# The cognitive cost of high-fat diet and what microglia have to do with it

# Le coût cognitif d'un régime riche en graisses et ce que la microglie a à voir avec cela

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# Diet matters

Western-style diet consumption is associated with deficits in cognitive processing.

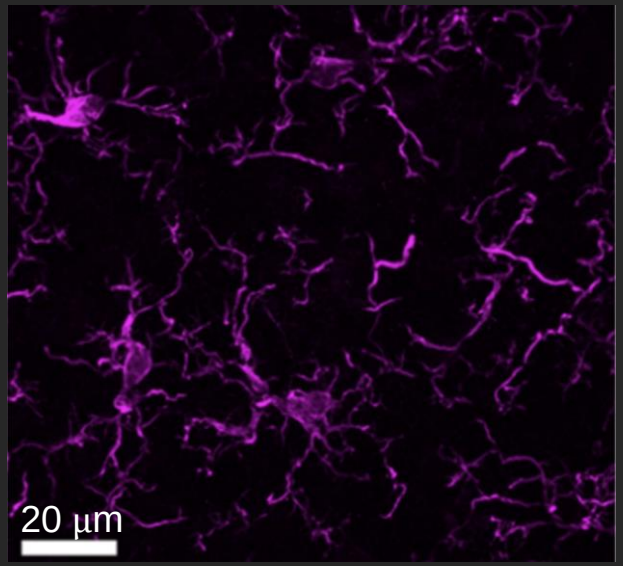
- higher BMI is associated with deficits in learning, memory, and executive functioning
- even after adjusting for age and education.

Barrientos et al, BBI, 2019; Lopez-Taboada et al, Front. Psychol., 2020.

# Diet matters

Western-style diet consumption is associated with deficits in cognitive processing.

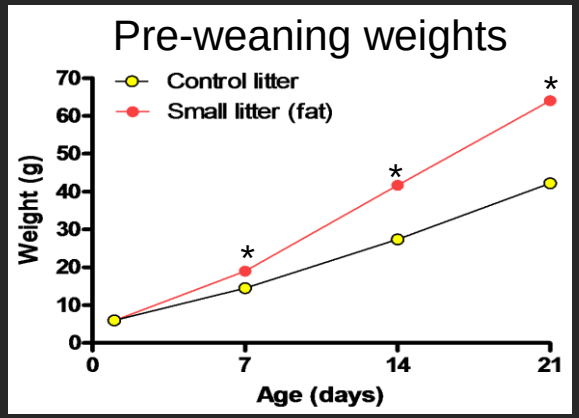
Microglia may mediate this connection.



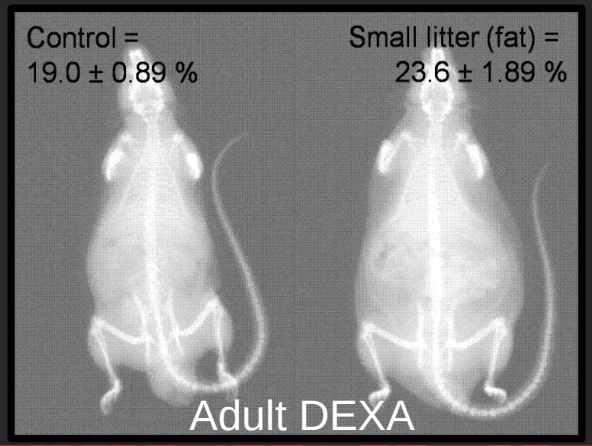

Barrientos et al, BBI, 2019; Lopez-Taboada et al, Front. Psychol., 2020.

# Rat model of childhood obesity

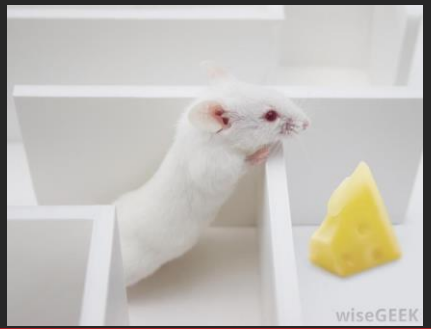






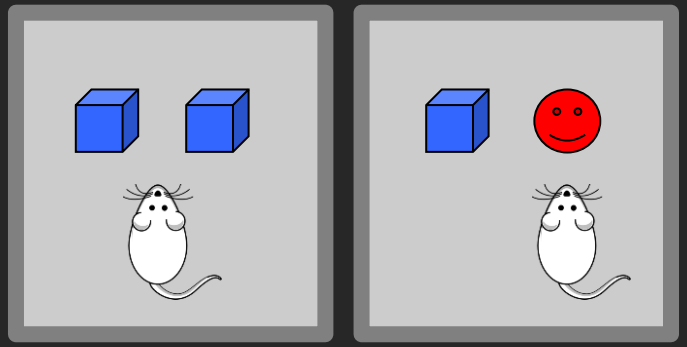


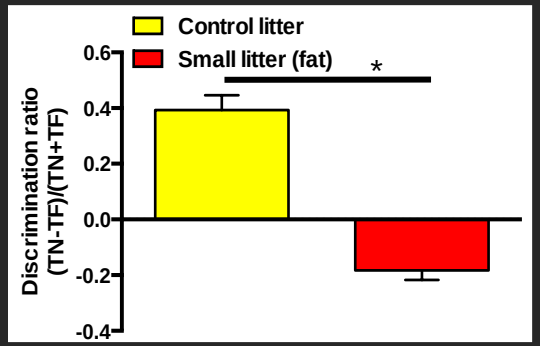

Cognition?



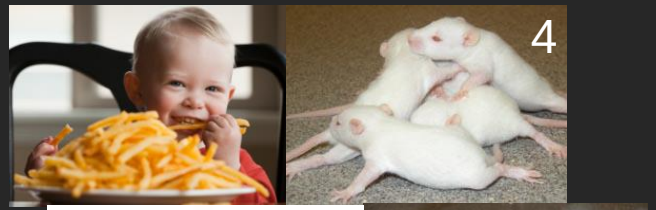

De Luca et al, J. Neuroinflammation, 2016.

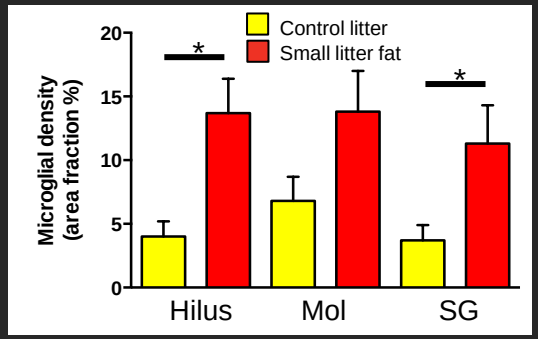
# Poor diet in early life leads to lasting cognitive deficits

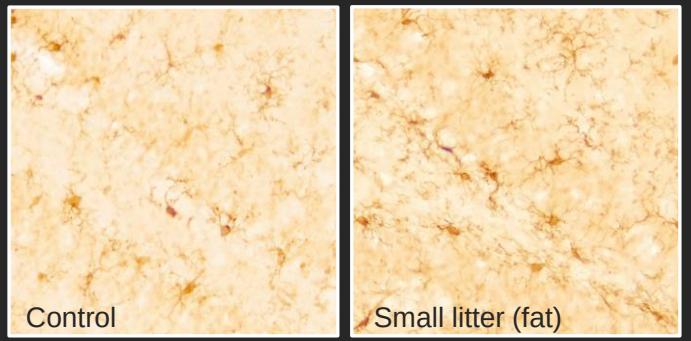





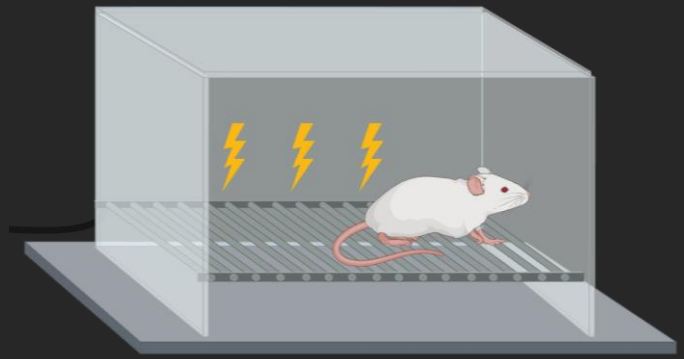
# Poor diet in early life leads to lasting cognitive deficits and microgliosis

