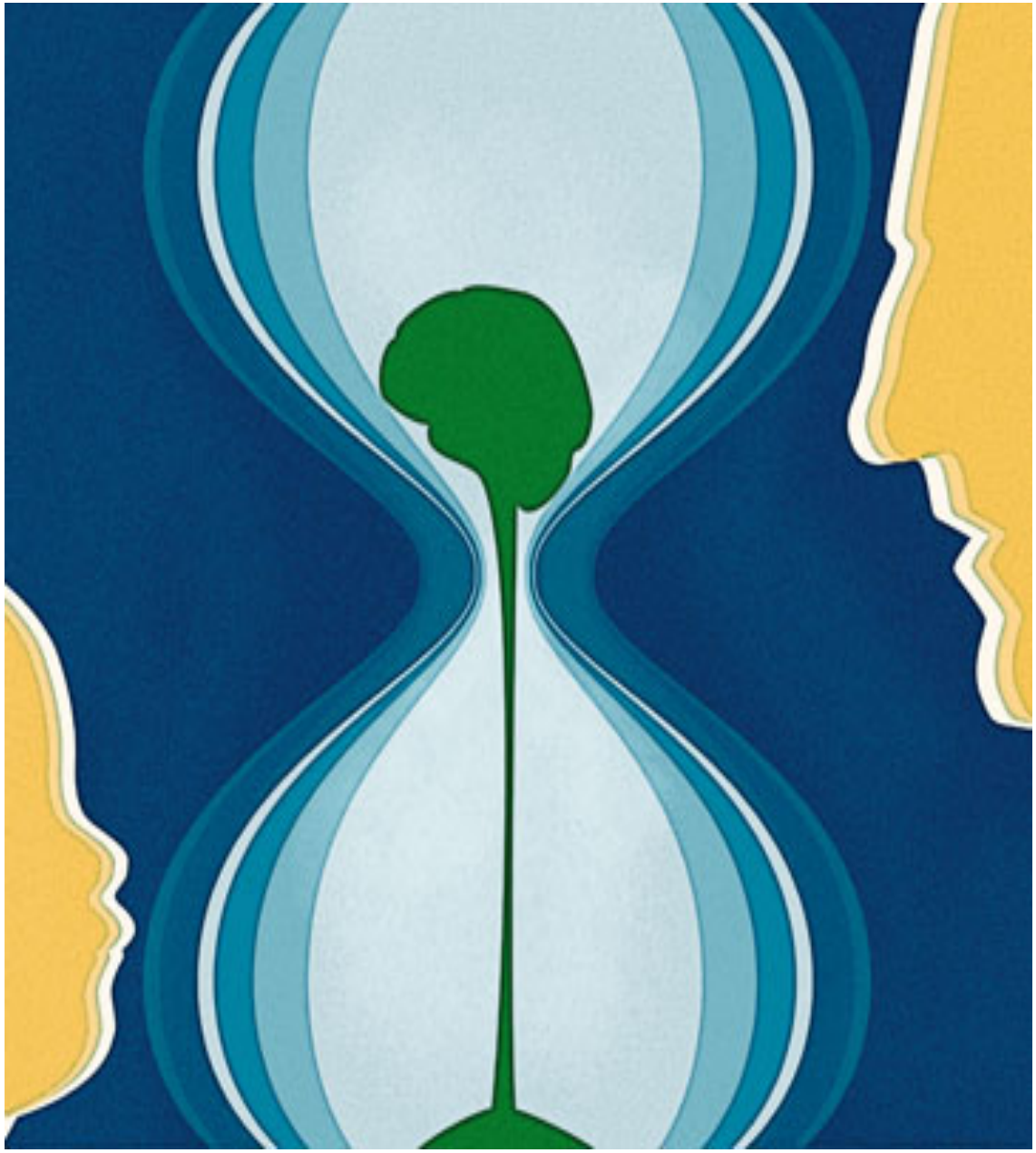
NIA Alzheimer's Disease Education and Referral (ADEAR) Center

1-800-438-4380 https://www.nia.nih.gov/alzheimers

- Alzheimer's disease information and referral center serving patients, caregivers, health care providers
- Information specialists available by toll-free phone



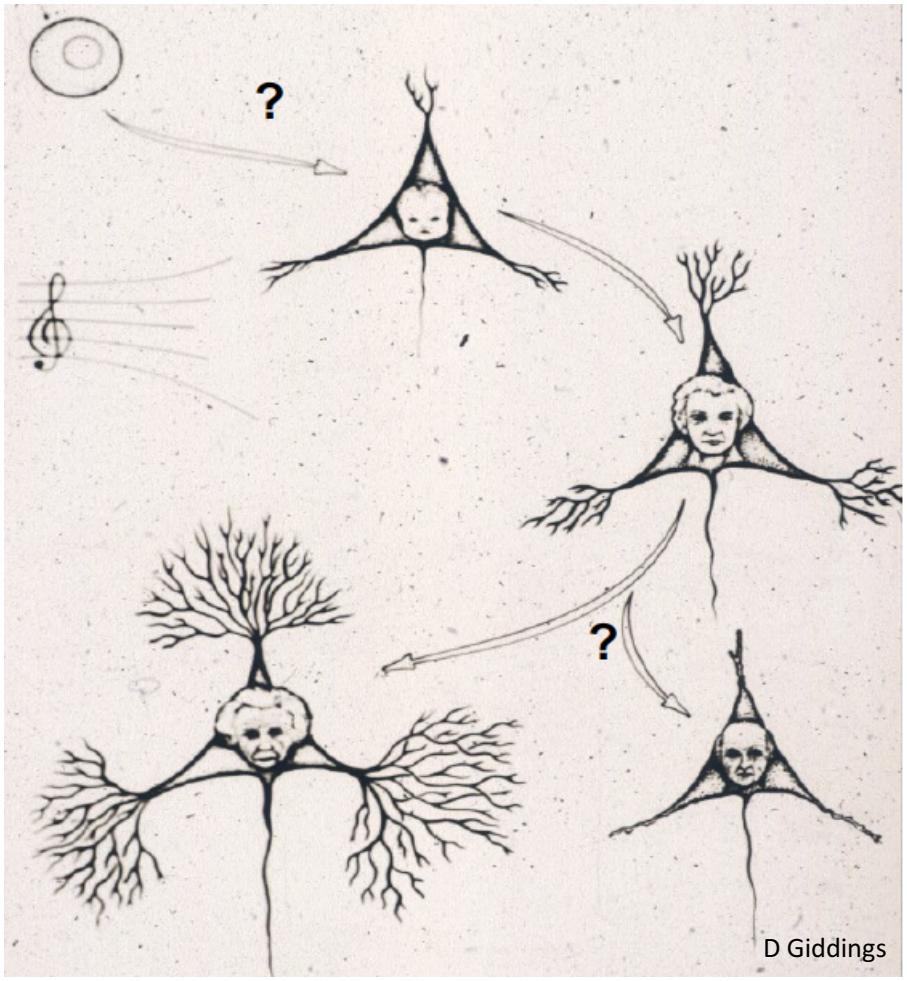
'The sands of time' by Kirsten Lee, inspired by the perspective on healthy brain aging in *Nature Reviews Neuroscience* (Stranahan and Mattson. 2012; 13:209-216).

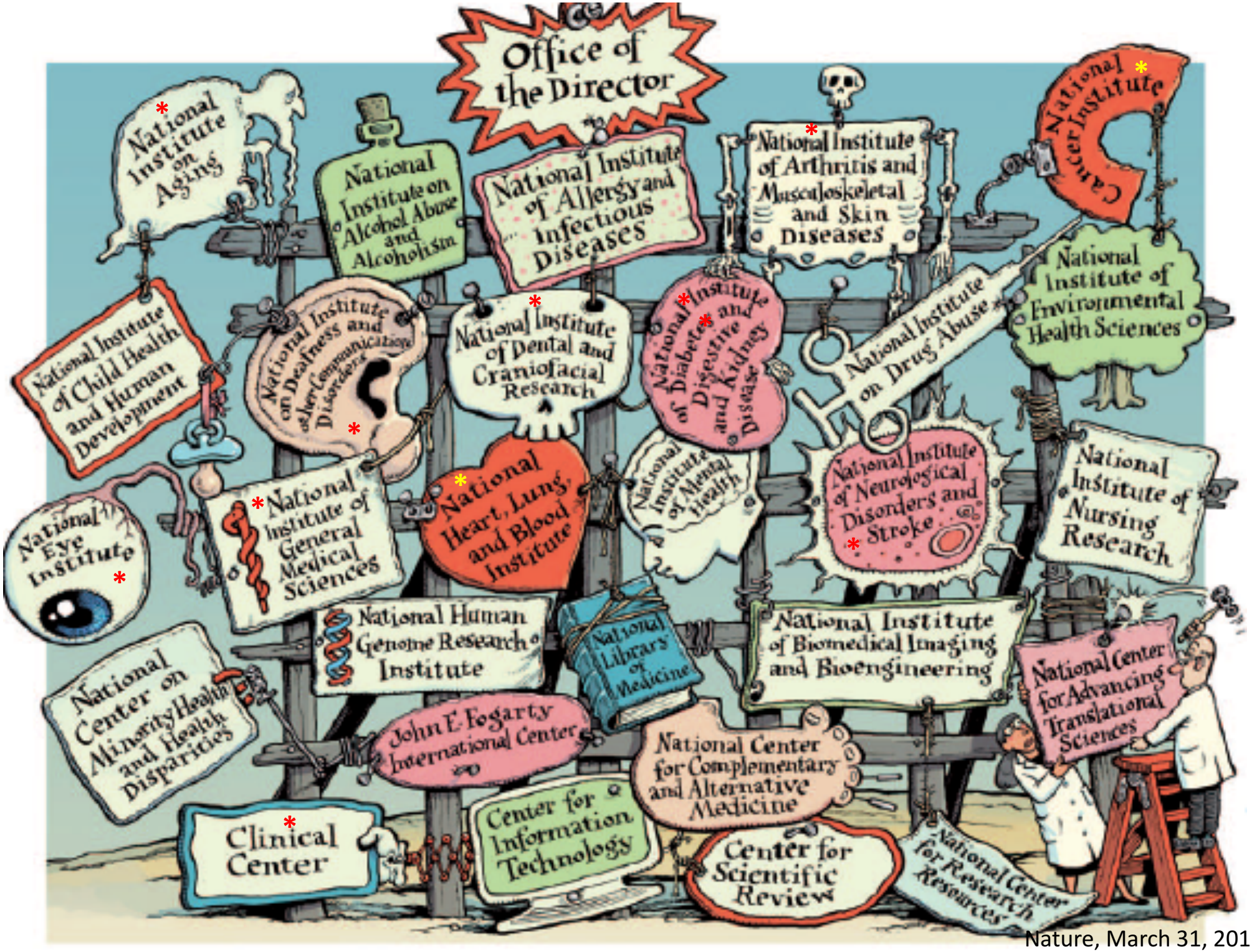
Intermittent Bioenergetic Challenges Improve Brain Health

"Challenges prolong life, while complacency hastens death."

Mark P. Mattson, Ph.D.

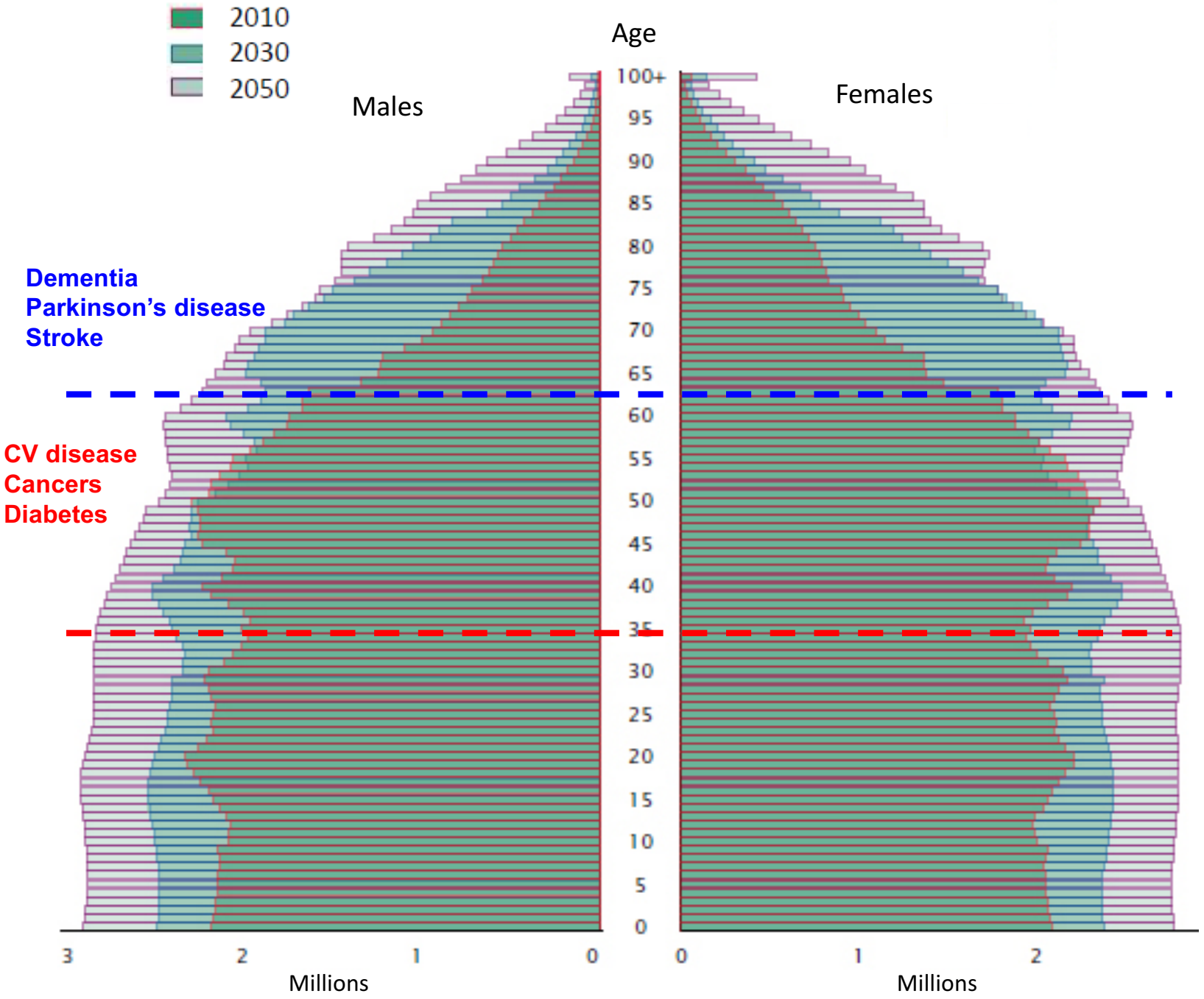
Chief, Laboratory of Neurosciences, NIA IRP, NIH
Professor, Department of Neuroscience, Johns Hopkins University



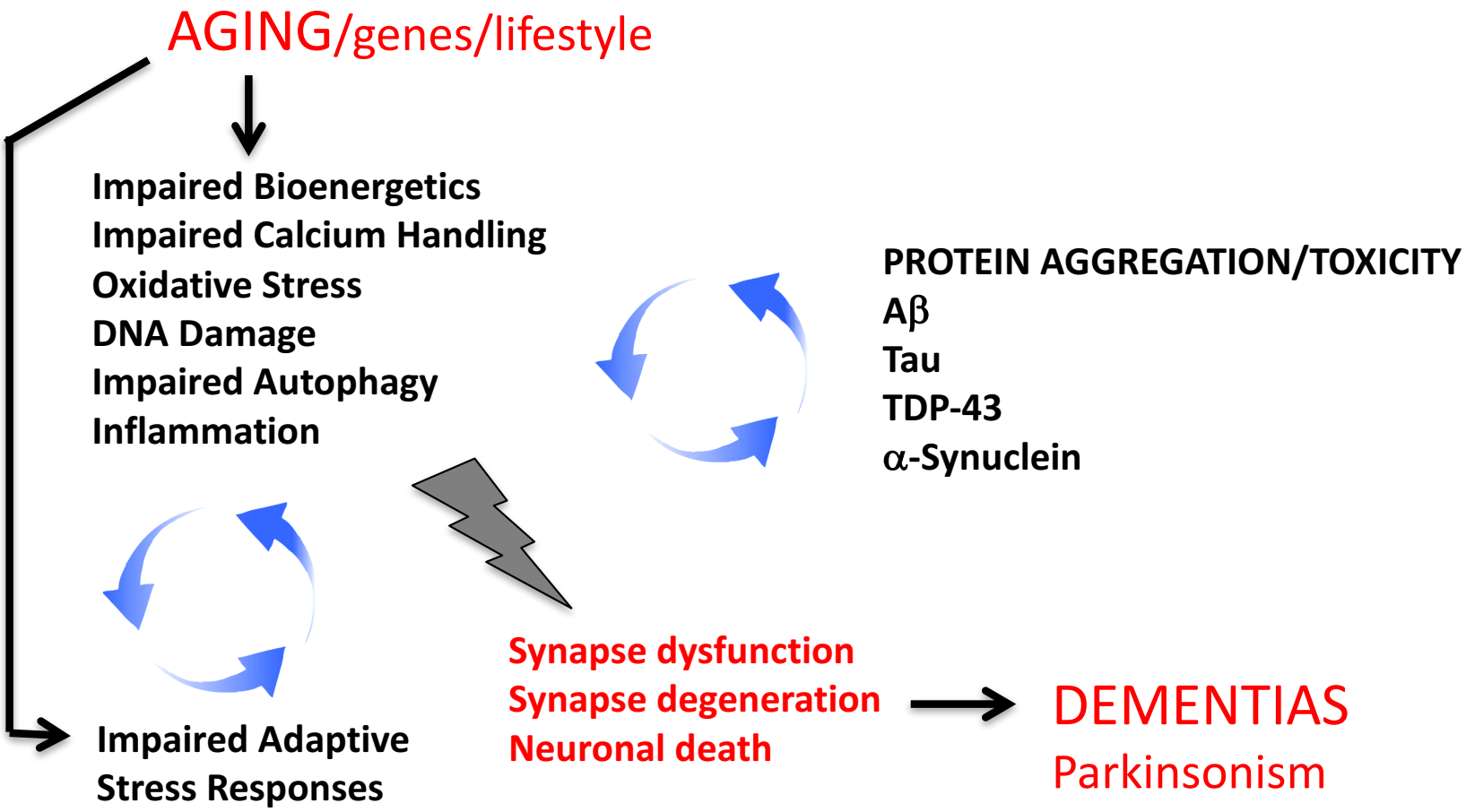


Nature, March 31, 2011

Age and Sex Structure of the US Population in 2010, 2030 and 2050



Mechanisms by Which Aging, Together with Genetic and Lifestyle Factors Promote Neurodegeneration



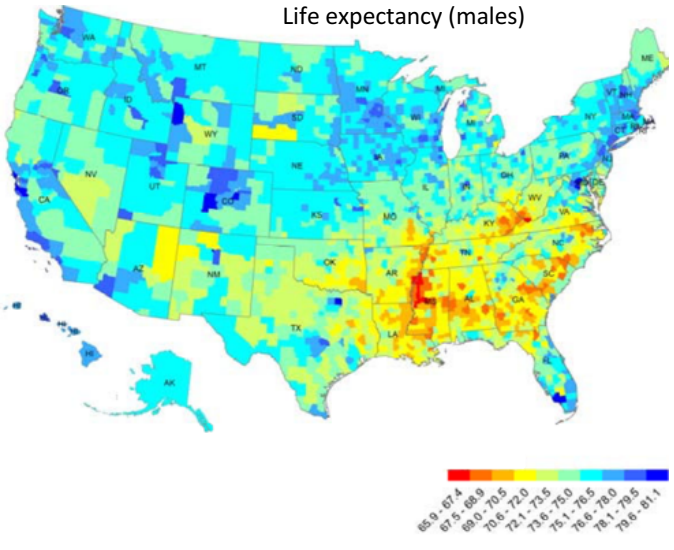
Mattson MP. 2004. Pathways towards and away from Alzheimer's disease. *Nature* 430:631-9.

Mattson MP, Magnus T. 2006. Ageing and neuronal vulnerability. *Nature Rev Neurosci.* 7(4):278-94.

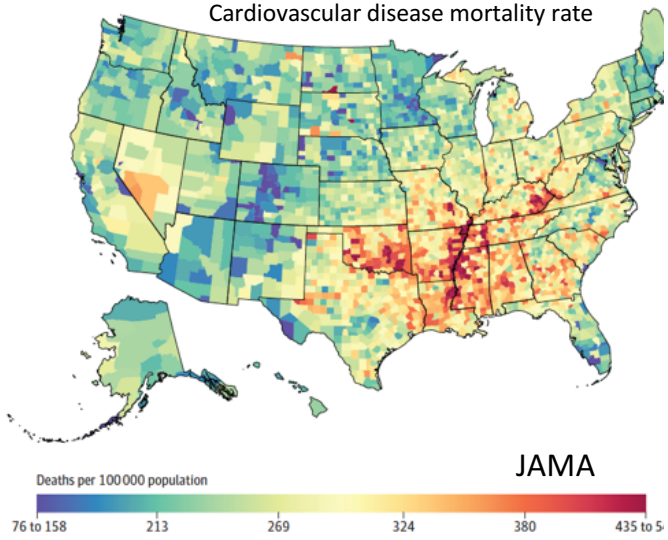
Lee EB, Mattson MP. 2014. The neuropathology of obesity. *Acta Neuropathol.* 127:3-28.

As time passes, the ‘obesity/diabetes belt’ will likely become the ‘dementia belt’

Life expectancy (males)

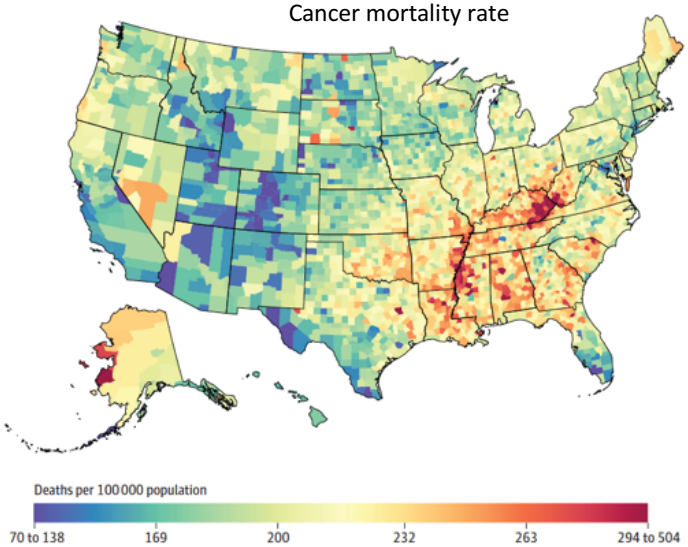


Cardiovascular disease mortality rate

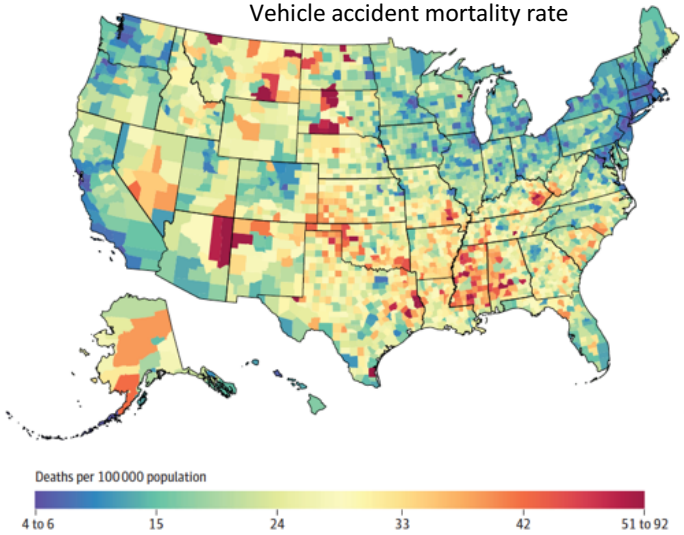


JAMA

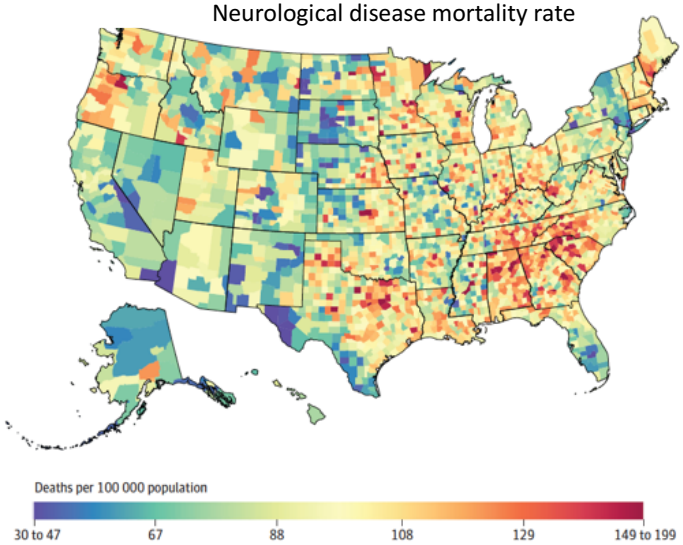
Cancer mortality rate



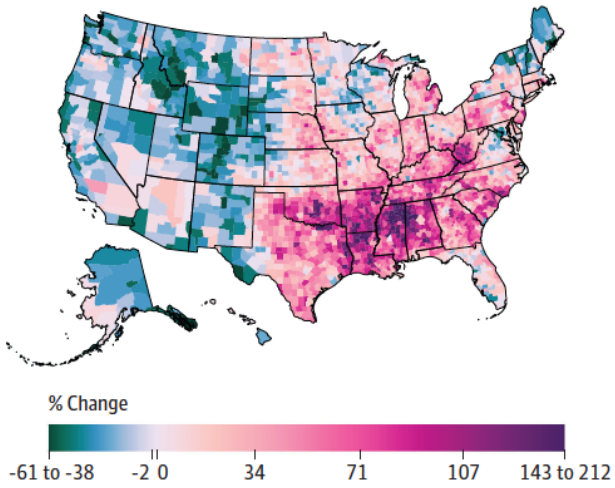
Vehicle accident mortality rate

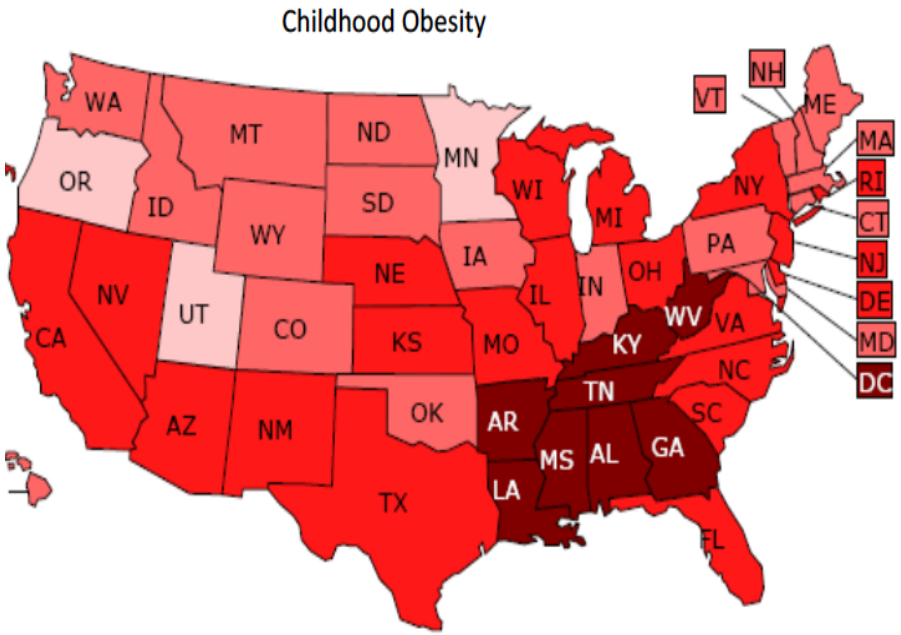


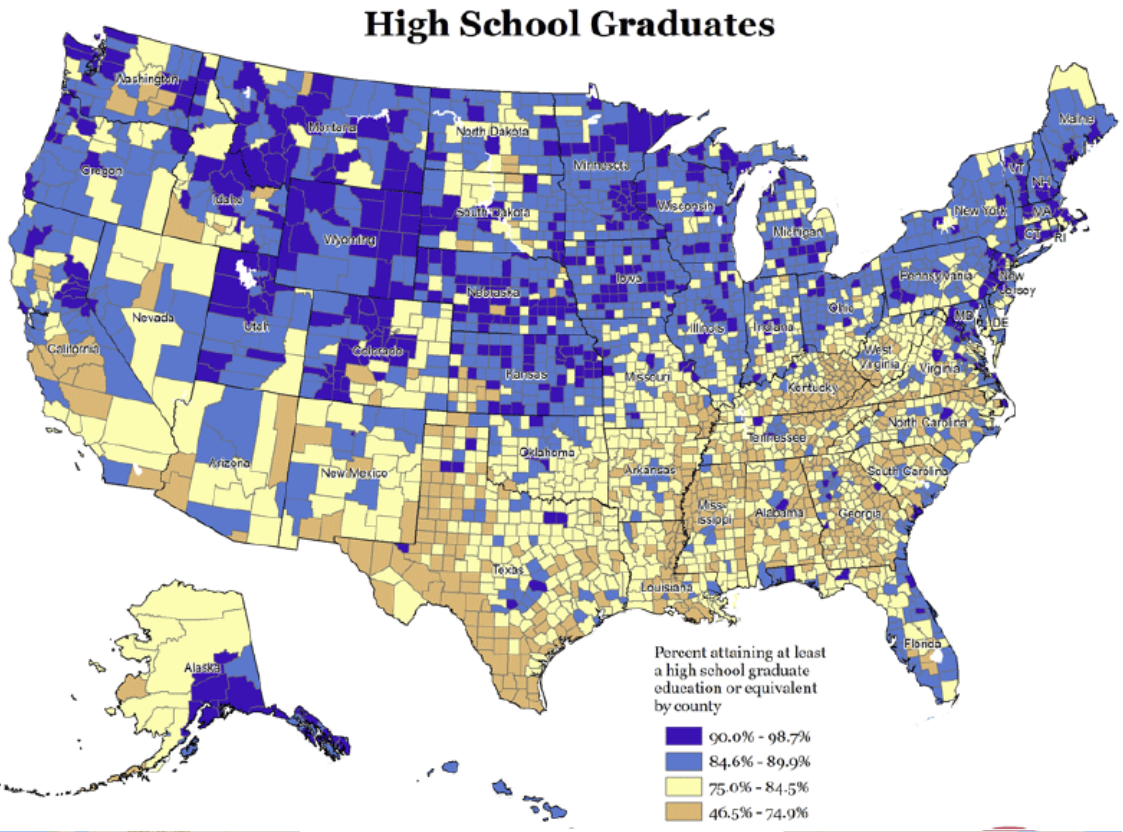
Neurological disease mortality rate

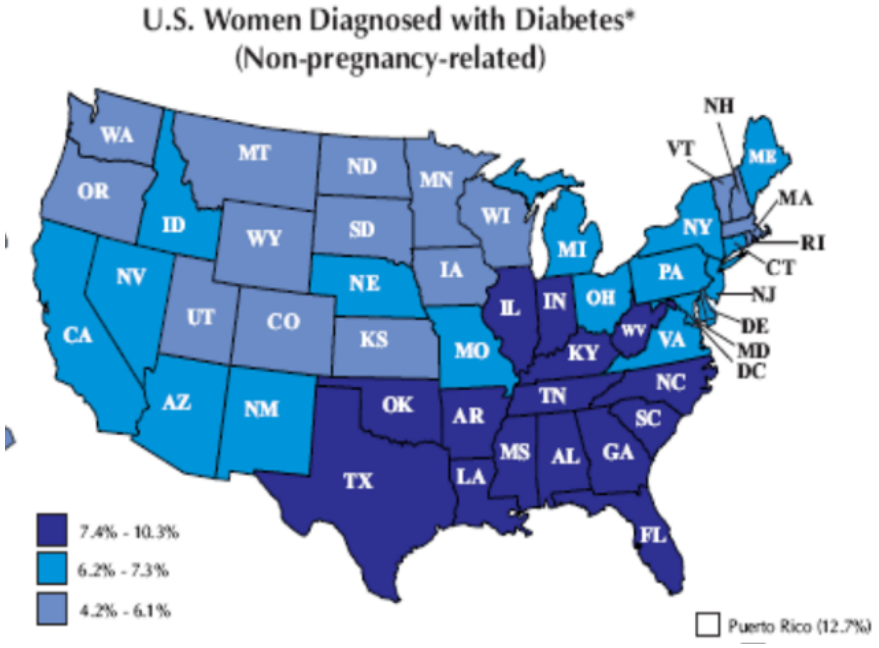


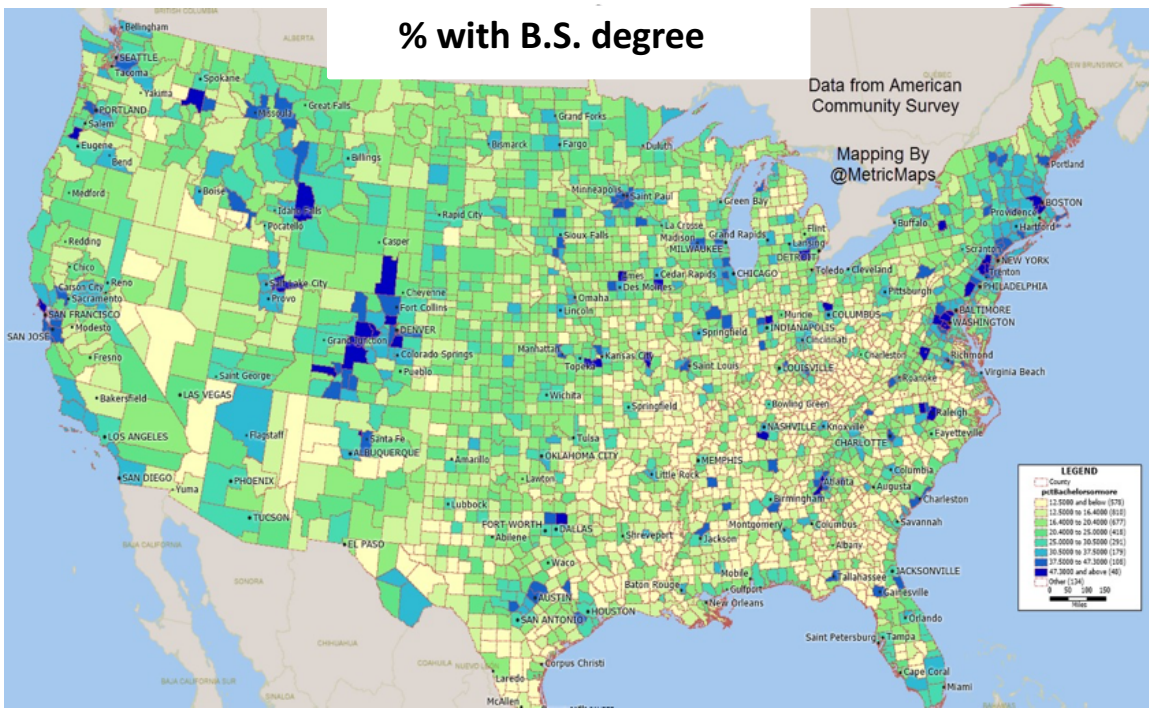
Percent change in age-standardized mortality rate from neurological disorders between 1980 and 2014, both sexes




Childhood Obesity
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
VA
NC
SC
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
DC


High School Graduates
Percent attaining at least a high school graduate education or equivalent by county
90.0% - 98.7%
84.6% - 89.9%
75.0% - 84.5%
46.5% - 74.9%

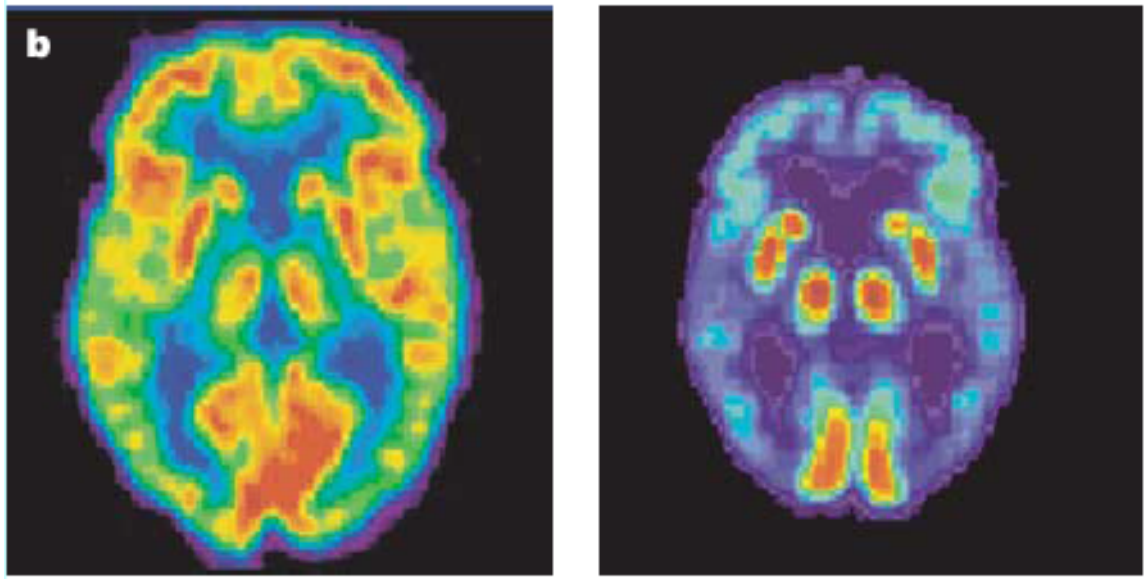

U.S. Women Diagnosed with Diabetes*
(Non-pregnancy-related)
7.4% - 10.3%
6.2% - 7.3%
4.2% - 6.1%
Puerto Rico (12.7%)


% with B.S. degree
Data from American Community Survey
Mapping By @MetricMaps

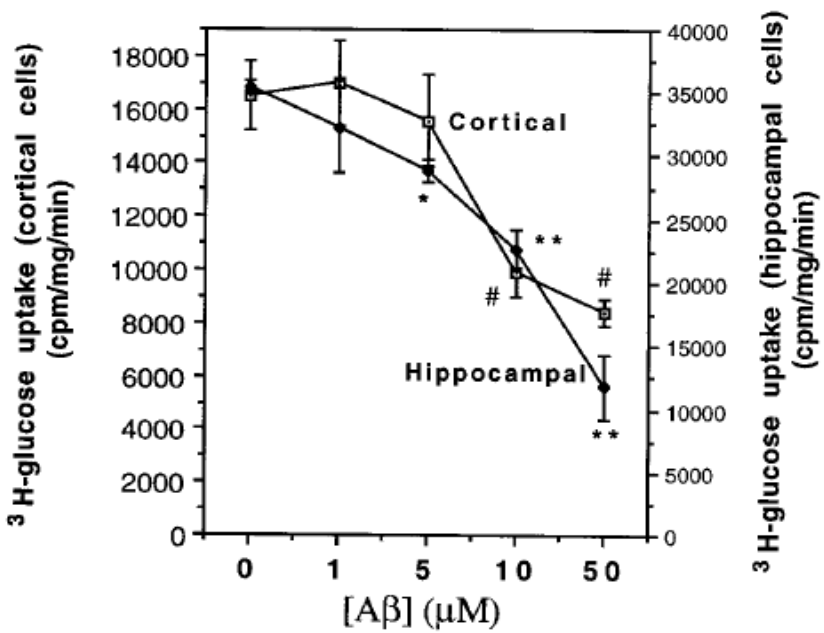
THIS DOES NOT BODE WELL FOR THE BRAIN HEALTH OF OUR CHILD

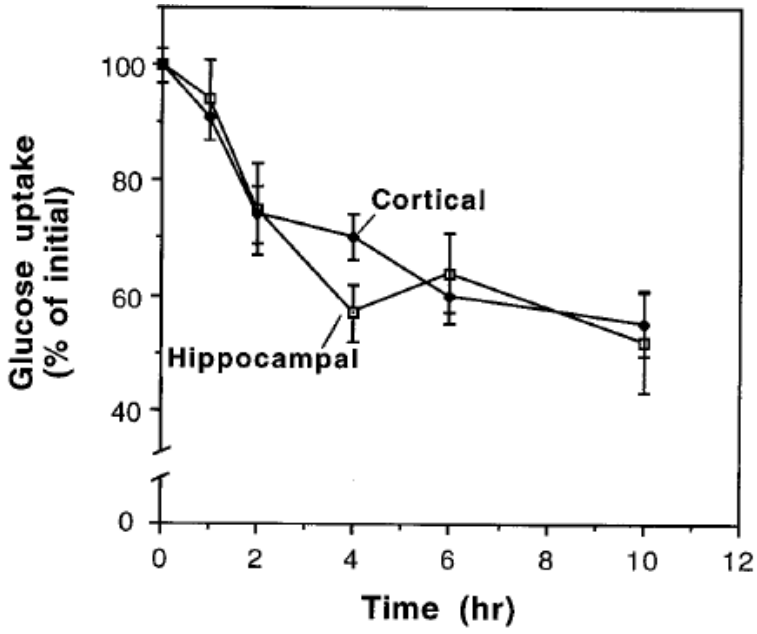
Regional glucose uptake is reduced in Alzheimer's disease

