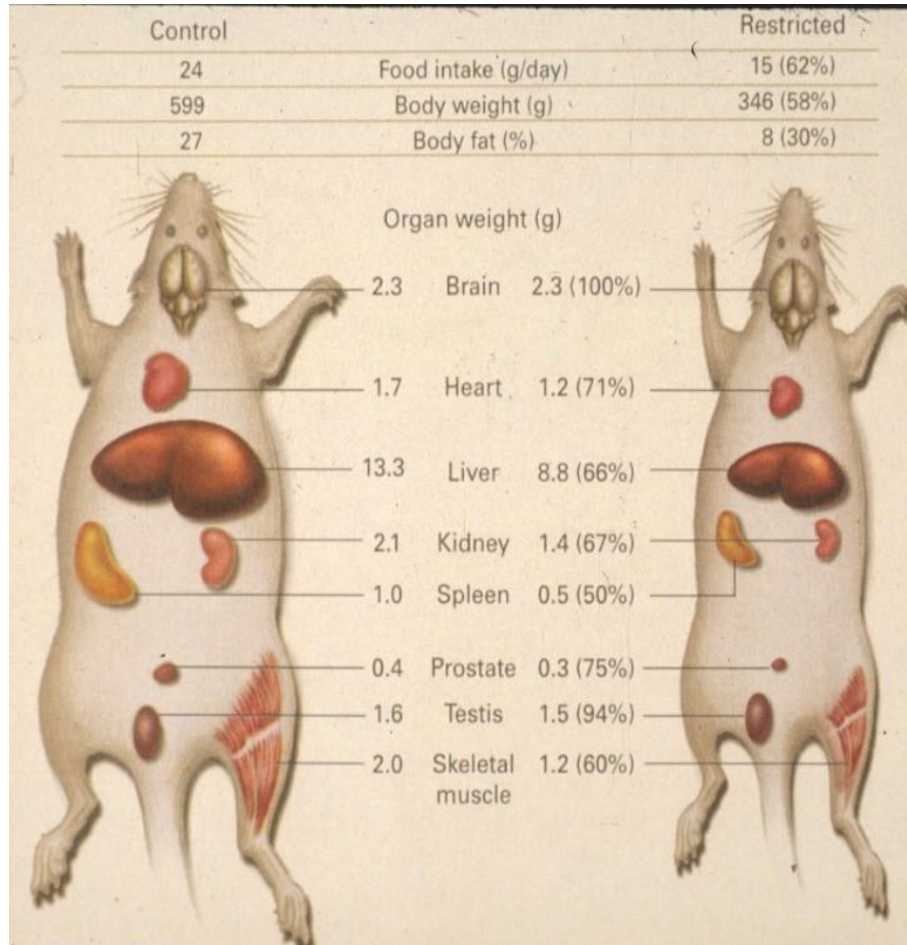
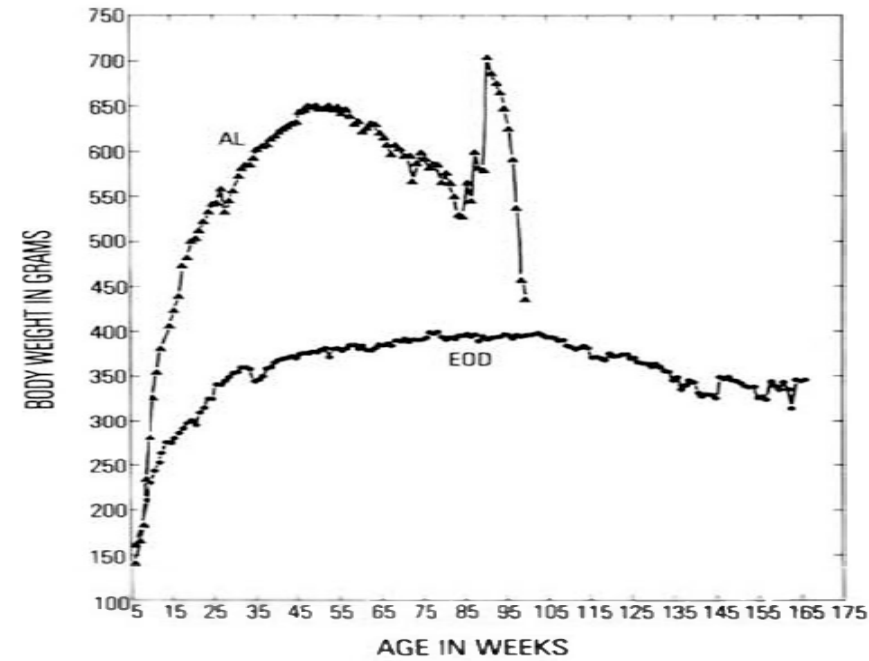
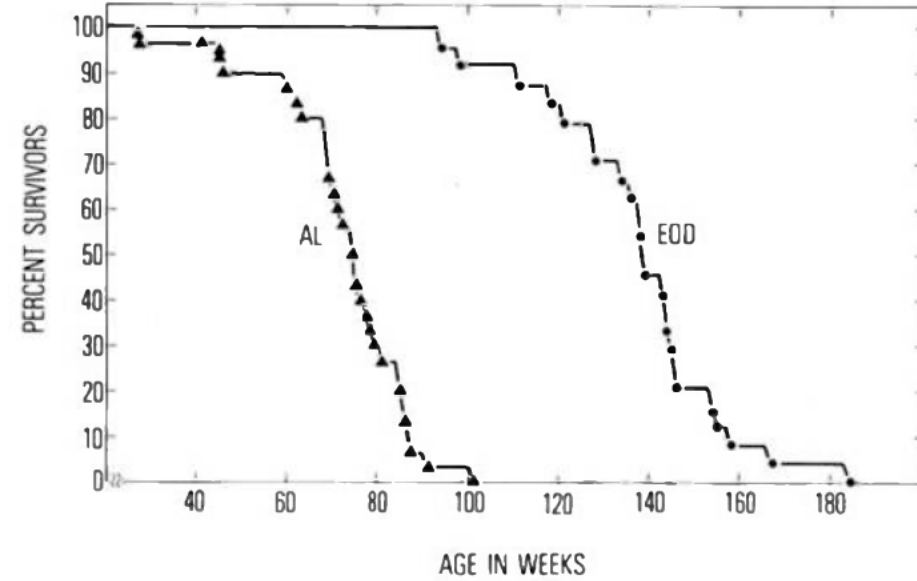


Long-term severe daily food restriction (40% CR) in rats reduces the size of all organs except the brain in males and females and testes in males



