Adaptive immune responses and post-stroke dementia

Stanford Stroke Center

Stanford | Neurosciences Institute

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Stroke

- 2nd leading cause of death worldwide, 5th in US
- 800,000 strokes/year in the US, 4.6 million survivors alive now
- A leading cause of long-term disability in the US

Heart Disease and Stroke Statistics—2013 Update
Circulation. 2013;127:e6-e245

Stroke Disability

- Among ischemic stroke survivors ≥65 years of age, the following disabilities were observed at 6 months after stroke:

Kelly-Hayes et. al., The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis. 2003;12:119–126.

Stroke Disability

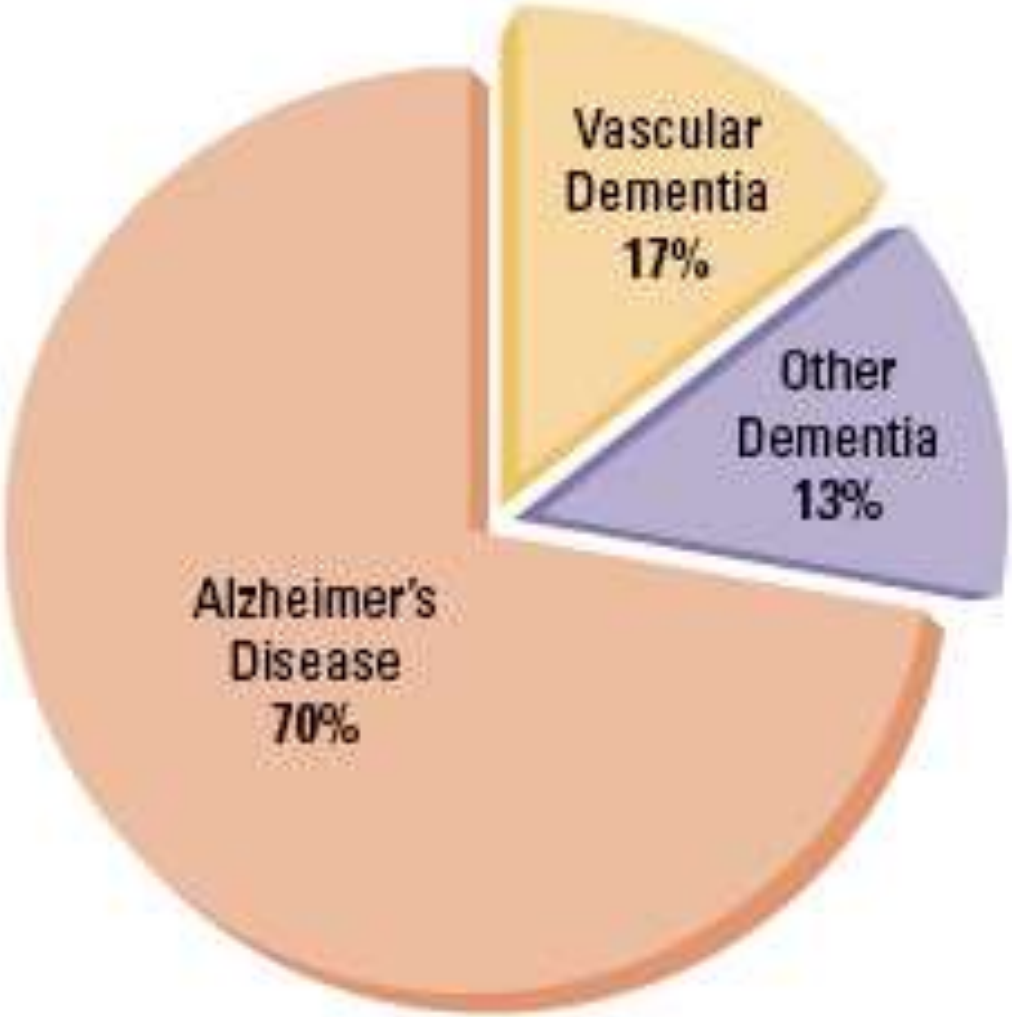
- Among ischemic stroke survivors ≥65 years of age, the following disabilities were observed at 6 months after stroke:
  - 50% had some hemiparesis
  - 30% were unable to walk without some assistance
  - **46% had cognitive deficits**
  - 35% had depressive symptoms
  - 19% had aphasia
  - 26% were institutionalized in a nursing home

Kelly-Hayes et. al., The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis. 2003;12:119–126.

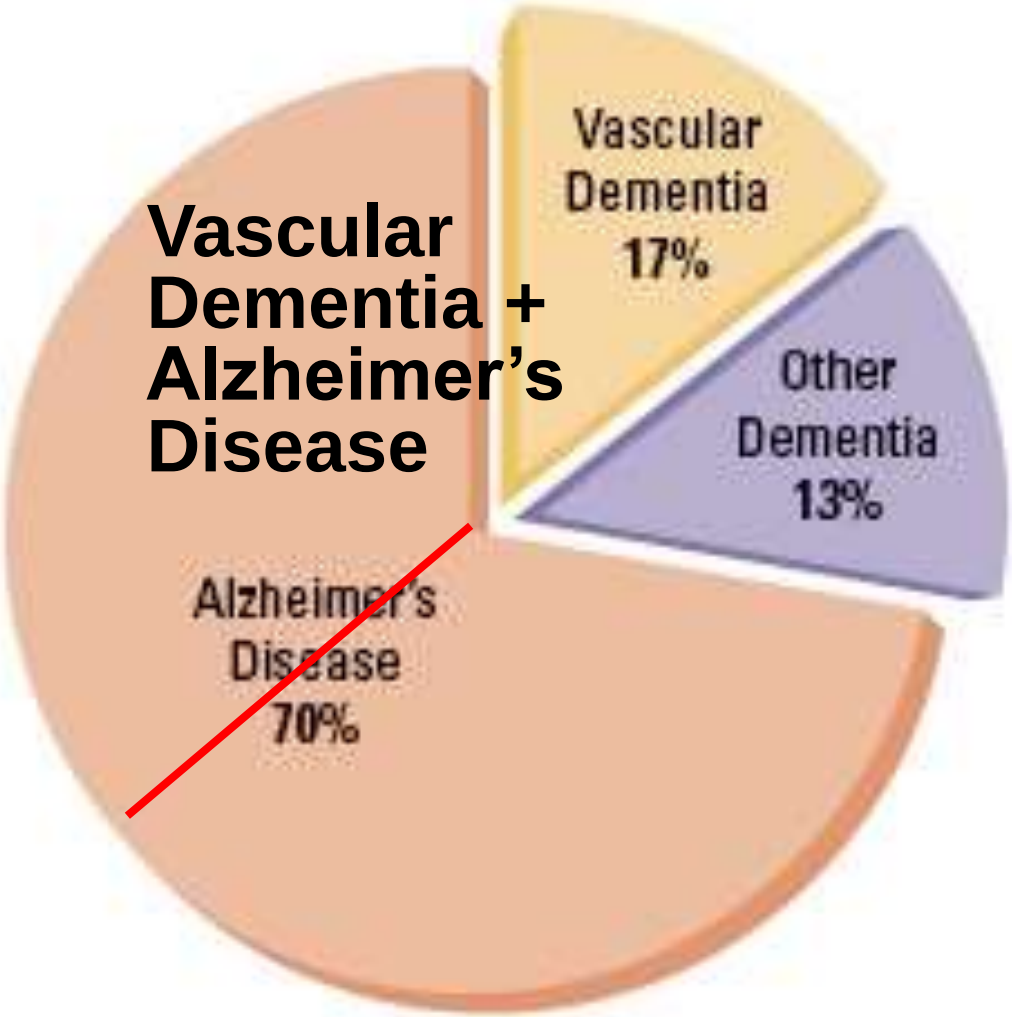
Dementia

- 35.6 million people living with dementia worldwide, expected to nearly double by 2030
- 7.7 million new cases per year, or one every 4 seconds
- Economics – costs $604 billion/year worldwide
- In the US, About 9 million people have dementia, 5 million of these have AD, 2 million vascular dementia.
- **But, up to 50% of those with AD have ischemic pathology on autopsy

Worldwide numbers are from 2010, WHO, http://www.who.int/features/factfiles/dementia/en/
American numbers are from http://www.alzfdn.org/AboutAlzheimers/statistics.html



Source: Plassman, BL; Langa, KM; Fisher, GG; Heeringa, SG; Weir, DR; Ofstedal, MB, et al. "Prevalence of Dementia in the United States: The Aging Demographics, and Memory Study. *Neuroepidemiology* 2007; 29:125-132.[31]



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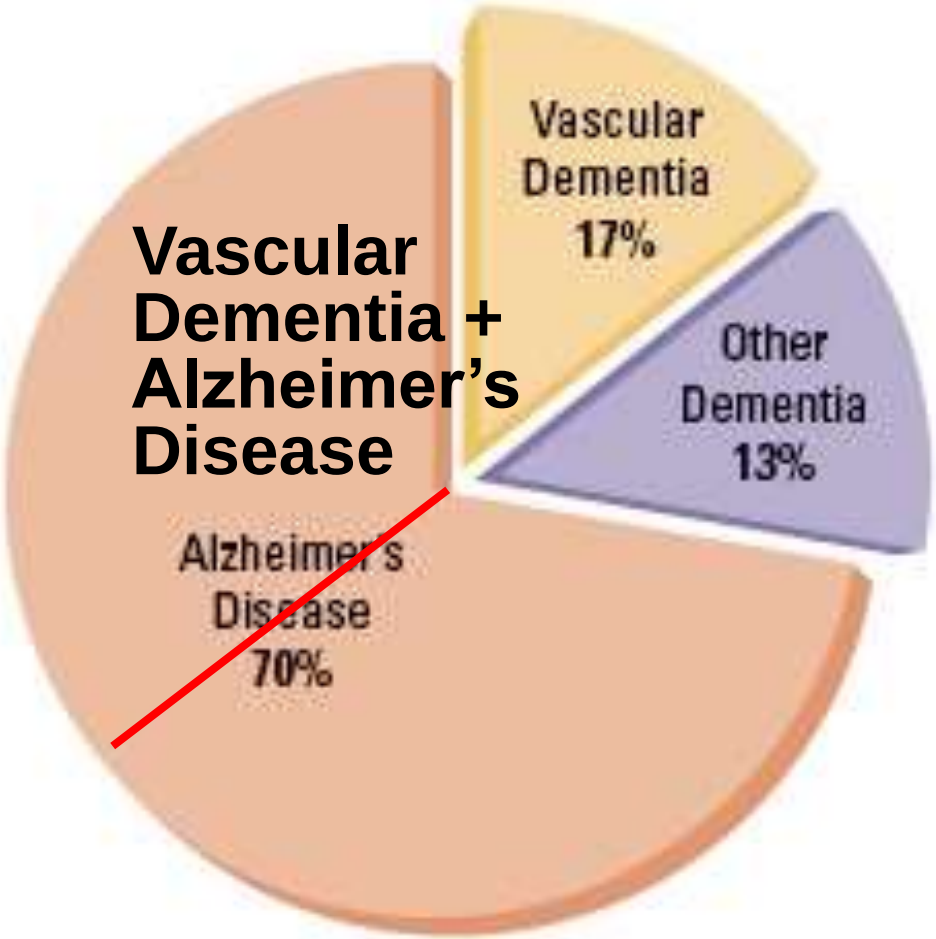
Post-Stroke Dementia is “all cause” dementia



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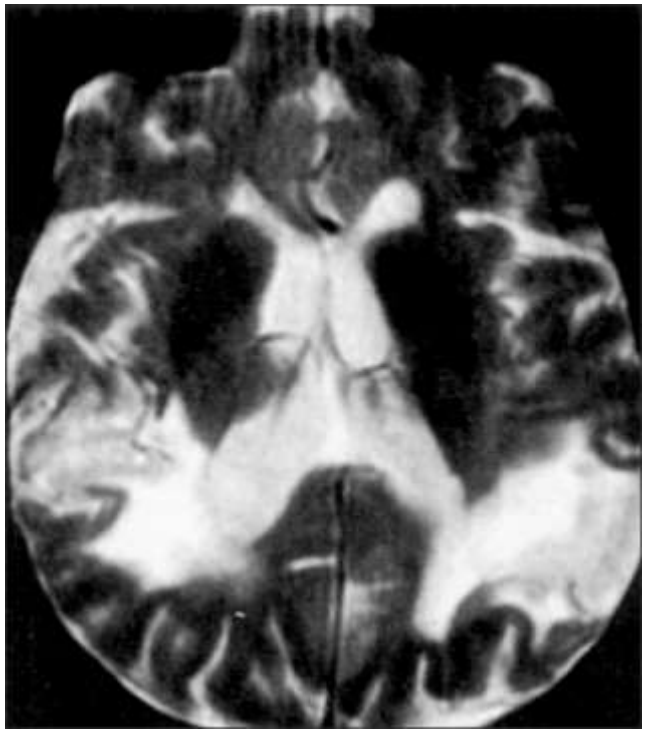
e, 1998

What is vascular dementia?

Subtypes of vascular dementia

Small Vessel Ischemic Disease

Multi-infarct Dementia



Post-stroke dementia

?

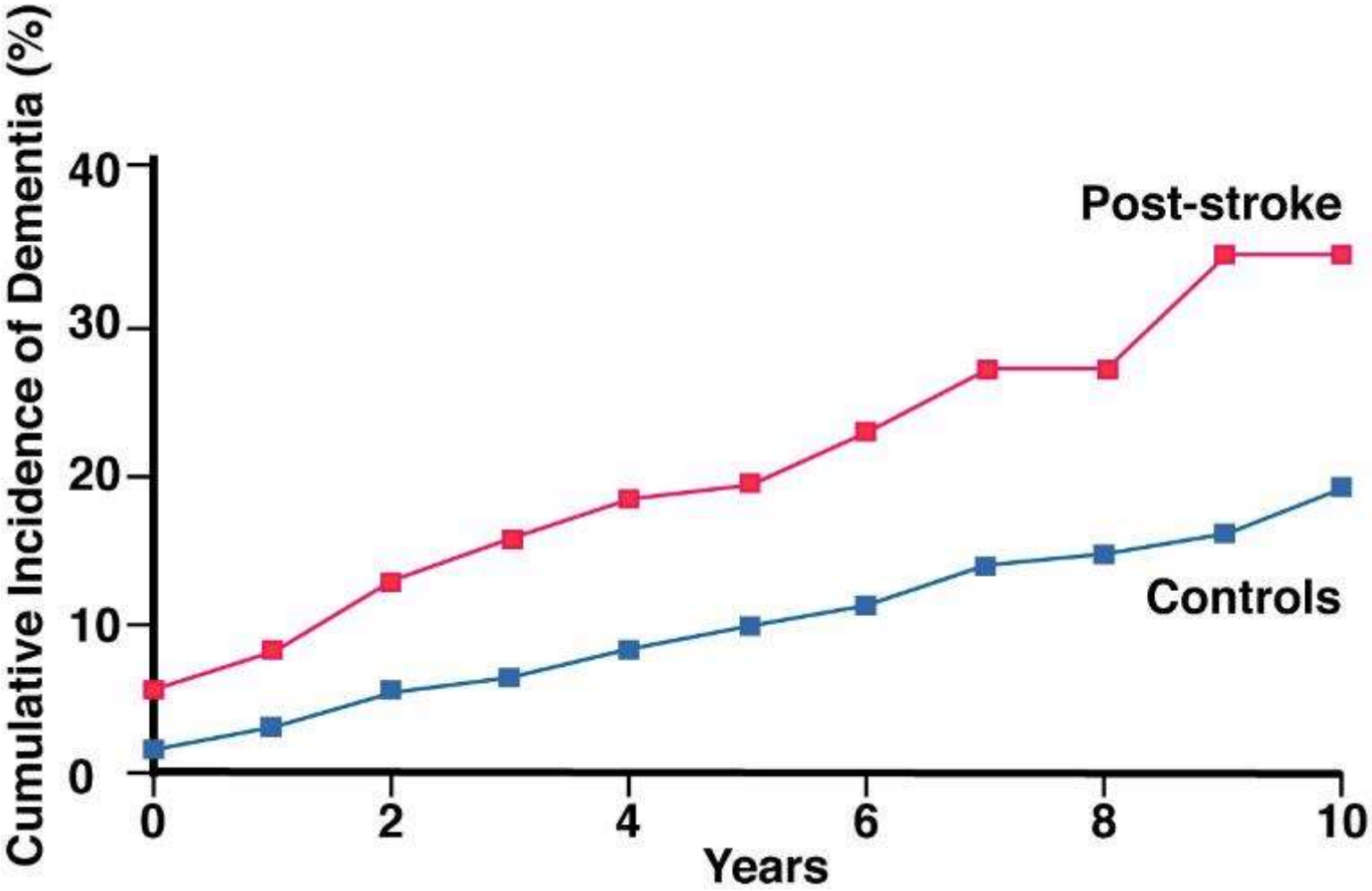
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Post-Stroke Dementia Risk: Framingham sub-study

