Microglial morphology and gene expression are altered in individuals resilient to Alzheimer's disease

Nicholas E. Karagas, Corbin S. C. Johnson, Alexandra N. Cochoit, Sainath Mamde, Isabel C. Smith, Aquene N. Reid, K. J. Green, C. Dirk Keene, Thomas J. Grabowski, Caitlin S. Latimer, Kevin Z. Lin, Suman Jayadev, and Katherine E. Prater

UW Medicine
DEPARTMENT OF NEUROLOGY

Alzheimer's Disease (AD) by the numbers

6.7 million

1 in 3

Seniors

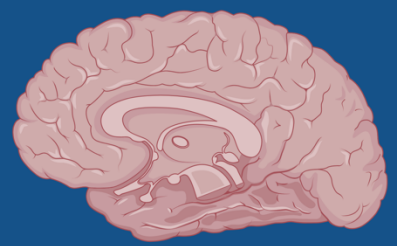
2023 cost:

$345 billion

Alzheimer's Association (www.alz.org)

Age

Genetics



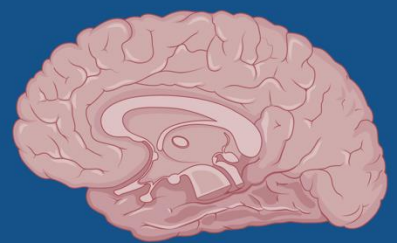
Environment

Lifestyle

Adapted from Latimer, Prater, Postupna, & Keene 2022 using BioRender.com

Age

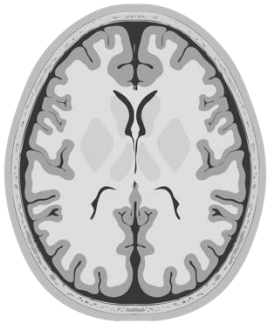
Genetics



Environment

Lifestyle

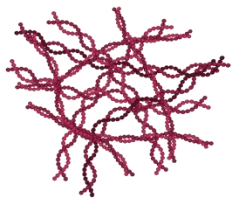
Resistance



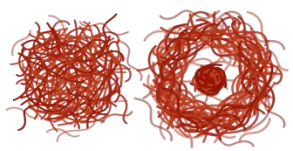
No Dementia

AD Pathology

Tau Tangles



Amyloid Plaques



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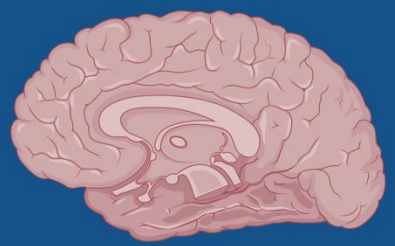
Age

Genetics



Environment

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AD Pathology

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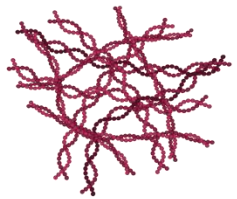

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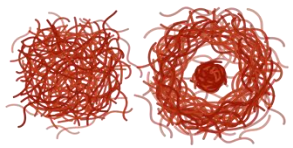
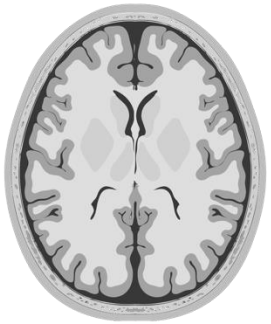
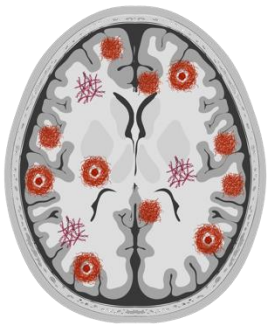


Resilience

Affected



No Dementia



Dementia

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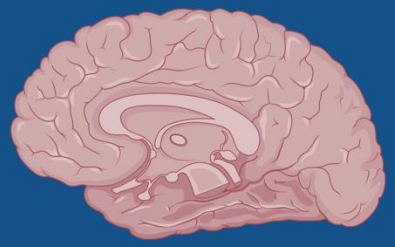
Age

Genetics



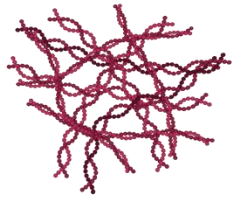
Environment

Lifestyle

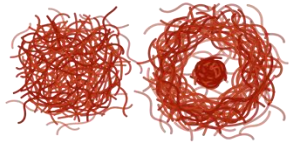
Resistance

AD Pathology

Tau Tangles

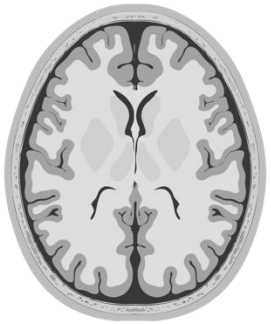


Amyloid Plaques

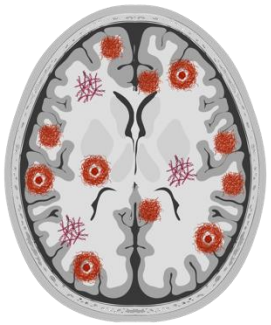


Resilience

Affected



No Dementia



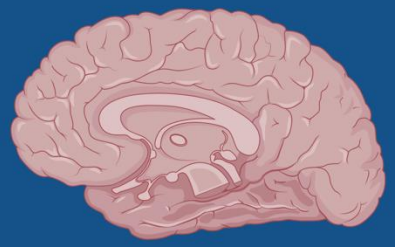
Dementia

What is the effect of pathology (keeping cognition constant)?

Adapted from Latimer, Prater, Postupna, & Keene 2022 using BioRender.com

Age

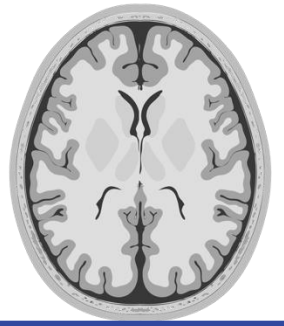
Genetics



Environment

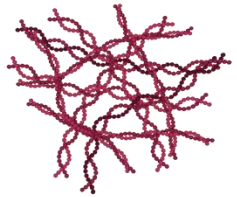
Lifestyle

Resistance



AD Pathology

Tau Tangles



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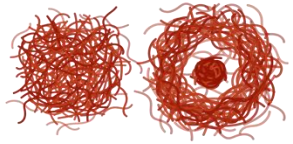

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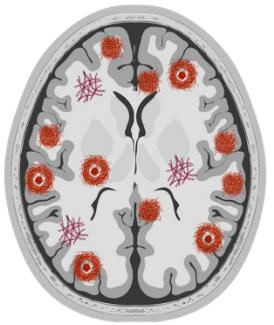
No Dementia



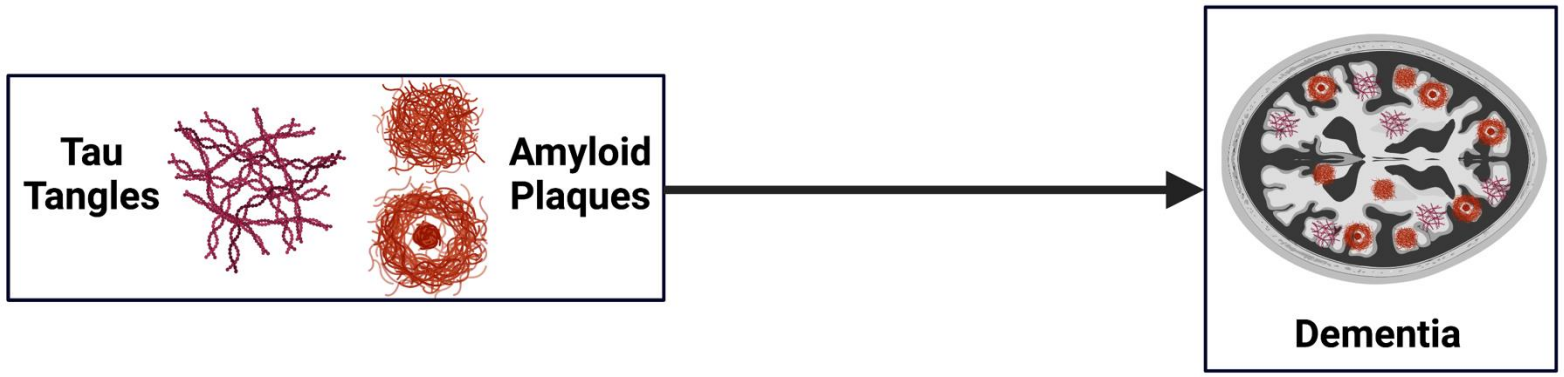
Affected

Dementia

What is the effect of cognitive decline (keeping pathology constant)?

