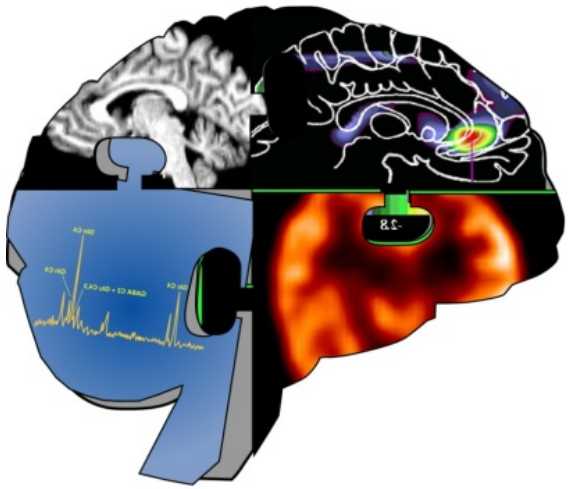
Positron Emission Tomography of Translocator Protein 18 kDa (TSPO) as a Biomarker of Neuroinflammation in Dementia and in Depression



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NIMH

Translocator Protein (TSPO)
aka Peripheral Benzodiazepine Receptor

1. Mitochondrial protein transports cholesterol to enzyme that synthesizes pregnenolone

2. Highly expressed in macrophages, activated microglia, and reactive astrocytes

3. Putative biomarker for activation of the immune system in brain: ‘neuroinflammation’

Major Findings

Alzheimer's Disease

1) TSPO binding increased in Alzheimer's disease but not mild cognitive impairment
2) Increased TSPO binding binding correlates with disease severity (cross sectional study) and with disease progression (longitudinal study)

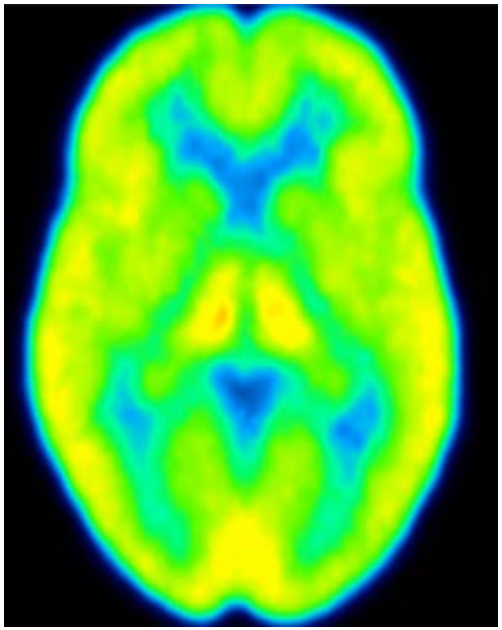
Major Depressive Episode

1) TSPO binding increased in unmedicated patients
2) TSPO binding not changed in medicated patients

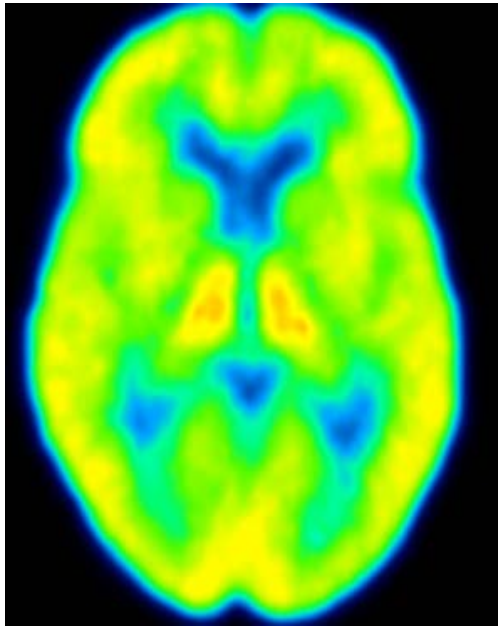
TSPO imaging in Alzheimer's disease

- Neuroinflammation a proposed contributor to Alzheimer's disease pathology
  - Unclear if early or late phenomenon
- Prior TSPO PET studies have shown conflicting results in AD and mild cognitive impairment
- PBR28 an improved TSPO radioligand
  - Genotype correction expected to detect differences in TSPO density in AD, MCI, and controls

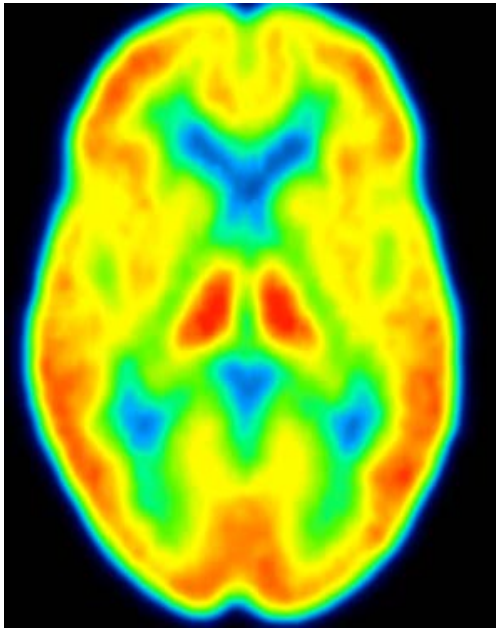
Increased TSPO in Alzheimer's Disease: Compared to Controls and MCI