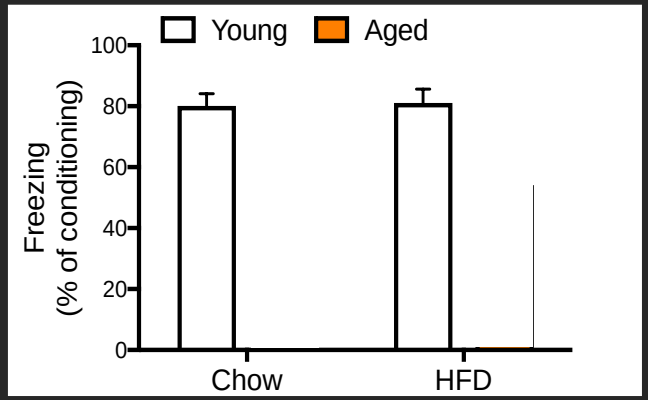


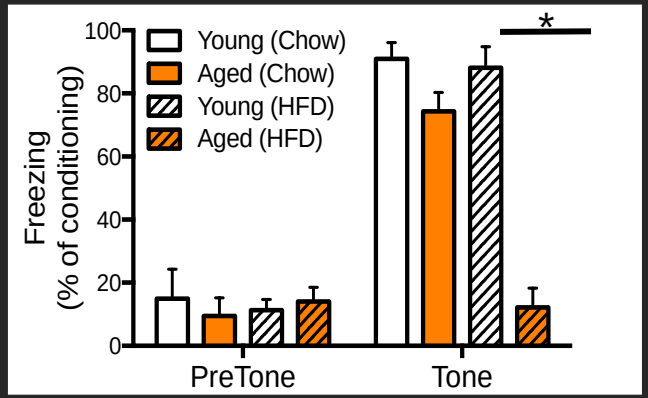



# High-fat diet in aging leads to lasting cognitive deficits and microgliosis






Contextual Memory




Cued-fear Memory

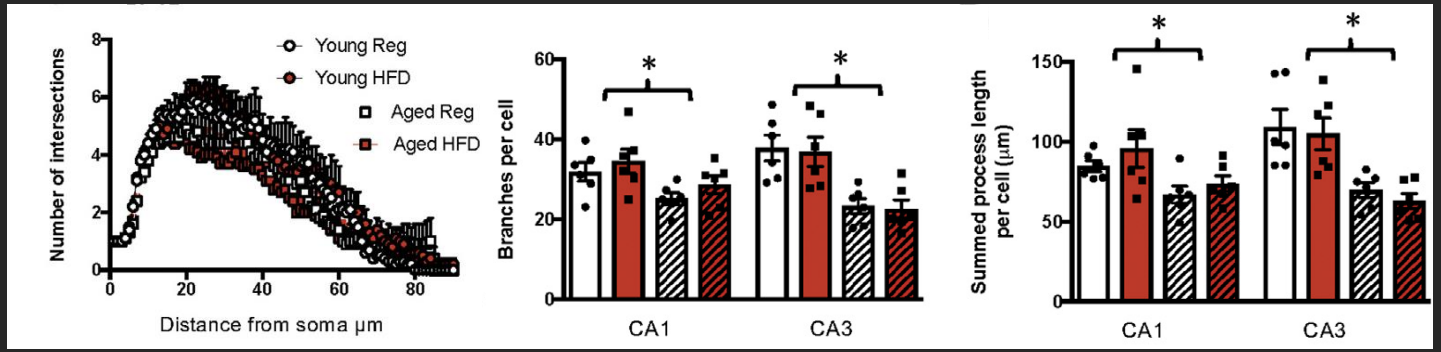
Spencer et al, Neurobiology of Aging, 2017.

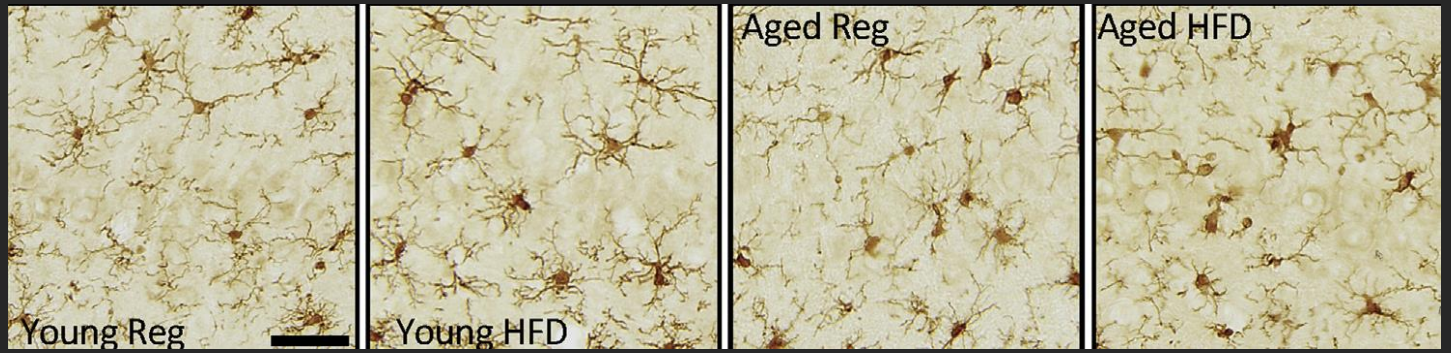
**IN COLLABORATION WITH A/Prof. RUTH BARRIENTOS; Ohio State Uni, USA**

# High-fat diet in aging leads to lasting cognitive deficits and microgliosis

CA3 Hippocampus

Young Reg
Young HFD
Aged Reg
Aged HFD




Spencer et al, Neurobiology of Aging, 2019.

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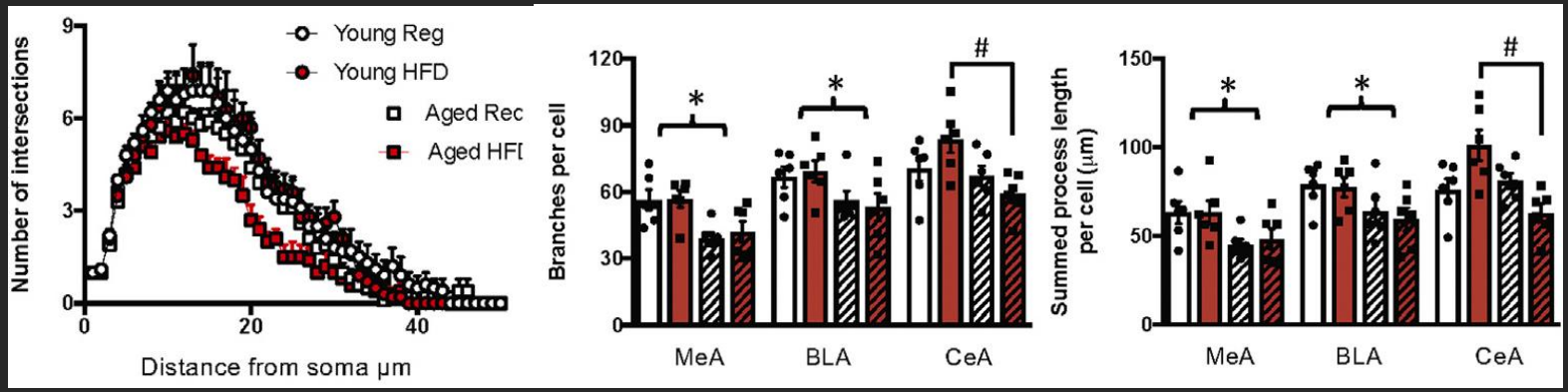
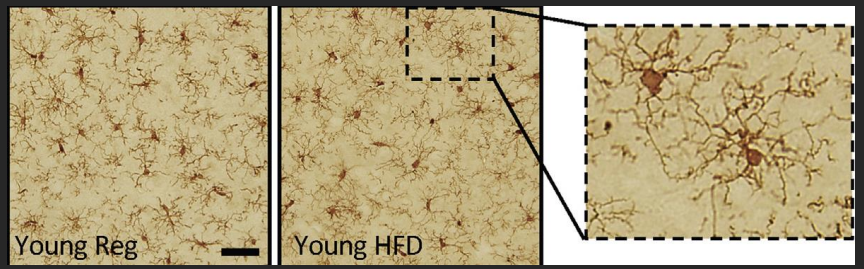
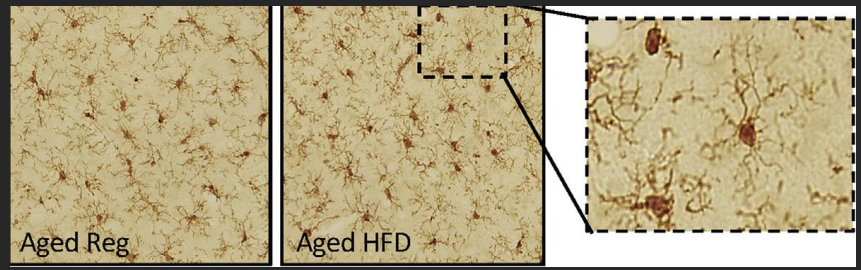
# High-fat diet in aging leads to lasting cognitive deficits and microgliosis

CeA Amygdala

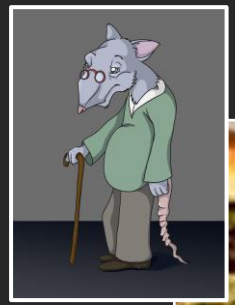
- Young Reg
- Young HFD
- Aged Reg
- Aged HFD

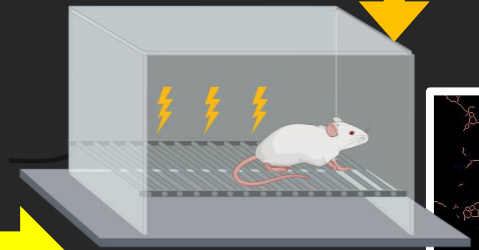


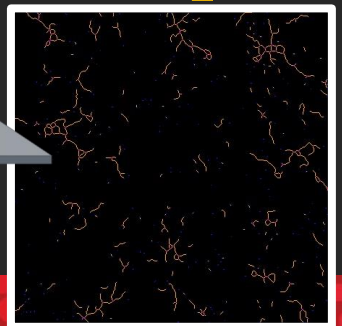



# Diet influences cognition and microglia







But, are the cognitive changes really due to microglia?

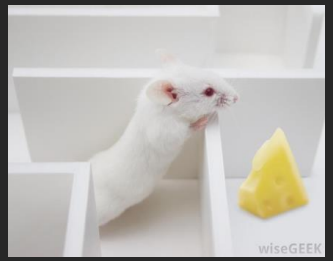
We therefore hypothesized that microglia dynamics play a direct role in cognitive health

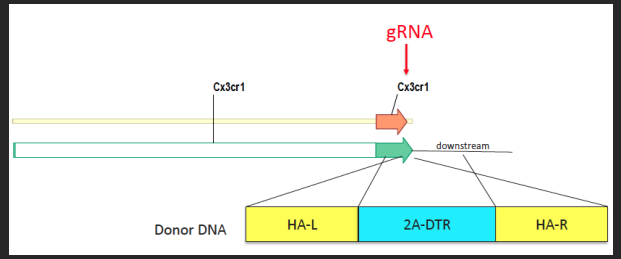
This microglial role is disrupted with poor diet and with aging.

