX-42/ITG α_m // CR3bi/Mac-1/ITG $\alpha_m\beta_2$

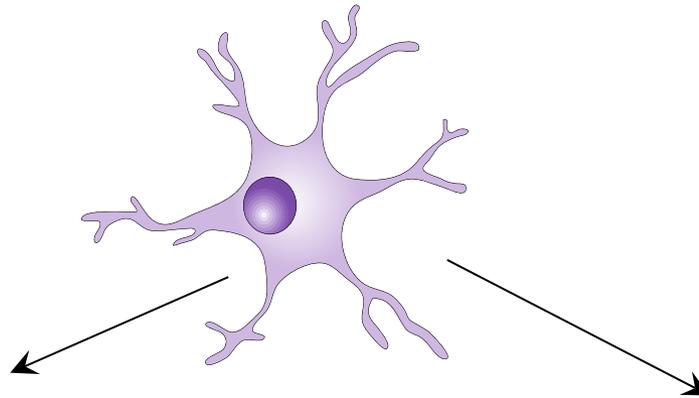
- activation \neq inflammation
- morphology \neq physiology
- ramified \neq resting
- amoeboid \neq activated
- cytokine release
- migration
- proliferation
- phagocytosis
- Need for operational definition of what we talk about

Microglia – the myeloid cell of the CNS: a potential biomarker view

Homeostatic

- Synaptic pruning
- Phagocytosis

- Growth factors



Neurotoxic

Responding

Repair

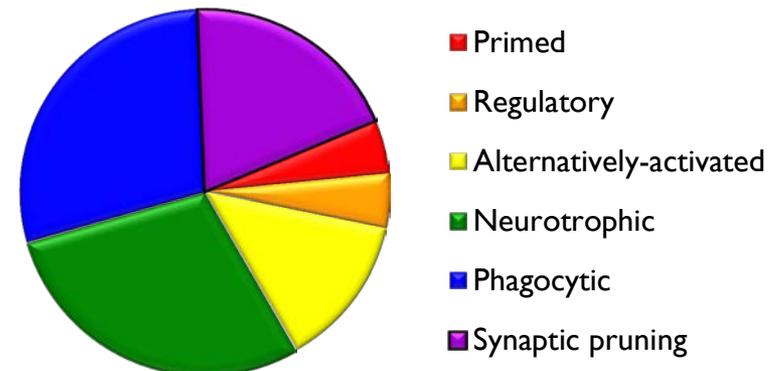
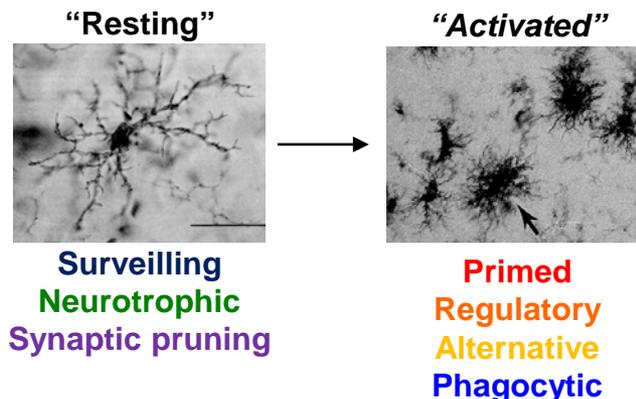
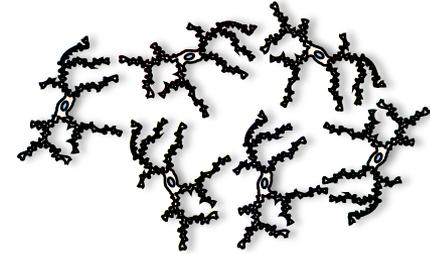
- ROS
- Pro-inflammatory mediators
- Excitatory Amino Acids