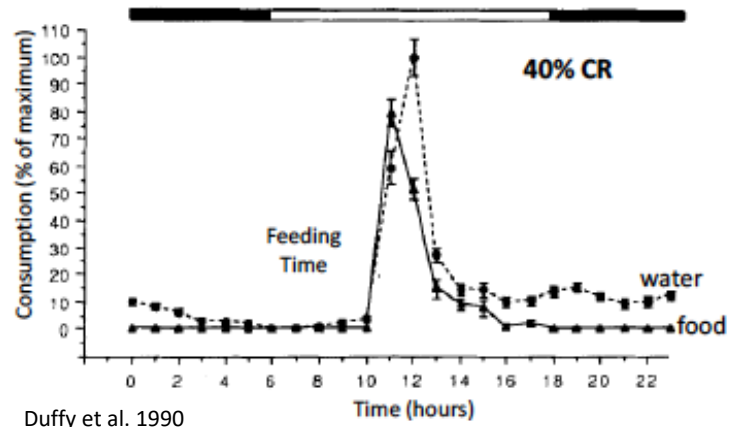
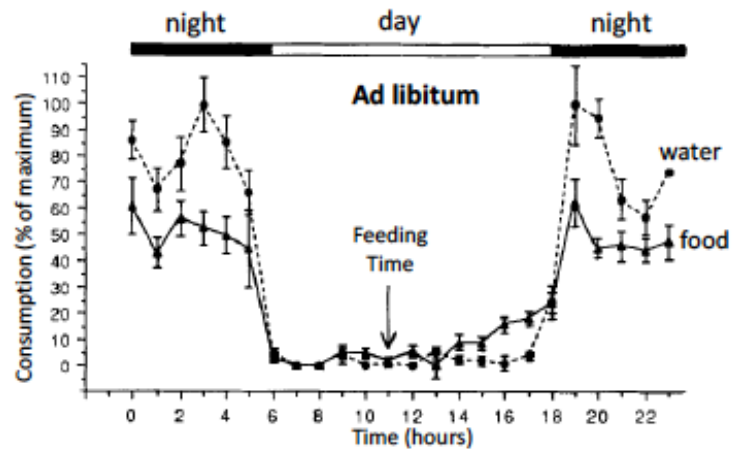
Weindruch R, Sohal R. 1997; *N Engl J Med.* 337:986-994.

Alternate day fasting extends lifespan in male rats

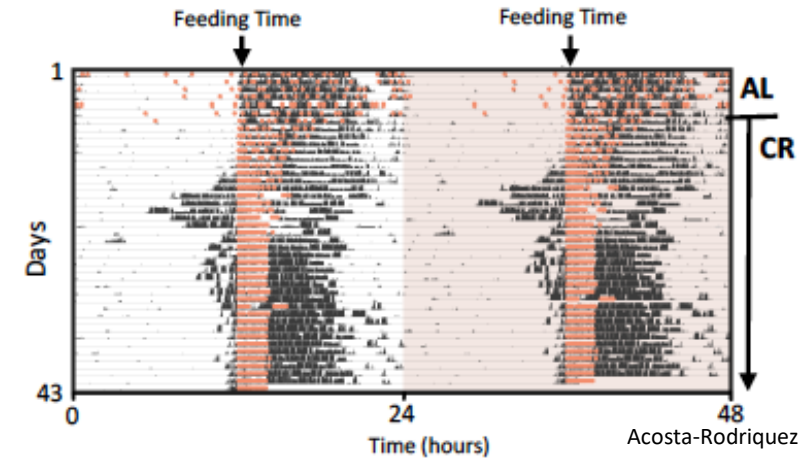
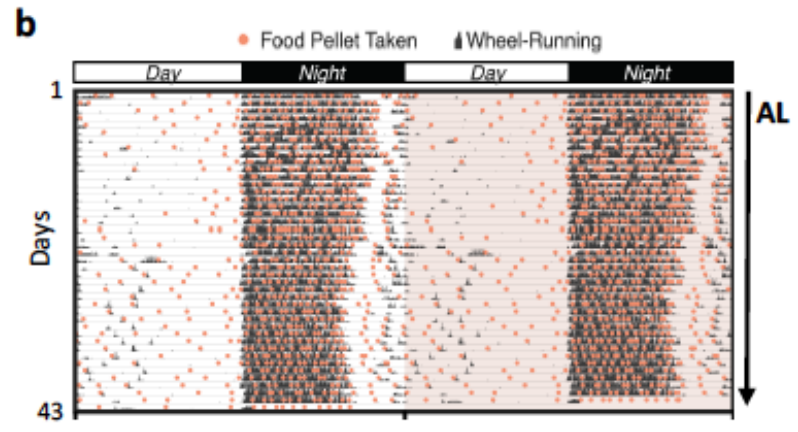


Goodrick CL, Ingram DK et al. 1982; *Gerontology* 28:233-241.

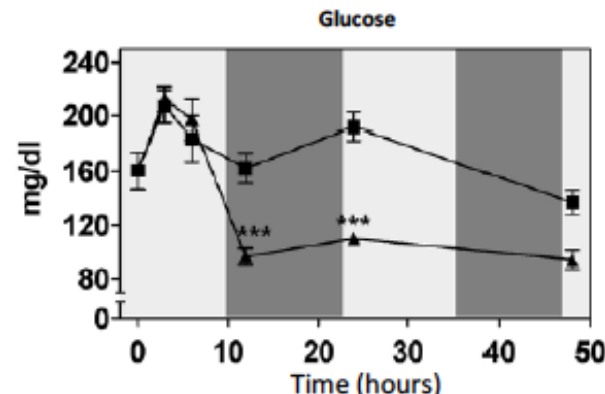
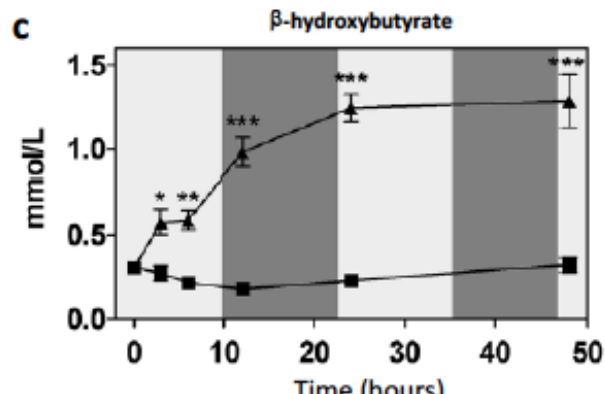
The most commonly used 'caloric restriction' protocols in rodents are also an intermittent fasting (IF) eating pattern with daily ketogenesis!



Duffy et al. 1990



Acosta-Rodriguez et al. 2017



Schupp et al. 2013

## Examples of studies demonstrating a dissociation from caloric intake of health benefits and disease-modifying effects of IF

Anson RM et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. *Proc Natl Acad Sci U S A.* 2003; **100**, 6216-20.

Harvie MN et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes.* 2011; **35**, 714-27.

Hatori M et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab.* 2012; **15**, 848-60.

Pak HH et al. Fasting drives the metabolic, molecular and geroprotective effects of a calorie-restricted diet in mice. *Nat Metab.* **3**, 1327-1341 (2021).

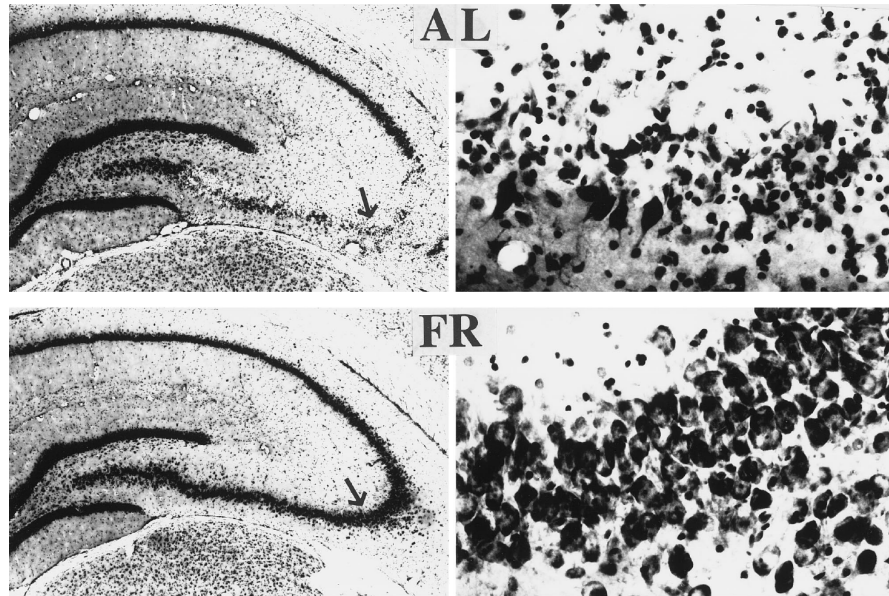
Jamshed H et al. Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity: A Randomized Clinical Trial. *JAMA Intern Med.* **182**, 953-962 (2022).

