A test of the hypothesis that factors acting to protect synapse function will lead to an understanding of the biological basis of cognitive reserve

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According to the frameworks developed by the Collaboratory, this study most closely assesses brain reserve

Cognitive Reserve

- Allows for better-than-expected cognitive performance given the degree of brain changes that accumulate across the lifespan.
- These mechanisms are often considered 'active' in that they compensate for brain changes associated with aging, injury, and disease.

Brain Reserve

- Reflects the neurobiological status of the brain.
- Brain reserve does not involve active adaptation to brain changes associated with aging, injury, and disease.
- Brain maintenance facilitates brain reserve.

Regardless of age, animals with more durable long-term potentiation (LTP) also have more durable memory. **Therefore, individual differences in plasticity at the synapse could be a brain property that contributes to individual differences in cognitive performance** (Barnes and McNaughton, 1985 *Behav. Neurosci.)*.

This study tests whether two distinct protein complexes that regulate synapse plasticity and structural stability are differentially expressed in high- vs. low-performing aging rats

The brain extracellular matrix (ECM) provides physical and biochemical support to neuronal structures, regulates membrane excitability, and are involved in mechanisms of plasticity.

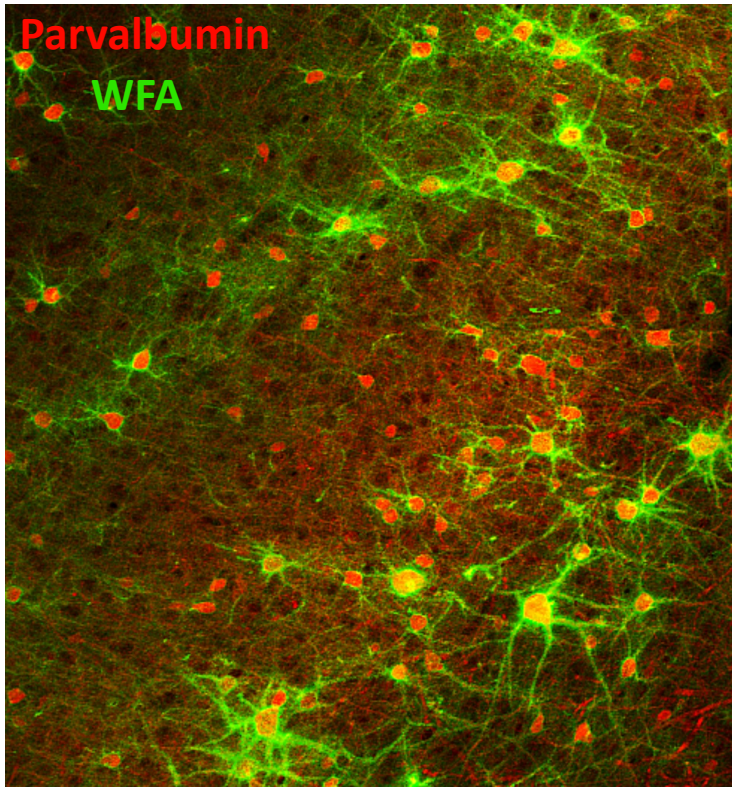
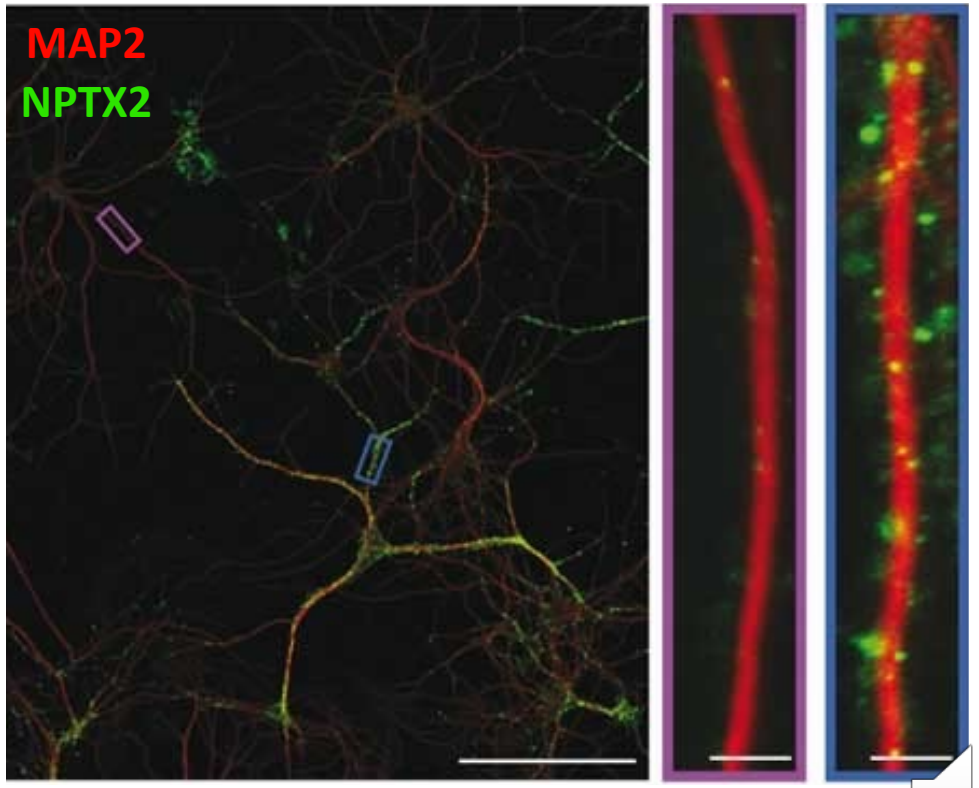