- Migration
- ECM modification
- Internalization

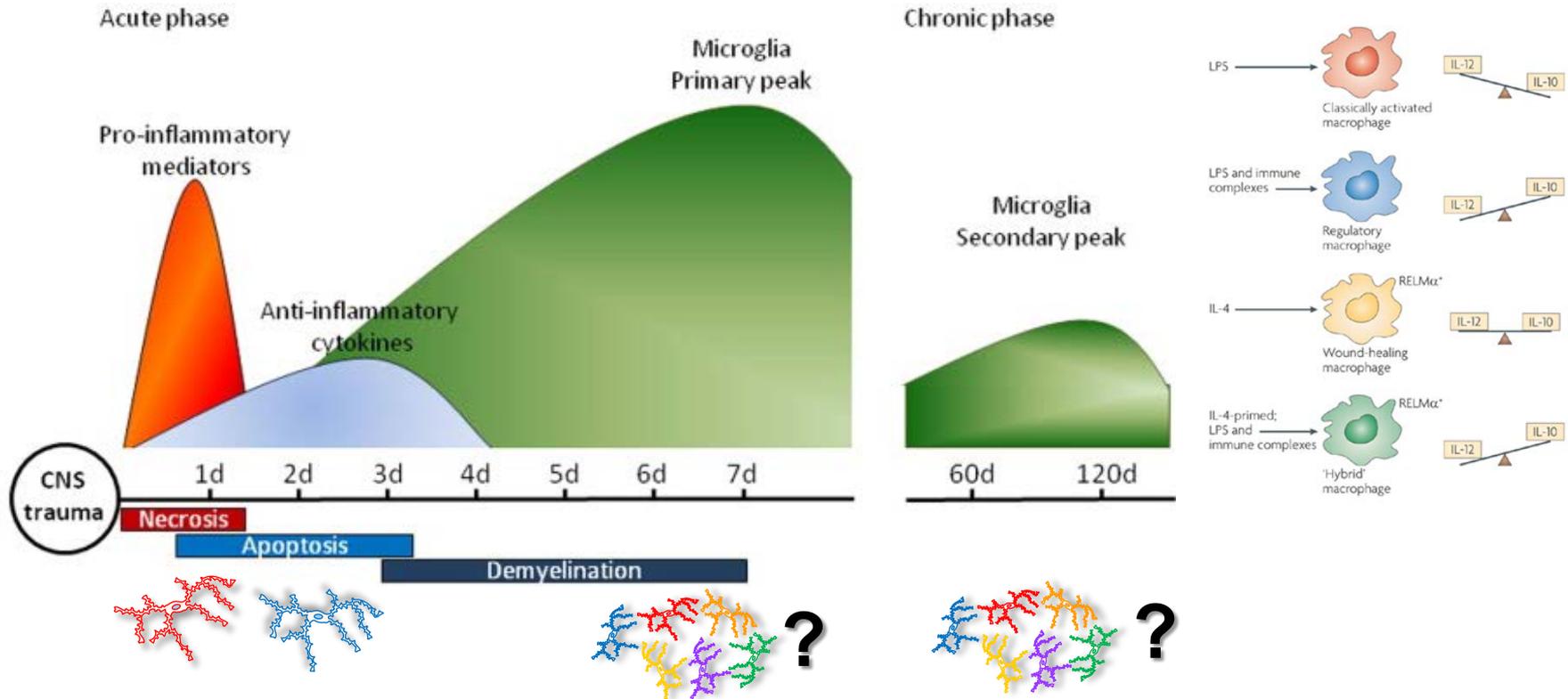
- Neuroprotective factors
- Anti-inflammatory mediators
- Pro-angiogenic factors

Microglia phenotypes - 2017

- Microglia may look alike, but ...
- Microglia are highly plastic cells
- Disease microenvironments create different phenotypes
- Microglia release cytokines, prostaglandins, microvesicles, miRNAs
- What are the consequences for a “sum” biomarker (CDF, PET)?
- Microglia “activation” needs to be operationally defined
- Can we identify biomarkers for different phenotypes?

