



Nutritional and pharmacological approaches to slow inflammation and degeneration of the aging brain

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ASU-Banner Neurodegenerative Disease Research Center

*Scan the QR
code to learn
more about the
Velazquez lab.*





At the Biodesign Institute, we are committed to catching disease before it catches us. We are finding creative and clean solutions for energy, air, and water. We are inventing diagnostics and treatments that are accessible and affordable. We are growing the next-gen researchers who will do the impossible.

-Joshua LaBaer, 2022

Executive Director, Biodesign Institute

ASU Biodesign
Institute
Arizona State University



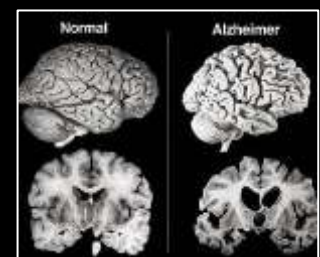
ASU-Banner Neurodegenerative Disease Research Center

biodesign.asu.edu

Lab focus: Determine the early events that contribute to the progression of **Alzheimer's disease**, with a strong focus on **inflammation and tau pathogenesis**. This includes environmental factors, such as **diet** and toxins, and neurodevelopmental disorders leading to neurodegeneration, in particular Down syndrome.

We use a variety of model symptoms and tools, which allows us to take a multidisciplinary approach when asking research questions.

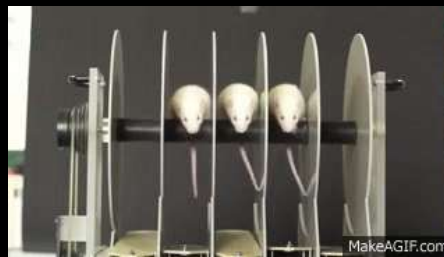
Human brain tissue



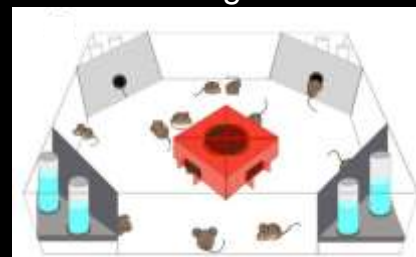
Mouse models



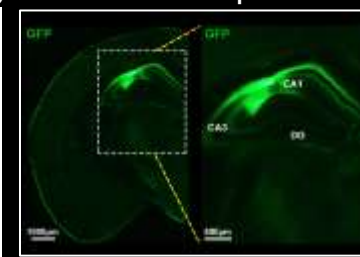
Rodent motor assessment



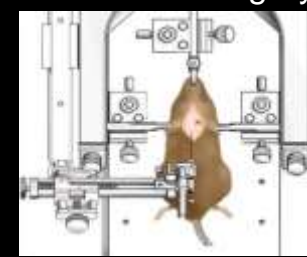
Automated cognitive testing



AAV development



Stereotaxic surgery



Drug studies



Our collaborative approach

We strongly believe that in order to progress outcomes in neurodegenerative disease research, collaborations across institutions and disciplines are required.



2023 ALZHEIMER'S DISEASE FACTS AND FIGURES



More than
6 million Americans
are living with Alzheimer's

Over 11 million
Americans
provide unpaid care for people with Alzheimer's or other dementias

These caregivers provided more than 18 billion hours valued at nearly

\$340 billion

1 in 3
seniors dies with Alzheimer's or another dementia

It kills more than
breast cancer
+
prostate cancer
combined

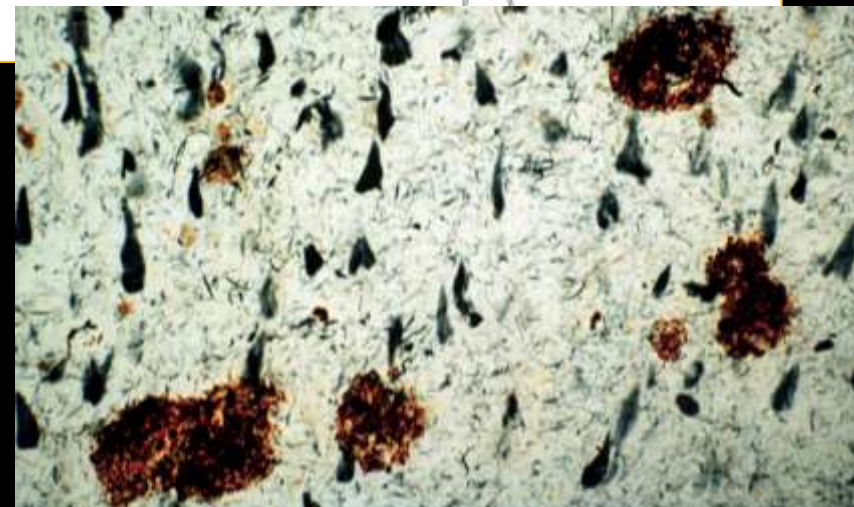
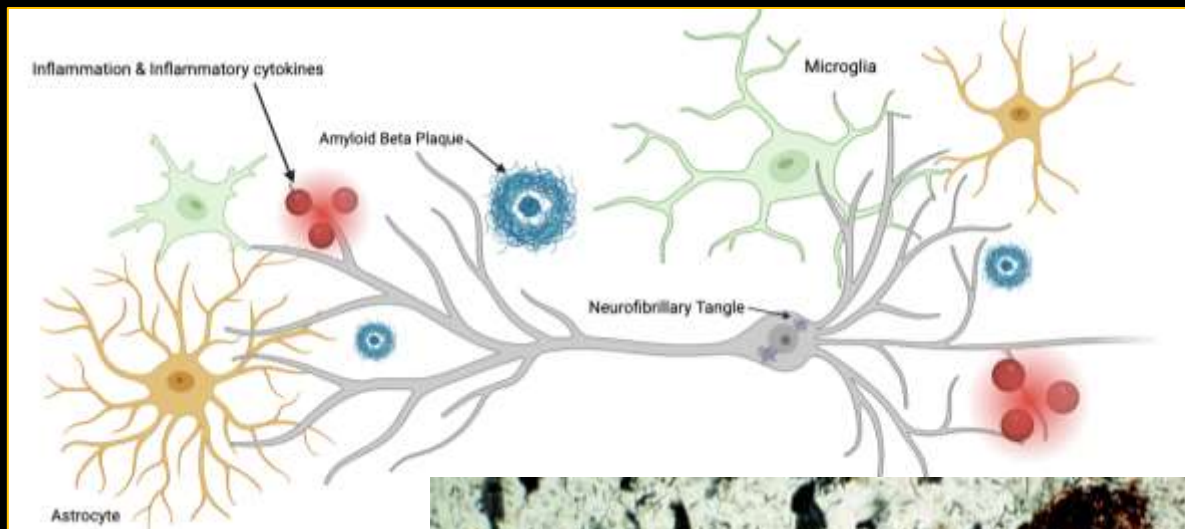
The lifetime risk for Alzheimer's at age 45 is
1 in 5 for women
+
1 in 10 for men

Between 2000 and 2019, deaths from heart disease has
decreased 7.3%

In 2023, Alzheimer's and other dementias will cost the nation
\$345 billion

By 2050, these costs could rise to nearly
\$1 trillion

ALZHEIMER'S ASSOCIATION





While aging is the most significant risk factor for AD, brain changes occur decades before clinical symptomology.

Can we identify preventive strategies to offset disease?

- * Worldwide, over 55 million affected with AD.
- * Estimated 153 million by year 2050.