Image from Barnes Lab Macaque Colony

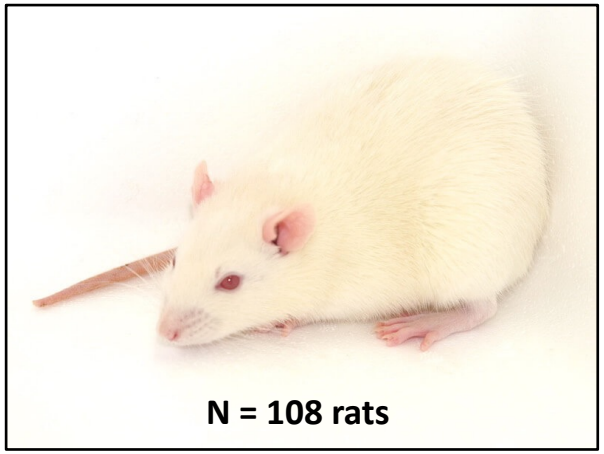
The plasticity-related protein neuronal pentraxin 2 (NPTX2) is critical in rebalancing network excitation/inhibition dynamics following episodes of increased activity.



Chang et al., 2010 *Nat. Neurosci.*

The Cognitive Aptitude Study (CAS) was designed to assess factors that contribute to individual differences in cognitive performance across the normative aging process

Animal model: adult (6-8mo), middle-aged (15-17mo) and aged (23-25mo) male F344 rats.

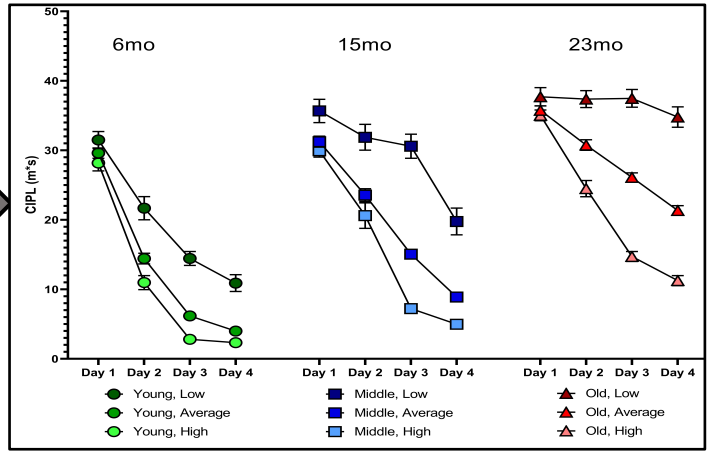


N = 108 rats

All rats underwent a behavioral battery over the course of 6 weeks.

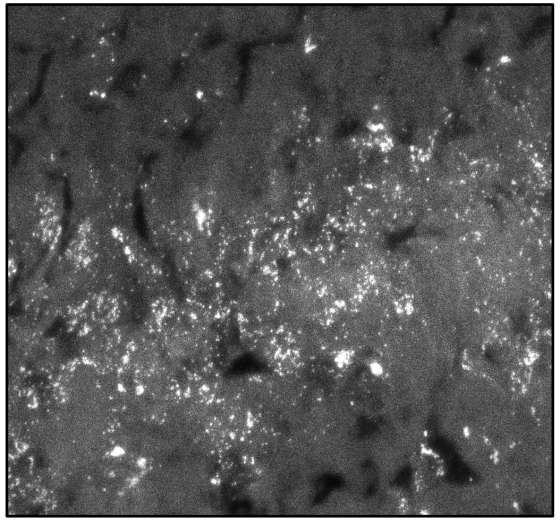
Week 1	Morris watermaze (spatial and cued)
Week 2	Spontaneous object recognition
Week 3 - 4	Working memory adaptation of Morris watermaze
Week 5-6	Spatial location/ temporal ordering task