Control



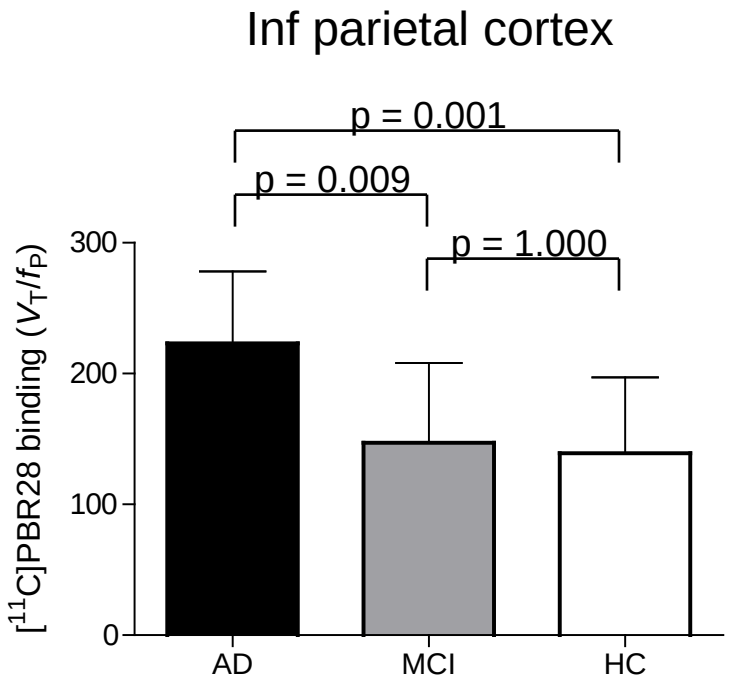
Mild Cognitive Impairment

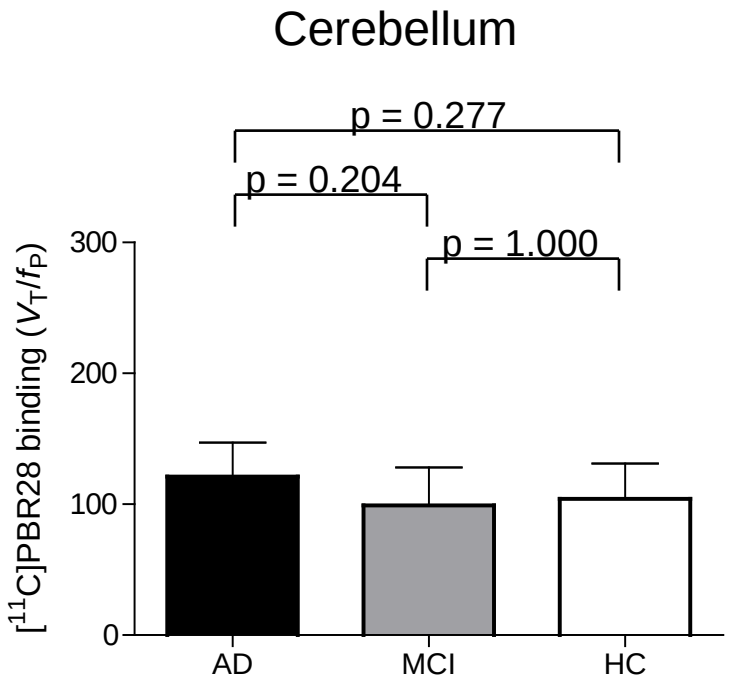


Alzheimer

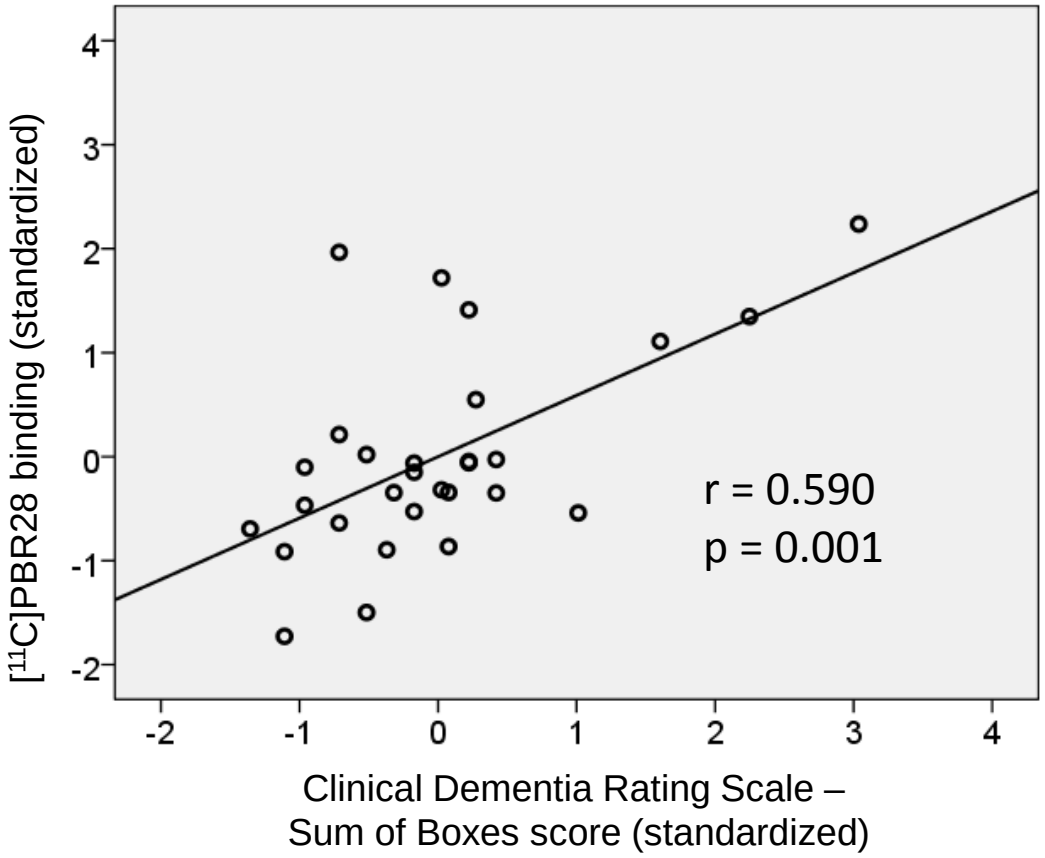
Kreisl, Brain. 2013

[^{11}C]PBR28 binding greater in Alzheimer's in target regions after correcting for TSPO genotype





[^{11}C]PBR28 binding correlates with clinical severity across Alzheimer's disease spectrum