Manoogian ENC et al. Feasibility of time-restricted eating and impacts on cardiometabolic health in 24-h shift workers: The Healthy Heroes randomized control trial. *Cell Metab.* **34**, 1442-1456.e7 (2022).

Gallage S et al. A 5:2 intermittent fasting regimen ameliorates NASH and fibrosis and blunts HCC development via hepatic PPARalpha and PCK1. *Cell Metab.* S1550-4131(24)00135-139 (2024).

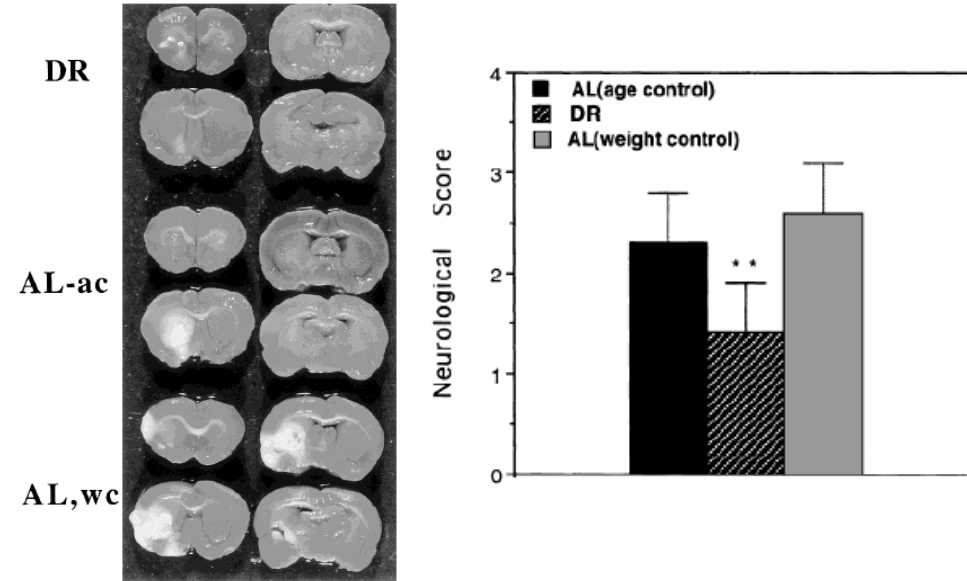
# Intermittent Fasting and/or CR) Protects Neurons Against Dysfunction and Degeneration in Animal Models of Epilepsy, Stroke, and Parkinson's and Huntington's Diseases

## Epilepsy (rat kainate model)



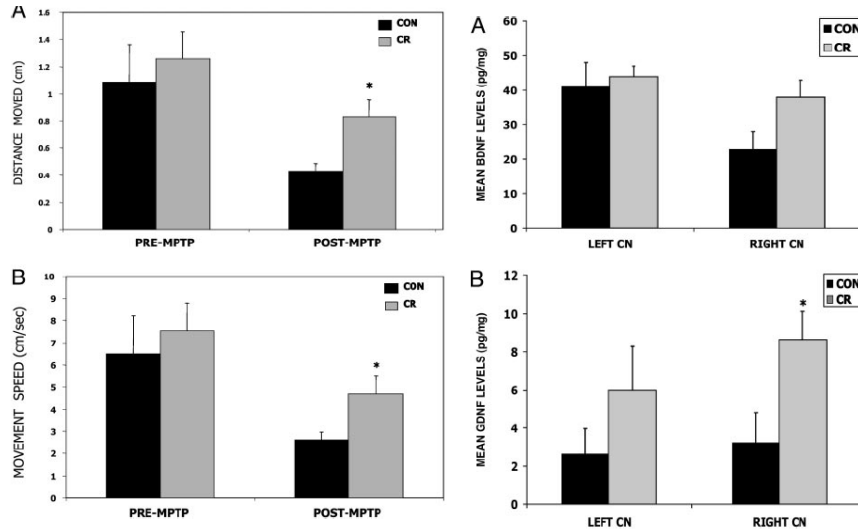
Bruce-Keller AJ et al. *Ann Neurol.* 1999; 45:8-15.

## Stroke (rat MCAO model)



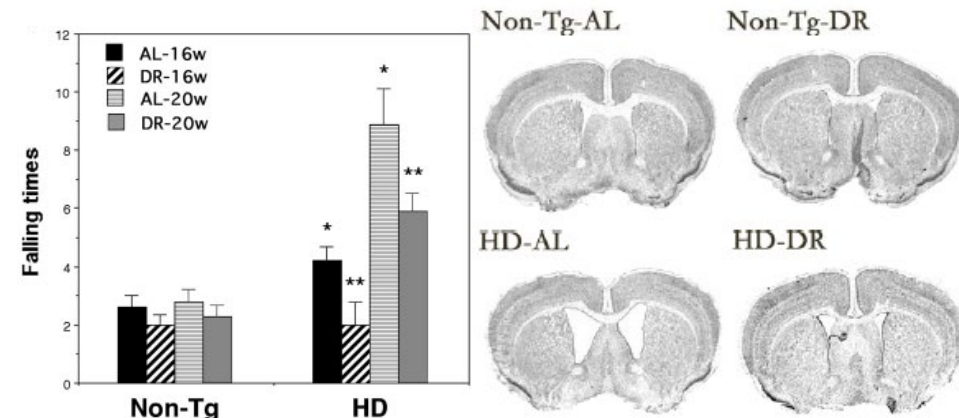
Yu ZF, Mattson MP. *J Neurosci Res.* 1999; 57:830-9.