SIMONE DE LUCA

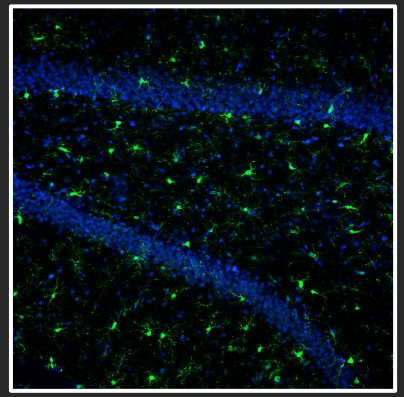
# Testing microglia's role in cognition

*Cx3cr1-Dtr*

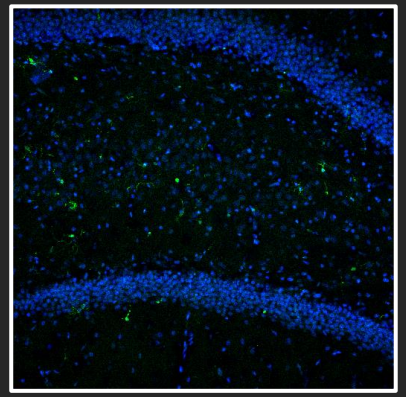


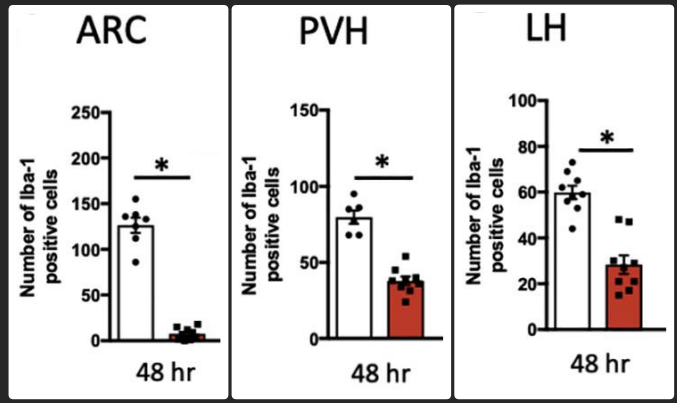




Wt 48 hr

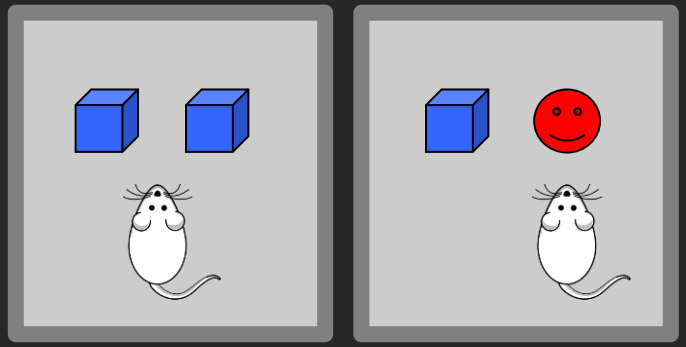


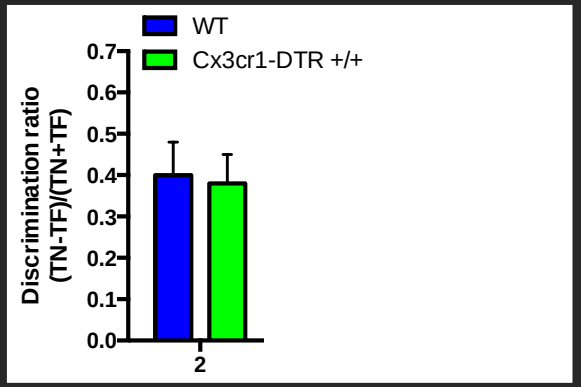
HOM 48 hr

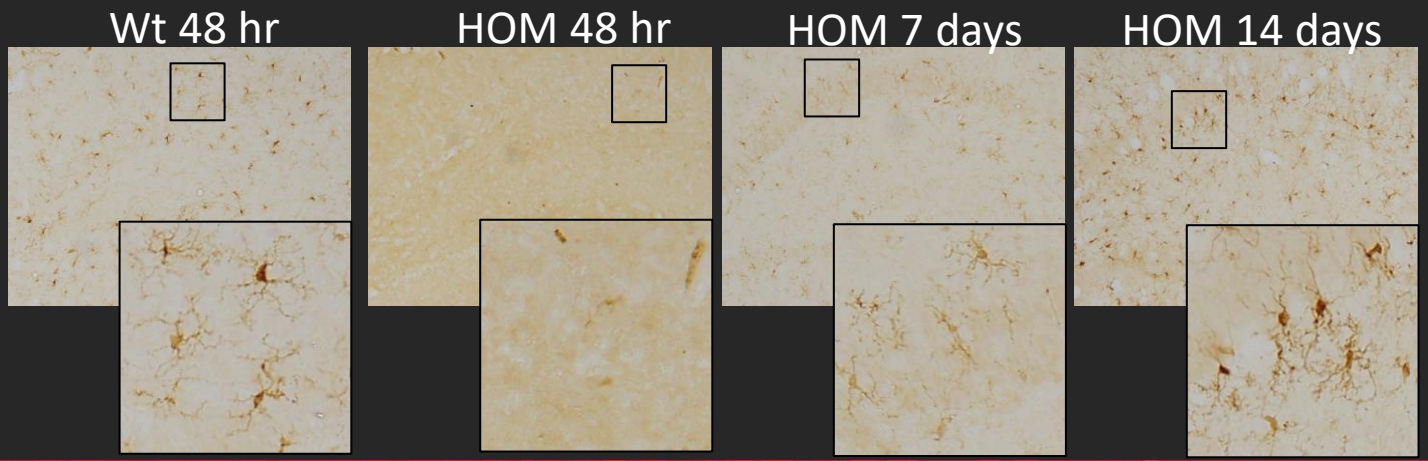




# Are microglia directly involved in cognition?





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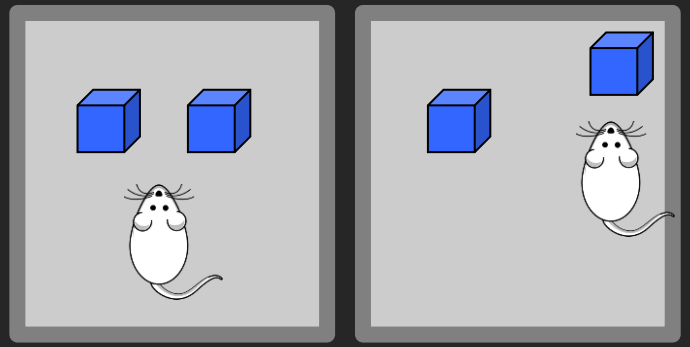
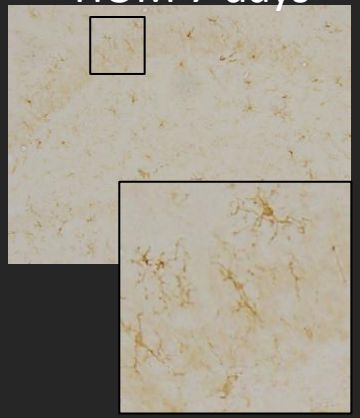
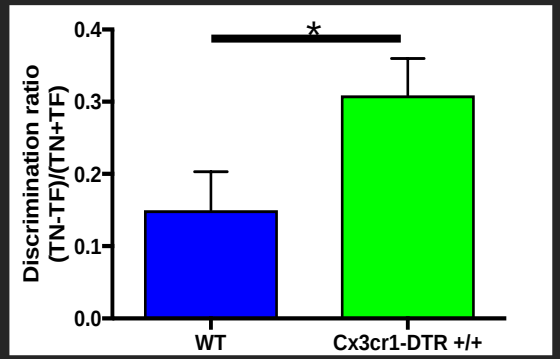


HOM 7 days





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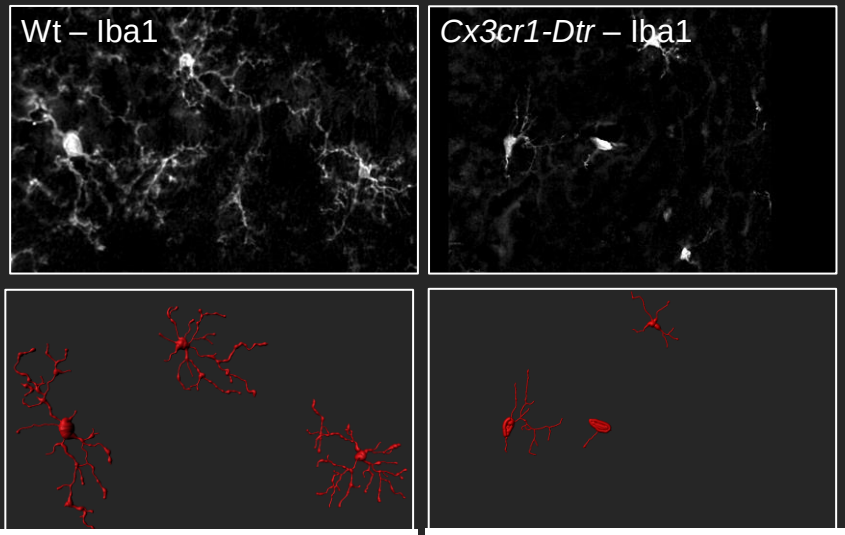
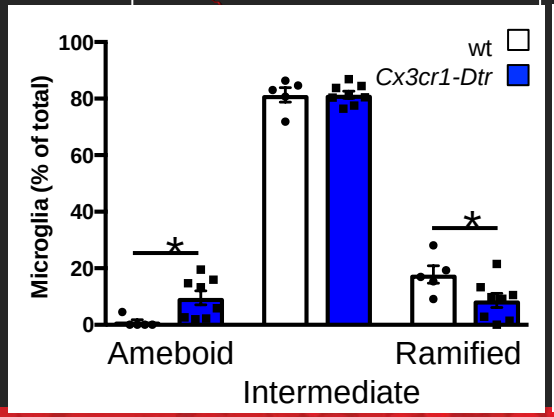
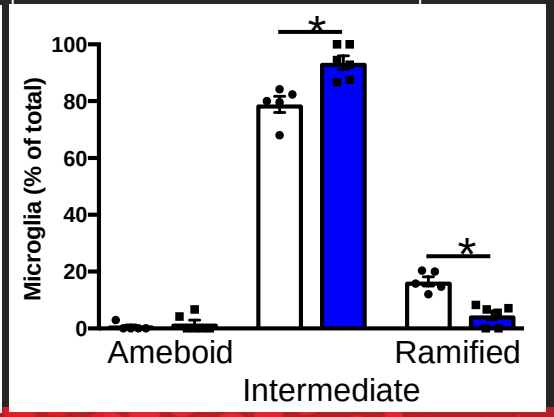



CA1



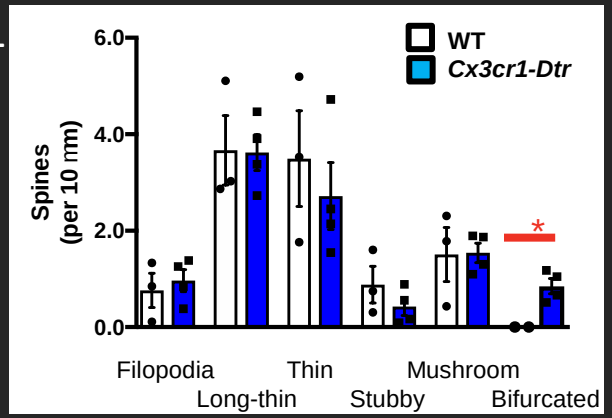




Hilus

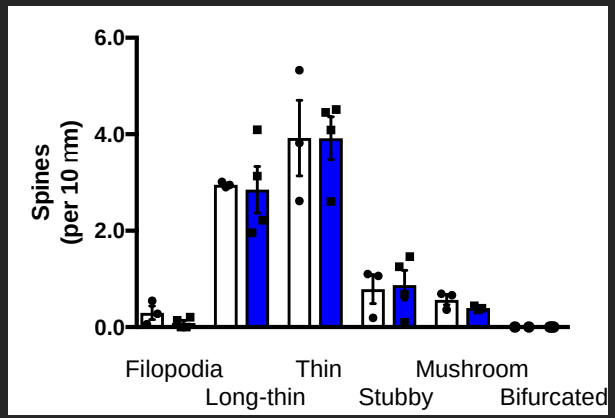
De Luca et al, J. Neuroinflam. 2020.