Current areas of investigation

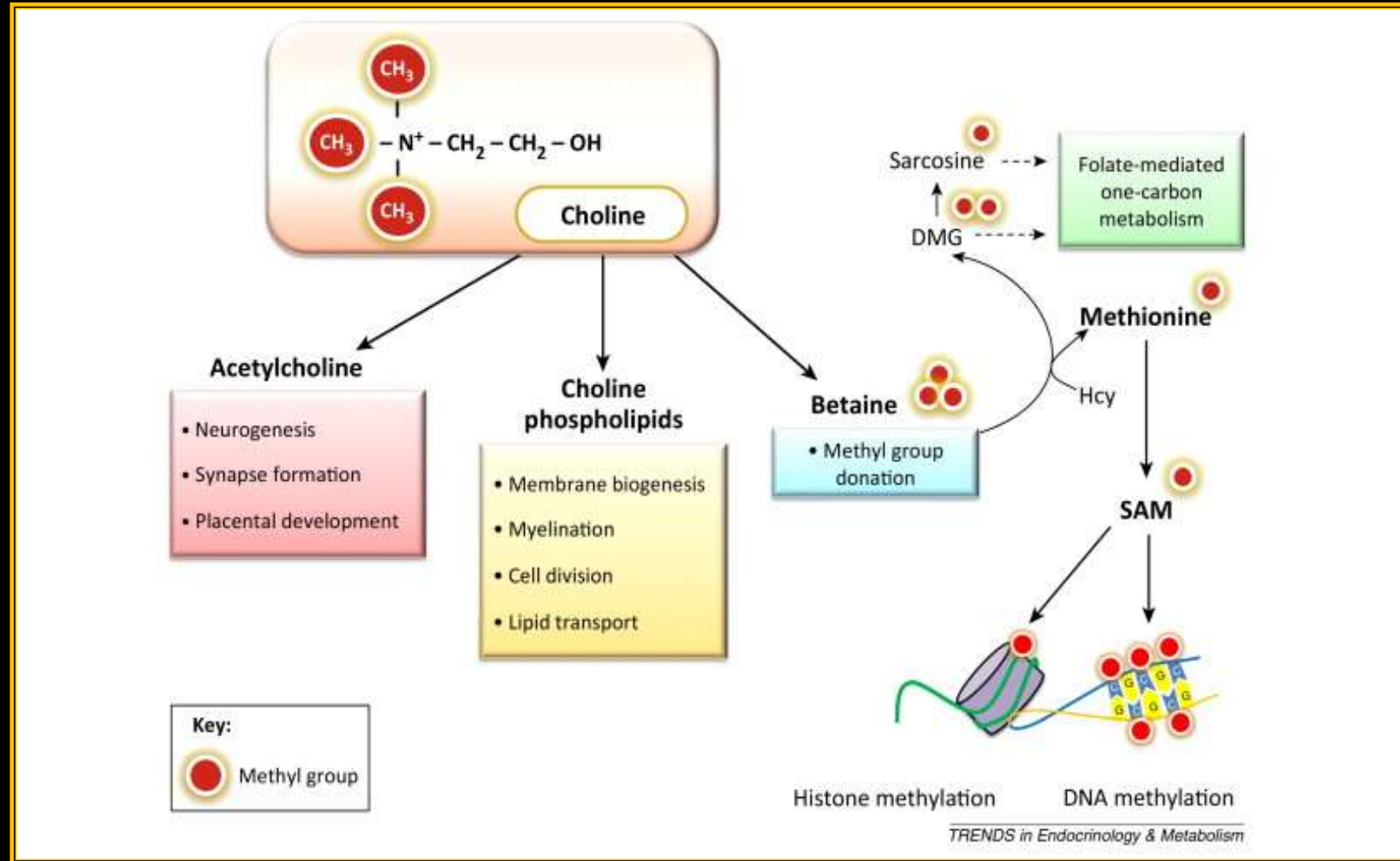
-  **The importance of dietary choline in the prevention of disease**
 - The role of herbicides in exacerbating neuroinflammation**
-  **Development of therapies against tau pathogenesis**

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Choline: Nutrient with essential roles in body and brain-related functions

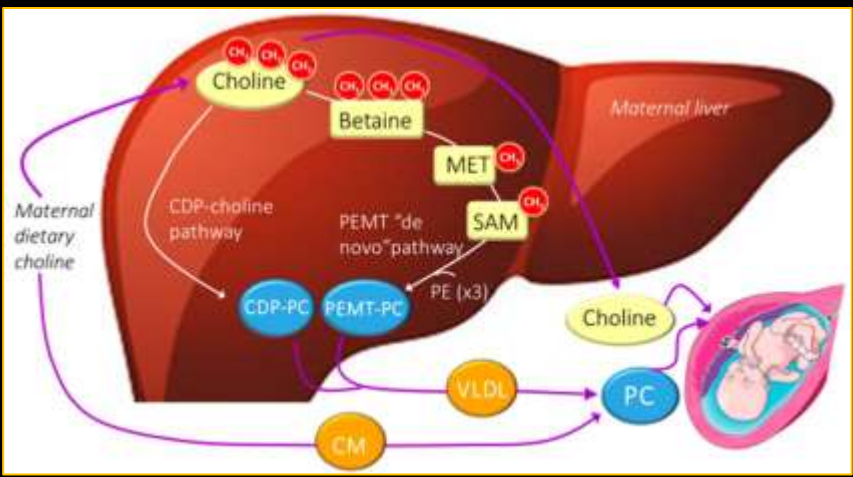


- Produced endogenously by the Phosphatidylethanolamine N-Methyltransferase (**PEMT**) protein in the liver, but not enough to meet bodily demands.



Choline: Dietary supplementation is required as recommended by the IOM in 1998

Men (550mg/day)
Women (425mg/day)
Pregnant (550mg/day)




Korsmo et al., 2019, *Nutrients*



	Beef liver, 3 ounces 65% DV		Cod Fish , 3oz. 13% DV
	1 large egg, hard boiled 27% DV		Potatoes, 1 large 10% DV
	Soybeans, 1/2 cup 19% DV		Wheat Germ, 1 oz. 9% DV
	Chicken breast, 3 oz. 13% DV		Kidney Beans, 1/2 cup 8% DV



~90% of Americans are deficient in dietary choline, and some countries do not have recommendations (PMID: 30853718).

 The American Journal of Clinical Nutrition
Volume 116, Issue 5, November 2022, Pages 1201-1207

Is dietary choline intake related to dementia and Alzheimer's disease risks? Results from the Framingham Heart Study



Jing Yuan^{1,2}, Xue Liu³, Chunyu Liu³, Alvin FA Ang^{2,4,5}, Joseph Massaro^{3,4}, Sherril A Devine^{2,4}, Sanford H Auerbach^{4,6}, Jan Krzysztof Blusztajn⁷, Rhoda Au^{2,4,5,6,8}, Paul F Jacques^{9,10}  

Hindawi
Behavioural Neurology
Volume 2021, Article ID 2962245, 11 pages
<https://doi.org/10.1155/2021/2962245>



Research Article

Choline Intake Correlates with Cognitive Performance among Elder Adults in the United States


Lu Liu,¹ Song Qiao,¹ Liying Zhuang,¹ Shanhu Xu,¹ Linhui Chen,¹ Qilun Lai¹ ¹ and Wenfeng Wang² 


Inflammation and the pathological progression of Alzheimer's disease are associated with low circulating choline levels

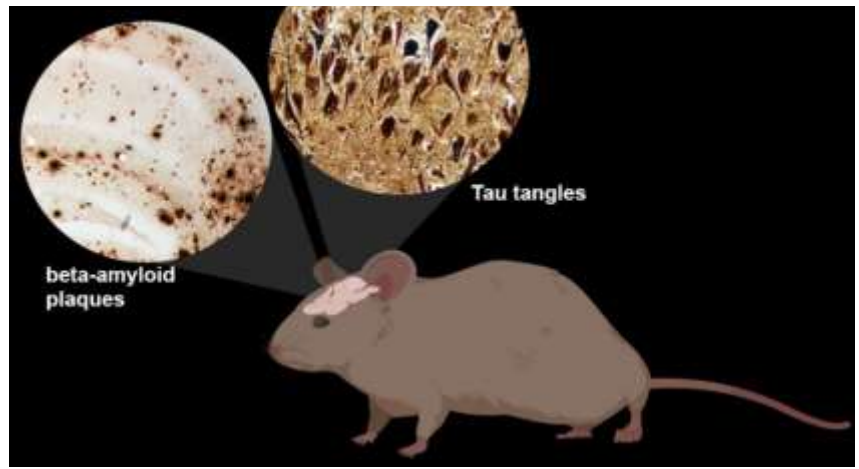
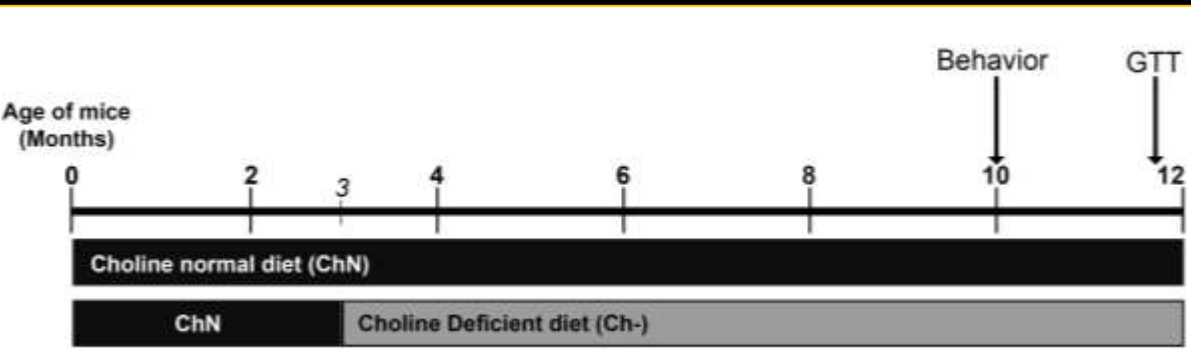
Original Paper | [Open access](#) | Published: 07 August 2023

Volume 146, pages 565–583, (2023) [Cite this article](#)