- Nested case control 1:5, 217 patients with 1 stroke and 1060 matched controls.
- All patients were dementia-free before the stroke (screened every 6 months)
- Cognition was followed for 10 years

Ivan et al, 2004. Stroke 35:1264-1269

Framingham sub-study



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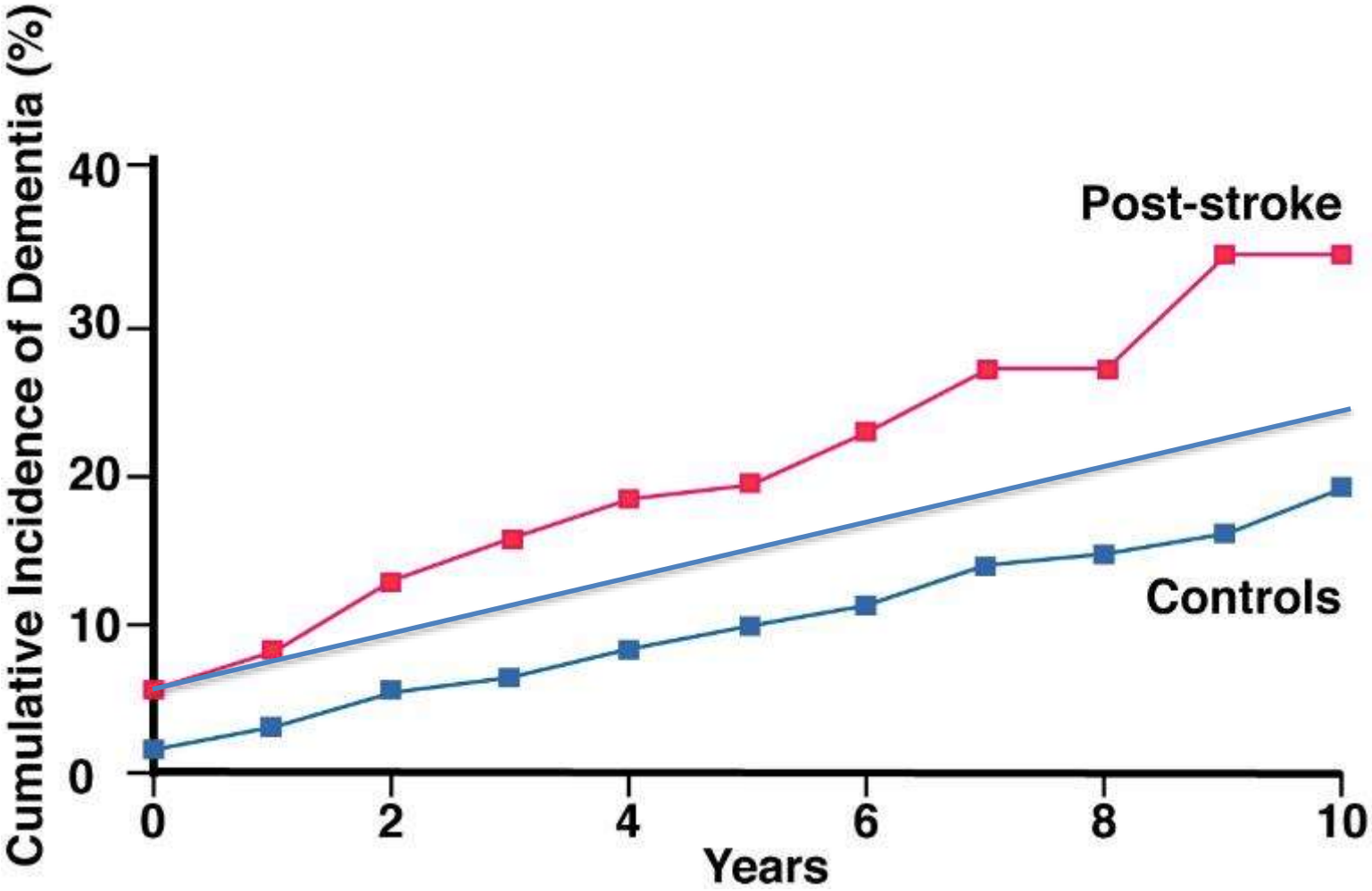

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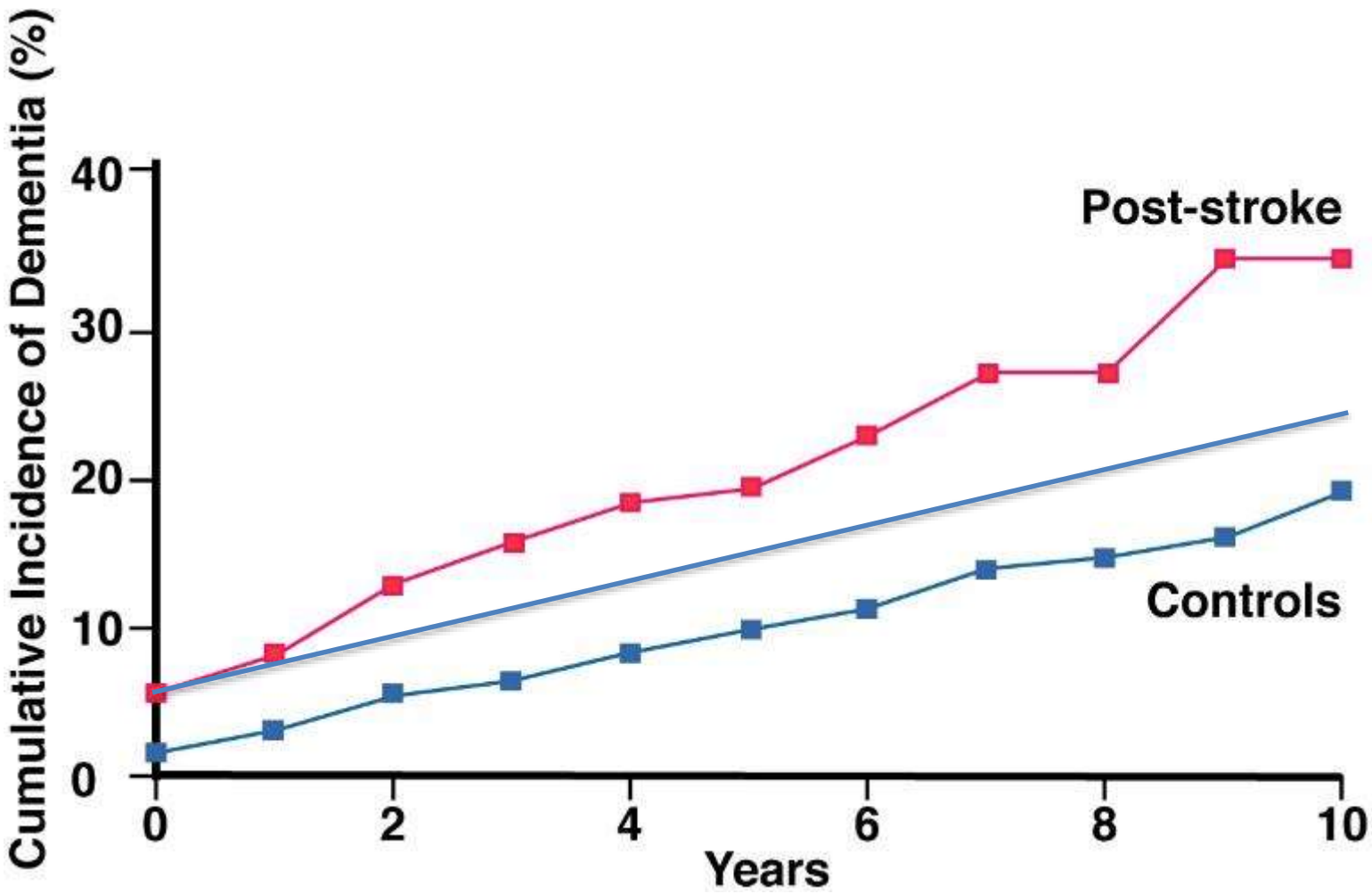

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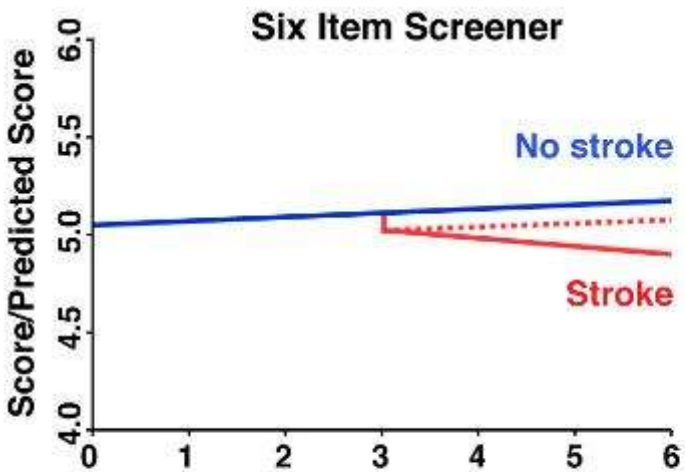
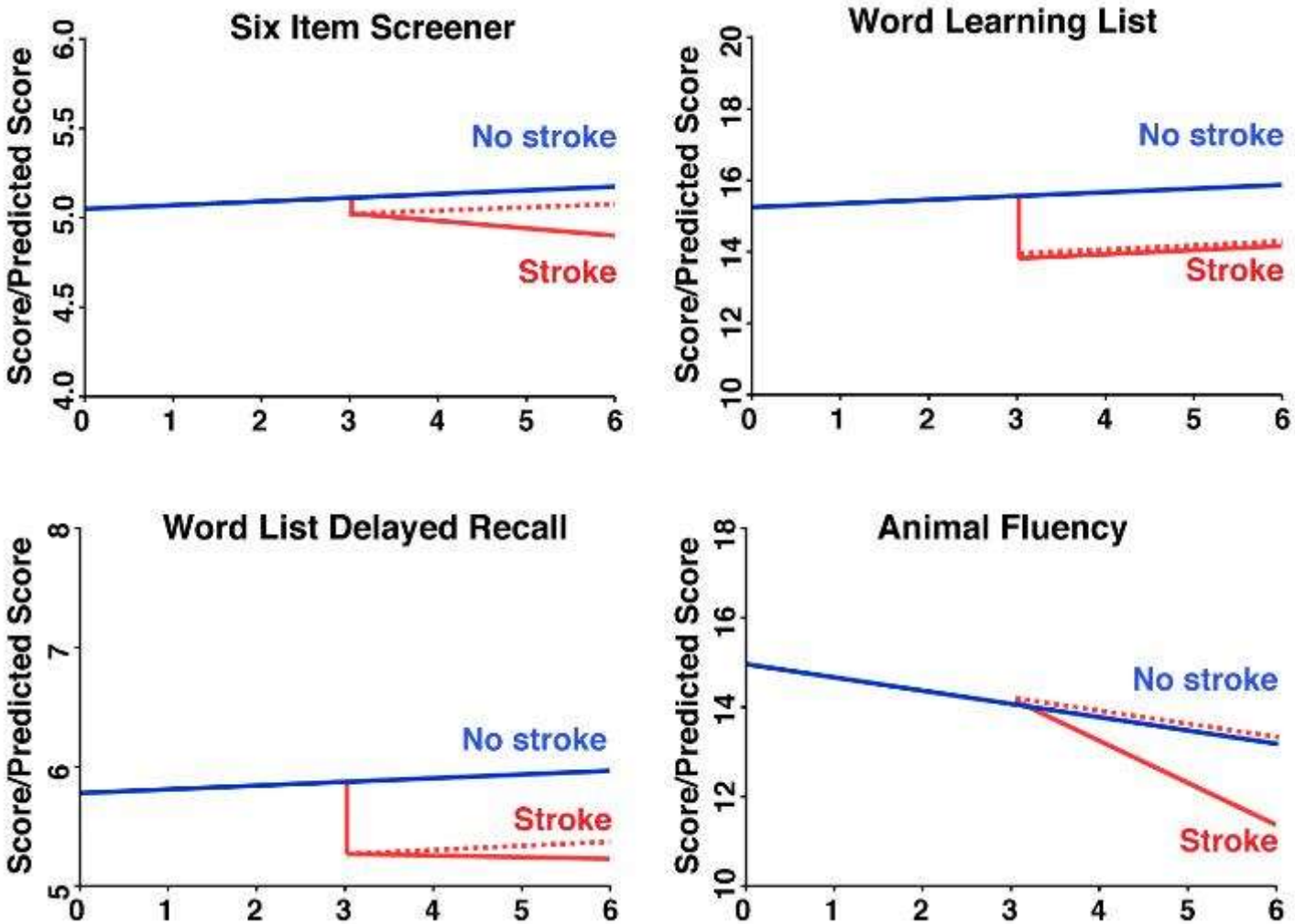
Cognitive trajectory after stroke-REGARDS cohort



Levine et al, 2015 JAMA 314:41-51.

Cognitive trajectory after stroke-REGARDS cohort



Levine et al, 2015 JAMA 314:41-51.

Post-Stroke Dementia

- Stroke doubles the risk of developing dementia in the year after a stroke
  - After accounting for common / known risk factors 10 – 20 % risk in first year of **incident** dementia
  - Unclear if this is one mechanism that interacts with others that cause dementia or if there is a "stand-alone" mechanism that causes post-stroke dementia

Hypothesis: stroke -> chronic inflammation -> dementia

http://www.neuroradiologycases.com/2012/09/ischemic-stroke-and-vascular.html

Histopathological changes after human acute ischemic stroke

Histopathological changes	n (%)
Astrogliosis	114 (83)
Polymorphonuclear leukocytes	31 (23)
Mononuclear inflammatory cells	61 (45)
Macrophages	103 (75)

n = 137

Mena et al, 2004. Acta Histopathologica 108:524-530.

Histopathological changes after human acute ischemic stroke

Histopathological changes	n (%)	Time
Astrogliosis	114 (83)	2 days-53 years
Neutrophils	31 (23)	1–37 days
Mononuclear inflammatory cells	61 (45)	3 days–53 years
Macrophages	103 (75)	3 days–53 years

n = 137

Mena et al, 2004. Acta Histopathologica 108:524-530.

Stroke “Scar”

Hypothesis: stroke ->

chronic inflammation ->

dementia

Modeling post-stroke dementia in a mouse

- Hypothesis: stroke ->

  chronic inflammation ->

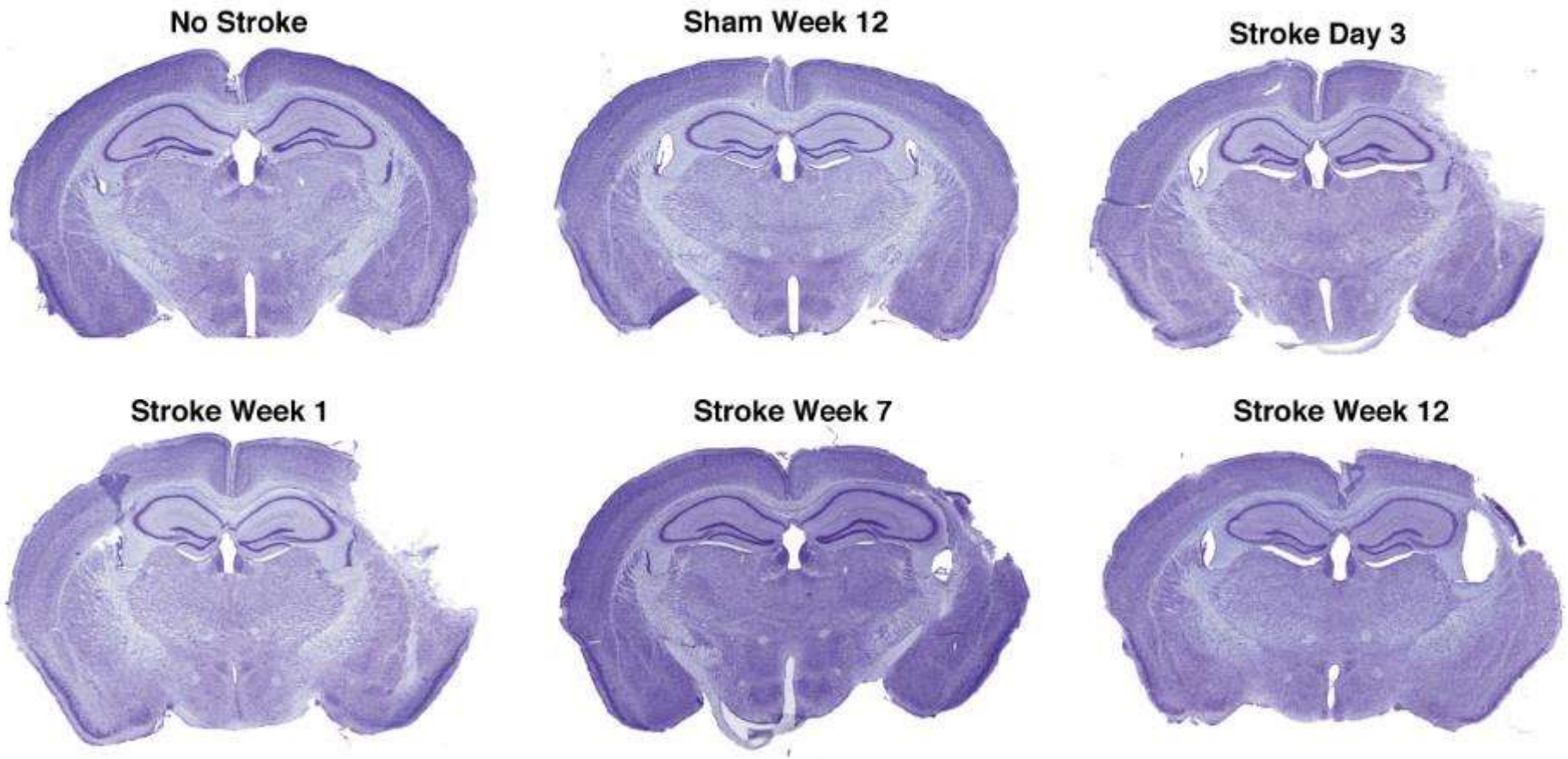
  dementia

Kristian Doyle

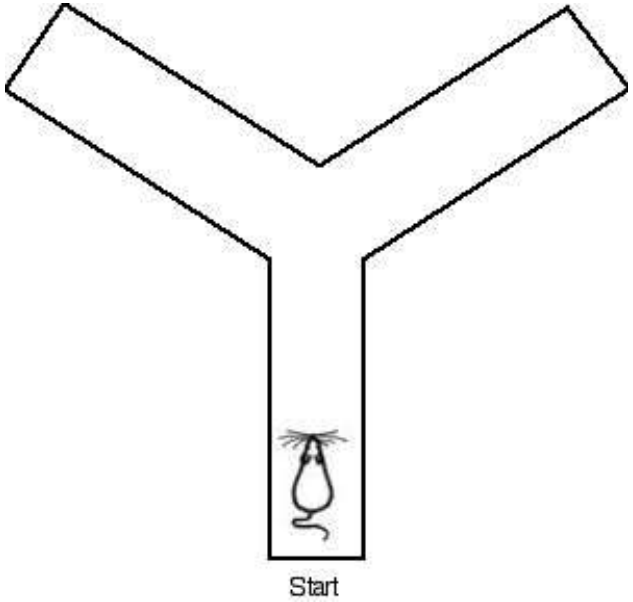
- Needed a mouse model that has no immediate cognitive impairment