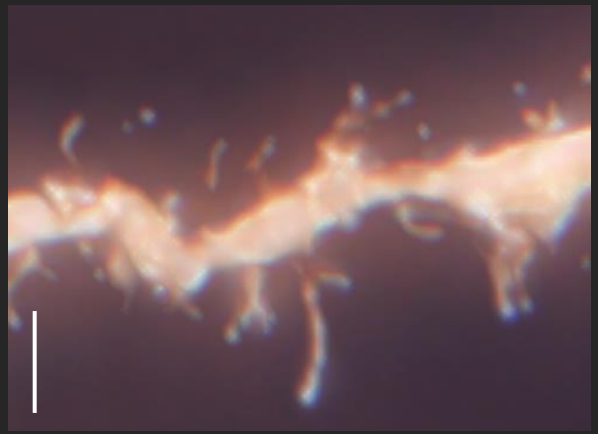
# Are microglia directly involved in cognition?

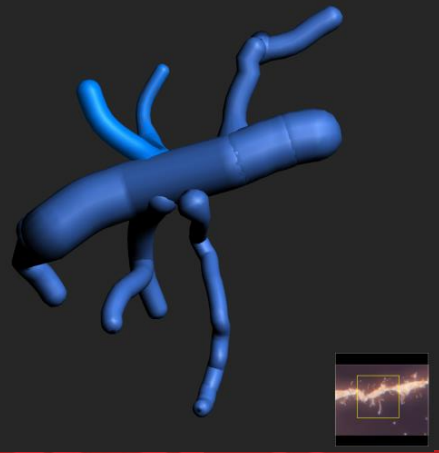
CA1




CA3





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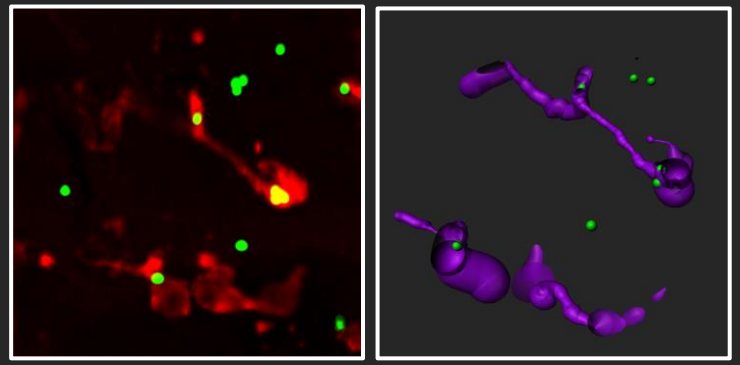
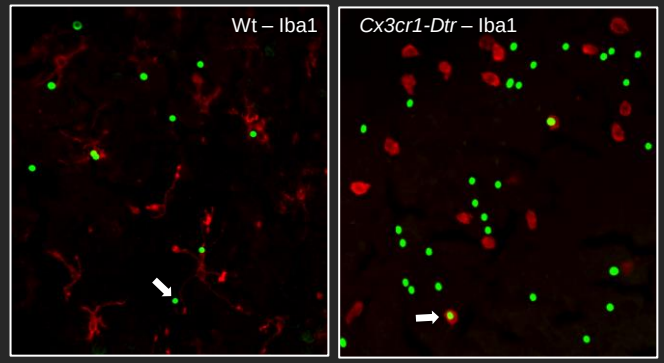
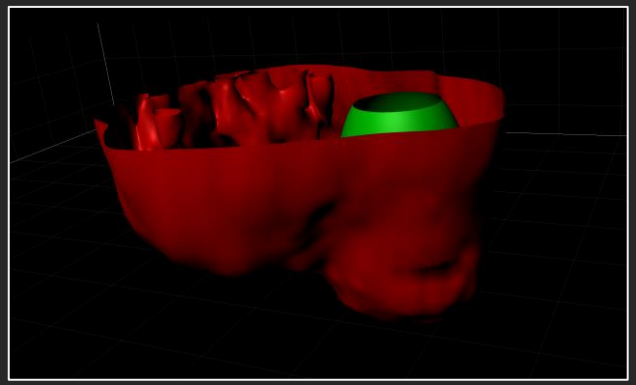
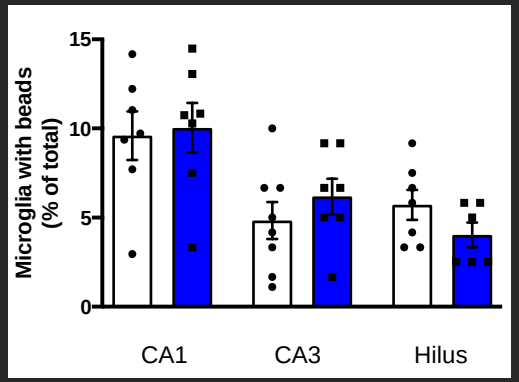
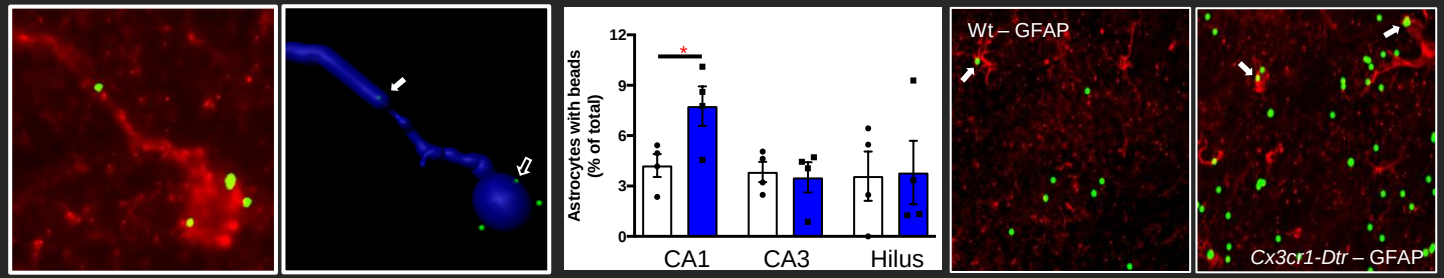


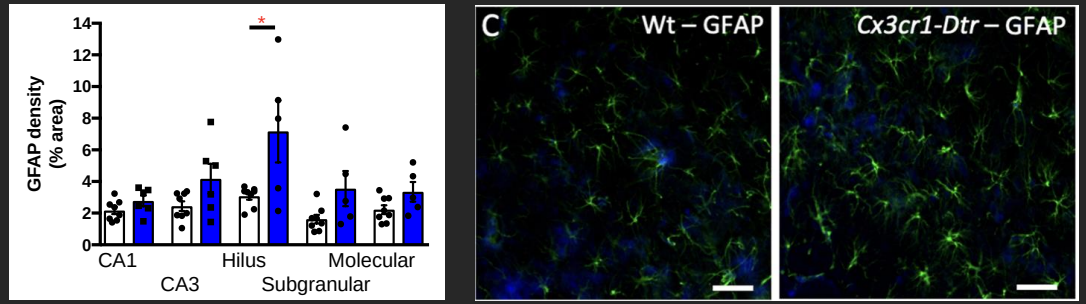


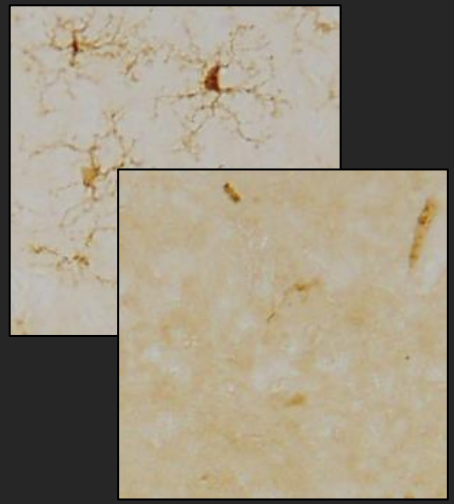


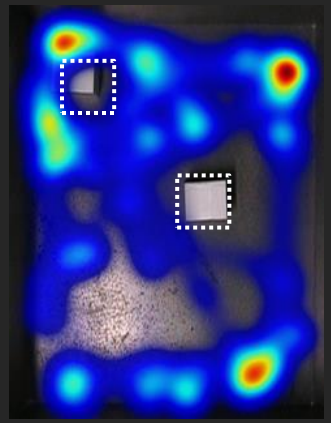
# Are astrocytes directly involved in cognition?