FDG PET



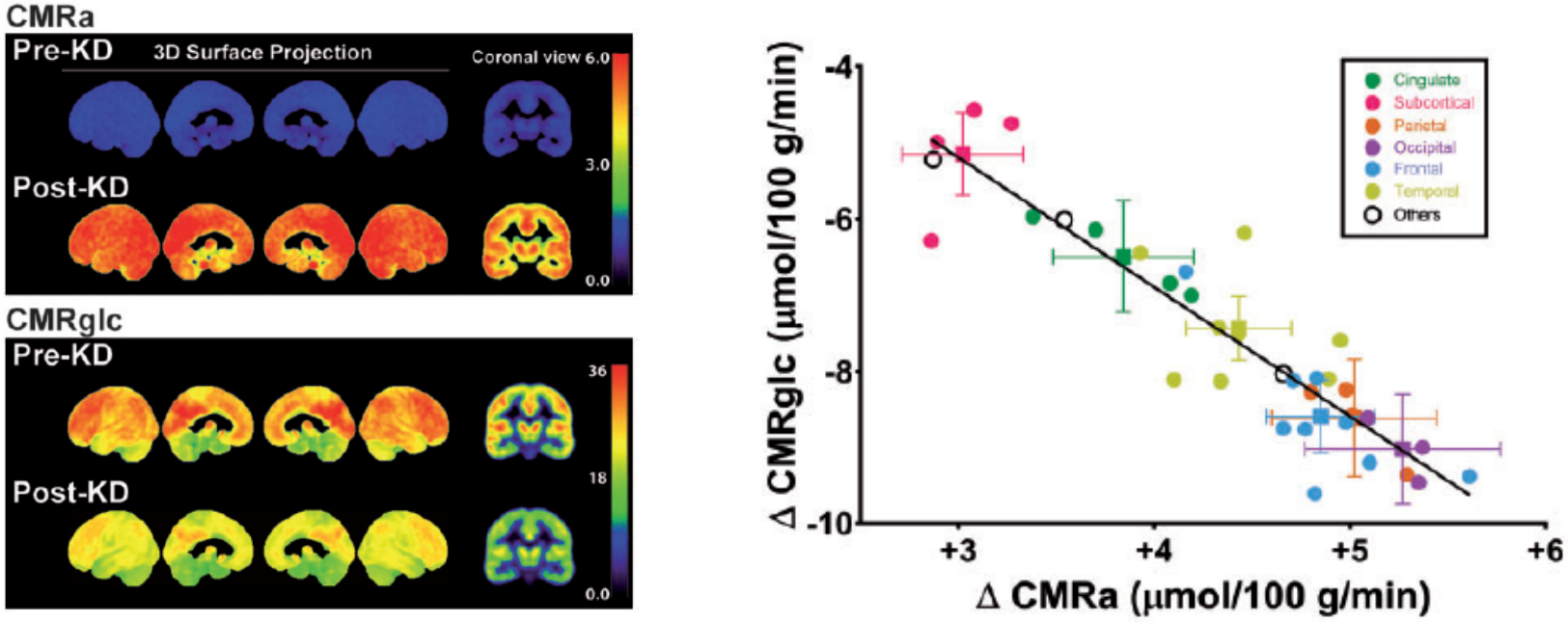
Amyloid β-peptide impairs neuronal glucose uptake in hippocampal and cortical neurons



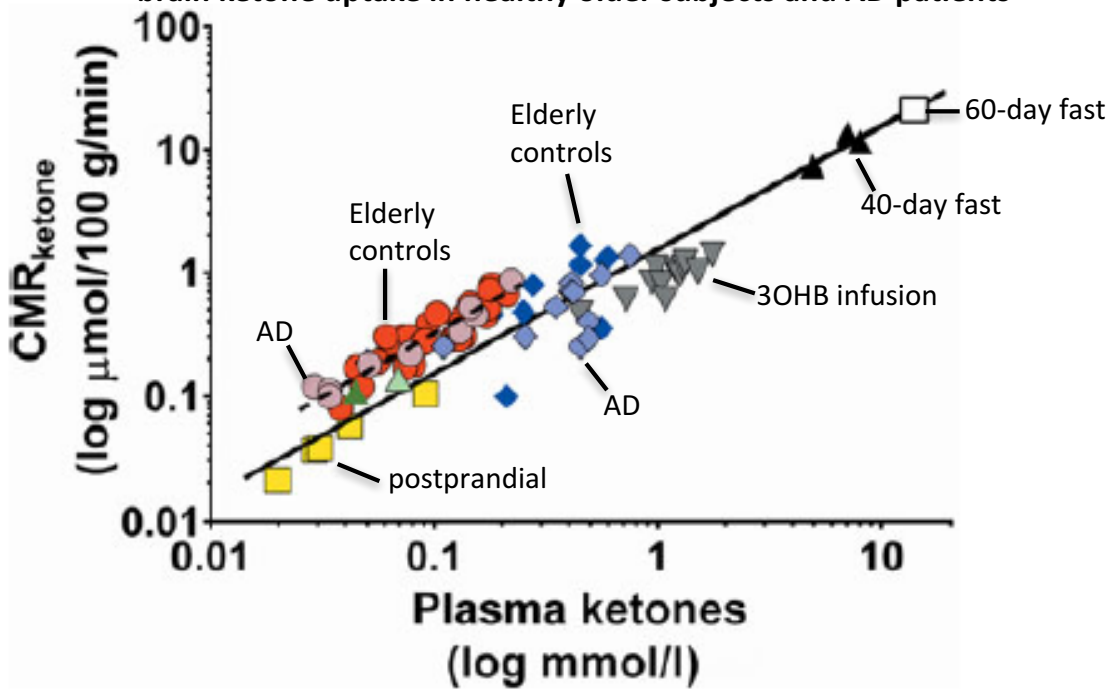


Mark et al. • β-Amyloid, Peroxidation, and Glucose Transport J. Neurosci., February 1, 1997, *17*(3):1046–1054

There is an inverse correlation between the regional change in cerebral metabolic rate (CMR) of acetoacetate and CMR of glucose pre- to post-ketogenic diet (4 days of KD including MCT).

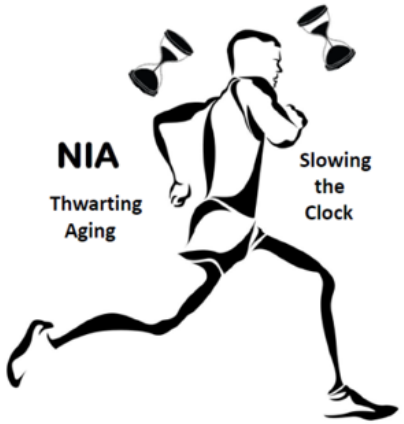


There is a direct, linear relation between plasma ketone concentration and brain ketone uptake in healthy older subjects and AD patients



Cunnane et al.
JCBFM and NYAS

EXERCISE
ENERGY RESTRICTION
INTELLECTUAL ENDEAVORS
CHEMICALS in FRUITS and VEGETABLES



Adaptive Responses
- 3-hydroxybutyrate (ketone)
- Neurotrophic factors (BDNF)
- Sirtuins
- Mitochondrial biogenesis
- GABAergic tone
- DNA repair proteins
- Protein chaperones

REDUCED PRODUCTION AND ENHANCED CLEARANCE OF PATHOGENIC PROTEINS
- Aβ
- Tau
- TDP-43
- α-Synuclein

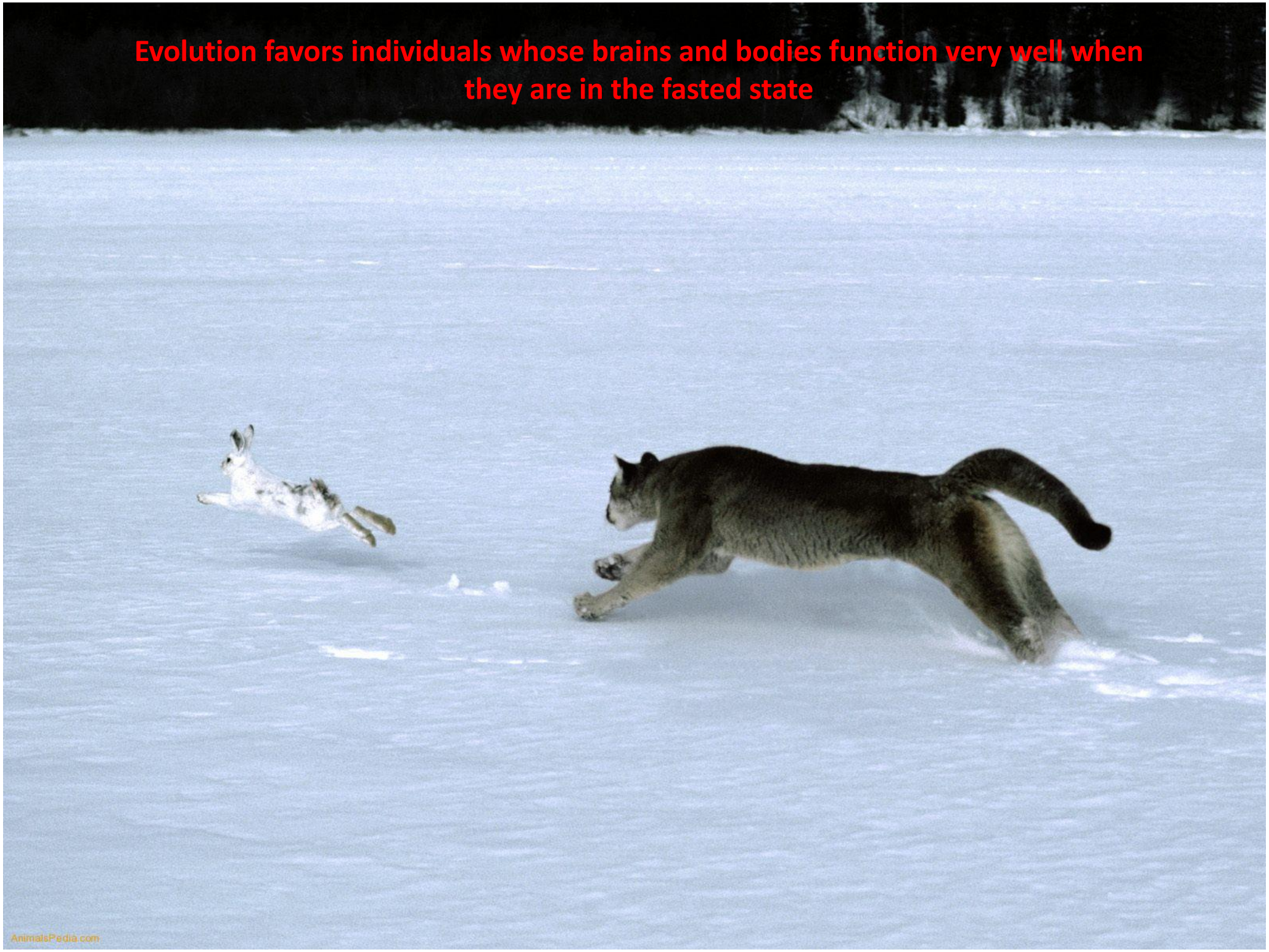
Bolstered Bioenergetics
Improved Calcium Handling
Reduced Oxidative Damage
Enhanced Autophagy
Reduced inflammation

Synaptic plasticity
Neuronal survival
Neurogenesis

OPTIMAL BRAIN FUNCTION AND RESISTANCE TO INJURY AND DISEASE

Mattson MP. 2012. *Cell Metab.* 16:706-722.
Stranahan AM, Mattson, MP. *Nat. Rev. Neurosci.* 13:209-216.
Raefsky S, Mattson MP. 2016. *Free Rad Biol. Med.* 102:203-216.

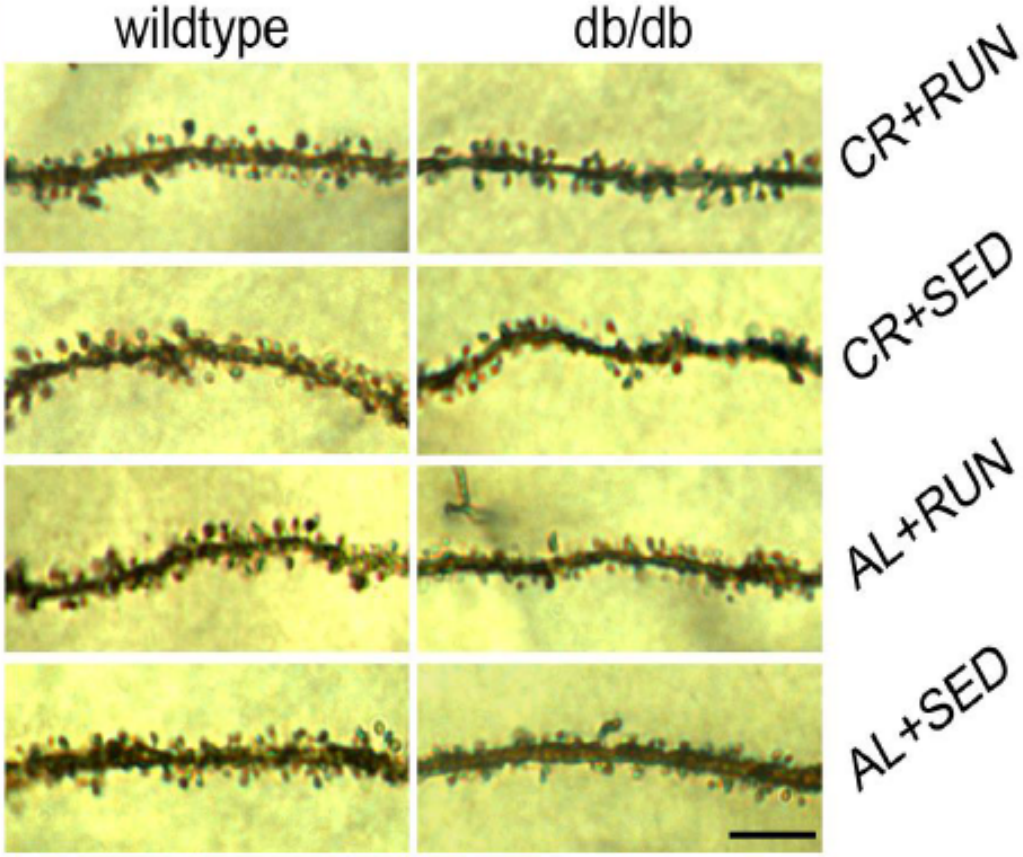
Evolution favors individuals whose brains and bodies function very well when they are in the fasted state



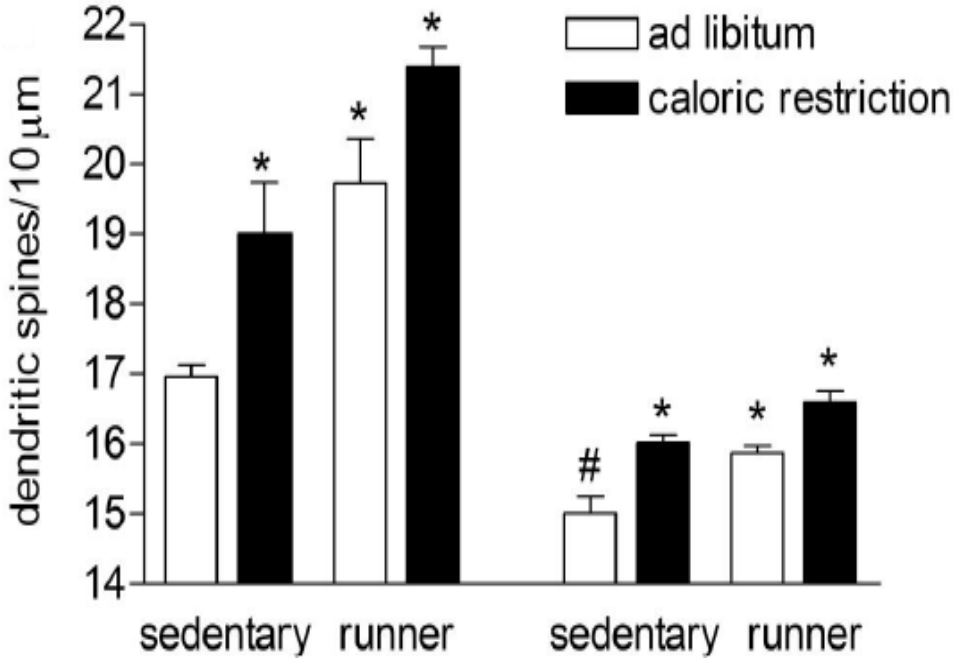
The need to acquire food has been a primary ‘driver’ of brain evolution, including the superior imagination and creativity of humans

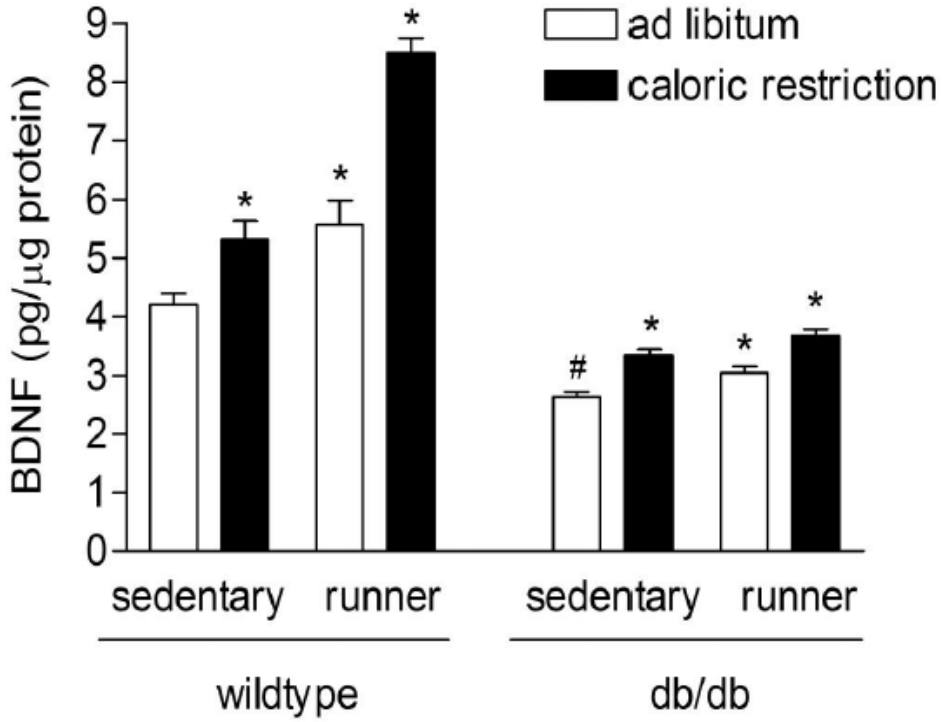
Mice that overeat and are diabetic (db/db mice) exhibit reduced synapse numbers and BDNF levels in the hippocampus, whereas dietary energy restriction and running increase synapse numbers and BDNF levels

Dendritic spines (postsynaptic structures) on hippocampal neurons



3 months of running and/or CR

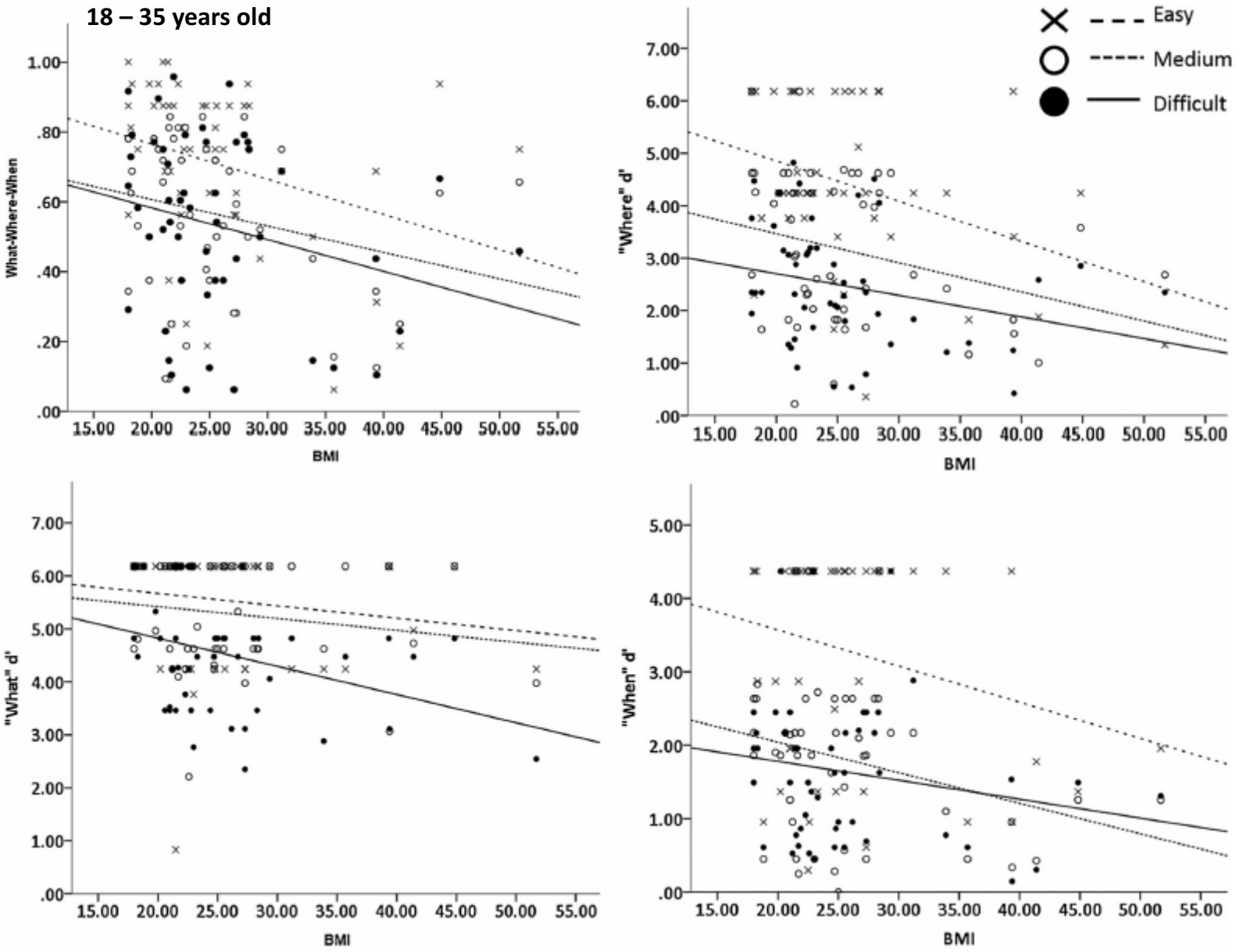




Stranahan et al. (2008) *Nature Neurosci.* 11: 309-317.
Stranahan et al. (2009) *Hippocampus* 19: 951-961.

Higher body mass index is associated with episodic memory deficits in young adults

18 – 35 years old



Lucy G. Cheke, Jon S. Simons, and Nicola S. Clayton
Department of Psychology, University of Cambridge, Cambridge, UK

THE QUARTERLY JOURNAL OF EXPERIMENTAL PSYCHOLOGY, 2016
Vol. 69, No. 11, 2305–2316, http://dx.doi.org/10.1080/17470218.2015.1099163

Children (10 years old) of overweight and obese mothers have reduced IQ and poorer executive brain function compared to children of normal or low body weight mothers

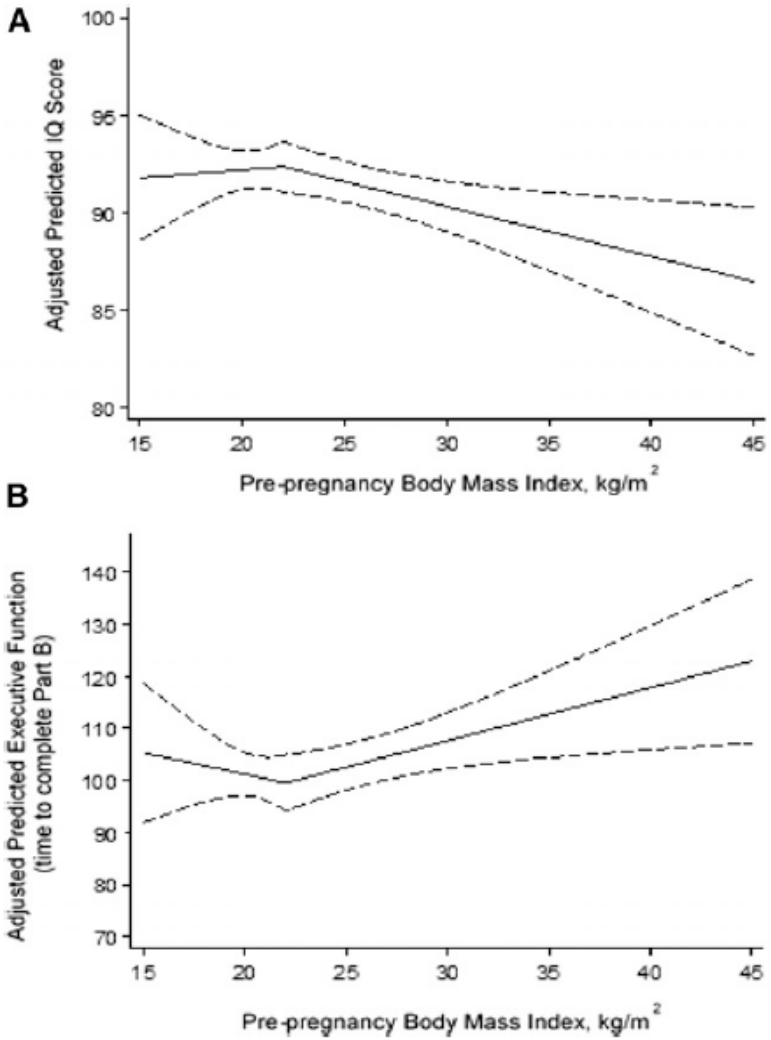


TABLE 3 Multivariable linear and negative binomial regression estimates of the association between prepregnancy BMI and offspring intelligence and executive function[1]

Prepregnancy BMI,[2] kg/m^2	IQ[3]	Executive function perseverative errors[3]	Executive function time to complete TMT-B,[3] s
18	−0.3 (−2.6, 1.9)	0.93 [0.9, 1.0]	3.3 (−6.0, 13)
20	−0.2 (−1.3, 0.9)	0.97 [0.9, 1.0]	1.7 (−3.1, 6.4)
22	0.0	1.0	0.0
24	−0.5 (−0.9, −0.1)	1.0 [1.0, 1.4]	2.0 (0.4, 3.6)
26	−1.1 (−1.8, −0.3)	1.0 [0.9, 1.1]	4.1 (0.9, 7.3)
28	−1.5 (−2.6, −0.4)	1.0 [0.9, 1.1]	6.0 (1.3, 11)
30	−2.1 (−3.6, −0.5)	0.9 [0.9, 1.1]	8.1 (1.8, 15)
32	−2.5 (−4.5, −0.6)	0.9 [0.9, 1.1]	10.1 (2.2, 18)
34	−3.2 (−5.6, −0.8)	0.9 [0.8, 1.1]	12.7 (2.8, 23)

530 children tested

Pugh SJ et al. *Journal of Nutrition* 2015; 145:2562-9.

Individuals with abdominal obesity and type 2 diabetes have significantly smaller sizes of brain regions critically involved in learning and memory (hippocampus and cerebral cortex)

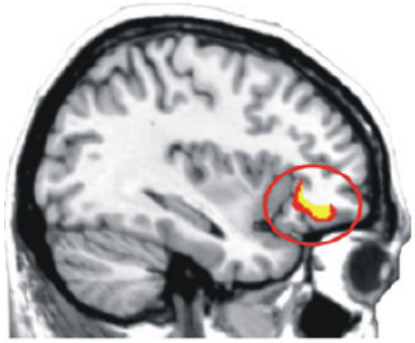
Table 2. Associations of type 2 diabetes mellitus (T2D), waist-hip ratio (WHR), body mass index (BMI), mean steps/day and cortical volumes (n = 560). β is unstandardized coefficient. CI–confidence interval. All regressions adjusted for age, sex and total intracranial volume.

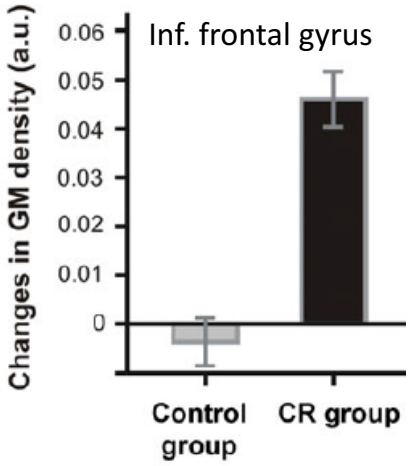
	T2D β (95% CI)	P value	WHR β (95% CI)	P value	BMI β (95% CI)	P value	Mean steps/day β (95% CI)	P value
Total gray matter volume (ml)	-10.04	0.001	-107.77	<0.001	-0.82	0.01	0.001	0.02
	(-15.89, -4.19)		(-146.81, -68.73)		(-1.47, 0.18)		(0.0001, 0.002)	
Left hippocampal volume (ml)	-0.39	<0.001	-1.48	<0.001	-0.01	0.03	0.00002	0.005
	(-0.47, -0.32)		(-2.03, -0.93)		(-0.01, -0.001)		(5.39^{-6}, 0.00003)	
Right hippocampal volume (ml)	-0.45	<0.001	-1.18	<0.001	-0.009	0.05	0.00002	0.002
	(-0.53, -0.37)		(-1.77, -0.59)		(-0.02, -0.00002)		(7.93^{-6}, 00003)	
Total hippocampal volume (ml)	-0.85	<0.001	-2.70	<0.001	-0.02	0.02	0.00004	0.001
	(-0.99, -0.70)		(-3.76, -1.64)		(-0.04, -0.003)		(0.00002, 0.00007)	

doi:10.1371/journal.pone.0142589.t002

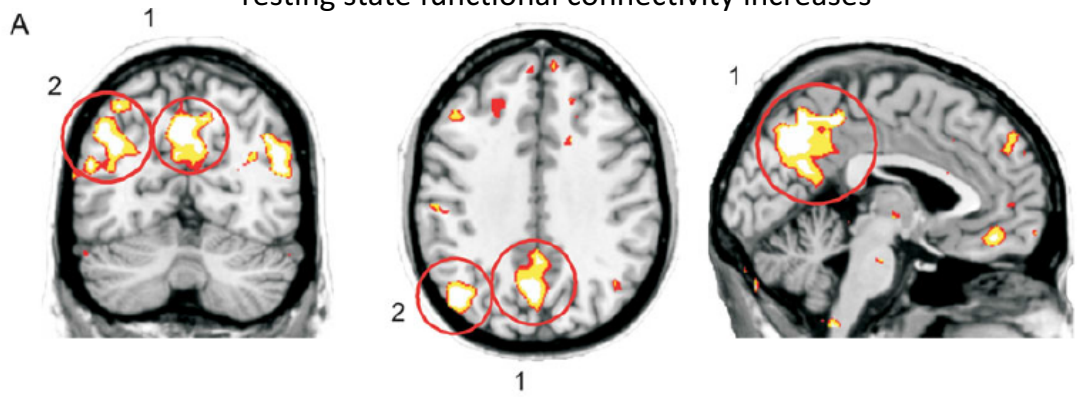
258 T2D patients 302 healthy controls

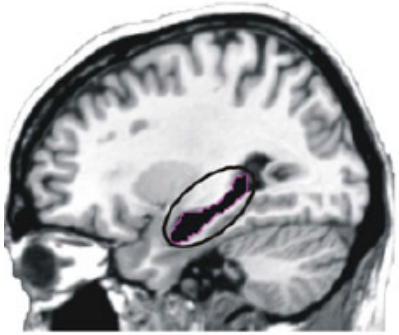
Caloric restriction results in increased sizes of brain regions critical for learning and memory, as well as increased communication (functional connectivity between these and other brain regions)

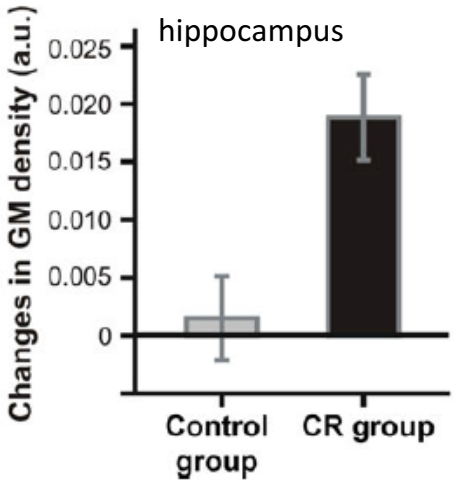


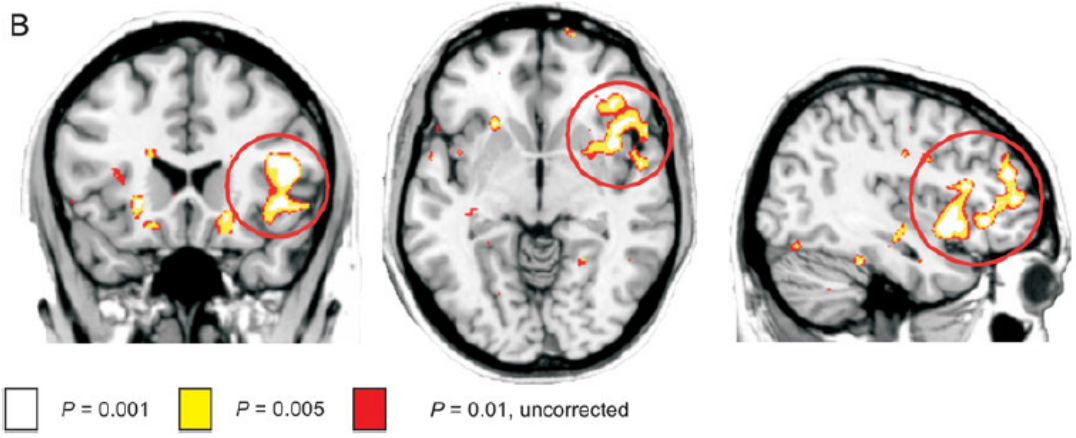


resting state functional connectivity increases









Agnes Flöel

Alternate Day Fasting During Training Enhances Performance in an Endurance Running Challenge

Ad libitum feeding (AL) sedentary
Alternate day fasting (ADF)

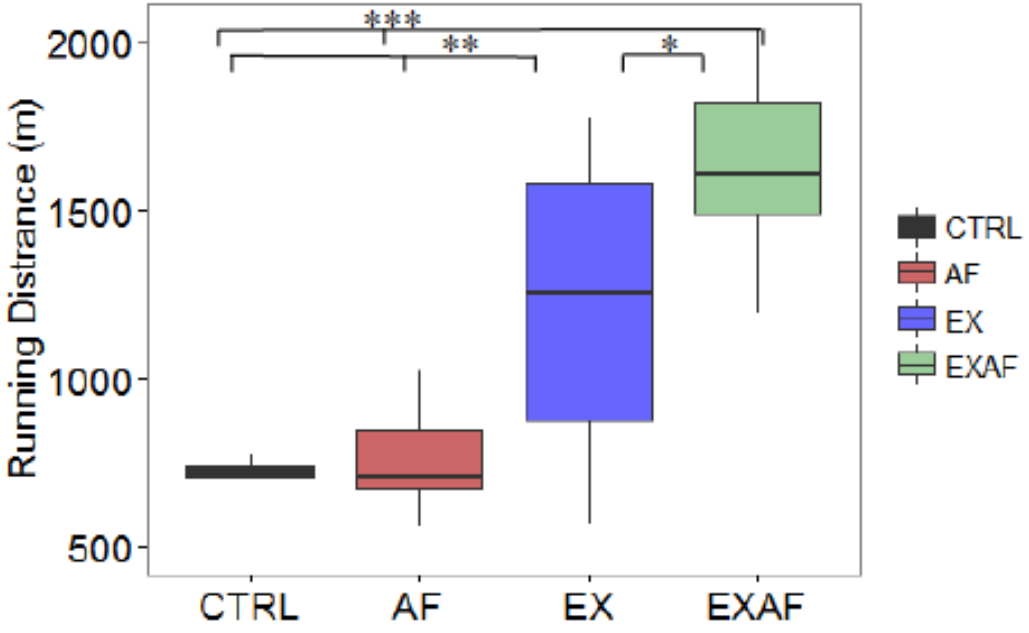
AL - exercise
ADF - exercise

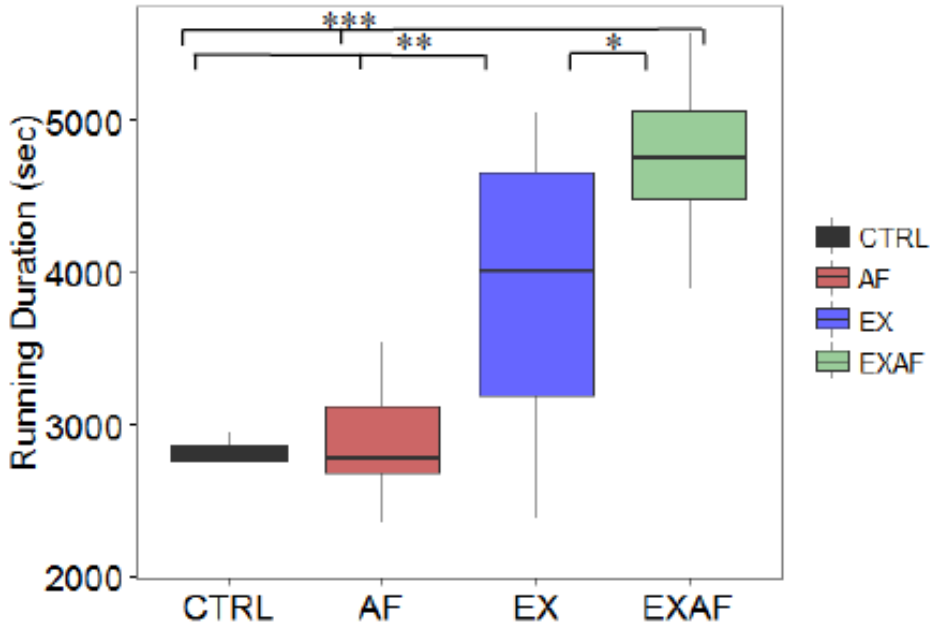
Training Protocol

Week	Duration	Speed	Incline
1	45 minutes	15 m/min	10˚
2	45 minutes	20 m/min	10˚
3	45 minutes	15 m/min	15˚
4	45 minutes	20 m/min	15˚