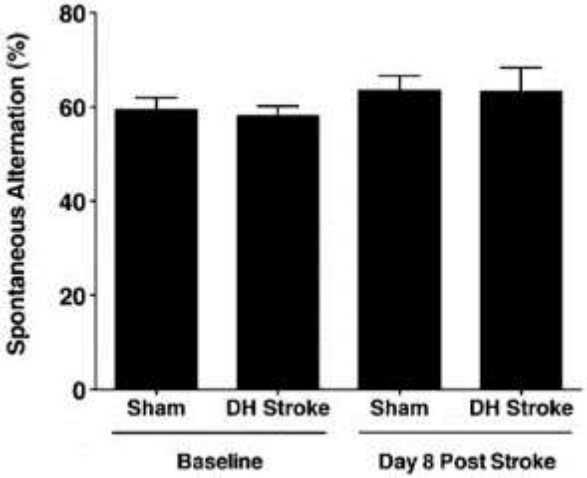
Doyle et al, 2012 J Neurosci methods.

Cresyl violet shows no gross hippocampal cell loss



DH stroke





Doyle et al, J Neurosci Methods 207 (2012) 31– 40

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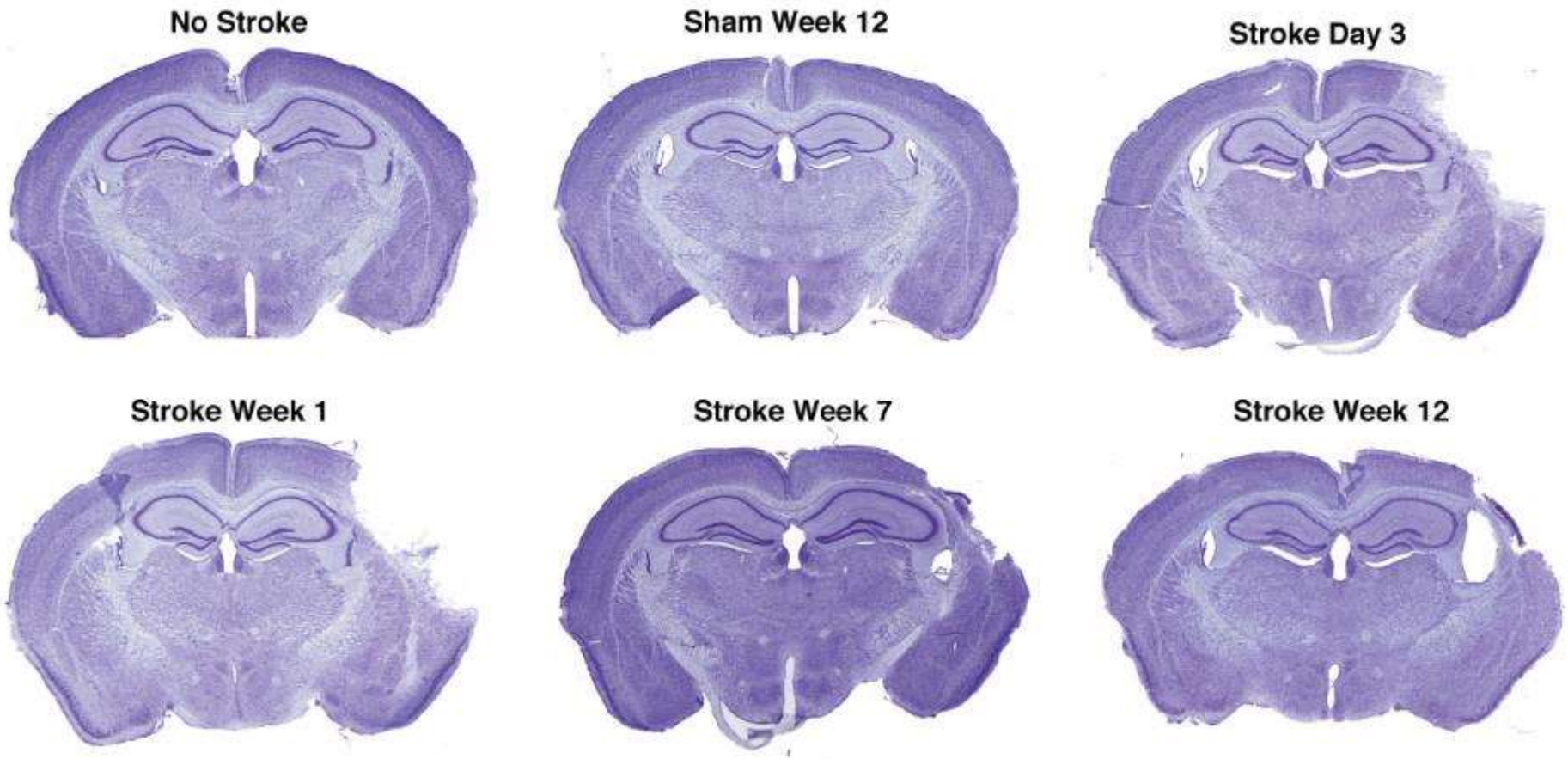
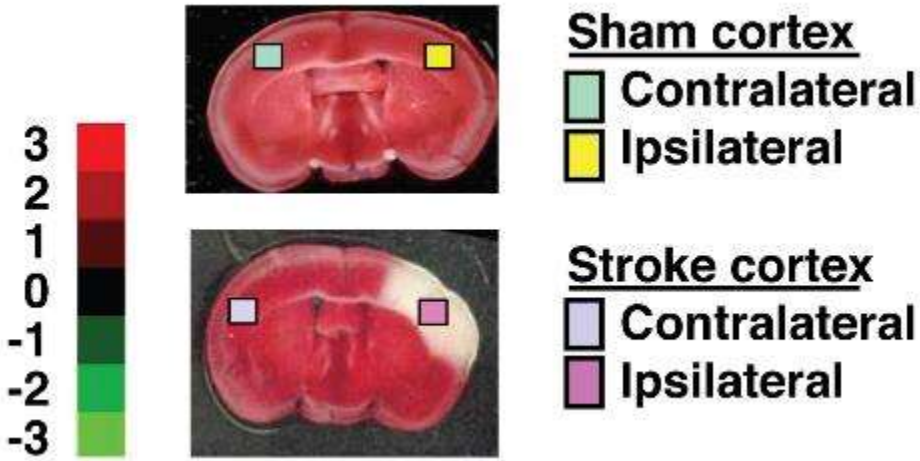


Inflammation 7 weeks after stroke



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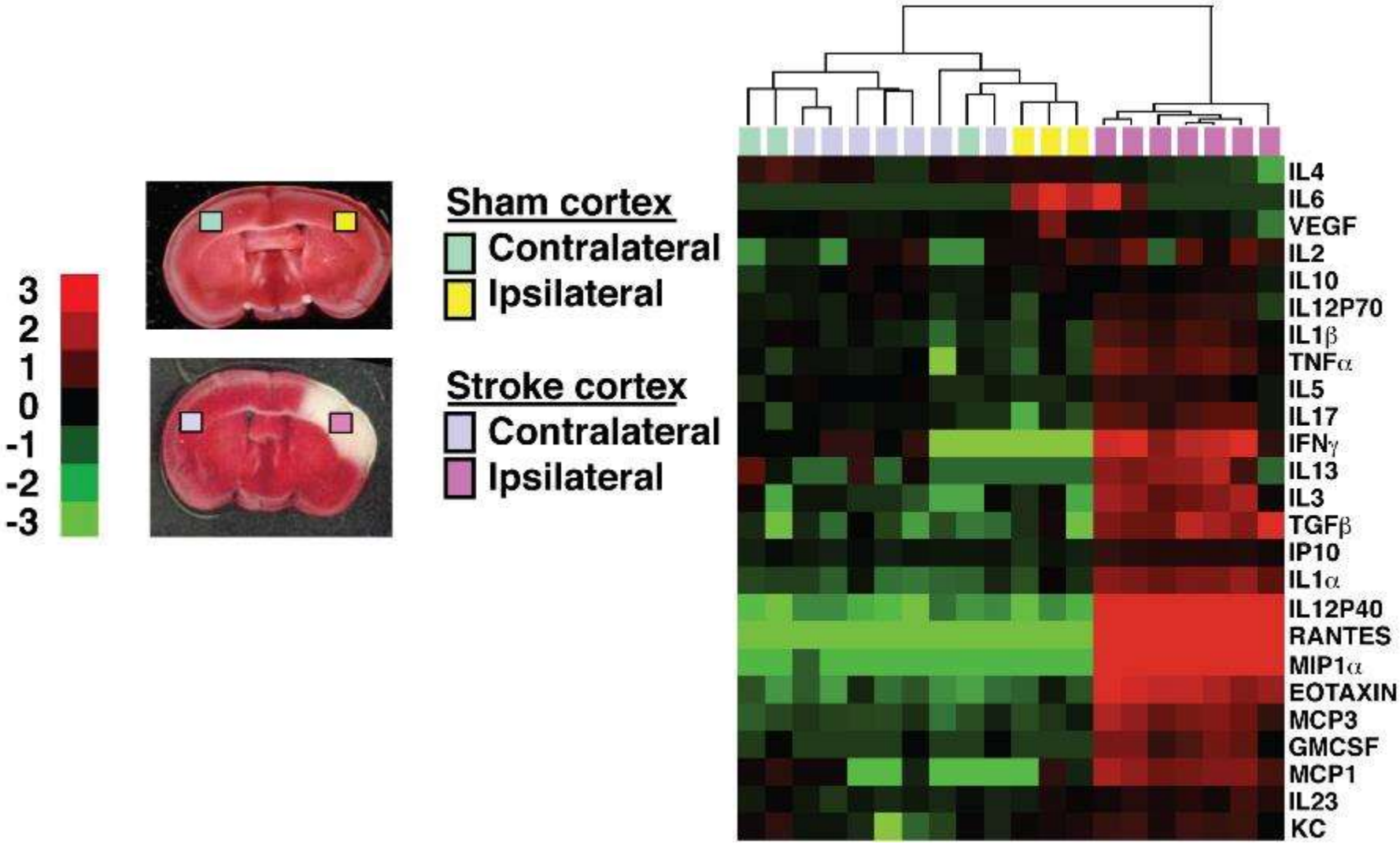
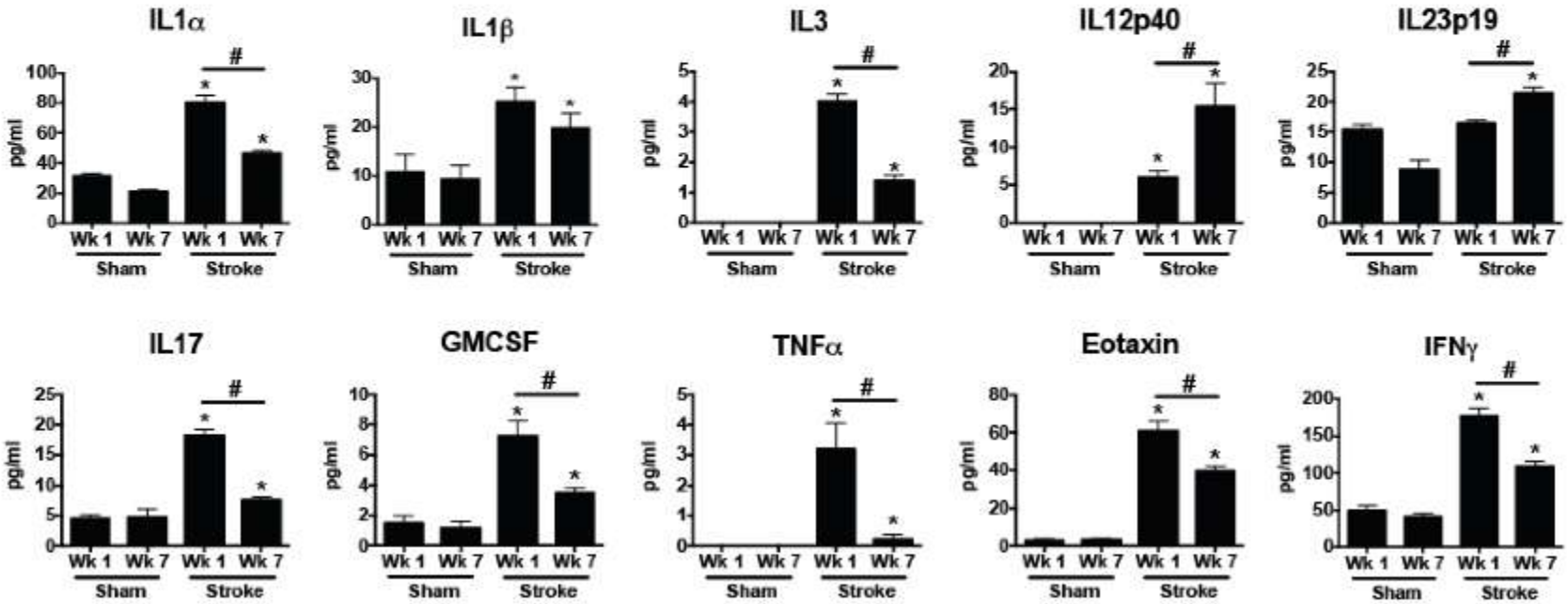
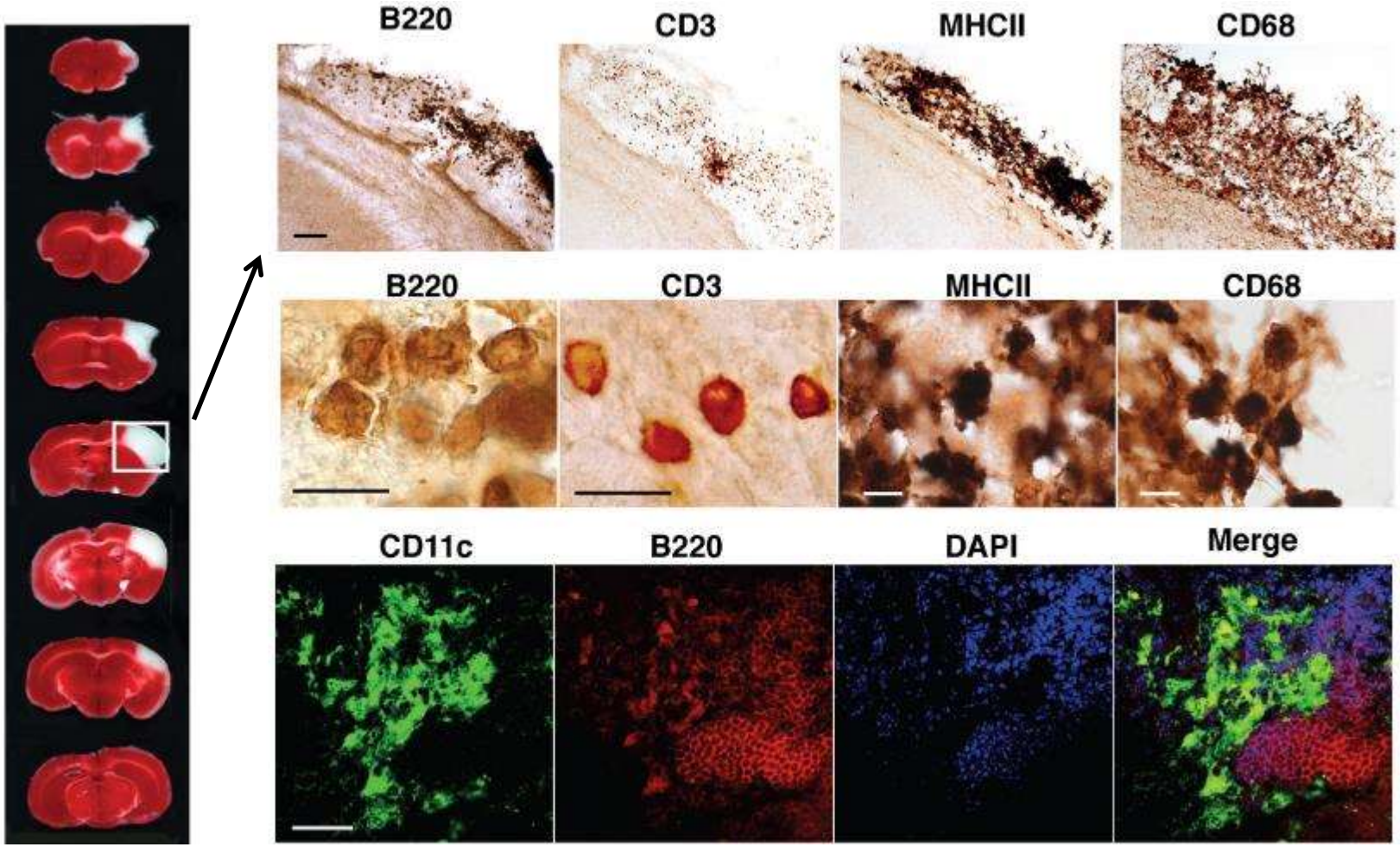