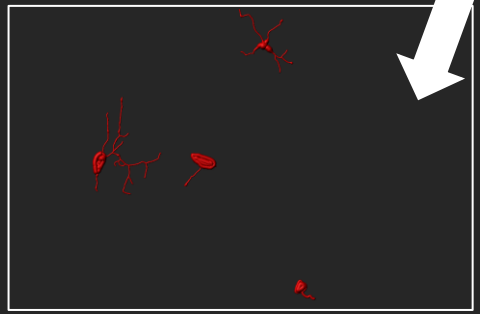


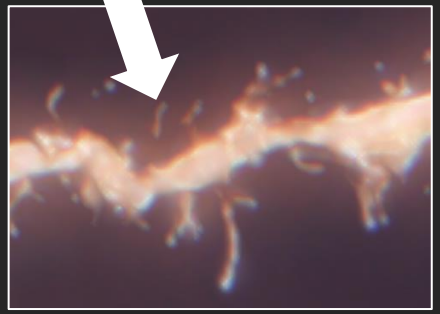



Ablating microglia leads to improved memory performance when the microglia repopulate the brain









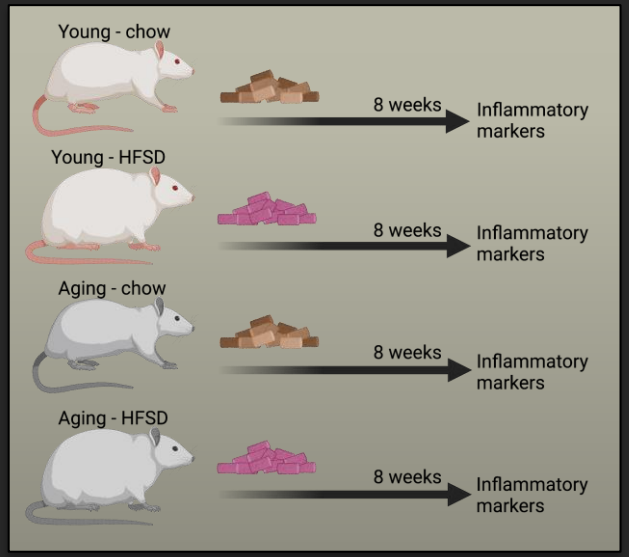
Associated with hyper-activated microglial morphology, and synaptic remodelling

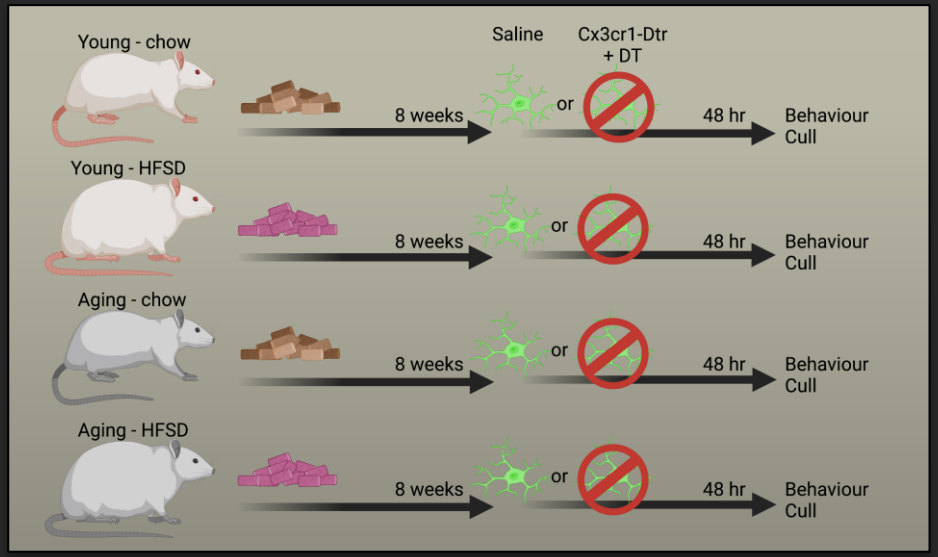
Microglia do have a direct role in cognition… is this role disrupted by high fat diet and aging?

# Cognition in neuroinflammaging

Microglia do have a direct role in cognition… is this role disrupted by high fat diet and aging?

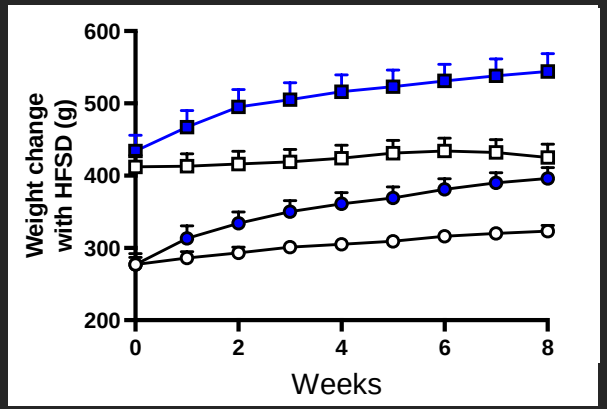
SAJIDA MALIK

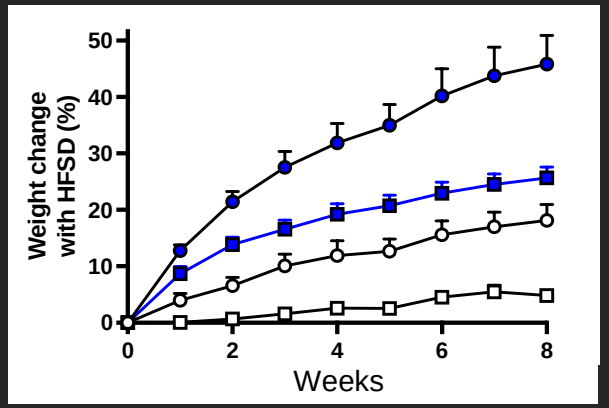


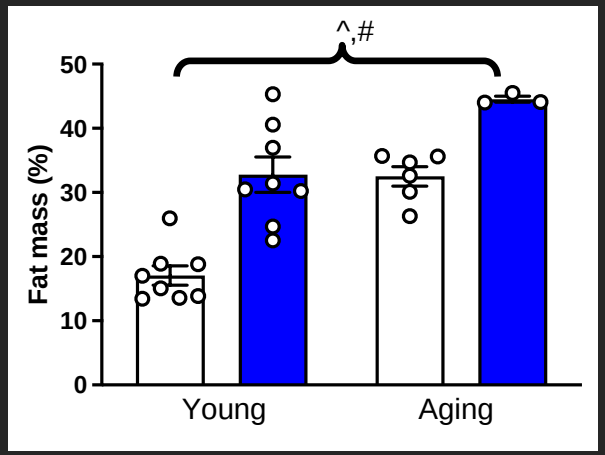
# HFSD causes weight gain in young and aging

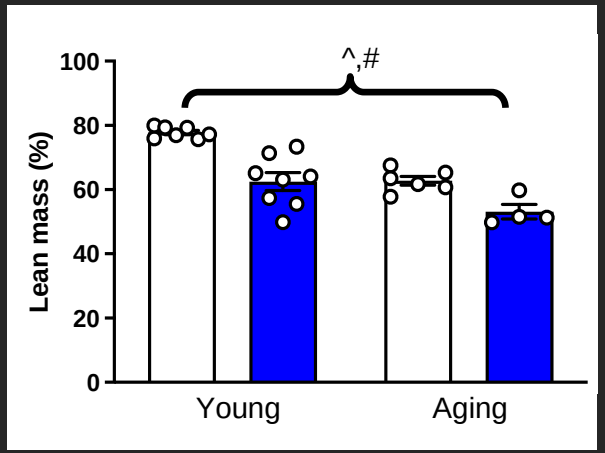
Chow young
HFSD young
Chow aging
HFSD aging