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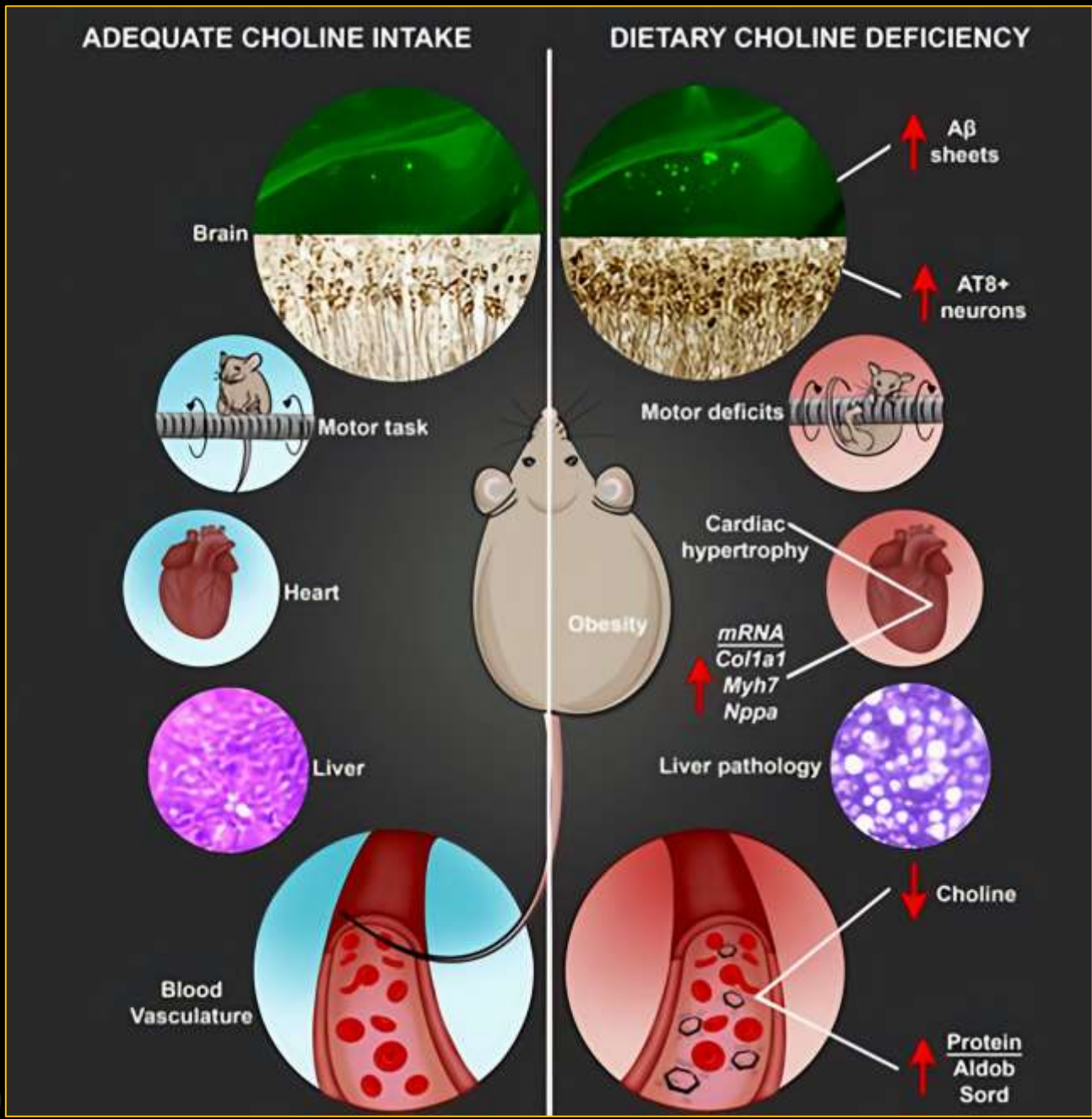
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Jessica M. Judd, Paniz Jasbi, Wendy Winslow, Geidy E. Serrano, Thomas G. Beach, Judith Klein-Seetharaman & Ramon Velazquez 



NonTg and 3xTg-AD

- Impairments in glucose metabolism in the GTT
- Elevations in pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ).



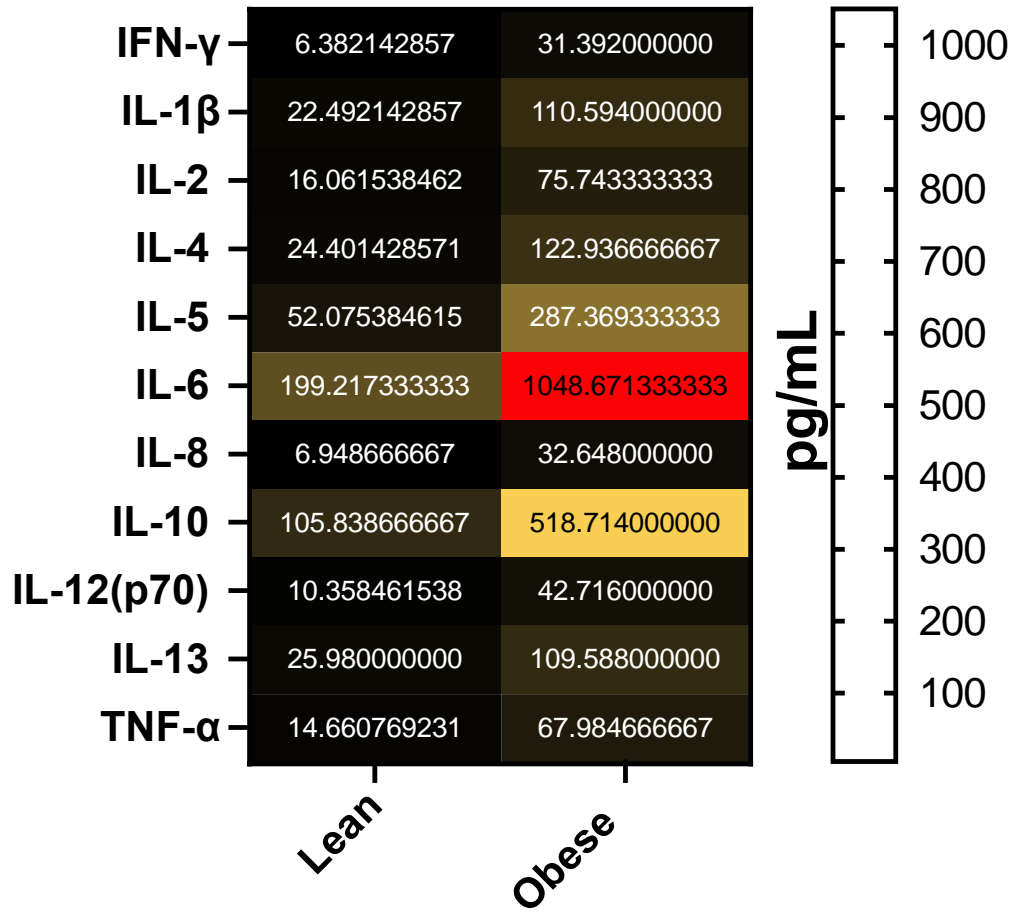
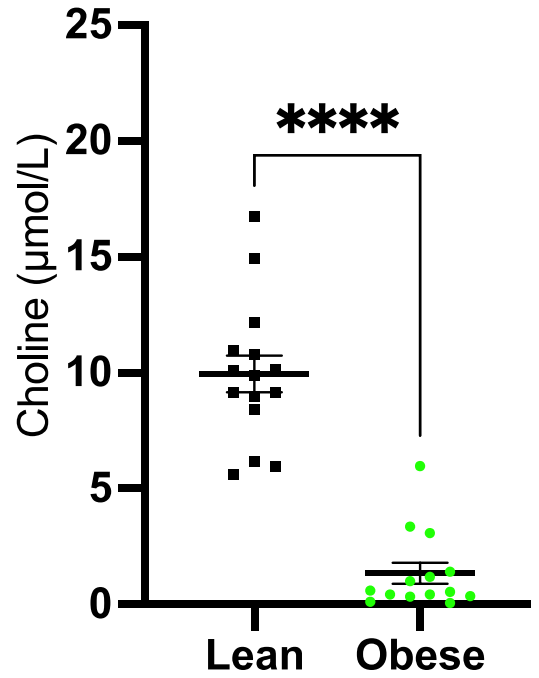


Prediabetic participants exhibit low circulating choline levels



Participant Profiles	Healthy weight (n=15)	Obese (n=13)
Age	M = 34.93	M = 33.23
BMI	M = 23.54	M = 35.49
A1C	M = 5.24	M = 5.62
HOMA-IR	M = 0.87	M = 2.79

Blood measures taken after 12 hours fasted. Abbreviations: Body mass index (BMI), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) where >1.9 indicates early IR.