Comparison of 1 and 7 weeks after stroke



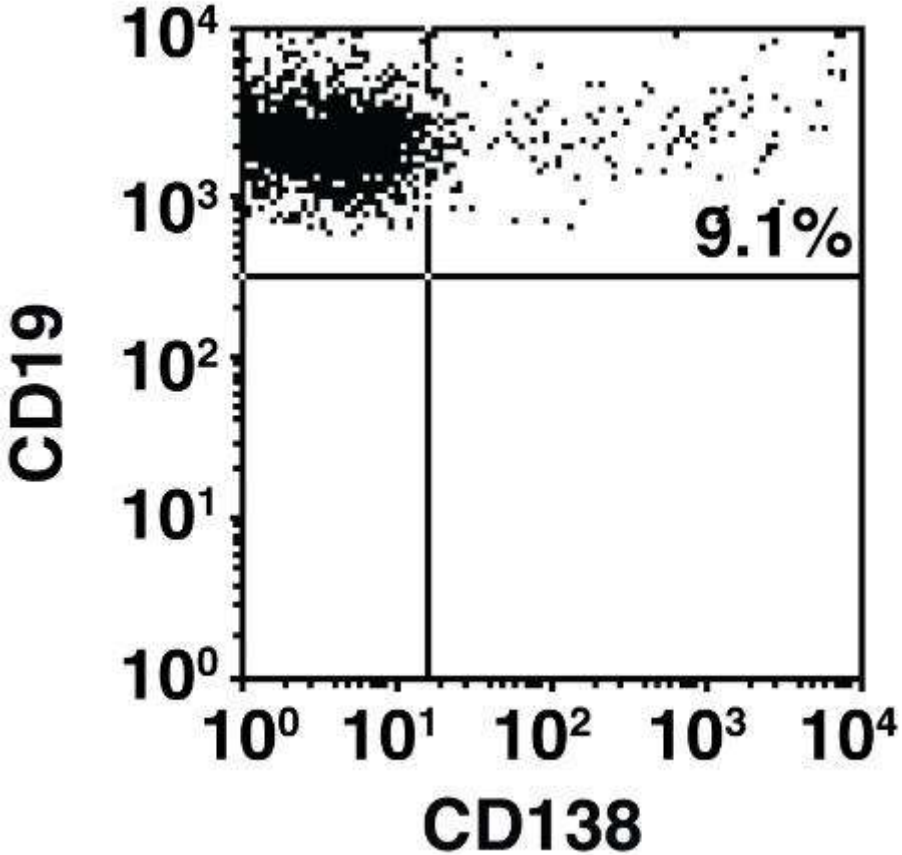
Doyle & Buckwalter, unpublished

The stroke core contains immune cells 7 weeks after stroke



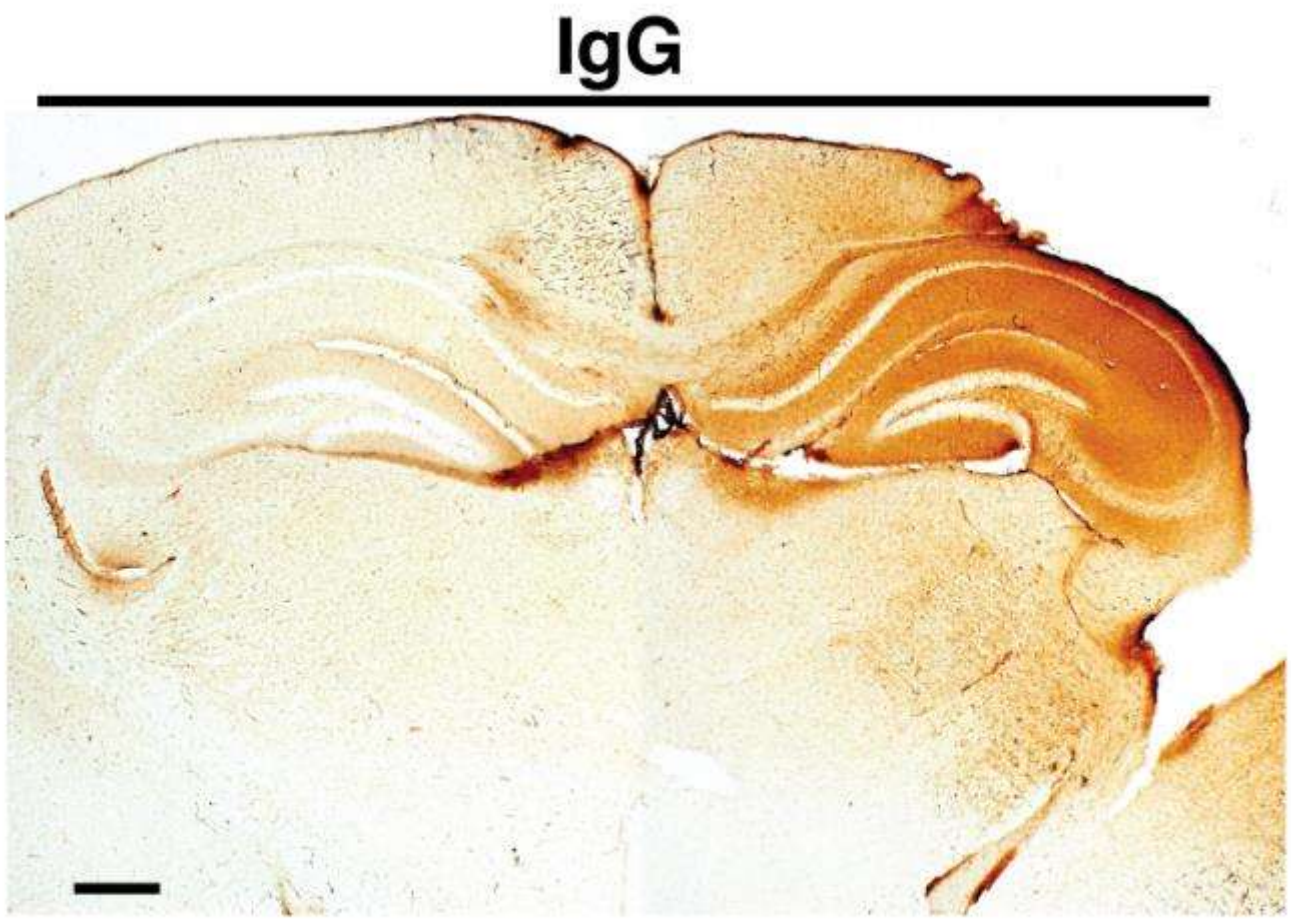
Doyle et al, J Neuroscience 2015

Plasma cells are also present in the stroke core

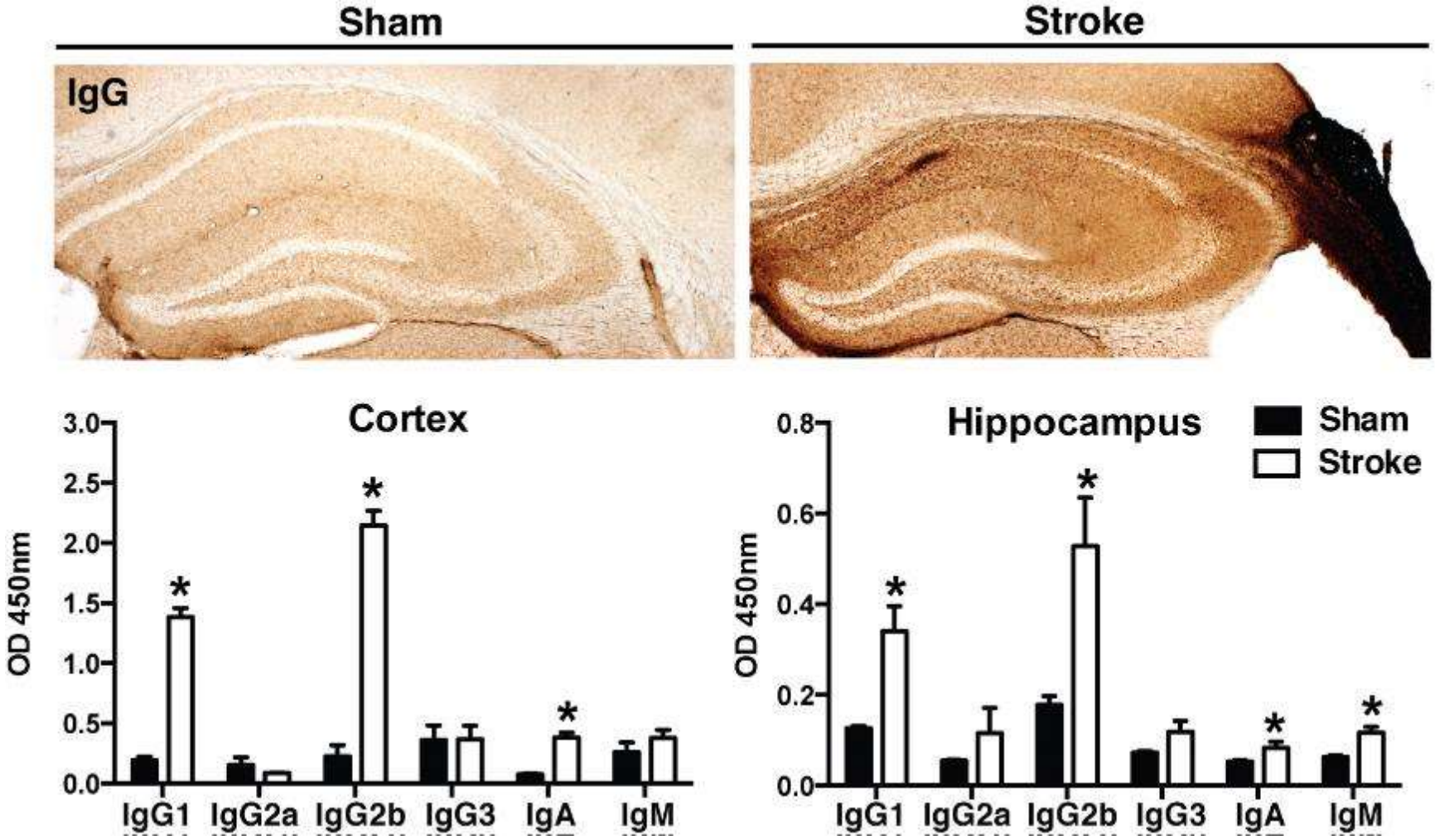


Doyle et al, J Neuroscience 2015

IgG is present in the mouse brains surrounding the stroke lesion

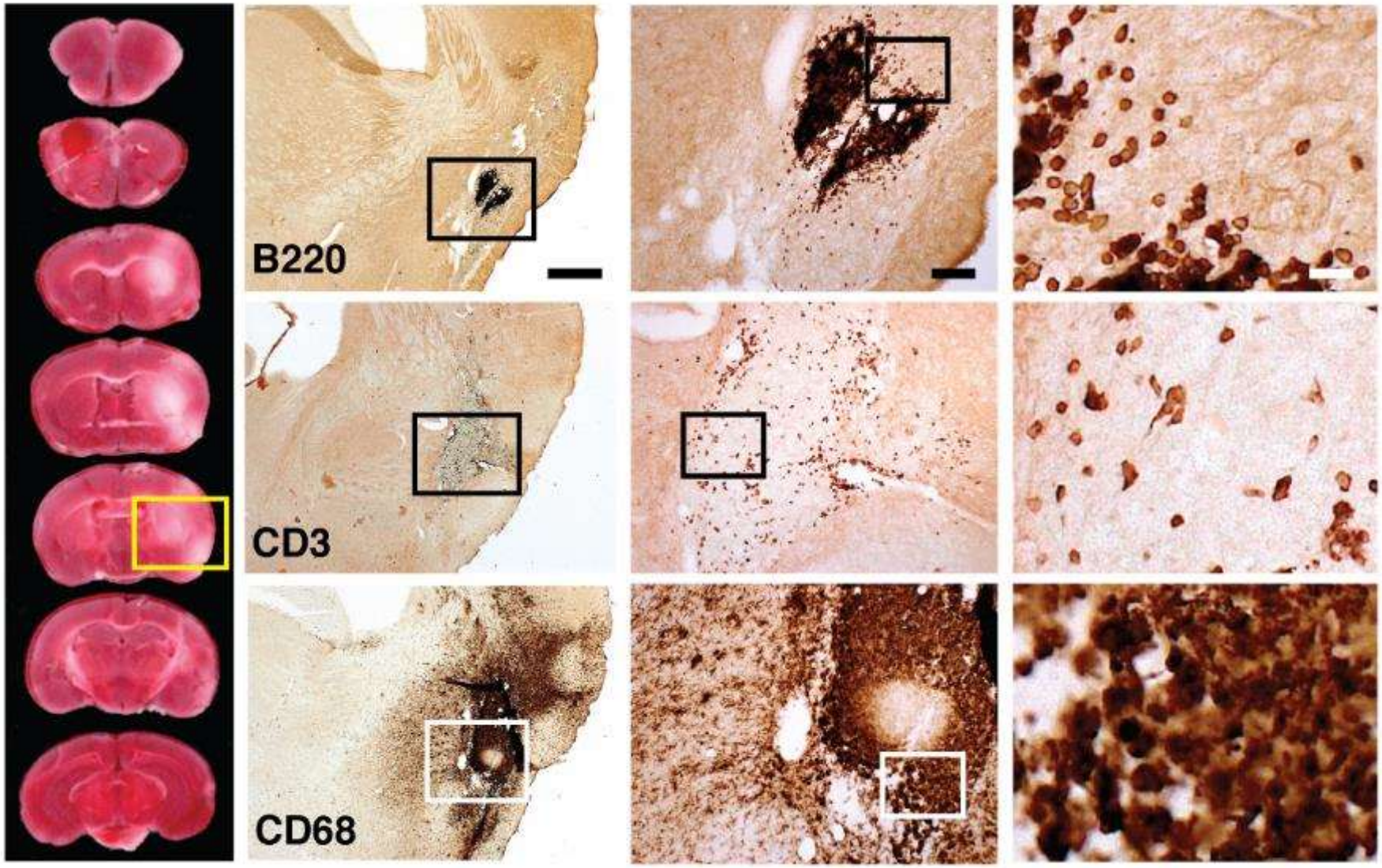


At 7 weeks after stroke, IgG is present in the tissue surrounding the stroke lesion



Doyle et al, J Neuroscience 2015

MCAO (Suture Model)



