Higher microglia densities are associated with reduced perineuronal net accumulation around parvalbumin-expressing neurons in the retrosplenial cortex of memory-impaired aged macaques

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Background

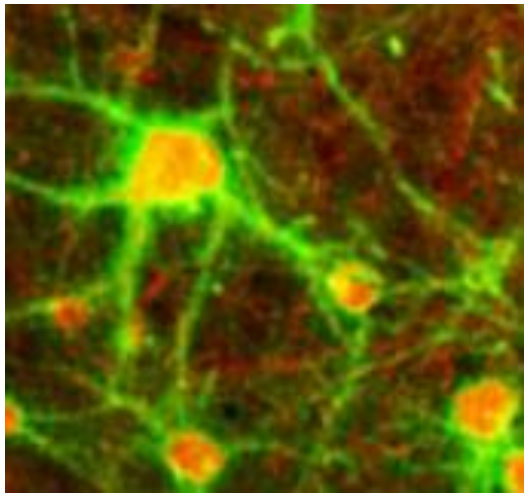
Neurobiological changes in the aging brain contribute to age-associated cognitive decline

Microglia

- Regulate synaptic plasticity
- Increased activity with aging

Perineuronal nets (PNNs)

- ECM structures that surround parvalbumin-containing GABAergic (PV) interneurons
- Reduce brain plasticity & maintain synapse function
  - Limited data in rodents show reduced PNNs in aged animals



PV interneuron
PNN

Goal: further understand possible contributions of PNN and microglia density to age-associated cognitive decline

Methods

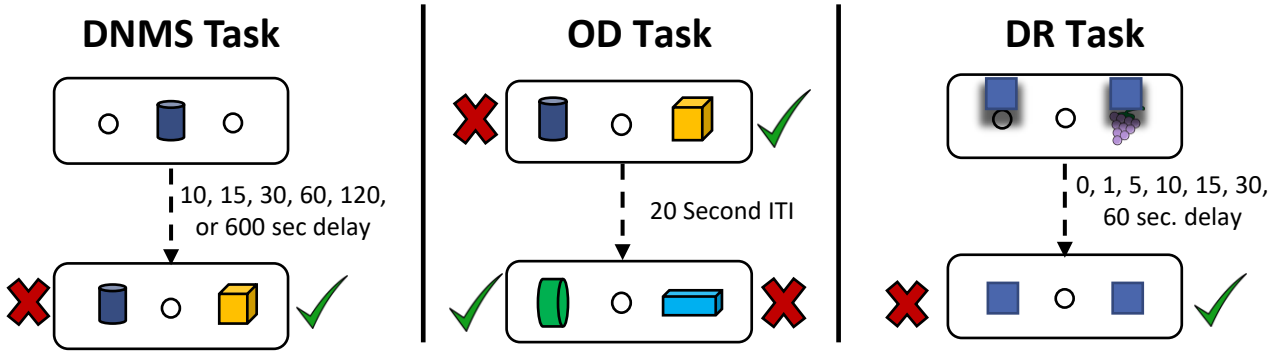
Subjects: 16 aged and 14 adult rhesus macaques

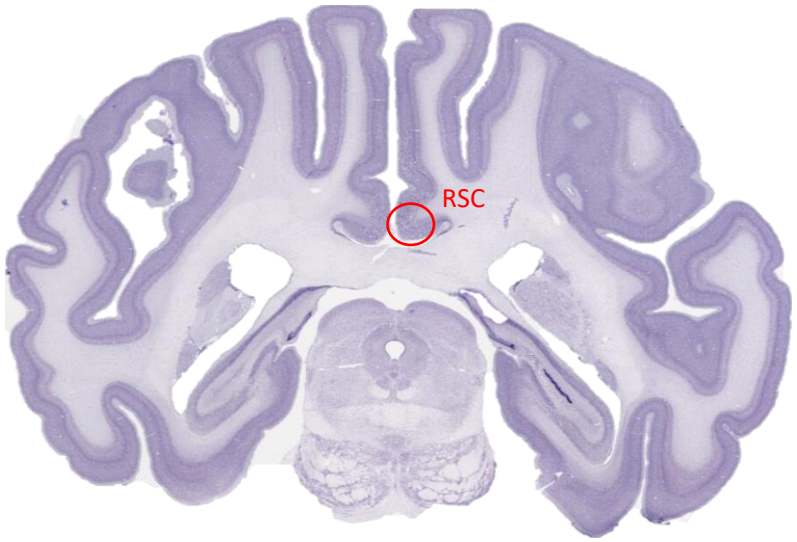
Cognitive Assessment:

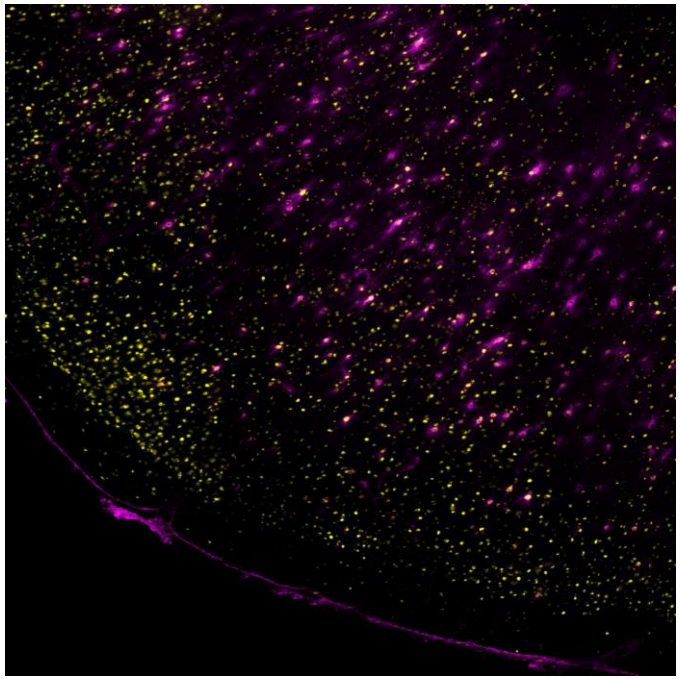
A. Delayed nonmatching-to-sample (**DNMS**) → object recognition memory

B. Object discrimination (**OD**) → stimulus-reward association memory

C. Delayed response (**DR**) → spatial short-term memory







Sections:

- Brains were fixed in 4% PFA, cut coronally at 30µm & hemisected

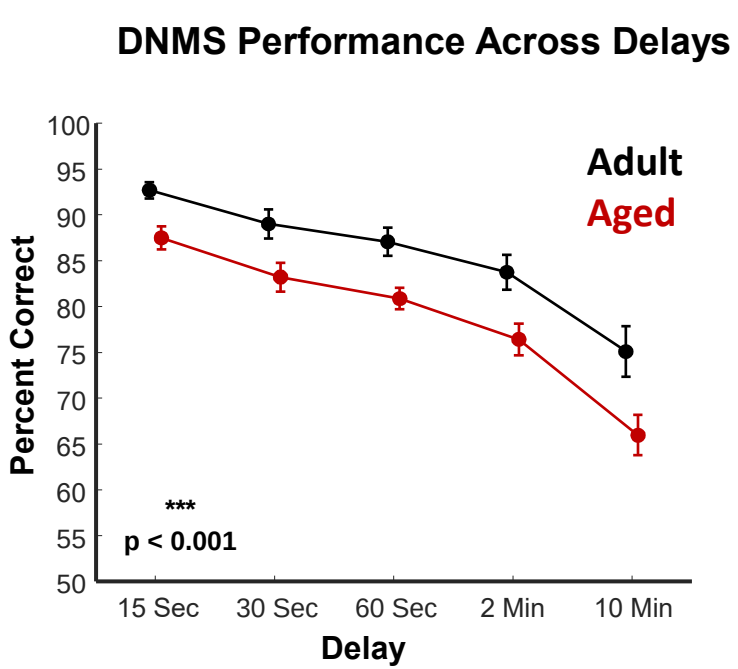
Immunohistochemical labelling:

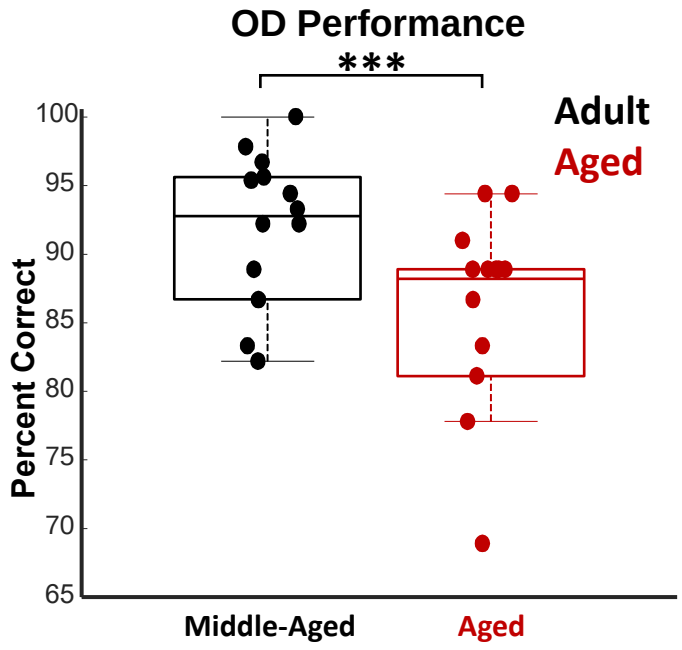
- Parvalbumin interneurons (**PV**)
- Component of PNNs (**WFA**)
- Aggrecan (**ACAN**) or microglia (**IBA1**)