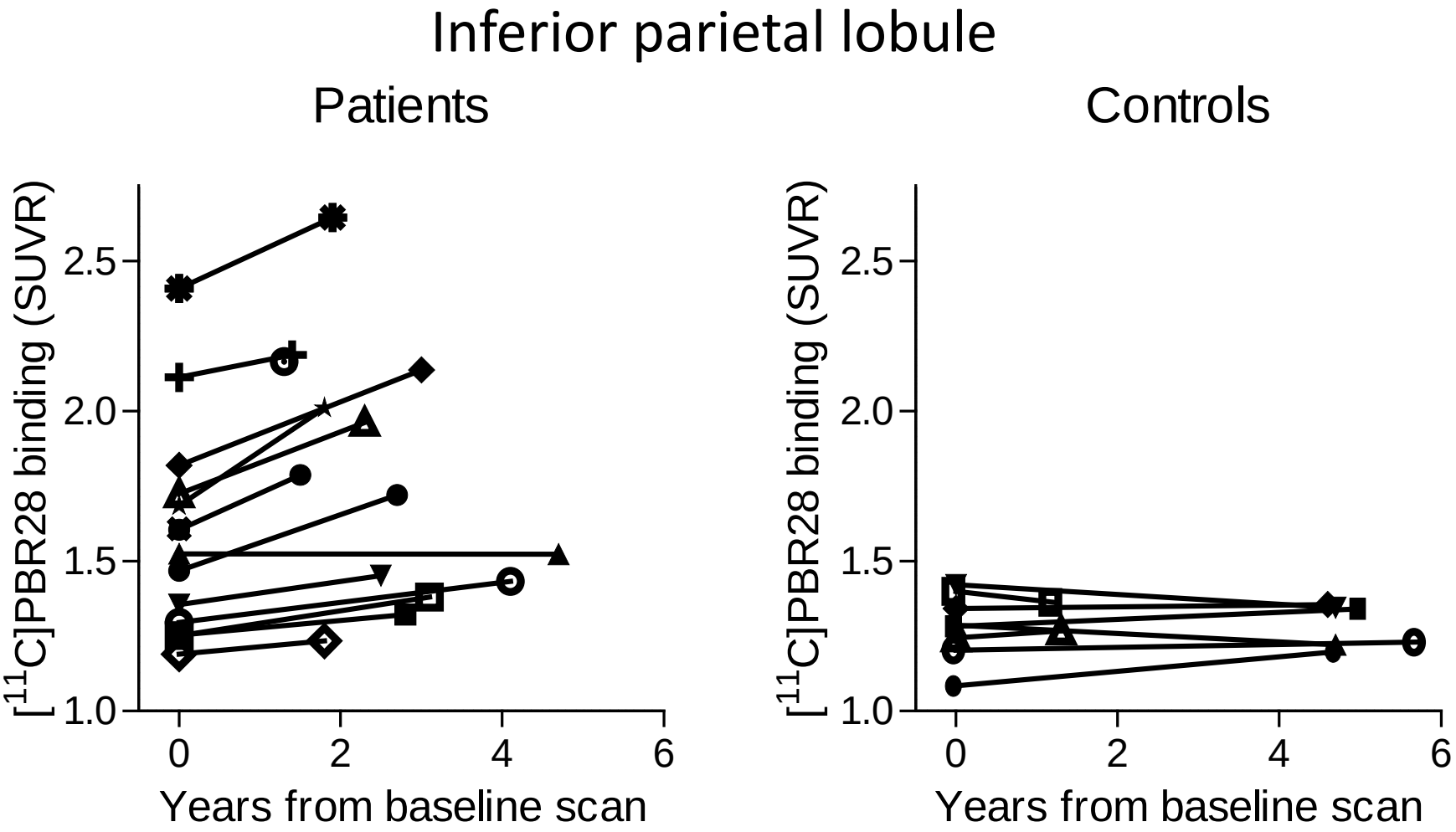


Longitudinal [^{11}C]PBR28 study

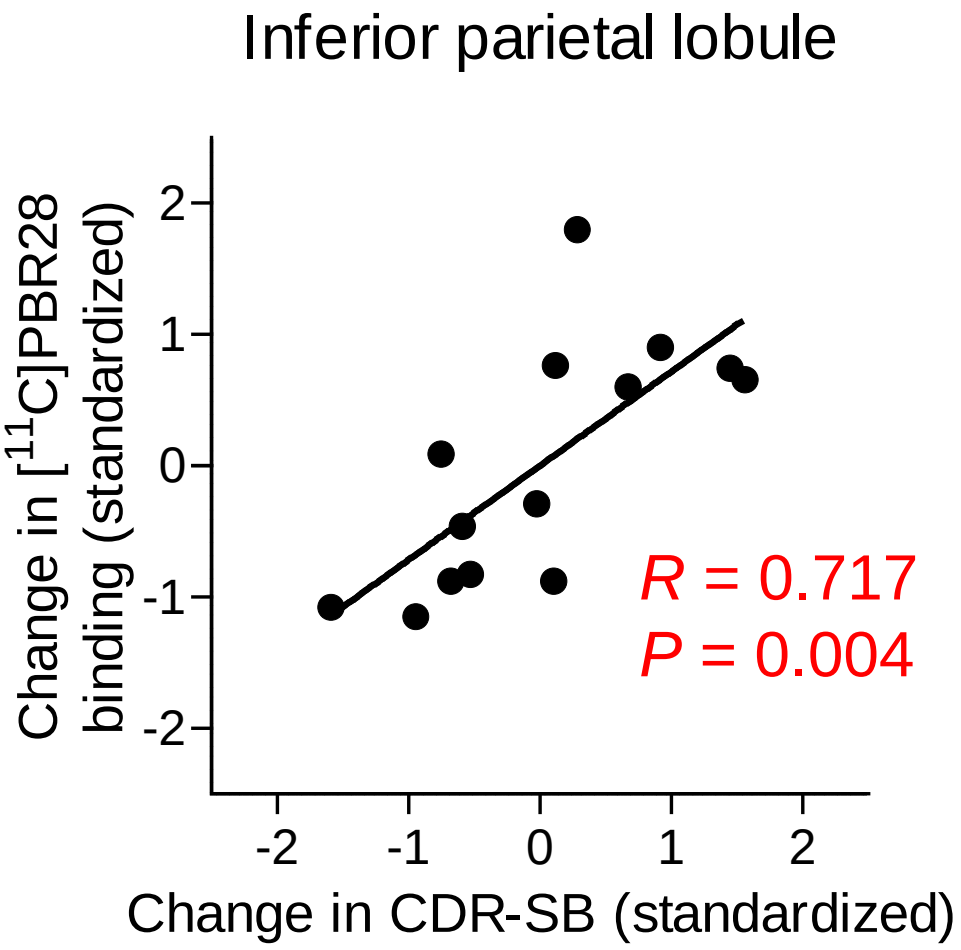
- Objective: Determine if TSPO binding increases during progression of AD and normal aging

- Methods:
  - 14 patients (5 AD + 9 MCI at baseline) and 8 controls returned for follow up
  - [^{11}C]PBR28 data analyzed using cerebellar ratio method (60 – 90 min scan data)
  - Image data analyzed with correction for partial volume effects

Results: [^{11}C]PBR28 binding increased in patients but not controls



Increased [^{11}C]PBR28 binding correlates with increased clinical severity



Conclusions from Alzheimer's disease study

- Cross-sectional study: Neuroinflammation occurs after conversion of MCI to AD and worsens with disease progression.

  Biomarker of disease severity

- Longitudinal study: [^{11}C]PBR28 increases in AD but not in controls and correlates with disease progression.