## Parkinson's disease (rhesus monkeys)



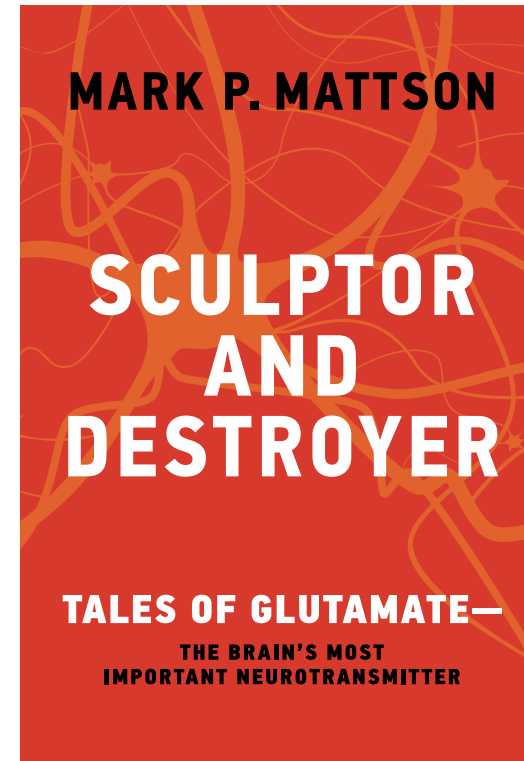
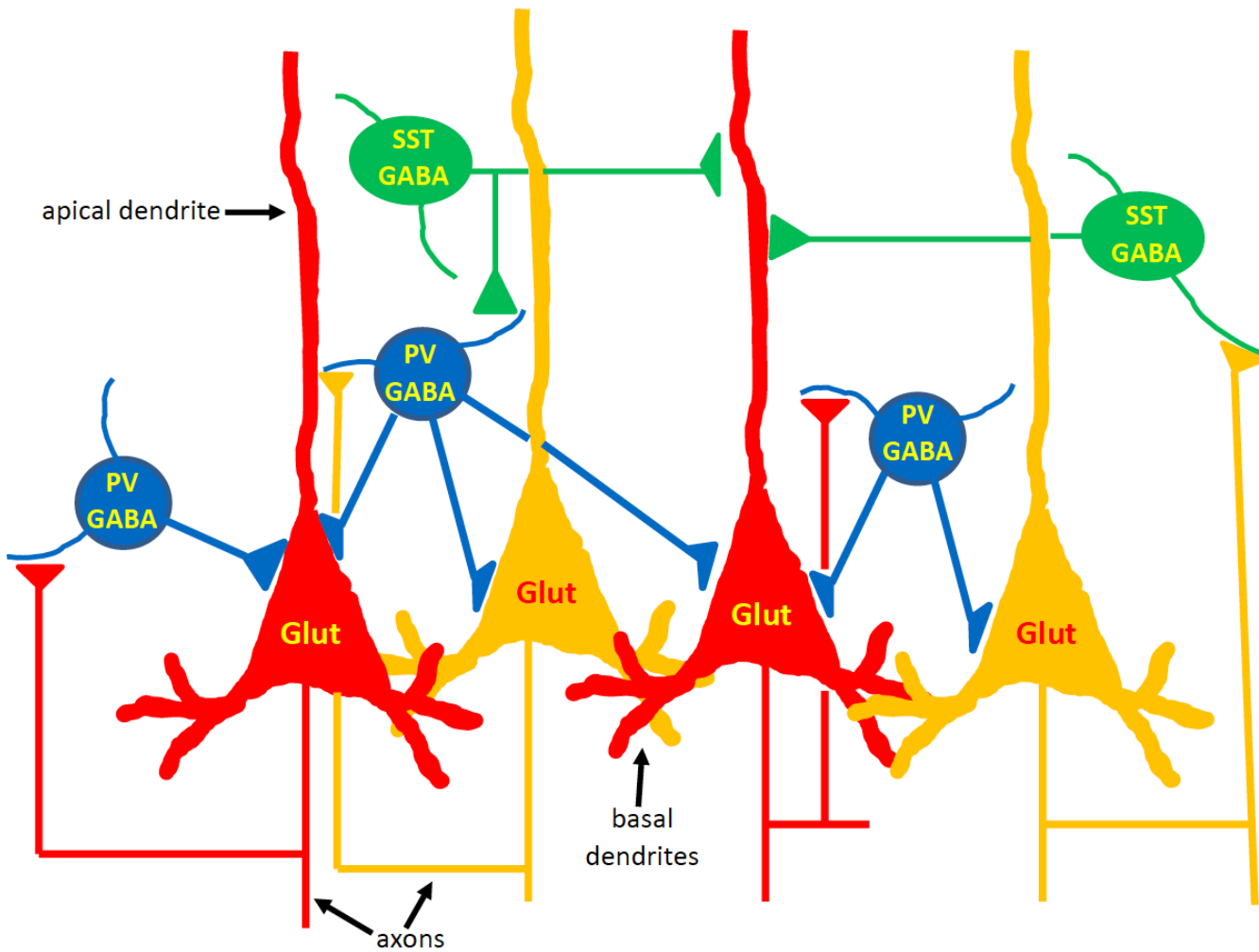
Maswood N et al. *PNAS* 2004; 101:18171-76.

## Huntington's disease (mutant htt transgenic mice)



Duan W et al. *PNAS* 2003; 100:2911-16.

Neural circuits throughout the brain are comprised of excitatory glutamatergic neurons and inhibitory GABAergic neurons.  
 (upwards of 90% of the neurons in the brain are glutamatergic and ~9% are GABAergic. The other ~1% deploy serotonin, dopamine, acetylcholine or norepinephrine)



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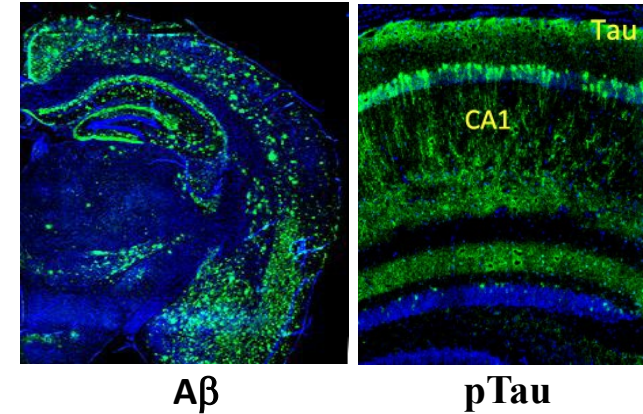
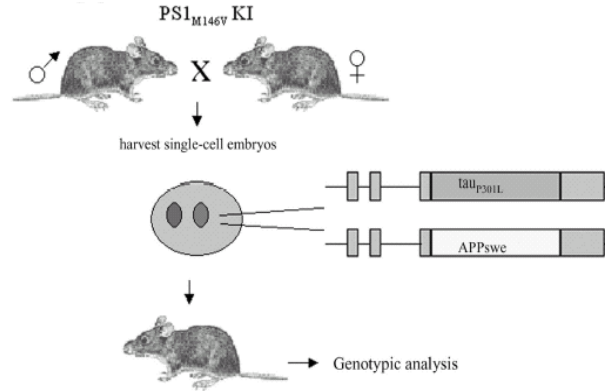
# CR (30%)/TRE, ADF, and a Dietary Ketone Ester Preserve Learning and Memory in a Transgenic Mouse Model of Alzheimer's Disease

Neuron, Vol. 39, 1-20, July 31, 2003, Copyright ©2003 by Cell Press

## Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular A $\beta$ and Synaptic Dysfunction

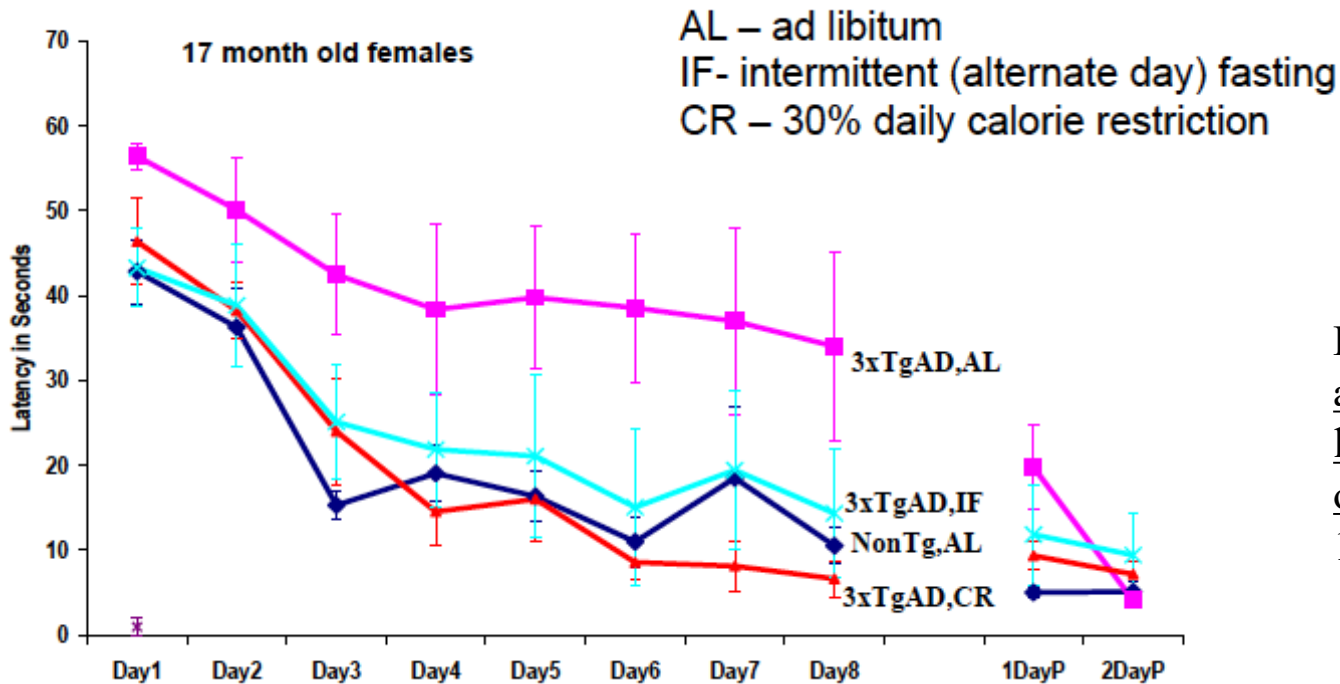
Salvatore Oddo,<sup>1</sup> Antonella Caccamo,<sup>1,5</sup> Jason D. Shepherd,<sup>1,5</sup> M. Paul Murphy,<sup>3</sup> Todd E. Golde,<sup>3</sup> Rakez Kaye,<sup>2</sup> Raju Metherate,<sup>1</sup> Mark P. Mattson,<sup>4</sup> Yama Akbari,<sup>1</sup> and Frank M. LaFerla<sup>1,4</sup>