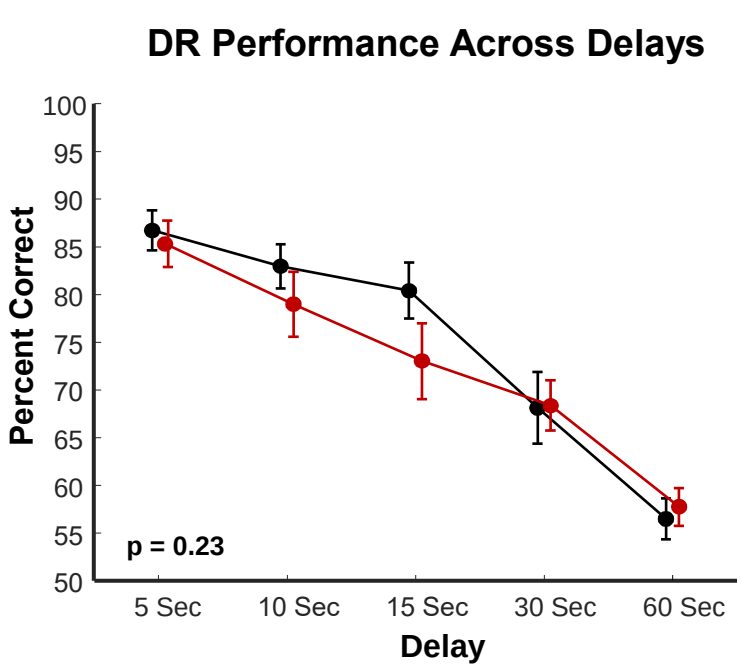
Imaging:

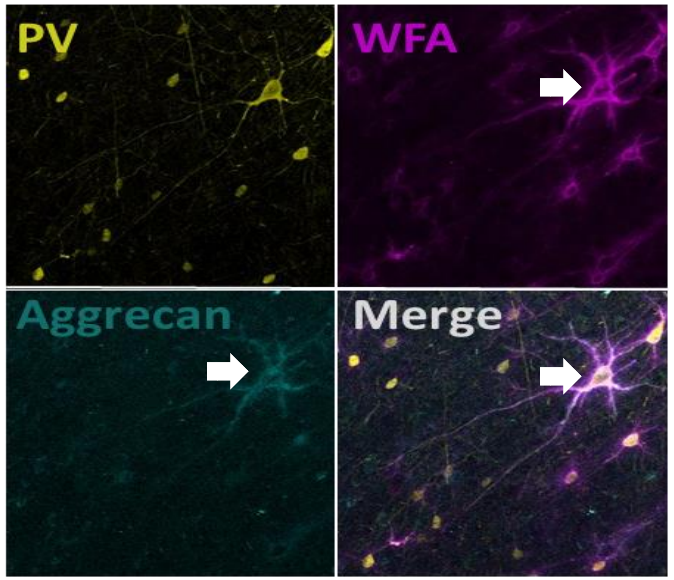
- Retrosplenial cortex (RSC) was imaged at 20x