  Biomarker of disease progression

TSPO Imaging in Major Depressive Episode

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Disclosure

- Supported by NIMH and Janssen / J&J

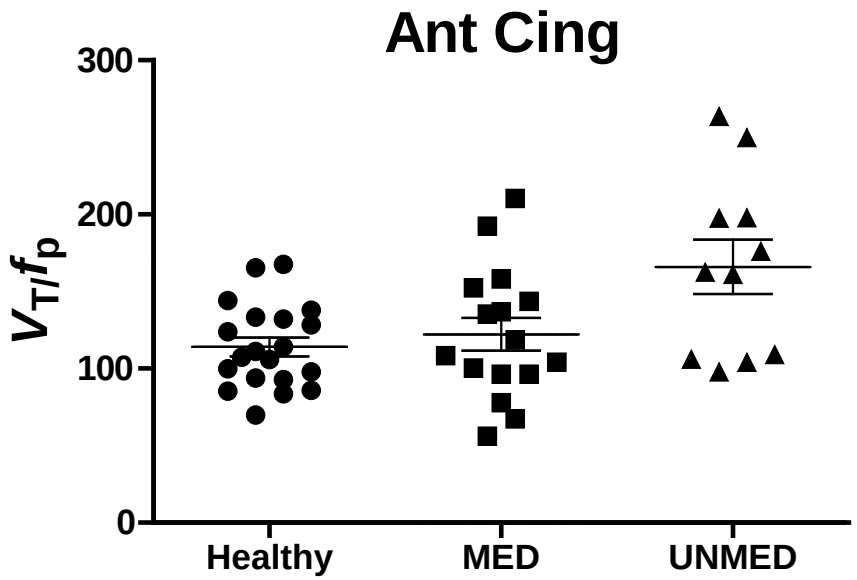
Study Aims

- To evaluate TSPO binding in MDE patients compared to healthy volunteers without a history of depression.

- To investigate any effects of medication on TSPO binding: half of MDE patients were on antidepressants.

TSPO binding in anterior cingulate was increased in unmedicated MDE patients

	V_T/f_p
Healthy	114 ± 27
Medicated MDE	122 ± 42
Unmedicated MDE	166 ± 58



Healthy vs. Unmed MDE	p = 0.002
Med MDE vs. Unmed MDE	p = 0.033
Healthy vs. Med MDE	not significant

In unmedicated patients, TSPO binding was increased by 31% compared to healthy controls and by 27% compared to medicated patients.

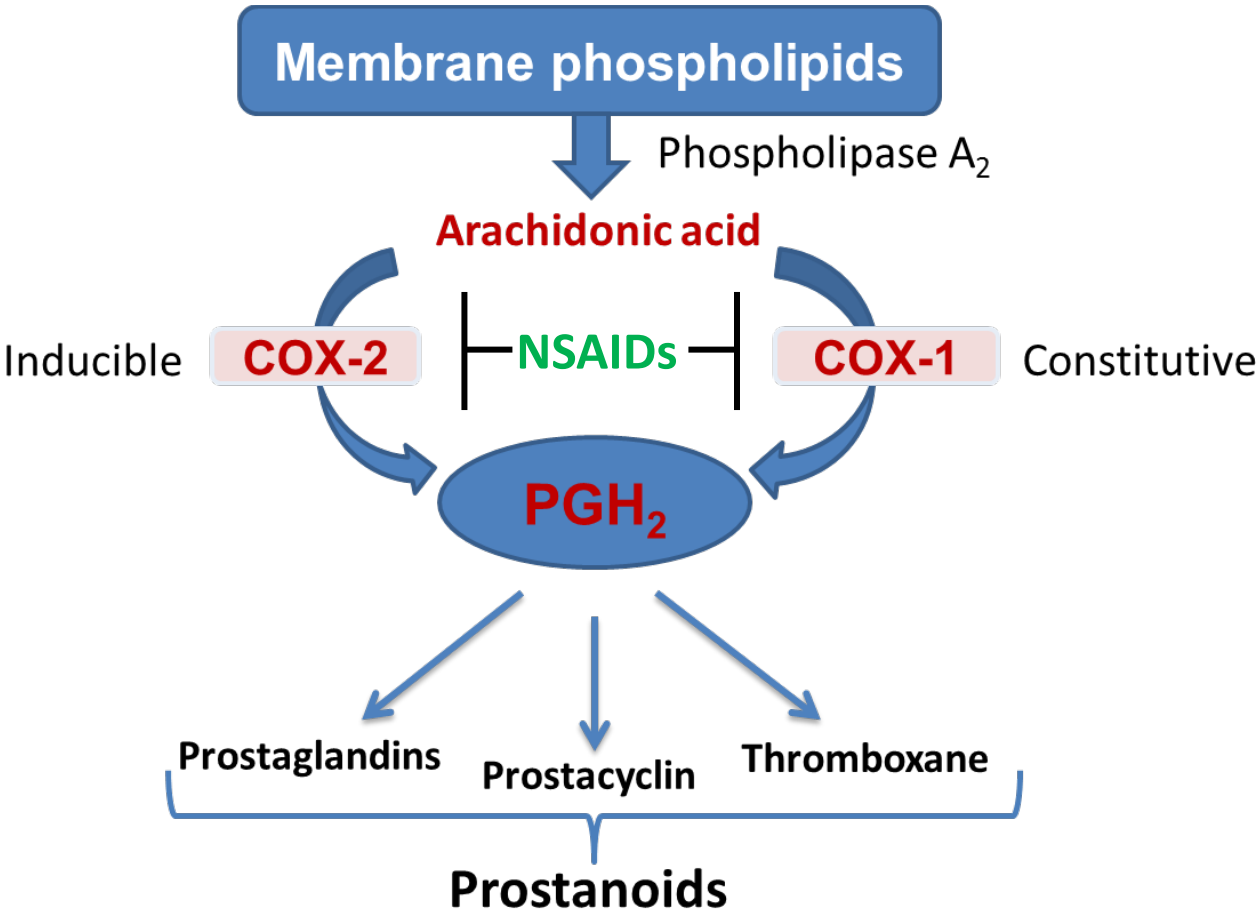
Major Findings

- TSPO binding showed widespread increase in unmedicated MDE patients compared to controls
  - Replicates findings of Meyer et al. (2015)
- But medicated MDE showed normal TSPO density
  - SSRI may modulate this PET inflammatory biomarker
- Need a longitudinal study of patients before and after treatment
  - Two treatments: SSRI and anti-inflammatory

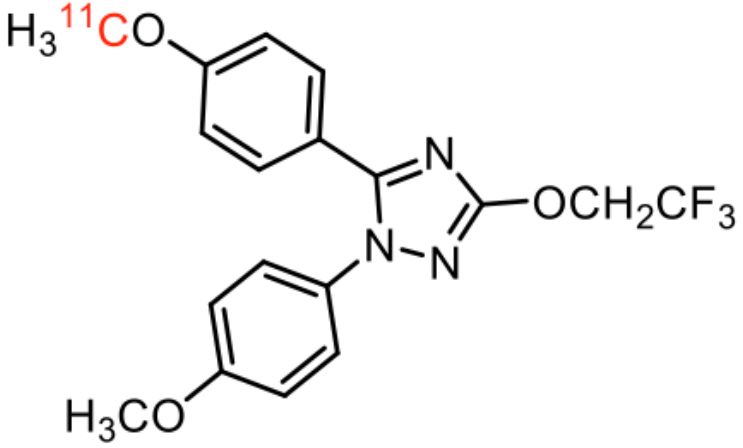
Summary

1. TSPO (translocator protein): marker of inflammation: activated microglia, reactive astrocytes, and macrophages
2. Alzheimer's disease: Increased TSPO binding correlates with disease severity (cross sectional) and with disease progression (longitudinal).
3. Major Depressive Episode: Confirms finding of Meyer et al. (2015) of increased TSPO binding, but also found medication effects
4. How can PET facilitate anti-inflammatory trials in dementia and depression?