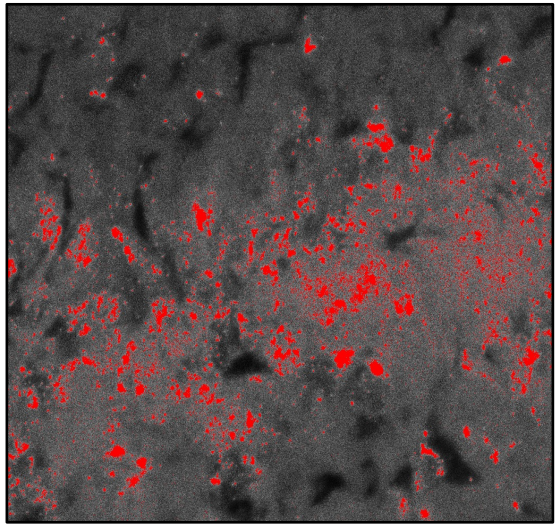
Animals in each age-group were statistically-classified as high-, average-, or low-performing for their age group.

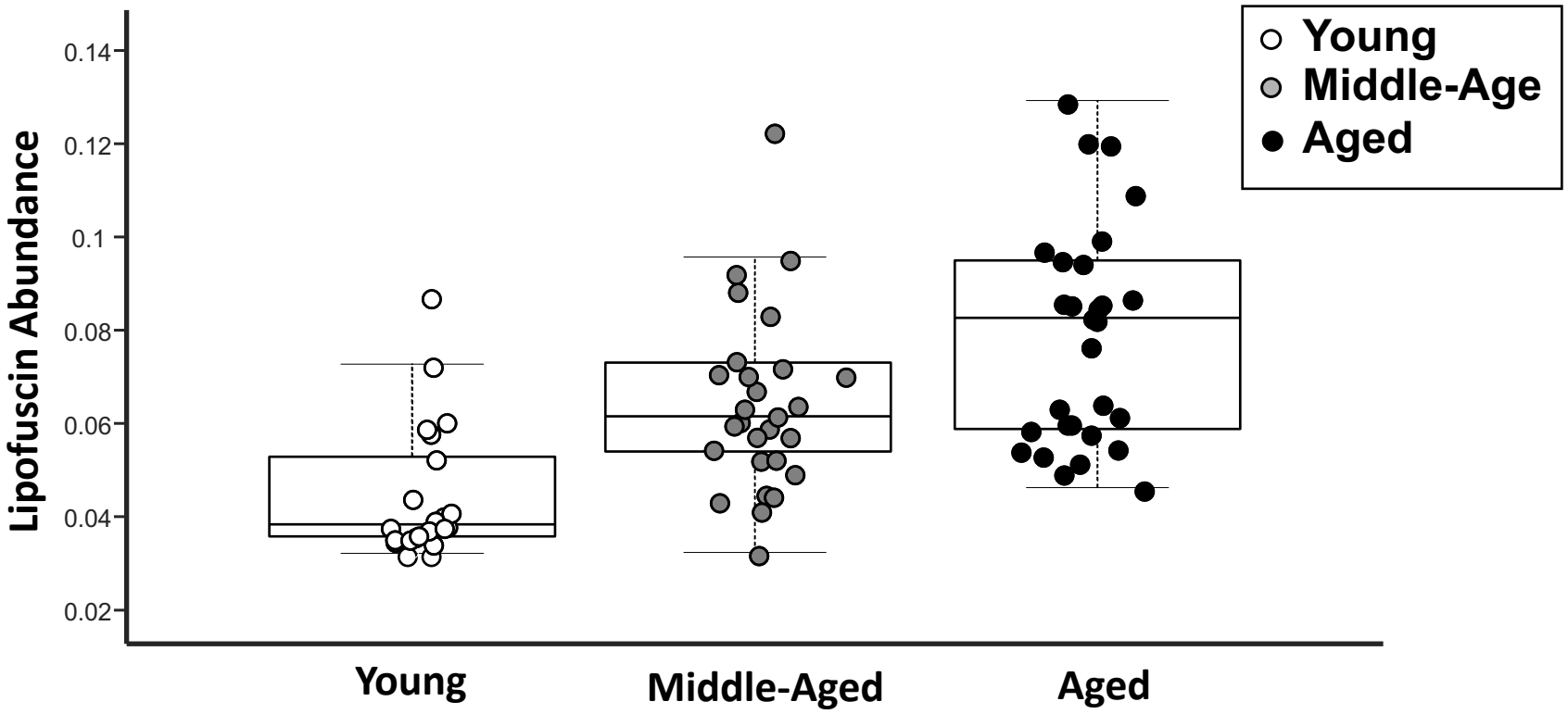


Brains from all rats were extracted fresh, flash frozen, and cut into coronal brain sections using a cryostat for *in situ* hybridization and immunohistochemical experiments.