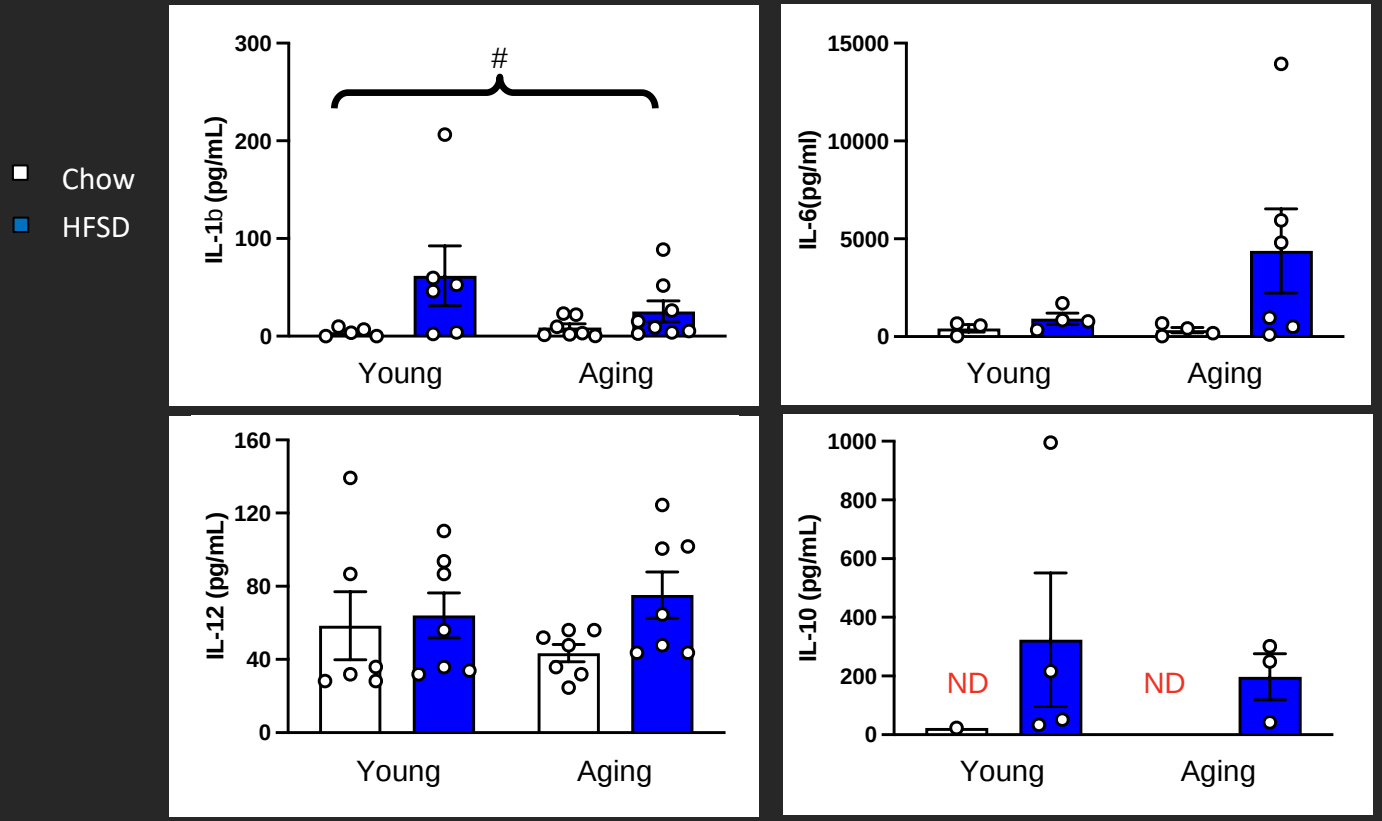

Chow
HFSD



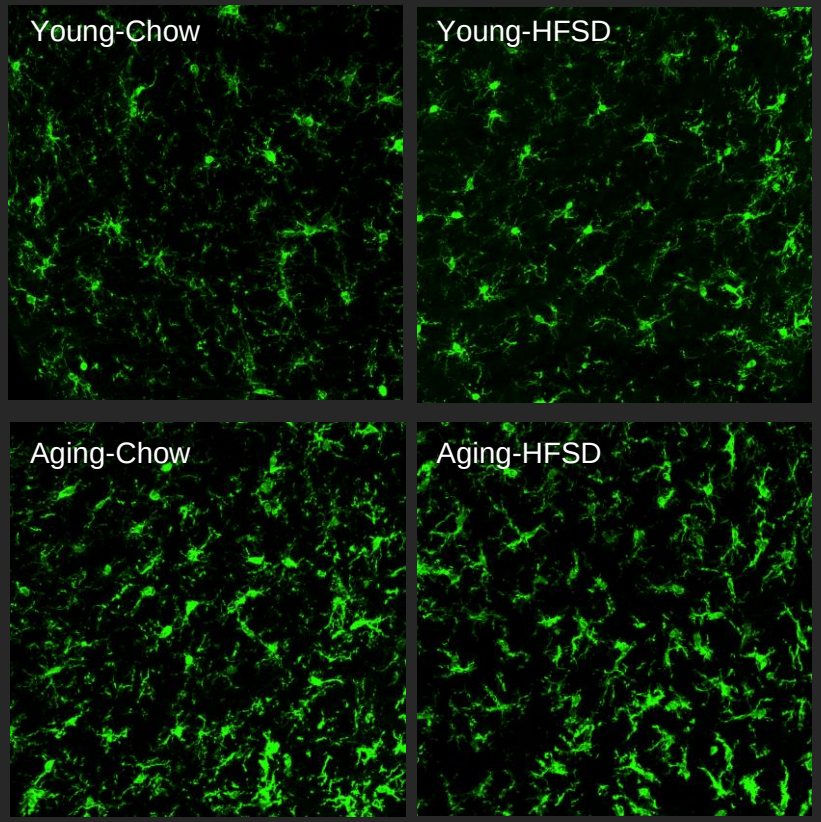

Malik, Spencer, et al unpublished.

# HFSD, but not aging, causes a mild inflammatory response

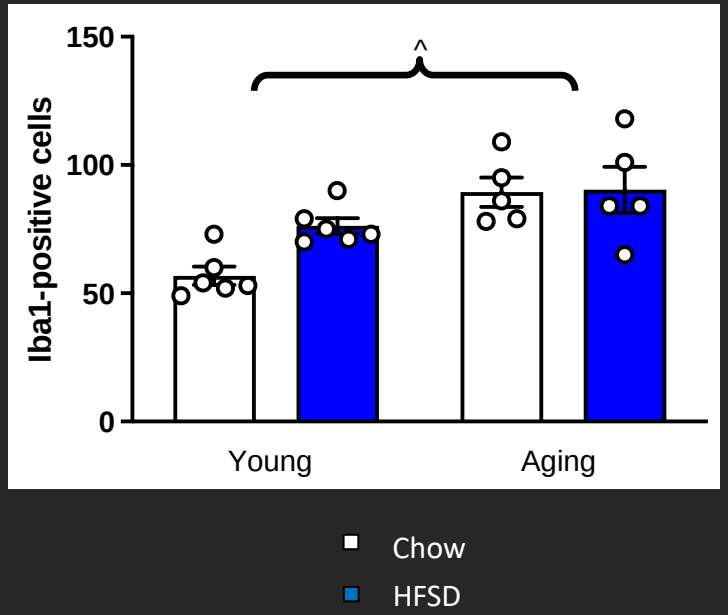



Malik, Spencer, et al unpublished.

# Aging, but not HFSD, causes microgliosis

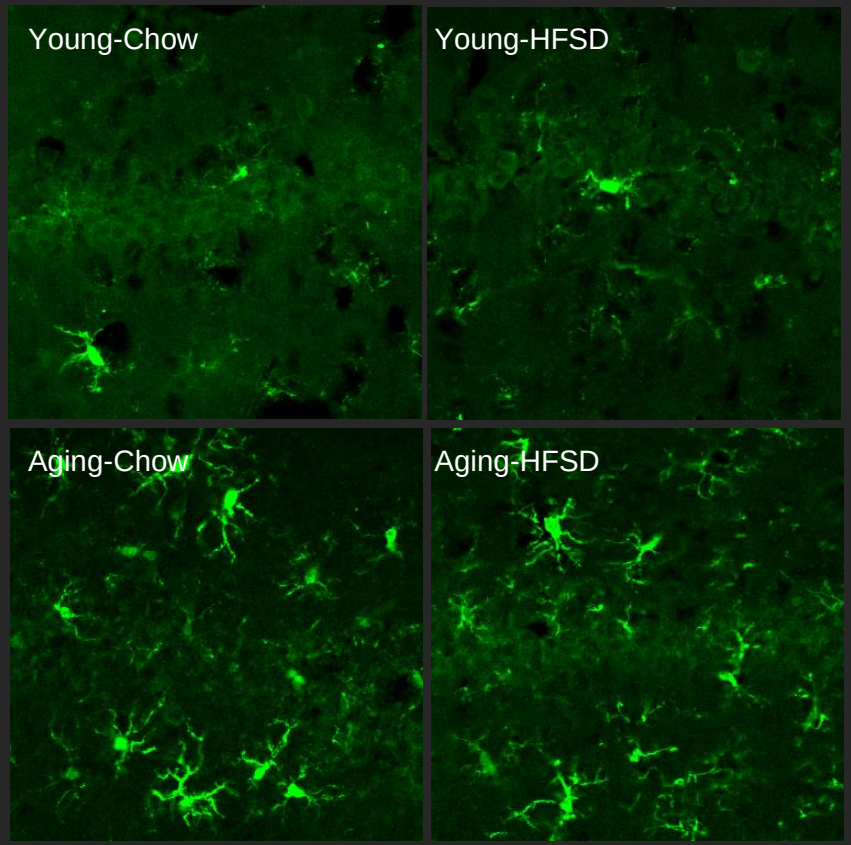



Arcuate

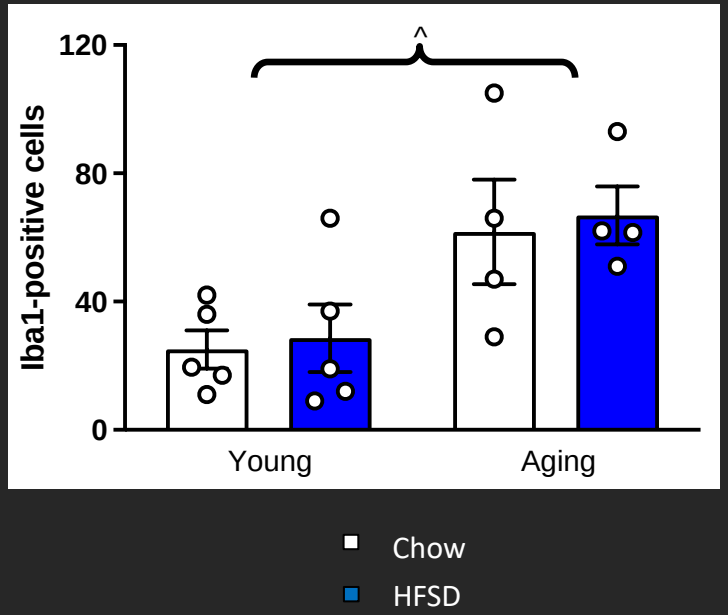



Malik, Spencer, et al unpublished.