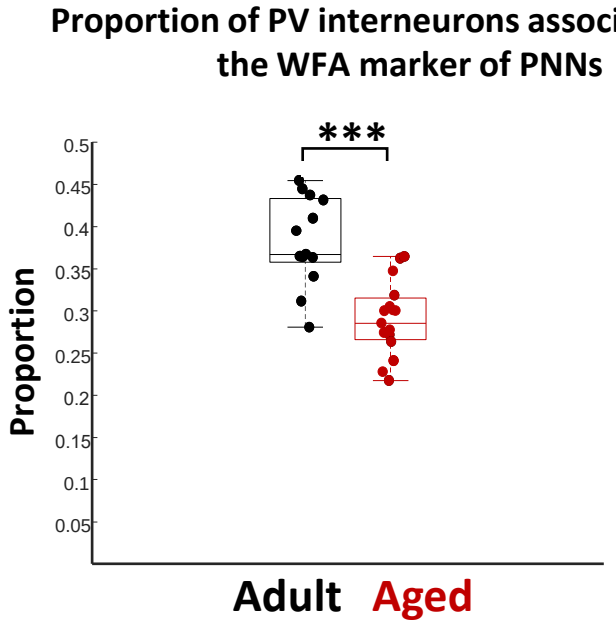
Behavior Results

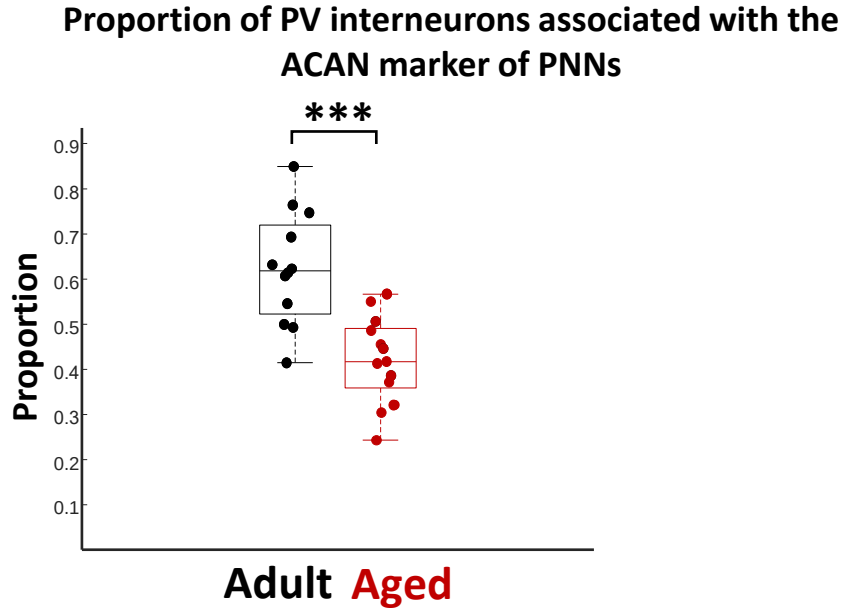


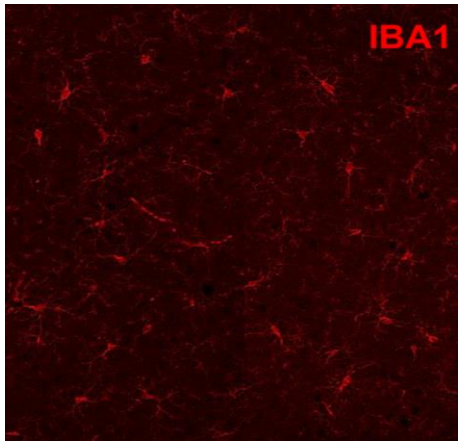


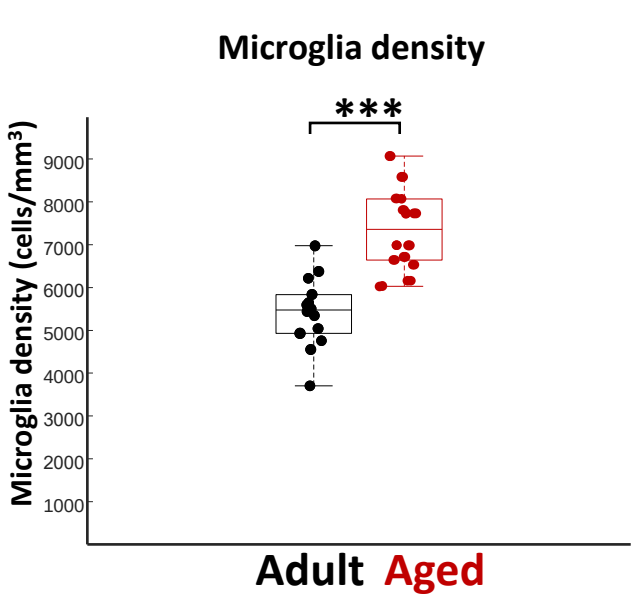


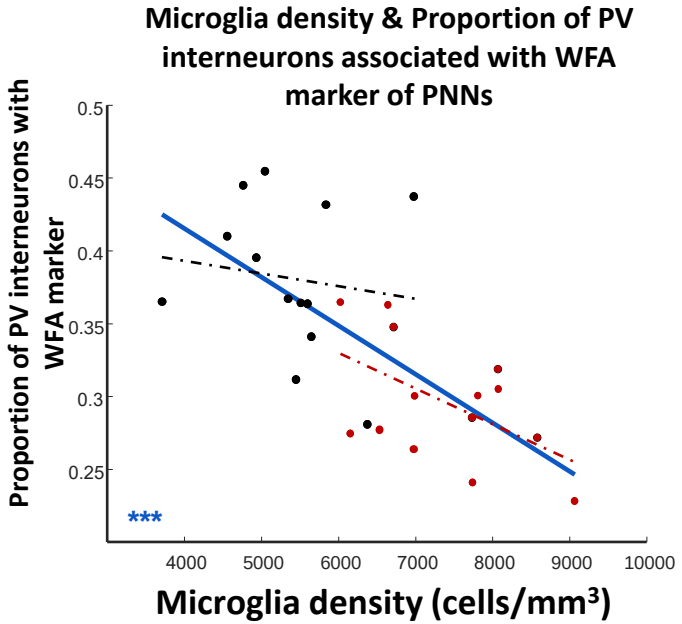

PV
WFA
Aggrecan
Merge

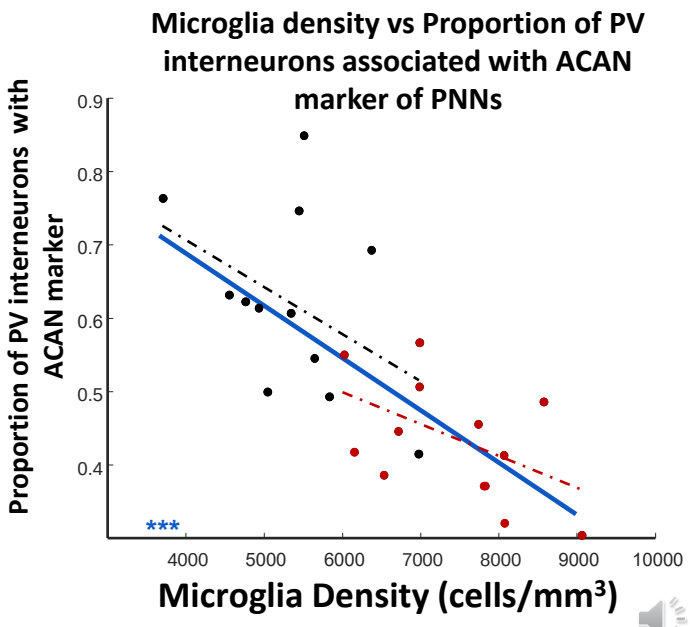

Proportion of PV interneurons associated with the WFA marker of PNNs
***
Proportion
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
Adult
Aged


Proportion of PV interneurons associated with the ACAN marker of PNNs