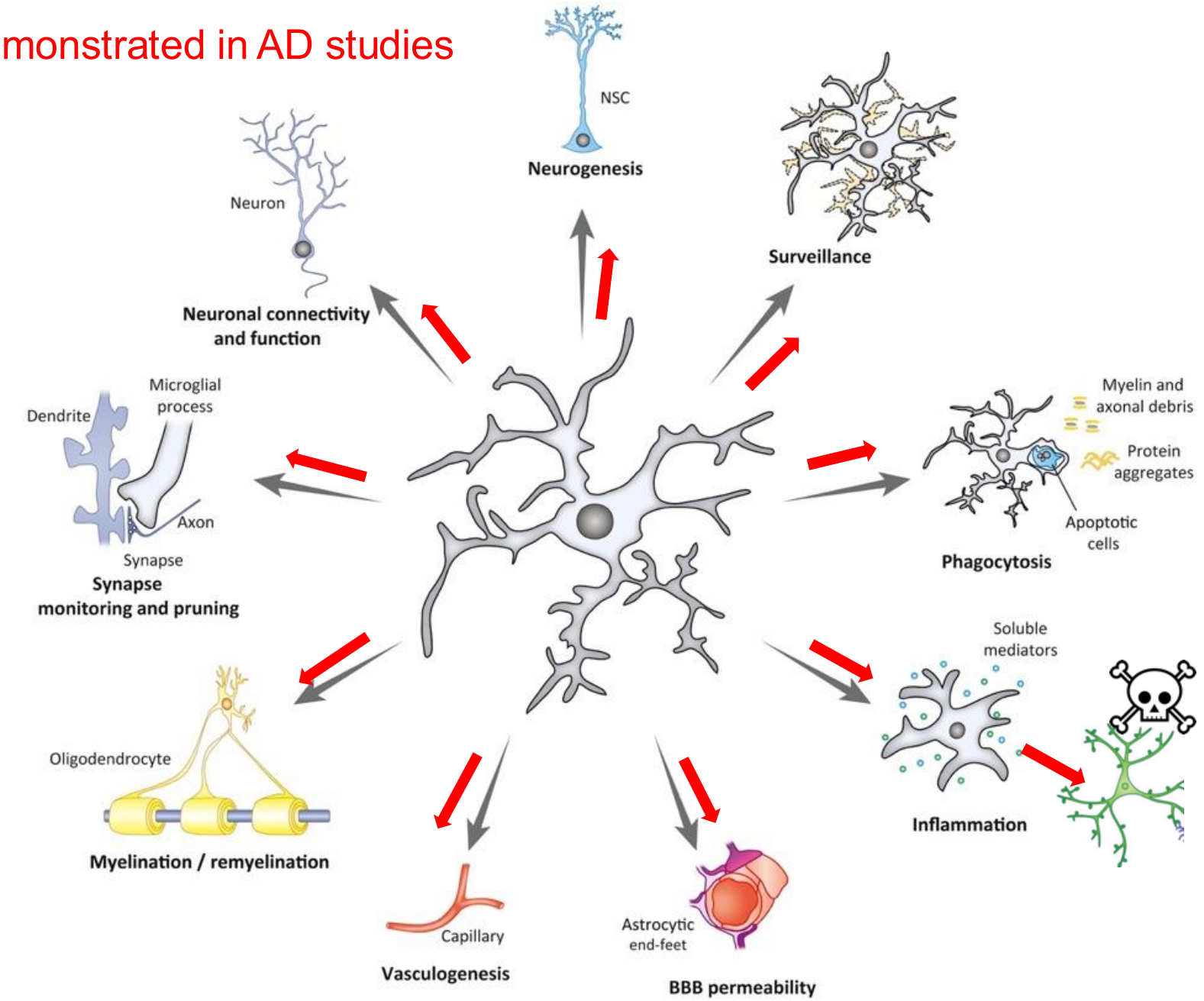
Adapted from Latimer, Prater, Postupn , & Keene 2022 using BioRender.com

The relationship between pathology and cognition is more complex than originally thought

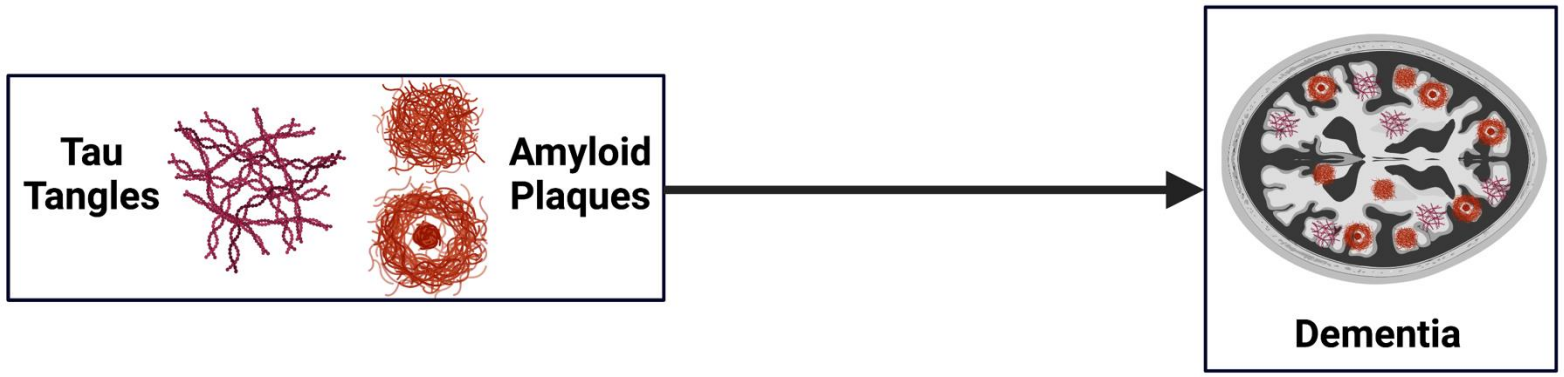


Microglia play both beneficial and detrimental roles

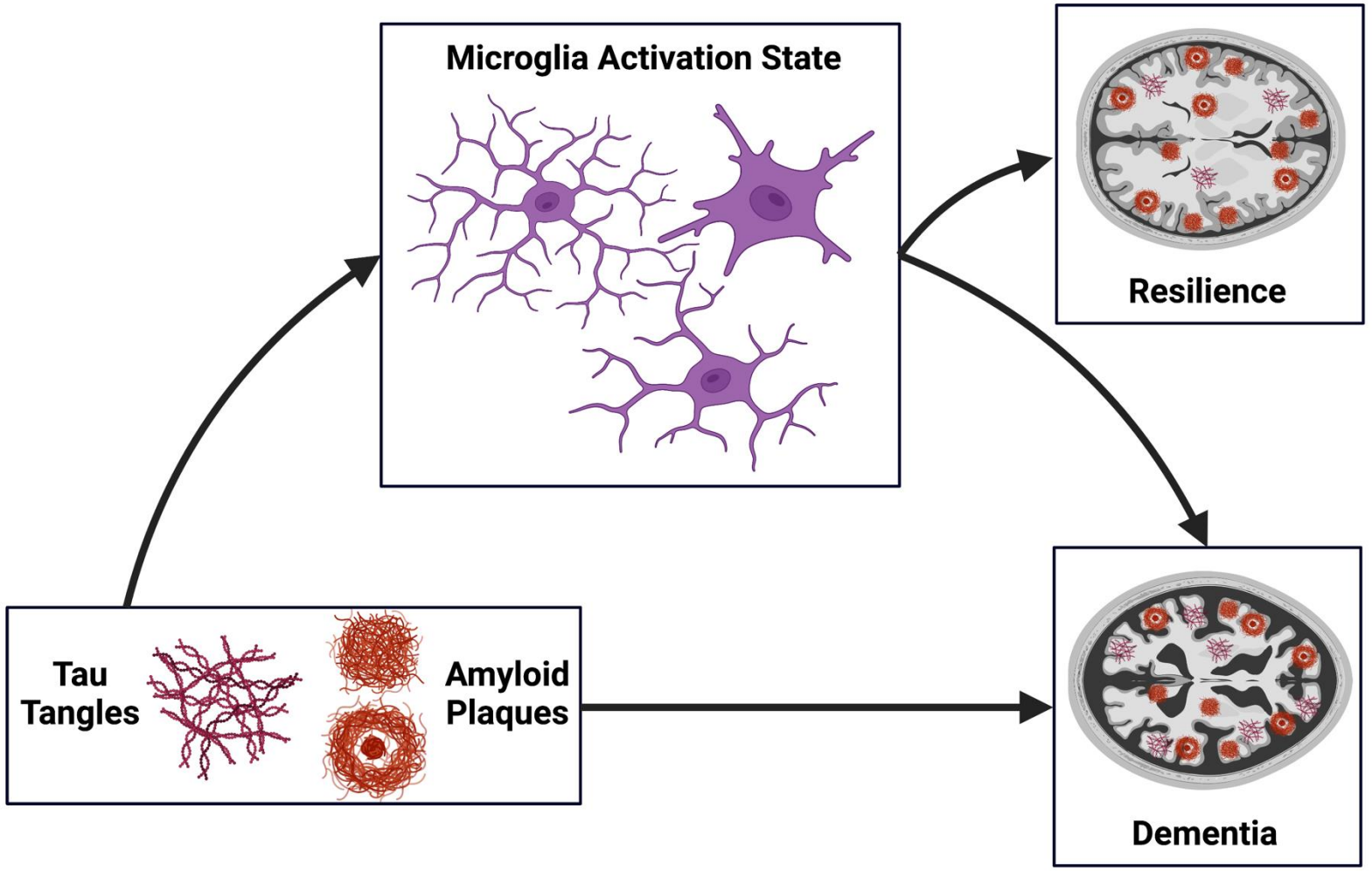
Demonstrated in AD studies



The relationship between pathology and cognition is more complex than originally thought