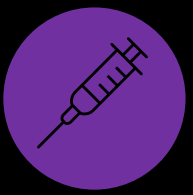


Collaborative opportunities



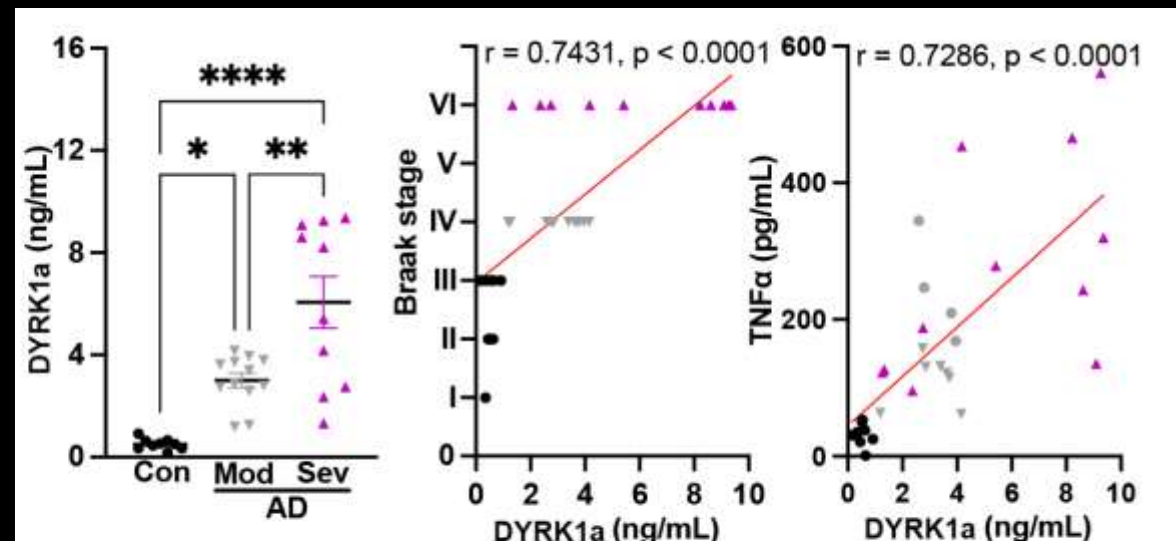
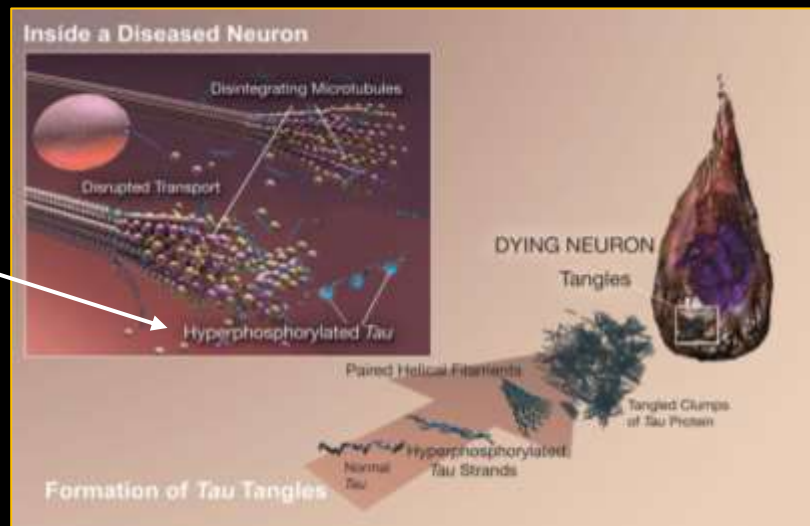
Examination of choline levels in blood





Development of novel DYRK1a inhibitors (US20220041590A1) to slow tau pathogenesis

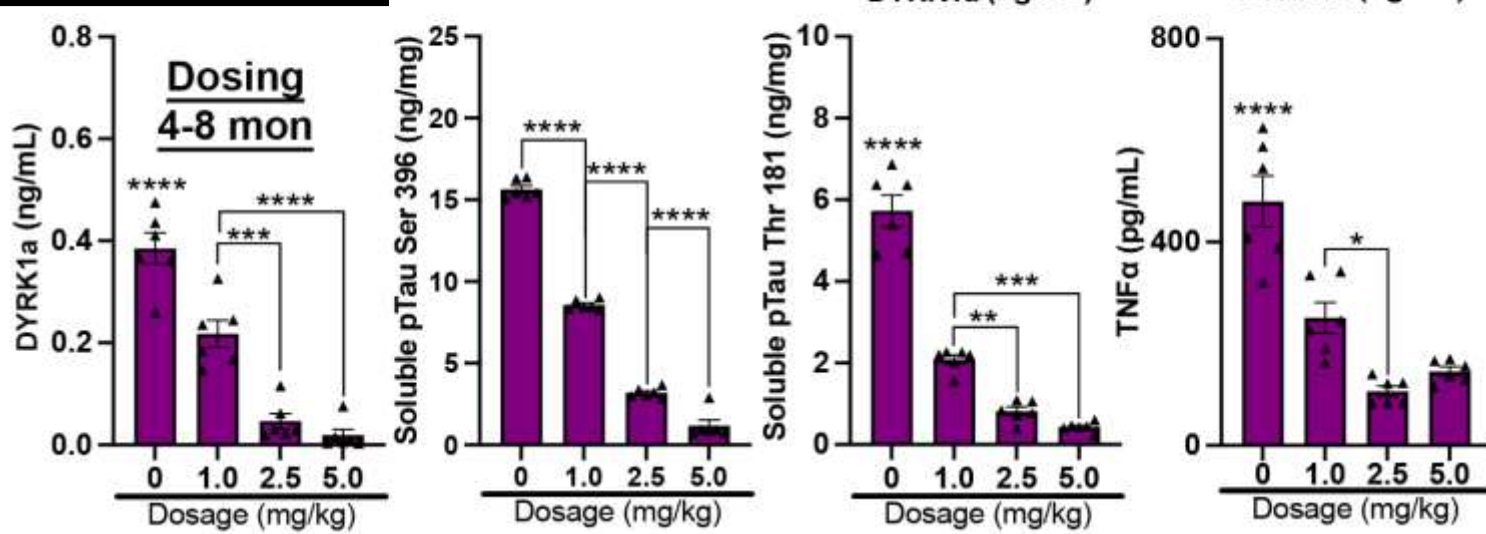
Dual specificity tyrosine-phosphorylation regulated kinase 1a (DYRK1a)



DYR533

- Small molecule Dyrk1a inhibitor
- 4-hour half life
- 100% oral bioavailability in mice
- High brain permeability

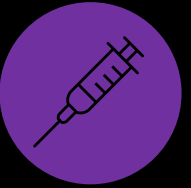
PS19 (P301S)



Collaborative opportunities

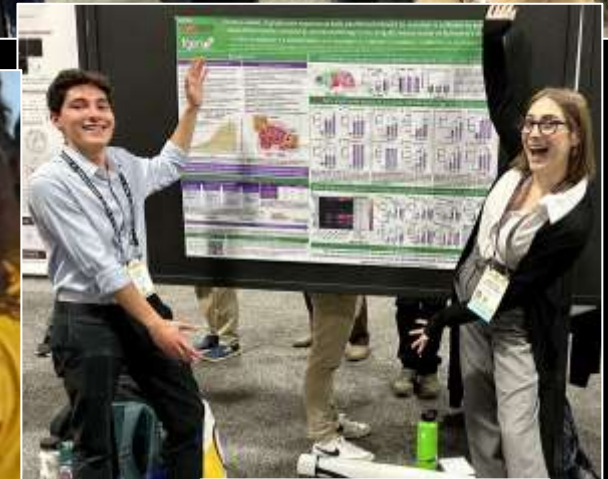
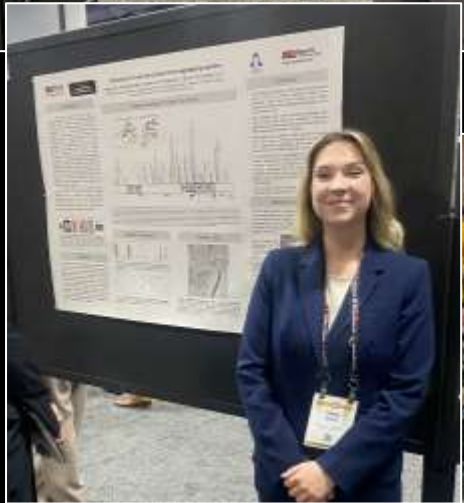
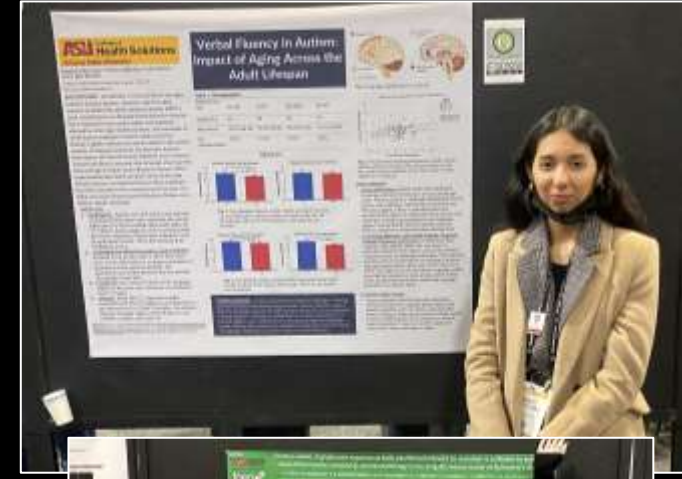
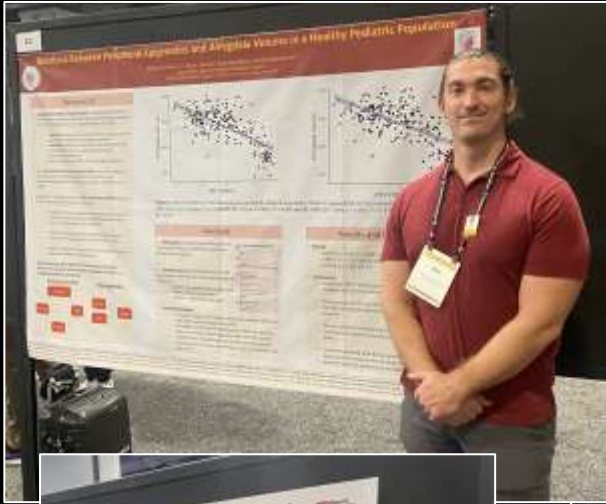
- Examination of choline levels in blood

 Testing novel therapeutic strategies utilizing preclinical models of disease

 Validating novel therapeutic targets utilizing blood plasma, serum and/or brain tissue from patients at various stages of disease.