Lipofuscin-associated autofluorescence increases with age

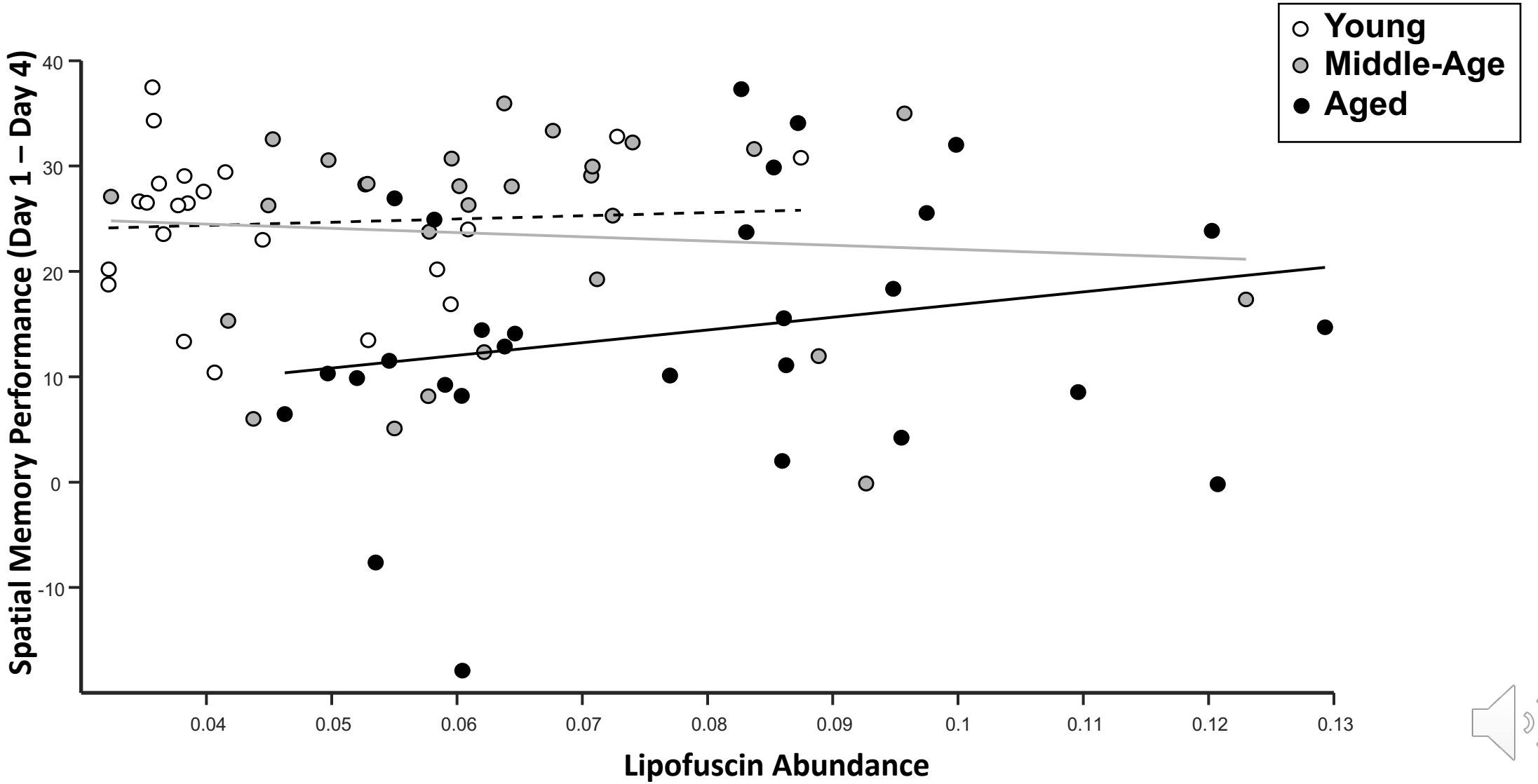




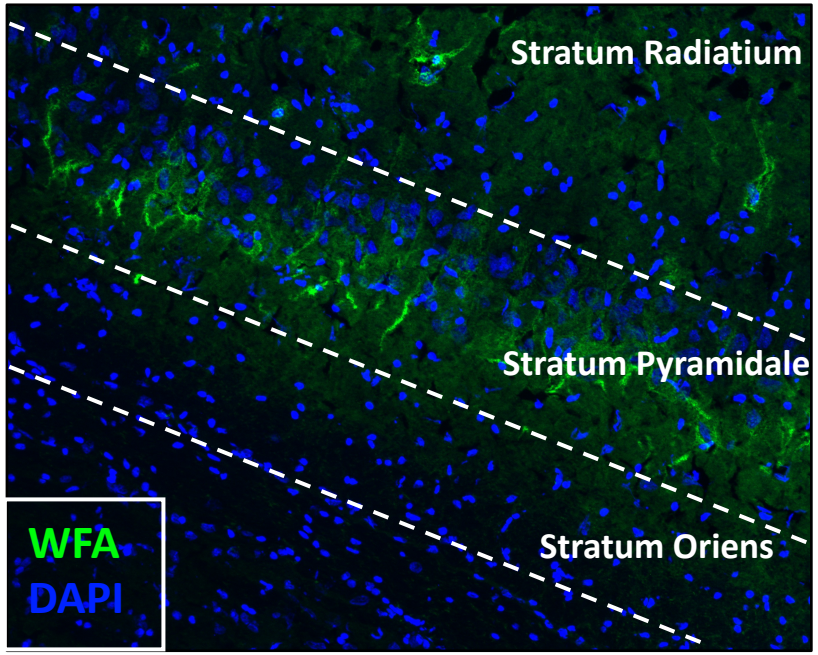


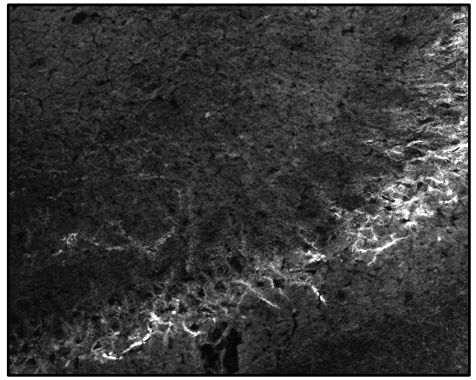
Note: lipofuscin is a fluorescent pigment that accumulates with age in lysosomal compartments in multiple tissue types, including the brain.

Lipofuscin-associated autofluorescence was not associated with spatial memory abilities in any age group