Microglia may mediate the relationship between pathology and cognition



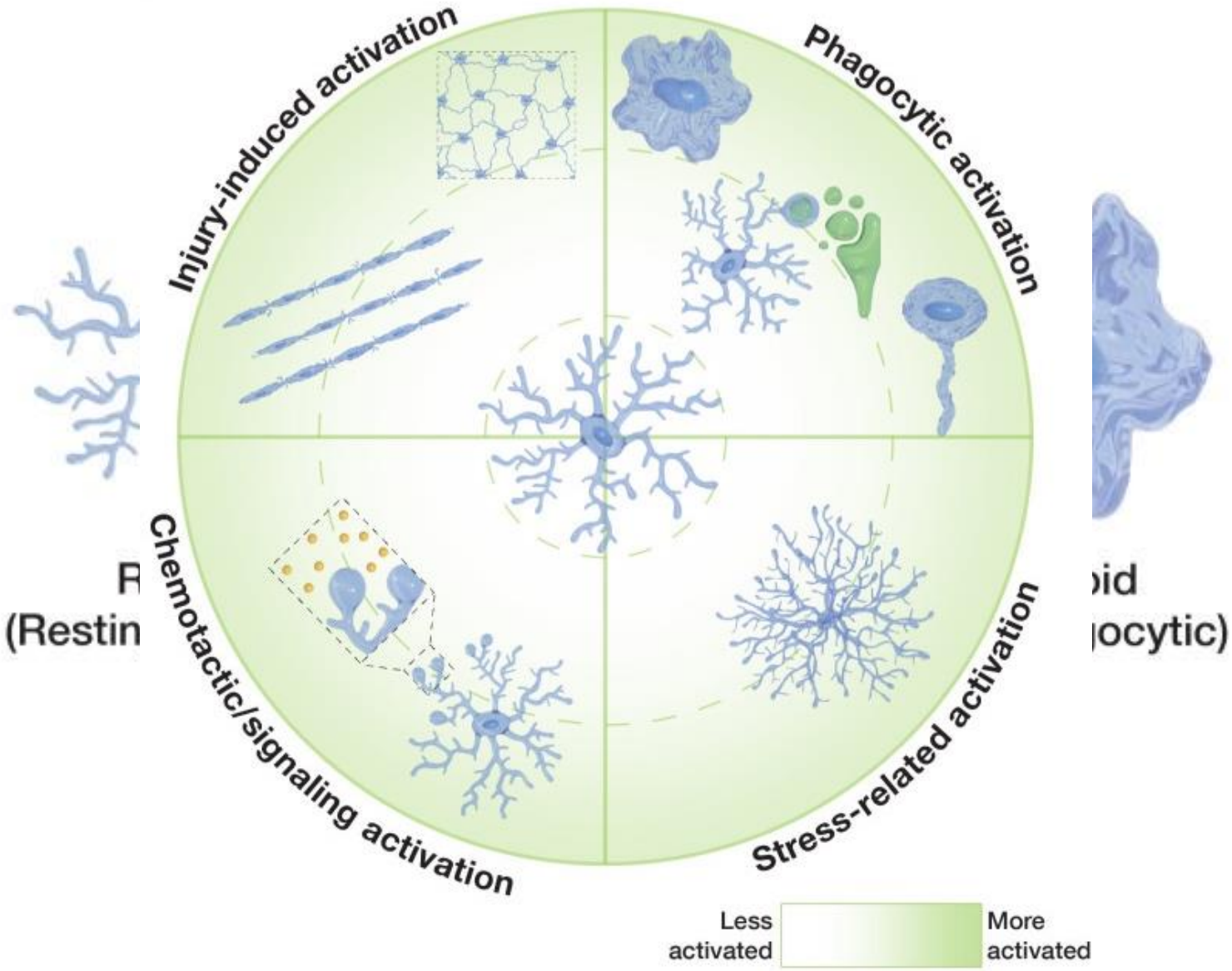
Created with BioRender.com

Our experimental questions:

1. Does microglial morphology differ in resilient individuals?

2. Does microglial gene expression differ in resilient individuals?

Microglial morphology



Vidal-Itriago et al., 2022

Our experimental questions:

1. Does microglial morphology differ in resilient individuals?

2. Does microglial gene expression differ in resilient individuals?

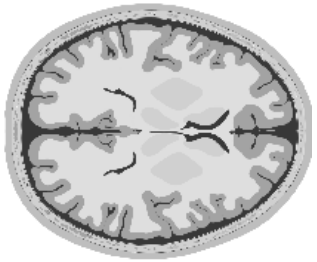
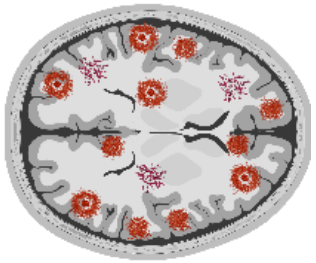
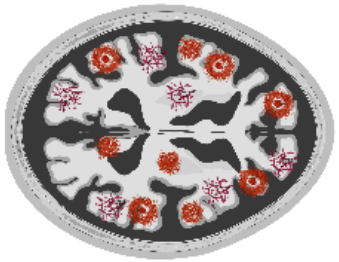
Dr. Nick Karagas MD, PhD