***
Proportion
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Adult
Aged


IBA1

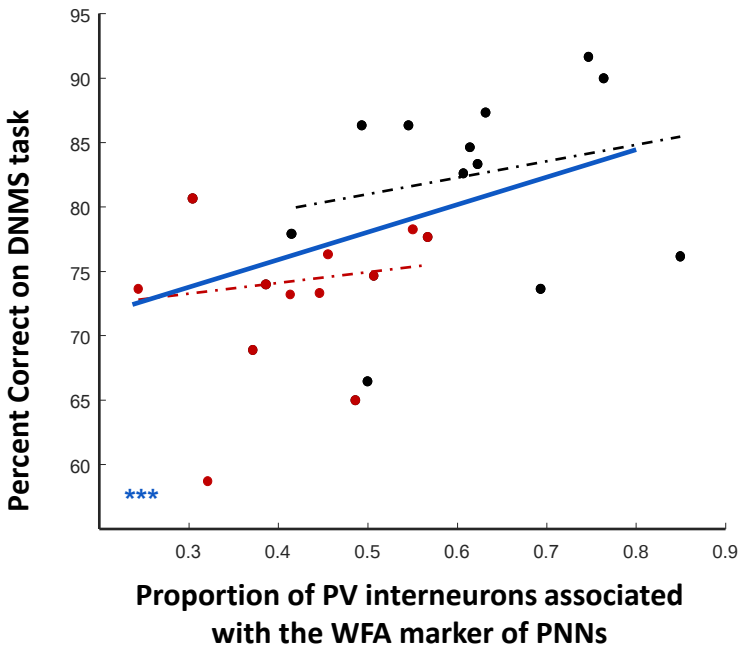

Microglia density
***
Microglia density (cells/mm³)
9000
8000
7000
6000
5000
4000
3000
2000
1000
Adult
Aged


Microglia density & Proportion of PV interneurons associated with WFA marker of PNNs
Proportion of PV interneurons with WFA marker
0.5
0.45
0.4
0.35
0.3
0.25
***
4000
5000
6000
7000
8000
9000
10000
Microglia density (cells/mm³)