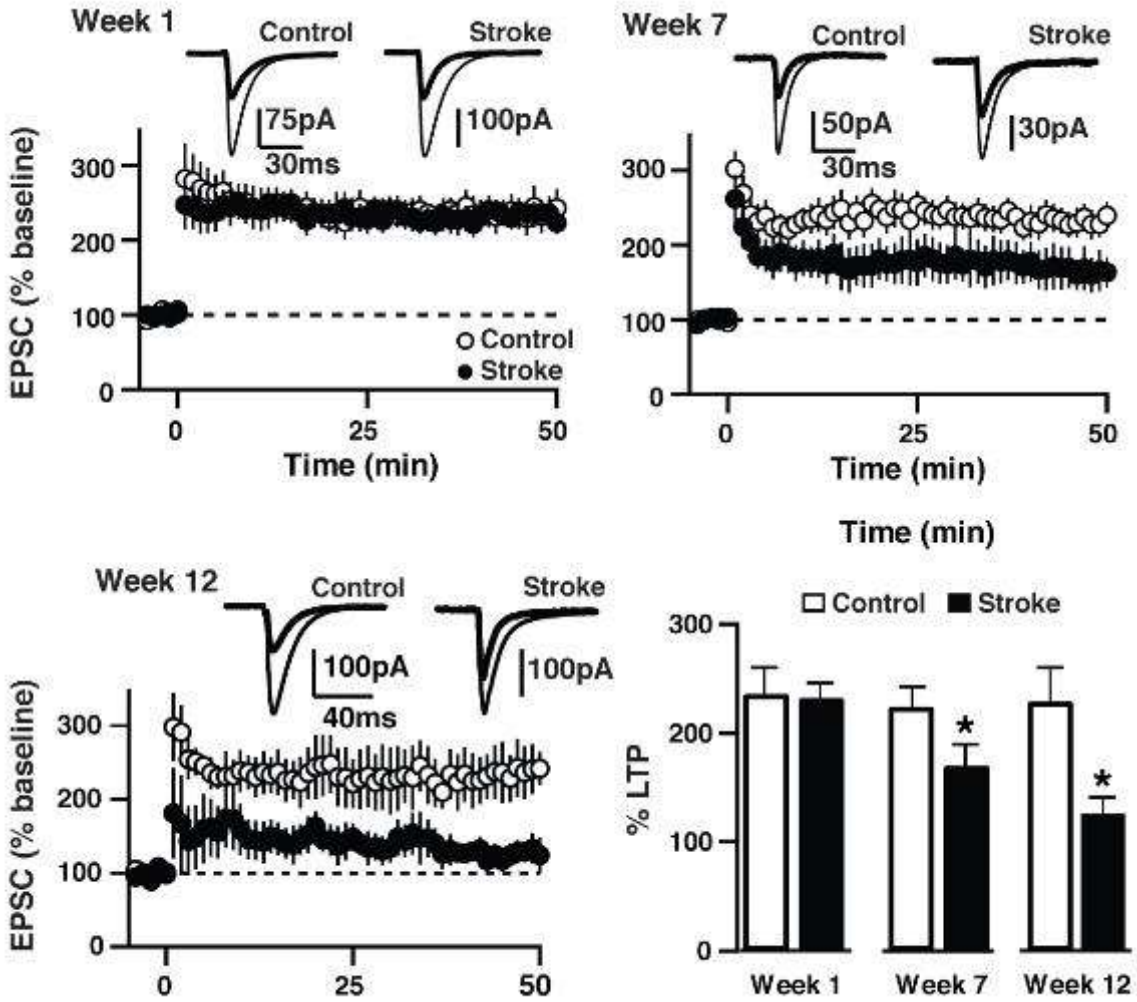
Doyle et al, J Neuroscience 2015

Hypothesis: stroke ->

chronic inflammation ->

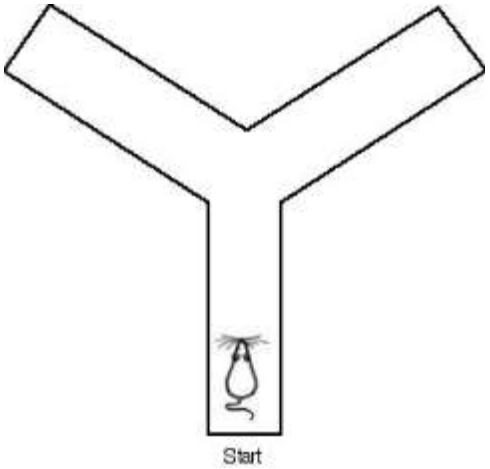
dementia

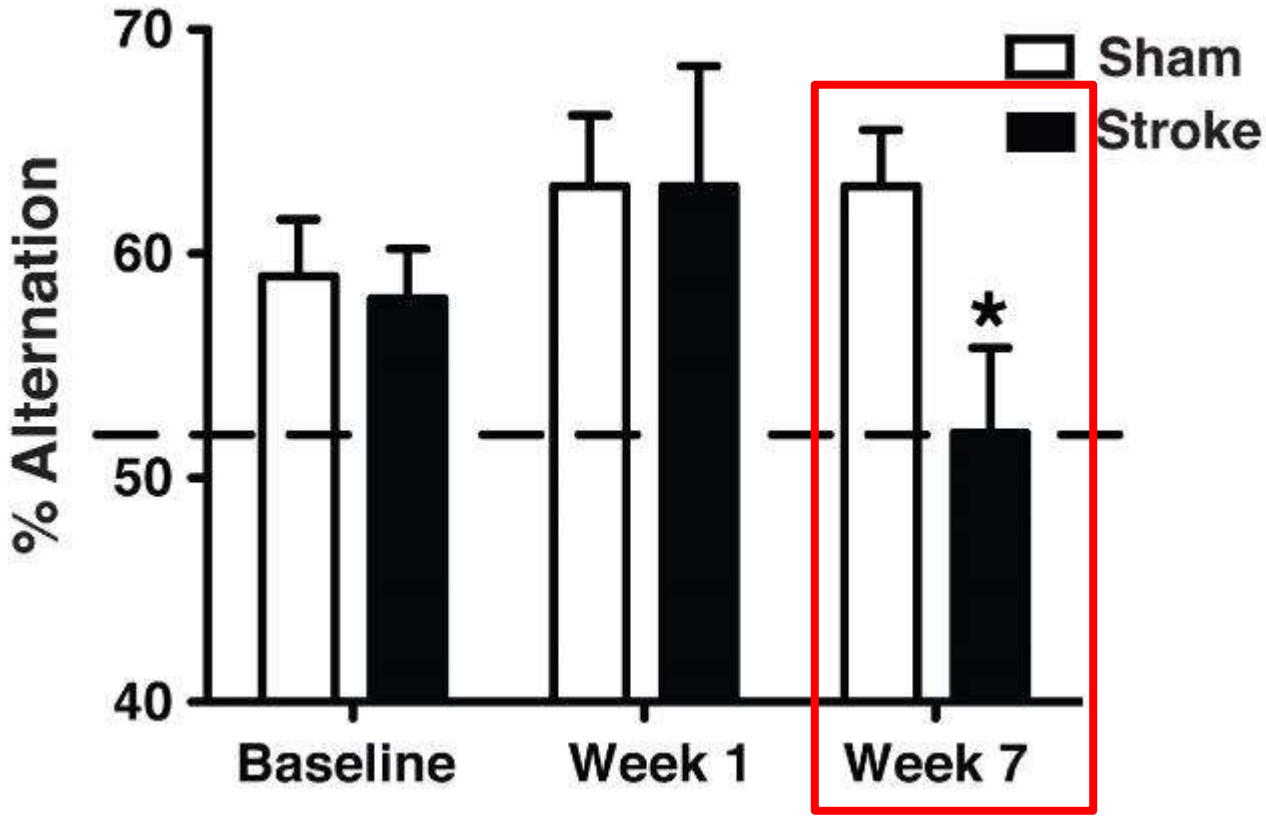
Hippocampal LTP is normal 1 week after stroke and then progressively worsens



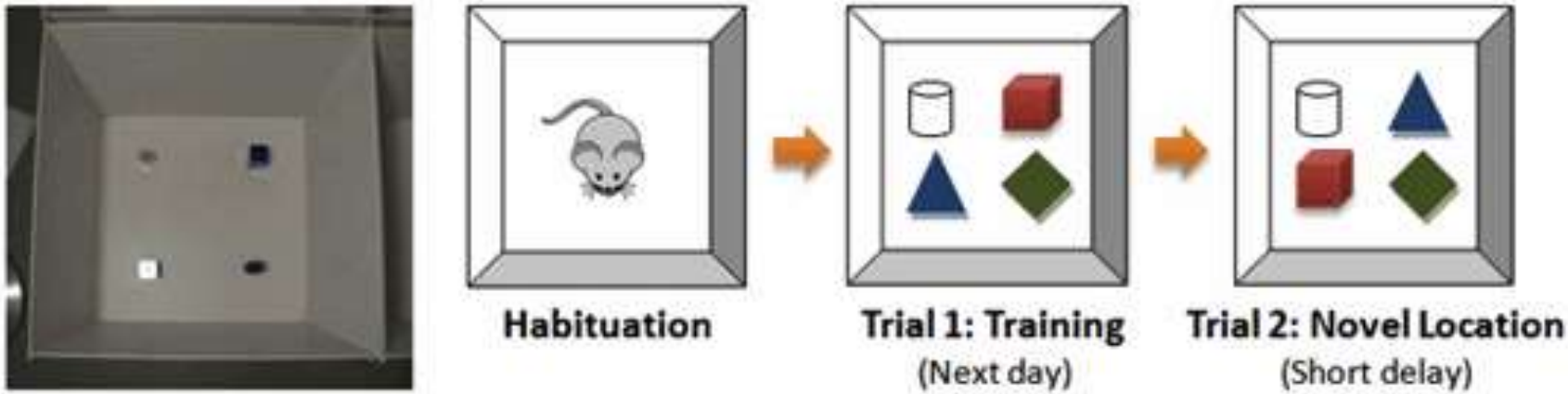
Doyle et al, J Neuroscience 2015

Y-maze performance deteriorates between weeks 1 and 7 after stroke

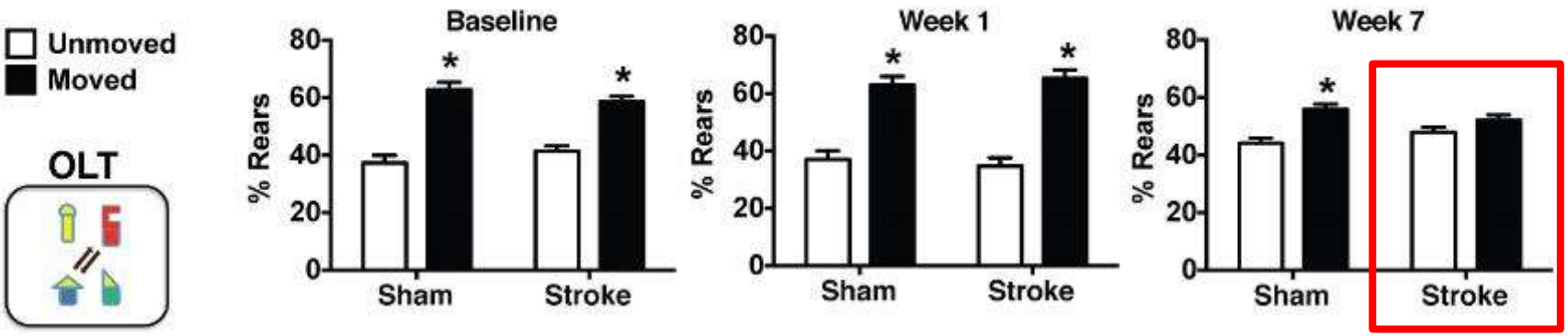




Object Location Task

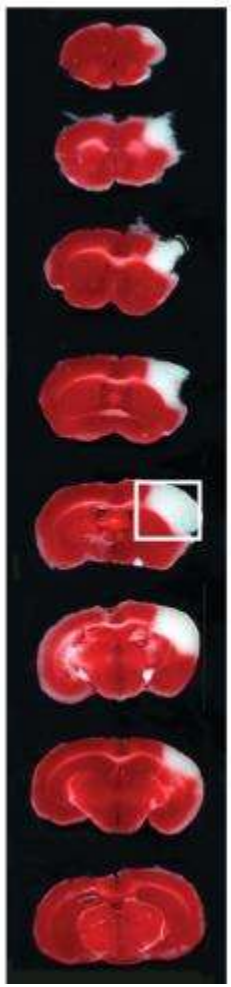


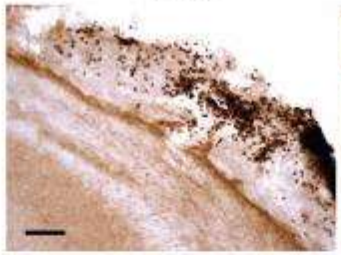
Deficits appear between weeks 1 and 7 in the Object Location Task



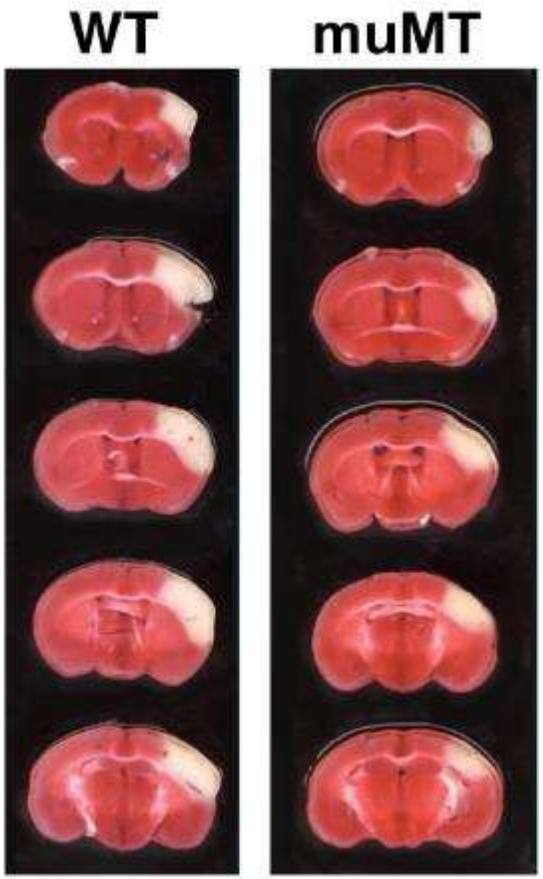
Doyle et al, J Neuroscience 2015

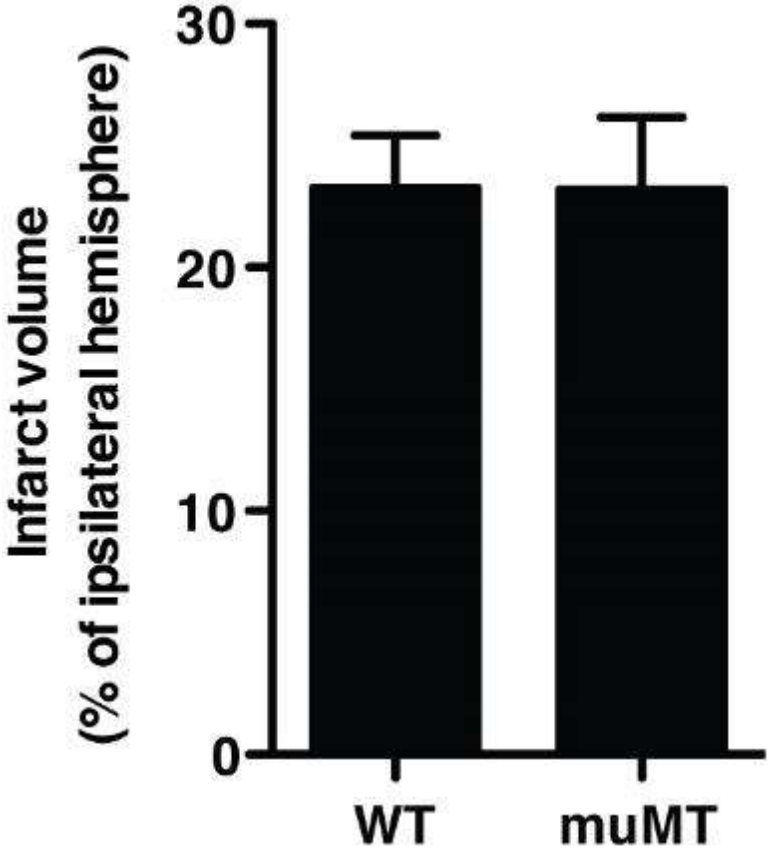
Are B lymphocytes necessary for the cognitive deficit?