The Cyclooxygenase System



^{11}C-PS13: COX-1

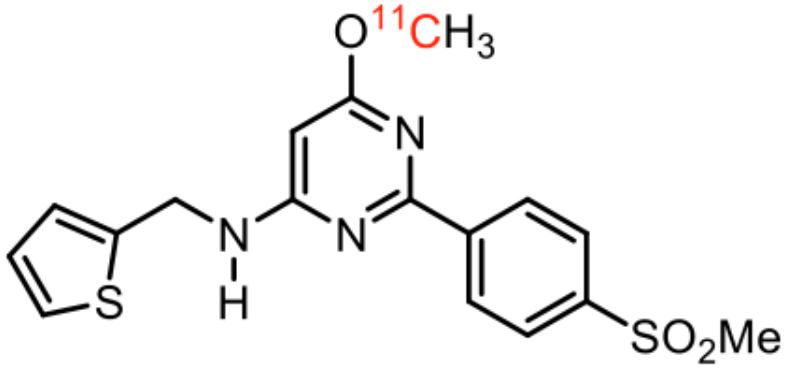


Human Enzyme	IC_{50} (nM)
COX-1	1
COX-2	>1,000

Constitutive

Microglia

^{11}C-MC1: COX-2



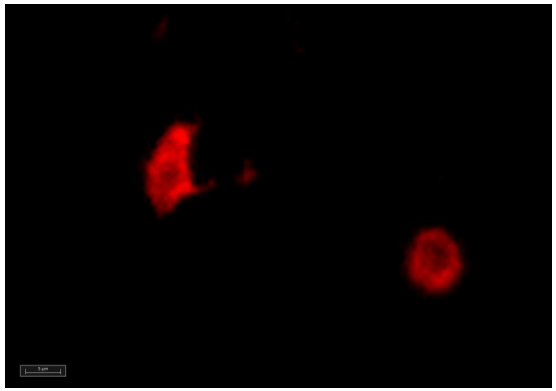
Human Enzyme	IC_{50} (nM)
COX-1	>1,000
COX-2	1