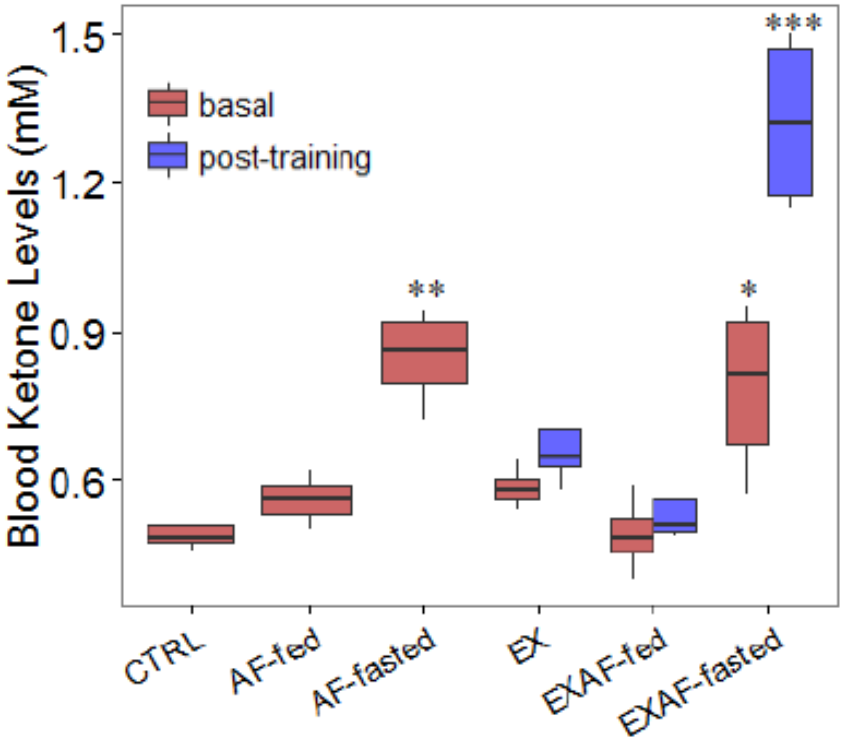
Endurance test

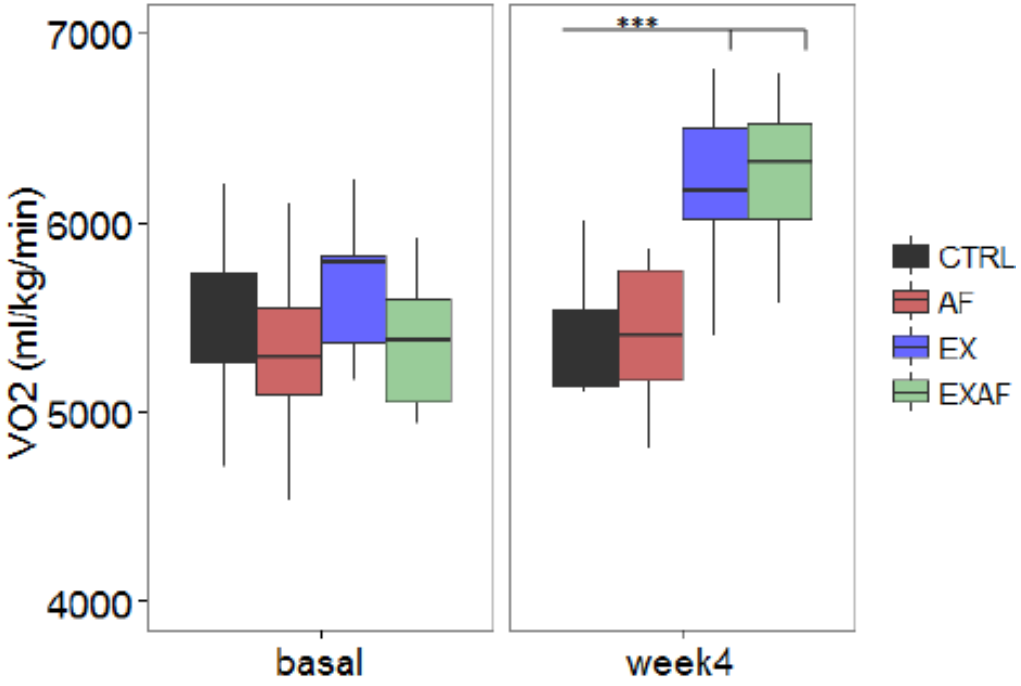
Time (min)	0-15	15-30	30-45	45-60	60-75	75+
Speed (m/min)	10	15	20	25	30	35

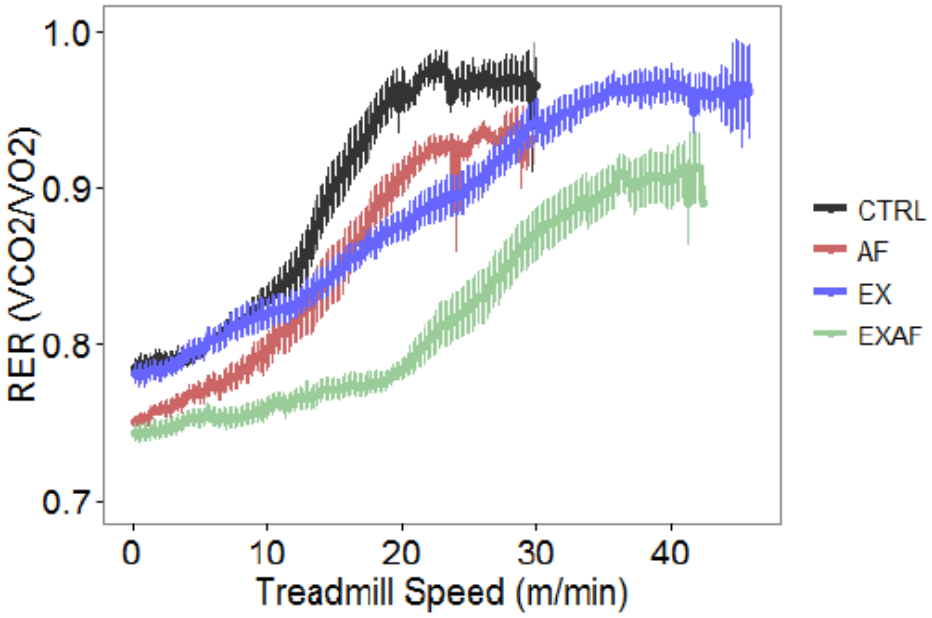


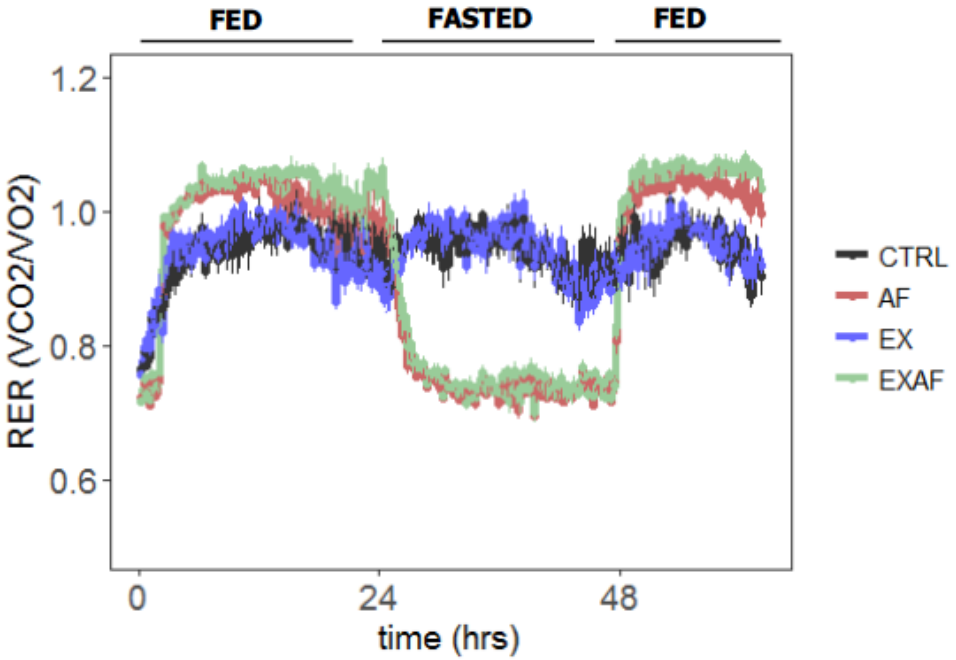


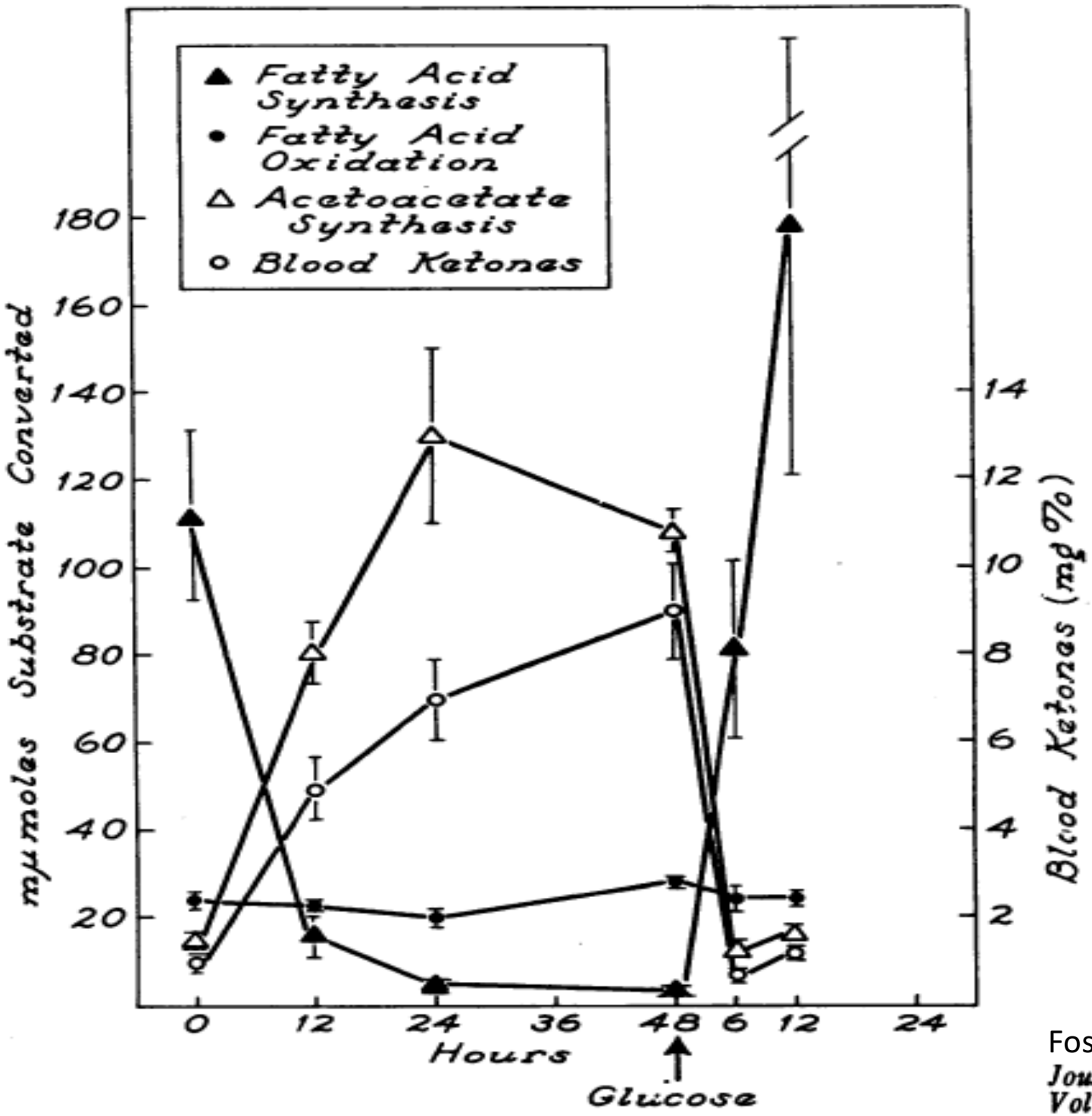
Keelin Moehl and Krisztina Marosi


Blood Ketone Levels (mM)
1.5
1.2
0.9
0.6
basal
post-training
***
**
*
CTRL
AF-fed
AF-fasted
EX
EXAF-fed
EXAF-fasted


VO2 (ml/kg/min)
7000
6000
5000
4000
***
basal
week4
CTRL
AF
EX
EXAF

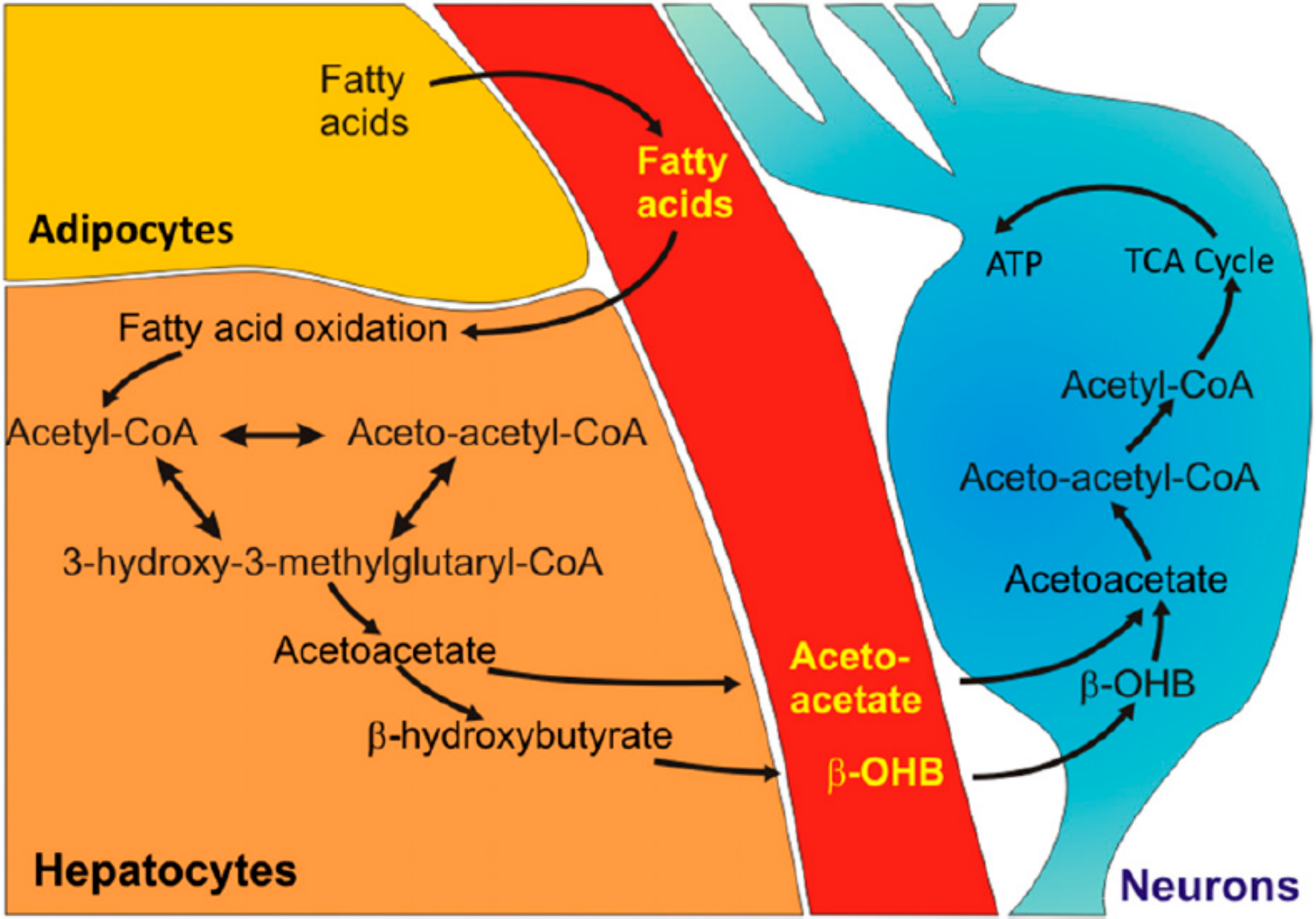

RER (VCO2/VO2)
1.0
0.9
0.8
0.7
0
10
20
30
40
Treadmill Speed (m/min)
CTRL
AF
EX
EXAF


FED
FASTED
FED
RER (VCO2/VO2)
1.2
1.0
0.8
0.6
0
24
48
time (hrs)
CTRL
AF
EX
EXAF

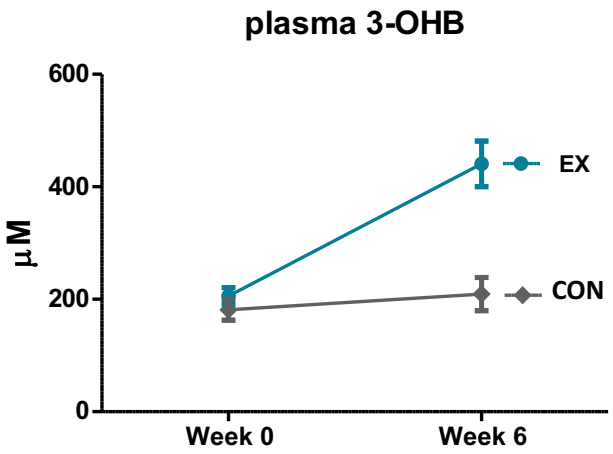


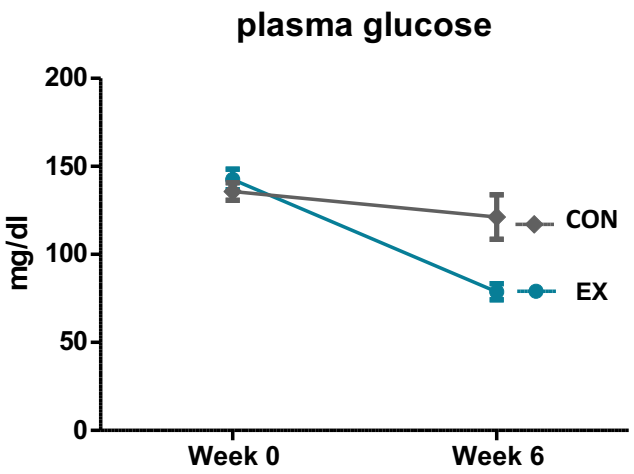
Foster DW

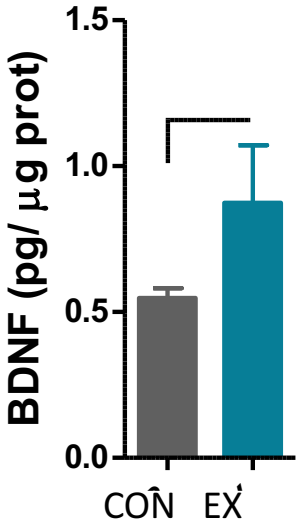
Journal of Clinical Investigation
Vol. 46, No. 8, 1967

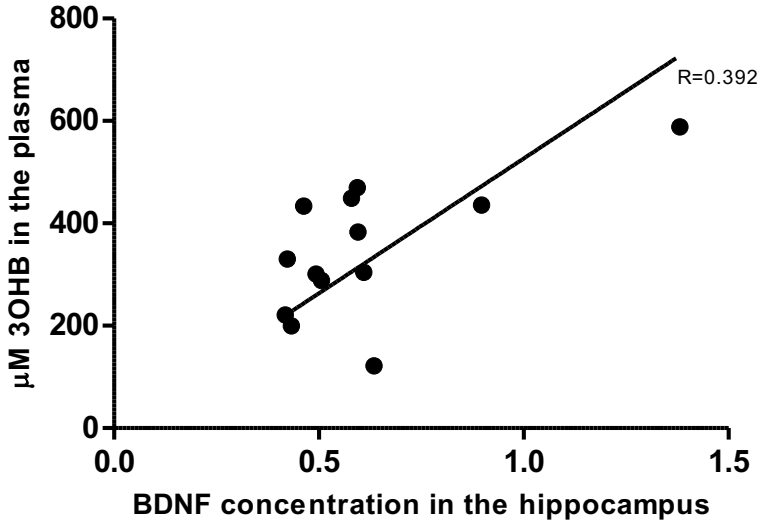

Fatty acids
Adipocytes
Fatty acids
Fatty acid oxidation
Acetyl-CoA
Aceto-acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
Acetoacetate
β-hydroxybutyrate
Hepatocytes
Aceto-acetate
β-OHB
ATP
TCA Cycle
Acetyl-CoA
Aceto-acetyl-CoA
Acetoacetate
β-OHB
Neurons

Running wheel exercise increases plasma 3OHB levels, and hippocampal BDNF levels are correlated with plasma 3OHB levels in mice



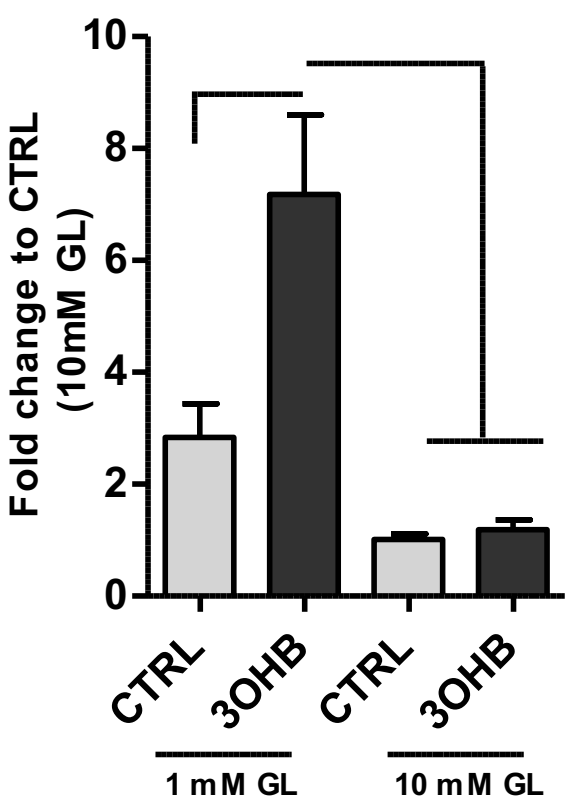


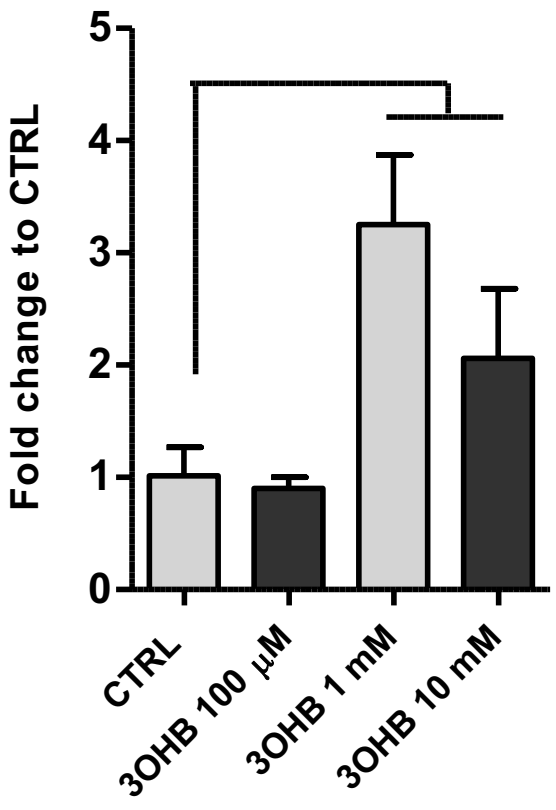


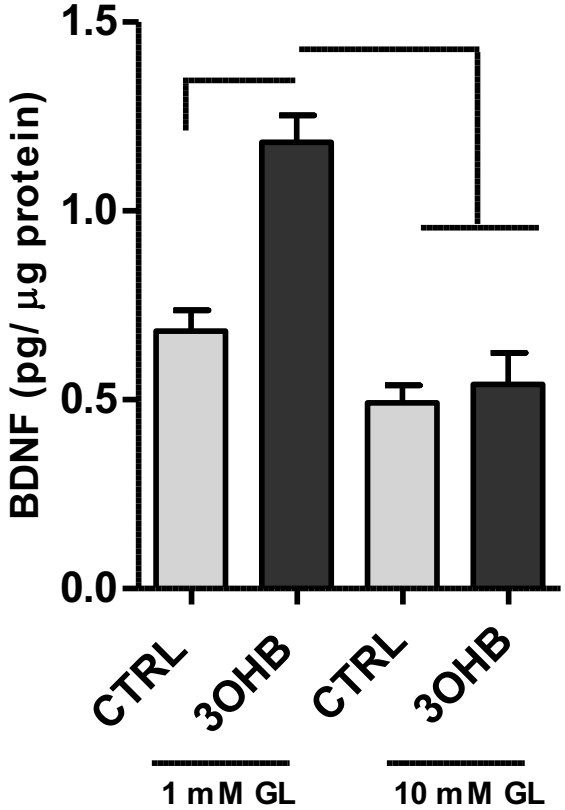


Marosi, K., S. W. Kim, K. Moehl, M. Scheibye-Knudsen, A. Cheng, R. Cutler, S. Camandola and M. P. Mattson (2016) 3-hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J. Neurochem.* In press.

The ketone 3-hydroxybutyrate (3OHB) induces expression of BDNF in cerebral cortical neurons





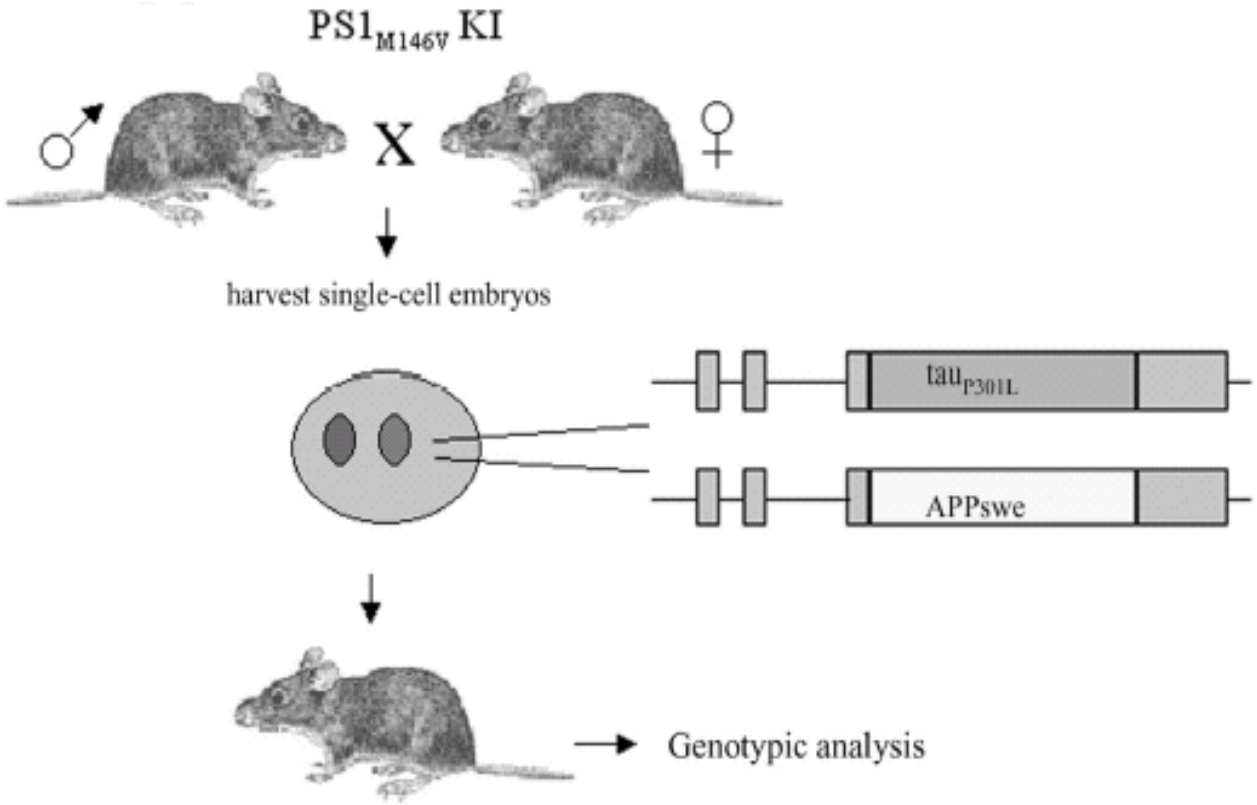


Marosi, K., S. W. Kim, K. Moehl, M. Scheibye-Knudsen, A. Cheng, R. Cutler, S. Camandola and M. P. Mattson (2016) 3-hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J. Neurochem.* In press.

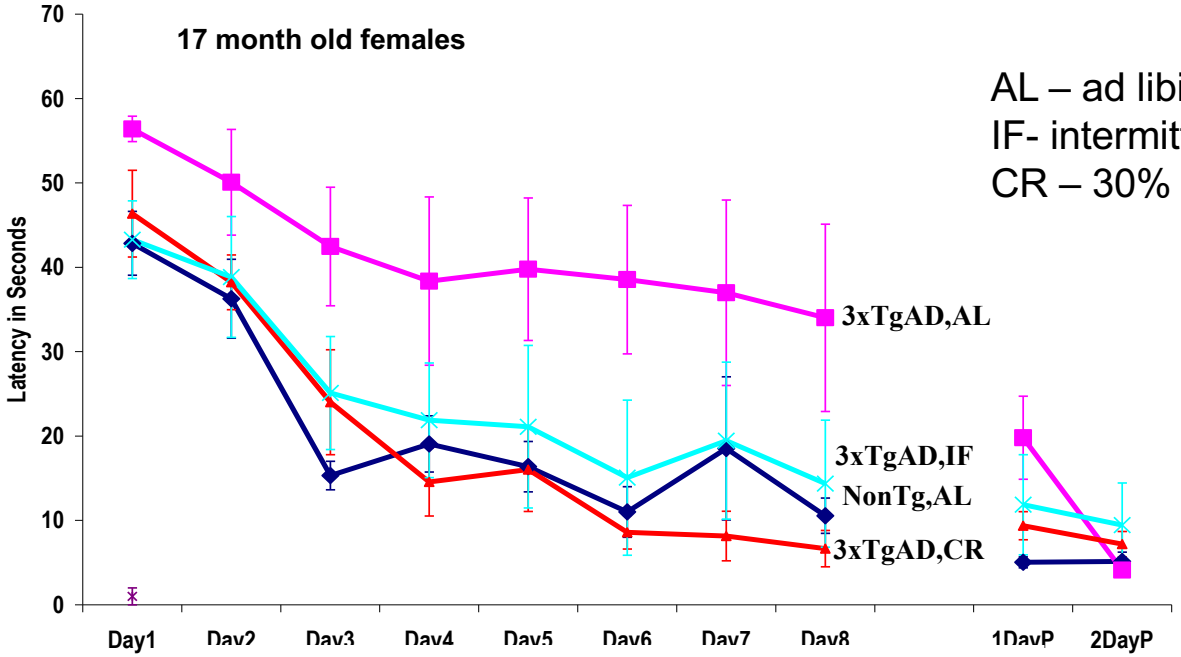
Neuron, Vol. 39, 1–20, July 31, 2003, Copyright ©2003 by Cell Press

Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

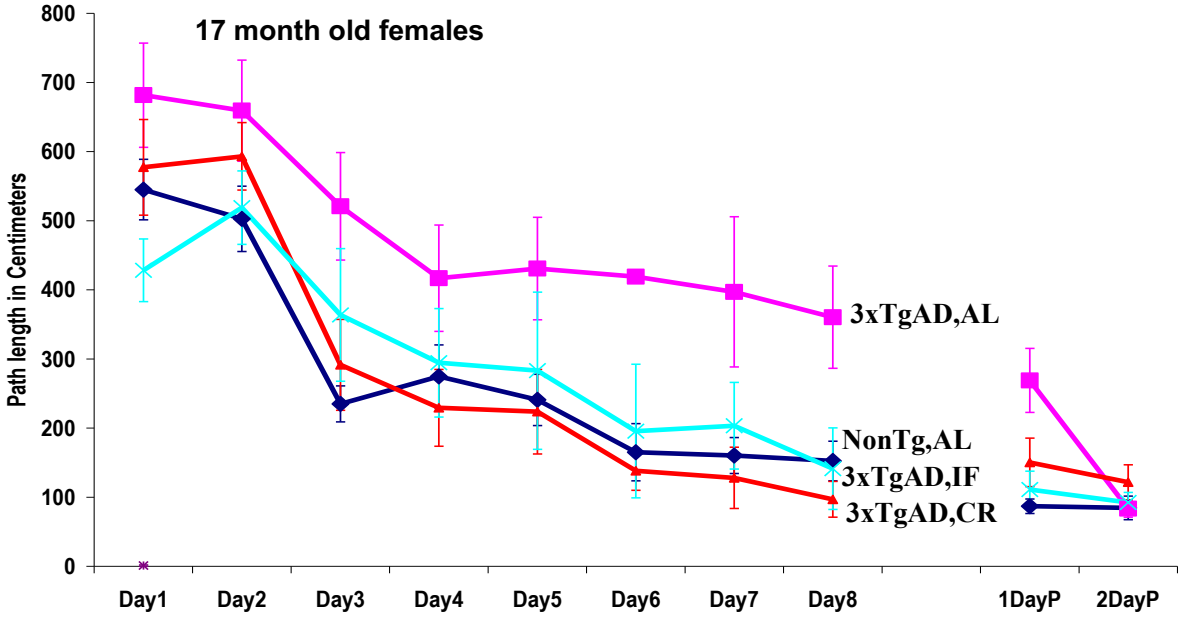
Salvatore Oddo,[1] Antonella Caccamo,[1,5]
Jason D. Shepherd,[1,5] M. Paul Murphy,[3]
Todd E. Golde,[3] Rakez Kayed,[2]
Raju Metherate,[1] Mark P. Mattson,[4]
Yama Akbari,[1] and Frank M. LaFerla[1,*]



Alternate day intermittent fasting and daily CR (time-restricted feeding) prevent cognitive deficits in a mouse model of Alzheimer's disease (3xTgAD mice)

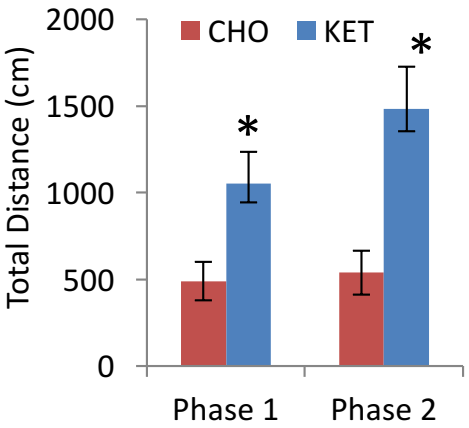


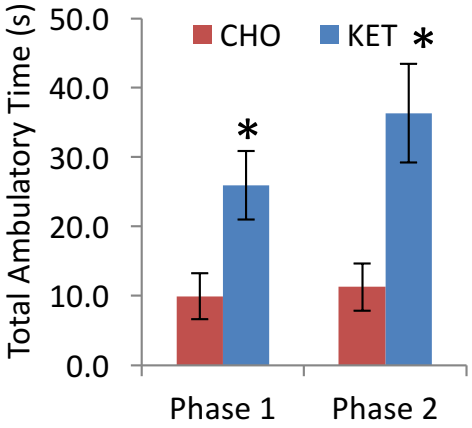
AL – ad libitum
IF- intermittent (alternate day) fasting
CR – 30% daily calorie restriction

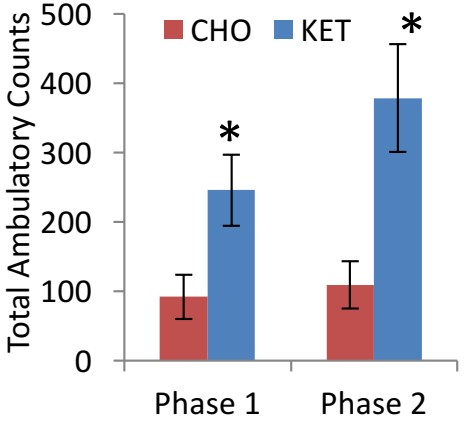


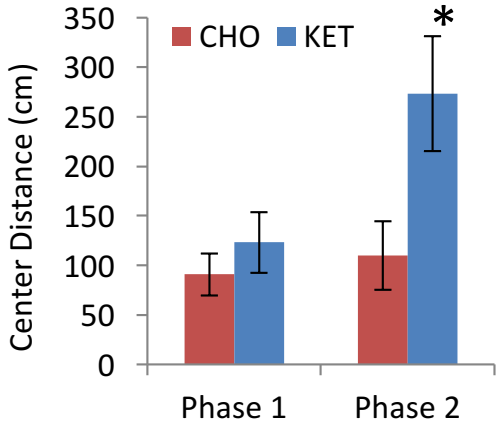
Halagappa VK et al (2007)
Neurobiol Dis. 26:212-20.

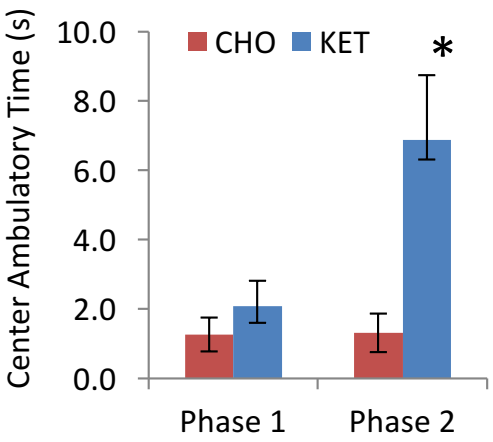
A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. Kashiwaya Y, Bergman C, Lee JH, Wan R, King MT, Mughal MR, Okun E, Clarke K, Mattson MP, Veech RL. Neurobiol Aging. 2013 Jun; 34:1530-9.