Workforce Inclusion in Neuroscience through Undergraduate Research Experience (WINURE) program



Acknowledgments

Velazquez Lab members

Wendy Winslow, BS
Jessica Judd, PhD
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Samantha Bartholomew, BS
Julie Turk, BS
Ian McDonough, BS
Nikhil Dave, MS
Hector Leon
Faizan Mistry
Rachel Etebari
Alison Martin



Collaborators

Thomas Beach (Banner)
Christos Katsanos (Mayo)
Travis Dunckley (ASU)
Christopher Hulme (UofA)



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NIH R01: AG062500
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NIH R25: NS107188

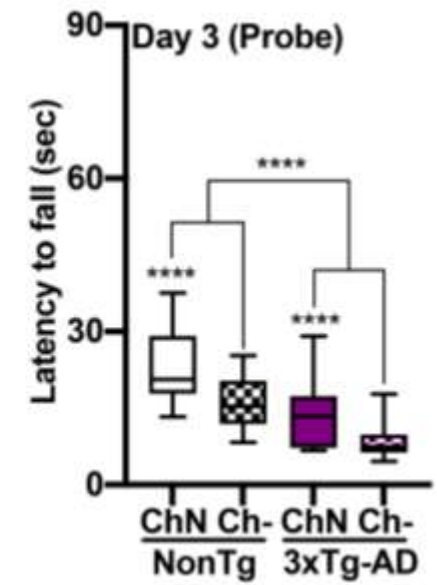
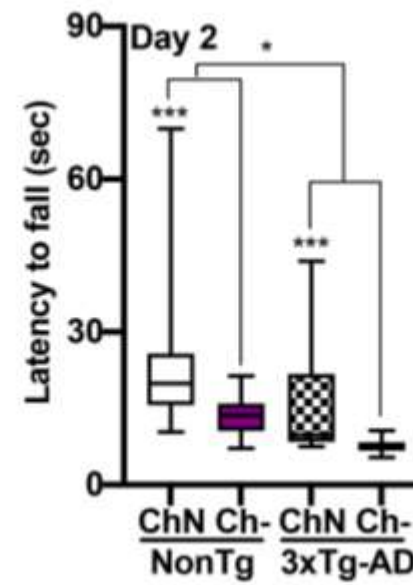
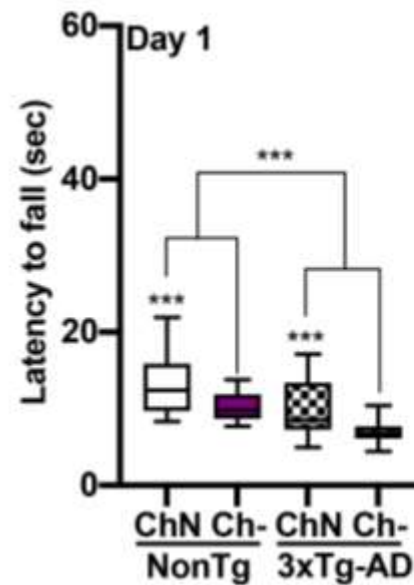
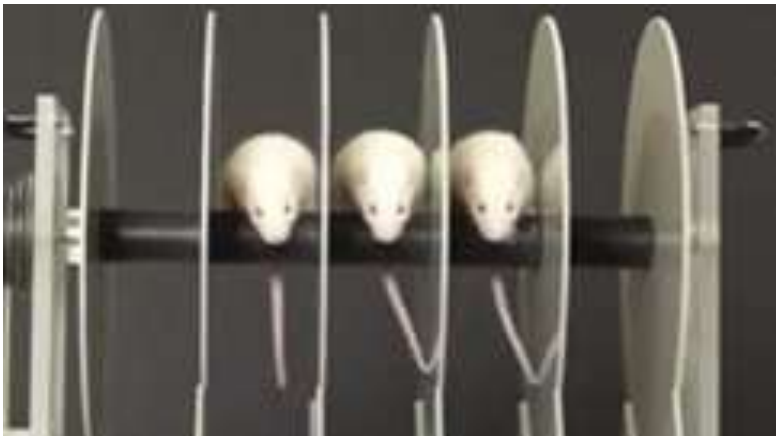
Supplementary Slides



Dietary choline deficiency impairs motor function

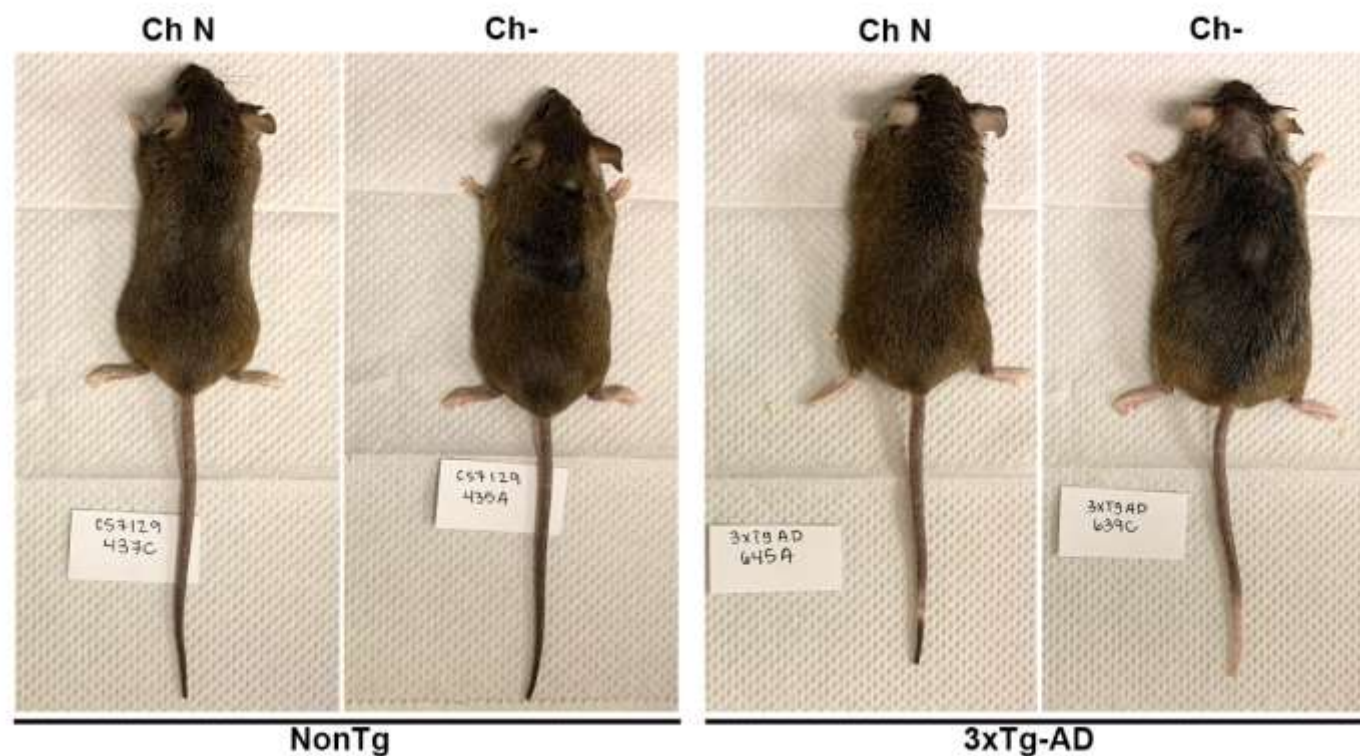
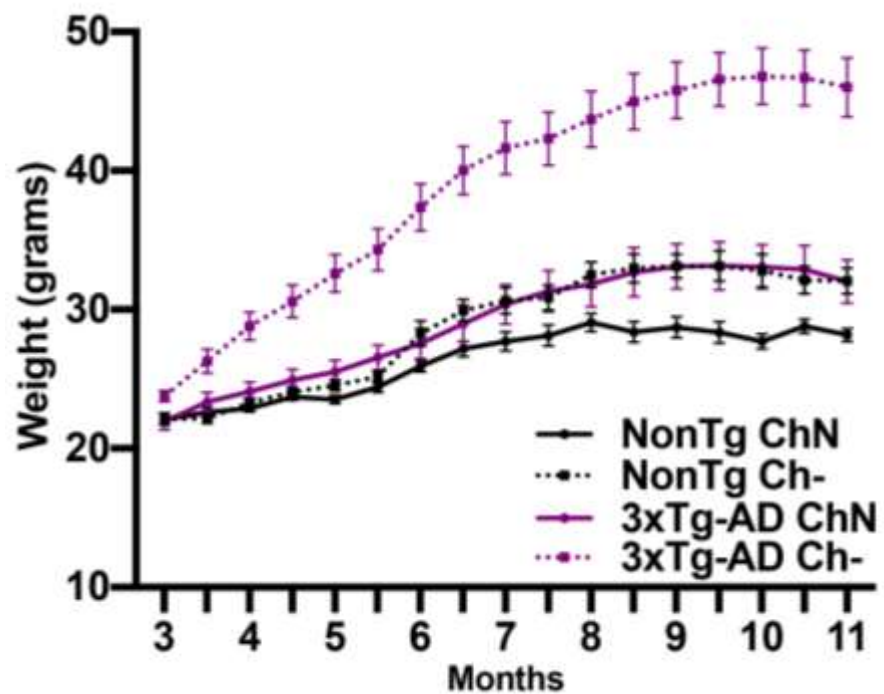
Why:

- Acetylcholine modulates nerve cells and muscles.
- To look at the effect on motor function due to deficiencies.