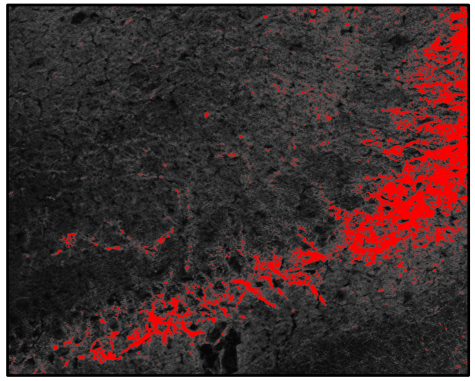


Supportive extracellular matrix proteins decline with age

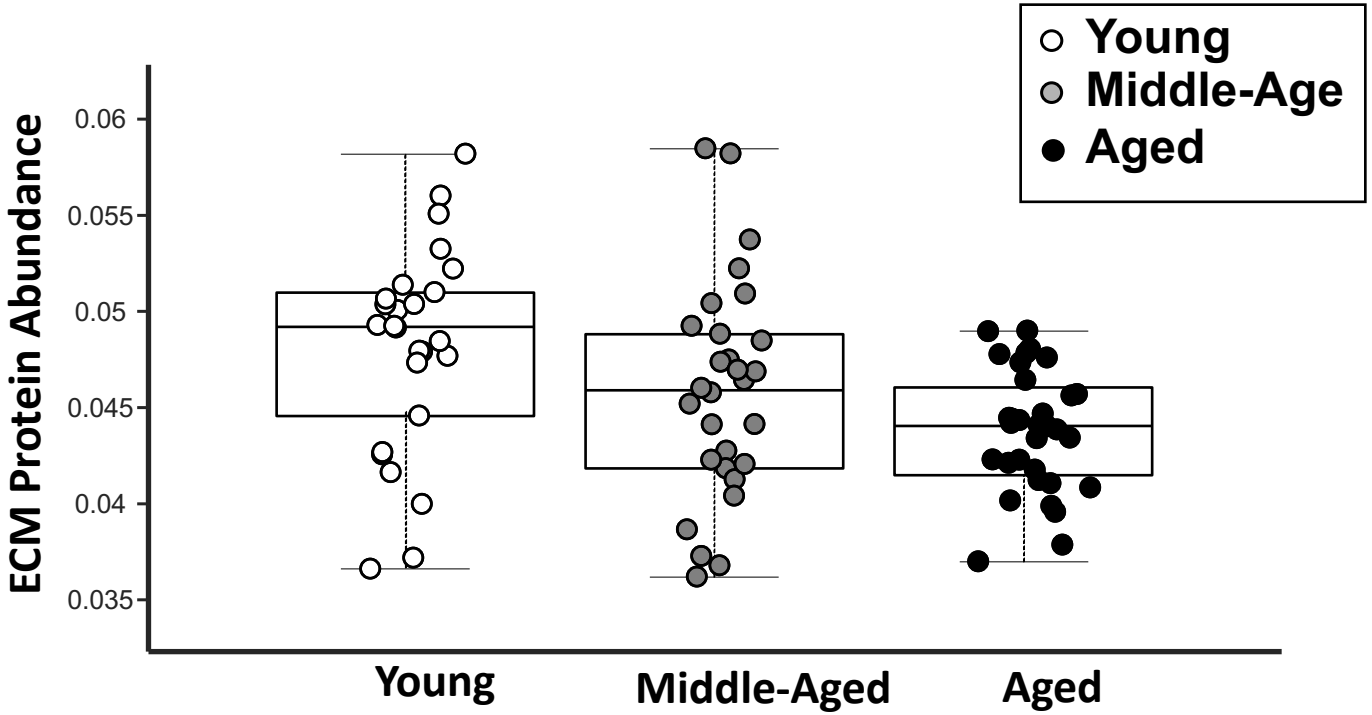




Raw Image

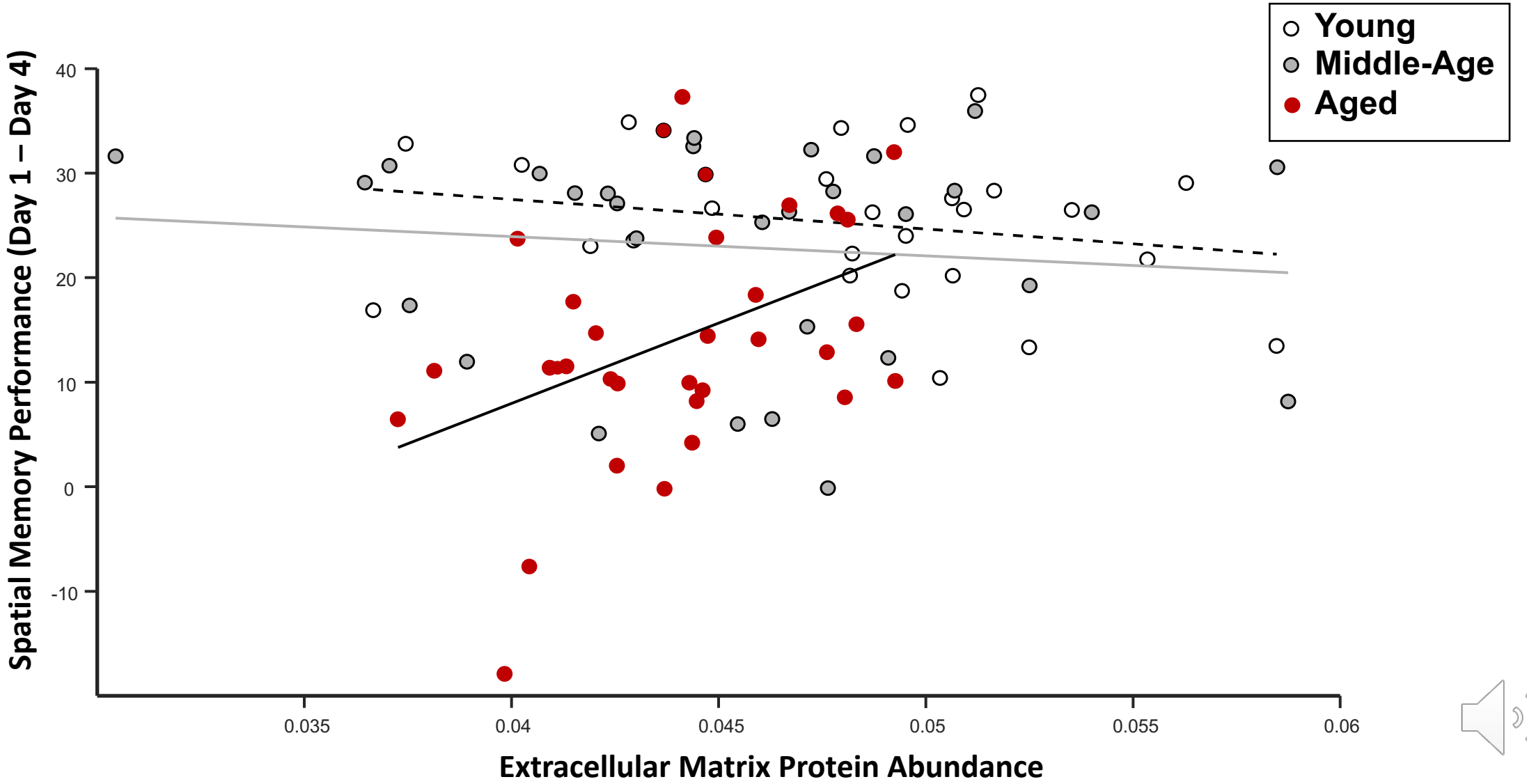


Threshold Image