overt neuronal degeneration (DeKosky and Scheff, 1981; Scheff et al., 1991). Notably, the memory decline observed in AD patients correlates the synaptic pathology more than either plaques and thus, synaptic dysfunction is likely to



A $\beta$

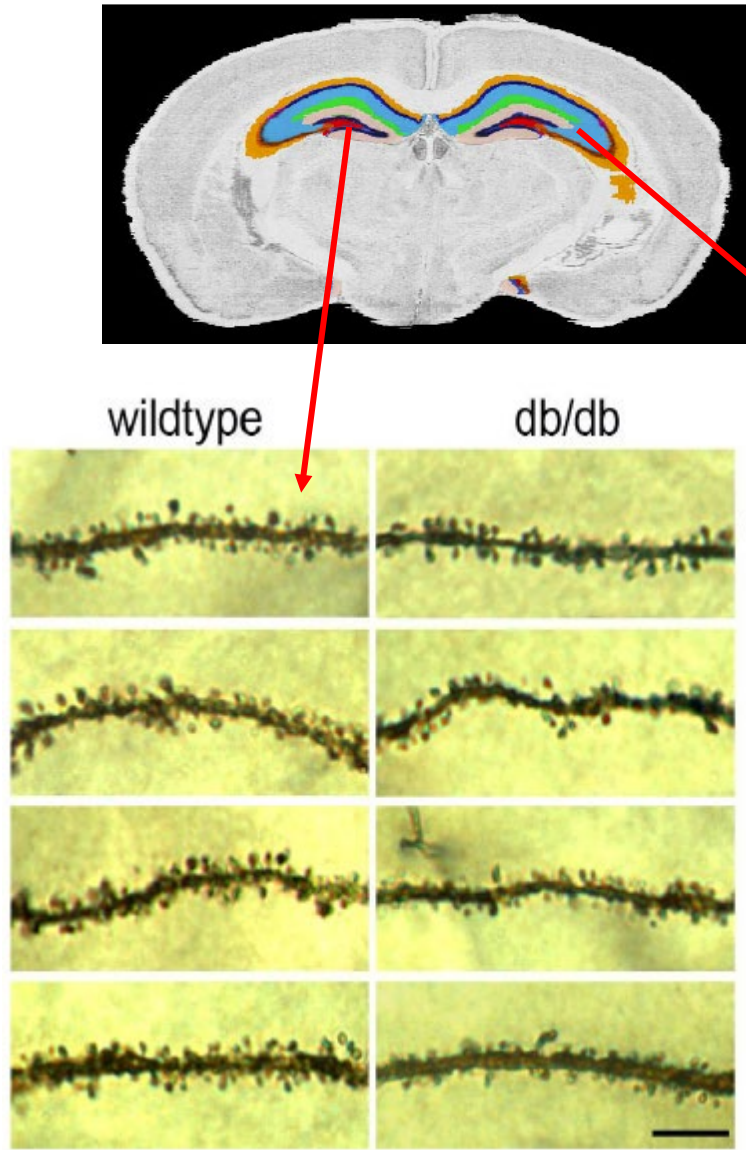
pTau



Halagappa VK et al (2007) *Neurobiol Dis.* 26:212-20.

Kashiwaya Y et al. A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. *Neurobiol Aging.* 2013; **34**, 1530-9.

Daily time-restricted eating (with 40%CR) and running increase synapse numbers and BDNF levels in the hippocampus, and partially restore synapse numbers and BDNF levels in leptin receptor mutant diabetic mice



wildtype

db/db

CR+RUN

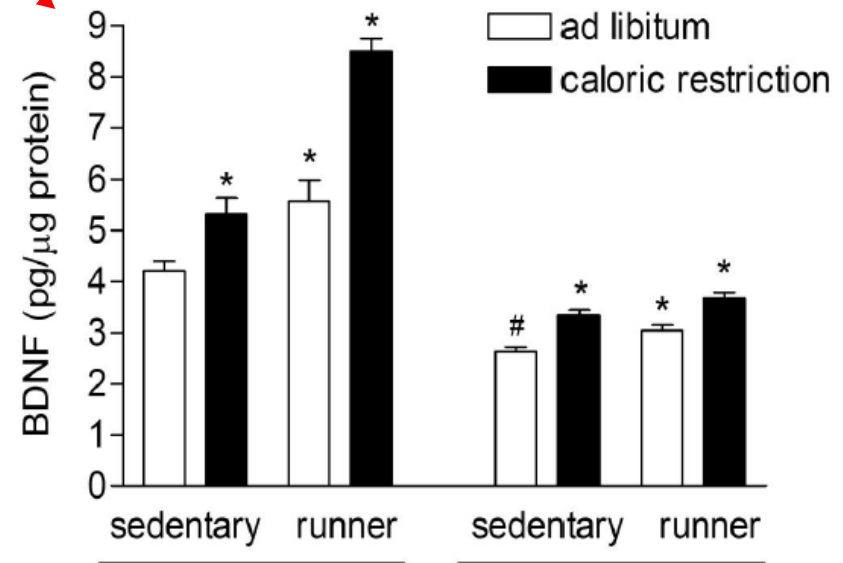
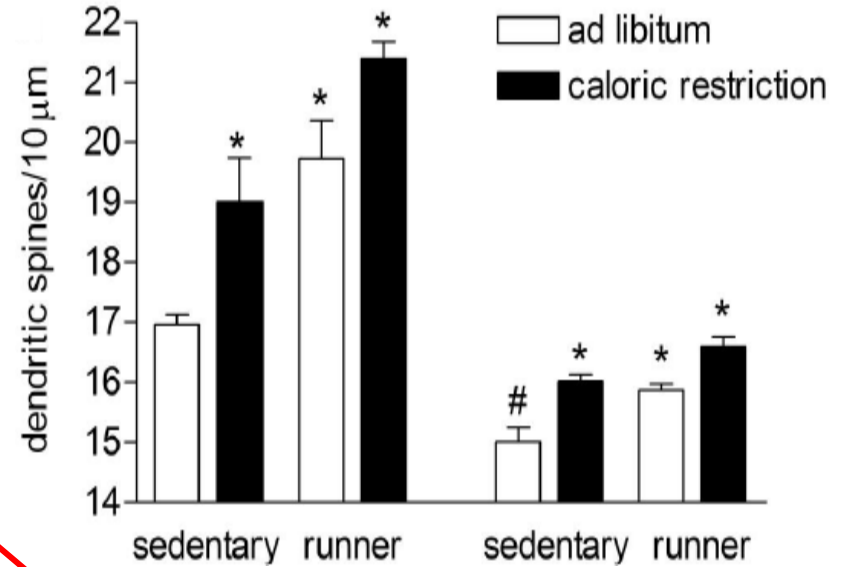
CR+SED