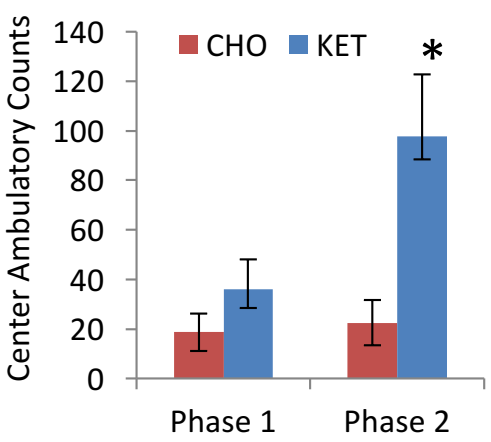


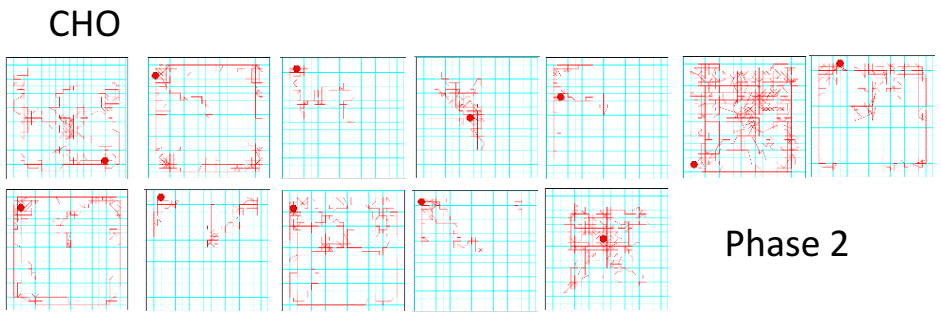


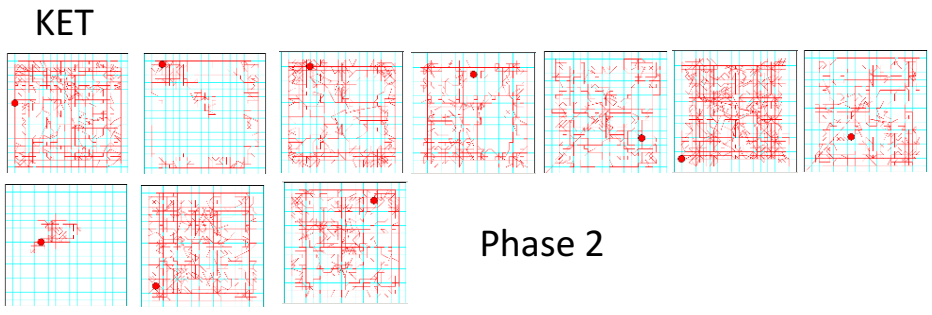




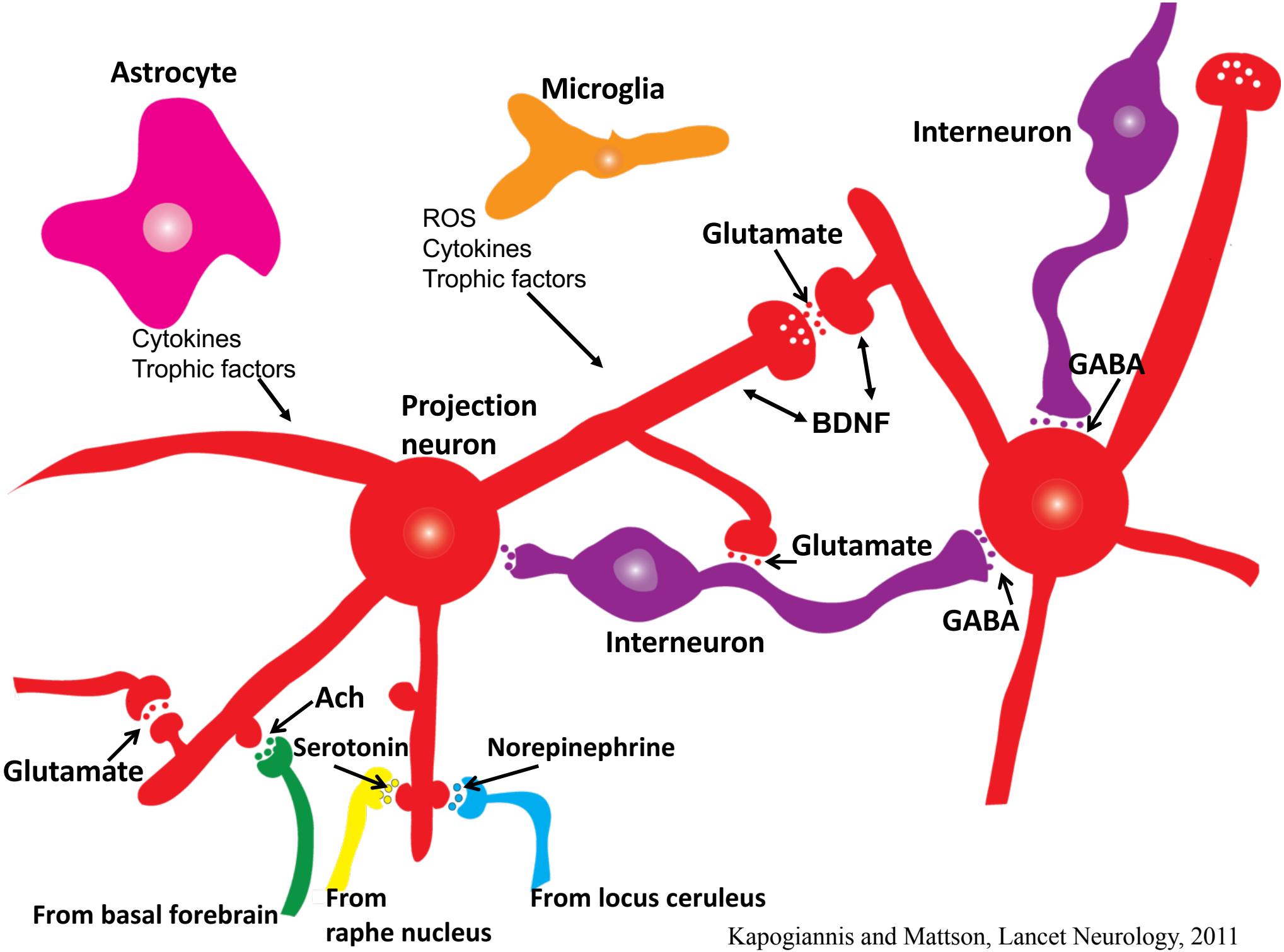








Open Field



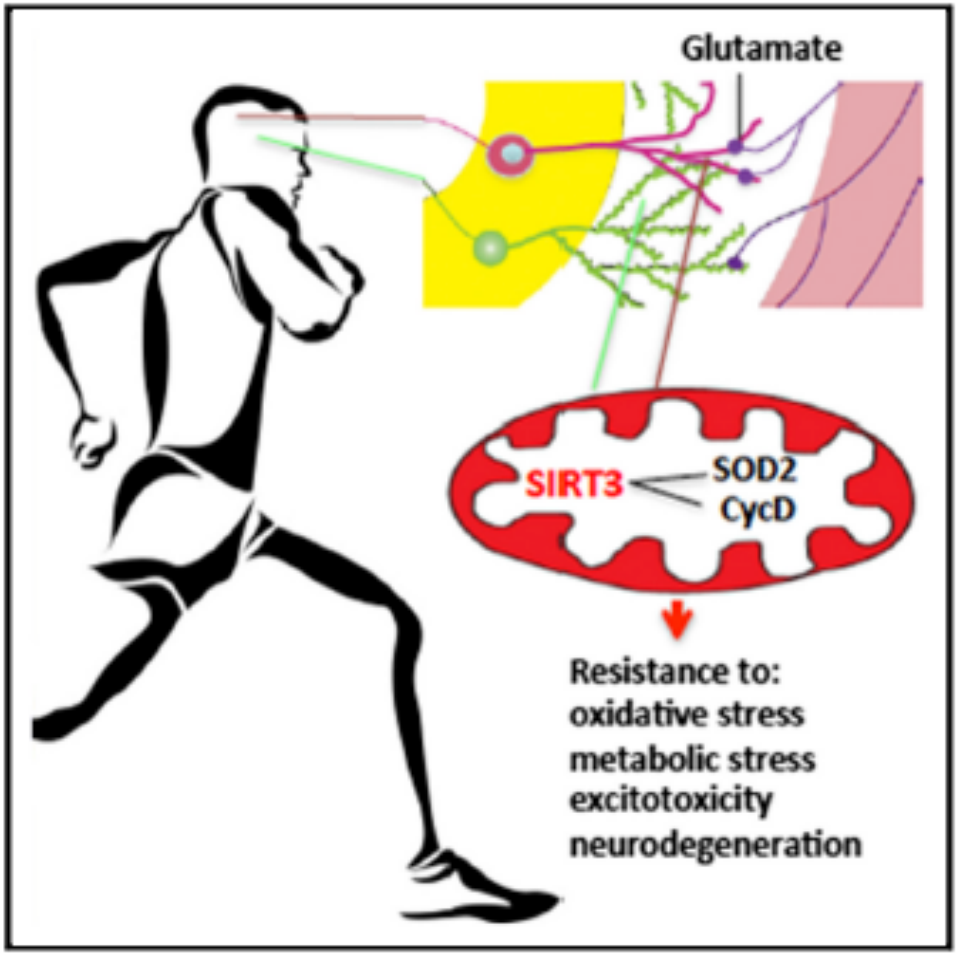
Kapogiannis and Mattson, Lancet Neurology, 2011

Article

Cell Metabolism

Mitochondrial SIRT3 Mediates Adaptive Responses of Neurons to Exercise and Metabolic and Excitatory Challenges

Graphical Abstract



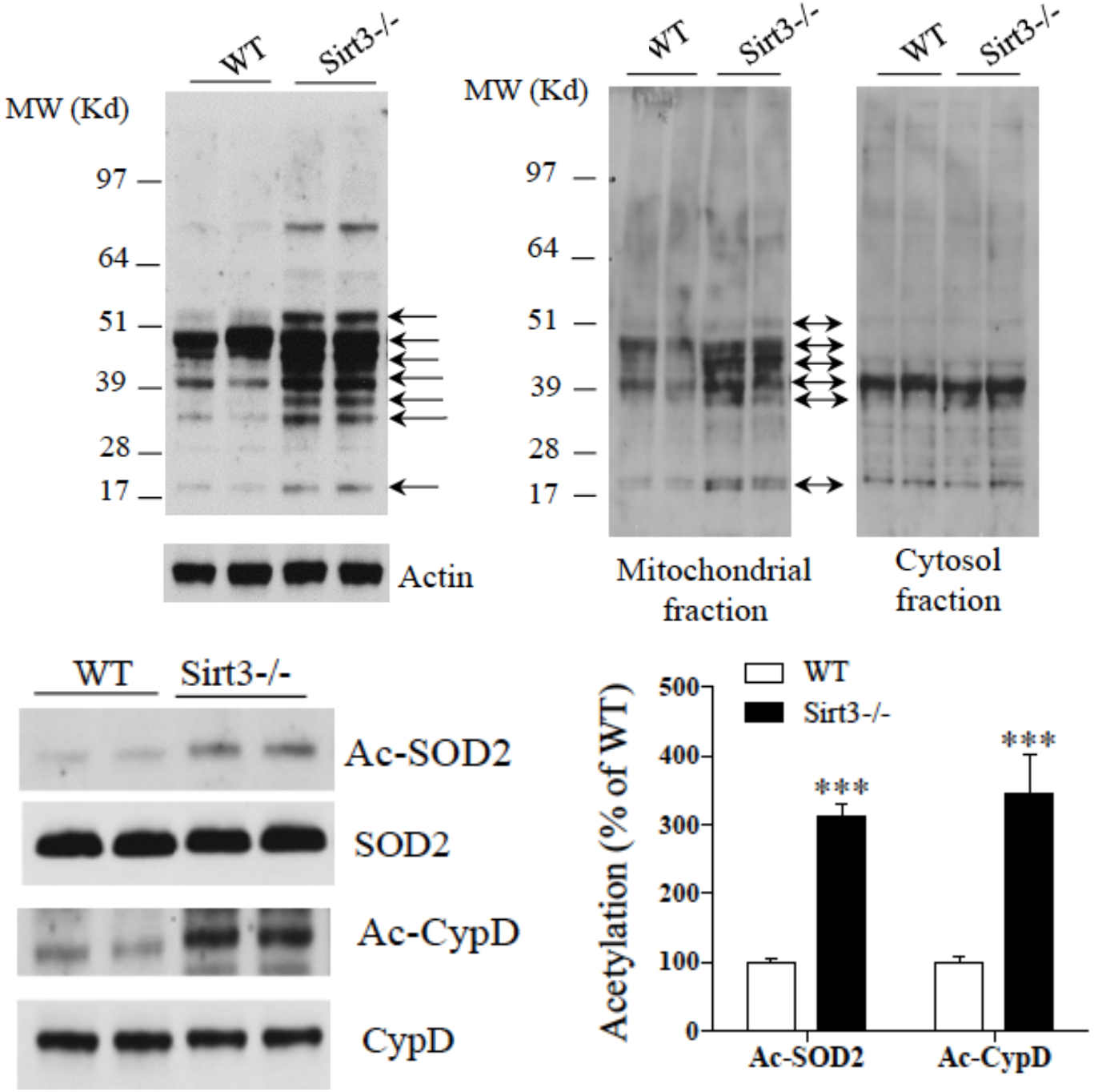
Authors

Aiwu Cheng, Ying Yang, Ye Zhou, ...,
Magdalena Misiak, Vilhelm A. Bohr,
Mark P. Mattson

Highlights

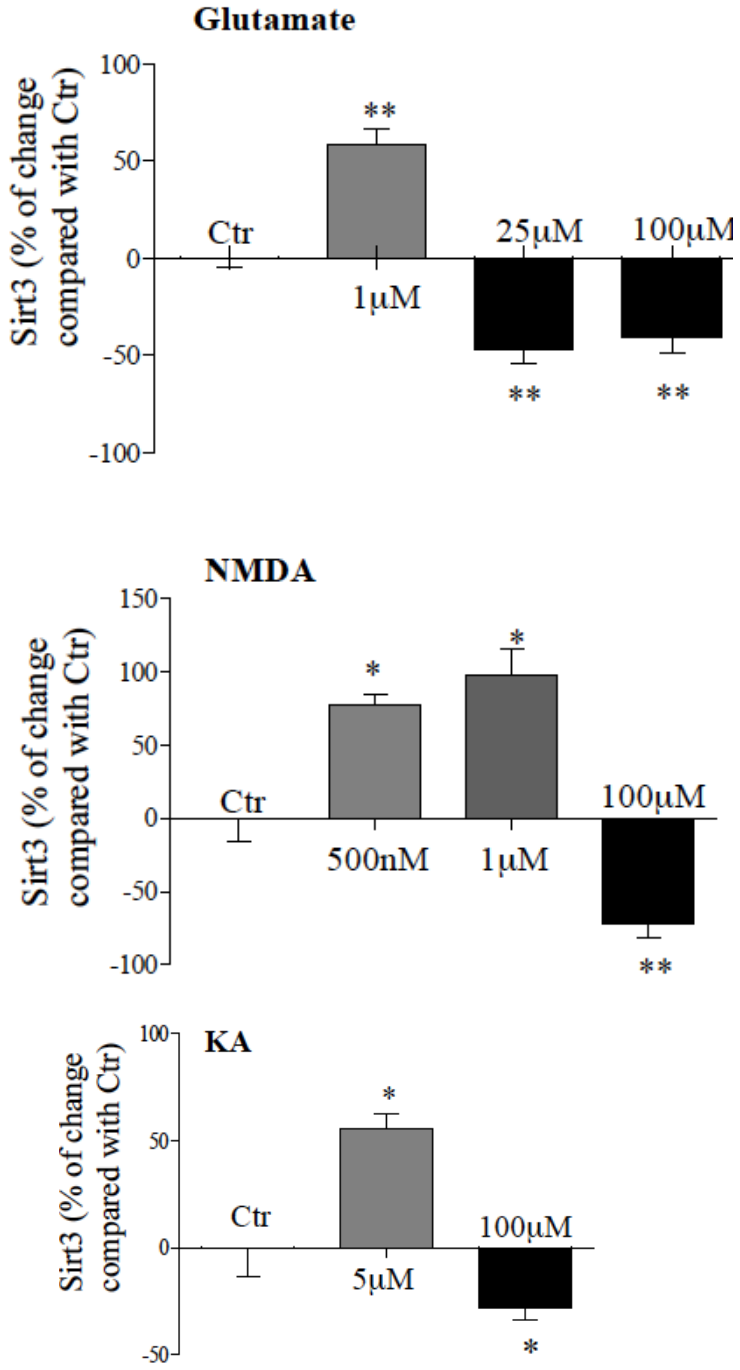
- Exercise and glutamatergic signaling induce SIRT3 expression in cortical neurons
- SIRT3 deacetylates SOD2 and cyclophilin D in neuronal mitochondria
- SIRT3 prevents neuronal death in mouse models of epilepsy and Huntington's disease
- SIRT3 mediates adaptive responses of neurons to excitotoxic and metabolic stress

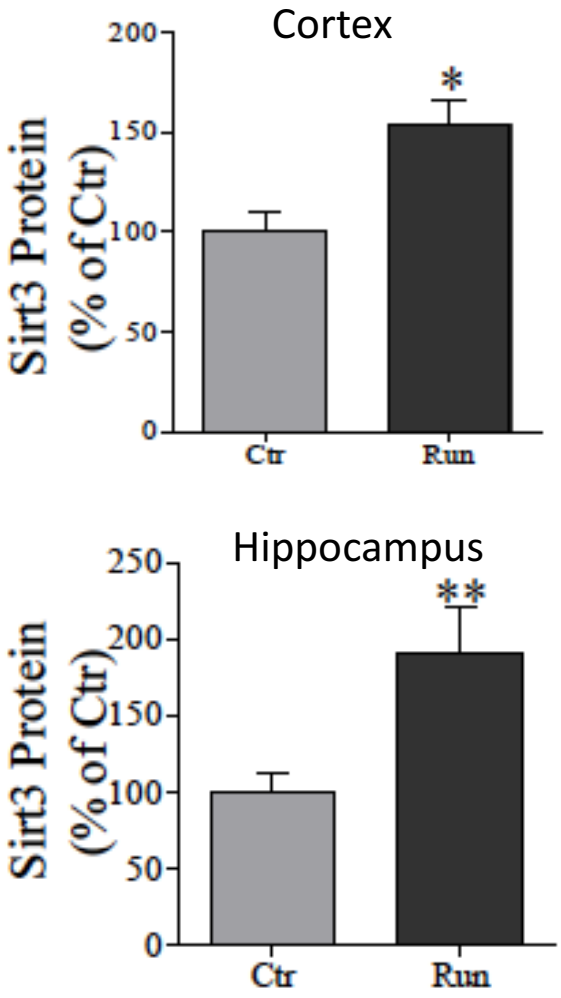
Sirt3 deficiency results in hyperacetylation of mitochondrial proteins including SOD2 and cyclophilin D



Cheng A et al. *Cell Metabolism*. 2016; 23: 128-142

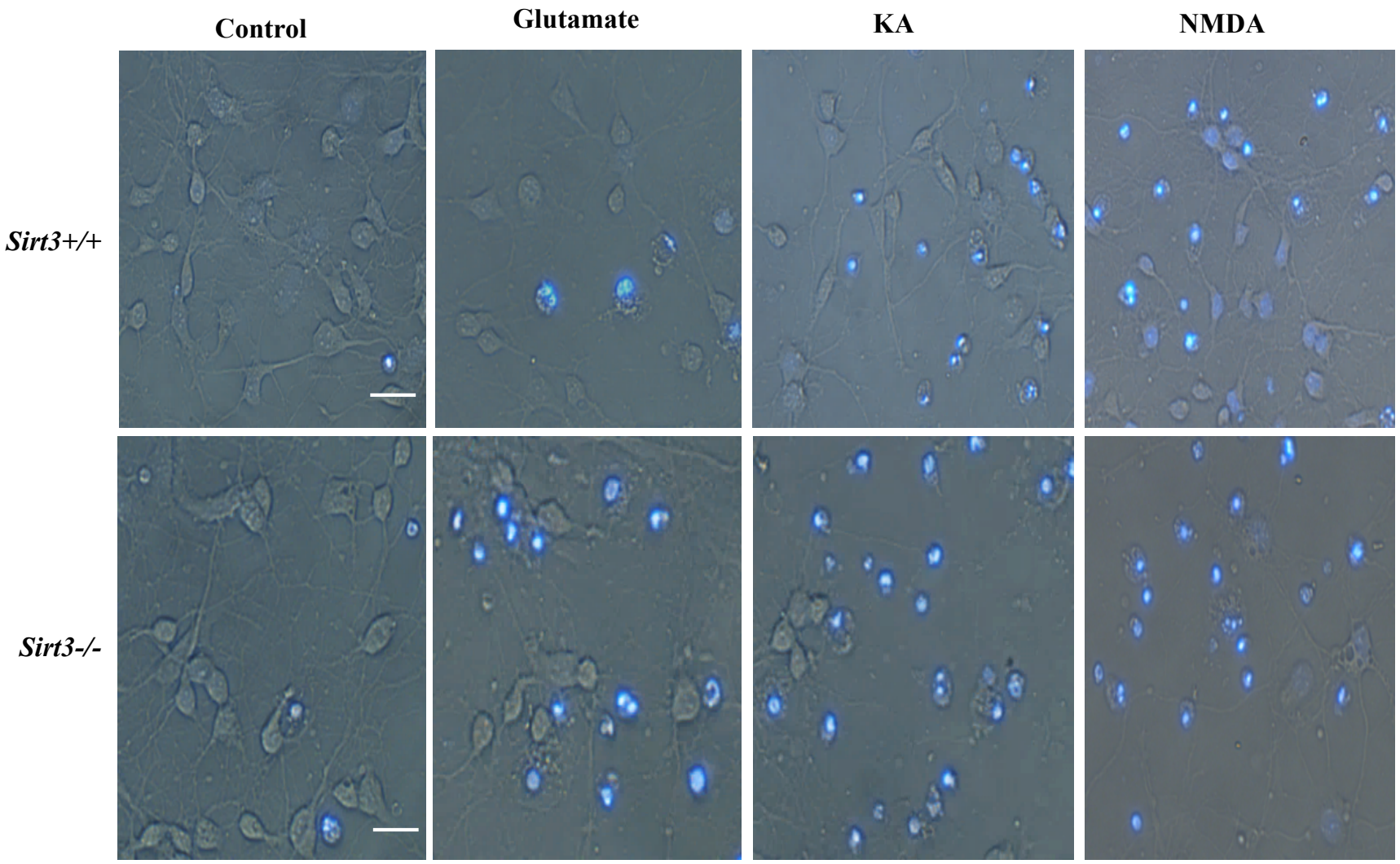
Glutamate receptor activation and running wheel exercise increase Sirt3 expression in brain cells



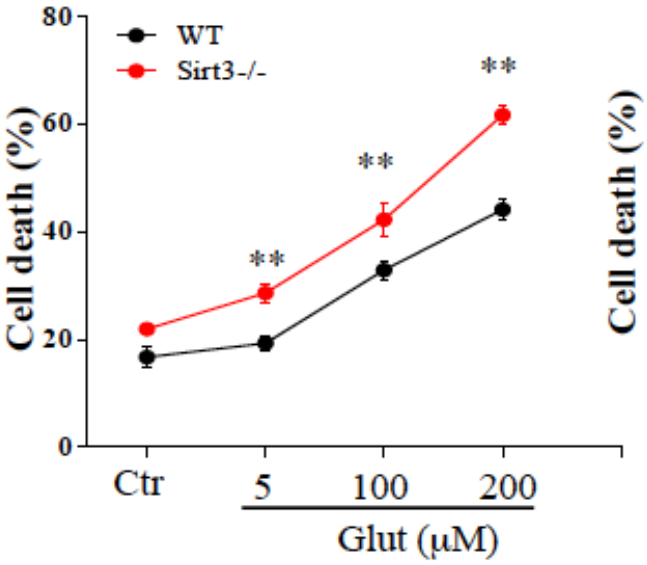


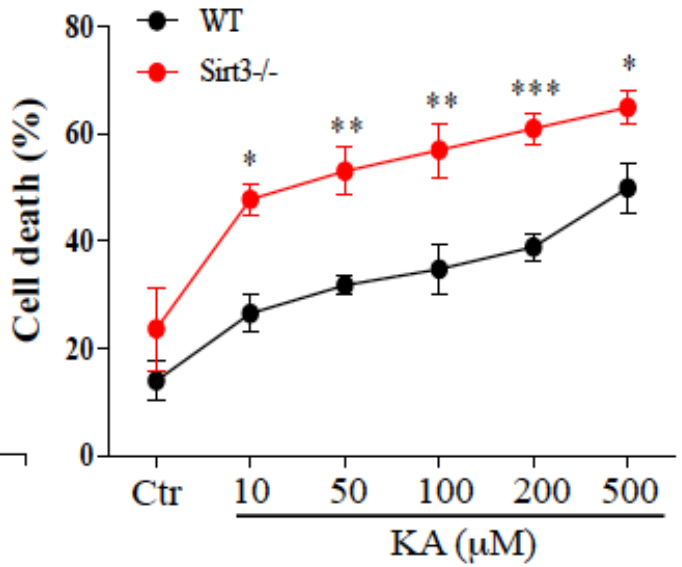
Cheng A et al. *Cell Metabolism*. 2016; 23: 128-142

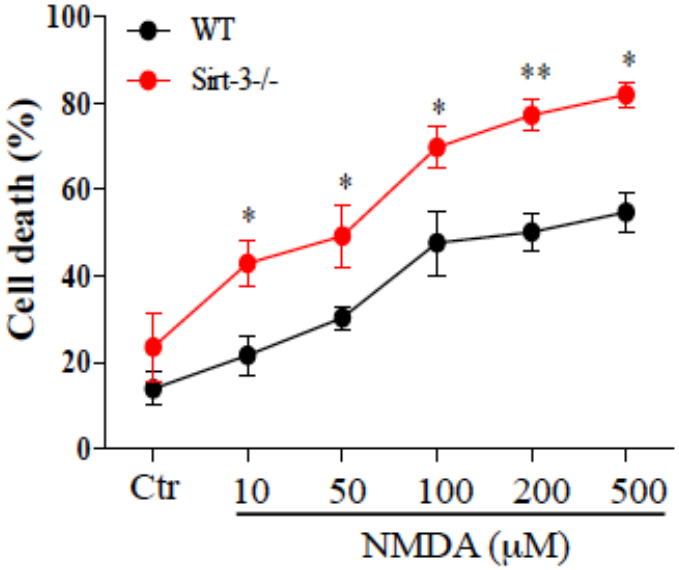
Sirt3 protects neurons against excitotoxicity

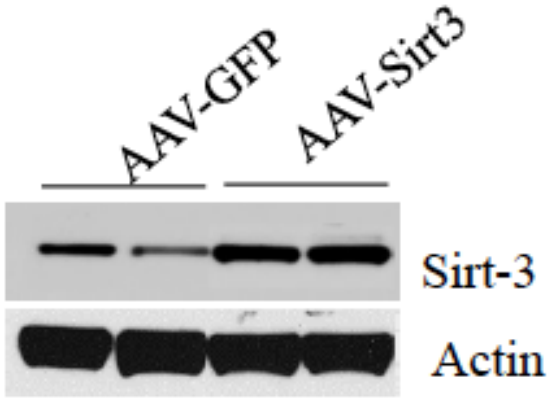


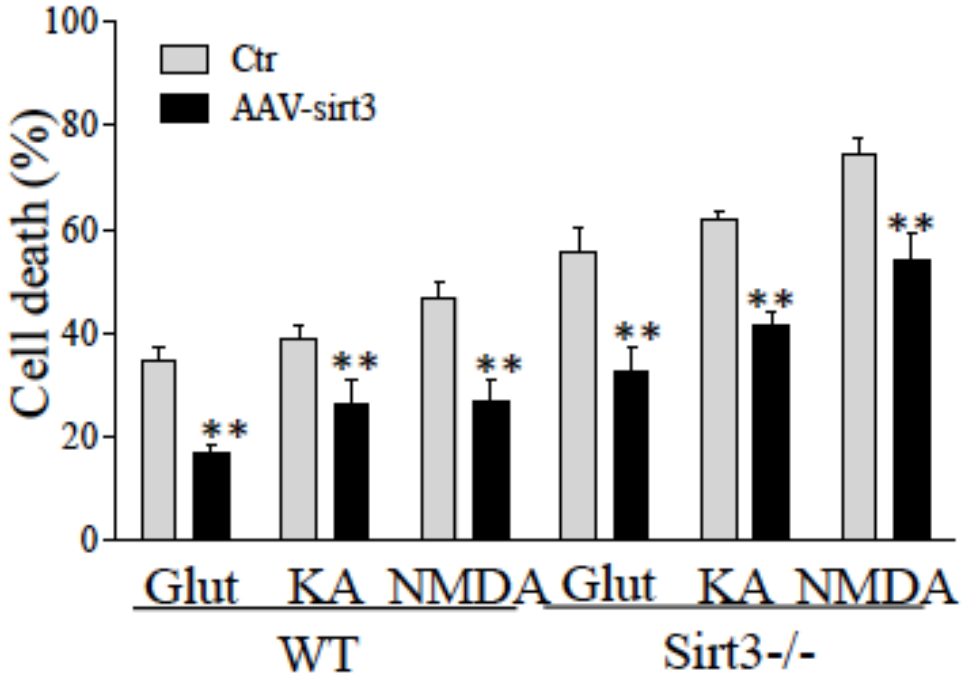
Sirt3 protects neurons against excitotoxicity



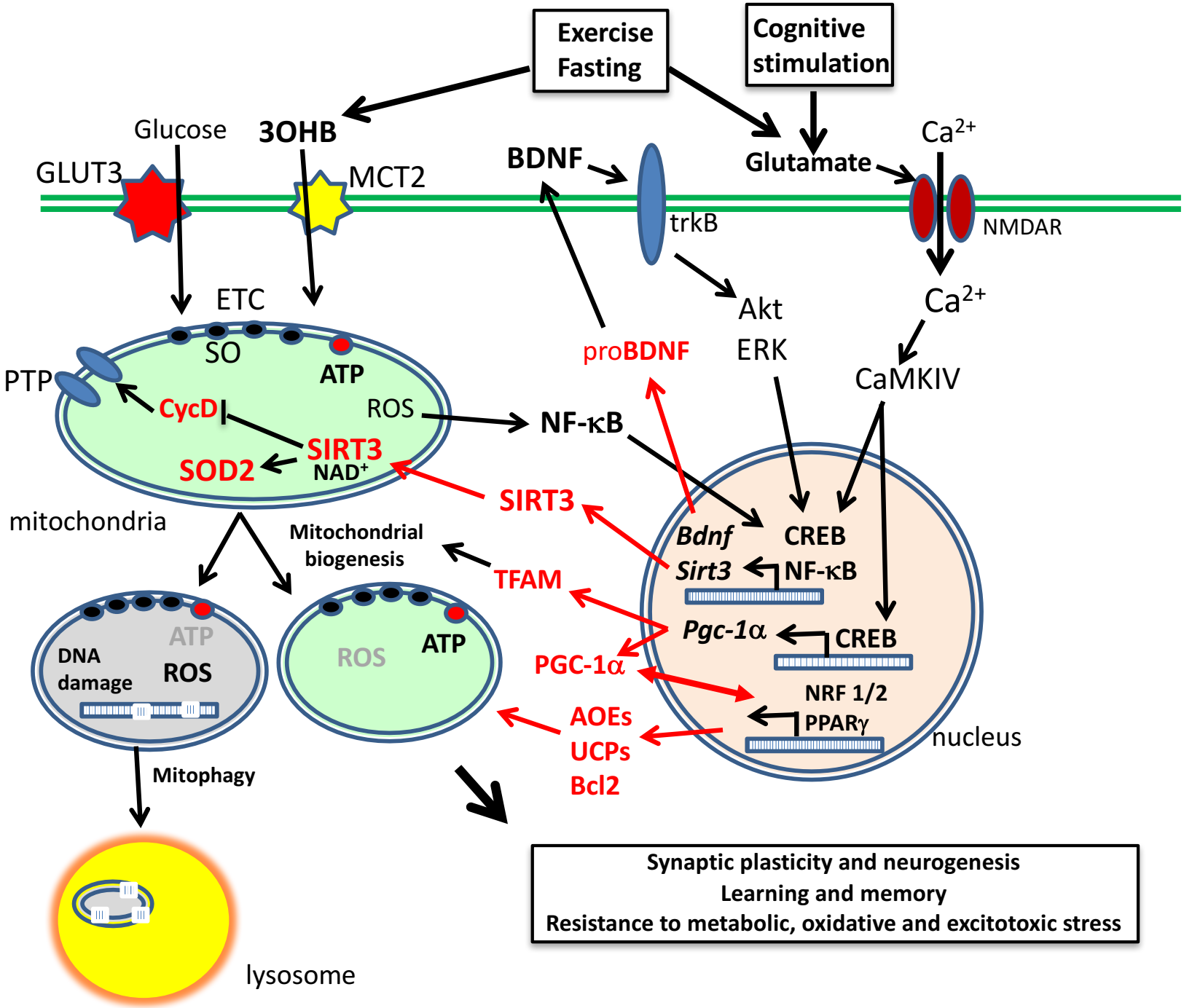




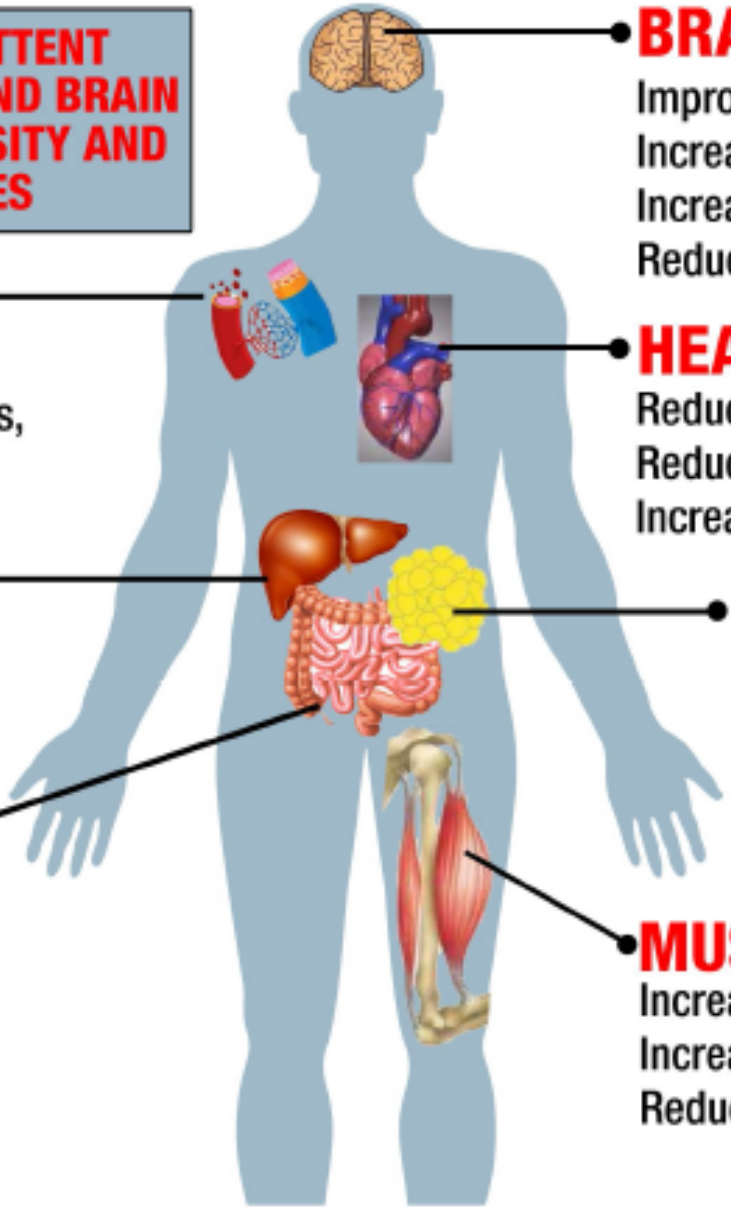




Cheng A et al. *Cell Metabolism*. 2016; 23: 128-142


Exercise
Fasting
Cognitive stimulation
Glucose
3OHB
BDNF
Glutamate
Ca2+
GLUT3
MCT2
trkB
NMDAR
ETC
Akt
ERK
Ca2+
proBDNF
CaMKIV
PTP
SO
ATP
ROS
CycD
SIRT3
SOD2
NAD+
NF-κB
mitochondria
SIRT3
Mitochondrial biogenesis
Bdnf
CREB
Sirt3
NF-κB
TFAM
Pgc-1α
CREB
PGC-1α
NRF 1/2
PPARγ
AOEs
UCPs
Bcl2
nucleus
DNA damage
ATP
ROS
ROS
ATP
Mitophagy
lysosome
Synaptic plasticity and neurogenesis
Learning and memory
Resistance to metabolic, oxidative and excitotoxic stress

EFFECTS OF INTERMITTENT FASTING ON THE BODY AND BRAIN THAT MAY THWART OBESITY AND CHRONIC DISEASES



BRAIN
Improved cognitive function
Increased neurotrophic factors
Increased stress resistance
Reduced inflammation

BLOOD
Decreased insulin, IGF-1 and leptin. Increased ketones, adiponectin and ghrelin.

HEART
Reduced resting heart rate
Reduced blood pressure
Increased stress resistance

LIVER
Increased insulin sensitivity
Ketone body production
Decreased IGF-1 levels

FAT CELLS
Lipolysis
Reduced leptin
Increased adiponectin
Reduced inflammation

INTESTINES
Reduced energy uptake
Reduced inflammation
Reduces cell proliferation

MUSCLE
Increased insulin sensitivity
Increased efficiency
Reduced inflammation

IF Promotes Fat 'Burning' and the Production of Beneficial Ketones

INTERMITTENT FASTING AND HEALTH: HUMAN STUDIES

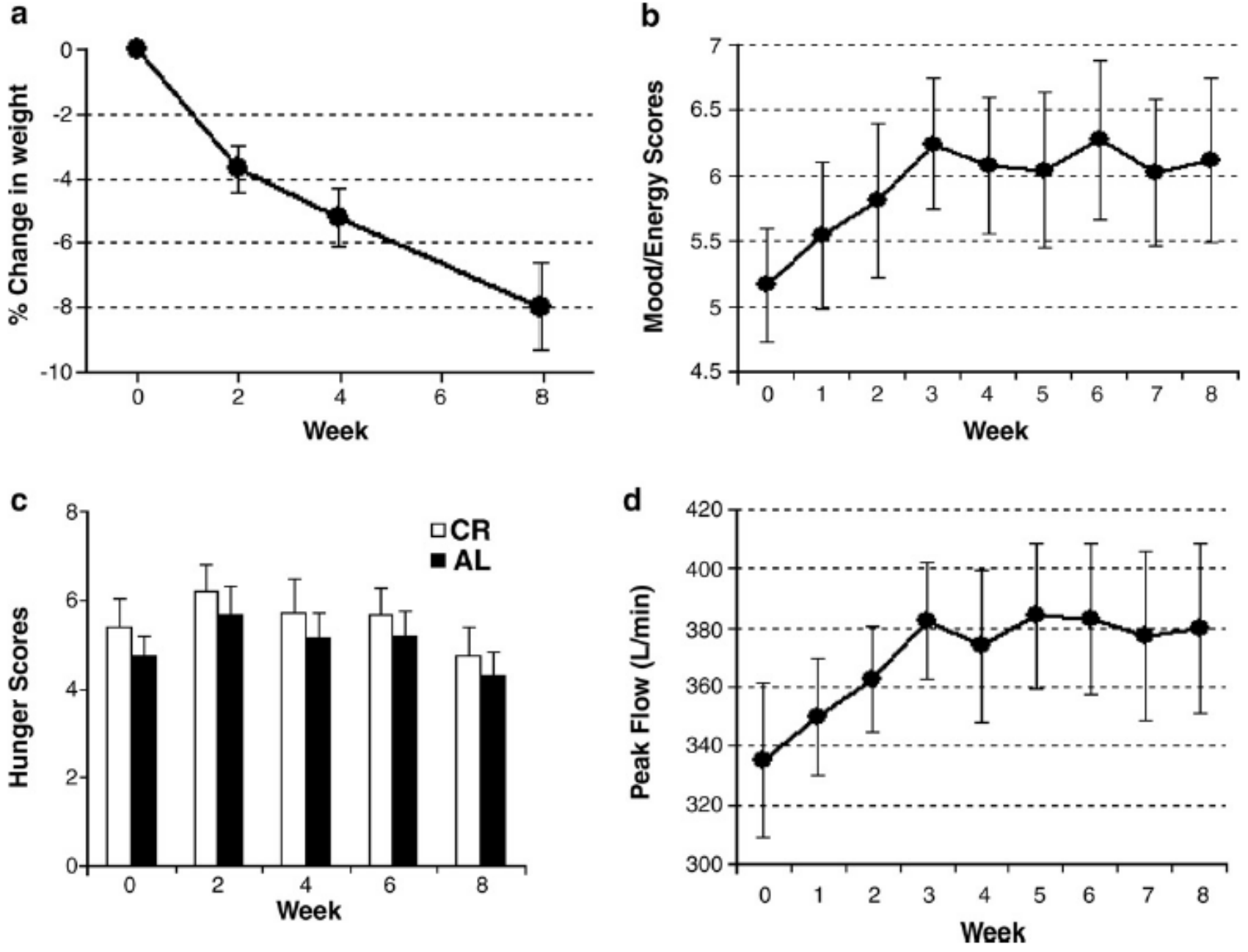
Johnson, J. B., W. Summer, R. G. Cutler, B. Martin, D. H. Hyun, V. D. Dixit, M. Pearson, M. Nassar, S. Maudsley, O. Carlson, S. John, D. R. Laub and M. P. Mattson (2007) Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Rad. Biol. Med.* 42: 665-674.