# Aging, but not HFSD, causes microgliosis

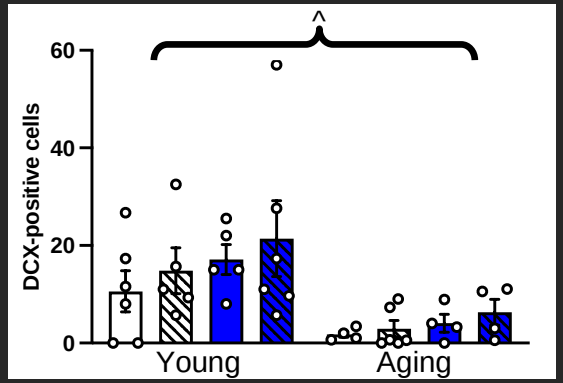



CA1

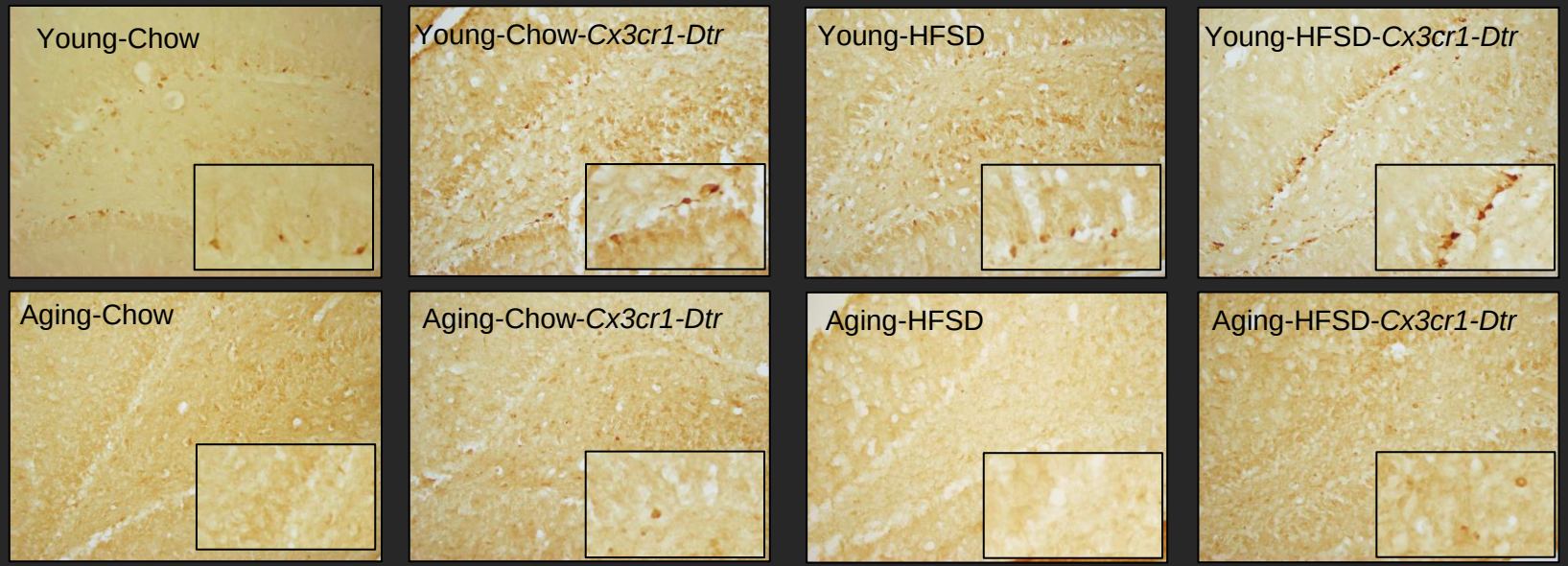



Malik, Spencer, et al unpublished.

# Aging, but not HFSD, reduces numbers of immature neurons



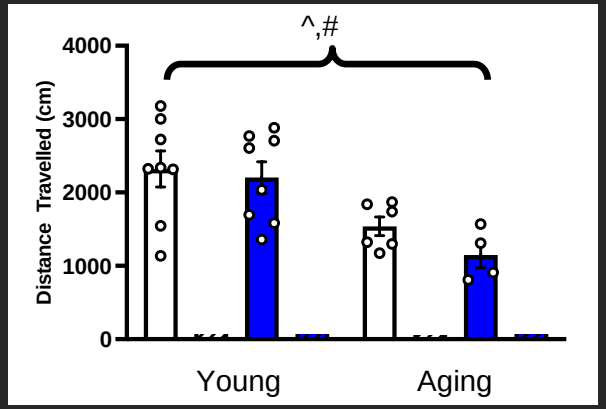

Chow
HFSD
Chow-Cx3cr1-Dtr
HFSD-Cx3cr1-Dtr

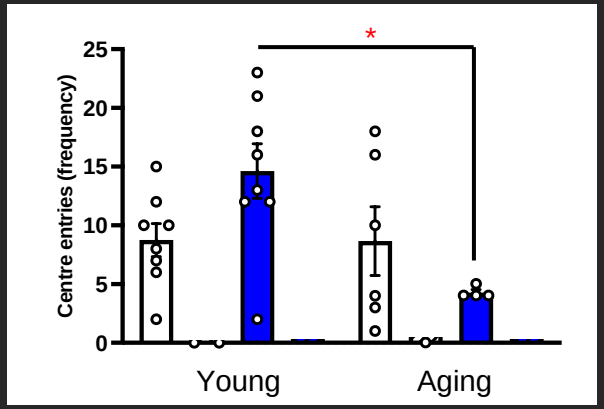



Malik, Spencer, et al unpublished.

# Aging AND HFSD reduce exploration

Chow
HFSD

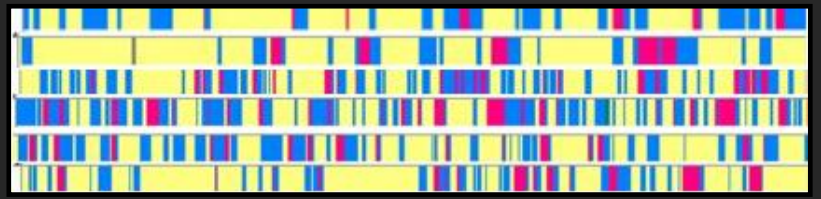



Freezing Grooming Walking Rearing Surveying

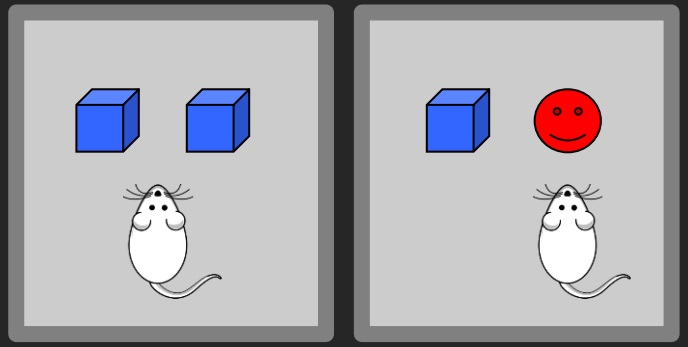
Young
- Chow

Ageing
- Chow

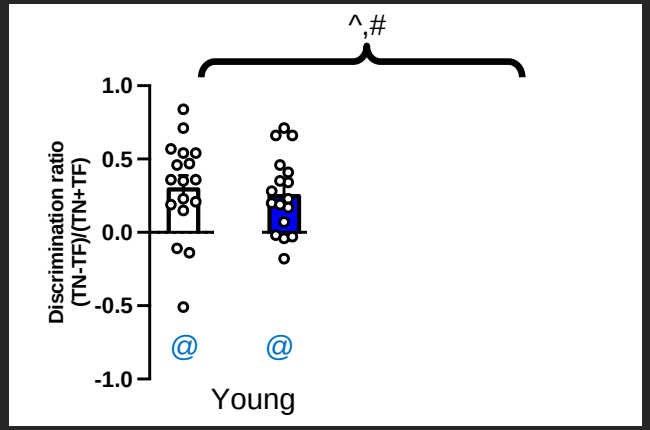


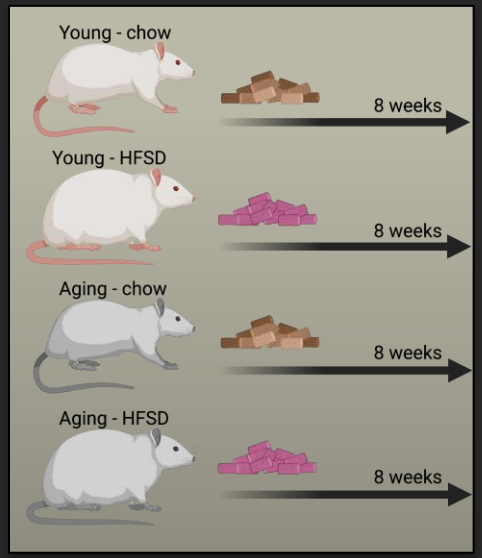
Malik, Spencer, et al unpublished.

# Aging AND HFSD impair novel object recognition memory

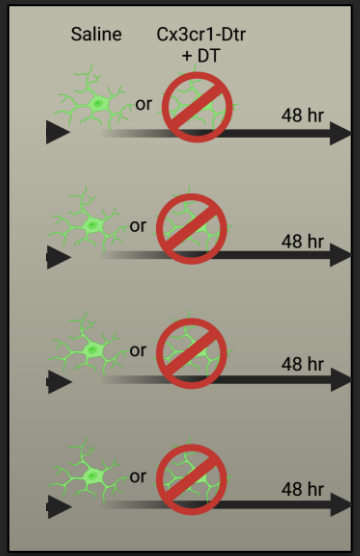


Chow
HFSD



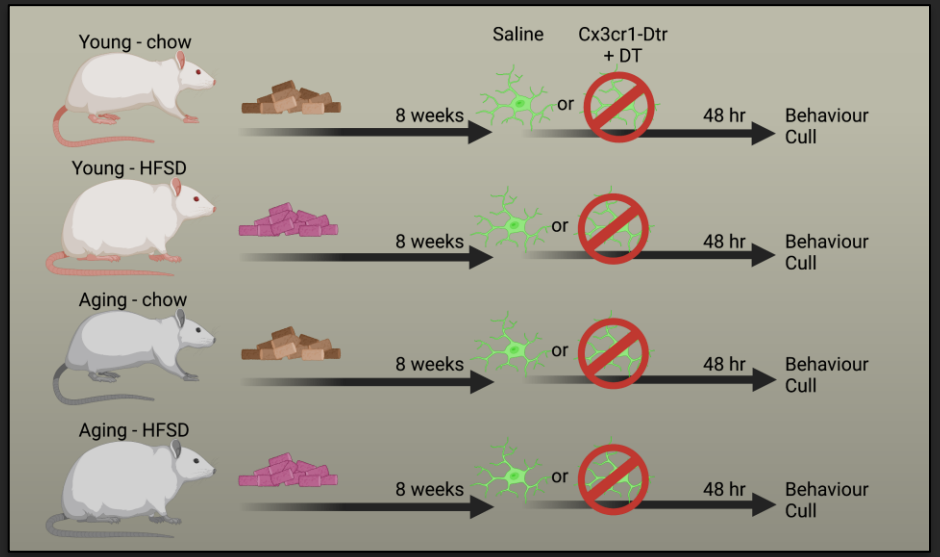


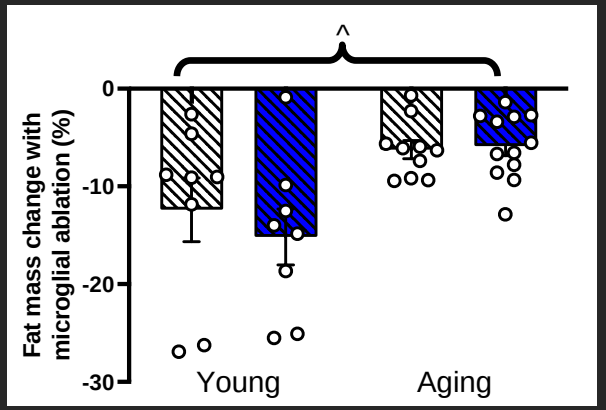

- HFSD increases weight and circulating inflammatory markers
- Aging increases weight, increases central inflammation (microgliosis), reduces numbers of new neurons (DCX)
- Aging + HFSD reduce exploration and impair NOR