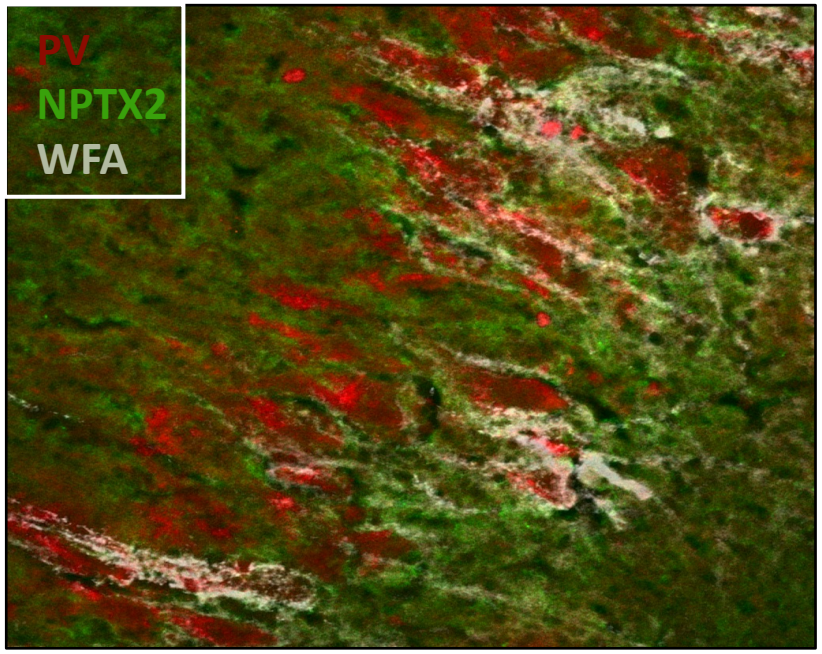


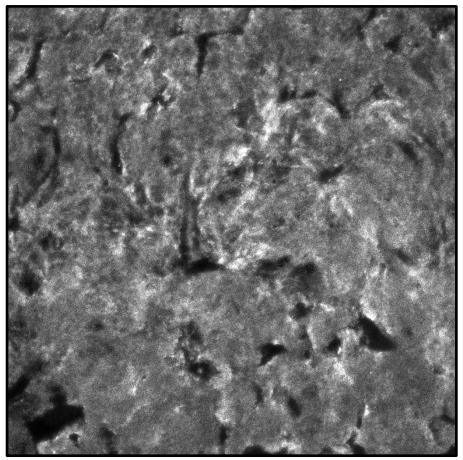
Note: Wisteria floribunda agglutinin (WFA) labels numerous glycoproteins within the extracellular matrix surrounding neurons.