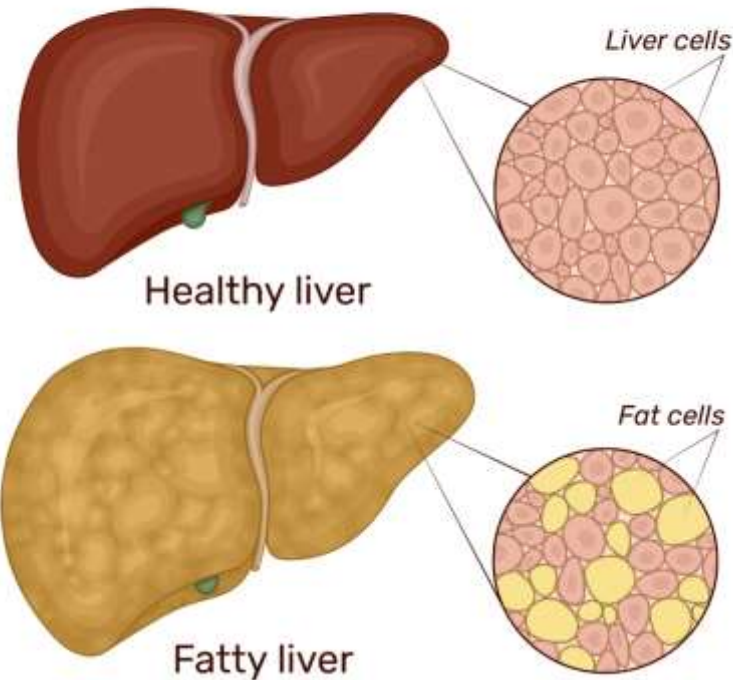
Dietary choline deficiency increases weight



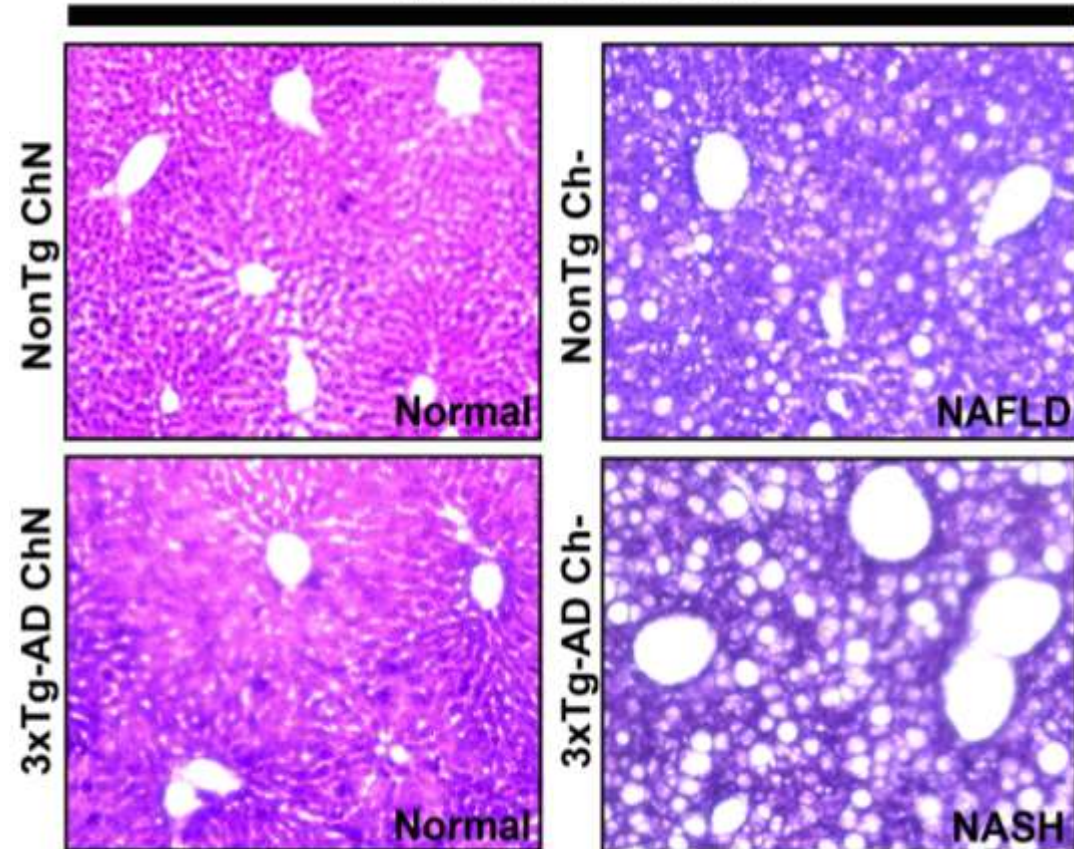


Dietary choline deficiency induces liver pathology and peripheral inflammation

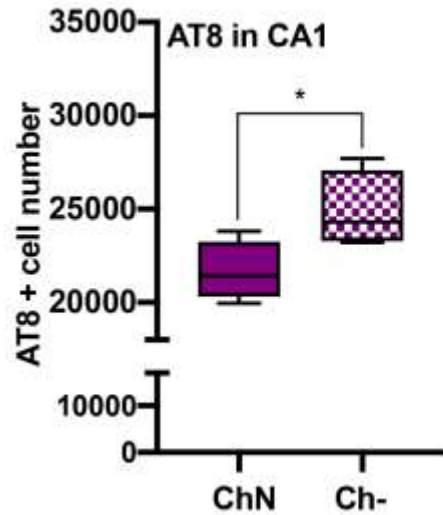
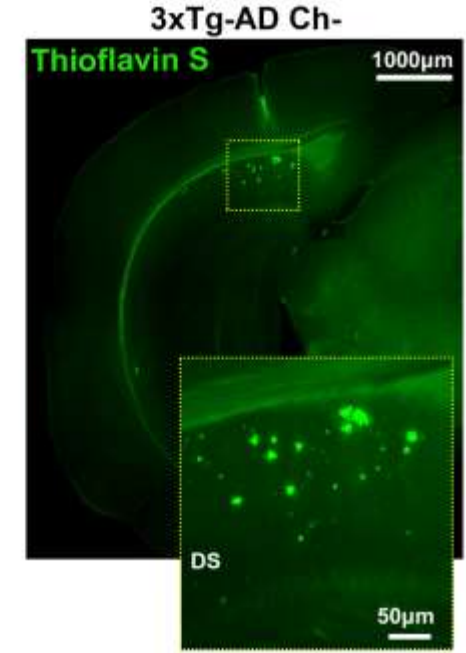
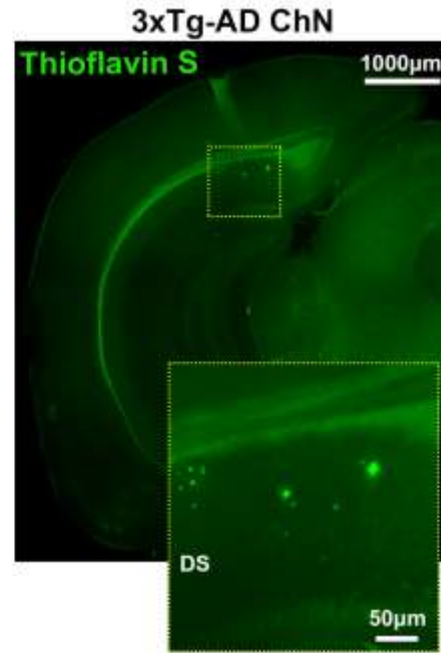
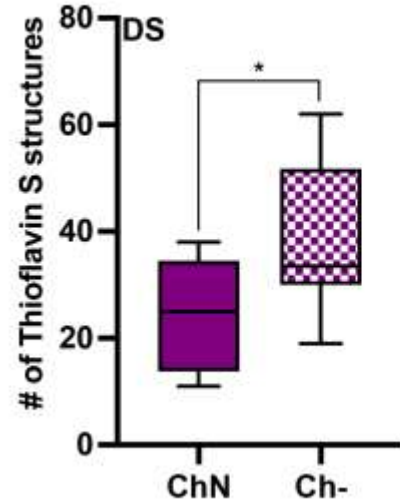
Non-alcoholic fatty liver disease