Mason Pirner

Vanessa Souders

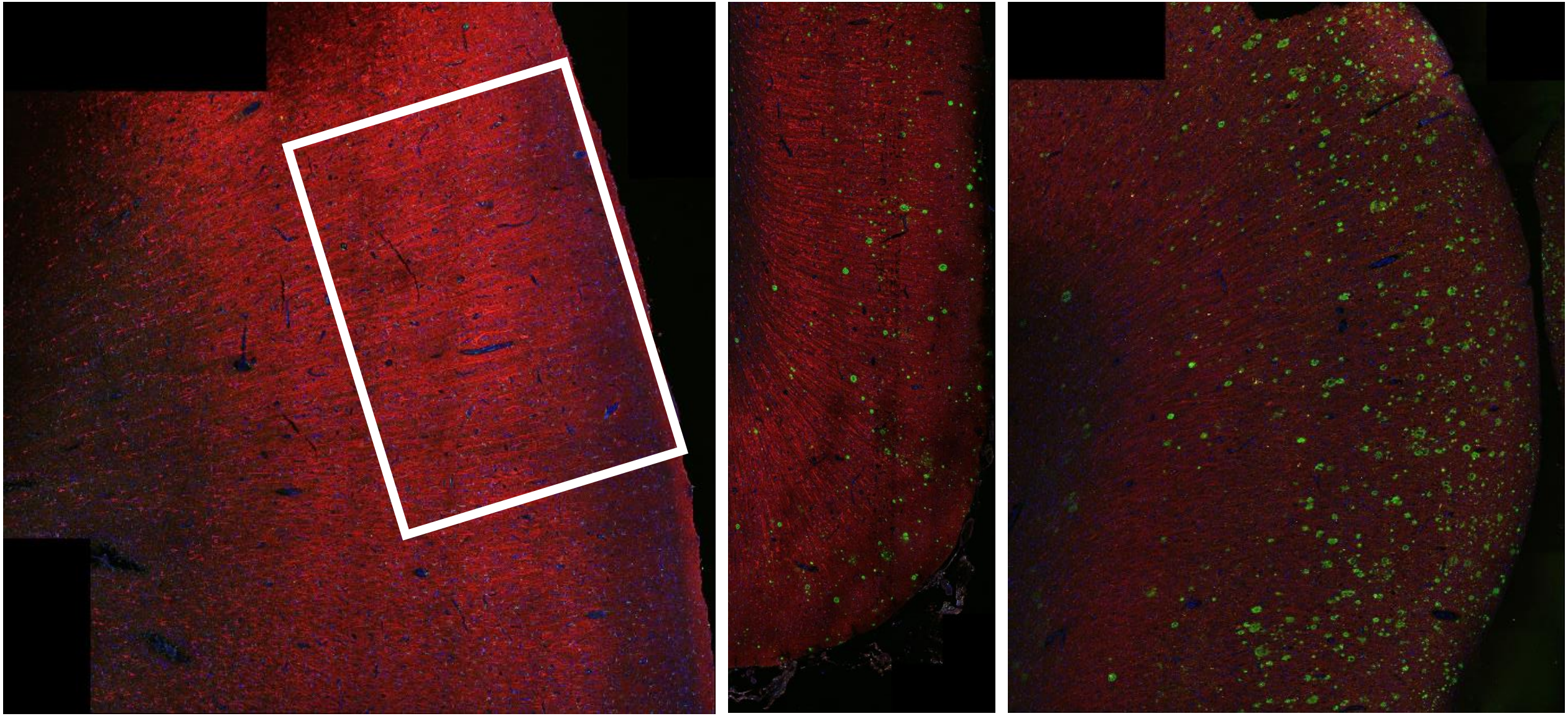
Rachel Blaine

Total cohort: 29 individuals **(25 ACT)**

#	Status	Sex	Age	MMSE	ADNC
7		4F/3M	86.14	28.14	0.71
13		8F/5M	90.69	26.61	2.38
9		7F/2M	85.11	18.44	2.88

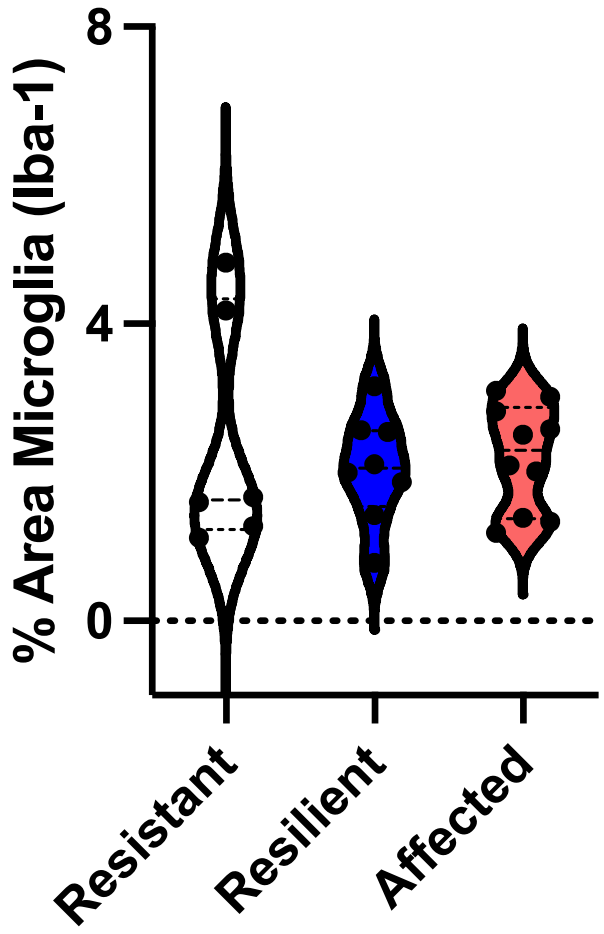
average PMI < 7.2Hrs

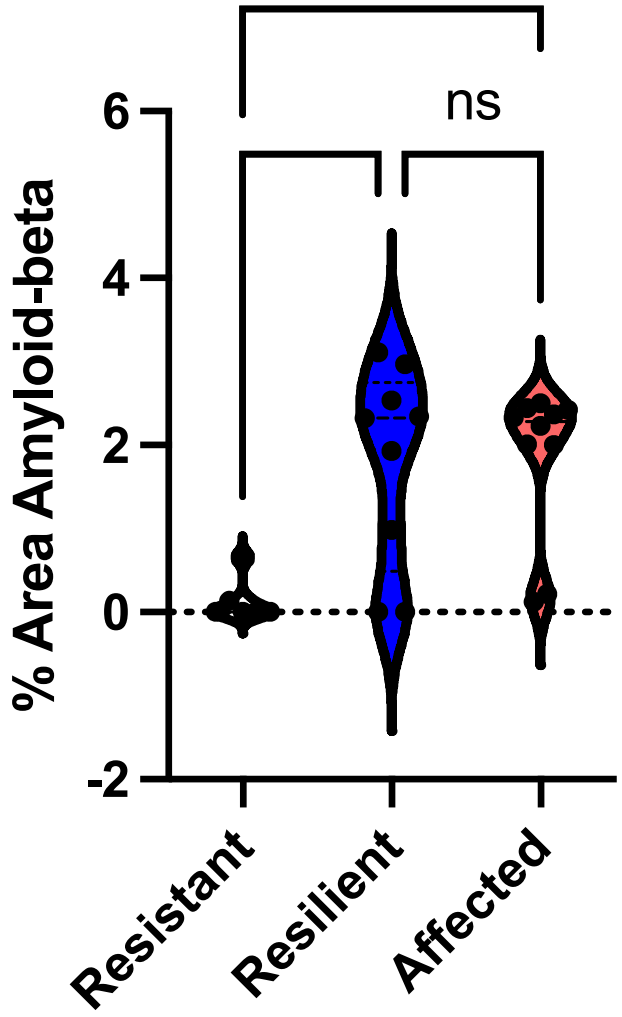
Resistant Resilient Affected

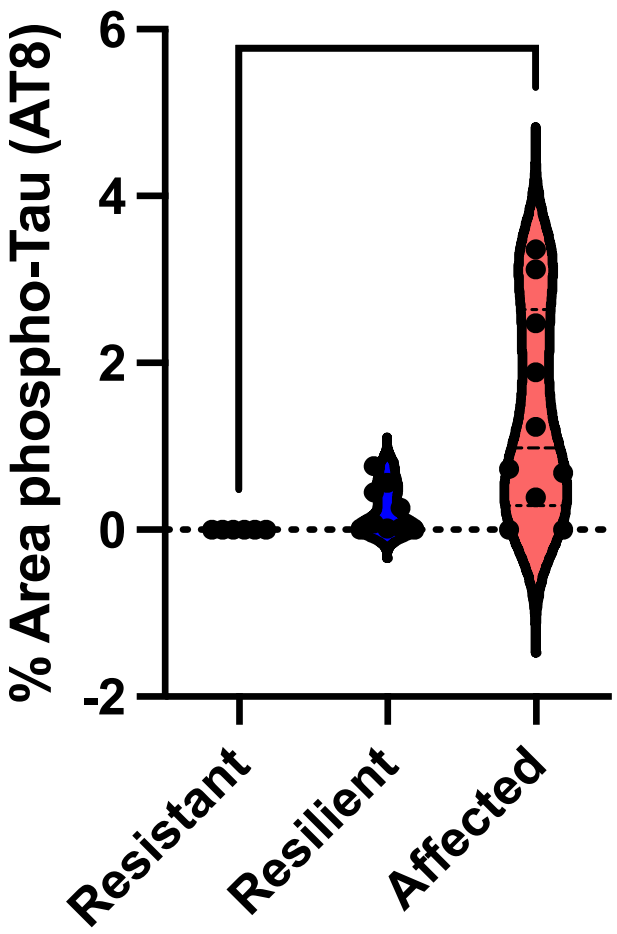


Neurons, Microglia, Amyloid beta, phospho-Tau, DAPI

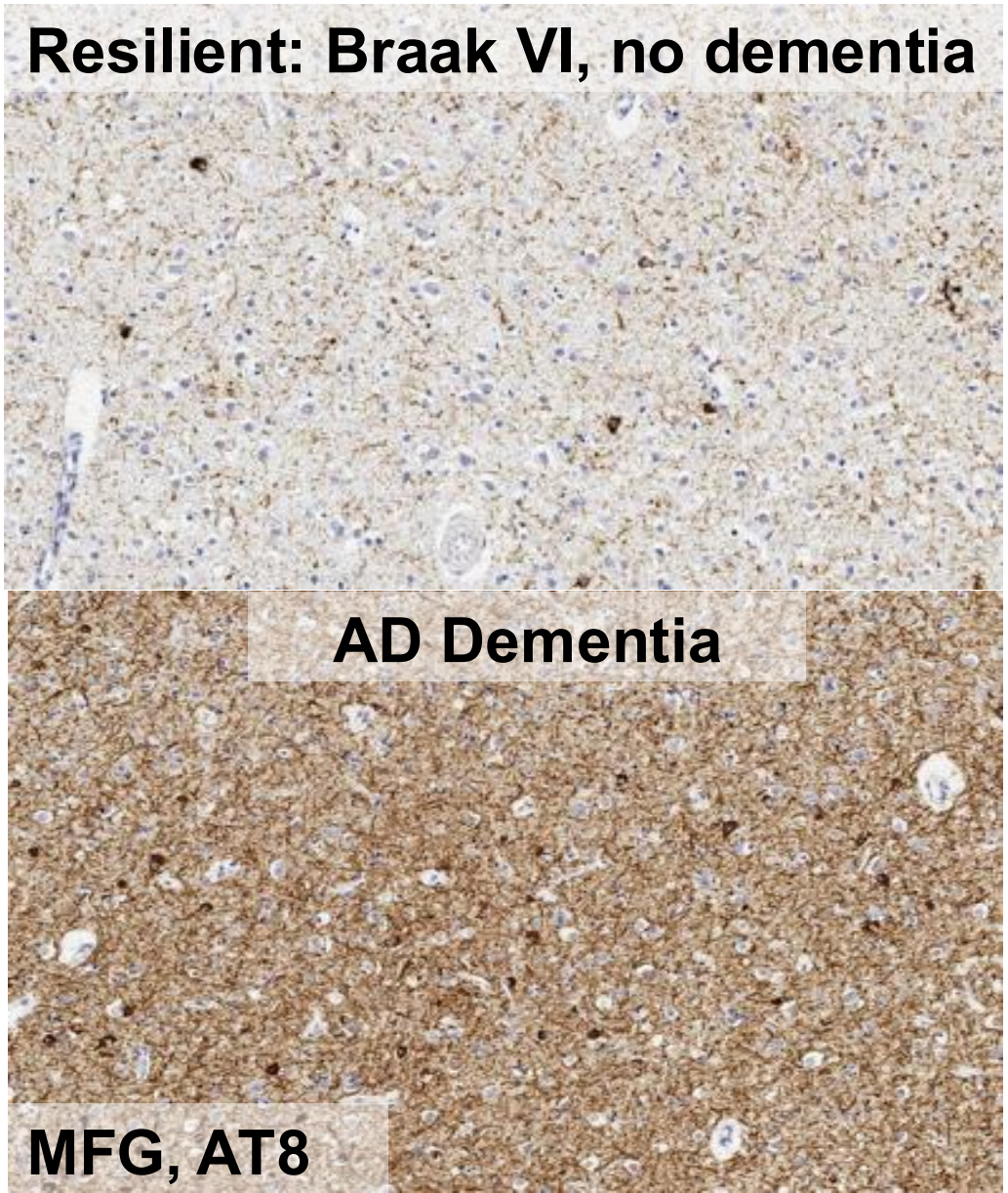
Differences in Abeta, not tau or microglia