Inducible

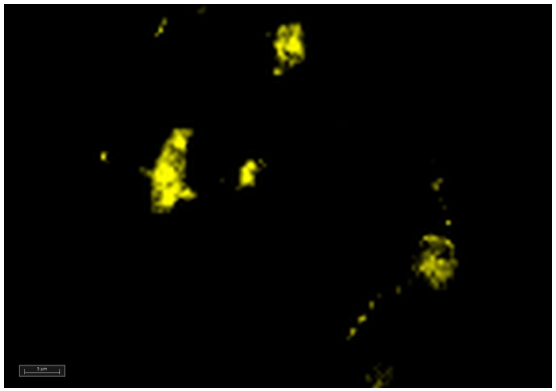
Neurons + Microglia

COX-1 is primarily in microglia: human epilepsy tissue

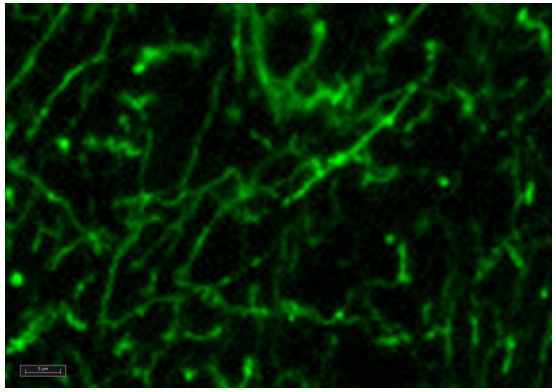
COX-1



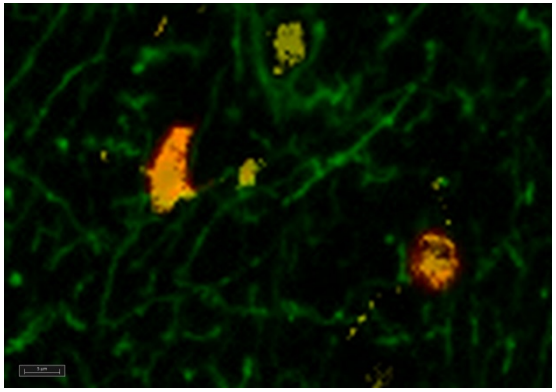
Microglia



Astrocytes

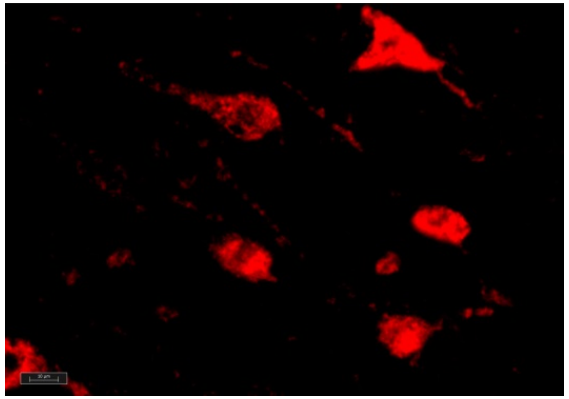


Merge

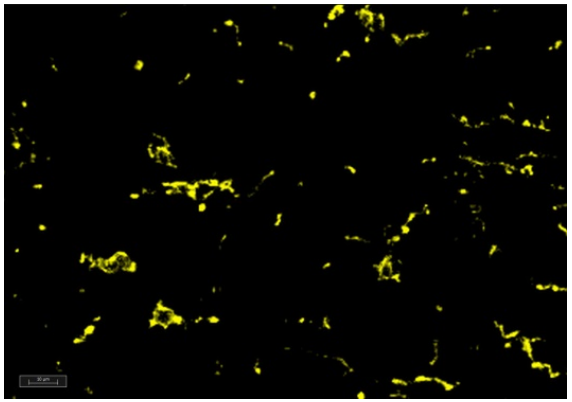