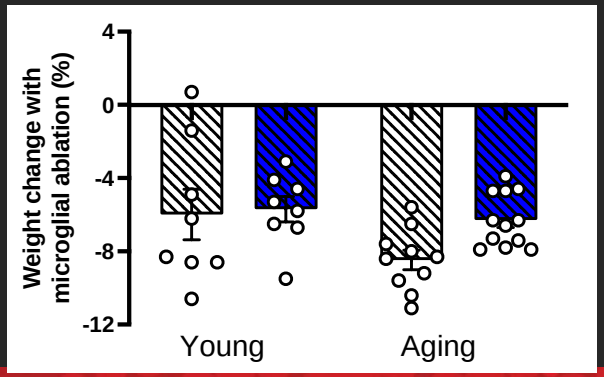



# Can microglial ablation mitigate these effects?

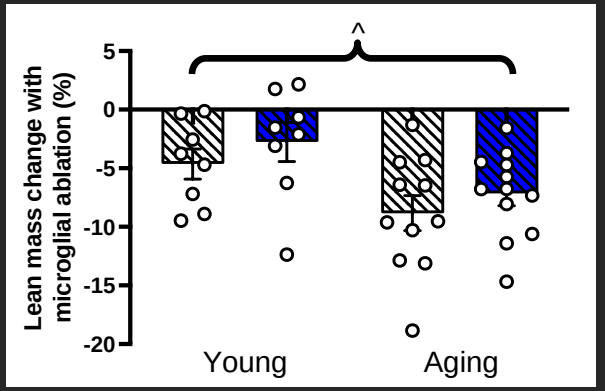
# Microglial ablation causes acute weight loss



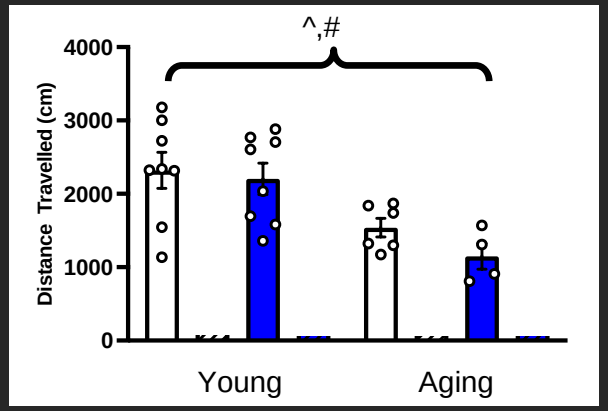

Chow
HFSD

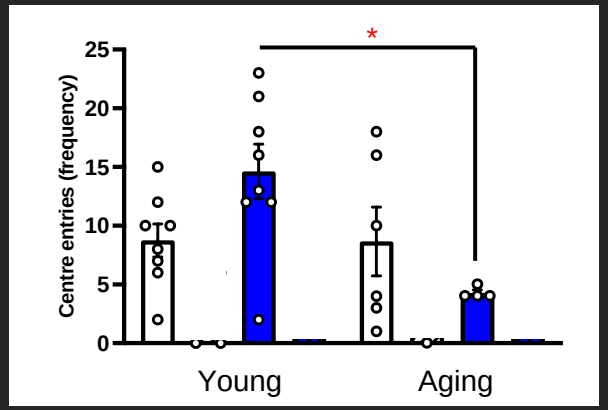



Malik, Spencer, et al unpublished.

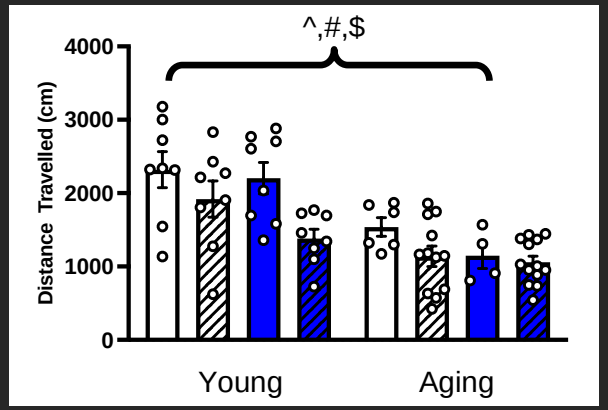
# HFSD and aging reduce exploration

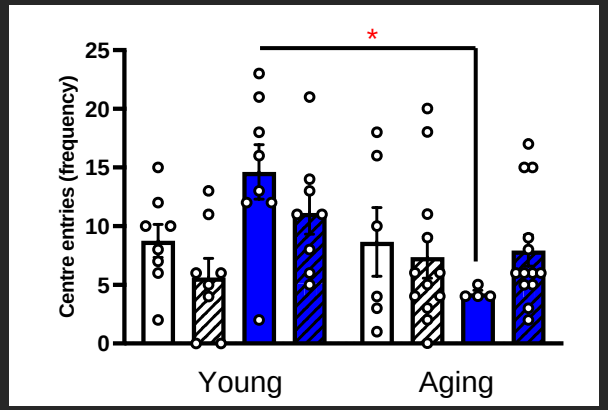
Chow
HFSD



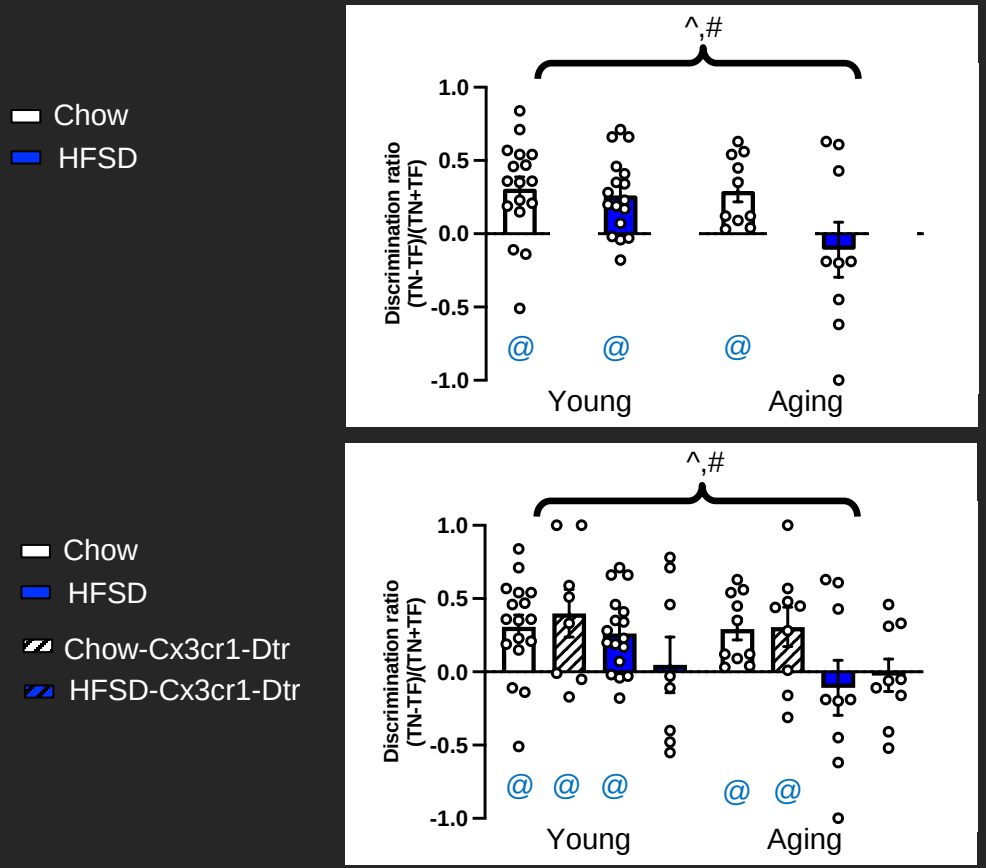

Chow
HFSD
Chow-Cx3cr1-Dtr
HFSD-Cx3cr1-Dtr




Microglial ablation does not reverse this

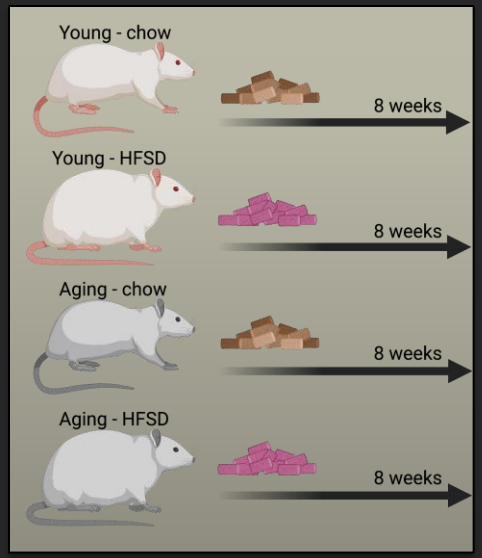
# HFSD and aging impair novel object recognition memory




Microglial ablation does not reverse this

Malik, Spencer, et al unpublished.

# Summary

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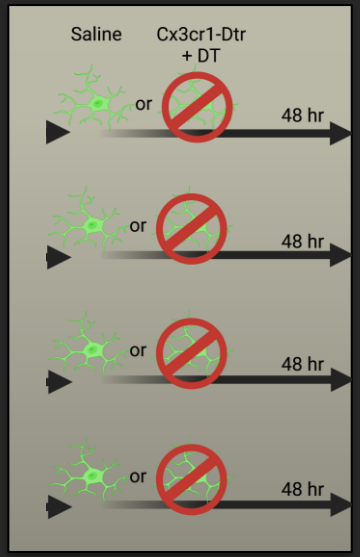


Microglial ablation does not reverse these effects

Malik, Spencer, et al unpublished.

# Summary

Microglia are not acutely responsible for the deficits caused by Aging and HFSD.

Likely involves brain regions other than hippocampus

The microglial contribution to memory decline is likely chronic

Probably impacts memory tasks with a long-term or sleep-phase consolidation period

# Team and funding

***This work***
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Brant Gibson (RMIT)
Philipp Reineck (RMIT)
& Ruth Barrientos (Ohio State University)

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Hasan Ul-Banna (PhD student)
Mary Slayo (PhD student)
Baha Mustafa (PhD student)
Bilal Muhammad (PhD student)

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SOLID Start To Cognitive Health

Sir Edward 'Weary' Dunlop MEDICAL RESEARCH FOUNDATION

Australian Government Australian Research Council

Australian Government National Health and Medical Research Council NHMRC

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