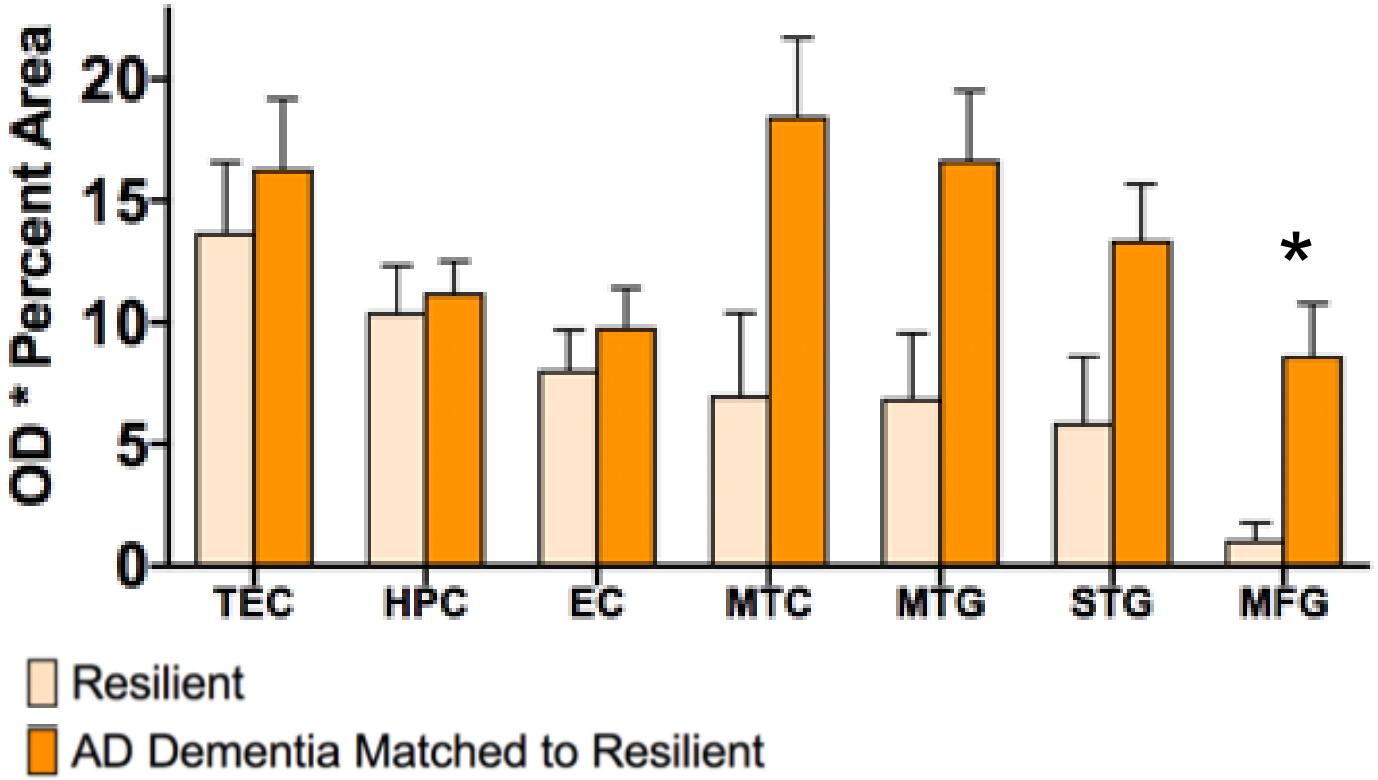




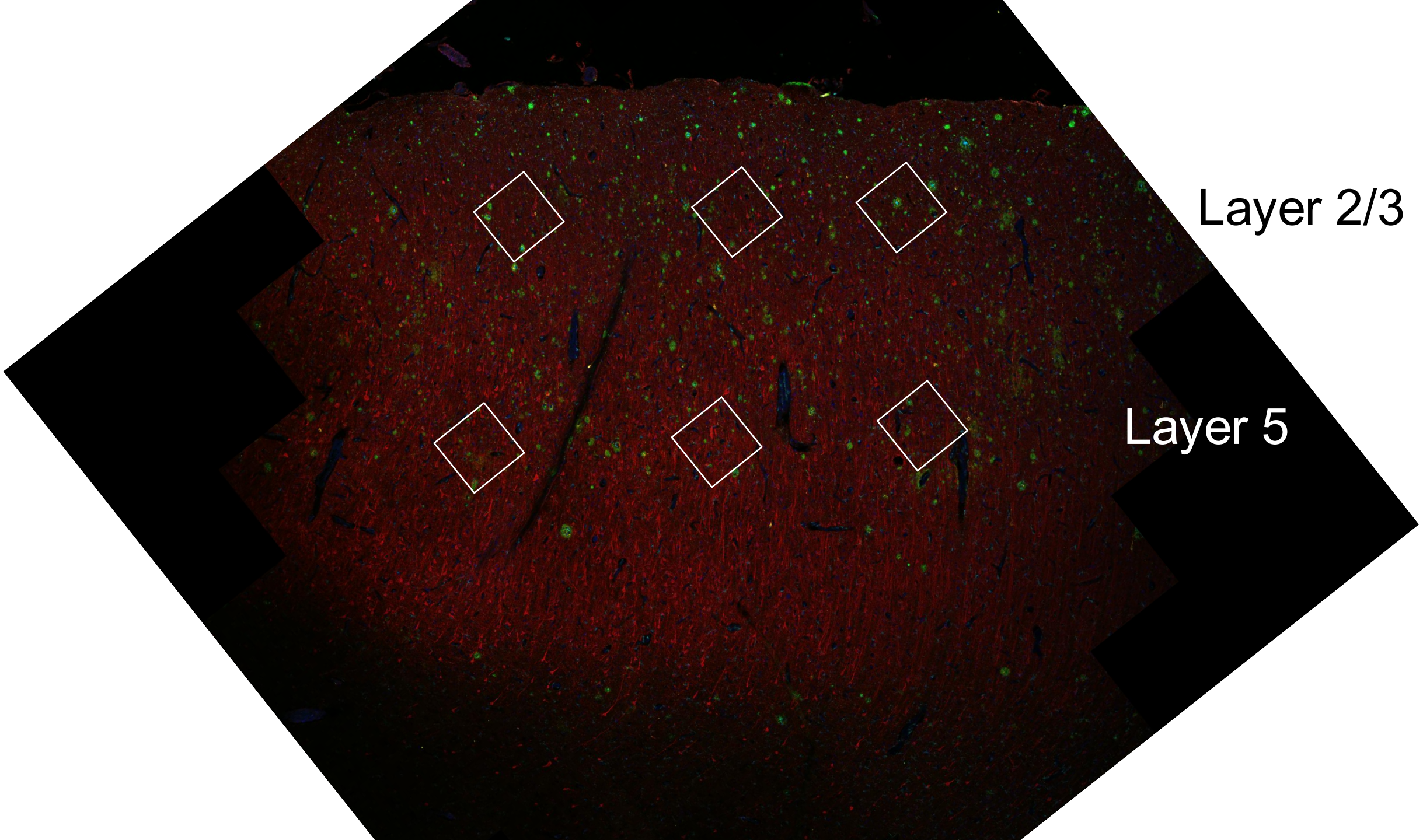


Resilient cases have less phospho-tau burden

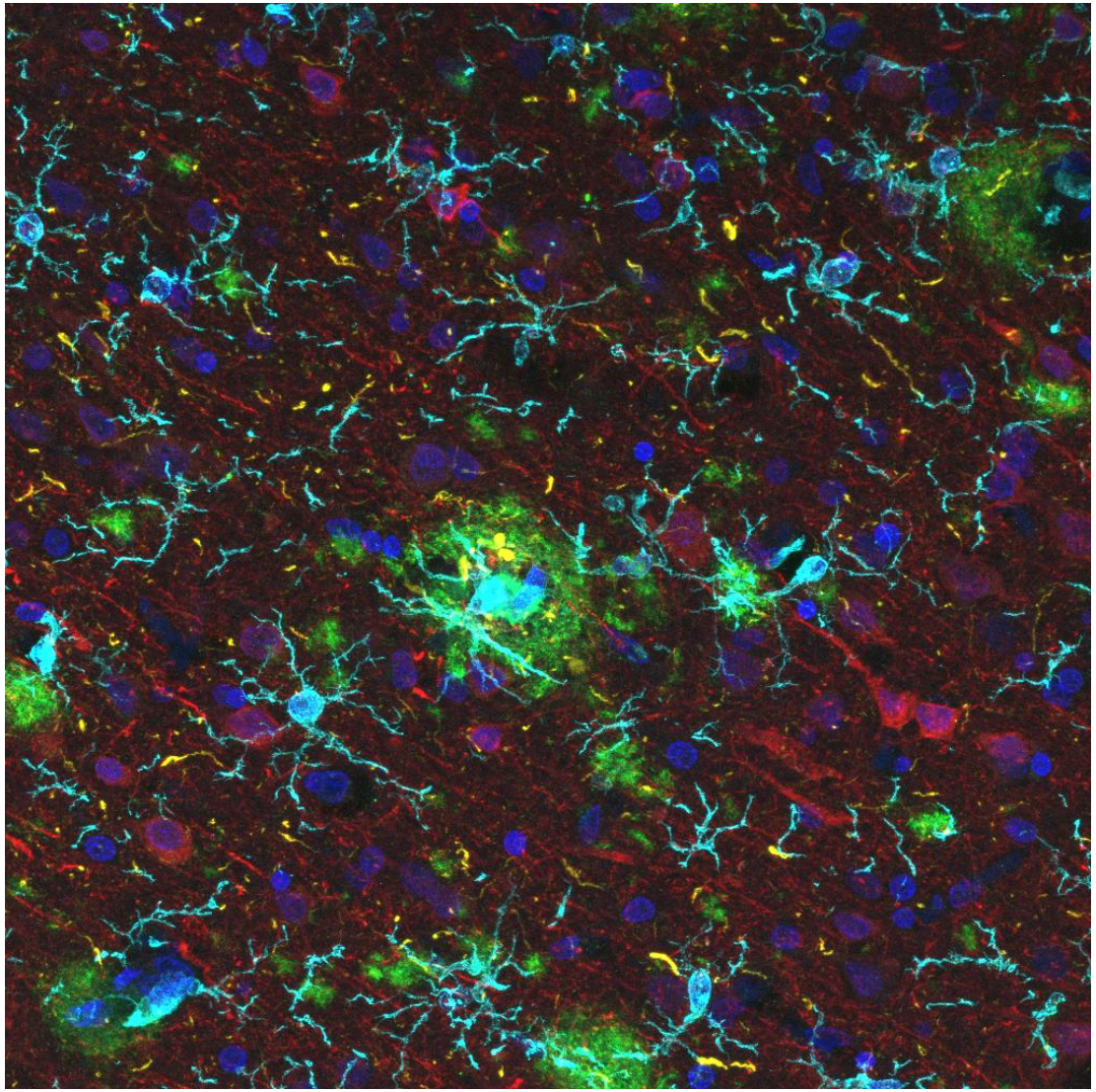


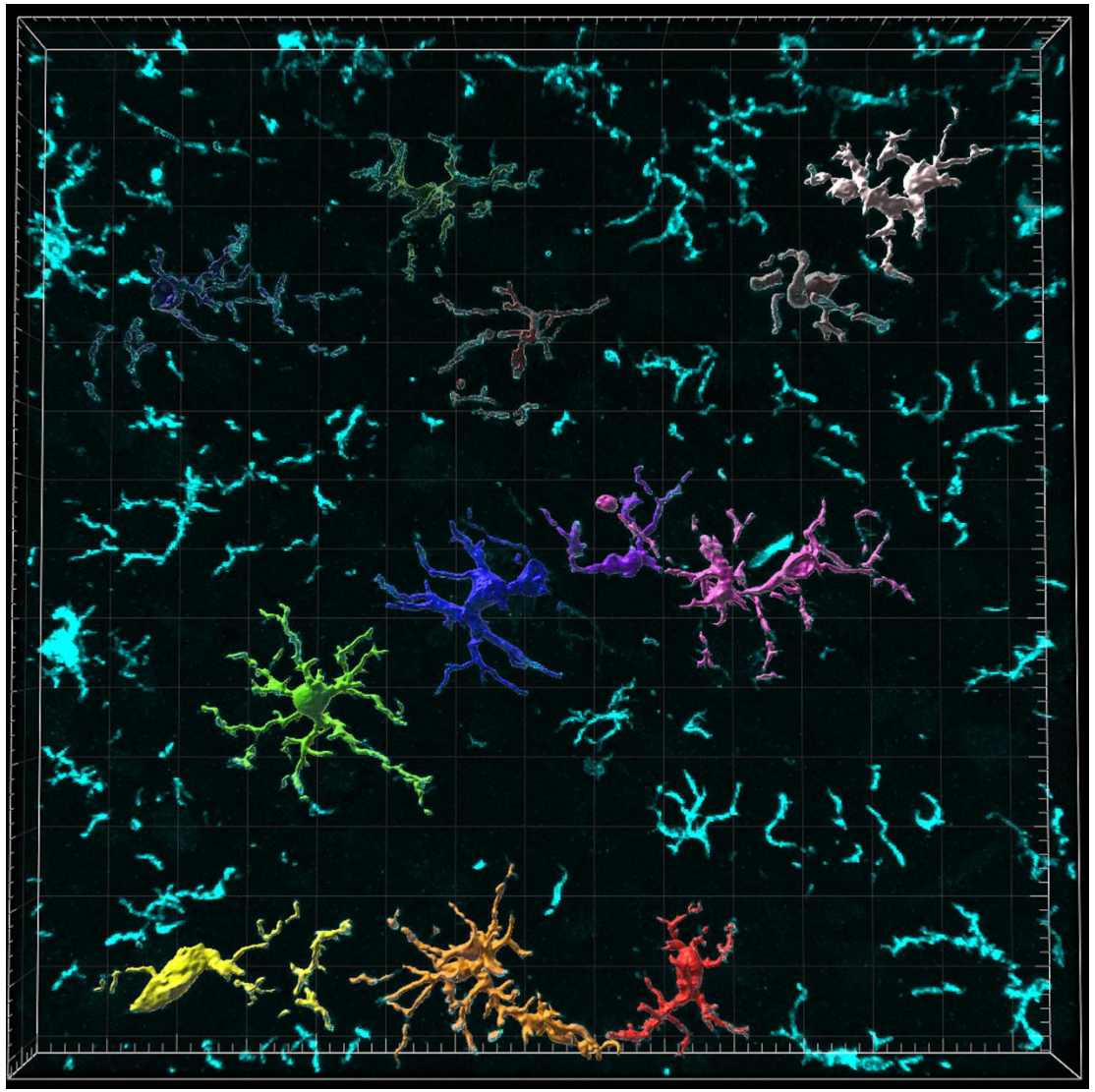


Latimer et al. 2019


Layer 2/3
Layer 5

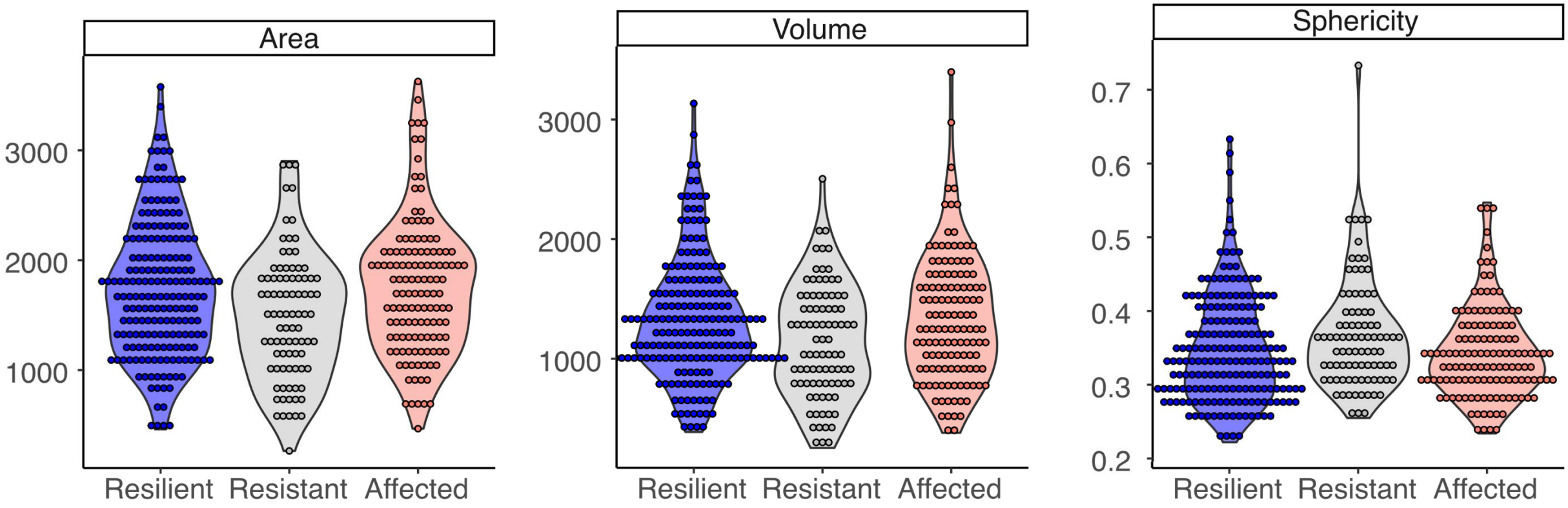
High resolution images to IMARIS surfaces



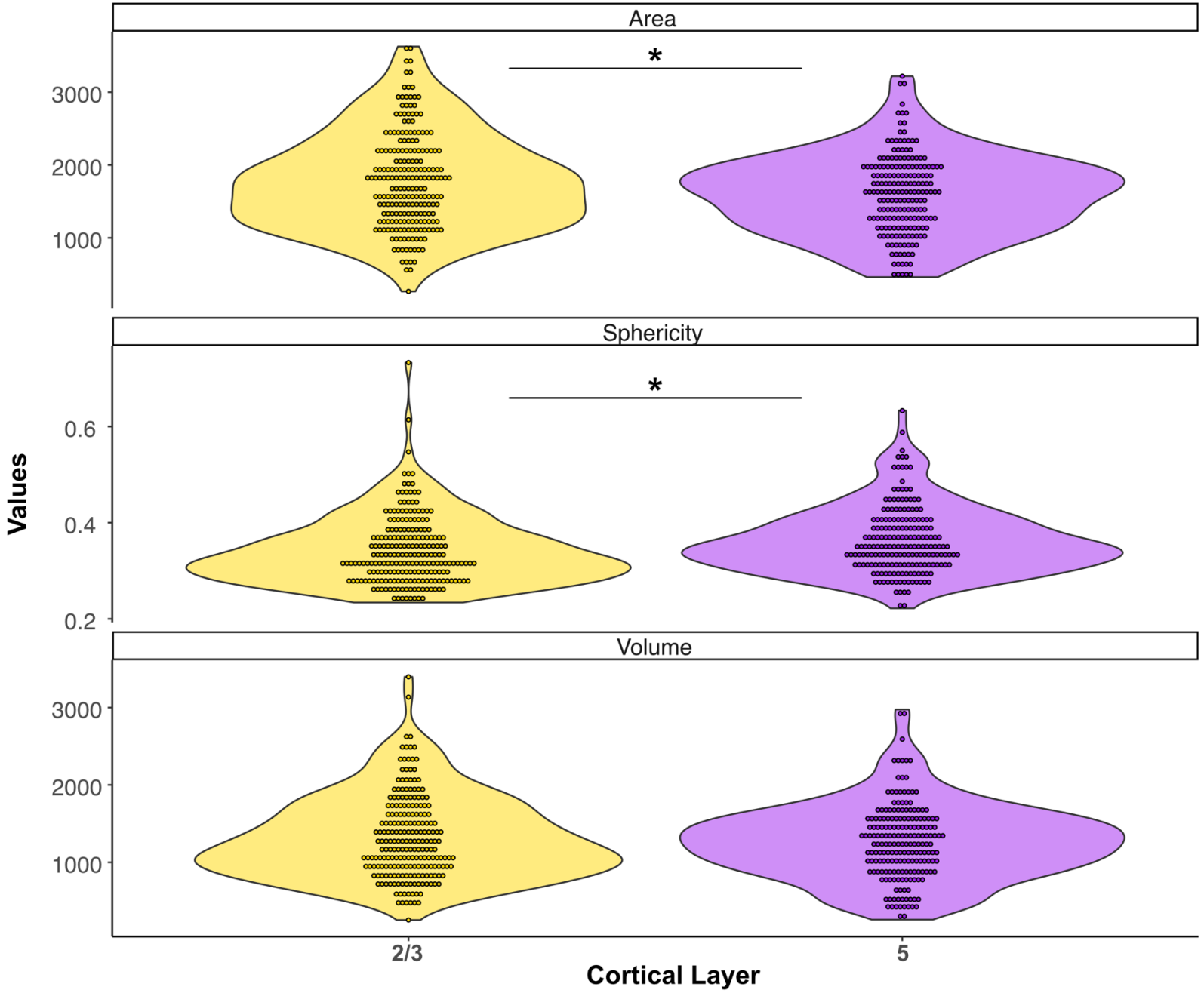


Neurons, Microglia, Amyloid beta, phospho-Tau, DAPI

Surface morphology does not differ by group



Surface morphology differs by layer

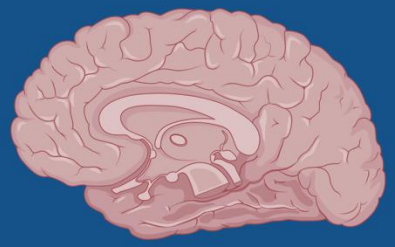


Our experimental questions:

1. **Does microglial morphology differ in resilient individuals?**
    1. We replicated the finding that resilient have less phospho-Tau in dlPFC
    2. There is no broad cortical change in Iba-1 signal
    3. Cortical layer 5 surfaces are more spherical and smaller area than layer 2/3 surfaces