AL+RUN

AL+SED

Dendritic spines (postsynaptic structures) on hippocampal neurons

3 month intervention



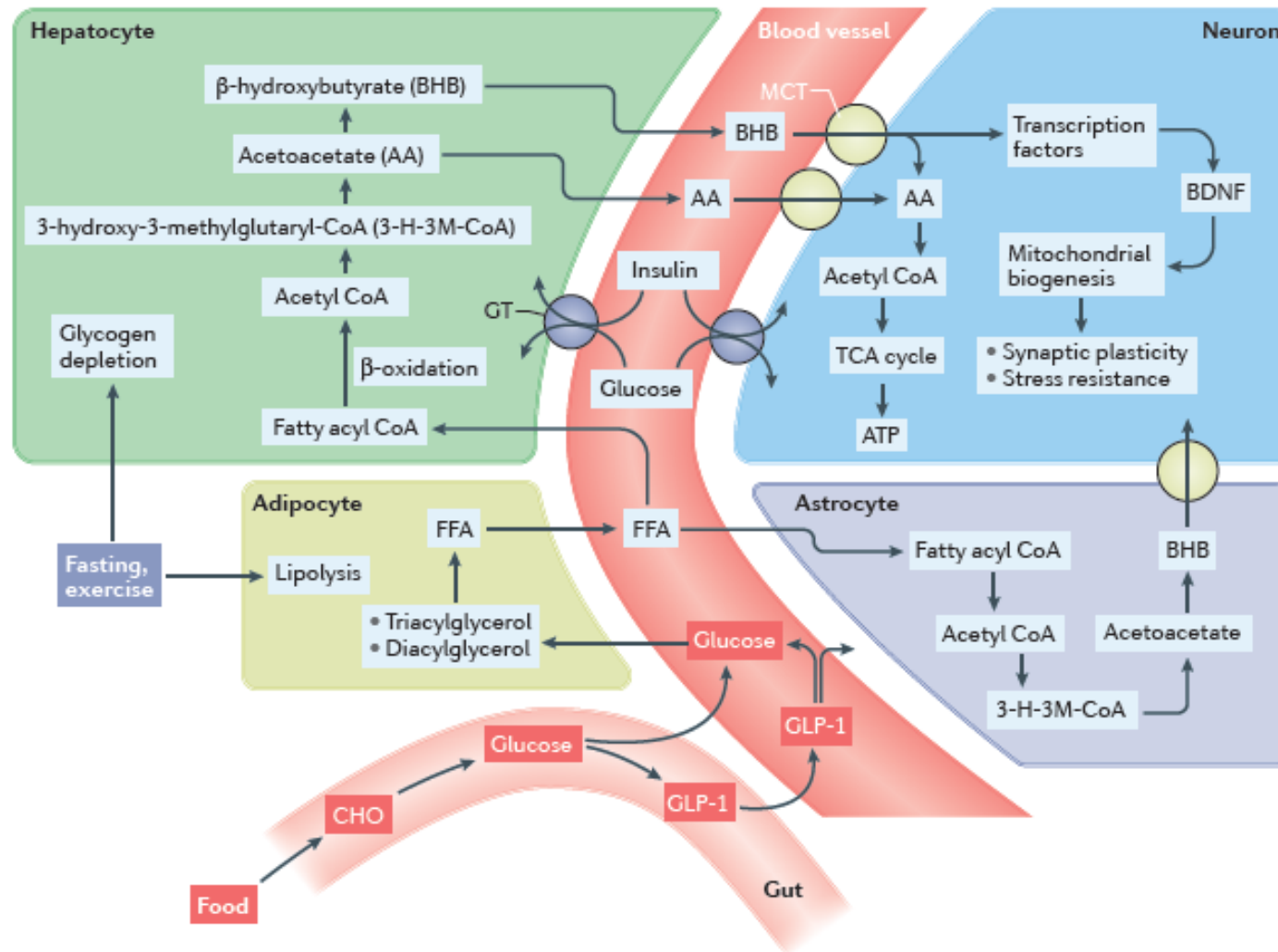
wildtype

db/db

Stranahan et al. (2008) *Nature Neurosci.* 11: 309-317.

Stranahan et al. (2009) *Hippocampus* 19: 951-961.

## $\beta$ -hydroxybutyrate enhances neuroplasticity and resilience by inducing the expression of BDNF



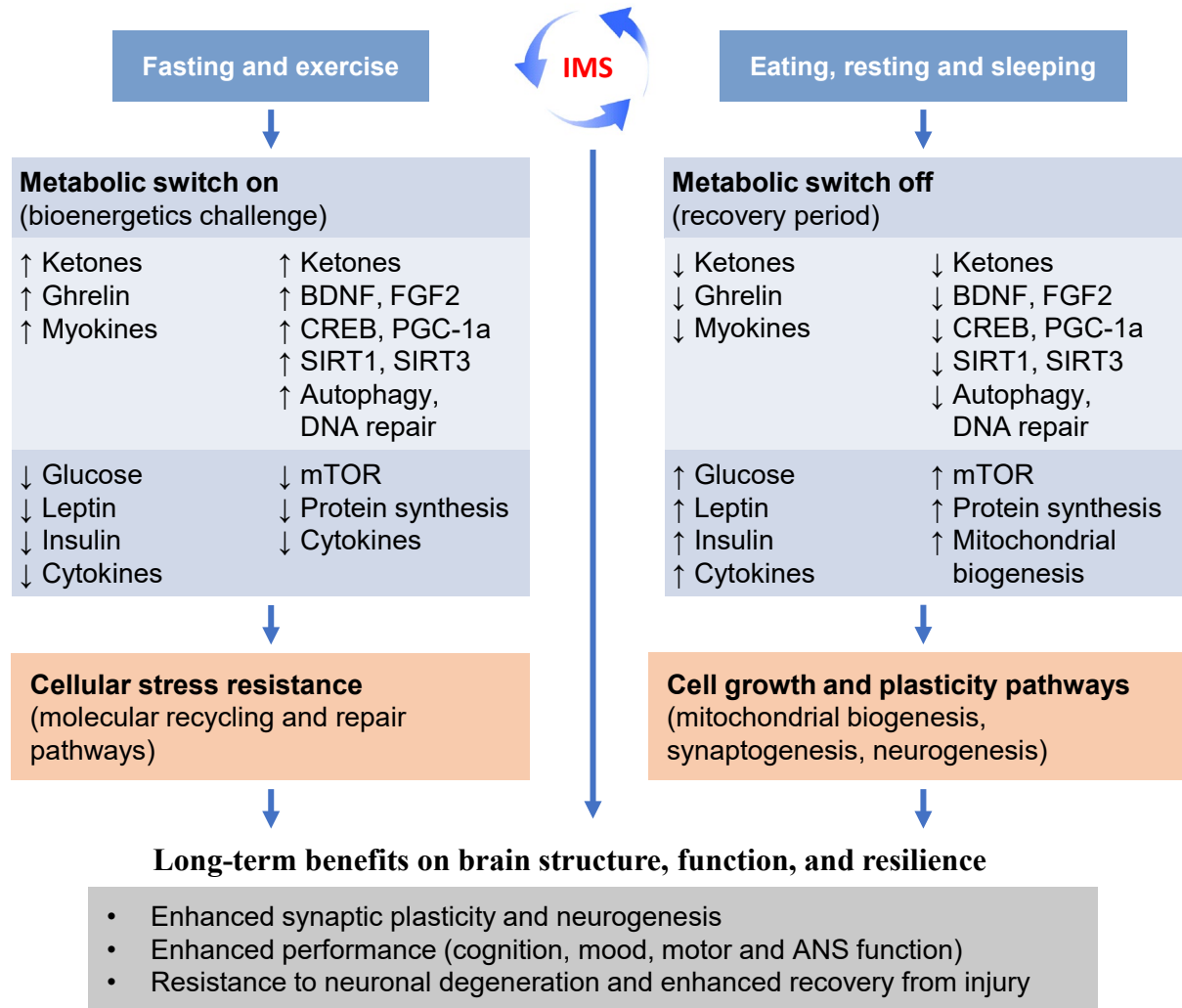
2018 Feb;19(2):63-80.  
Nature Reviews | **Neuroscience**