The levels of extracellular matrix proteins hypothesized to protect synapses are associated with spatial memory abilities only in aged rats



NPTX2 abundance is not different with age





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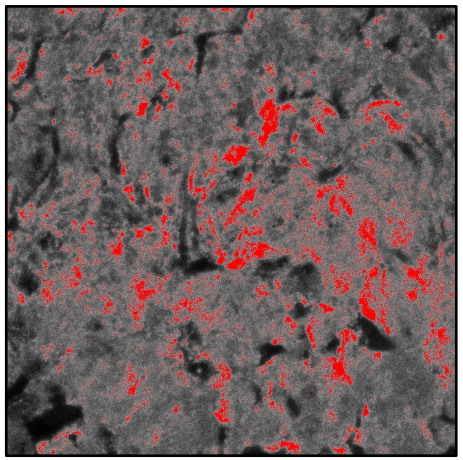

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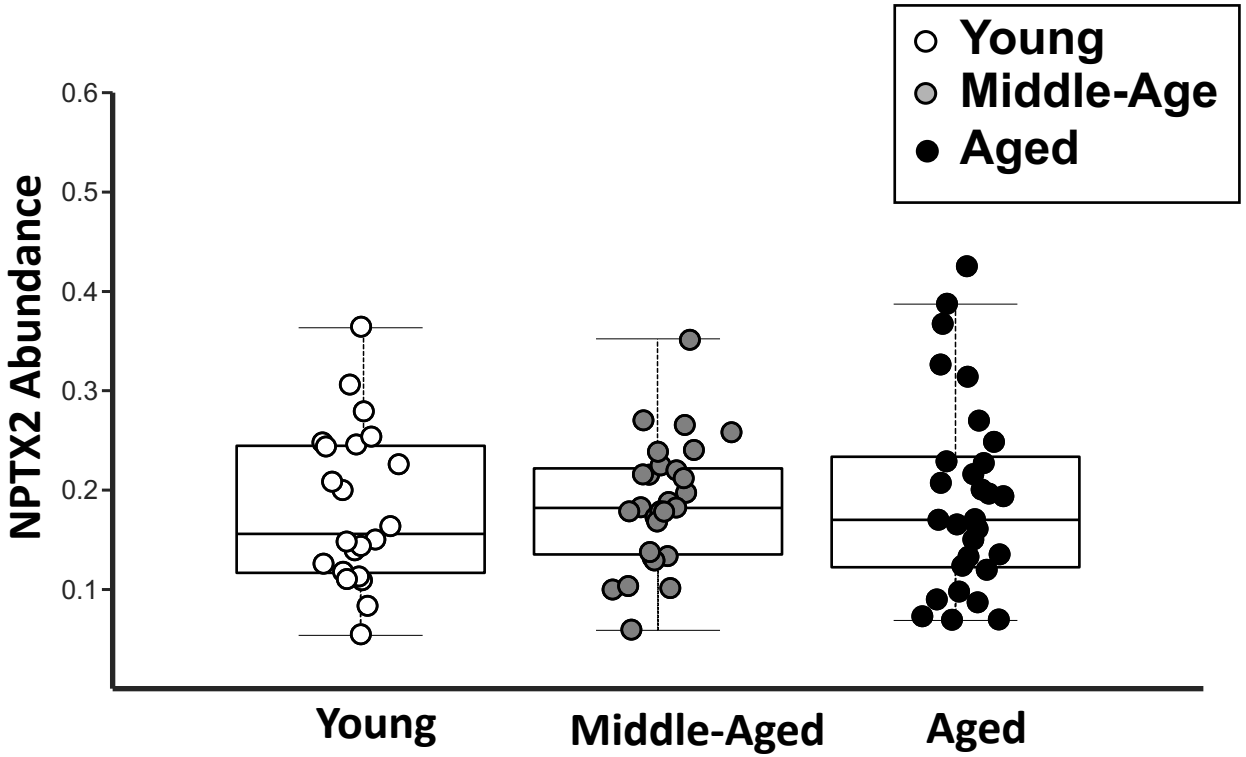

Note: this preparations does not distinguish between intracellular and extracellular NPTX2.

- This dataset provides examples of neurobiological variables that do not correlate with cognition in any age group:
  - 1) Lipofuscin levels do increase with age in CA3.
  - 2) NPTX2 levels do not decline with age in CA3.

- This dataset also provides an example of a neurobiological variable that does correlate with cognition in aged rats.
  - 3) Extracellular matrix protein levels do decline with age in CA3.

These observations are consistent with the hypothesis that extracellular matrix structures provide support to hippocampal circuit function that **is most engaged later in the lifespan.**

These data may suggest that **the structural and biochemical support provided by the extracellular matrix could be among the factors that contribute to brain reserve at hippocampal synapses**.