        1. Additional fine-grained tracing of microglial processes will start once the surfaces are finalized
        2. Analysis of the layer x group interaction might detect differences?

Age

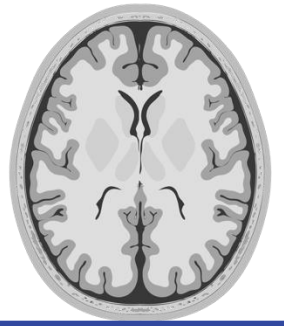
Genetics



Environment

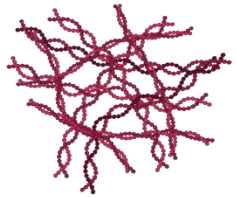
Lifestyle

Resistance

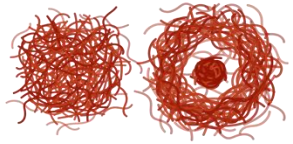


AD Pathology

Tau Tangles

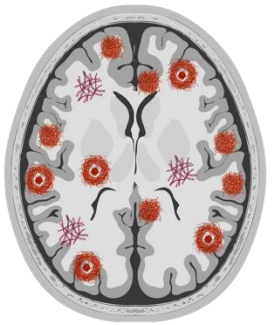


Amyloid Plaques



Resilience

No Dementia



Affected

Dementia

What is the effect of cognitive decline (keeping pathology constant)?

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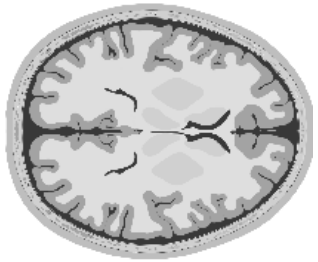
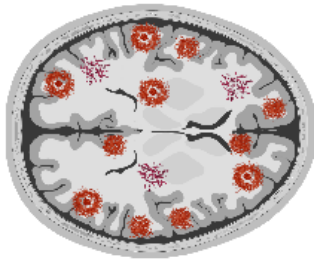
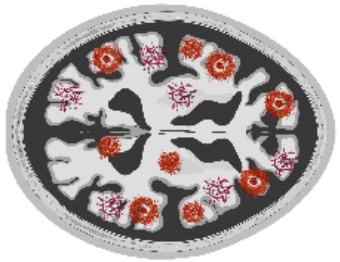
2. Does microglial gene expression differ in resilient individuals?