Marosi K et al. 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J Neurochem.* 2016 Dec;139(5):769-781.

Sleiman SF et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. *Elife.* 2016 Jun 2;5:e15092.

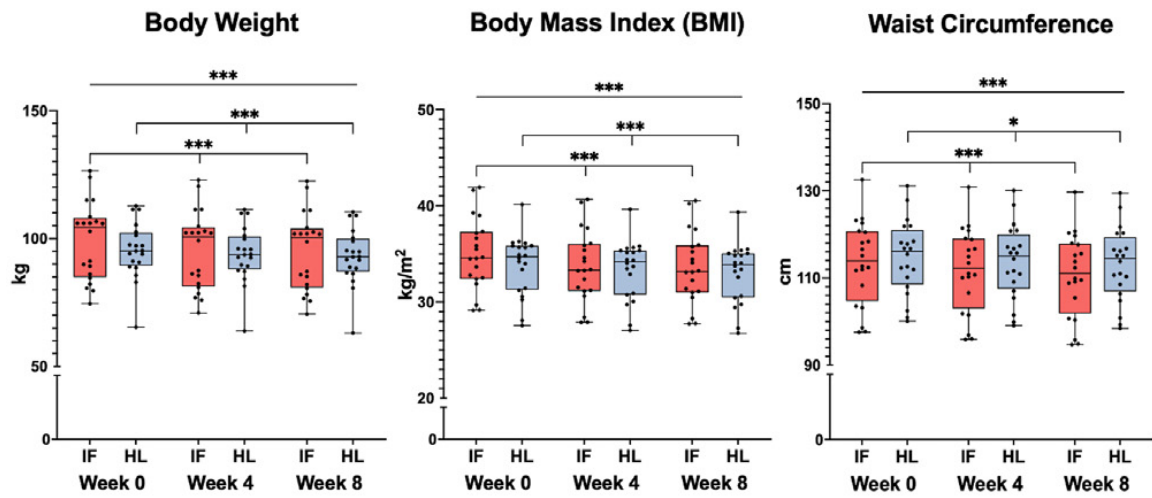


# Enhancing Neuroplasticity, Counteracting Brain Aging and Bolstering Disease Resistance via Challenge – Recovery Cycles

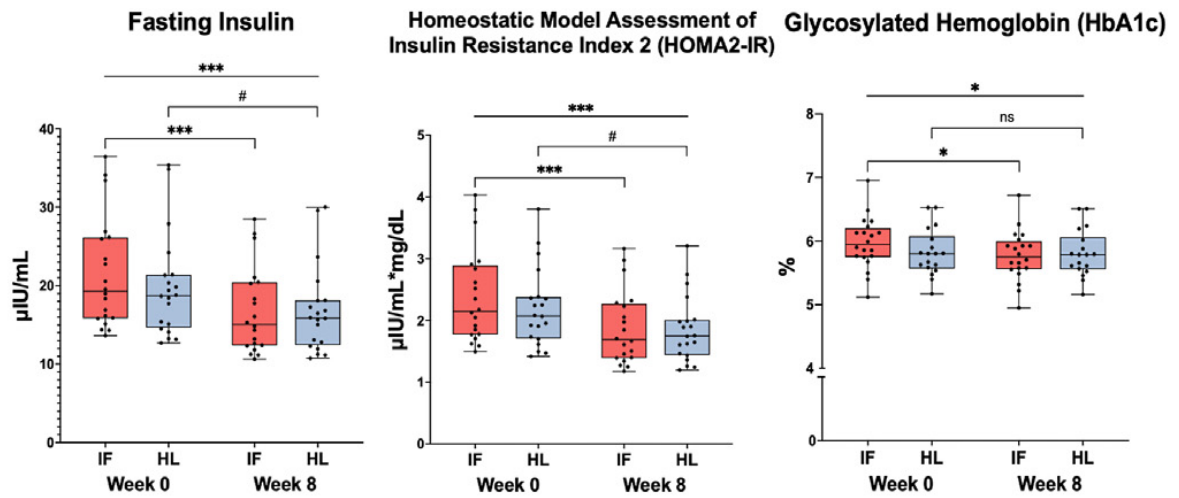


# Brain responses to intermittent fasting and the USDA healthy living diet in older adults with obesity and insulin resistance

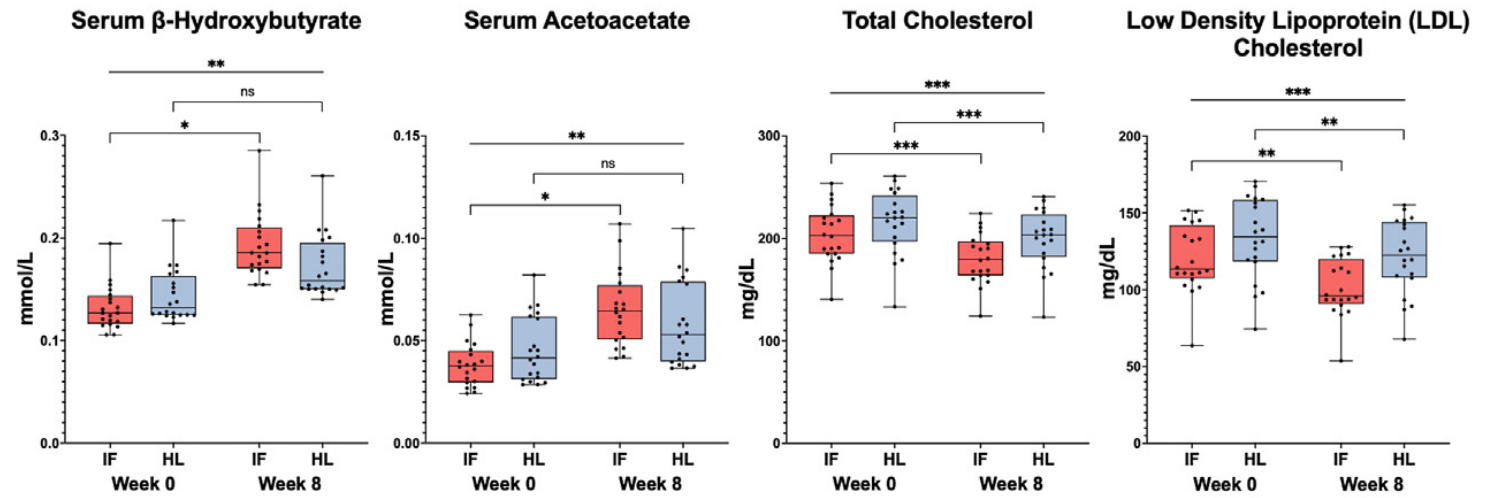
## Anthropometrics



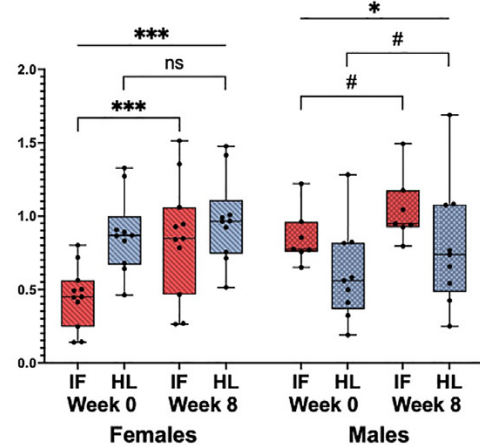
## Systemic Insulin Resistance and Glycemia