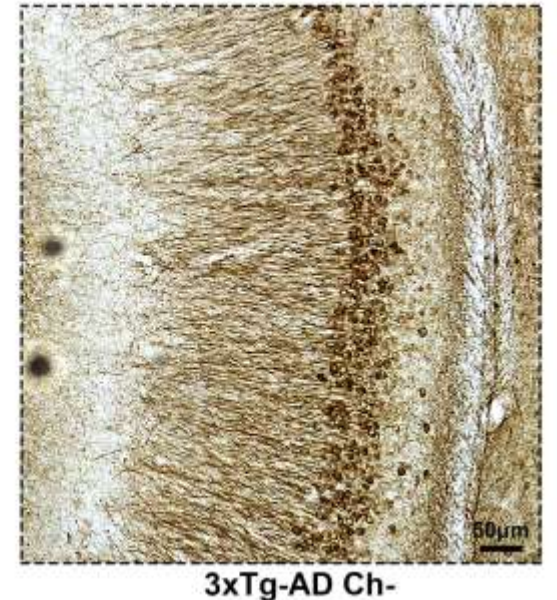
H&E of Liver tissue



Choline deficiency increases Thioflavin S sheet and AT8 + cell number



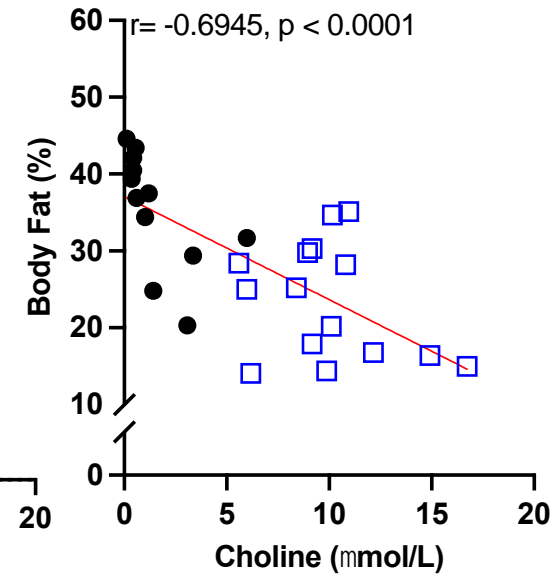
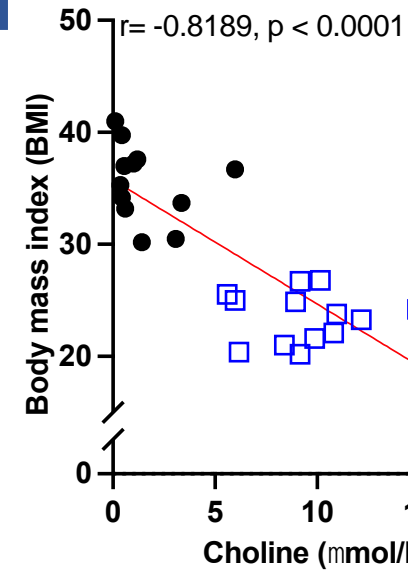
AT8 (Ser202/Thr205)



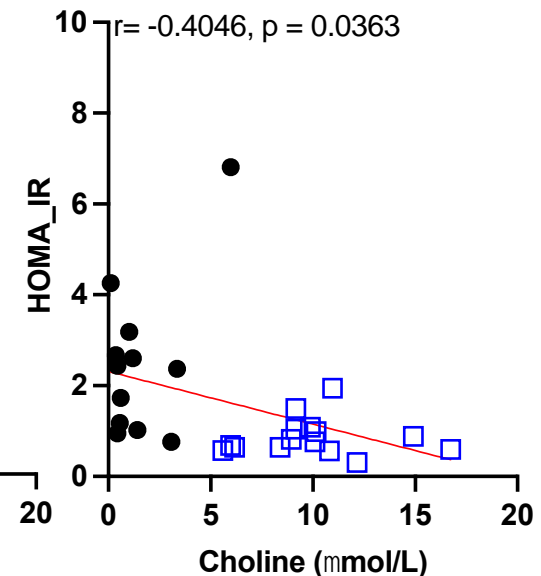
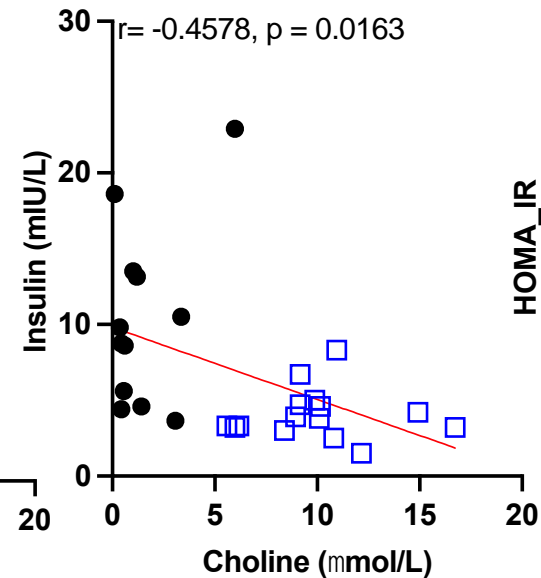
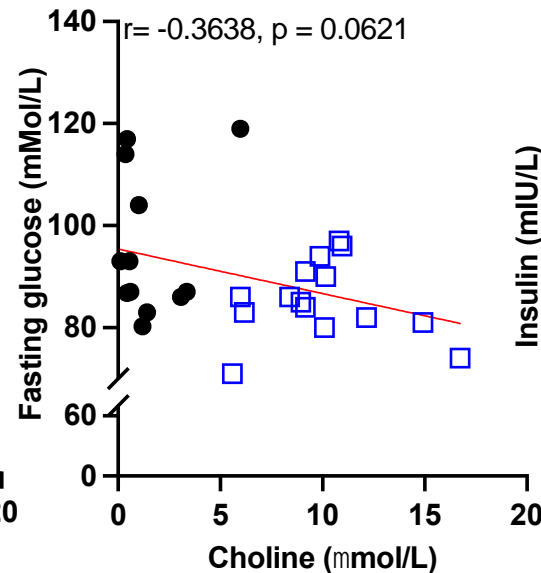
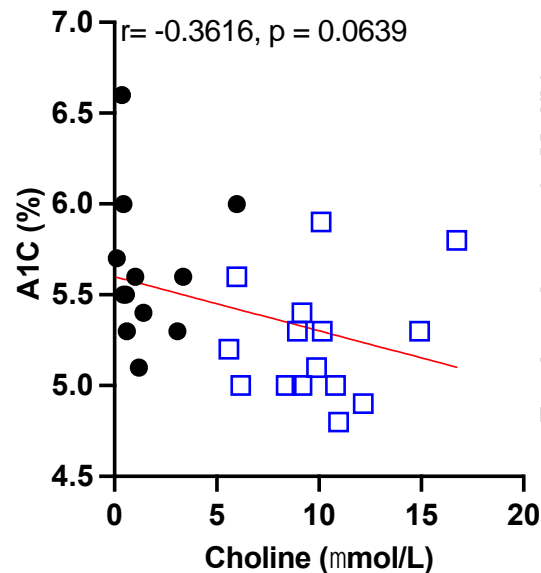
Healthy BMI versus obese participant characteristics

Participant Profiles	Healthy weight (n=15)	Obese (n=13)
Age	M = 34.93; SD = 9.95	M = 33.23; SD = 8.98
BMI	M = 23.54; SD = 2.38	M = 35.49; SD=3.19
A1C	M = 5.24; SD = 0.32	M = 5.62; SD = 0.39
HOMA-IR	M = 0.87; SD = 0.41	M = 2.79; SD = 1.94

Table 2. Characteristics of participants classified as controls with a healthy BMI, and obese BMI with prediabetes. Blood measures taken after 12 hours fasted. *Abbreviations:* Body mass index (BMI), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) where >1.9 indicates early IR.