Dr. Corbin Johnson PhD

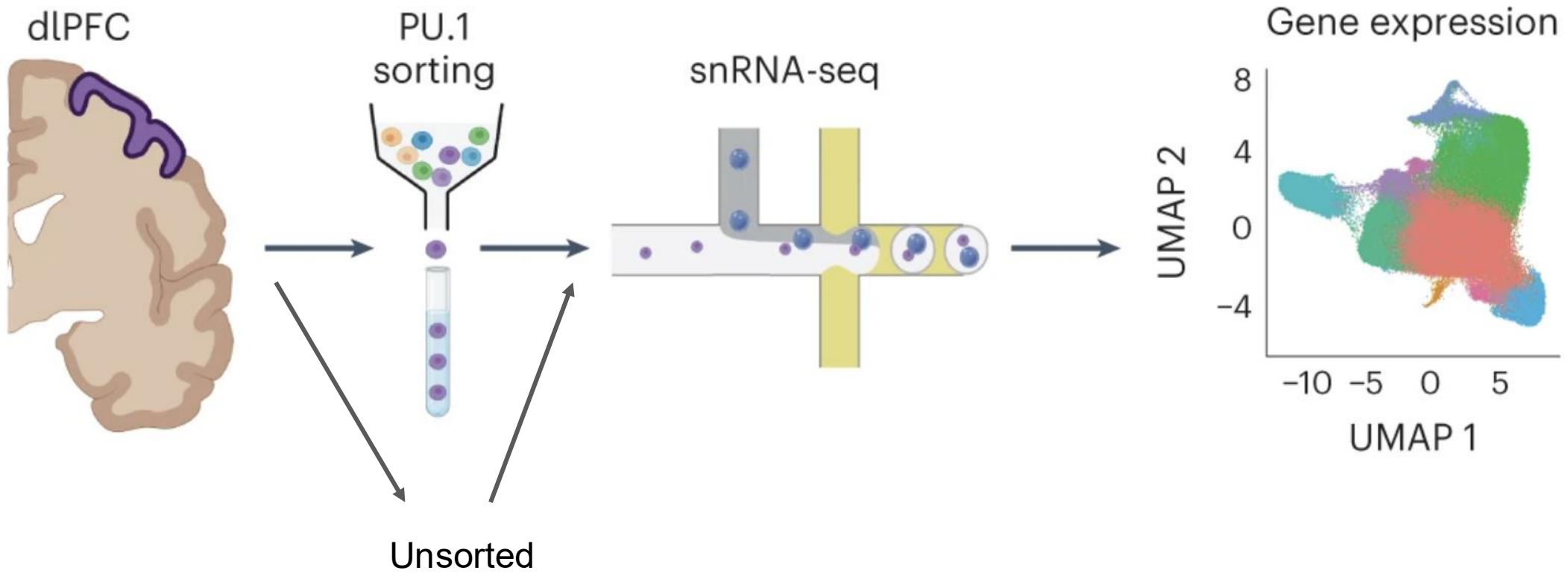
Lexi Cochoit

Isa Smith

Total cohort: 33 individuals **(30 ACT)**

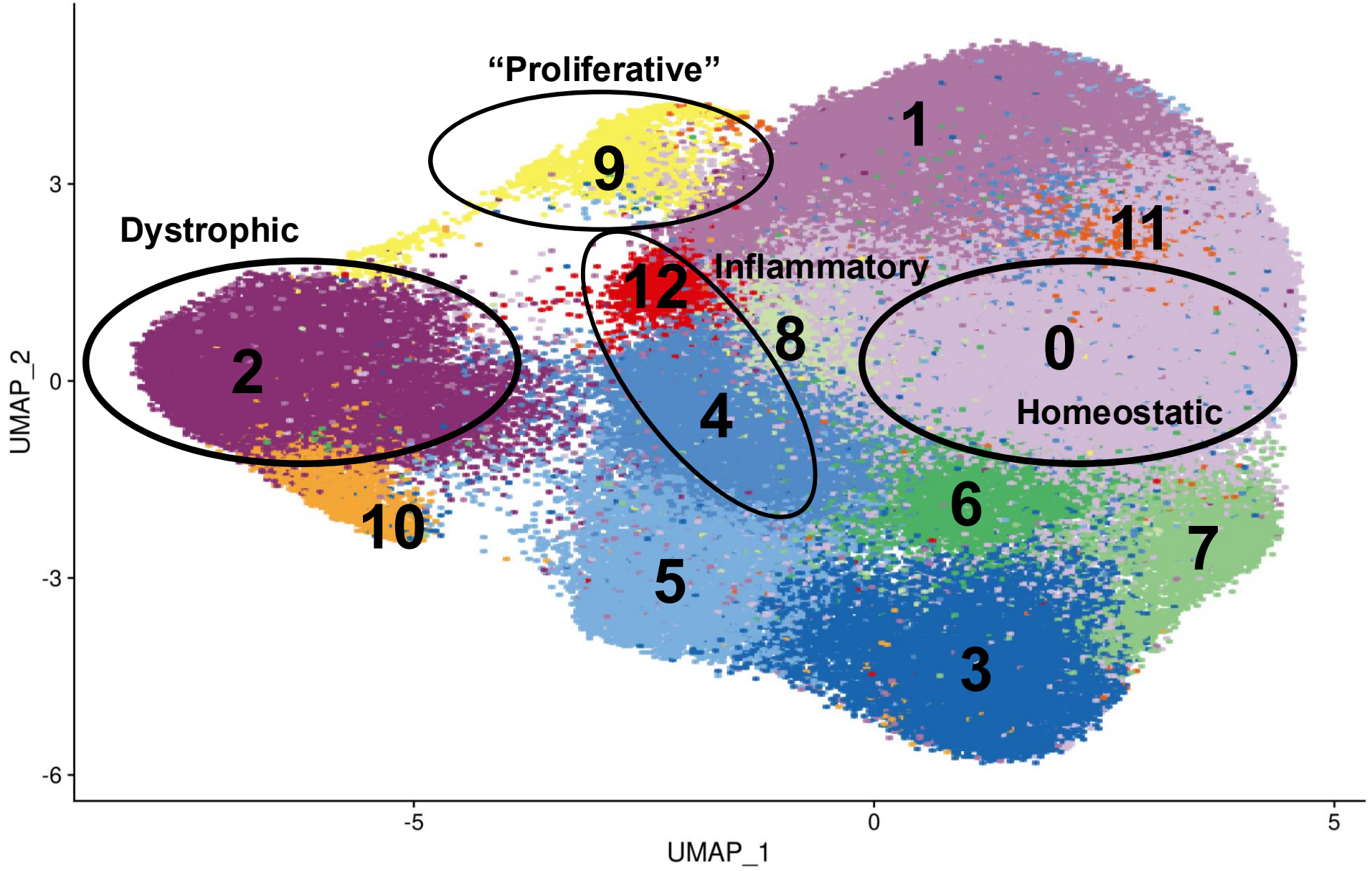
#	Status	Sex	Age	MMSE	ADNC
10		5F/5M	84.10	27.80	0.70
13		9F/4M	91.92	26.62	2.23
10		6F/4M	87.70	20.60	2.90