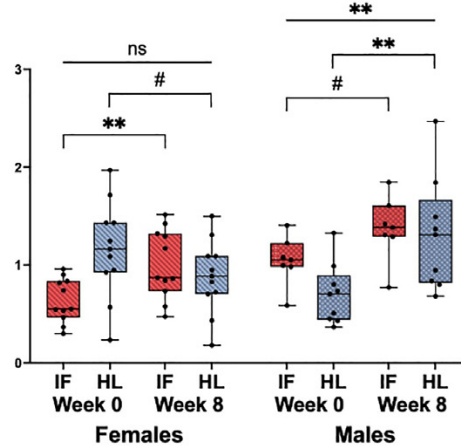
## Blood Ketones and Lipids



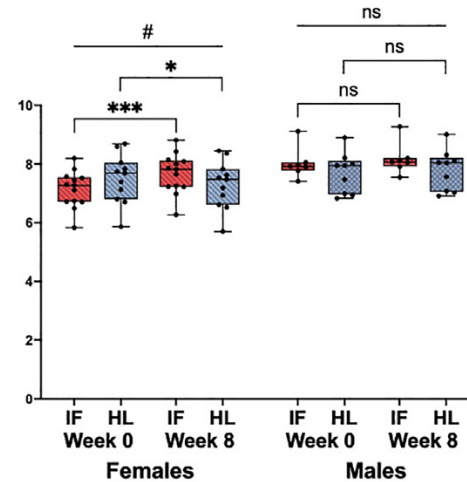
### Executive Function; Composite Score



### Fluency Factor

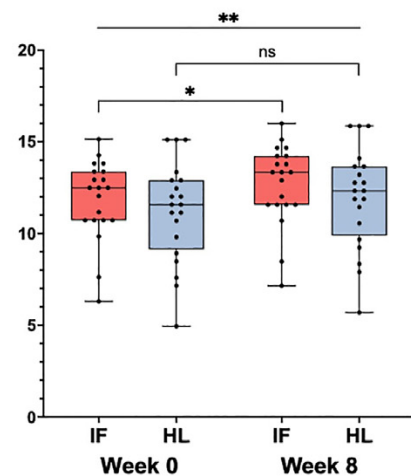


### Dimensional Set Shifting

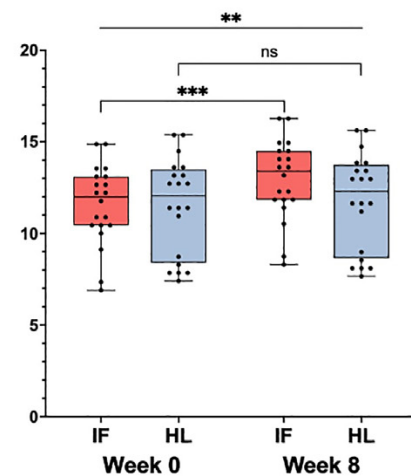


## Memory

### California Verbal Learning Test; Short Delay Cued Recall

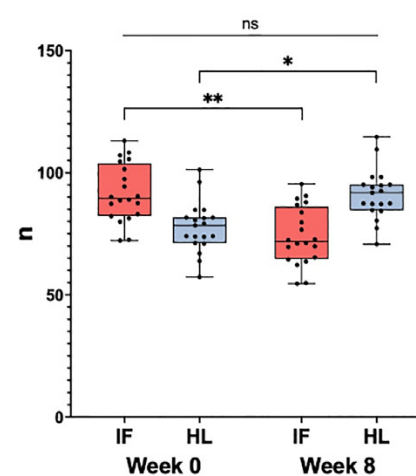


### California Verbal Learning Test; Long Delay Cued Recall

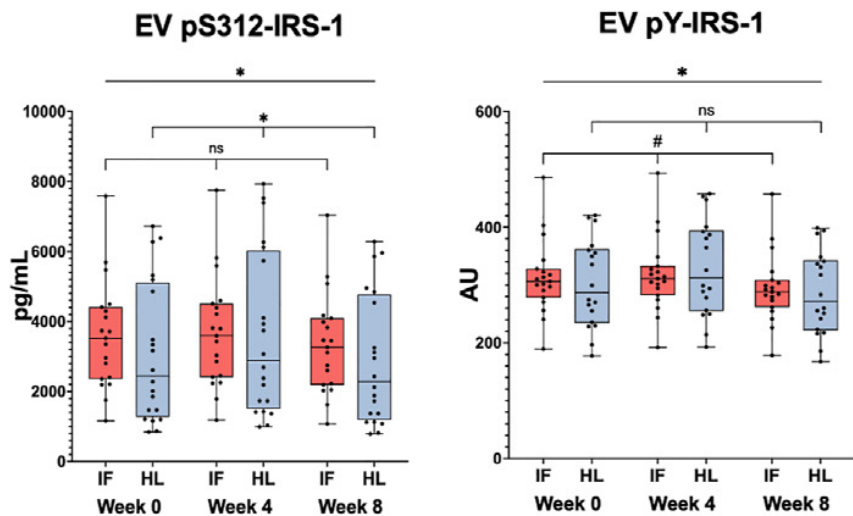


## Actigraphy

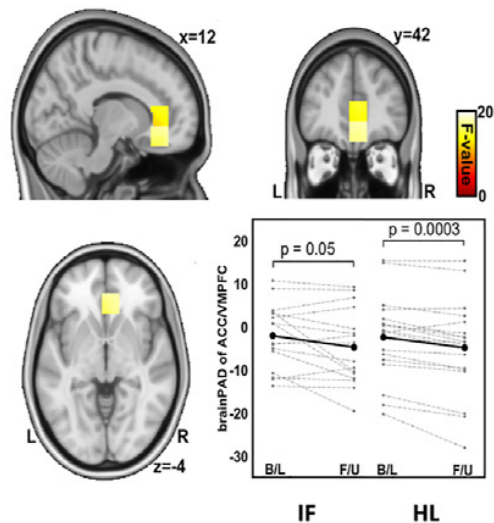
### Total Sedentary Bouts



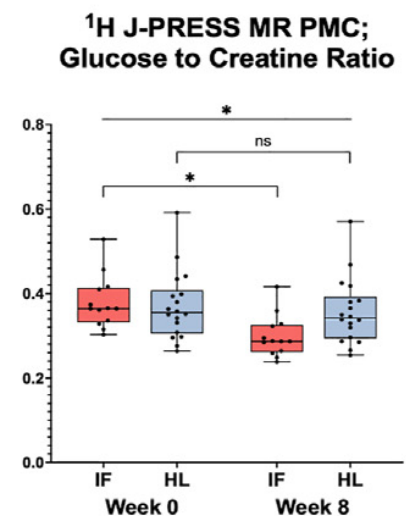
### Brain insulin resistance



### Brain AGE



### Brain MRS glucose



### CSF AD/ADRD Biomarkers

D