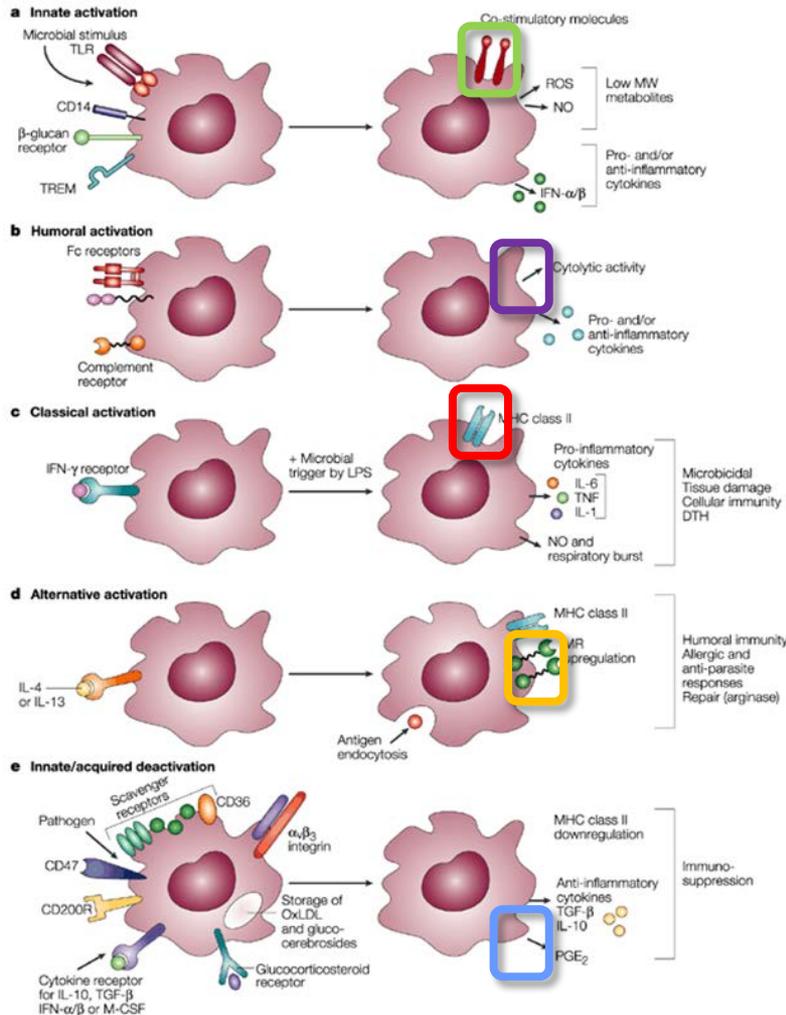


Is timing important for biomarkers?



- Which microglia phenotype(s) drive primary and secondary peak?
- What are the potential detrimental or protective functions?
- What are the consequences for biomarkers?