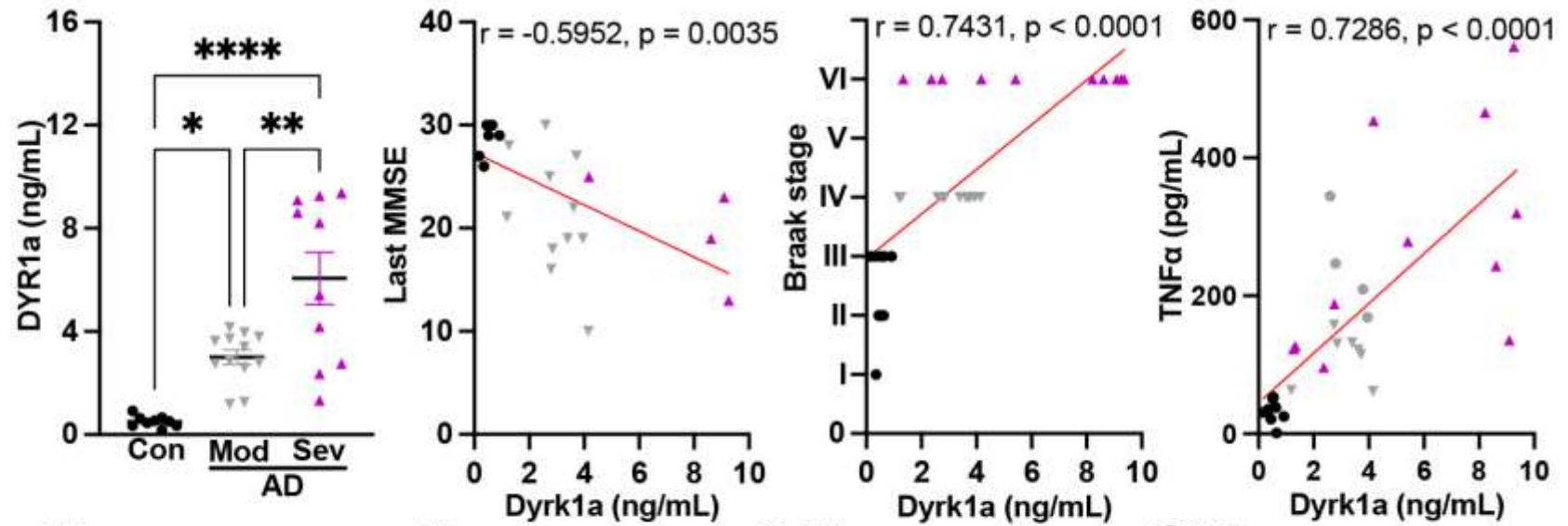


□ Healthy BMI
● Obese BMI

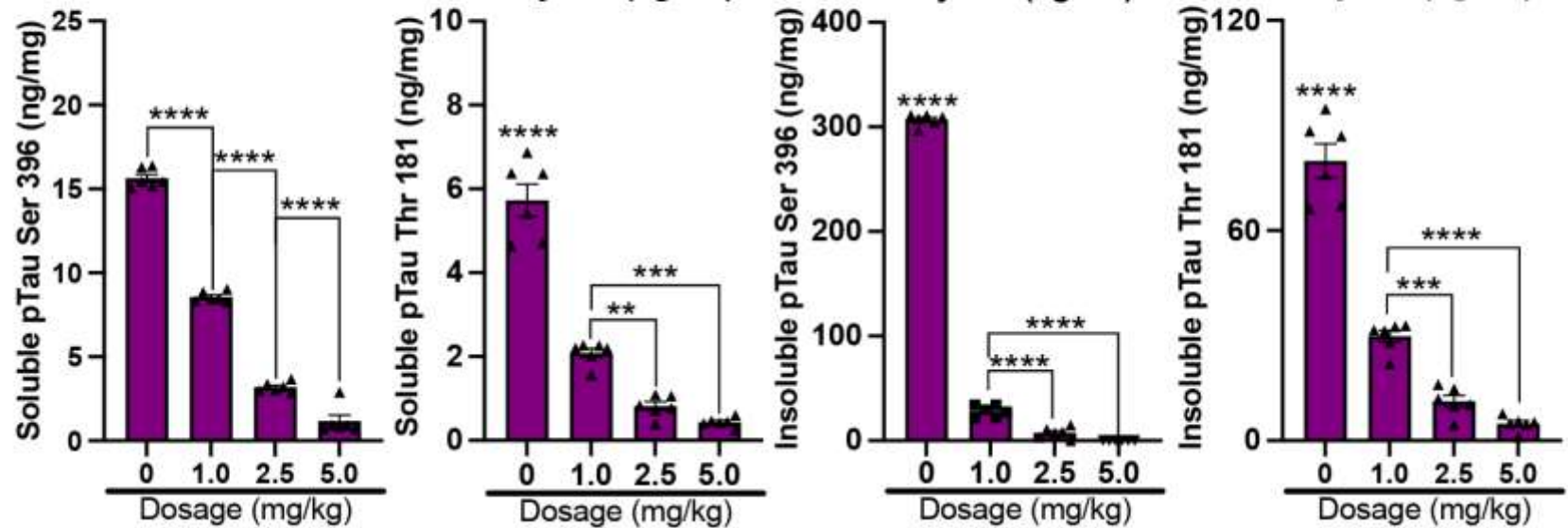


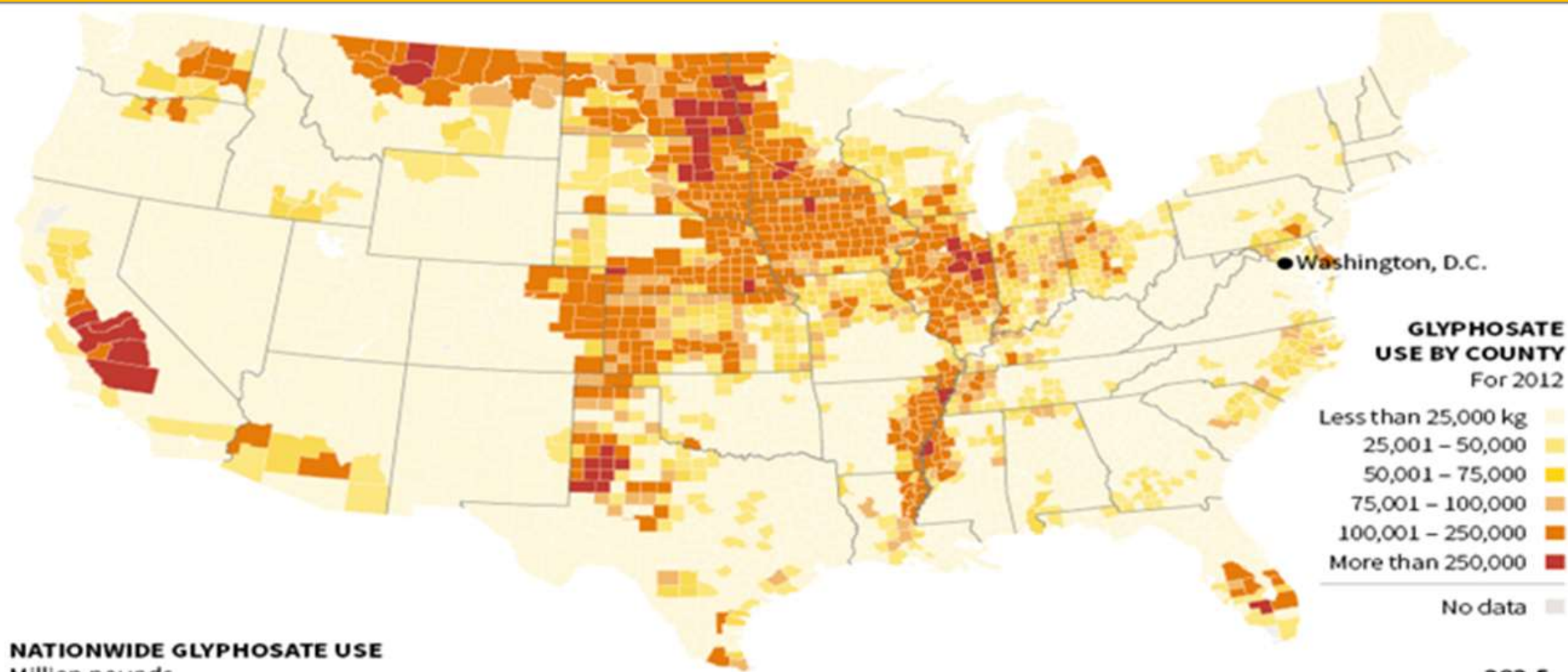
DYRK1a human and DYR533 PS19 supplemental data

Human

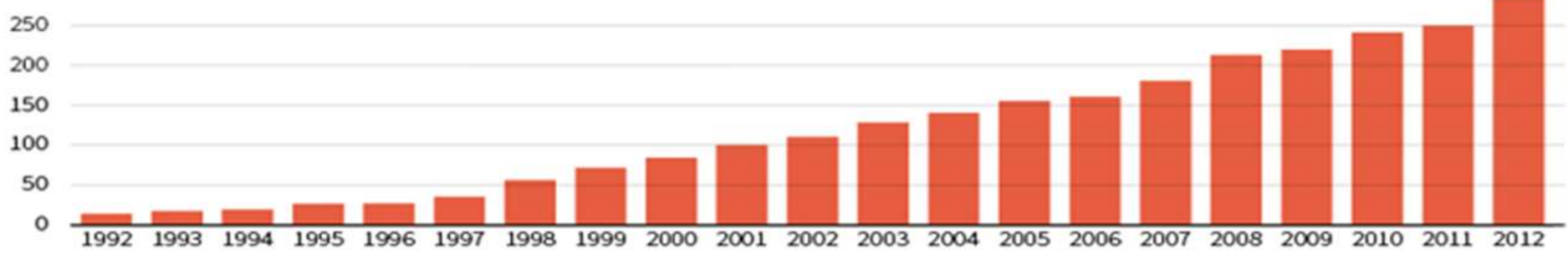


PS19 mouse





NATIONWIDE GLYPHOSATE USE
Million pounds



Source: Baker, N.T. and Stone, W.W., U.S. Geological Survey

C. Chan, 24/03/2015

REUTERS

Figure 1. Glyphosate use in the United States (Baker & Stone, 2015).

Research | [Open access](#) | [Published: 28 July 2022](#)

Glyphosate infiltrates the brain and increases pro-inflammatory cytokine TNF α : implications for neurodegenerative disorders

[Joanna K. Winstone](#), [Khyatiben V. Pathak](#), [Wendy Winslow](#), [Ignazio S. Piras](#), [Jennifer White](#), [Ritin Sharma](#), [Matthew J. Huentelman](#), [Patrick Pirrotte](#) & [Ramon Velazquez](#) ✉

[Journal of Neuroinflammation](#) **19**, Article number: 193 (2022) | [Cite this article](#)

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THE NEW LEDE

NEWS OPI



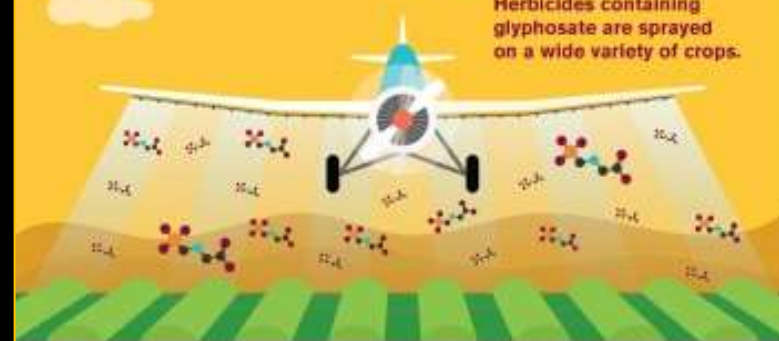
AUGUST
19
2022

New study says glyphosate may be linked to neurodegenerative diseases



Served with a side
of glyphosate.

Herbicides containing
glyphosate are sprayed
on a wide variety of crops.



Glyphosate ends up in common food
items such as tofu and cereal.



Glyphosate is able to cross
the blood-brain barrier.