average PMI < 7.5Hrs

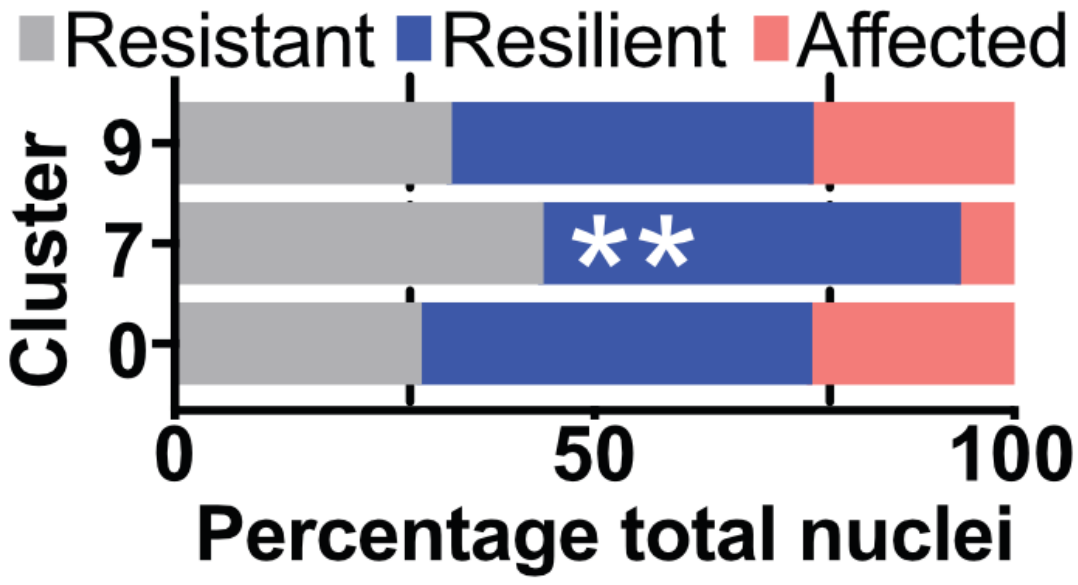


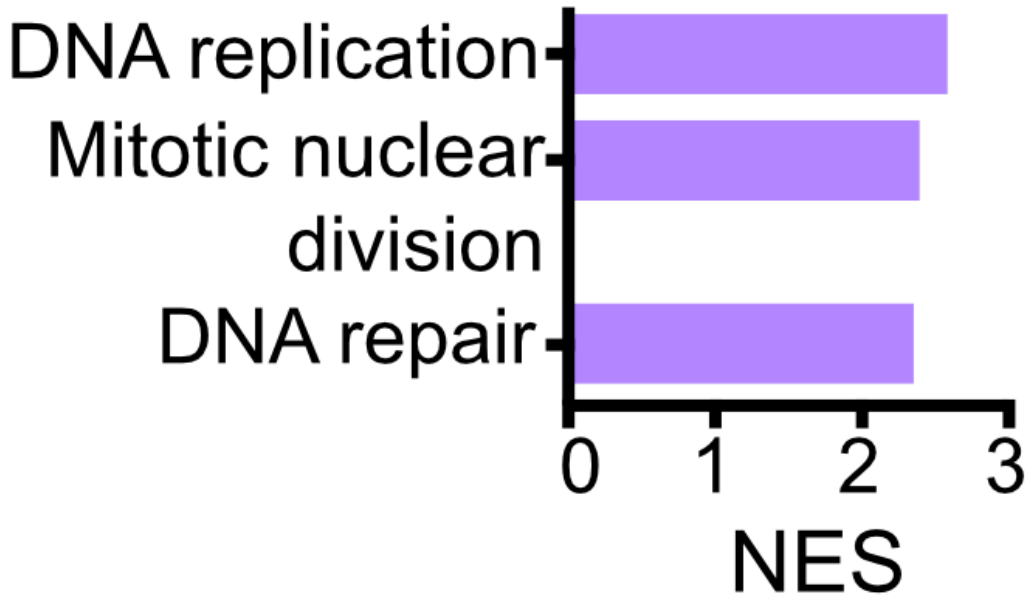
Prater & Green, Nature Aging 2023

160,094 microglial nuclei

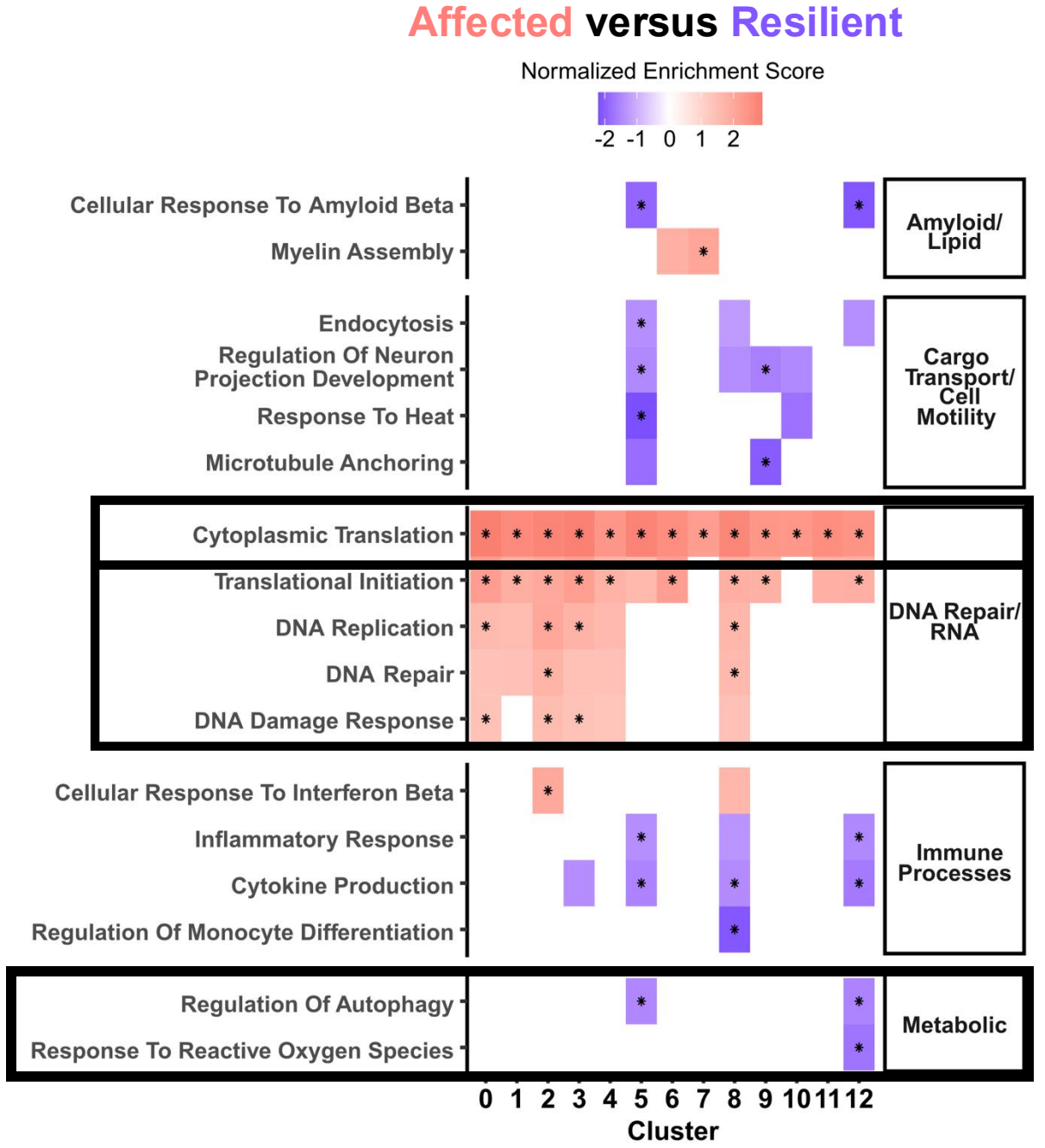


A specific state of microglia appears lost in AD





Microglial gene expression shifts with cognitive decline



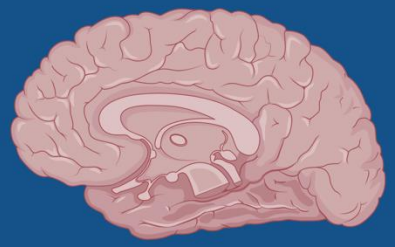
Our experimental questions:

1. Does microglial morphology differ in resilient individuals?

2. Does microglial gene expression differ in resilient individuals?
    1. The “proliferative” microglial cluster may help maintain cognition in the presence of pathology
    2. Gene expression shifts with cognitive decline

Age

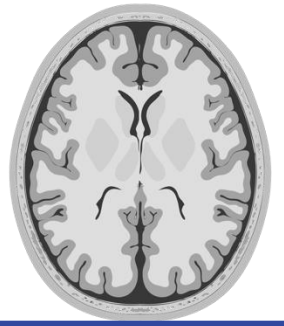
Genetics



Environment

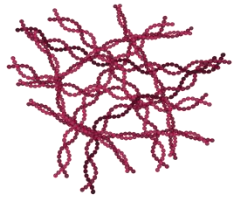
Lifestyle

Resistance

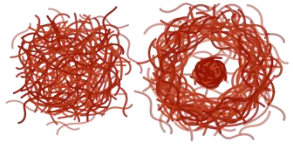


AD Pathology

Tau Tangles

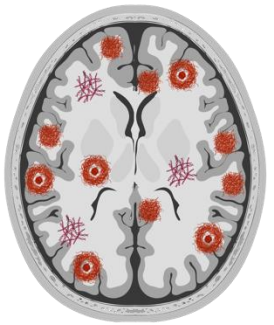


Amyloid Plaques



Resilience

No Dementia



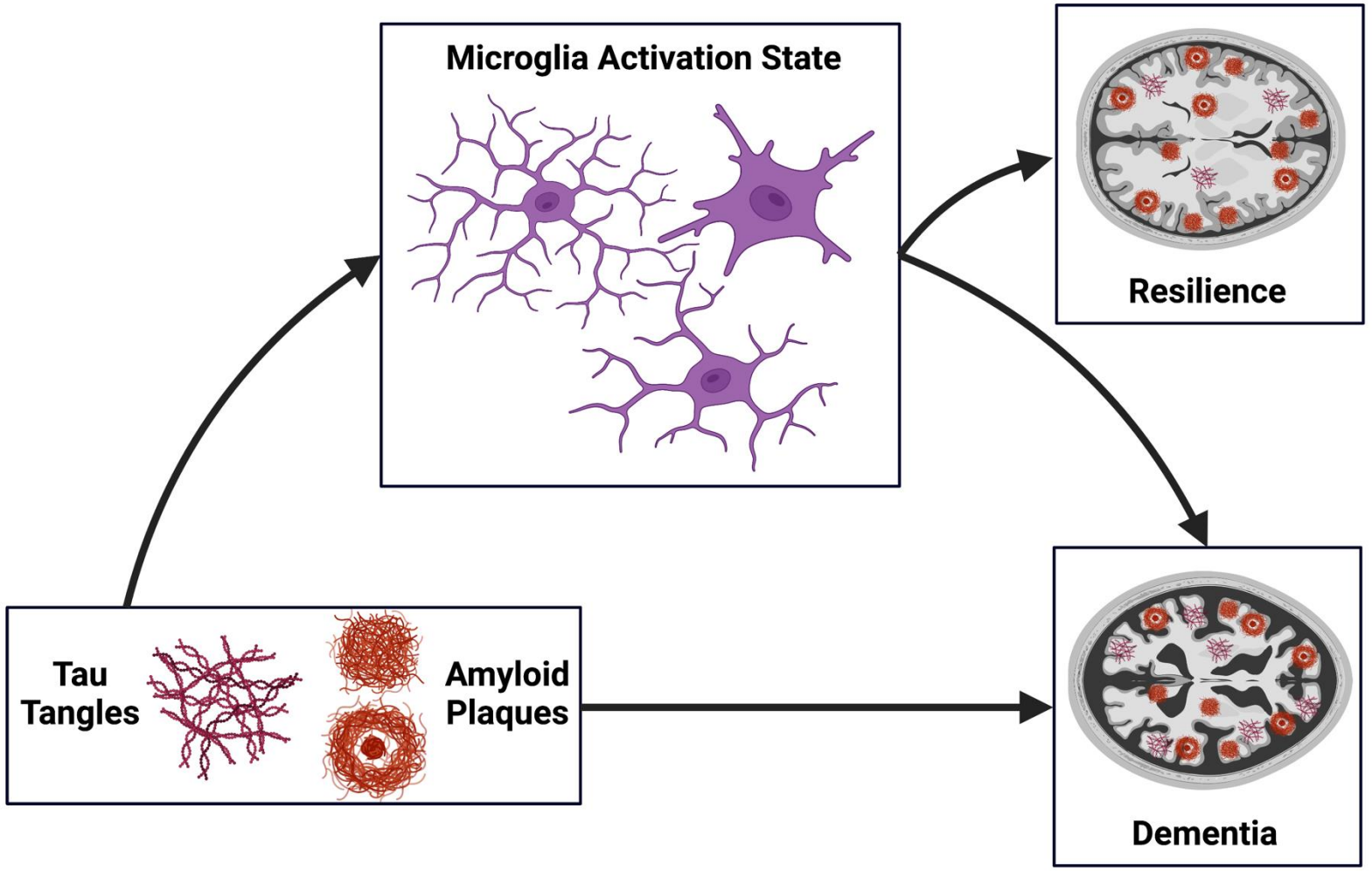
Affected

Dementia

What is the effect of cognitive decline (keeping pathology constant)?

Adapted from Latimer, Prater, Postupn , & Keene 2022 using BioRender.com

Microglia may mediate the relationship between pathology and cognition



Created with BioRender.com

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DEPARTMENT OF NEUROLOGY EVALUATIONS

SCAN ME!

THANK YOU!

neurology.uw.edu/teaching-evaluations/

Questions/Thoughts?

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