Microglia phenotype imaging

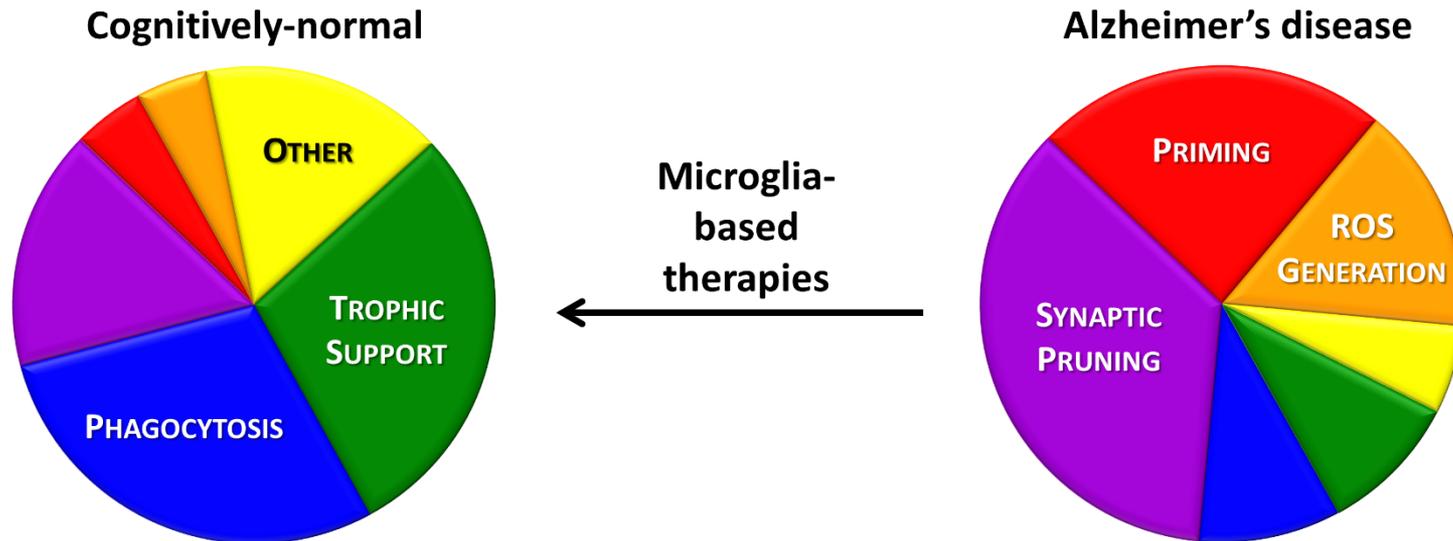


- Marker for different phenotypes?
- Better correlation with specific diseases?
- Patient segmentation?

This is not about M1/M2. Different markers may be needed to capture the different “flavors” of microglial states.

Affecting microglia phenotypes

Hypothetical spectrum of microglial phenotypes

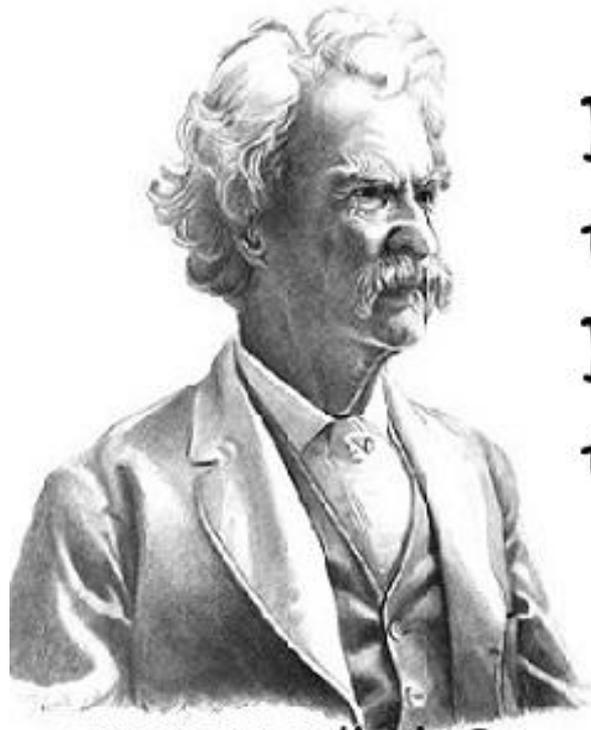


- Microglia-based interventions should preferably target specific phenotype(s)
- Specific interventions might allow for more specific biomarkers
- Interventions should spare beneficial phenotypes

More in Sessions 1, 2, and 3

- S1: The Acute to Chronic Neuroinflammation Continuum
- S2: Neuroimaging biomarkers - current initiatives and opportunities
 - What are the (unique) features of neuroinflammation in acute diseases such as trauma and stroke?
 - What are the consequences and needs for biomarkers in an acute setting?
 - How are slowly proceeding neurodegenerative diseases defined?
 - Why do different disease etiologies and overtly different pathophysiologies give rise to the same TSPO signal?
- S3: CSF and other Fluid Biomarkers of Neuroinflammation
 - Are fluid biomarkers useful in identifying neuroinflammation in patients, or defining endophenotypes?
 - Do peripheral biomarkers reflect neuroinflammation?
- Do we need to think about biomarkers for disease specific glial “phenotypes?”

The end



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It ain't what you don't know
that gets you into trouble.
It's what you know for sure
that just ain't so.

Mark Twain