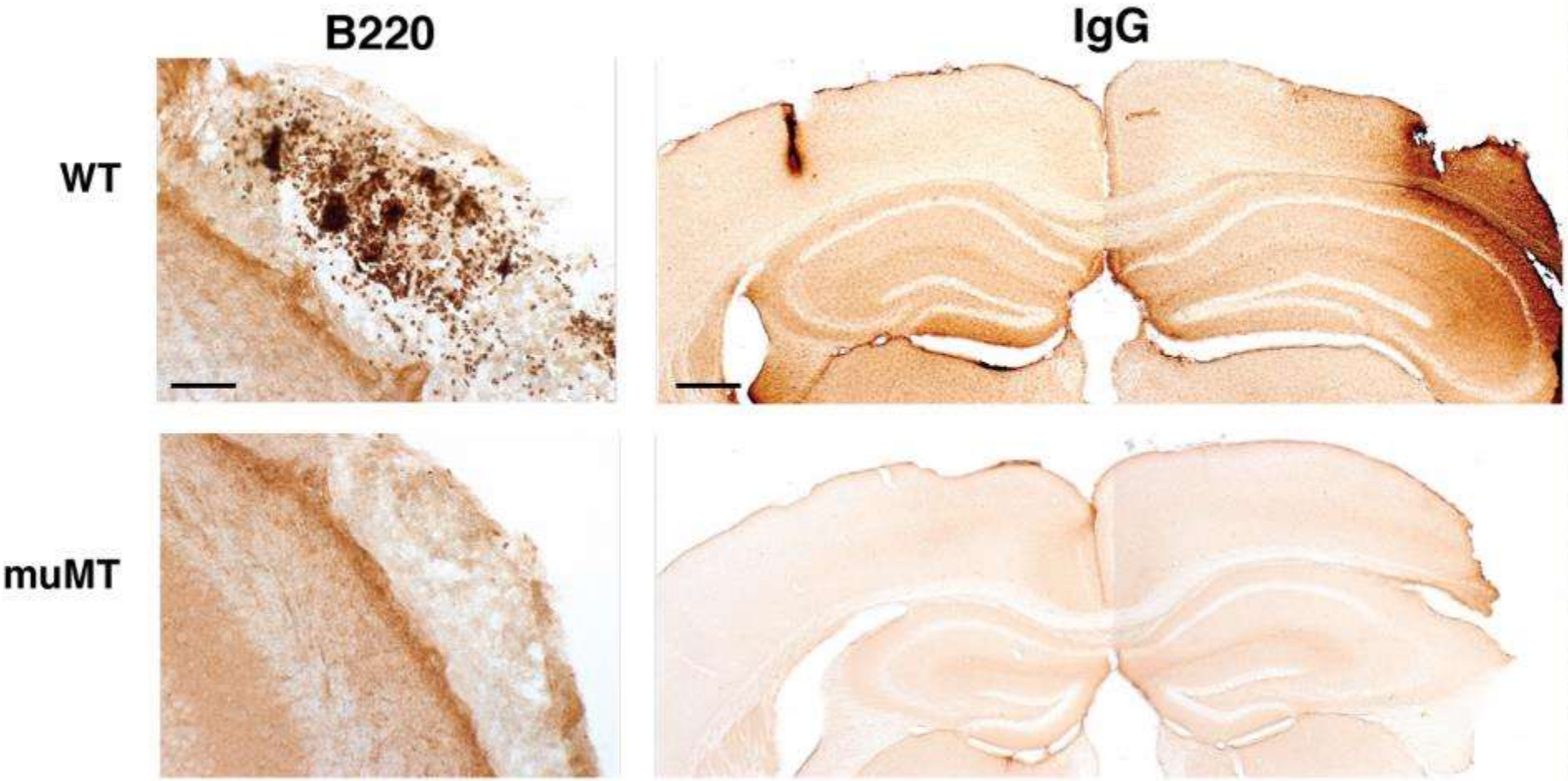


Are B lymphocytes responsible for the cognitive deficit?

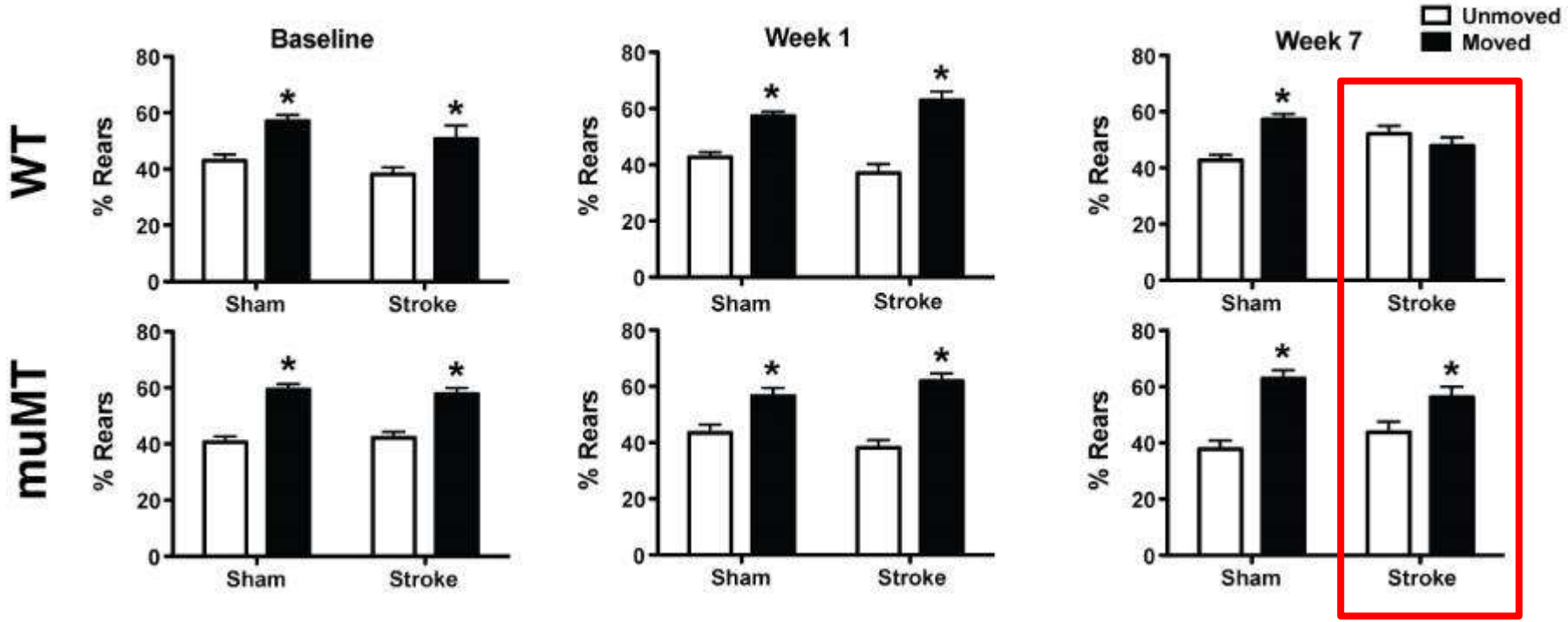




Validation of muMT mice

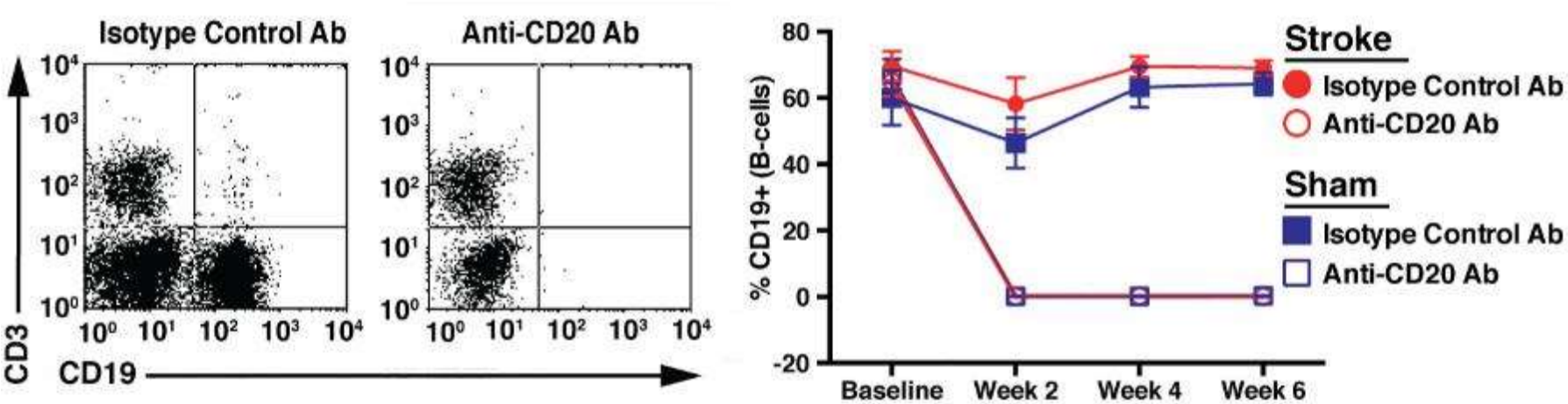


MuMT mice do not get delayed OLT impairment



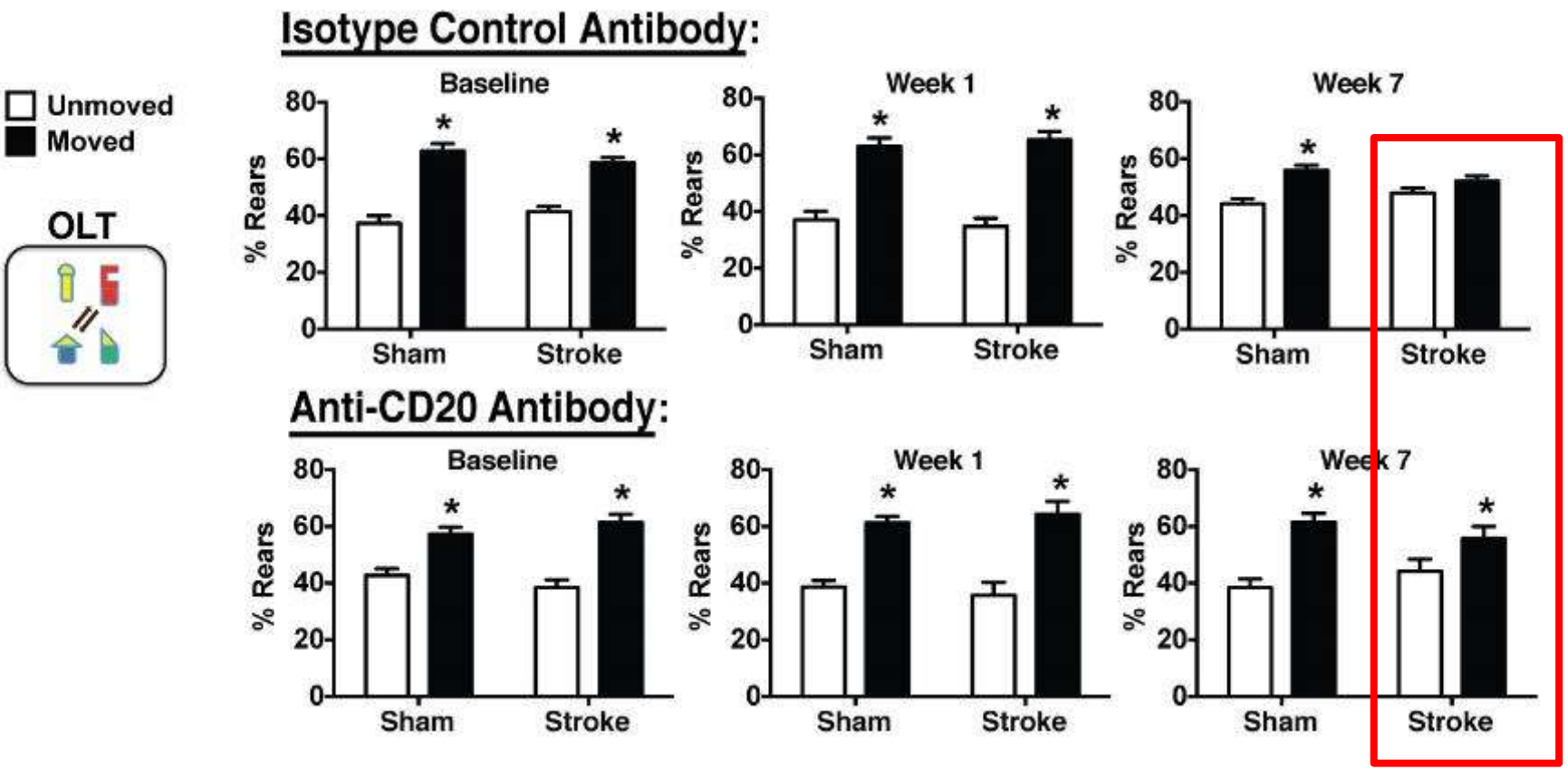
Doyle et al, J Neuroscience 2015

Anti-CD20 Antibody treatment 5 days after stroke ablates B cells



Doyle et al, J Neuroscience 2015

Anti-CD20-treated mice do not develop cognitive deficits

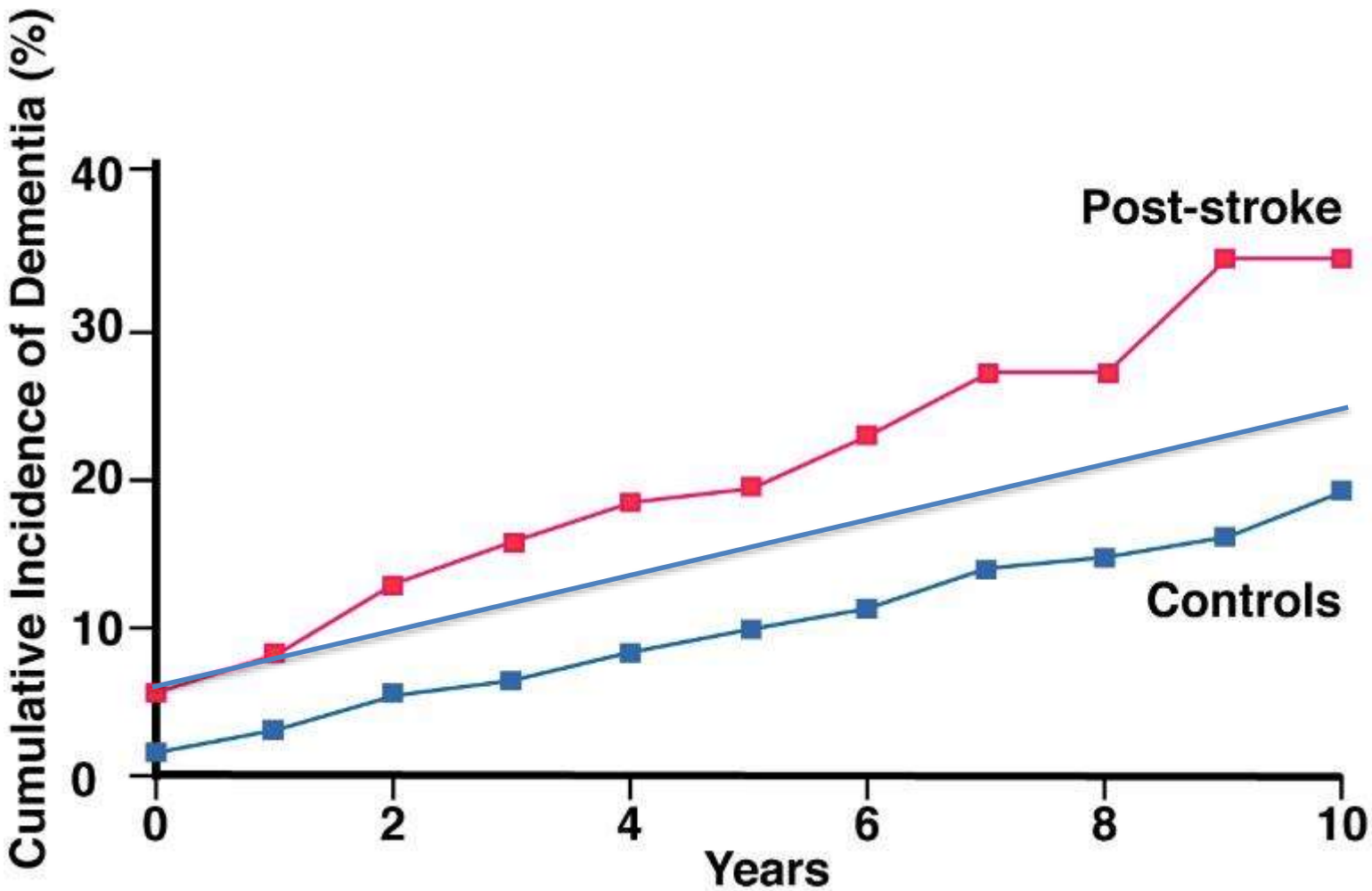


Doyle et al, J Neuroscience 2015

Post-Stroke Dementia

- Normal mice can develop delayed cognitive impairment after stroke
- This is associated with prolonged inflammation in the stroke core that includes B lymphocytes
- In the absence of B cells mice do not develop delayed cognitive impairment after stroke