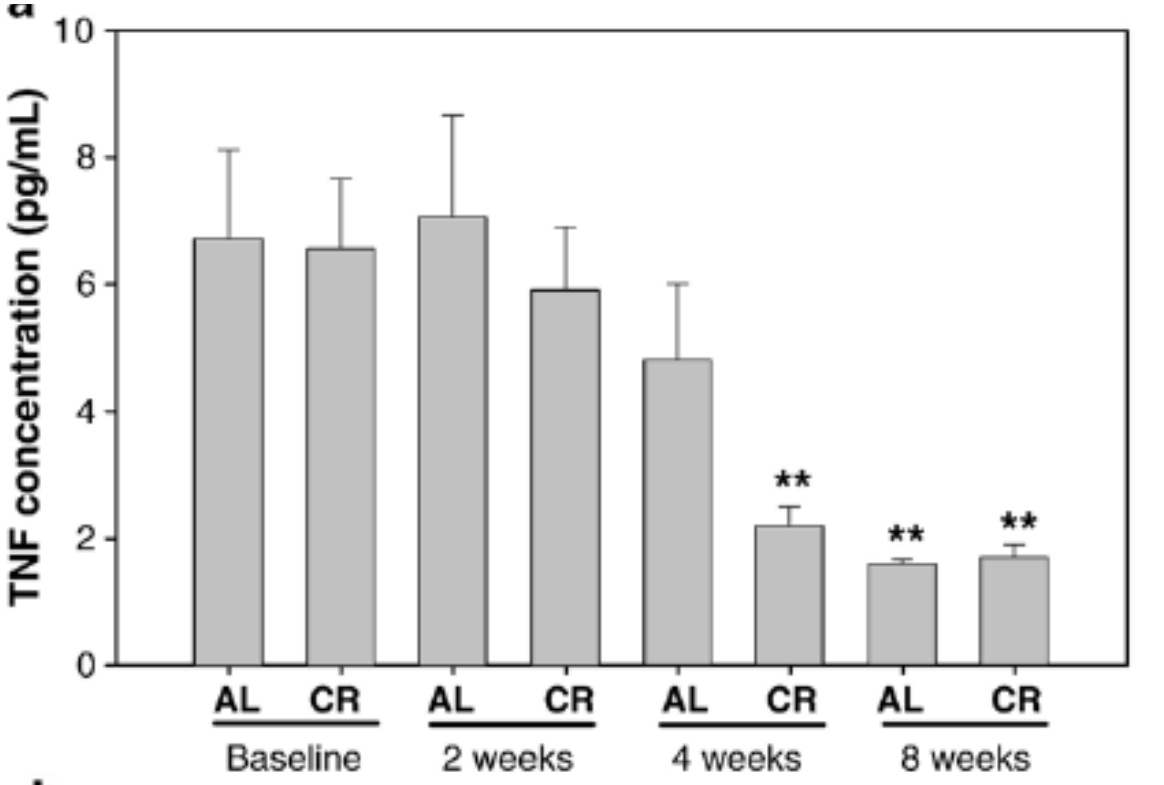
Harvie, M. N., M. Pegington, M. P. Mattson, J. Frystyk, B. Dillon, G. Evans, J. Cuzick, S. Jebb, B. Martin, R. G. Cutler, T. G. Son, S. Maudsley, O. D. Carlson, J. M. Egan, A. Flyvbjerg and A. Howell (2010) The effects of intermittent and continuous energy restriction on weight loss, and metabolic disease risk markers: a randomized trial in young overweight women. *Int. J. Obesity.* 35: 714-727.

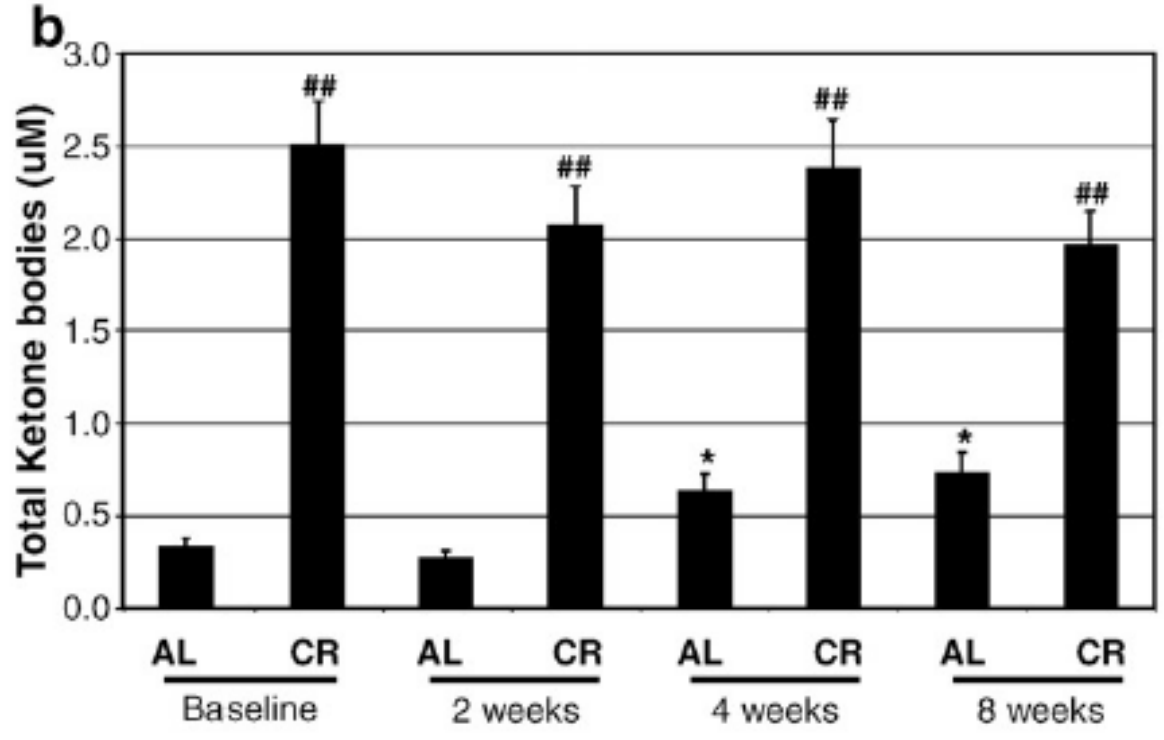
A TRIAL OF INTERMITTENT FASTING SUBJECTS AT RISK FOR COGNITIVE IMPAIRMENT (active). Dimitrios Kapogianis et al.

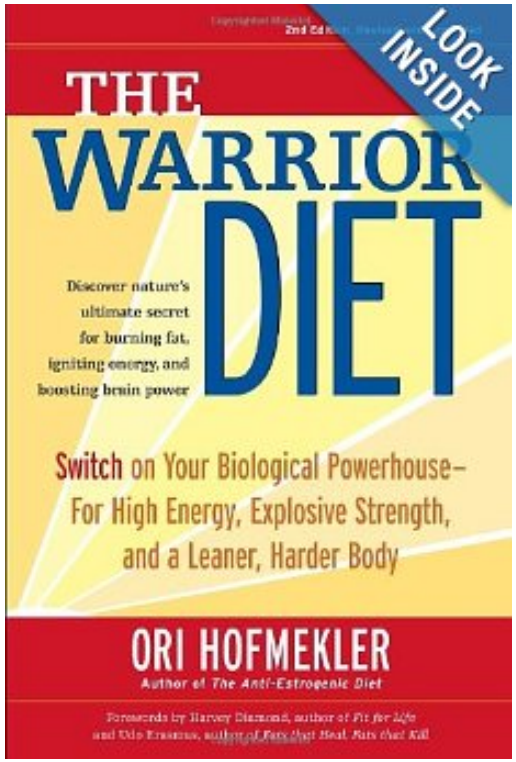
Ages 55 – 70. Overweight and insulin resistant.
Cognitive testing – executive function
Structural and functional MRI (regional volumes, DMN, executive function circuits)
MRS spectroscopy – GABA, glutamate, energy metabolism markers
Cerebrospinal fluid – BDNF, Aβ, pTau, markers of oxidative stress and inflammation
Plasma energy-regulating hormones and various markers of interest
ANS function – heart rate variability

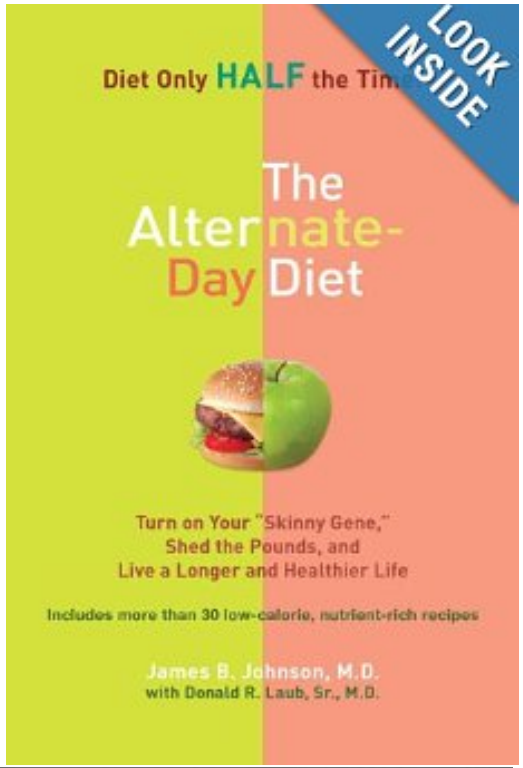
Johnson, J. B., W. Summer, R. G. Cutler, B. Martin, D. H. Hyun, V. D. Dixit, M. Pearson, M. Nassar, S. Maudsley, O. Carlson, S. John, D. R. Laub and **M. P. Mattson** (2007) Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Rad. Biol. Med.* 42: 665-674.

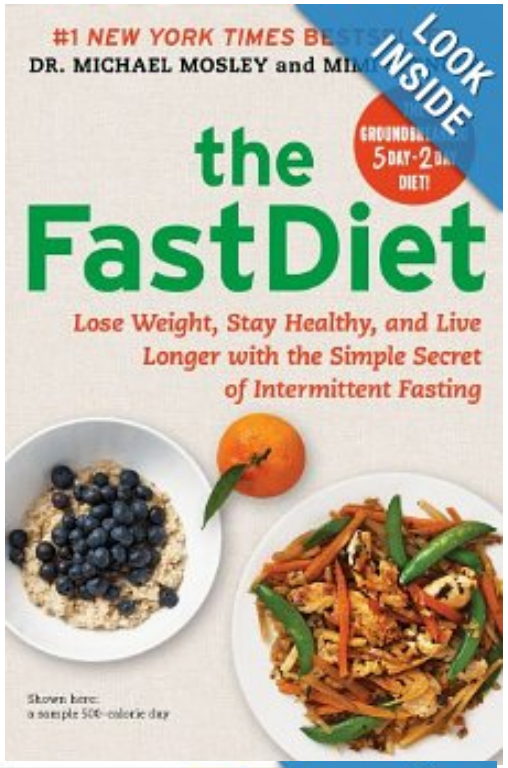


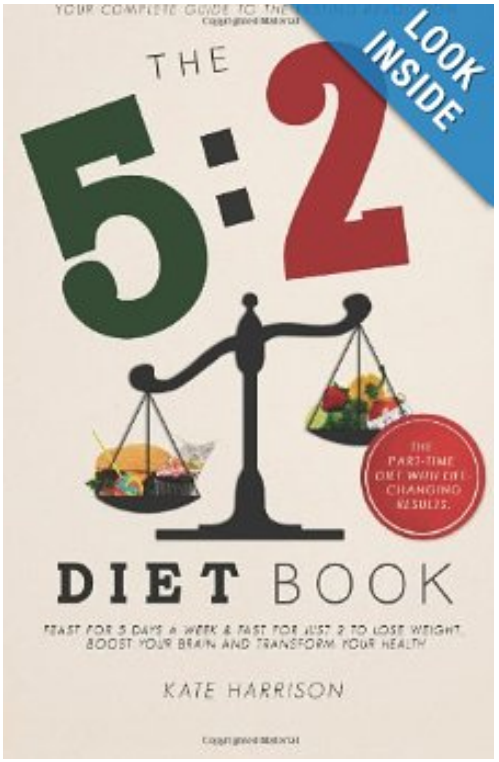

TNF concentration (pg/mL)
10
8
6
4
2
0
**
**
**
AL
CR
AL
CR
AL
CR
AL
CR
Baseline
2 weeks
4 weeks
8 weeks

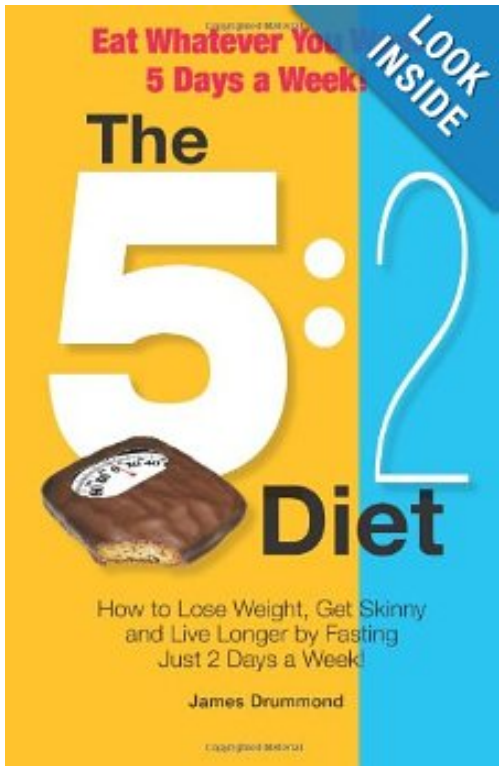

b
Total Ketone bodies (uM)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
##
##
##
##
*
*
AL
CR
AL
CR
AL
CR
AL
CR
Baseline
2 weeks
4 weeks
8 weeks

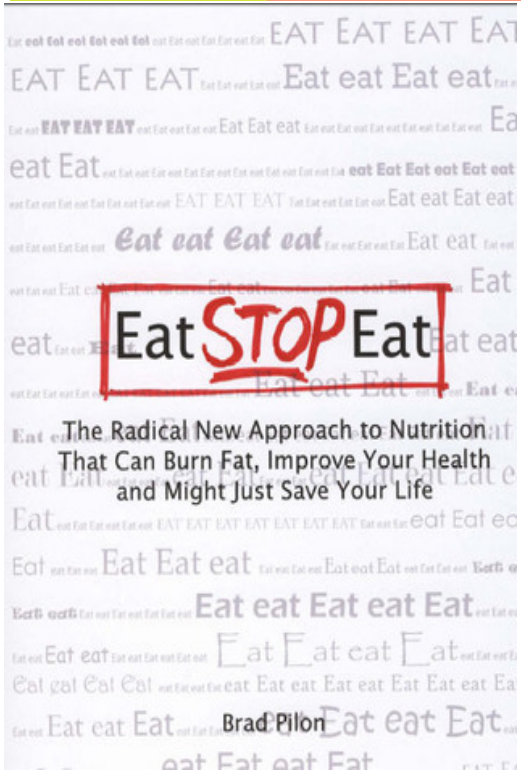

LOOK INSIDE
THE WARRIOR DIET
Discover nature's ultimate secret for burning fat, igniting energy, and boosting brain power
Switch on Your Biological Powerhouse– For High Energy, Explosive Strength, and a Leaner, Harder Body
ORI HOFMEKLER
Author of The Anti-Estrogenic Diet

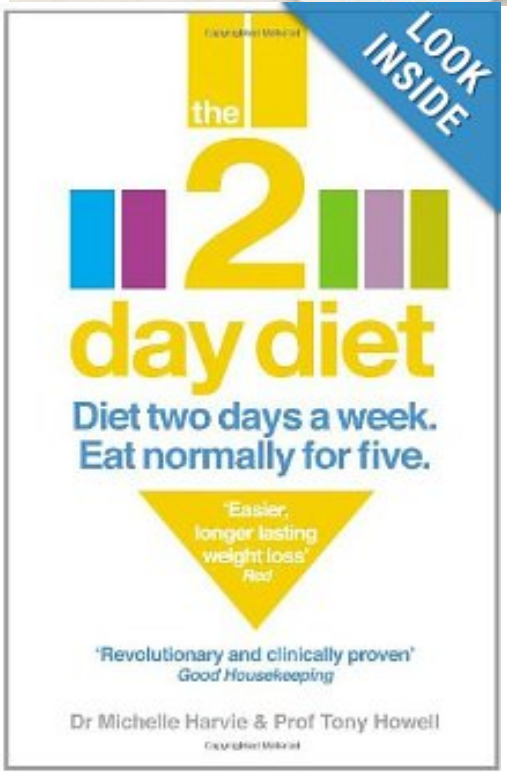

LOOK INSIDE
Diet Only HALF the Tim
The Alternate-Day Diet
Turn on Your "Skinny Gene," Shed the Pounds, and Live a Longer and Healthier Life
Includes more than 30 low-calorie, nutrient-rich recipes
James B. Johnson, M.D.
with Donald R. Laub, Sr., M.D.


LOOK INSIDE
#1 NEW YORK TIMES BE
DR. MICHAEL MOSLEY and MI
the FastDiet
Lose Weight, Stay Healthy, and Live Longer with the Simple Secret of Intermittent Fasting


LOOK INSIDE
THE
5:2
DIET BOOK
KATE HARRISON


LOOK INSIDE
Eat Whatever You
5 Days a Week
The 5:2 Diet
How to Lose Weight, Get Skinny and Live Longer by Fasting Just 2 Days a Week!
James Drummond


Eat STOP Eat
The Radical New Approach to Nutrition That Can Burn Fat, Improve Your Health and Might Just Save Your Life
Brad Pilon


LOOK INSIDE
the 2 day diet
Diet two days a week. Eat normally for five.
'Easier, longer lasting weight loss' Red
'Revolutionary and clinically proven' Good Housekeeping
Dr Michelle Harvie & Prof Tony Howell

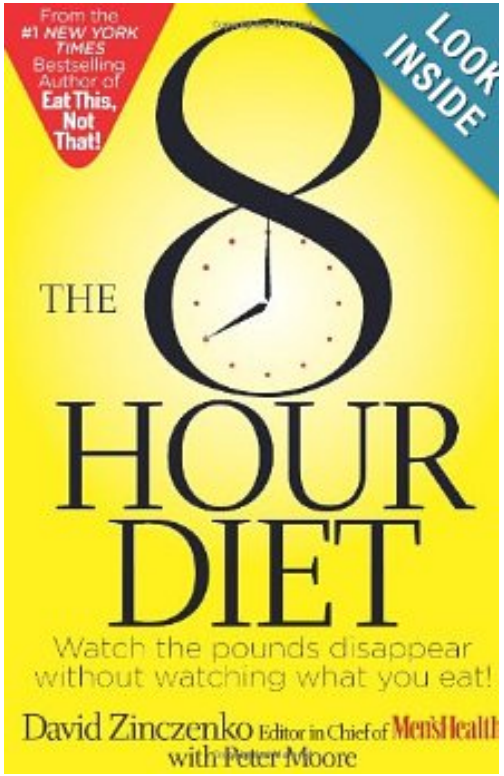
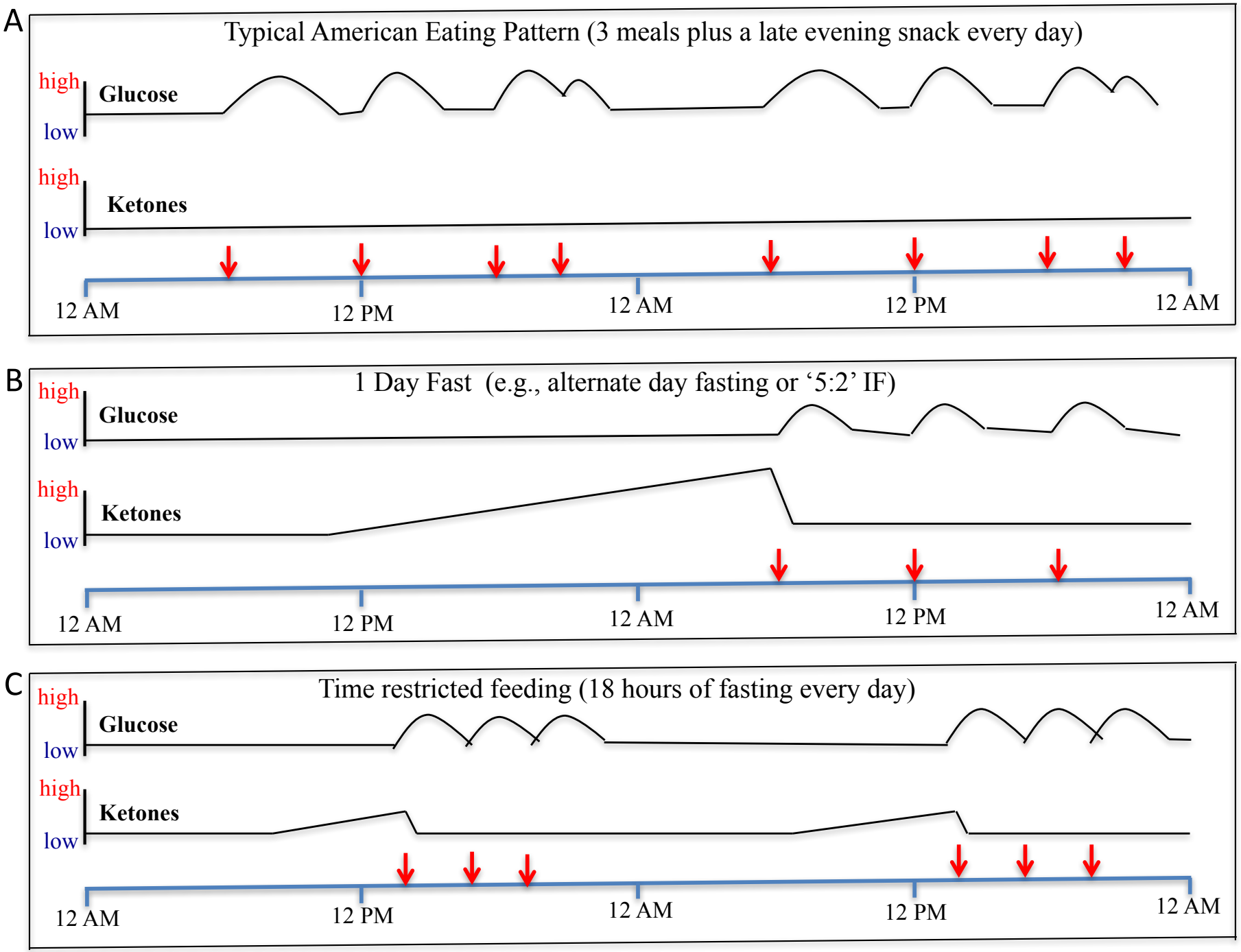
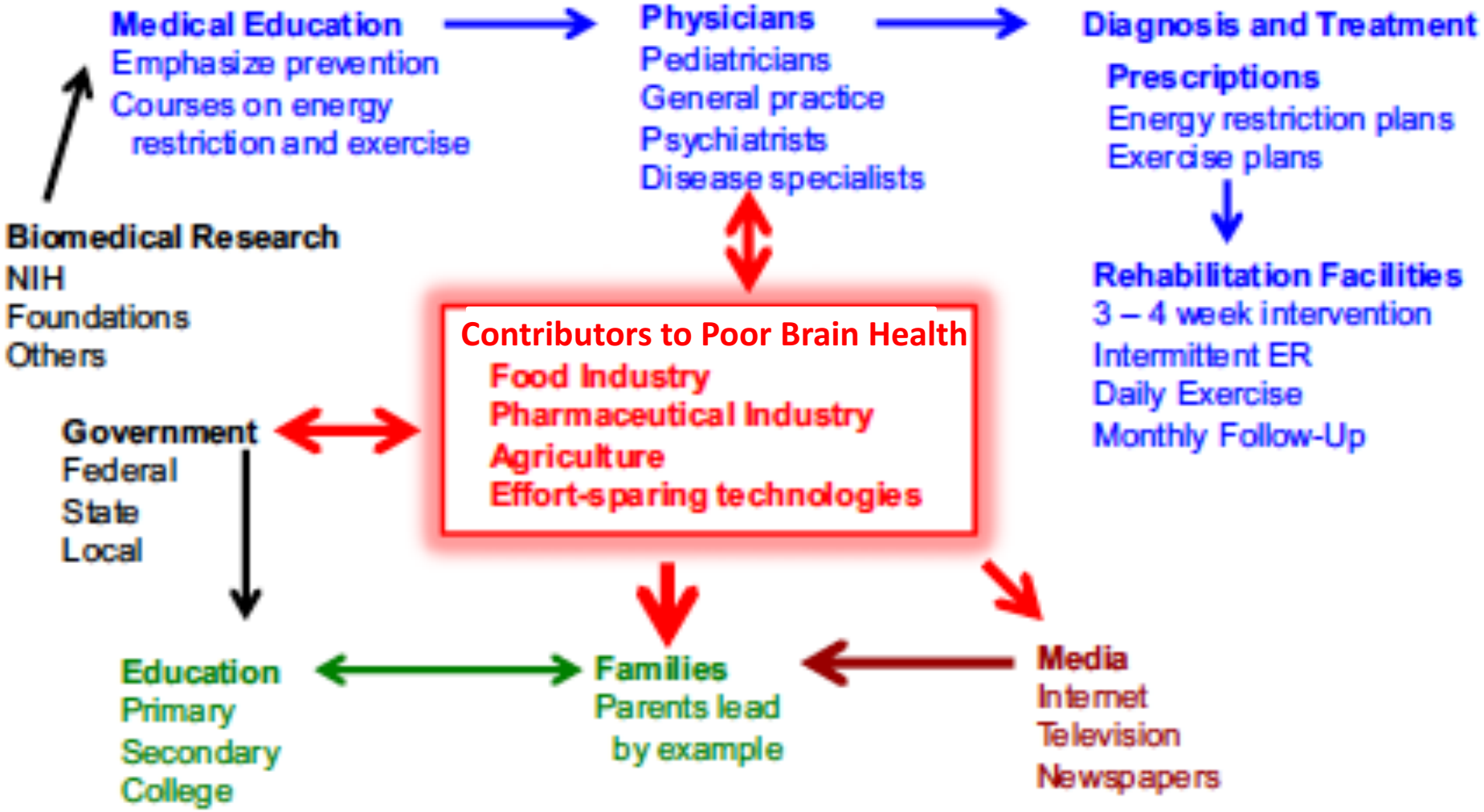

LOOK INSIDE
From the #1 NEW YORK TIMES Bestselling Author of Eat This, Not That!
THE 8 HOUR DIET
Watch the pounds disappear without watching what you eat!
David Zinczenko Editor in Chief of Men's Health
with Peter Moore

Figure 1


A
Typical American Eating Pattern (3 meals plus a late evening snack every day)
high
Glucose
low
high
Ketones
low
12 AM
12 PM
12 AM
12 PM
12 AM
B
1 Day Fast (e.g., alternate day fasting or '5:2' IF)
high
Glucose
low
high
Ketones
low
12 AM
12 PM
12 AM
12 PM
12 AM
C
Time restricted feeding (18 hours of fasting every day)
high
Glucose
low
high
Ketones
low
12 AM
12 PM
12 AM
12 PM
12 AM



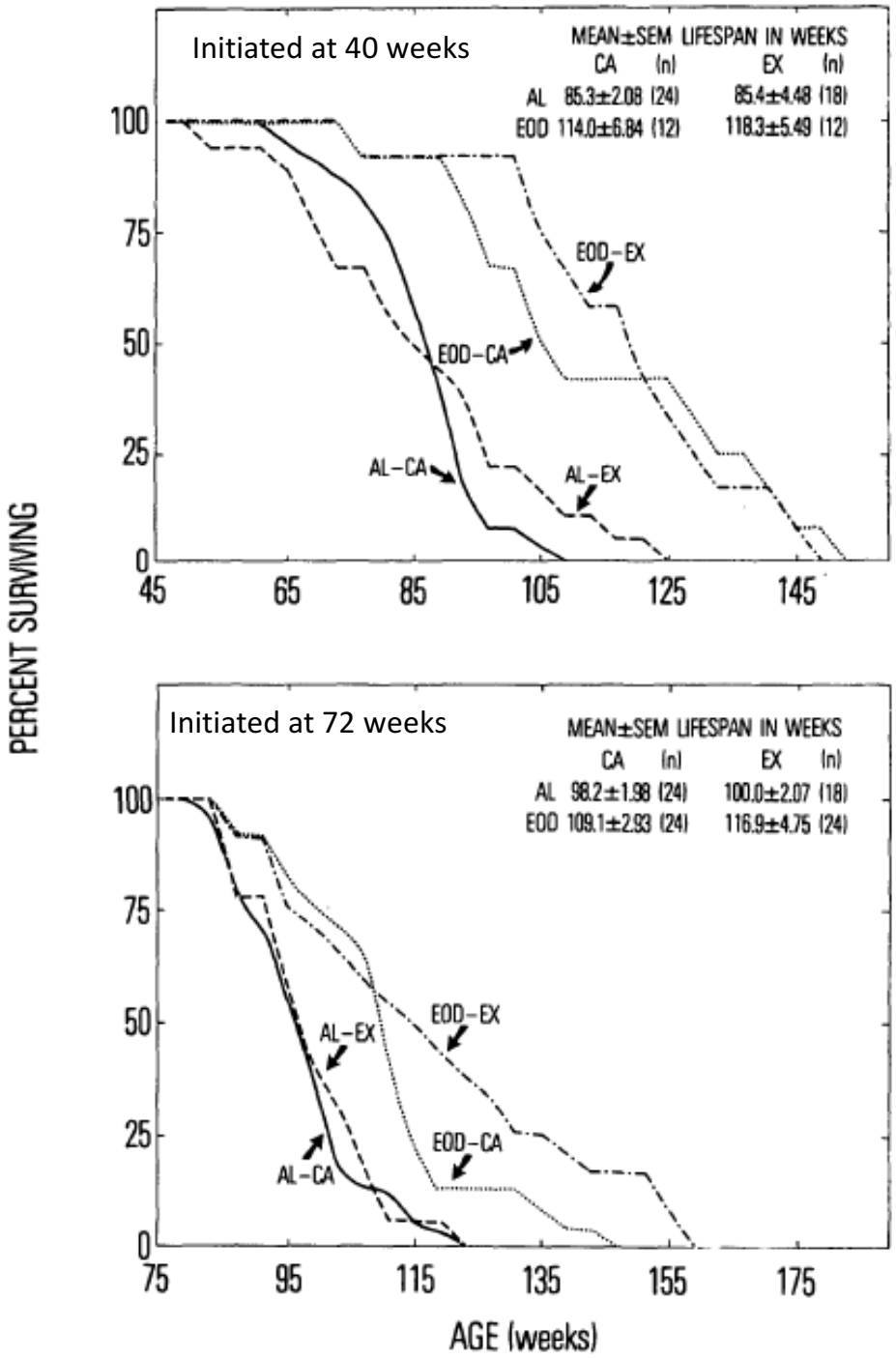
Mattson MP. (2012) Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab. 16:706-722.

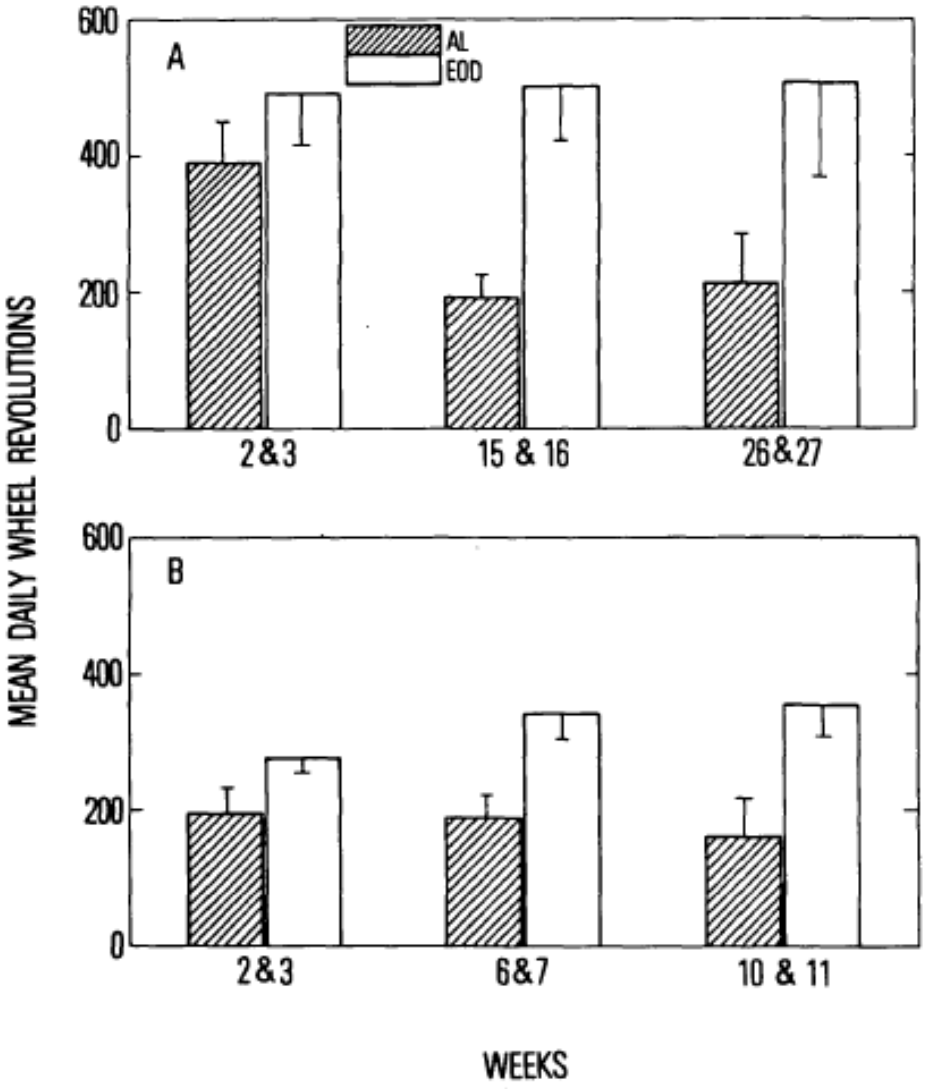
NIA

Thwarting Aging

Slowing the Clock

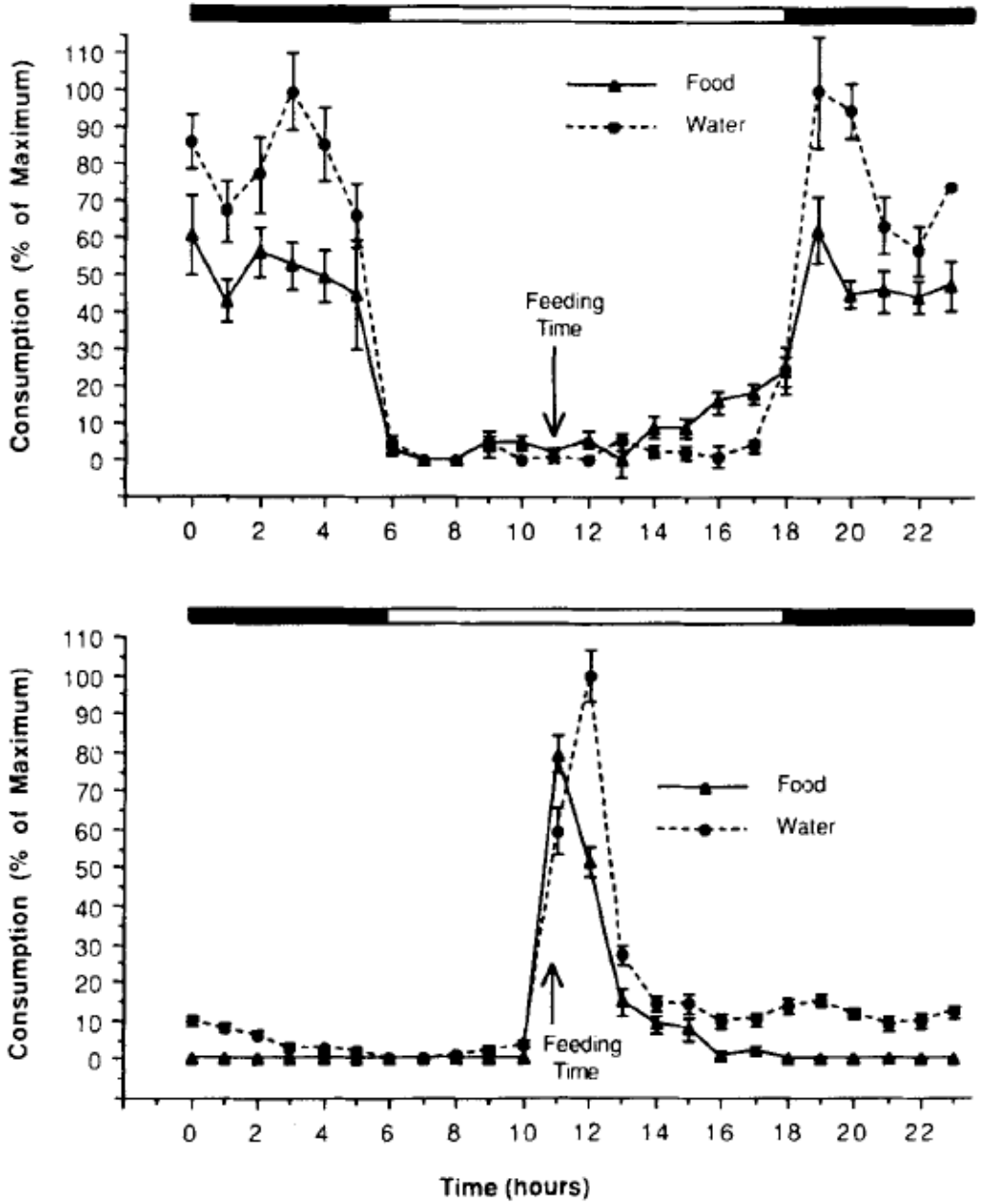
Alternate day fasting extends average and maximum lifespan in Wistar rats, whereas exercise is only modestly beneficial