COX-2: neurons and microglia: human epilepsy tissue

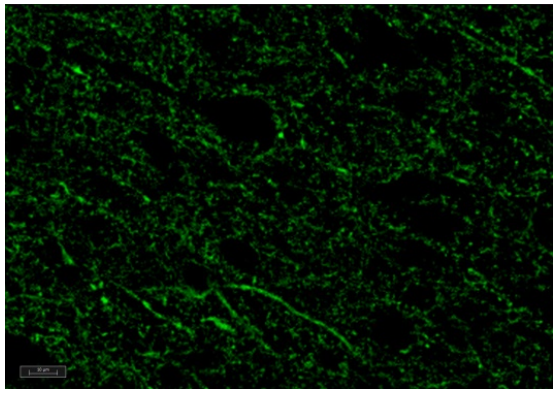
COX-2



Microglia



Astrocytes



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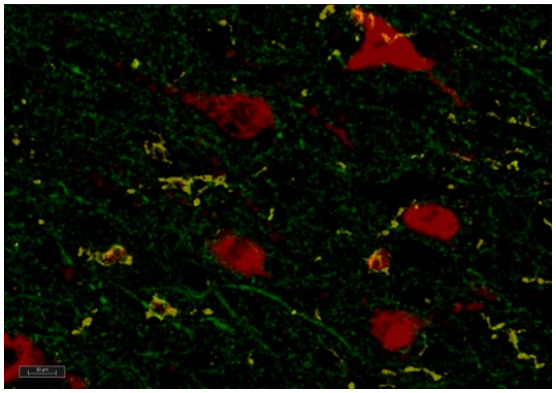
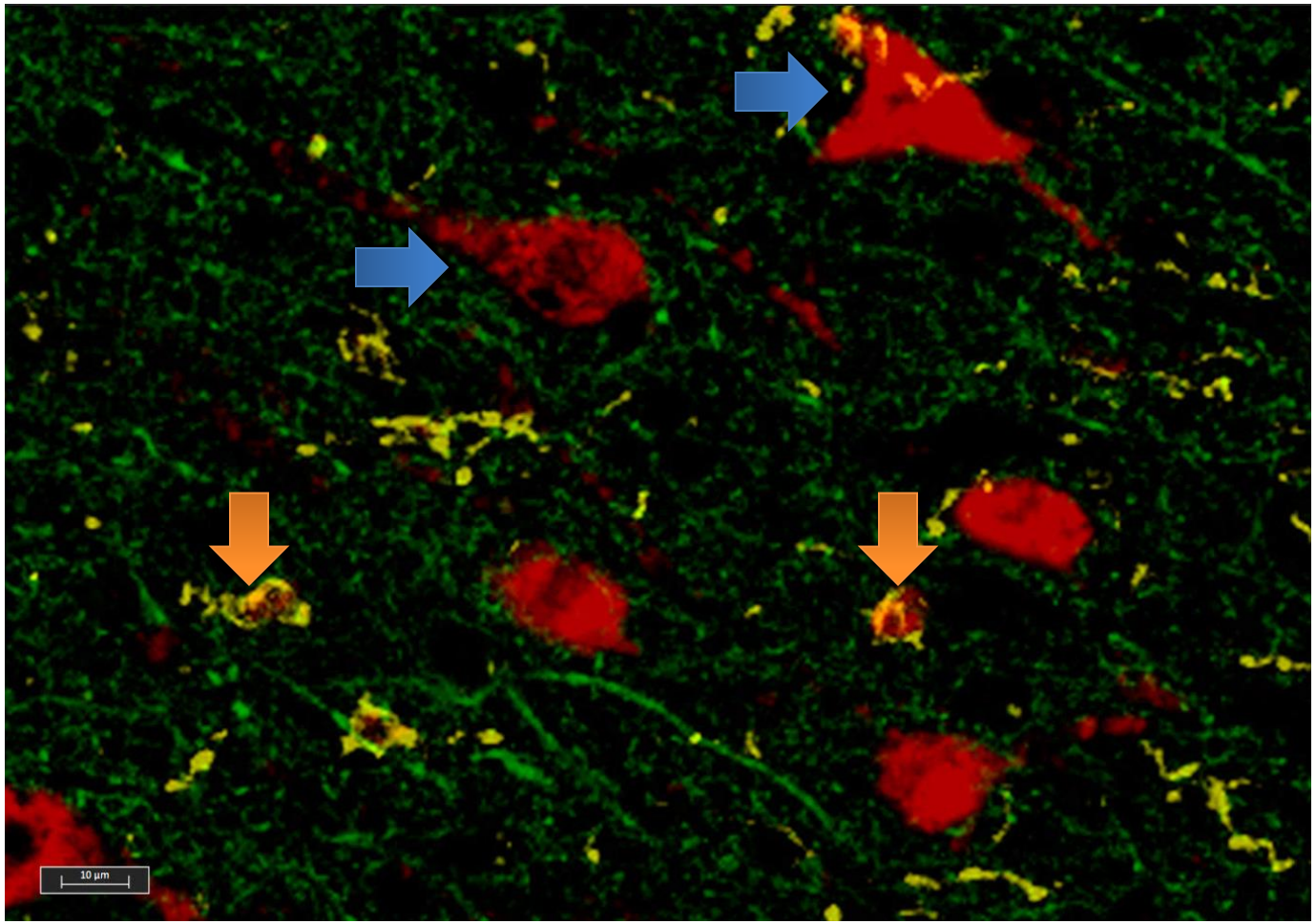
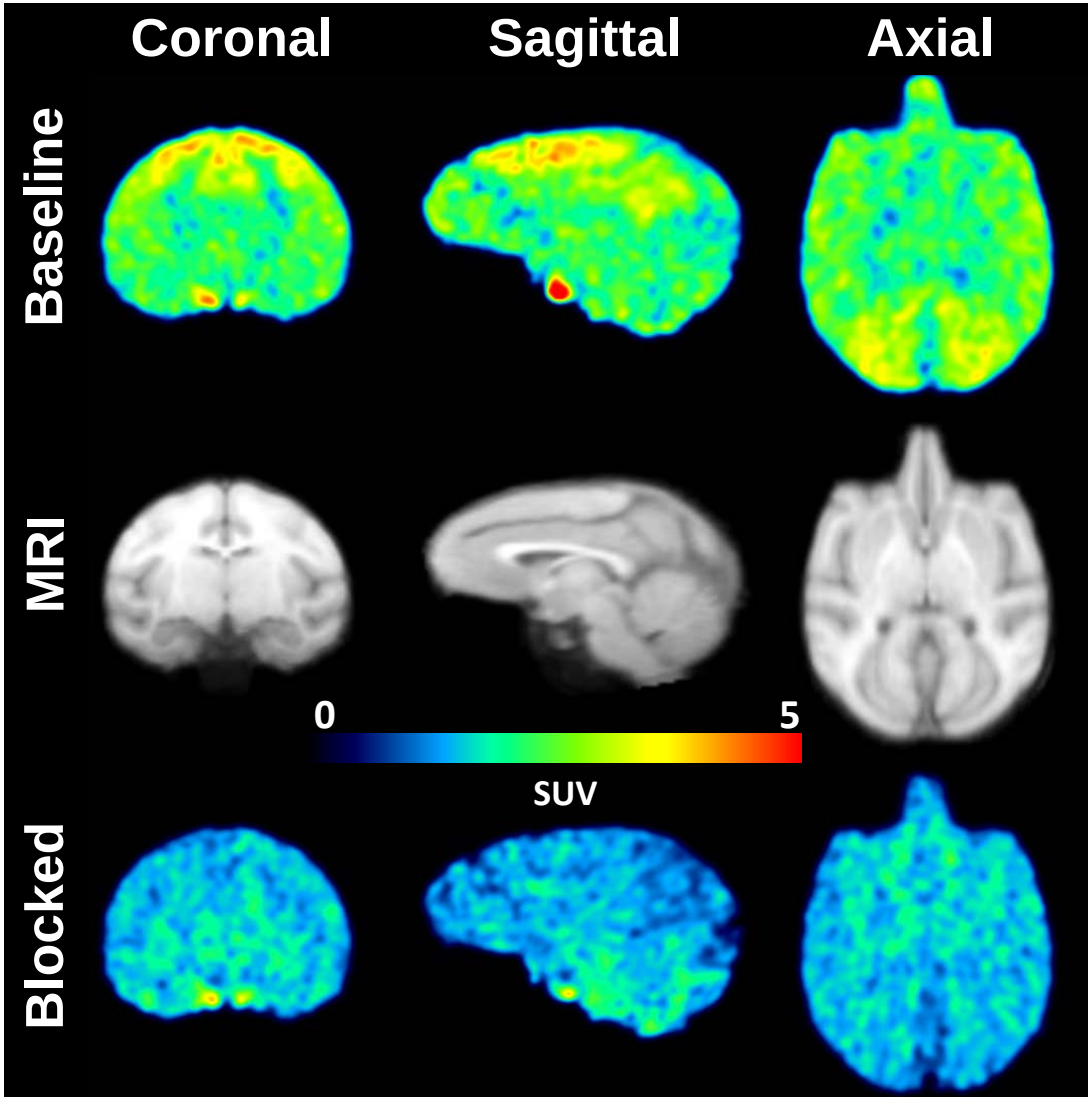