Framingham sub-study



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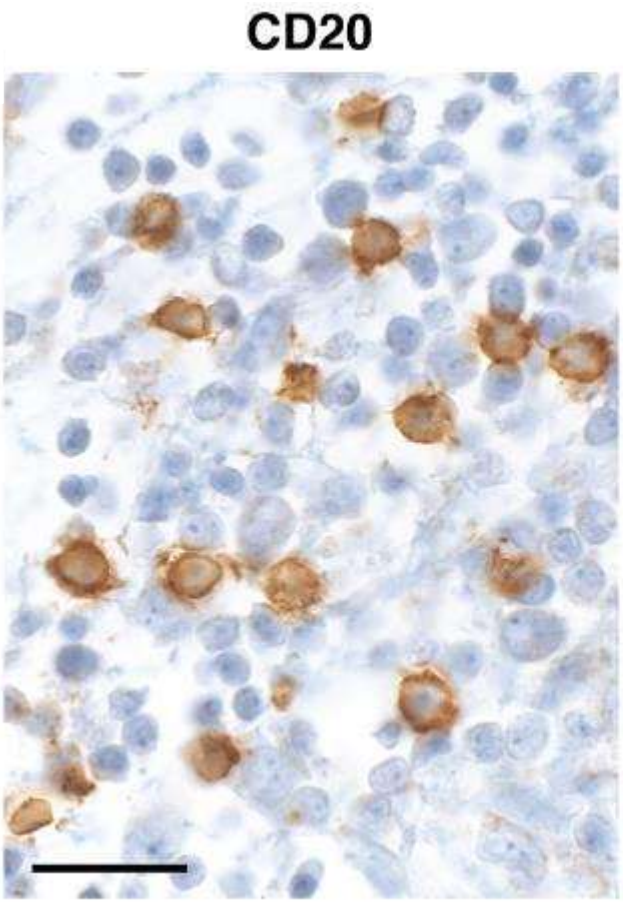
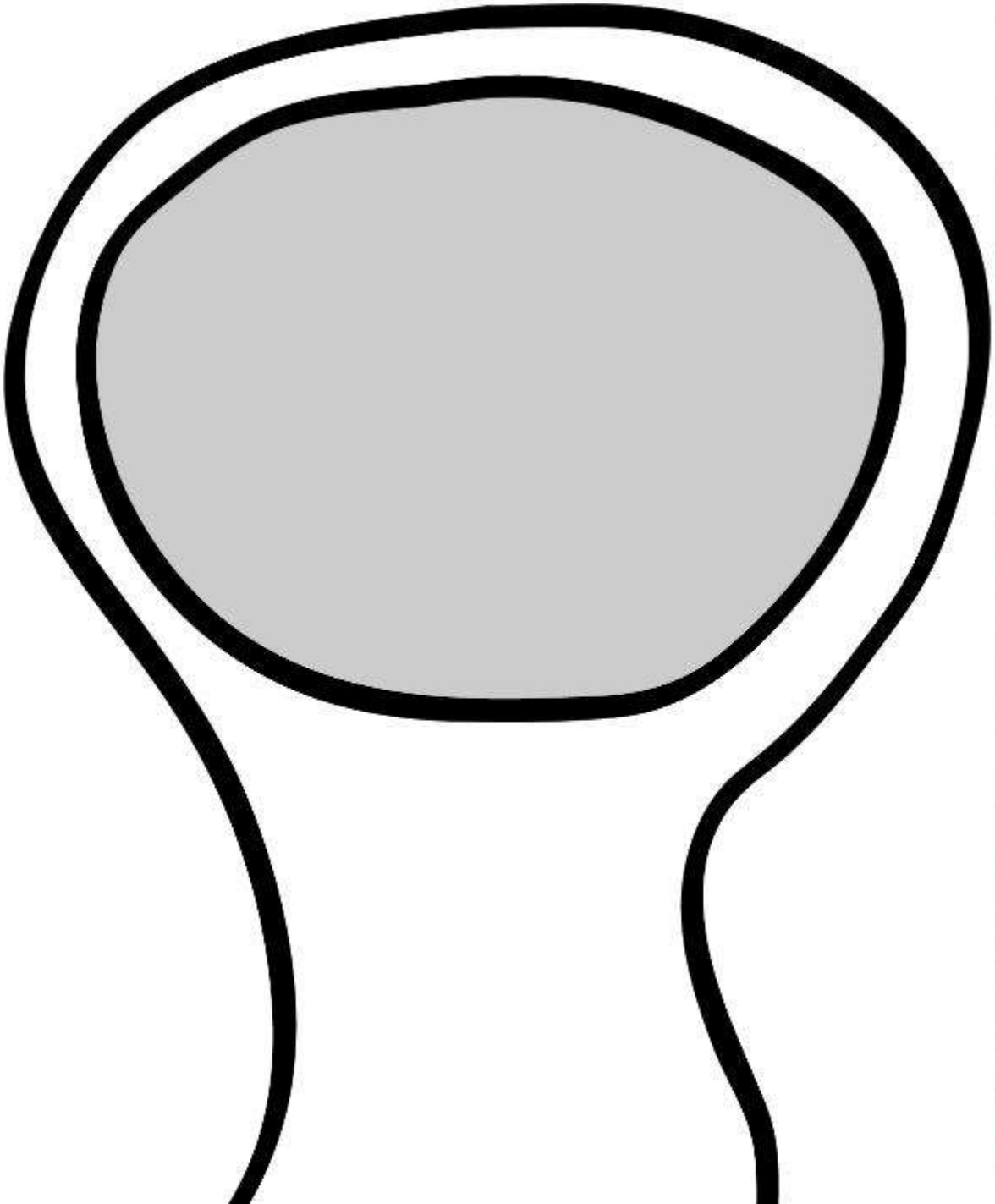
Ivan et al, 2004. Stroke 35:1264-1269

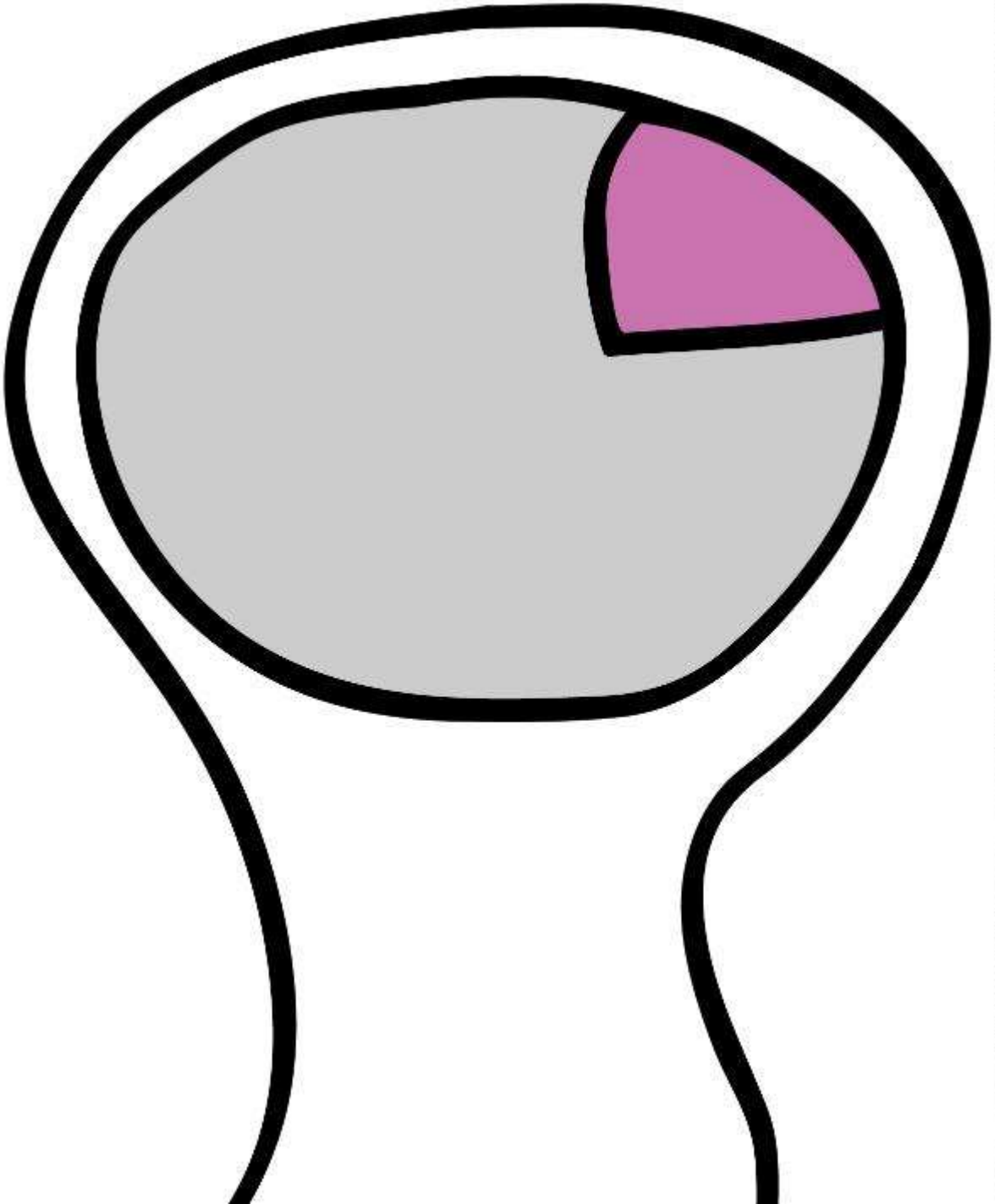
Human Brain Pathology - Rush

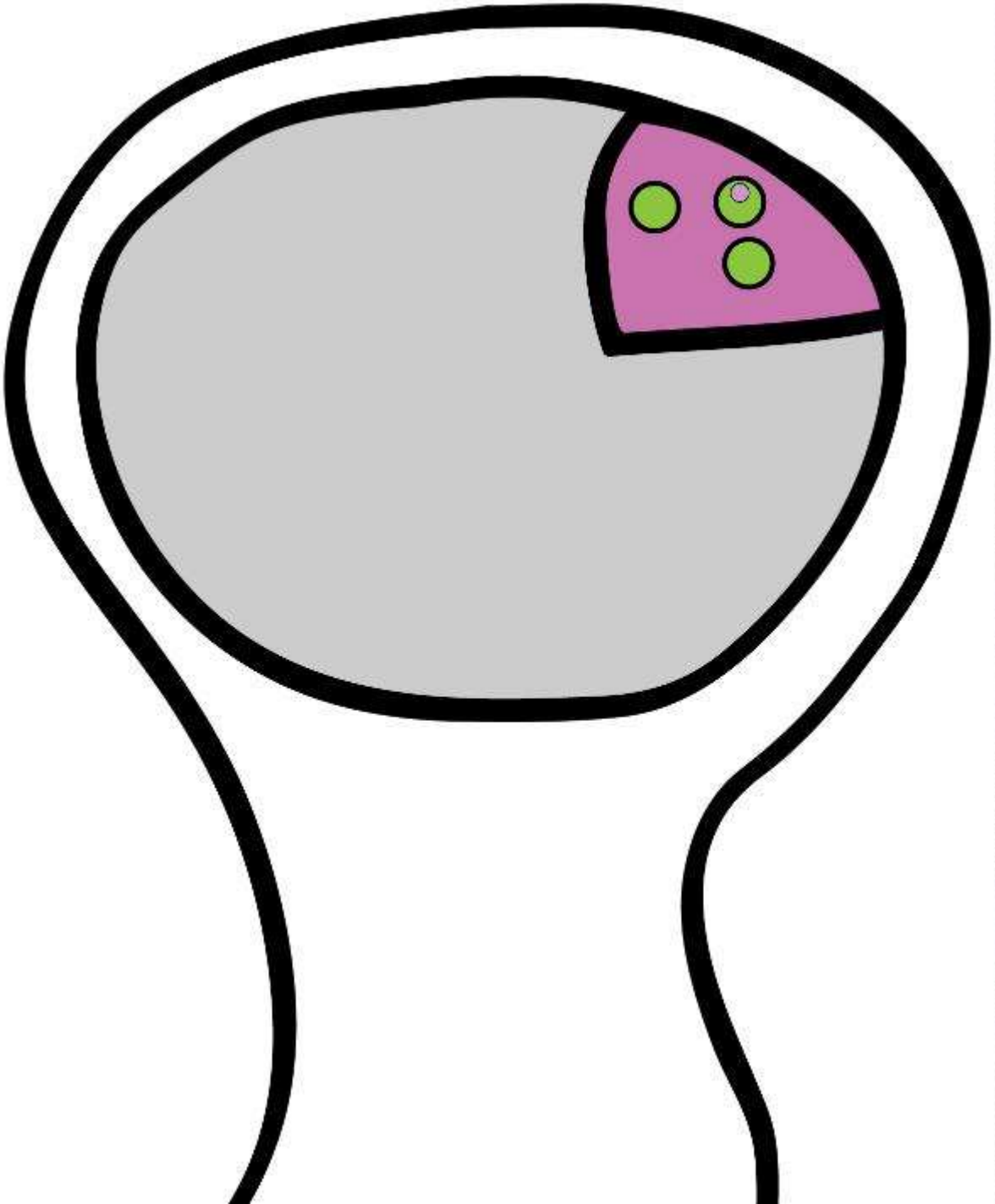
- ROS
  - The Rush Religious Orders Study
  - subjects recruited beginning in 1994,
  - Older nuns, priests, and monks, from >40 groups within the US.
- MAP
  - The Rush Memory and Aging Study
  - subjects recruited beginning in 1997
  - older lay people from the Chicago metropolitan area.
- Participants ≥ 65 years of age are enrolled without dementia
- Undergo yearly cognitive evaluations, with serum collection
- Donate their brains after death.
- Over 1300 brains have been collected from those with at least 2 cognitive evaluations

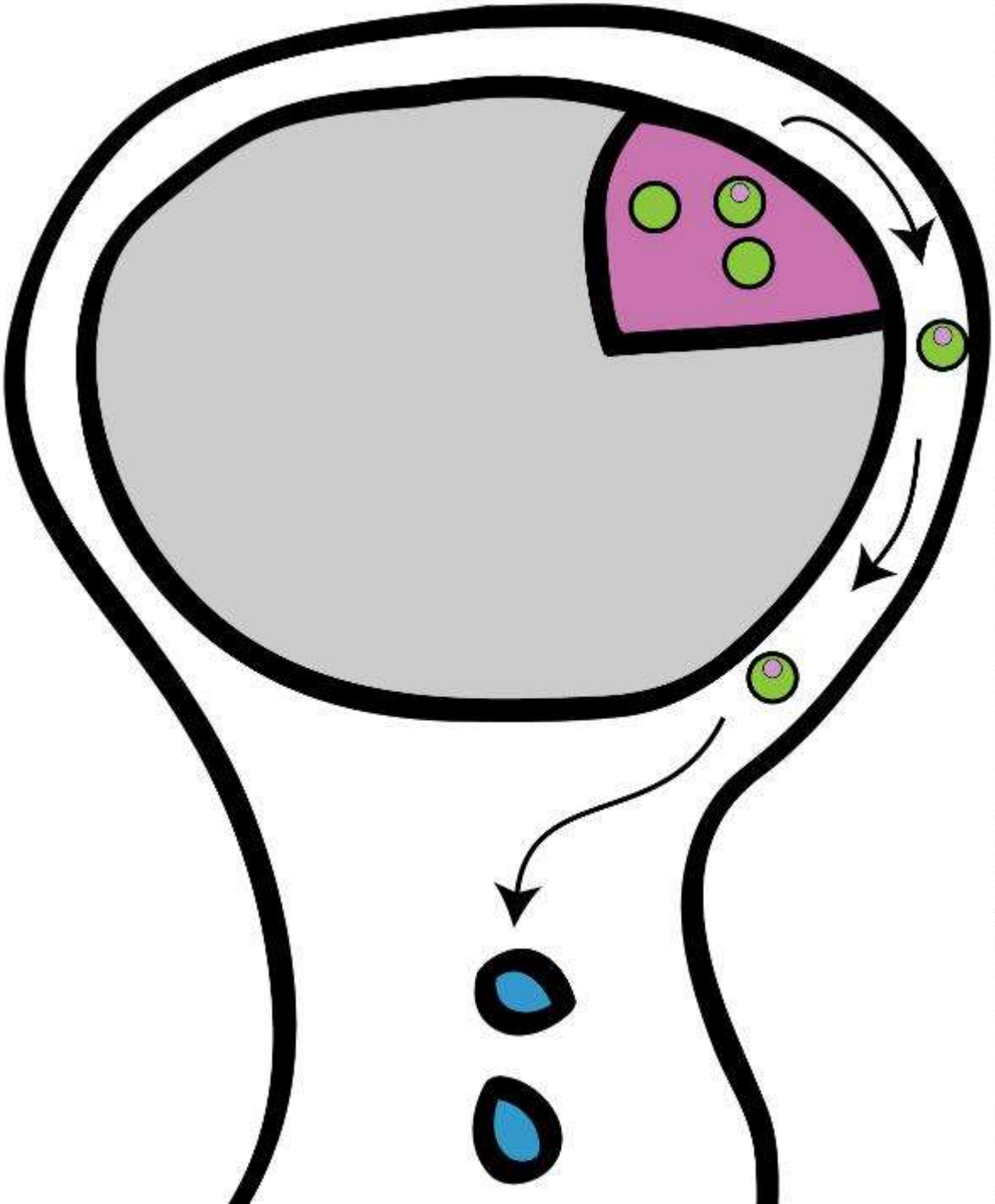
B lymphocytes in the stroke core of a person with dementia and stroke