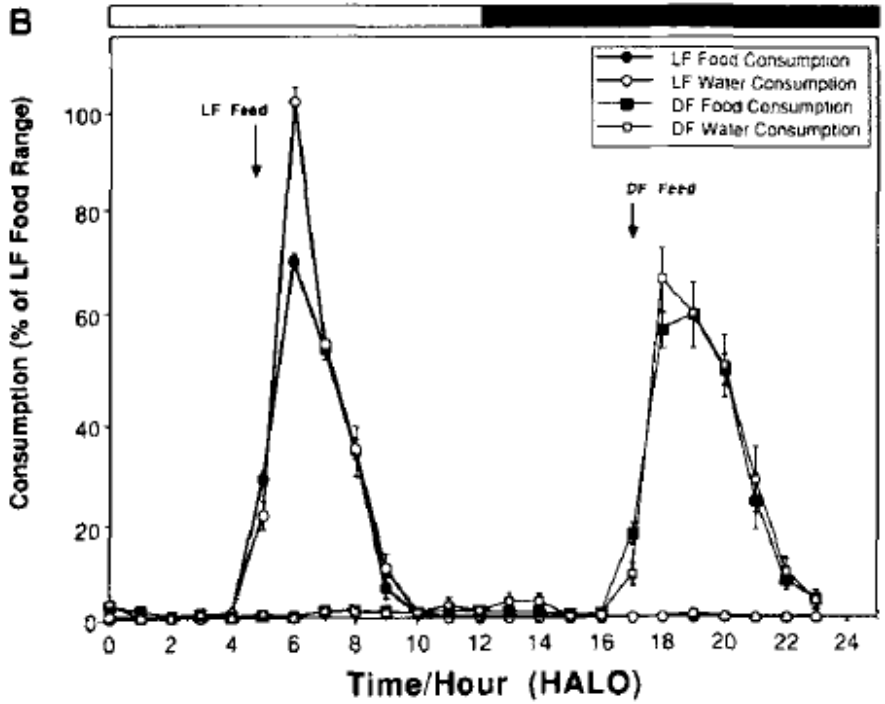


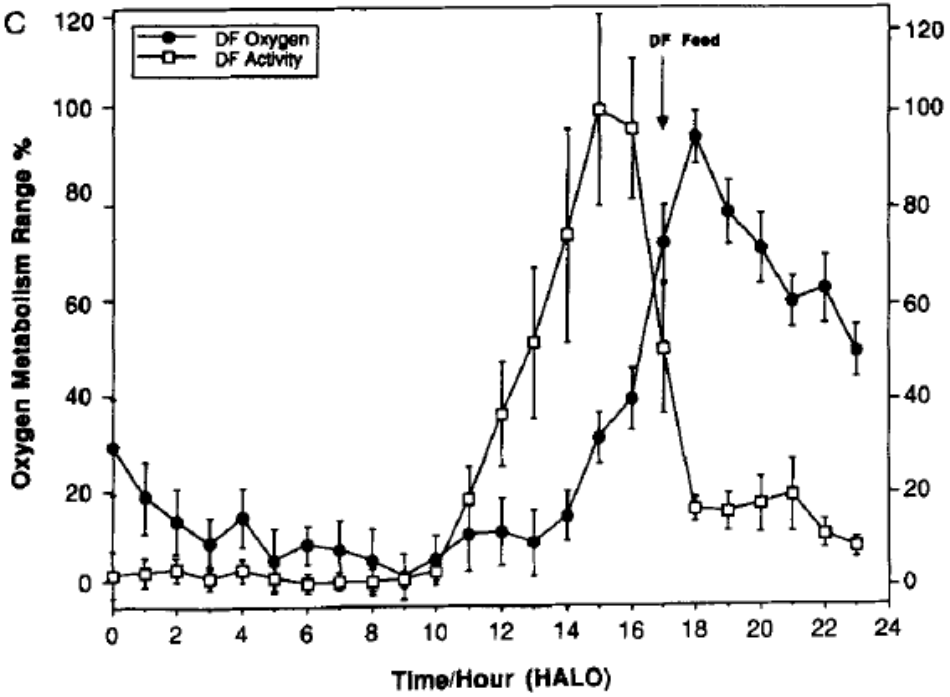


GOODRICK, INGRAM, REYNOLDS, FREEMAN, AND CIDER 1983

When on a 40% caloric restriction diet, rats and mice eat all food within a 4 – 6 hour time window

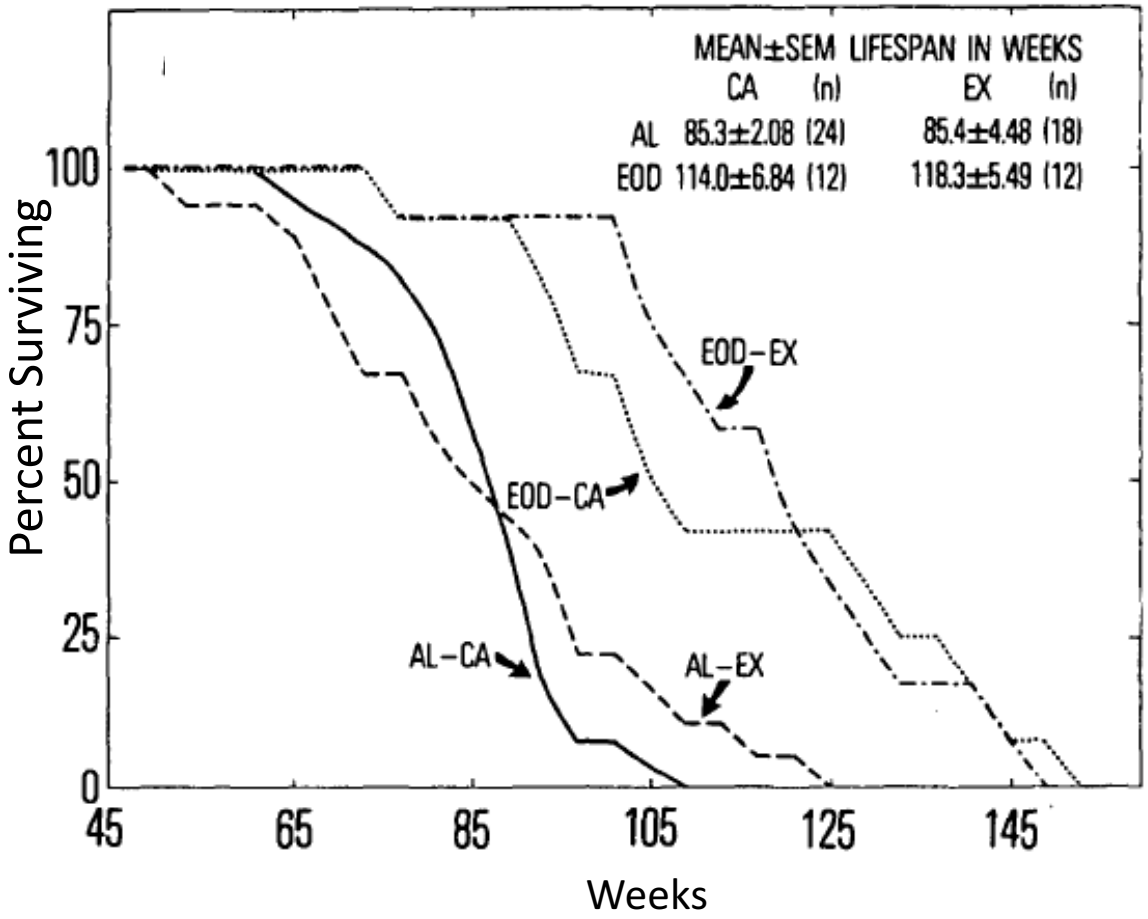


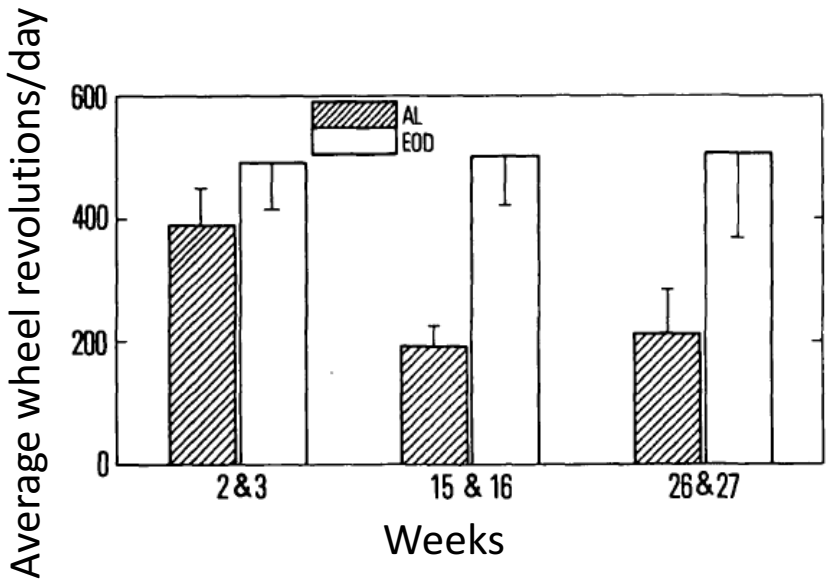


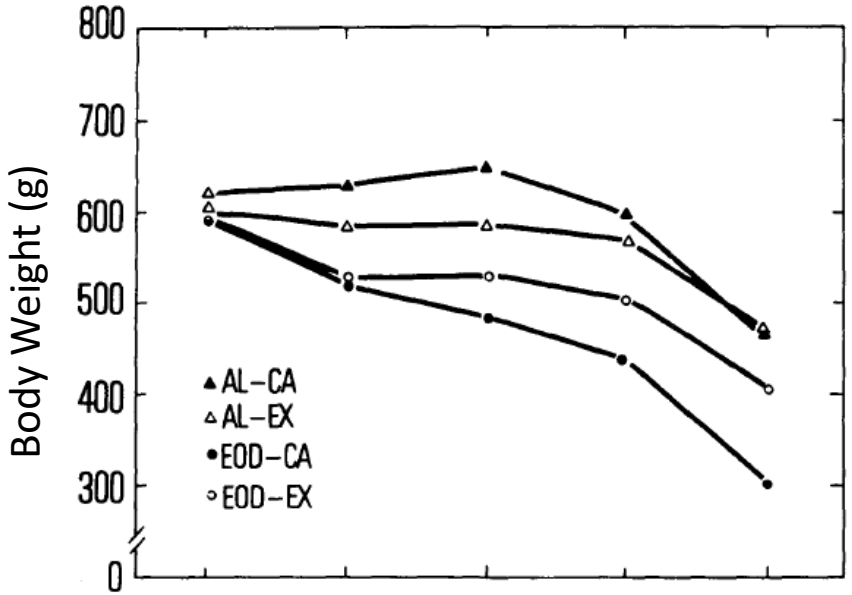


Chronobiology International, Vol. 7. pp. 113–124, 1990
pp. 291–303, 1990

When initiated at 10 months of age, intermittent fasting extends lifespan by 30% in rats



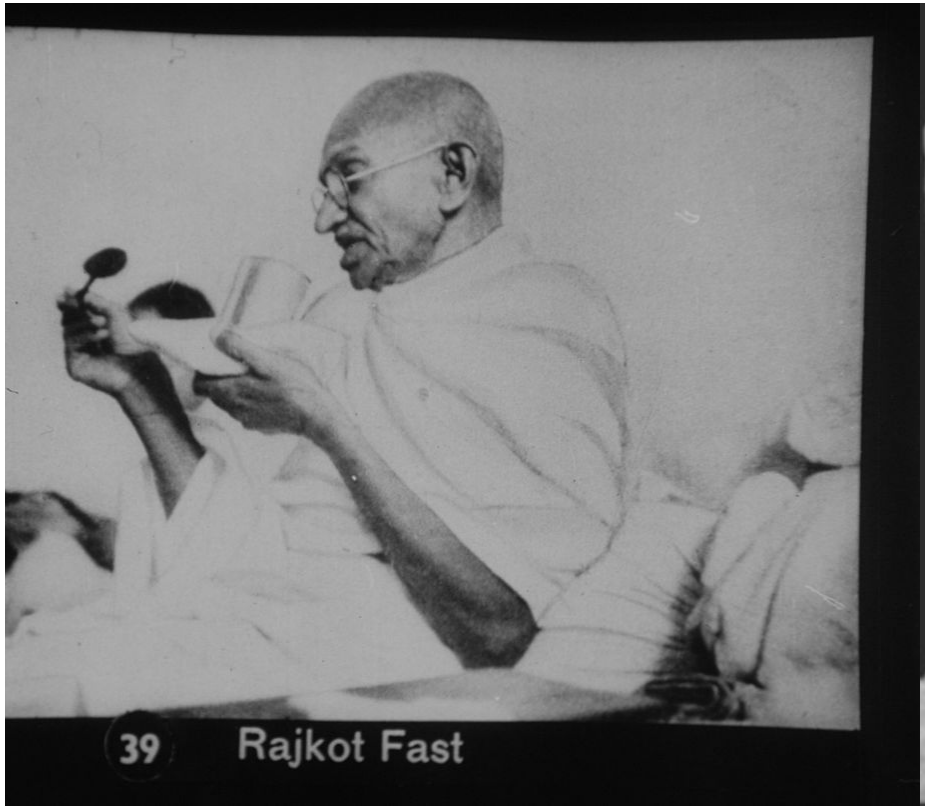


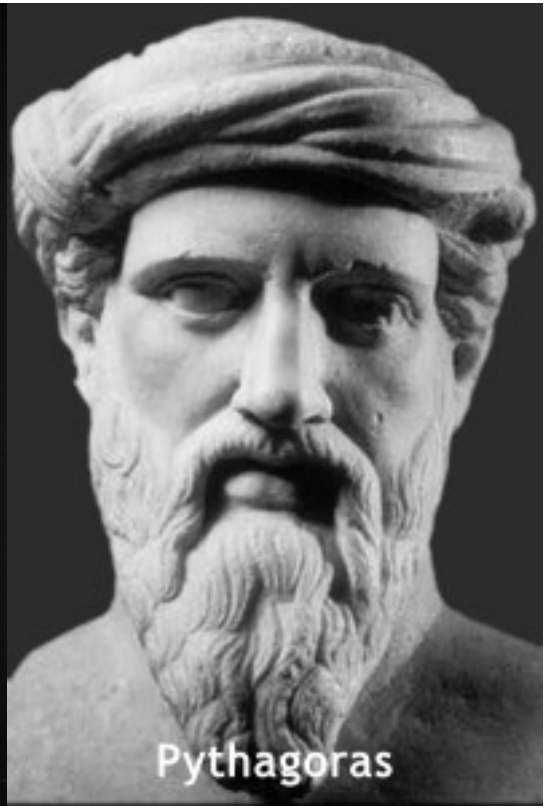


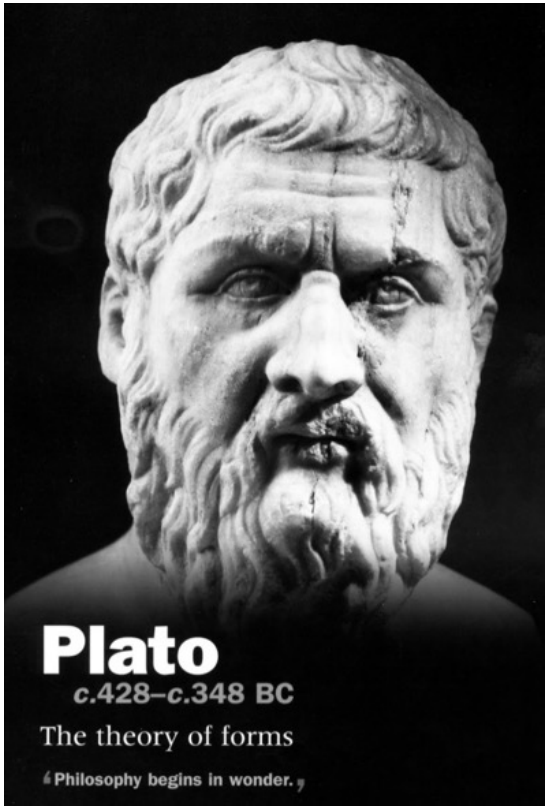
Goodrick et al.

Journal of Gerontology
1983, Vol. 38, No. 1, 36–45

Historical Perspective "I fast for greater physical and mental efficiency." Plato







"Fasting is the greatest remedy-- the physician within."

Philippus Paracelsus, one of the three fathers of Western medicine

"A little starvation can really do more for the average sick man than can the best medicines and the best doctors." Mark Twain

"Humans live on one-quarter of what they eat; on the other three-quarters lives their doctor."

Egyptian pyramid inscription, 3800 B.C.

"A full belly makes a bad brain" Ben Franklin

The Fasting Cure

by

UPTON SINCLAIR

IN the *Cosmopolitan Magazine* for May, 1910, and in the *Contemporary Review* (London) for April, 1910, I published an article dealing with my experiences in fasting. I have written a great many magazine articles, but never one which attracted so much attention as this. The

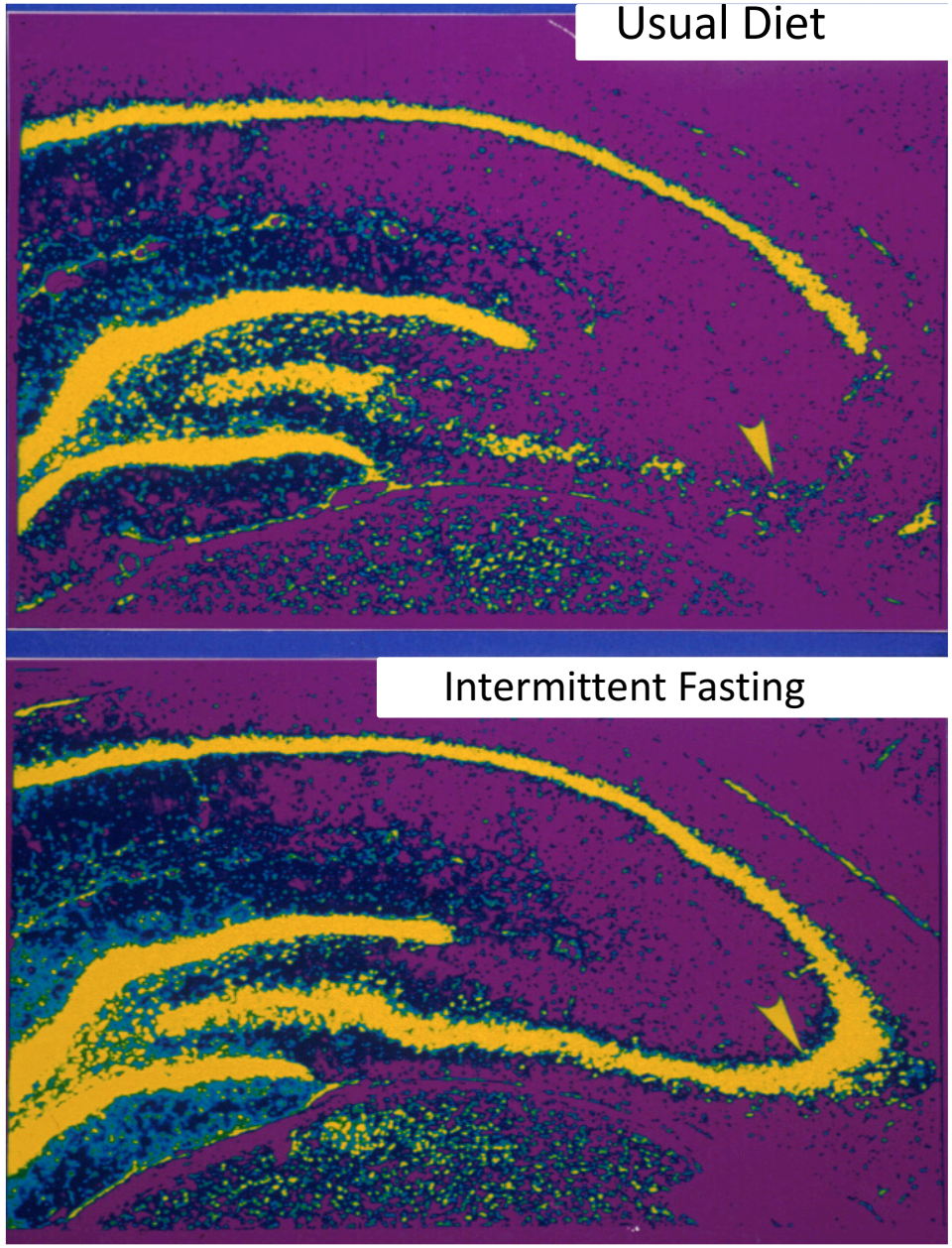
My object in publishing this book is two-fold: first, to have something to which I can refer people, so that I will not have to answer half a dozen "fasting letters" every day for the rest of my life; and second, in the hope of attracting sufficient attention to the subject to interest some scientific men in making a real investigation of it. To-day we know certain facts about what is called "autointoxication"; we know them because Metchnikoff, Pawlow and others have made a thorough-going inquiry into the subject. I believe that the subject of fasting is one of just as great importance. I have stated facts in this book about myself; and I have quoted many letters which are genuine and beyond dispute. The cures which they record are altogether without precedent, I think. The reader will find in the course of the book (page 63) a tabulation of the results of 277 cases of fasting. In this number of desperate cases, there were only about half a dozen definite and unexplained failures reported. Surely it cannot be that medical men and scientists will continue for much longer to close their eyes to facts of such vital significance as this.

Upton Sinclair

DISPELLING THE DEMONS (epileptic seizures)

Romans: Fasting

Bruce-Keller, A. J., G. Umberger, R. McFall and M. P. Mattson (1999) **Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults.** *Ann. Neurol.* 45: 8-15.



IF prevents obesity and protects the heart and brain against damage and disease in animal models

Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, Ingram DK, Lane MA, Mattson MP. (2003) 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. 100:6216-6220.

Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, Gill S, Leblanc M, Chaix A, Joens M, Fitzpatrick JA, Ellisman MH, Panda S. (2012) Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet.
Cell Metab. 15:848-860.

Mager DE, Wan R, Brown M, Cheng A, Wareski P, Abernethy DR, Mattson MP. (2006) Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB J. 20:631-637.

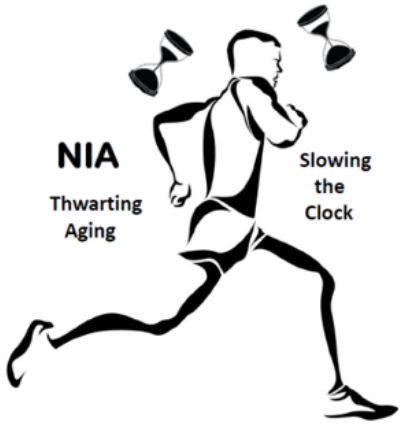
Ahmet I, Wan R, Mattson MP, Lakatta EG, Talan M. (2005) Cardioprotection by intermittent fasting in rats. Circulation 112:3115-3121.

Bruce-Keller AJ, Umberger G, McFall R, Mattson MP. (1999) Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. Ann Neurol. 45:8-15.

Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. (2003b) Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci U S A. 100:2911-2916.

Griffioen KJ, Rothman SM, Ladenheim B, Wan R, Vranis N, Hutchison E, Okun E, Cadet JL,Mattson MP. (2013) Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein. Neurobiol Aging. 34:928-935.

EXERCISE
ENERGY RESTRICTION
INTELLECTUAL ENDEAVORS
HORMETIC PHYTOCHEMICALS



Adaptive Responses
3-hydroxybutyrate (ketone)
Neurotrophic factors (BDNF)
Sirtuins
Mitochondrial biogenesis
DNA repair proteins
Protein chaperones

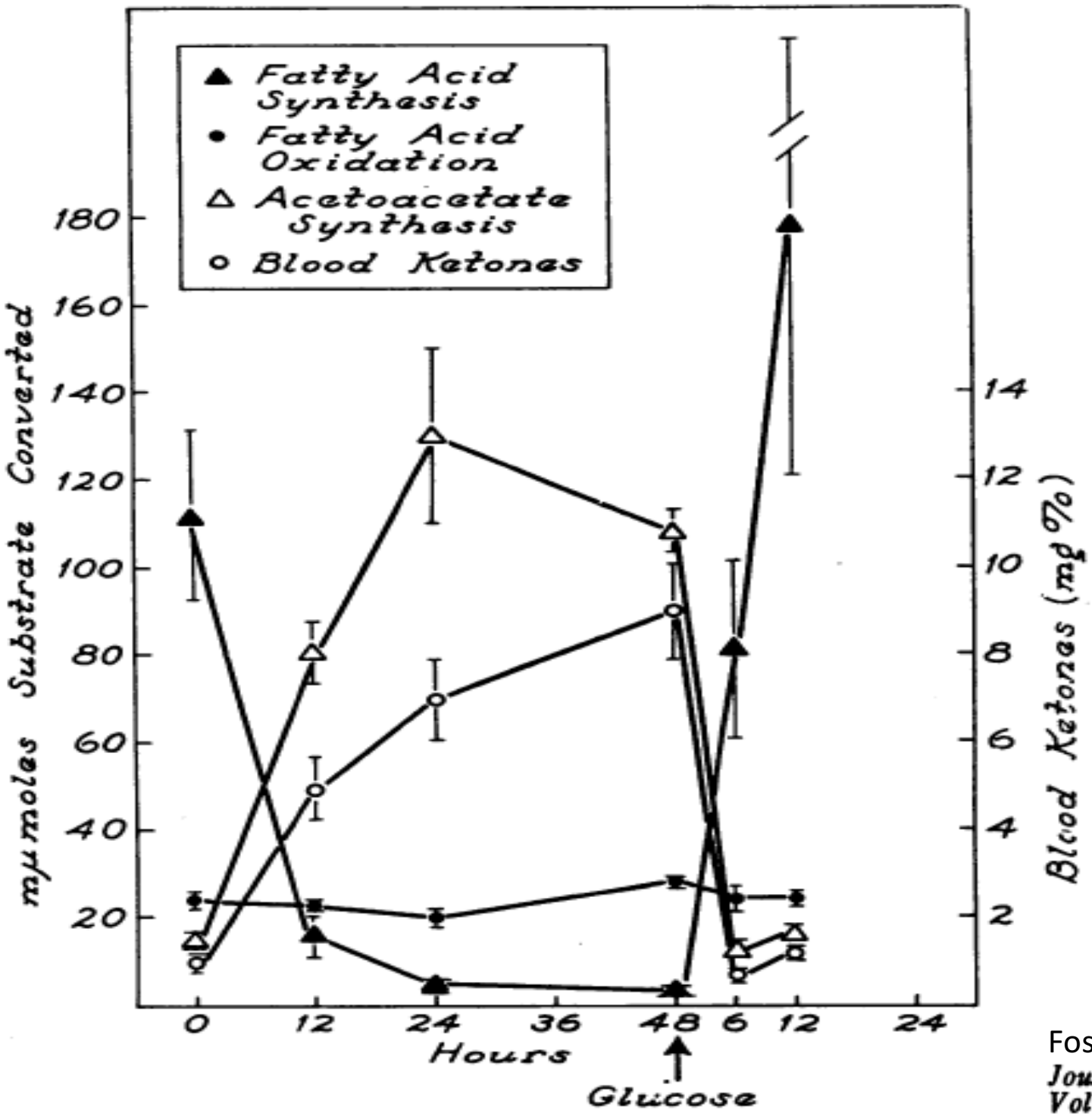
REDUCED PRODUCTION AND ENHANCED CLEARANCE OF PATHOGENIC PROTEINS
Aβ
Tau
TDP-43
α-Synuclein

Bolstered Bioenergetics
Improved Calcium Handling
Reduced Oxidative Damage
Enhanced Autophagy
Reduced inflammation

Synaptic plasticity
Neuronal survival
Neurogenesis

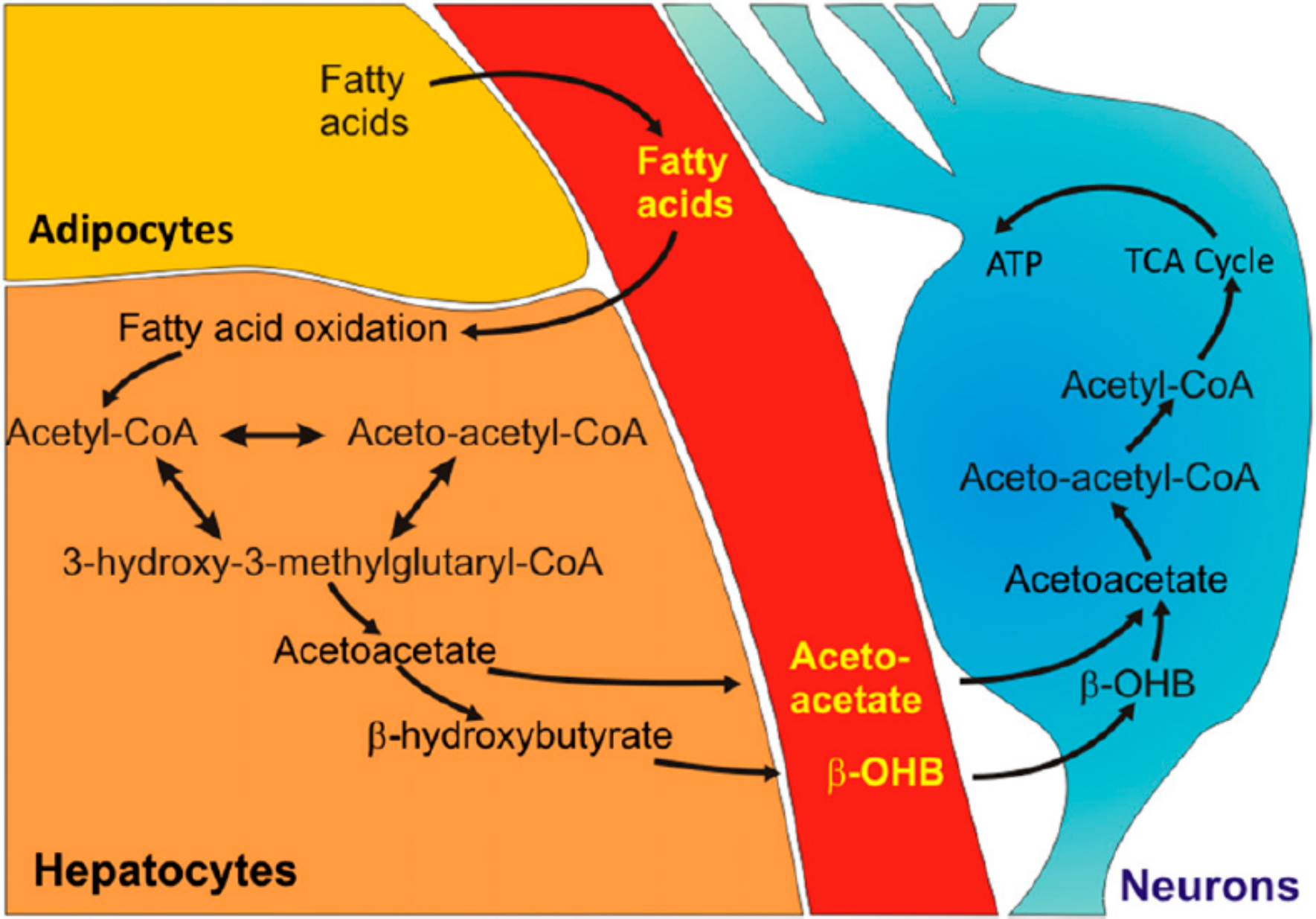
OPTIMAL BRAIN FUNCTION AND RESISTANCE TO INJURY AND DISEASE

Mattson MP. 2012. *Cell Metab.* 16:706-722.
Stranahan AM, Mattson, MP. *Nat. Rev. Neurosci.* 13:209-216.
Raefsky S, Mattson MP. 2016. *Free Rad Biol. Med.* 102:203-216.

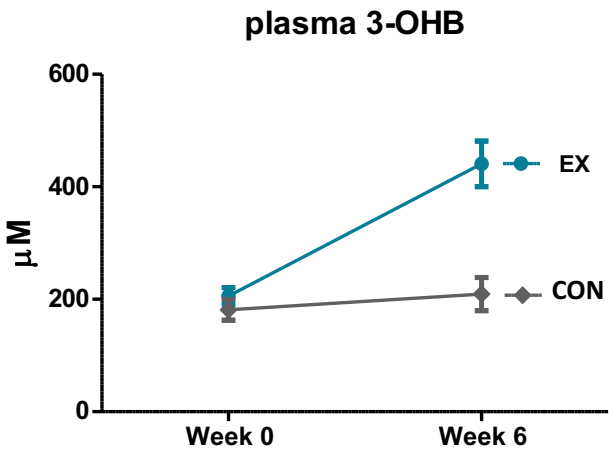


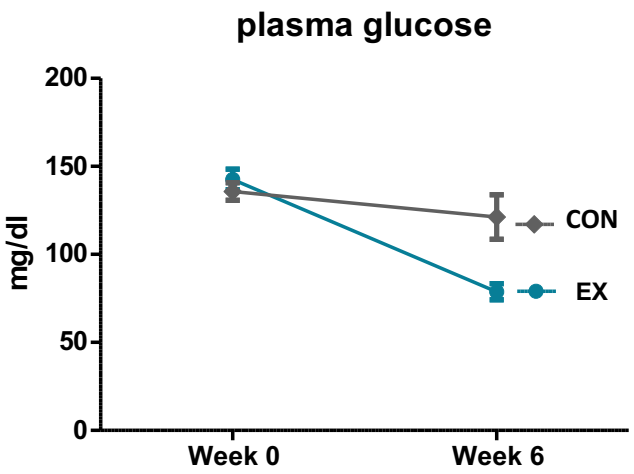
Foster DW

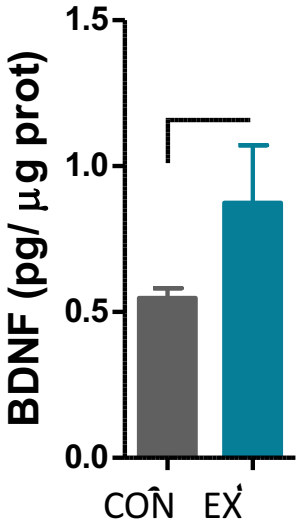
Journal of Clinical Investigation
Vol. 46, No. 8, 1967

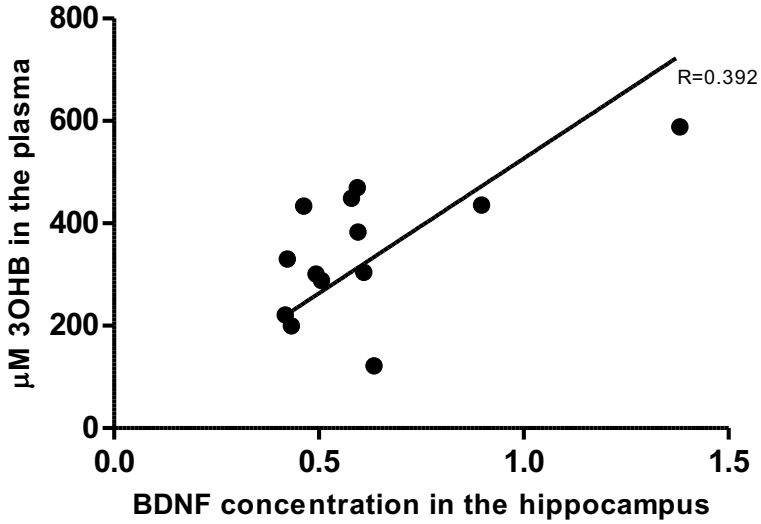

Fatty acids
Adipocytes
Fatty acids
Fatty acid oxidation
Acetyl-CoA
Aceto-acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
Acetoacetate
β-hydroxybutyrate
Hepatocytes
Aceto-acetate
β-OHB
ATP
TCA Cycle
Acetyl-CoA
Aceto-acetyl-CoA
Acetoacetate
β-OHB
Neurons

Running wheel exercise increases plasma 3OHB levels, and hippocampal BDNF levels are correlated with plasma 3OHB levels in mice



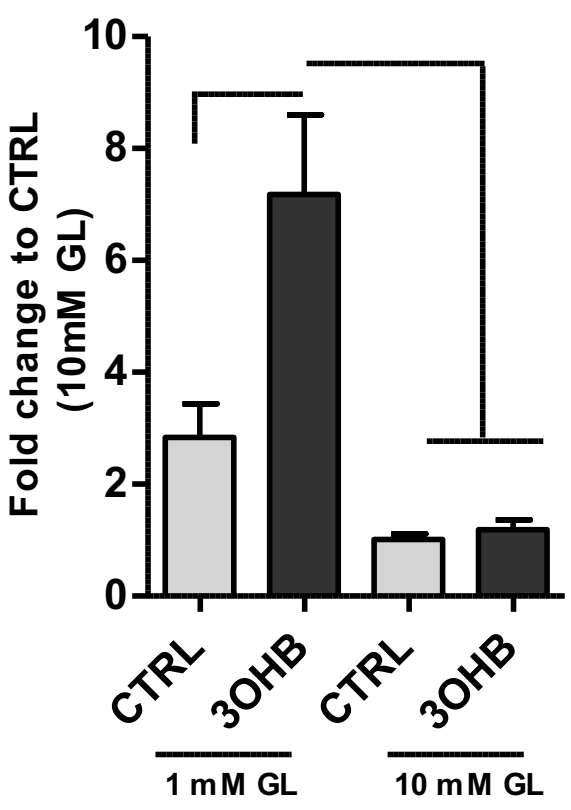


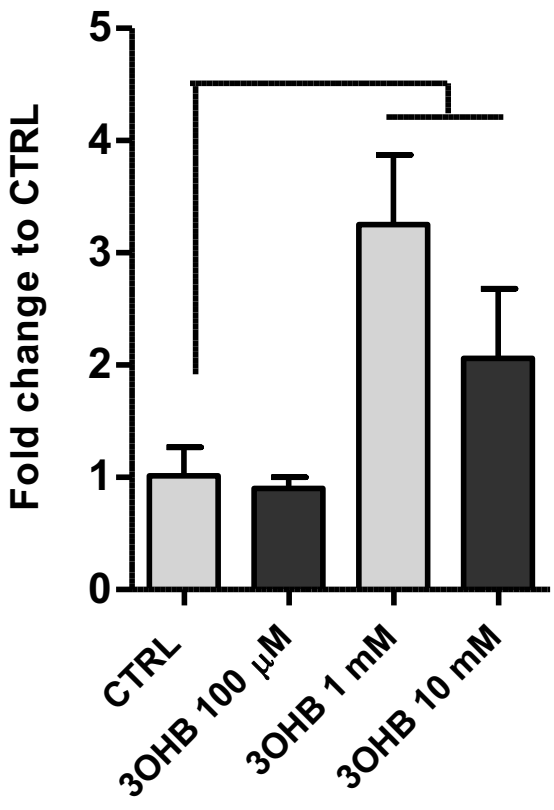


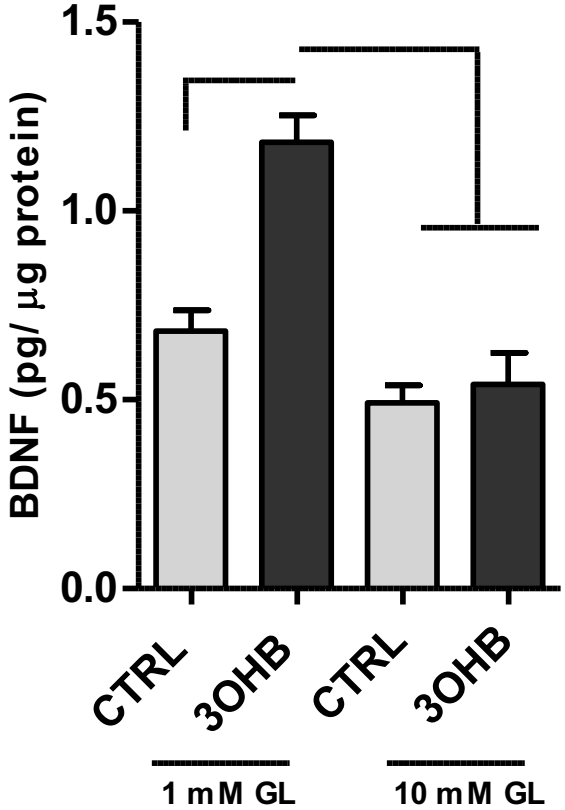


Marosi, K., S. W. Kim, K. Moehl, M. Scheibye-Knudsen, A. Cheng, R. Cutler, S. Camandola and M. P. Mattson (2016) 3-hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J. Neurochem.* Epub online Oct 14.