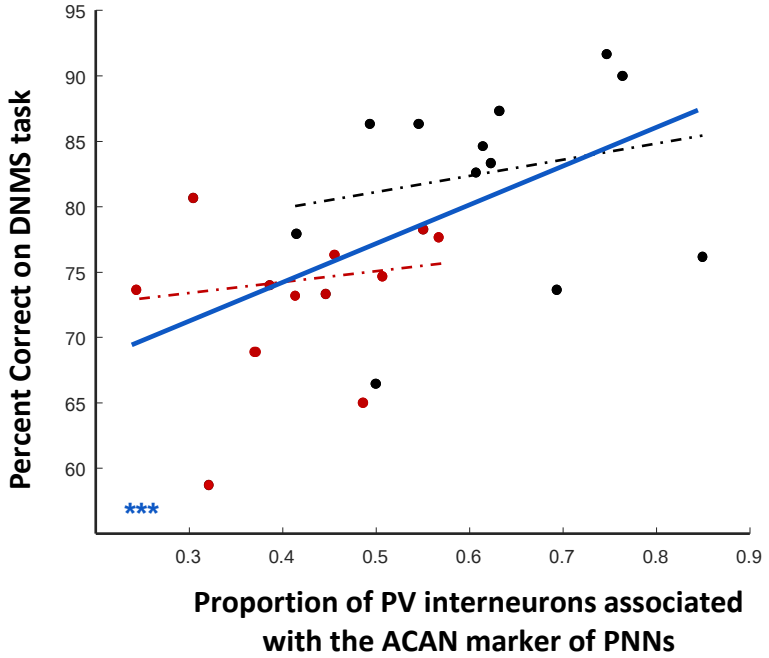

Microglia density vs Proportion of PV interneurons associated with ACAN marker of PNNs
Proportion of PV interneurons with ACAN marker
0.9
0.8
0.7
0.6
0.5
0.4
***
4000
5000
6000
7000
8000
9000
10000
Microglia Density (cells/mm³)

Anatomy and Delayed Nonmatching-to-Sample Task

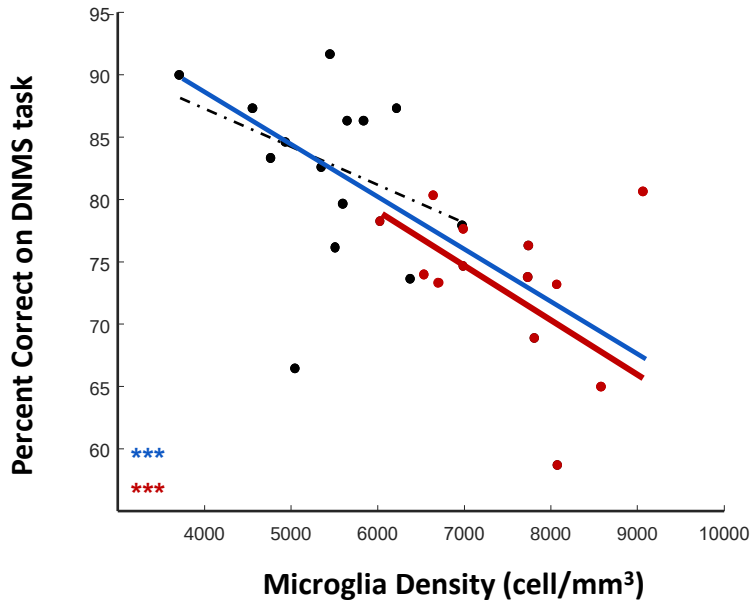
DNMS Performance & Proportion of PV interneurons associated with the WFA marker of PNNs



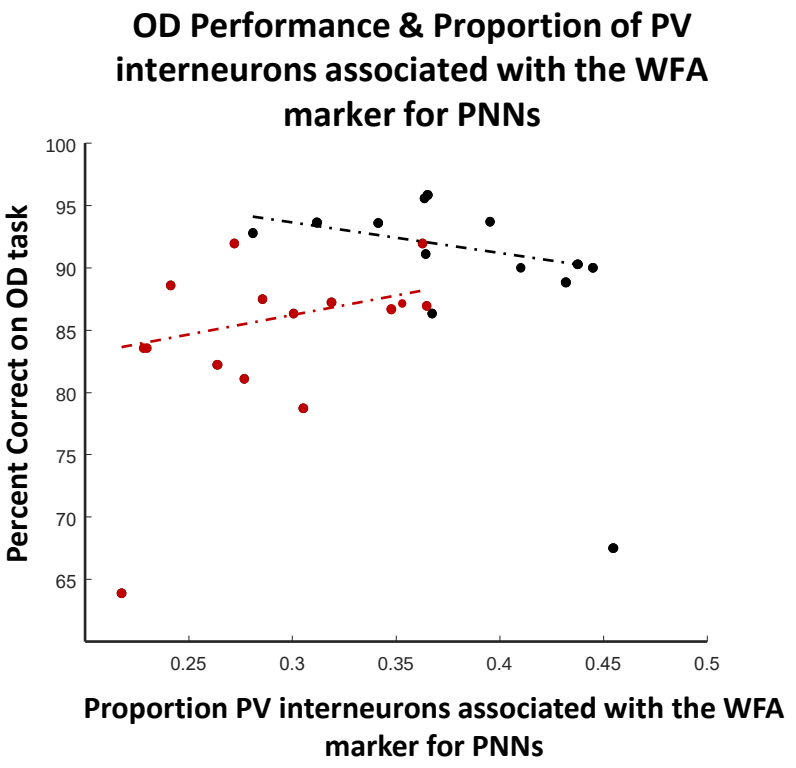
DNMS Performance & Proportion of PV interneurons associated with the ACAN marker of PNNs