COX-2: neurons and microglia human epilepsy tissue

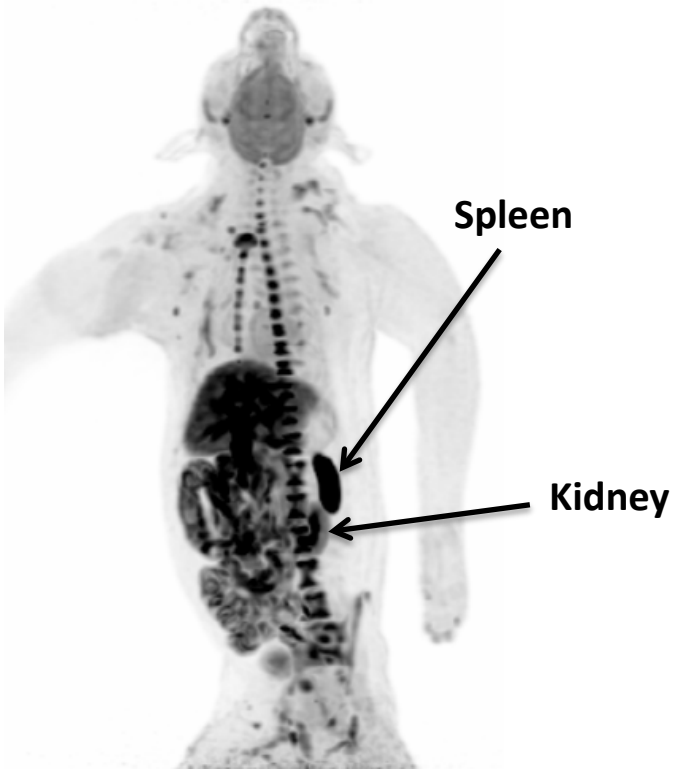


[^{11}C]PS13: Specific binding to COX-1 in monkey brain



[^{11}C]PS13: specific binding to COX-1 in brain, spleen, GI tract, and kidney

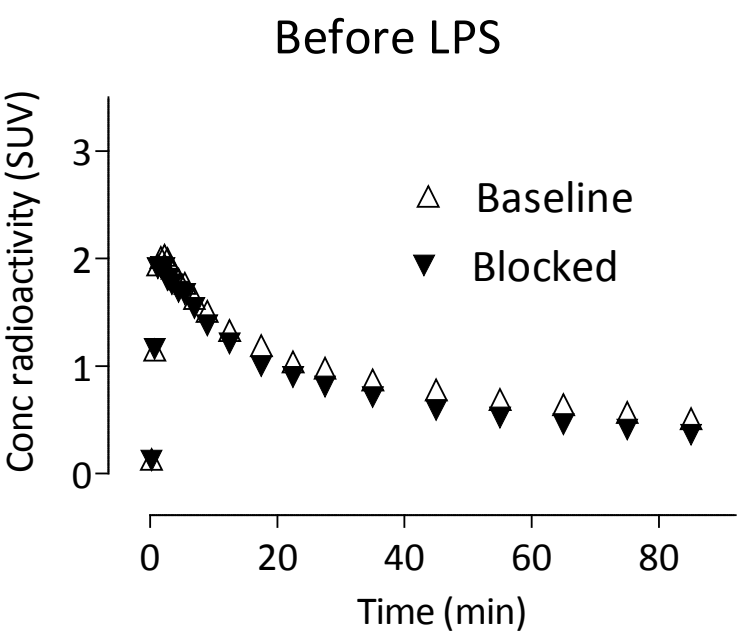
Baseline

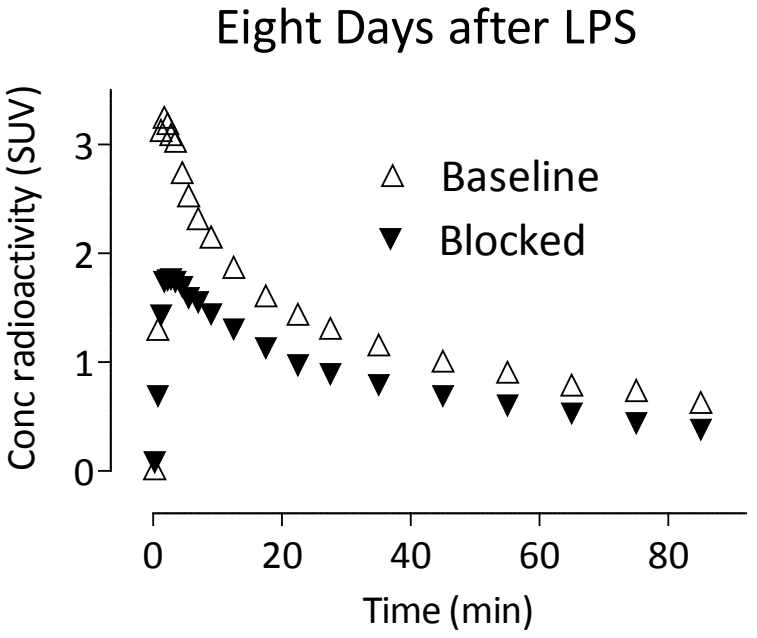


Blocked

PS13 (0.3 mg/kg)

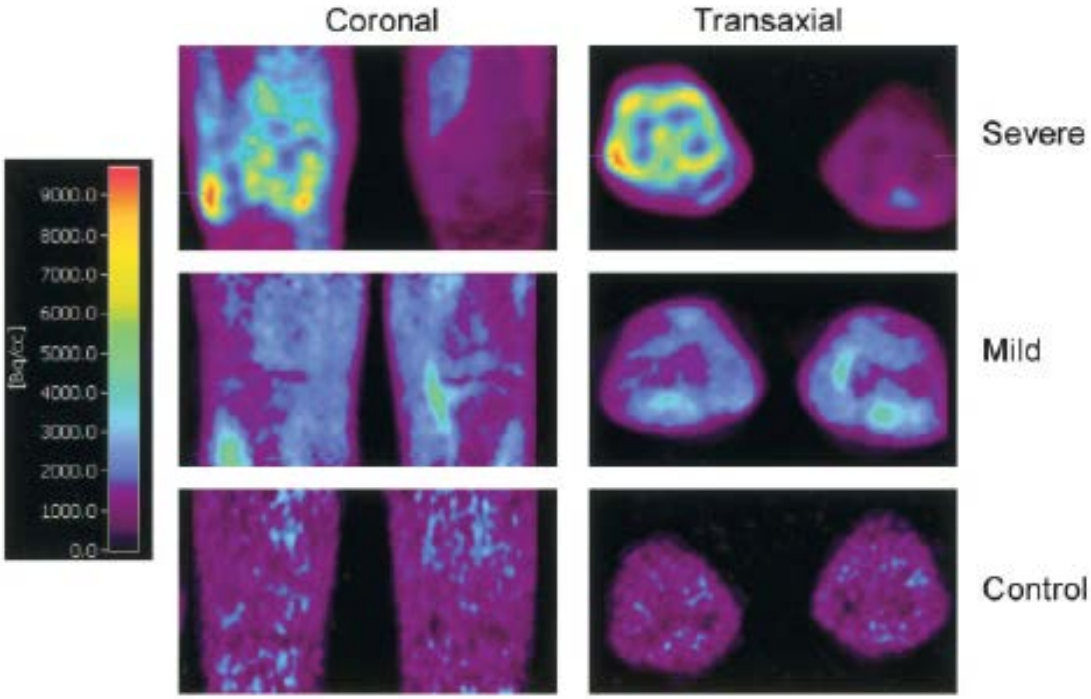
^{11}C-MC1: Specific / Displaceable binding to COX-2 only after inflammogen LPS





Macrophages in Rheumatoid Arthritis (RA)

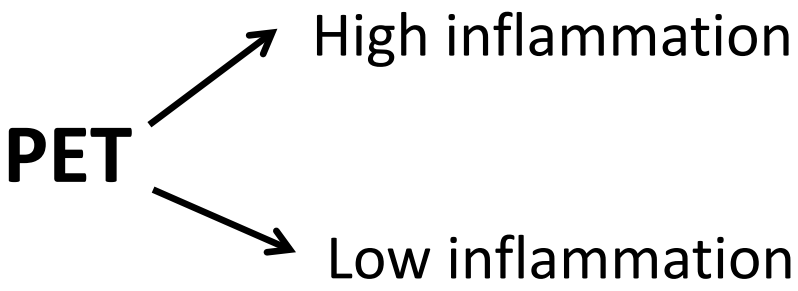
- Macrophages and RA pathogenesis
  - Disease activity is associated with activated macrophages in joint lining
  - All disease-modifying drugs directly or indirectly reduce macrophage number and activity in joint tissues
  - Macrophages produce most of the key cytokines in joint tissues
- PET imaging with older TSPO ligand 11C-]-PK11195 showed increased uptake in RA synovitis that correlated with clinical activity



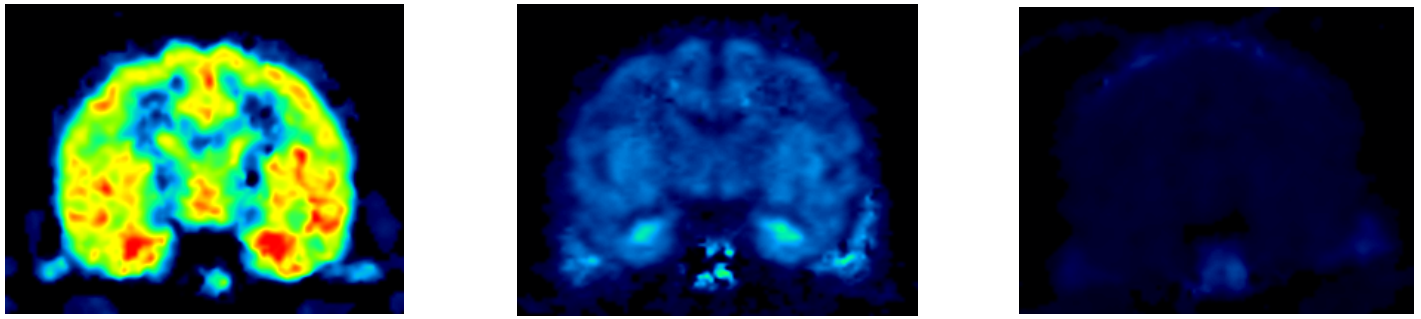
Laken et al..Arthritis & Rheumatism, 2008

Using PET to Guide Treatment Trials

Patient Stratification: Precision Medicine



Drug Delivery to Brain: Target Engagement



No blockade | partial blockade | complete blockade

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Radiochemistry and clinical staff in labs of Pike and Innis