The ketone 3-hydroxybutyrate (3OHB) induces expression of BDNF in cerebral cortical neurons

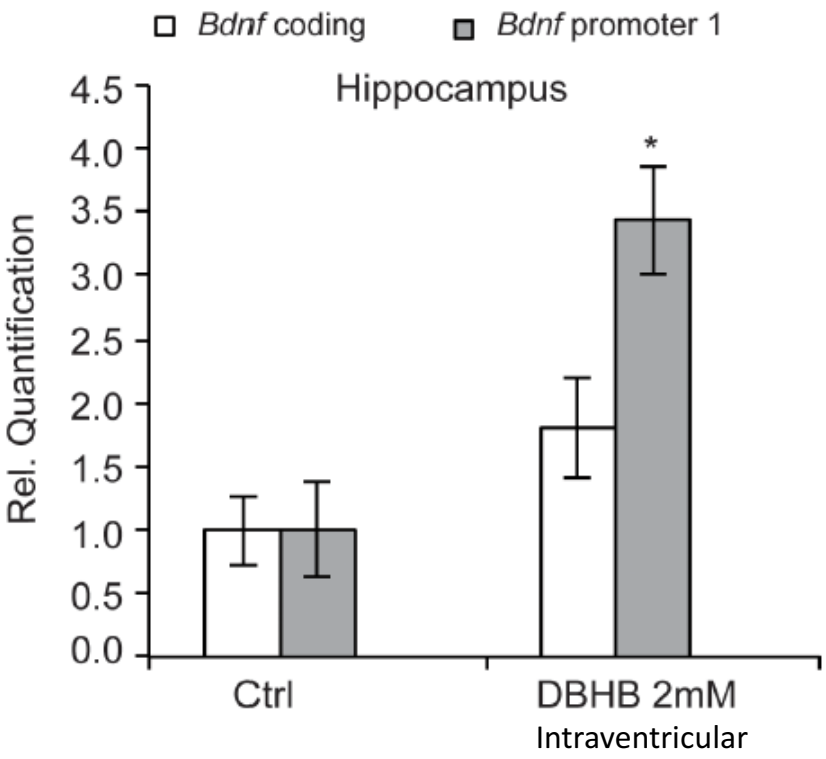


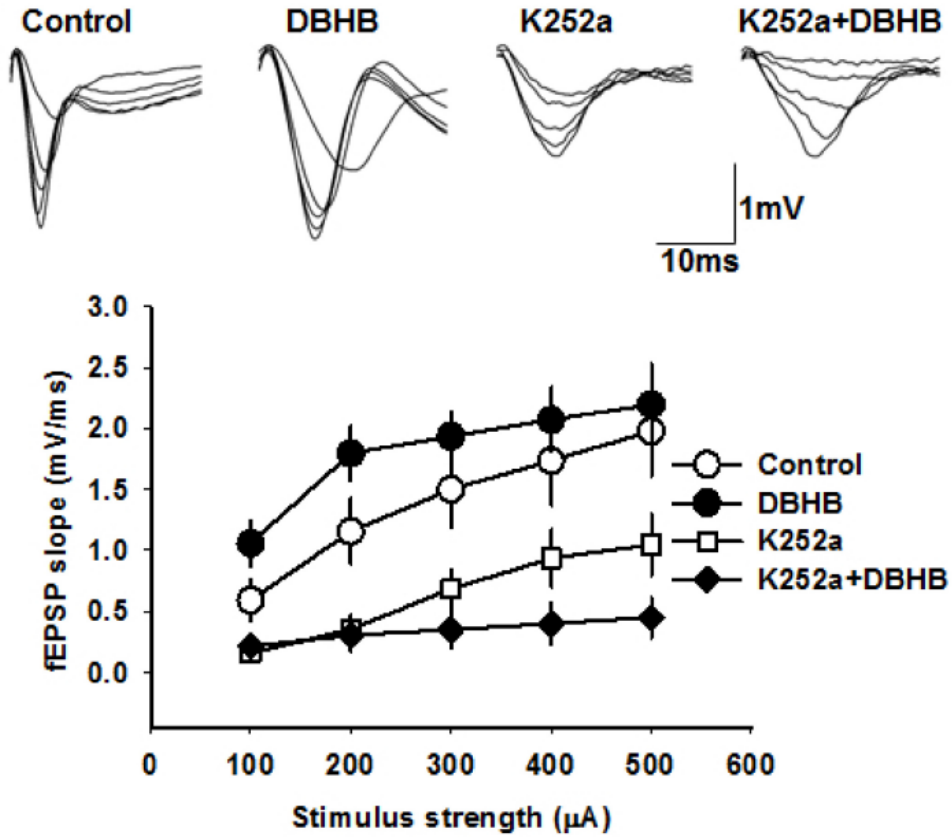




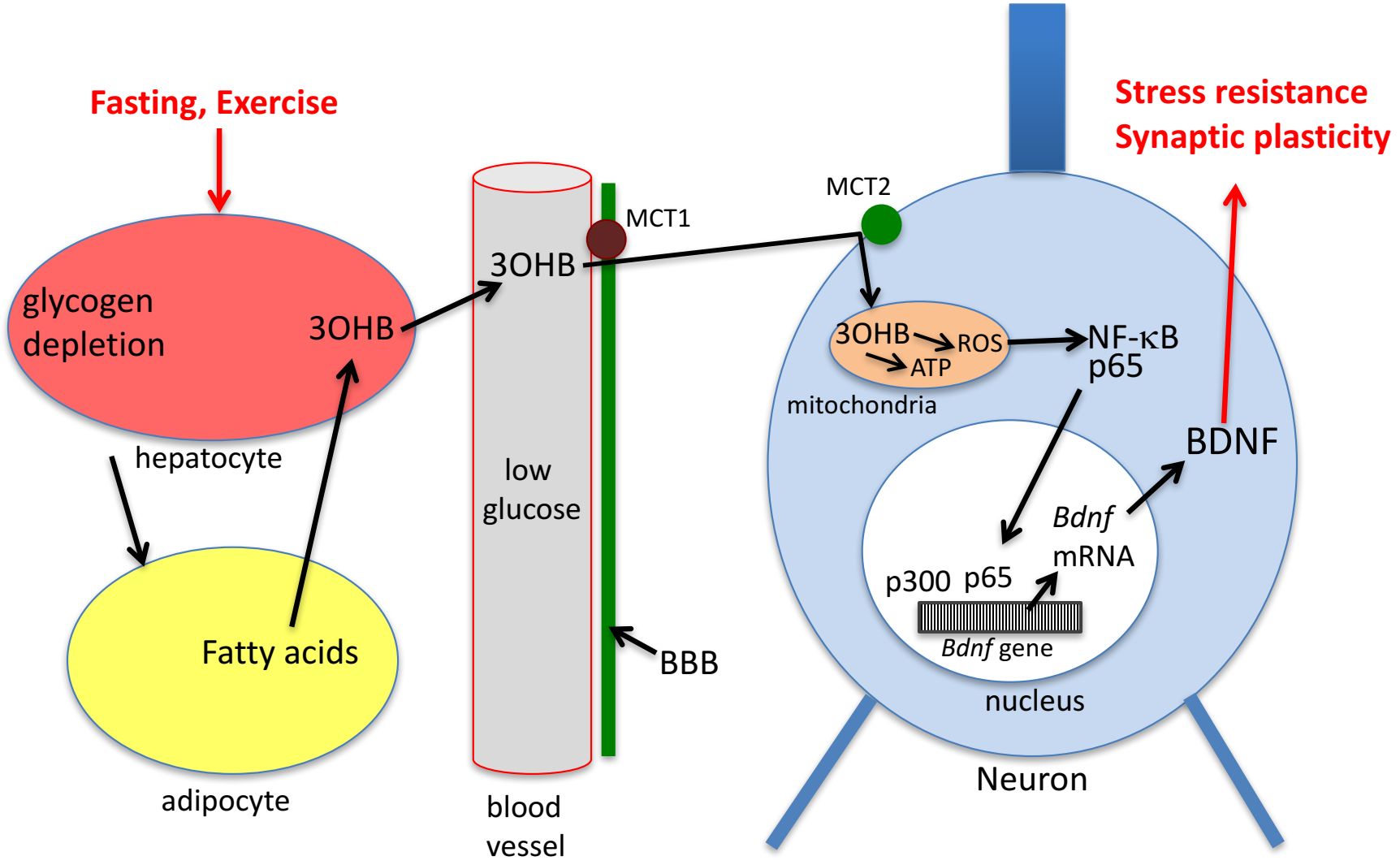
Marosi, K., S. W. Kim, K. Moehl, M. Scheibye-Knudsen, A. Cheng, R. Cutler, S. Camandola and M. P. Mattson (2016) 3-hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J. Neurochem.* Epub online Oct 14.

The ketone 3-hydroxybutyrate induces expression of BDNF in the hippocampus vivo, and increases excitatory synaptic transmission in hippocampal slices



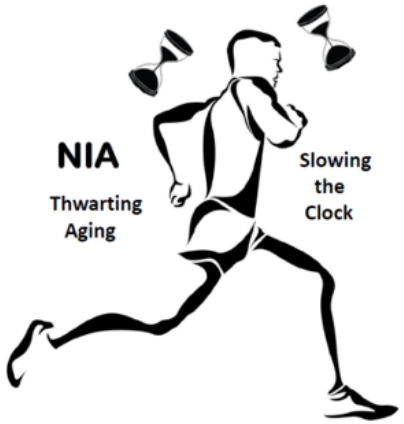


Sleiman et al. (2016) eLife



Marosi, K., S. W. Kim, K. Moehl, M. Scheibye-Knudsen, A. Cheng, R. Cutler, S. Camandola and M. P. Mattson (2016) 3-hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J. Neurochem.* Epub online Oct 14.

EXERCISE
ENERGY RESTRICTION
INTELLECTUAL ENDEAVORS
HORMETIC PHYTOCHEMICALS



Adaptive Responses
- 3-hydroxybutyrate (ketone)
- Neurotrophic factors (BDNF)
- Increases GABA tone
- Sirtuins
- Mitochondrial biogenesis
- DNA repair proteins
- Protein chaperones

REDUCED PRODUCTION AND ENHANCED CLEARANCE OF PATHOGENIC PROTEINS
- Aβ
- Tau
- TDP-43
- α-Synuclein

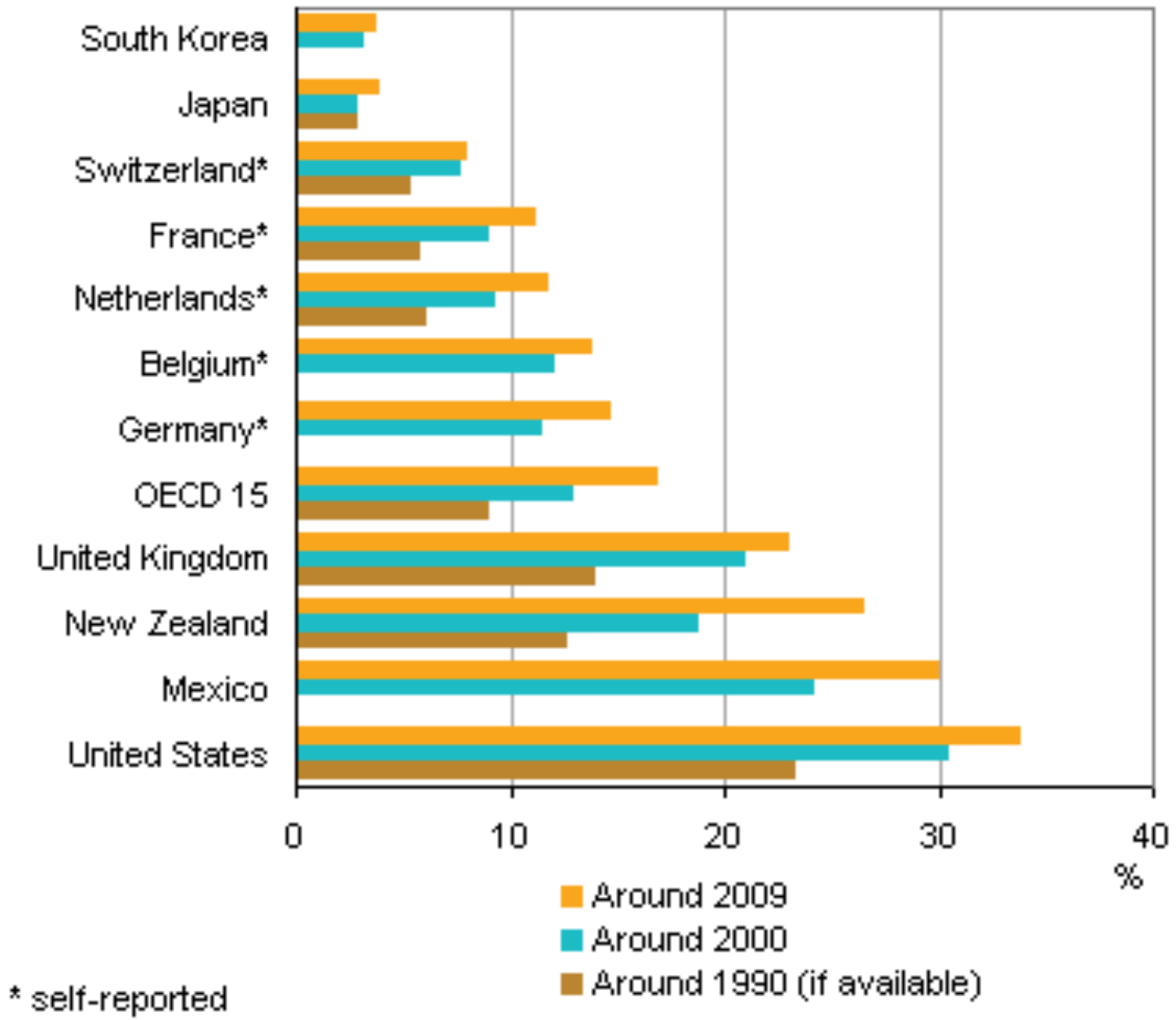
Bolstered Bioenergetics
Improved Calcium Handling
Reduced Oxidative Damage
Enhanced Autophagy
Reduced inflammation

Synaptic plasticity
Neuronal survival
Neurogenesis

OPTIMAL BRAIN FUNCTION AND RESISTANCE TO INJURY AND DISEASE

Mattson MP. 2012. *Cell Metab.* 16:706-722.
Stranahan AM, Mattson, MP. *Nat. Rev. Neurosci.* 13:209-216.
Raefsky S, Mattson MP. 2016. *Free Rad Biol. Med.* 102:203-216.

Obesity Rates



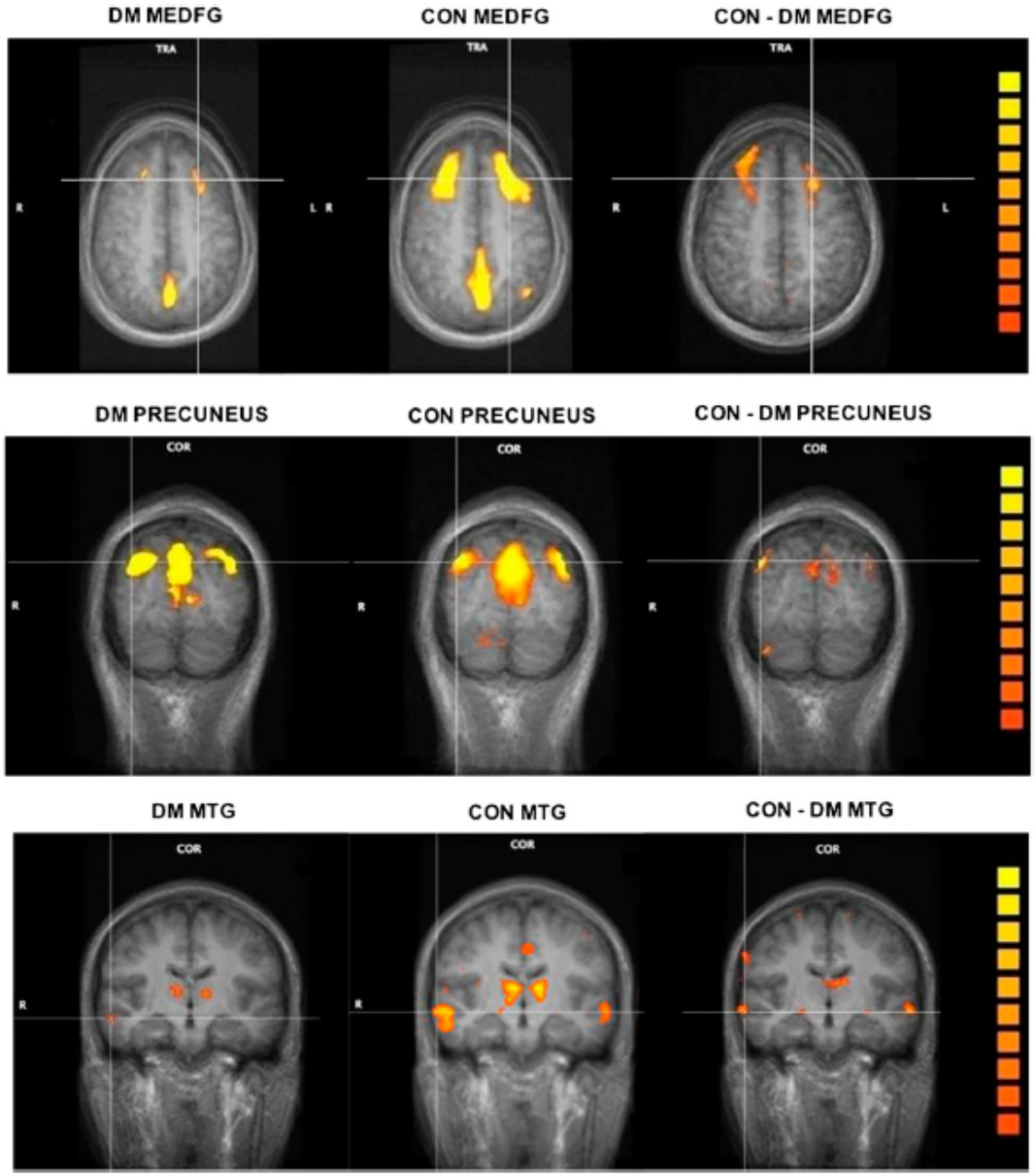
* self-reported

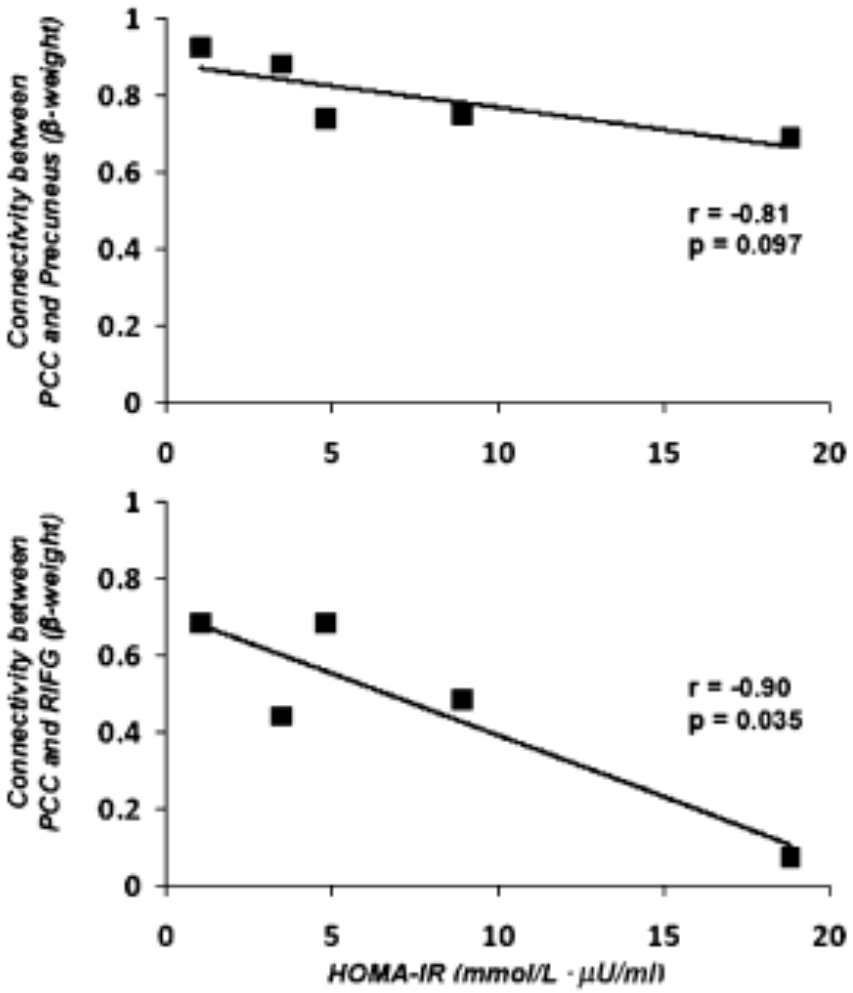
Source: OECD, CBS

USA: the leader in obesity, health care spending, and drug development

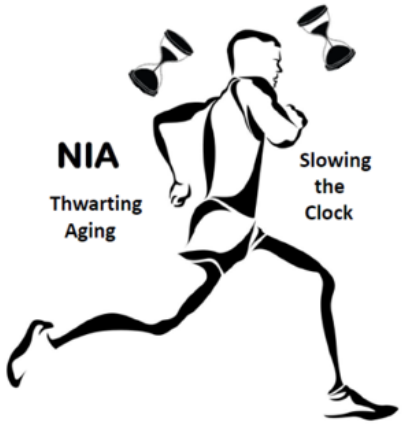
Netherlands

Functional Connectivity Between Brain Regions is Reduced in Patients with Diabetes





EXERCISE
ENERGY RESTRICTION
INTELLECTUAL ENDEAVORS
HORMETIC PHYTOCHEMICALS



Adaptive Responses
3-hydroxybutyrate (ketone)
Neurotrophic factors (BDNF)
Sirtuins
Mitochondrial biogenesis
DNA repair proteins
Protein chaperones

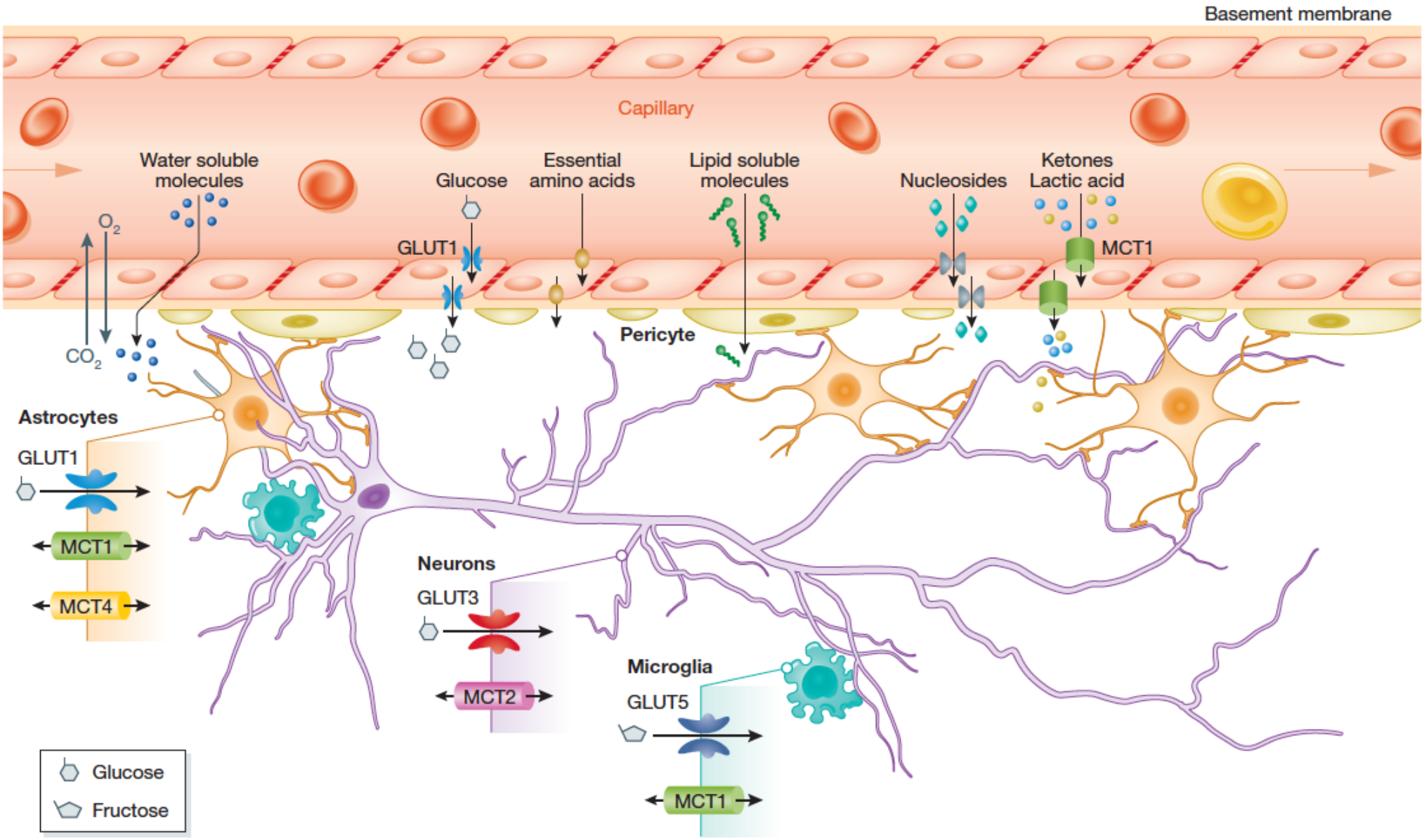
REDUCED PRODUCTION AND ENHANCED CLEARANCE OF PATHOGENIC PROTEINS
Aβ
Tau
TDP-43
α-Synuclein

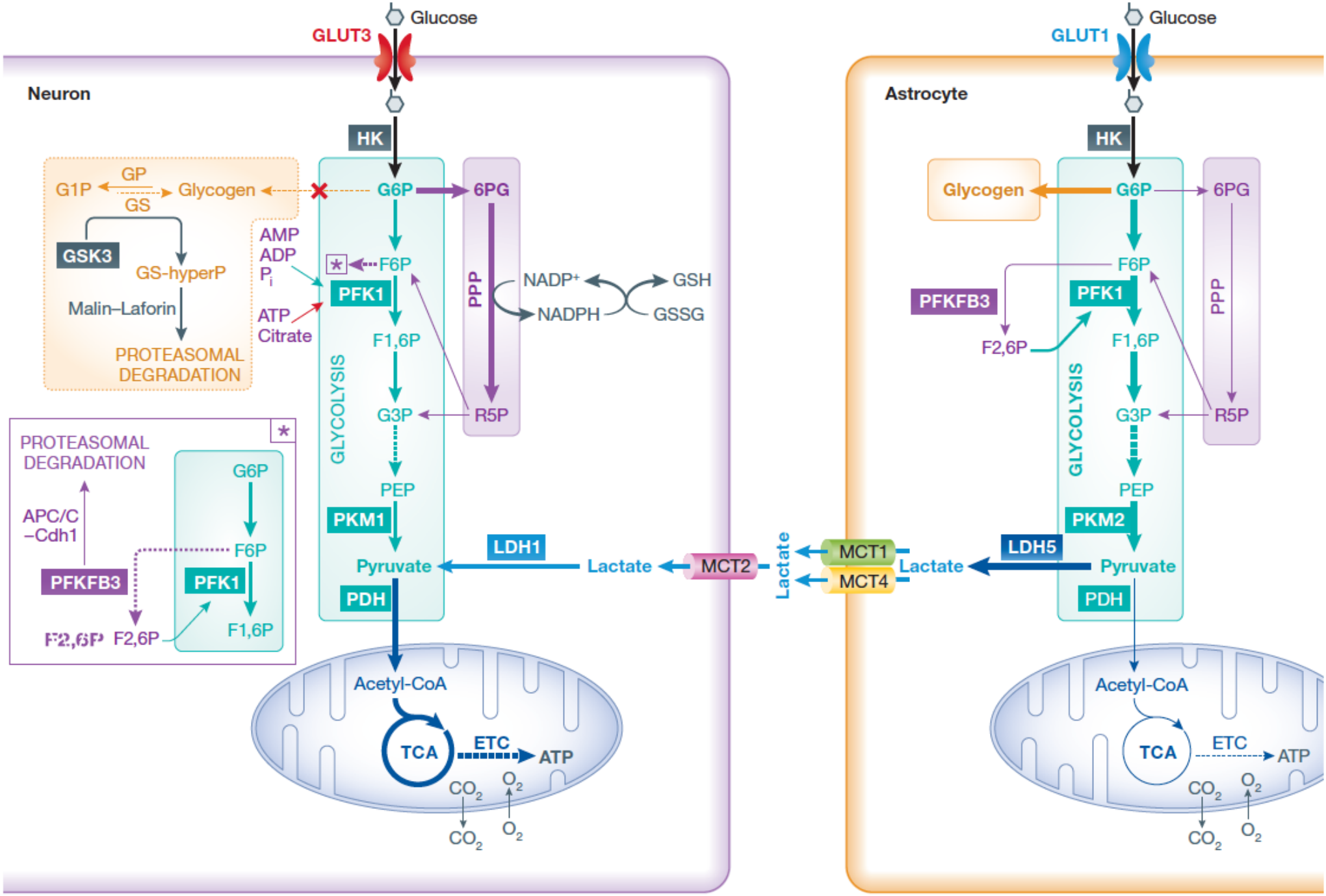
Bolstered Bioenergetics
Improved Calcium Handling
Reduced Oxidative Damage
Enhanced Autophagy
Reduced inflammation

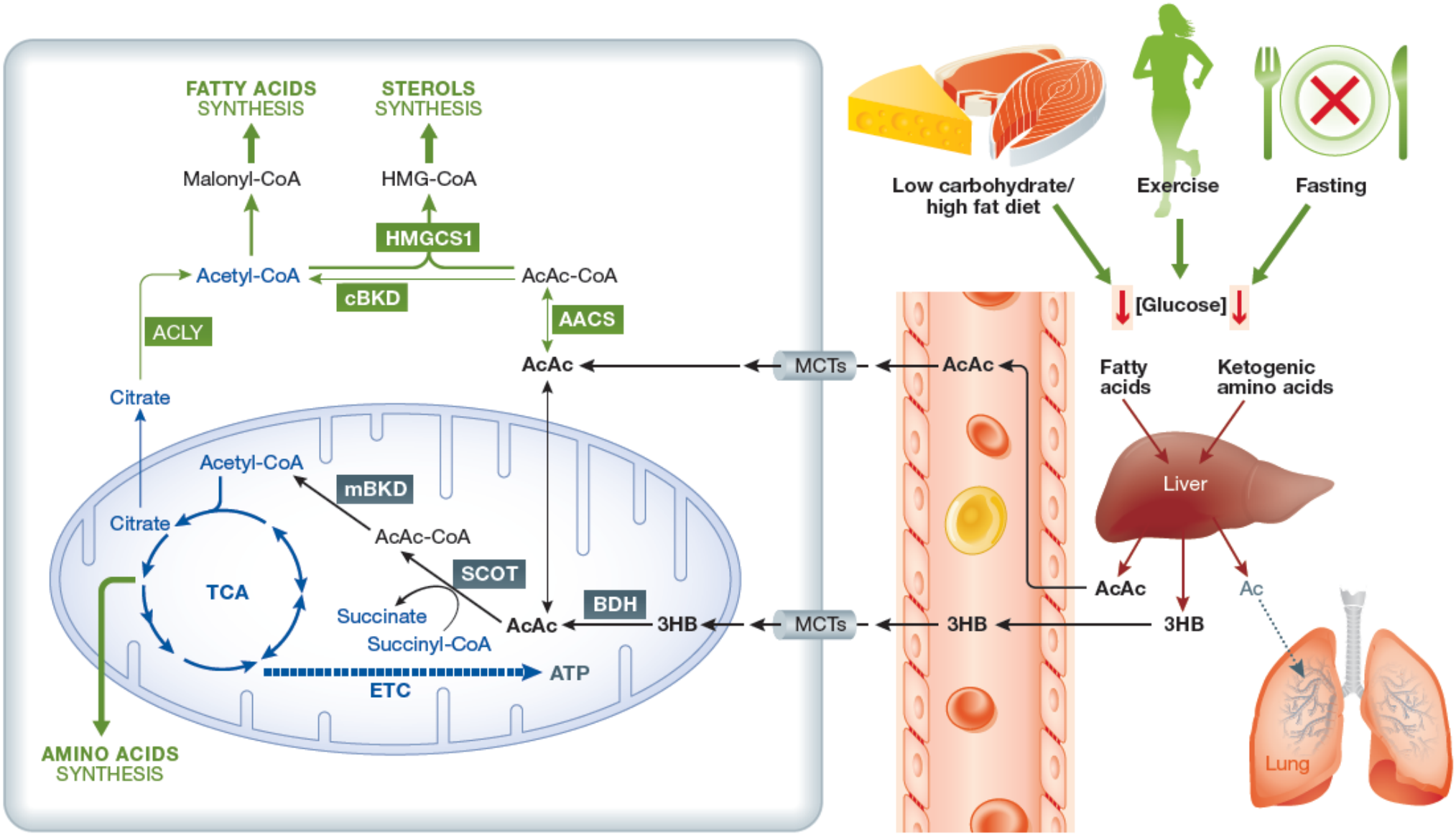
Synaptic plasticity
Neuronal survival
Neurogenesis

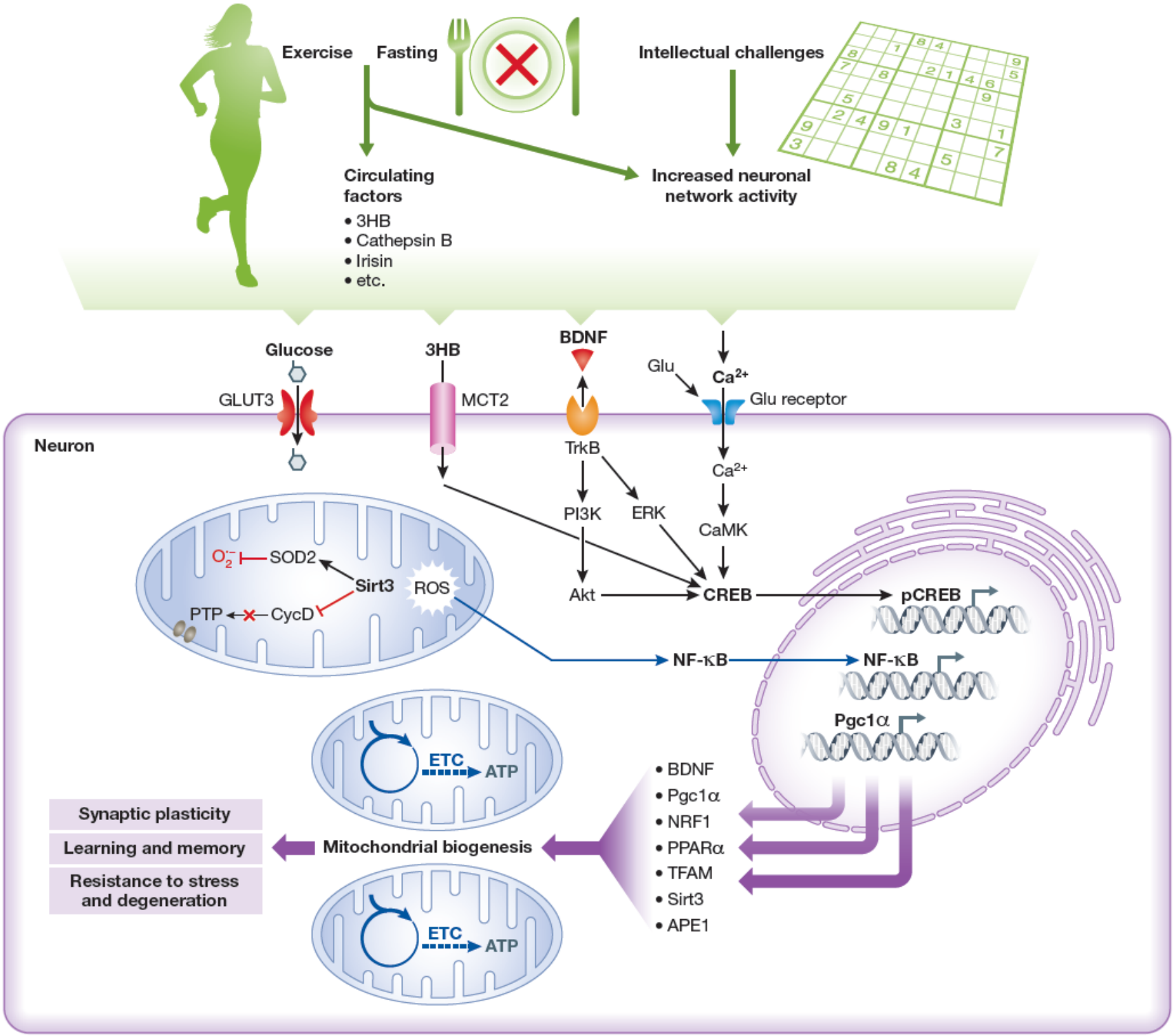
OPTIMAL BRAIN FUNCTION AND RESISTANCE TO INJURY AND DISEASE

Mattson MP. 2012. *Cell Metab.* 16:706-722.
Stranahan AM, Mattson, MP. *Nat. Rev. Neurosci.* 13:209-216.
Raefsky S, Mattson MP. 2016. *Free Rad Biol. Med.* 102:203-216.

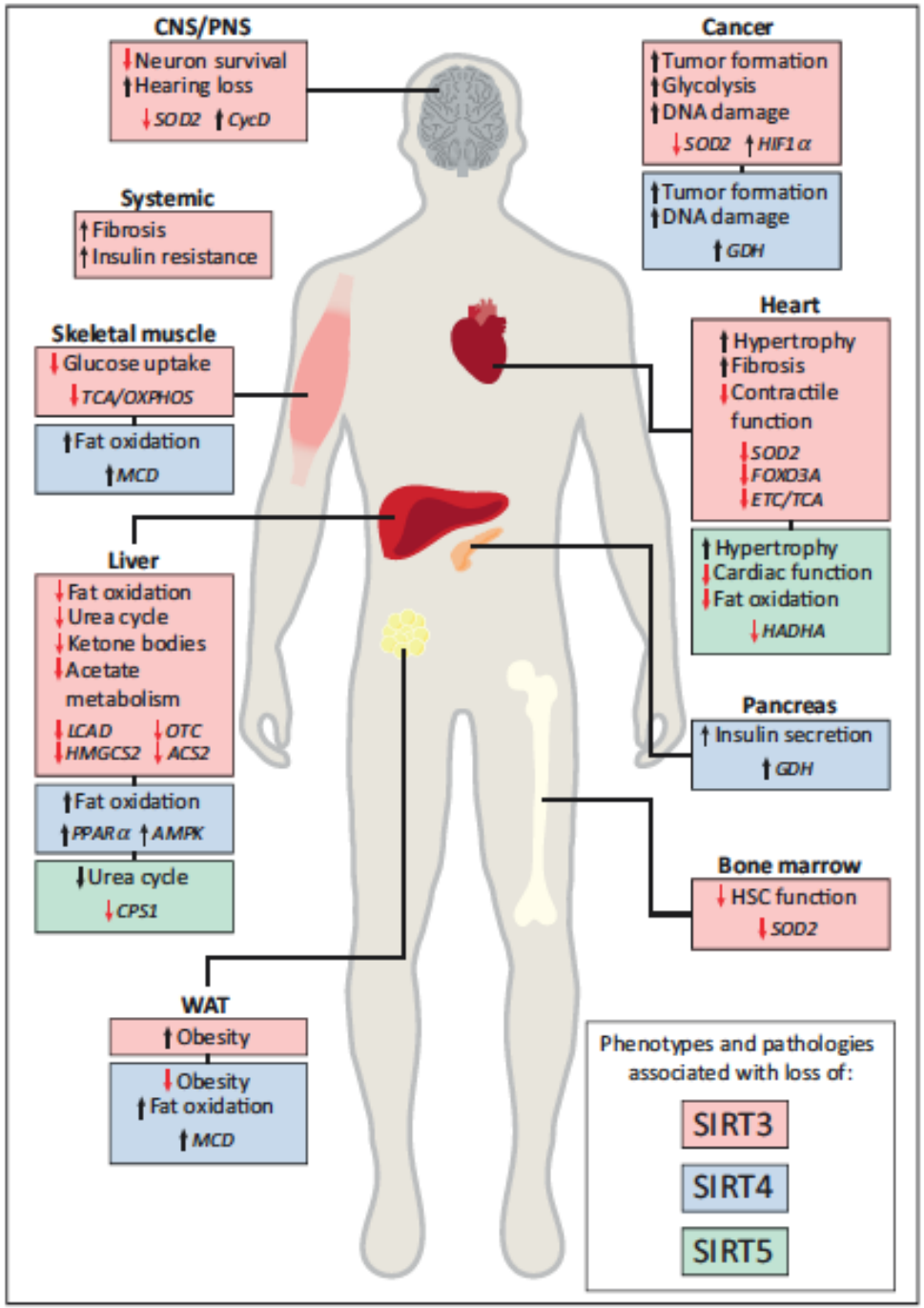

Basement membrane
Capillary
Water soluble molecules
Glucose
Essential amino acids
Lipid soluble molecules
Nucleosides
Ketones Lactic acid
O_2
CO_2
GLUT1
MCT1
Pericyte
Astrocytes
GLUT1
MCT1
MCT4
Neurons
GLUT3
MCT2
Microglia
GLUT5
MCT1
Glucose
Fructose


Neuron
Astrocyte
Glucose
GLUT3
GLUT1
HK
G6P
6PG
F6P
F1,6P
G3P
PEP
Pyruvate
R5P
PPP
GLYCOLYSIS
PFK1
PFKFB3
F2,6P
PKM1
PKM2
PDH
LDH1
LDH5
Lactate
MCT1
MCT2
MCT4
Glycogen
GP
GS
G1P
GSK3
GS-hyperP
Malin–Laforin
PROTEASOMAL DEGRADATION
AMP
ADP
Pi
ATP
Citrate
NADP+
NADPH
GSH
GSSG
APC/C –Cdh1
Acetyl-CoA
TCA
ETC
ATP
CO2
O2


FATTY ACIDS SYNTHESIS
STEROLS SYNTHESIS
Malonyl-CoA
HMG-CoA
HMGCS1
Acetyl-CoA
AcAc-CoA
cBKD
ACLY
AACS
AcAc
Citrate
Acetyl-CoA
mBKD
Citrate
AcAc-CoA
SCOT
TCA
Succinate
Succinyl-CoA
BDH
AcAc
3HB
ATP
ETC
AMINO ACIDS SYNTHESIS
MCTs
AcAc
MCTs
3HB
Low carbohydrate/ high fat diet
Exercise
Fasting
[Glucose]
Fatty acids
Ketogenic amino acids
Liver
AcAc
3HB
Ac
Lung


Exercise
Fasting
Intellectual challenges
Circulating factors
• 3HB
• Cathepsin B
• Irisin
• etc.
Increased neuronal network activity
Glucose
GLUT3
3HB
MCT2
BDNF
TrkB
Glu
Ca2+
Glu receptor
Neuron
PI3K
ERK
Ca2+
CaMK
O2•−
SOD2
Sirt3
ROS
PTP
CycD
Akt
CREB
pCREB
NF-κB
NF-κB
Pgc1α
ETC
ATP
ETC
ATP
Synaptic plasticity
Learning and memory
Resistance to stress and degeneration
Mitochondrial biogenesis
• BDNF
• Pgc1α
• NRF1
• PPARα
• TFAM
• Sirt3
• APE1

Loss of SIRT3, SIRT4, and SIRT5 Can Cause Age-Related Pathologies.