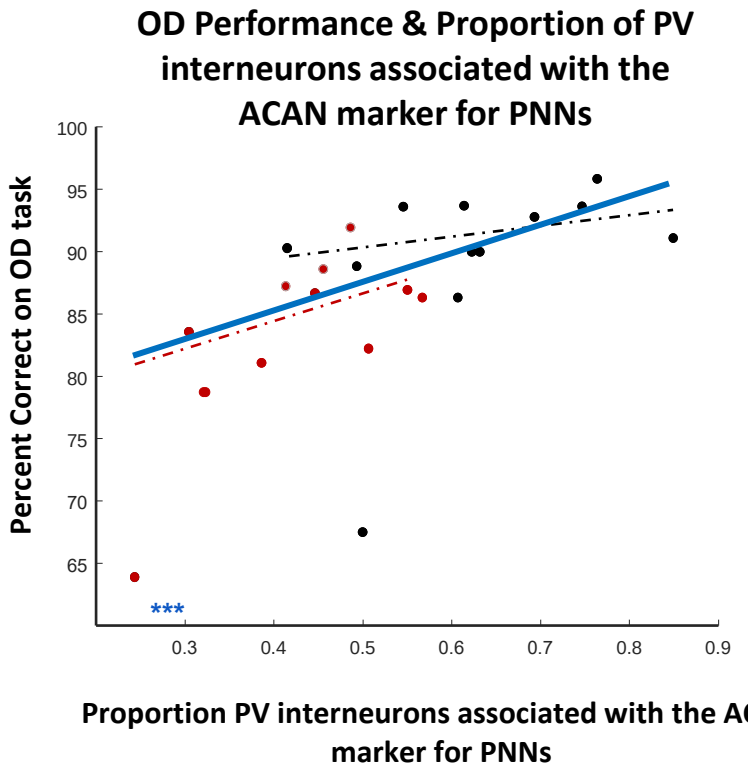


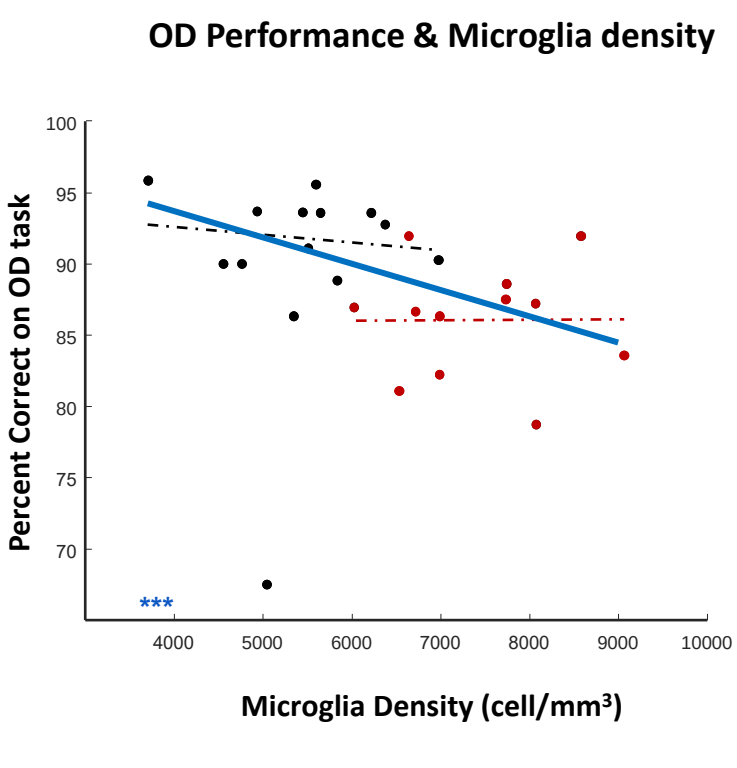
DNMS Performance & Microglia Density



Anatomy and Object Discrimination Task

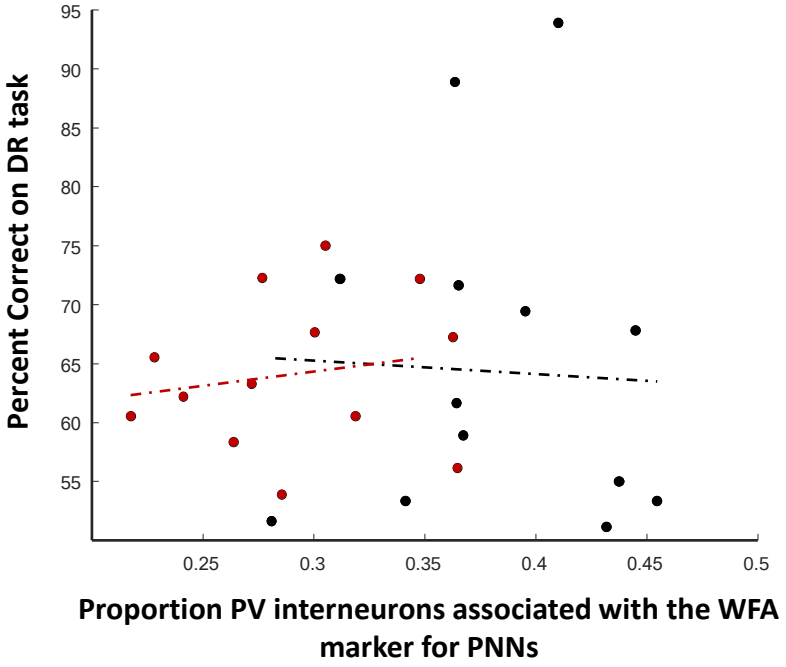




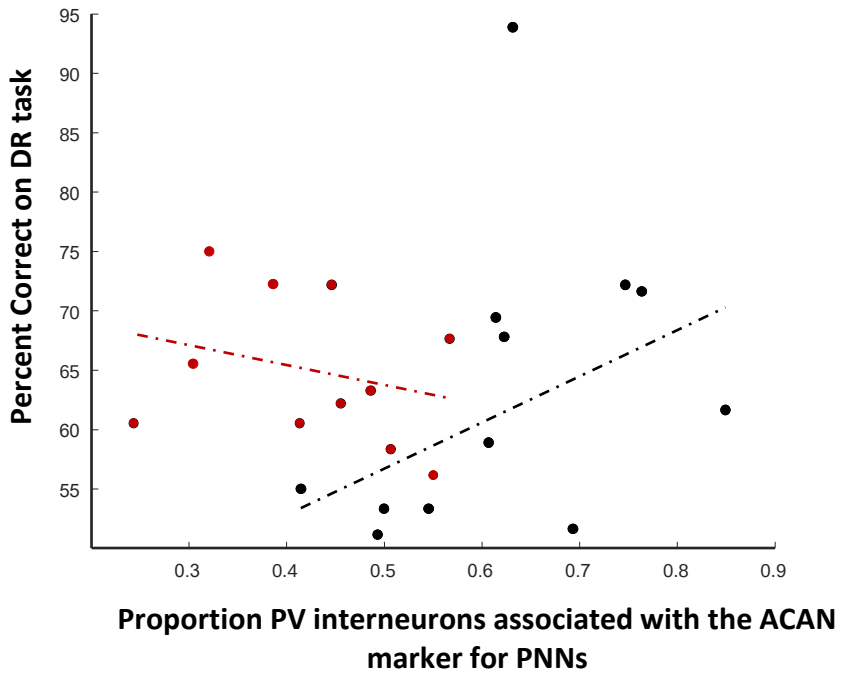


Anatomy and Delayed Response Task

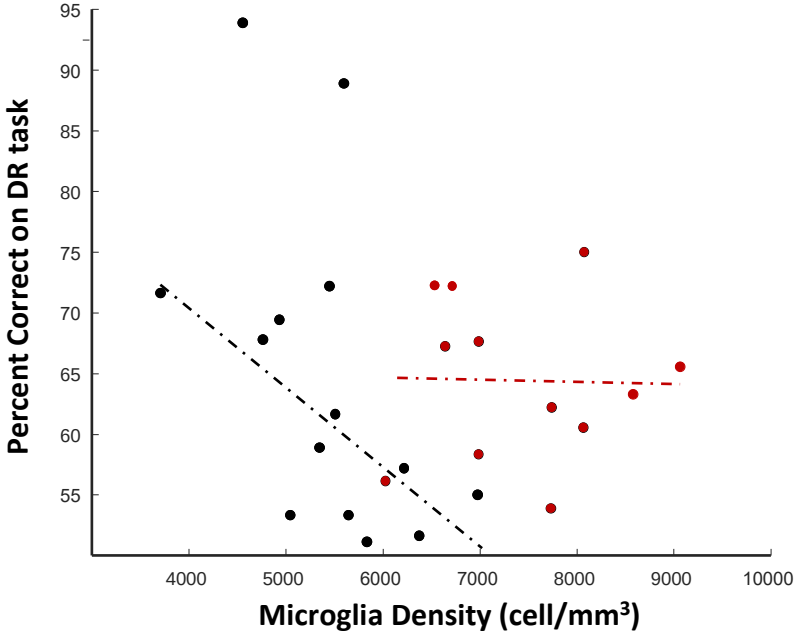
DR Performance & Proportion of PV interneurons associated with the WFA marker for PNNs



DR Performance & Proportion of PV interneurons associated with the ACAN marker for PNNs



DR Performance & Microglia density



Summary & Conclusions

Summary

- Aged animals have a lower proportion of PV interneurons associated with PNN's in the RSC compared to younger animals
  - Correlates with impaired performance on object recognition tasks
- Aged animals have higher microglia densities in the RSC than younger animals
  - Correlates with impaired performance on object recognition tasks

Conclusions

- Increased microglia activity seen with aging may contribute to age-associated degradation of ECM structures that has a circuit-specific impact on cognition in aged monkeys

Acknowledgments

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