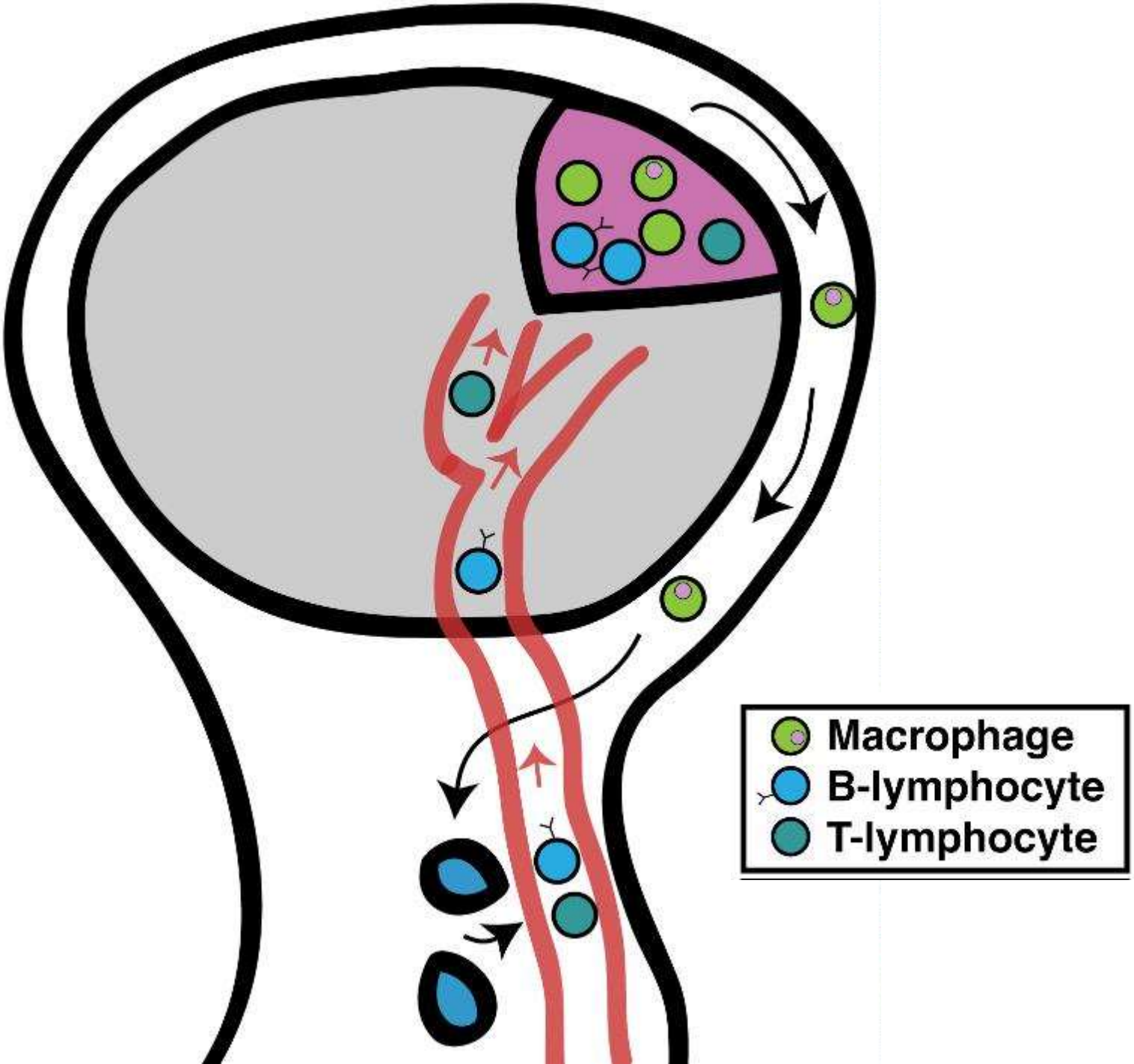


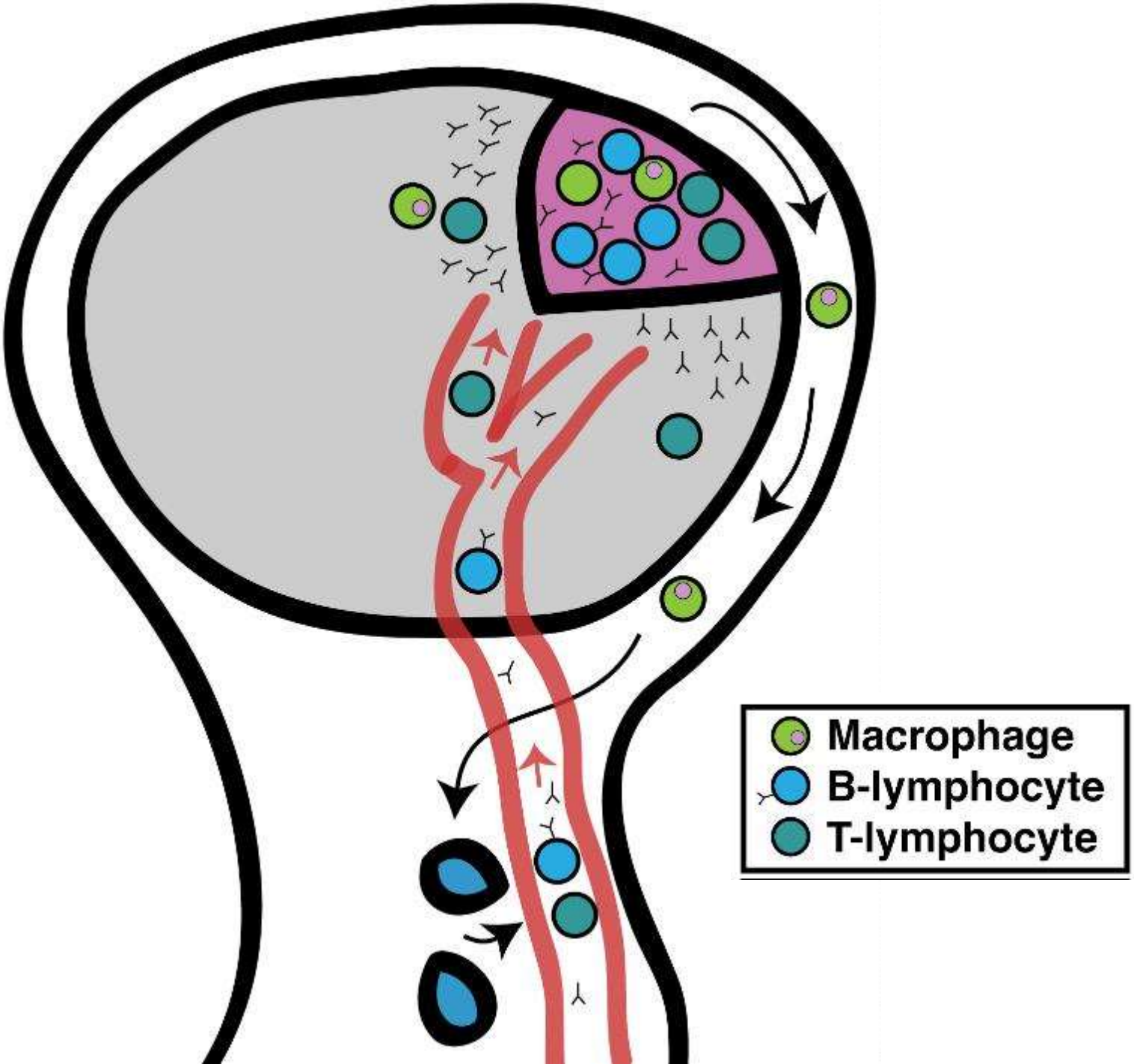









Macrophage
B-lymphocyte
T-lymphocyte


Macrophage
B-lymphocyte
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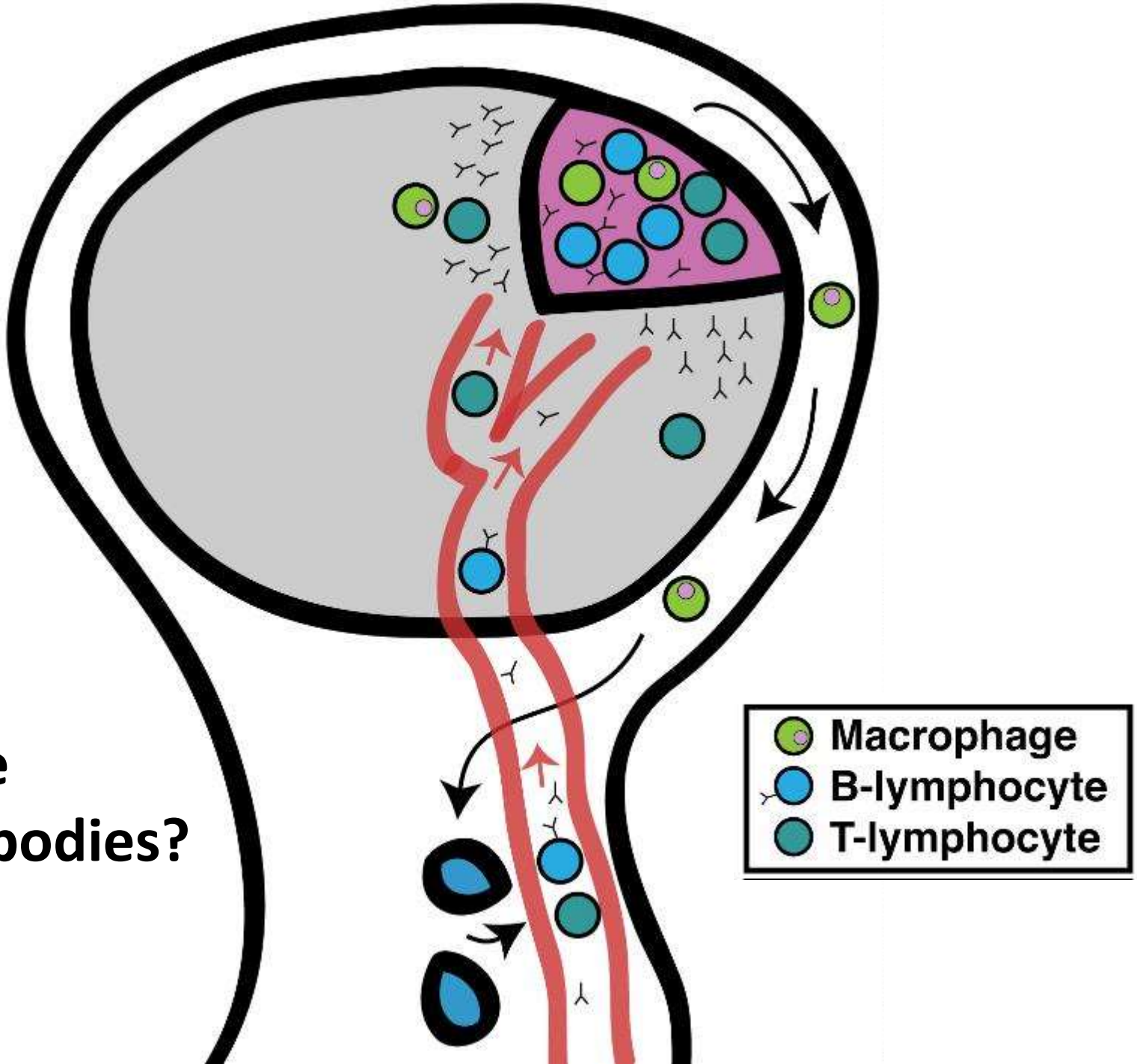
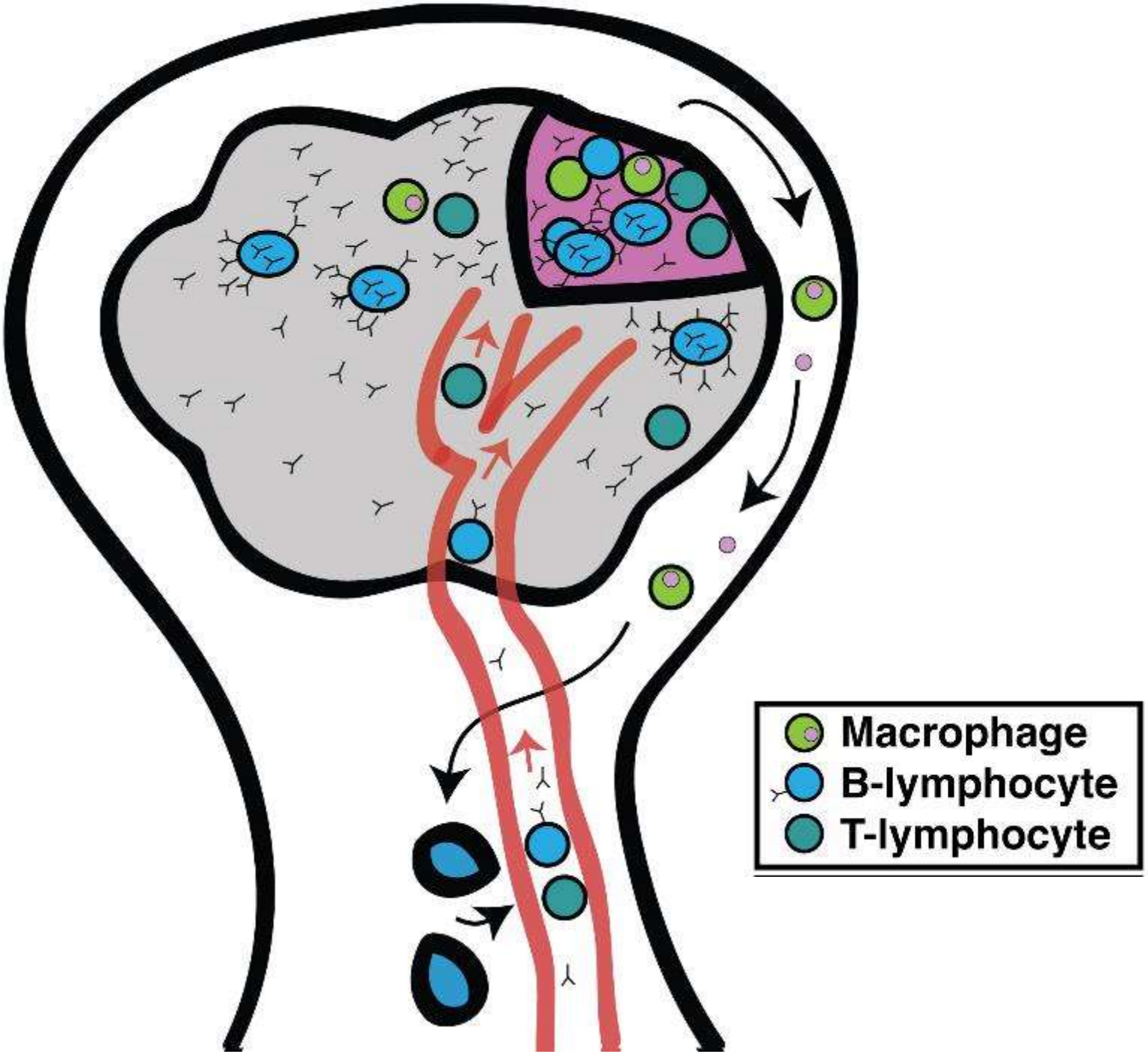
Are there autoantibodies?




Macrophage
B-lymphocyte
T-lymphocyte

Depression and Fatigue after stroke

- Stroke confers a 9-fold risk of depression, and 25-33% of stroke survivors get depression
- Fatigue is even more common, up to 75% of stroke survivors
- Perhaps related to “sickness behavior”

Post-stroke Depression

- Risk factors are prior history of depression, worse disability, and poorer social support
- More negative than positive symptoms
- An independent predictor of poor long term outcomes
- Associated with cognitive impairment

Is post-stroke depression related to long term inflammation?

- Inflammation is common after stroke
- Inflammation is linked to depression
- Depression is common after stroke

Thus, there seems as if there should be a link between PSD and inflammation. However there is no definitive link to date.

- Small studies have linked post-stroke depression to high CRP and low Vitamin D (immunoregulatory)
- Some links to anti-inflammatory use in a large observational Danish cohort – less depression early after stroke and more after one year

Becker, Neurotherapeutics (2016) 13:801–810
Wium-Anderson, J Psychiatry Neurosci 2017, 42(5)

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Frank Longo
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