SIRT3

ROS balance	SOD2 IDH2 FOXO3A
TCA cycle	IDH2 SDHA* OGDH PDH
ETC/OXPHOS	complex I complex I complex III complex IV ATP synthase
Fatty acid metabolism	LCAD ACADM AGK
Amino acid catabolism	GDH
Ketone body metabolism	AceCS2 HMGCS2
Urea cycle	OTC
UPRmt	LonP CLPX CLPB HSPE1 DNAJA3
mtDNA function	TFAM POLDIP2 PNPT1 LRPPRC1
Mitochondrial translation	28S subunits 39S subunits ATAD3B tRNA ligases
Transporters	SLC25A10 SLC25A11 SLC25A12 SLC25A13 ABCF2

SIRT4

ROS balance	SOD2
TCA cycle	PDH OGDH
Fatty acid metabolism	MCAD ACADM
Amino acid catabolism	GDH
Transporters	SLC25A3 SLC25A11 SLC12A13

SIRT5

ROS balance	SOD1 IDH2 FOXO3A
TCA cycle	IDH2 PDH
Fatty acid metabolism	ECHA
Urea cycle	CPS1

nature COMMUNICATIONS

ARTICLE

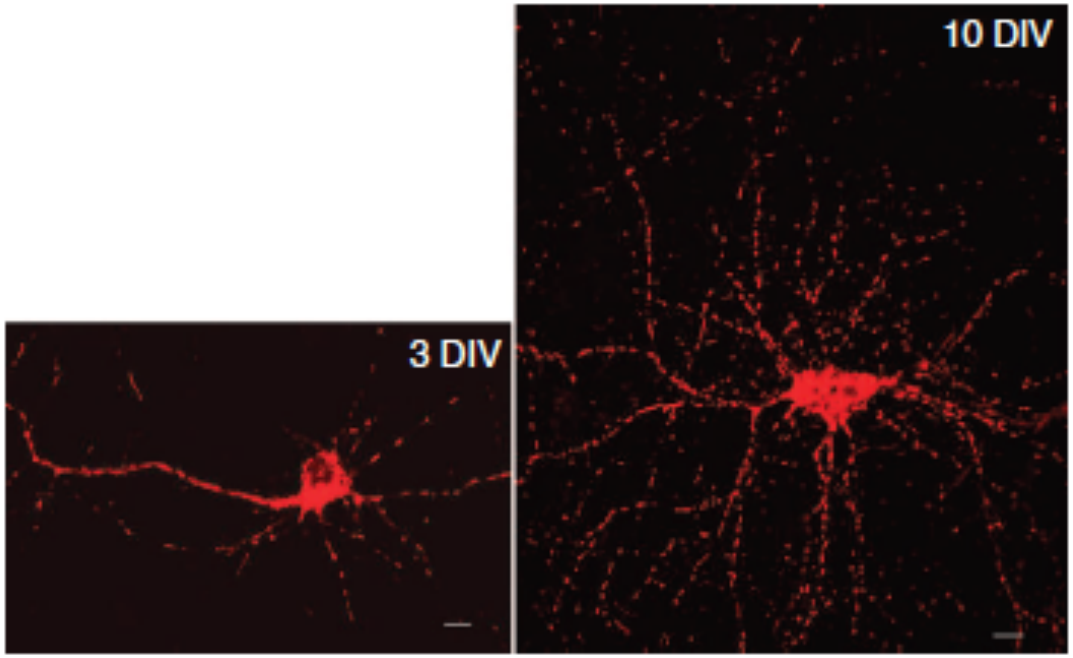
Received 28 Aug 2012 | Accepted 31 Oct 2012 | Published 4 Dec 2012

DOI: 10.1038/ncomms2238

Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines

Aiwu Cheng[1], Ruiqian Wan[1], Jenq-Lin Yang[1,2], Naomi Kamimura[1,3], Tae Gen Son[1], Xin Ouyang[1], Yongquan Luo[1], Eitan Okun[1] & Mark P. Mattson[1,4]

dentate granule neurons *in vivo*. We further show that brain-derived neurotrophic factor stimulates proliferator-activated receptor γ co-activator-1α-dependent mitochondrial biogenesis by activating extracellular signal-regulated kinases and cyclic AMP response element-binding protein. Proliferator-activated receptor γ co-activator-1α knockdown inhibits brain-derived neurotrophic factor-induced dendritic spine formation without affecting expression and activation of the brain-derived neurotrophic factor receptor tyrosine receptor kinase B. Our findings suggest that proliferator-activated receptor γ co-activator-1α and mitochondrial biogenesis have important roles in the formation and maintenance of hippocampal dendritic spines and synapses.



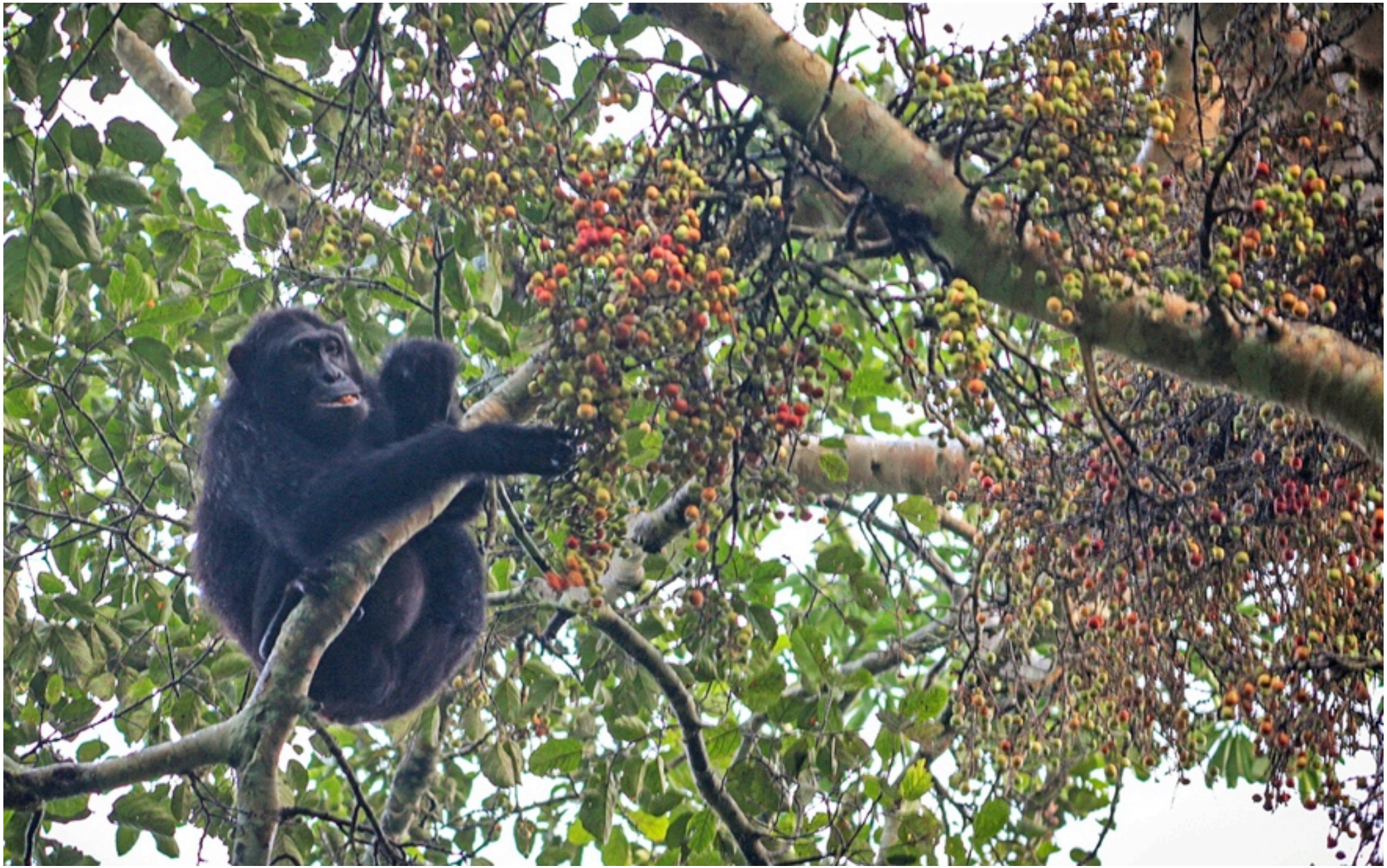
Obesity impairs academic attainment in adolescence: findings from ALSPAC, a UK cohort

JN Booth[1], PD Tomporowski[2], JME Boyle[3], AR Ness[4], C Joinson[4], SD Leary[4] and JJ Reilly[3]

International Journal of Obesity (2014) **38,** 1335–1342

Obesity and stature in adolescence and earnings in young adulthood. Analysis of a British birth cohort.

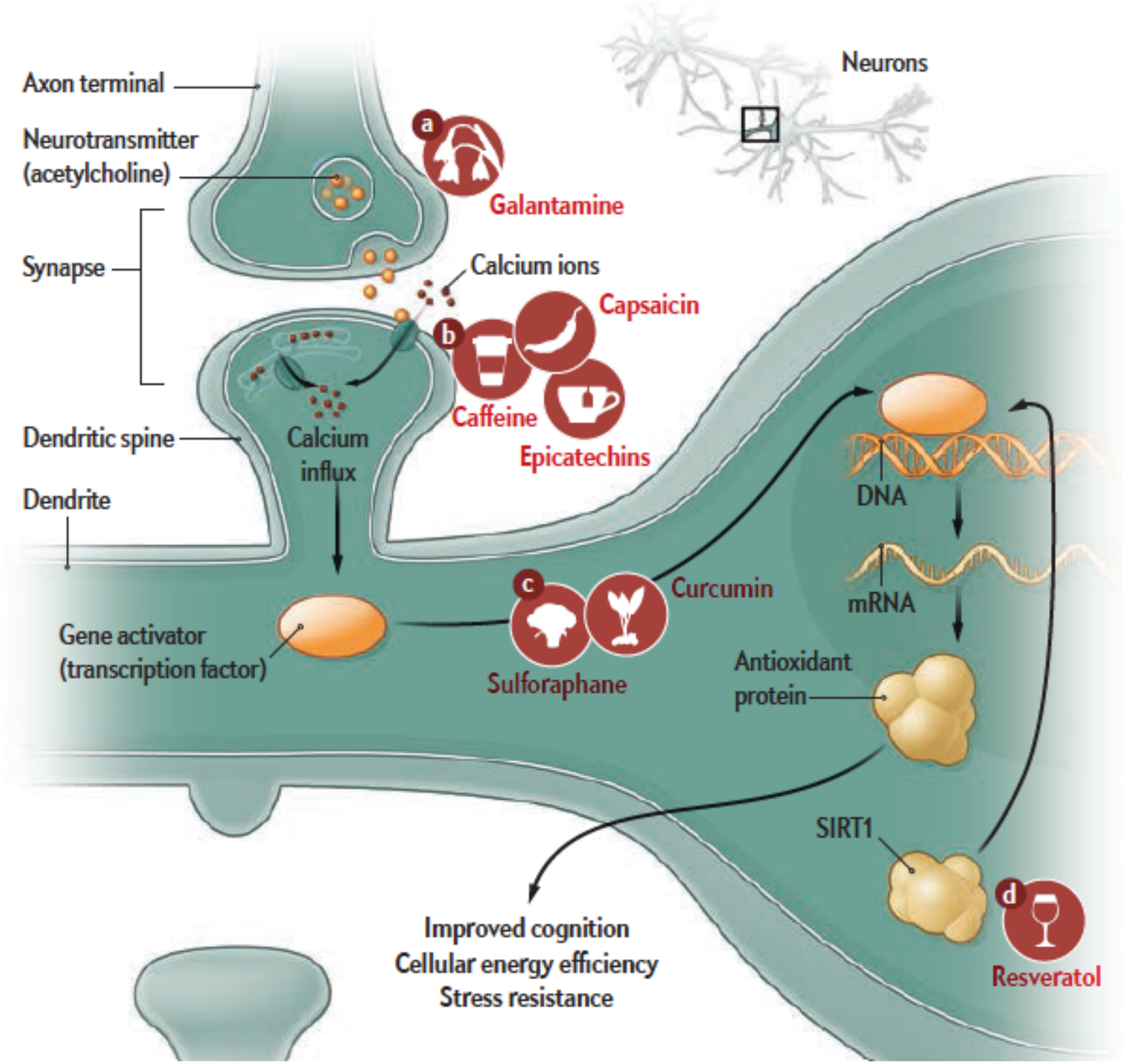
Arch Pediatr Adolesc Med 1994; 148:681-687.
Sargent JD, Blanchflower DG.
Men and women who had been obese at age 16 years had significantly fewer years of schooling than did their nonobese peers. Obese women performed poorly on math and reading tests at ages 7, 11, and 16 years when compared with their nonobese peers. Regression analyses indicated no relationship between obesity at any age and earnings at age 23 years in males. In contrast, **there was a statistically significant inverse relation between obesity and earnings in females, independent of parental social class** and ability test scores of the child. Female adolescents who were in the top 10% of the body mass index at age 16 years earned 7.4% less (95% confidence interval, -11% to -3.8%) than their nonobese peers; those in the top 1% earned 11.4% less (-21% to -1.5%).



Plants do not have the option of fleeing predators. As a consequence, they have developed an elaborate set of chemical defenses to ward off insects and other creatures that want to make them into a meal.

Toxins that plants use against predators are consumed by us at low levels in fruits and vegetables. Exposure to these chemicals causes a mild stress reaction that lends resilience to cells in our bodies.

Adaptation to these stresses, a process called hormesis, accounts for a number of health benefits, including protection against brain disorders, that we receive from eating broccoli and blueberries.


Neurons
Axon terminal
Neurotransmitter
(acetylcholine)
a
Galantamine
Synapse
Calcium ions
Capsaicin
b
Caffeine
Epicatechins
Dendritic spine
Calcium
influx
Dendrite
DNA
mRNA
c
Curcumin
Gene activator
(transcription factor)
Sulforaphane
Antioxidant
protein
SIRT1
d
Resveratol
Improved cognition
Cellular energy efficiency
Stress resistance

How do Cycles of Challenges and Recovery Periods Bolster Brain Health and Disease Resistance?

CHALLENGES
Fasting
Exercise
Intellectual
Phytochemicals

RECOVERY
Eating
Relaxation
Sleeping

Enhancement of:
Learning and Memory
'Cognitive Reserve'
Motor Function
Stress resistance

Calcium
ROS
Ketones
AMPK, CREB, PGC-1α
Neurotrophic factors
Autophagy
Antioxidant enzymes
DNA repair enzymes

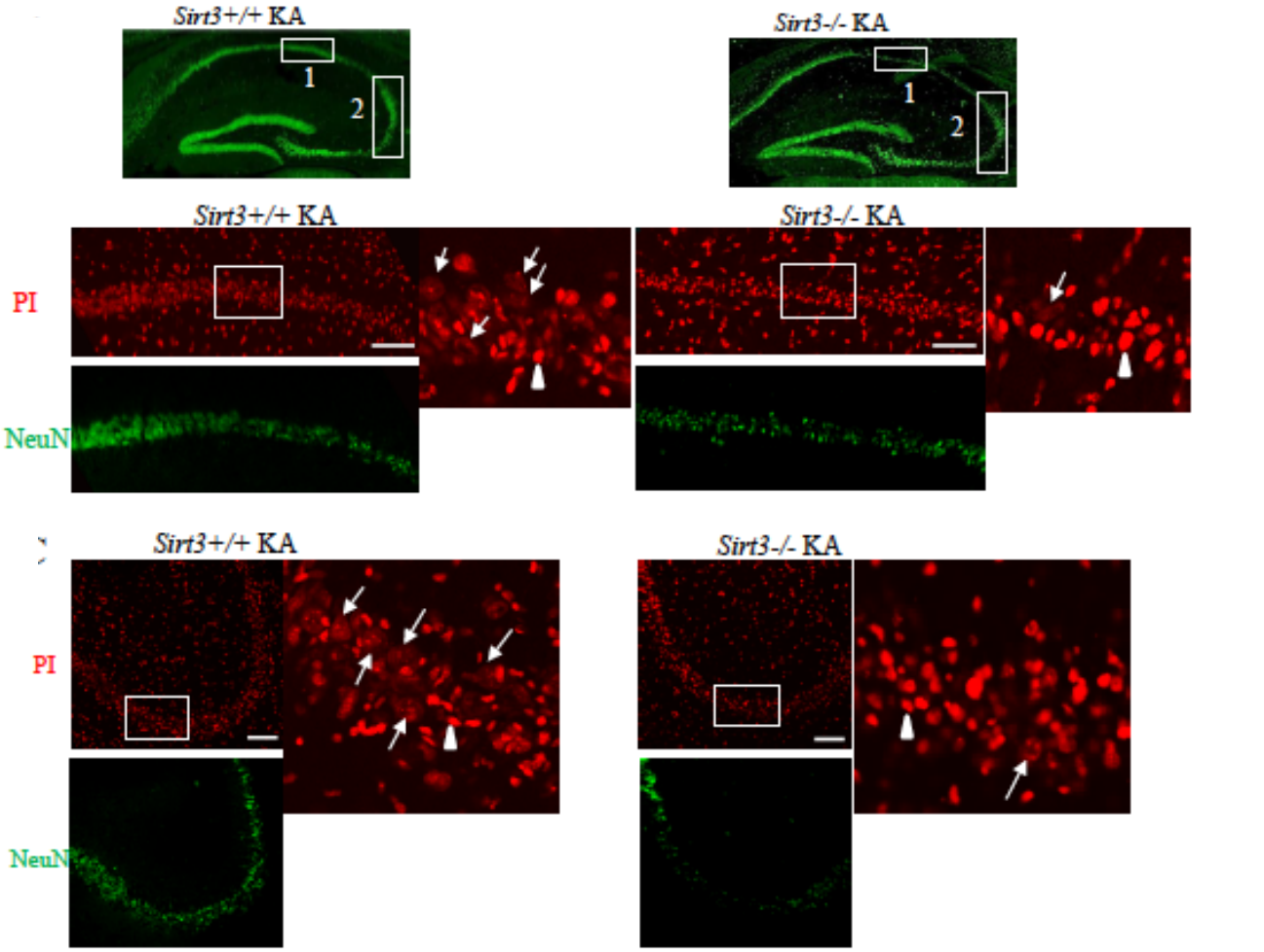
mTOR
Protein synthesis
ATP

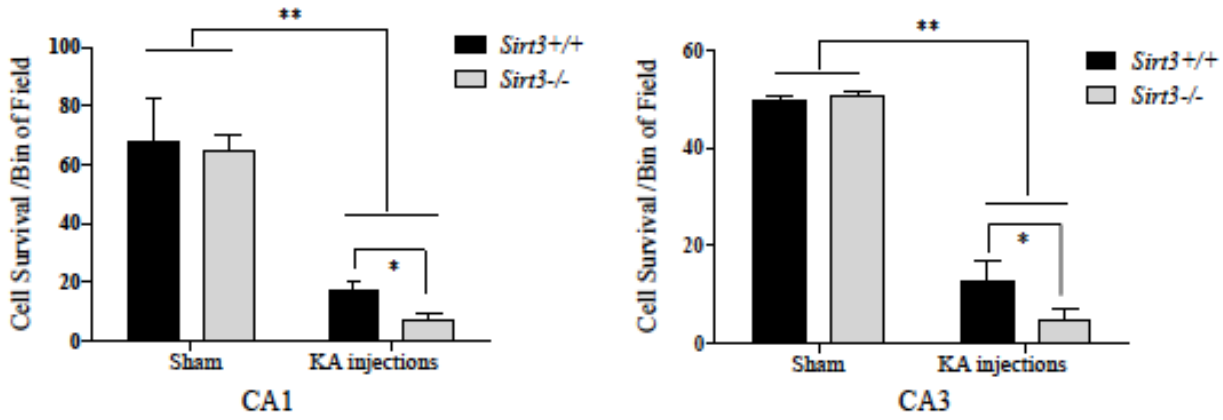
mTOR
Protein synthesis
Mitochondrial biogenesis
ATP
Neurite outgrowth
Synaptic plasticity
Neurogenesis

ROS
Oxidative damage
DNA damage
Protein aggregation

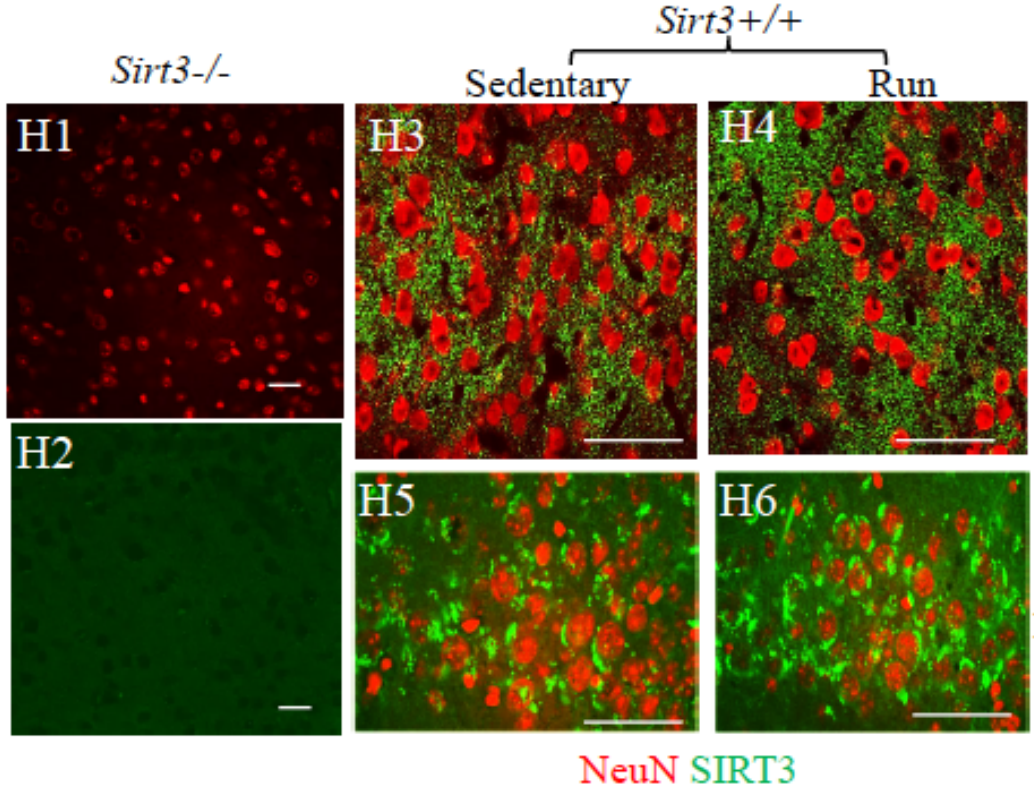
Healthy Brain Aging
Resistance to Dementia

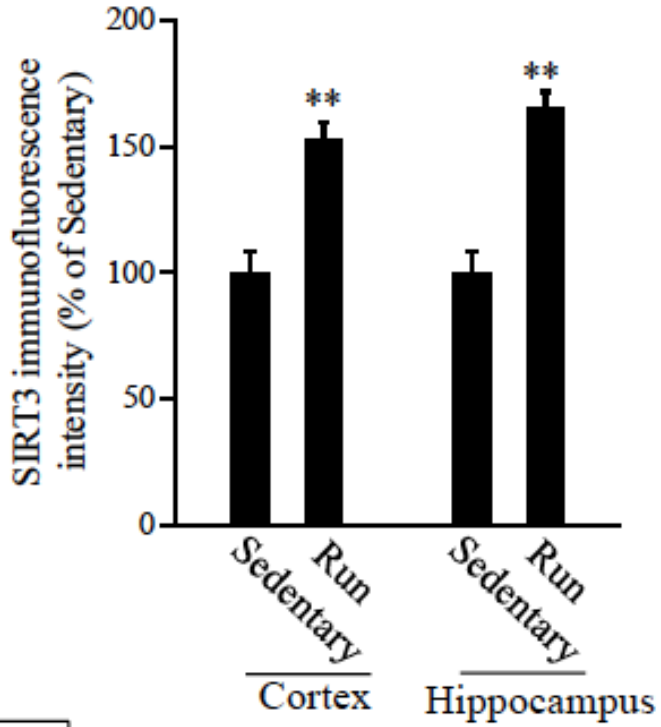
SIRT3 deficiency renders hippocampal neurons vulnerable to epileptic seizure-induced damage

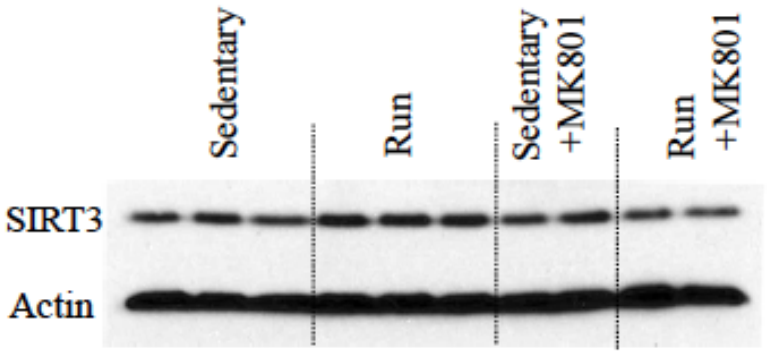


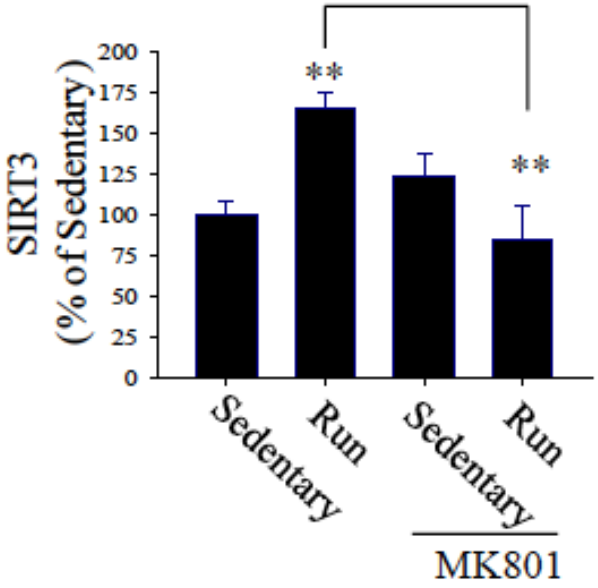


Exercise-induced SIRT3 expression is mediated by NMDA receptor activation



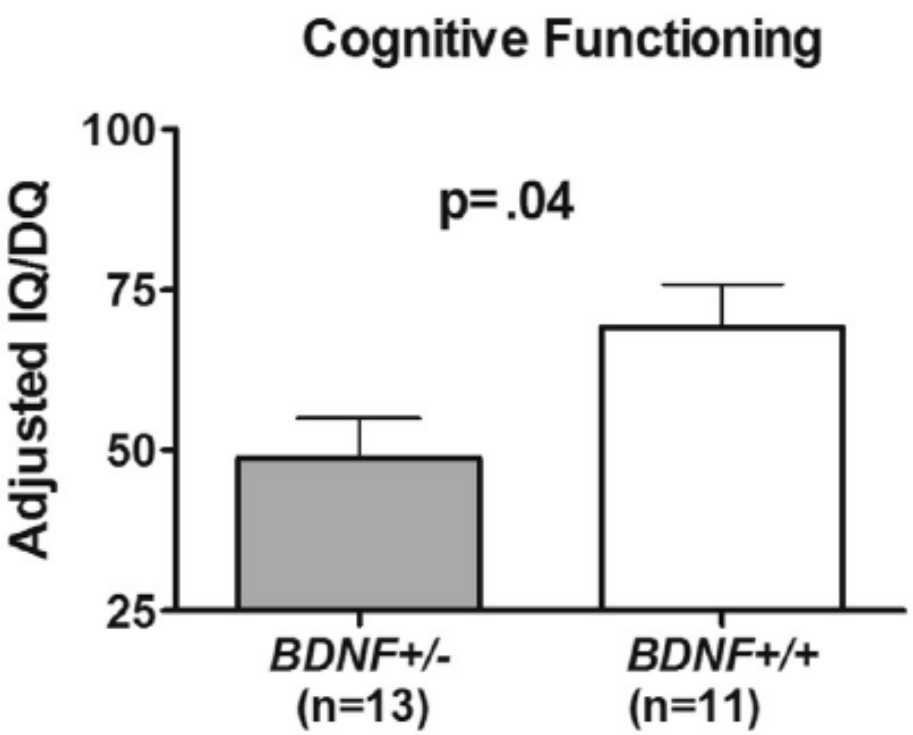


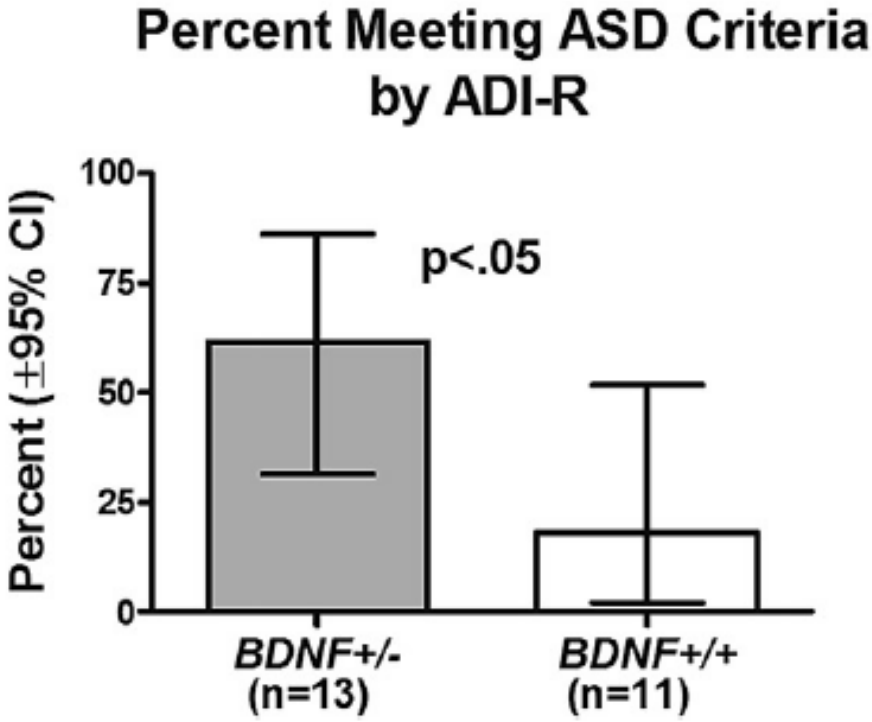




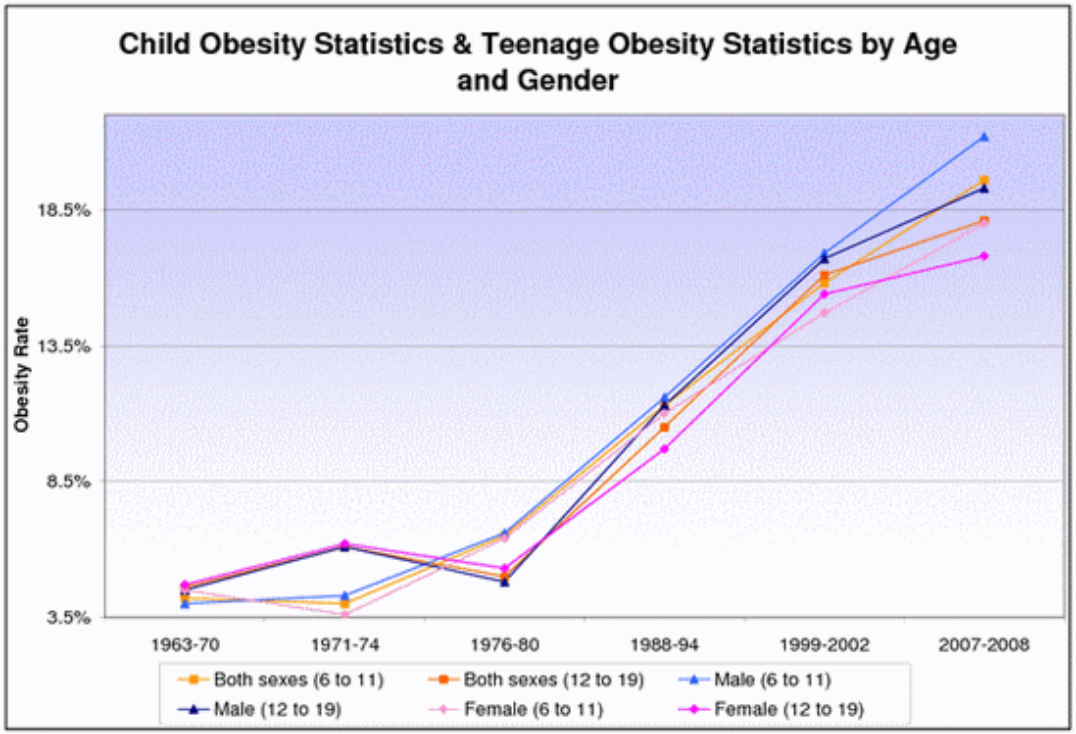
Cheng A et al. *Cell Metabolism*. 2016; 23: 128-142

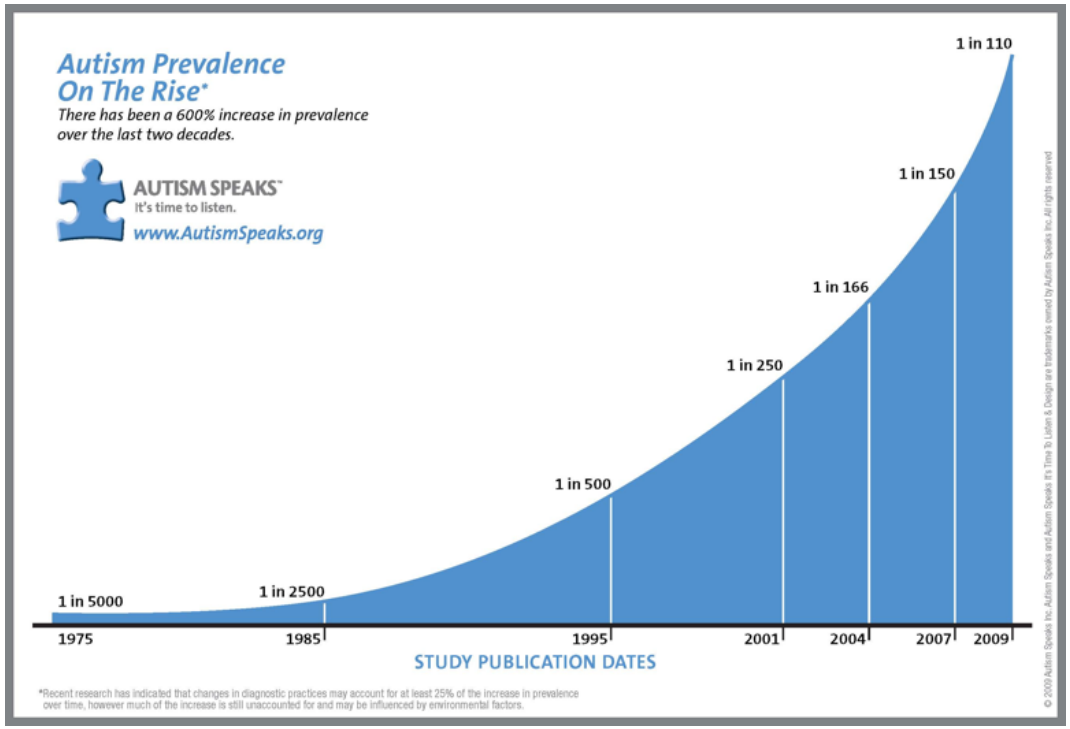
BDNF haploinsufficiency results in reduced cognitive functioning and increased autism-like behaviors in adolescent and young adult humans





Han JC et al. Association of brain-derived neurotrophic factor (BDNF) haploinsufficiency with lower adaptive behaviour and reduced **cognitive** functioning in WAGR/11p13 deletion syndrome. Cortex. 2013 Nov-Dec;49(10):2700-10.


Child Obesity Statistics & Teenage Obesity Statistics by Age and Gender
Obesity Rate
18.5%
13.5%
8.5%
3.5%
1963-70
1971-74
1976-80
1988-94
1999-2002
2007-2008
Both sexes (6 to 11)
Both sexes (12 to 19)
Male (6 to 11)
Male (12 to 19)
Female (6 to 11)
Female (12 to 19)


Autism Prevalence On The Rise*
There has been a 600% increase in prevalence over the last two decades.
AUTISM SPEAKS
It's time to listen.
www.AutismSpeaks.org
1 in 5000
1 in 2500
1 in 500
1 in 250
1 in 166
1 in 150
1 in 110
1975
1985
1995
2001
2004
2007
2009
STUDY PUBLICATION DATES
*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.
© 2009 Autism Speaks Inc. Autism Speaks and Autism Speaks It's Time To Listen & Design are trademarks owned by Autism Speaks Inc. All rights reserved