



The caloric restriction paradigm: implications for healthy human aging

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Rationale for caloric restriction research

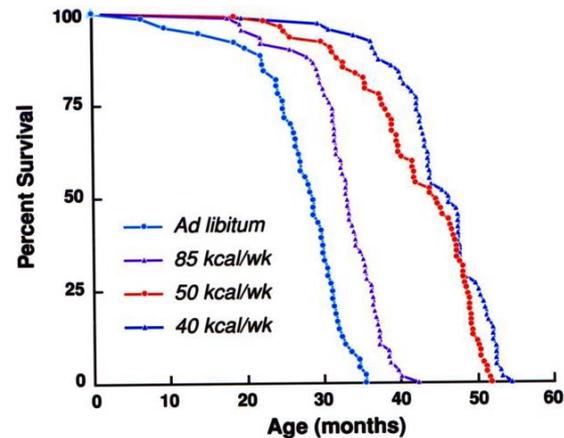
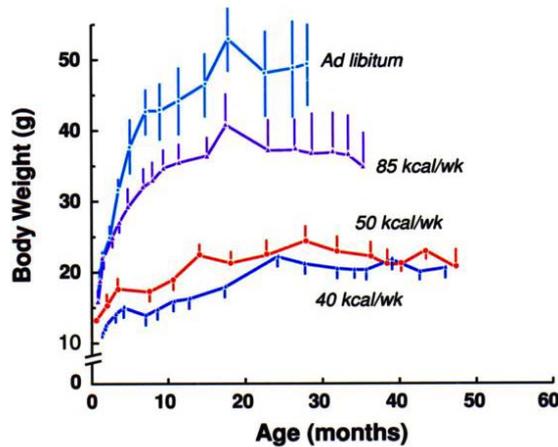
- (i) Aging itself is the **most significant risk factor** for a range of diseases including cancer, neurodegenerative disease, cardiovascular disease and diabetes.
- (ii) Elucidation of the factors contributing to the aging process will identify **novel targets for disease prevention and treatment.**

Caloric restriction as a model of delayed aging is a research tool to determine the **underlying causes** of age-associated disease vulnerability





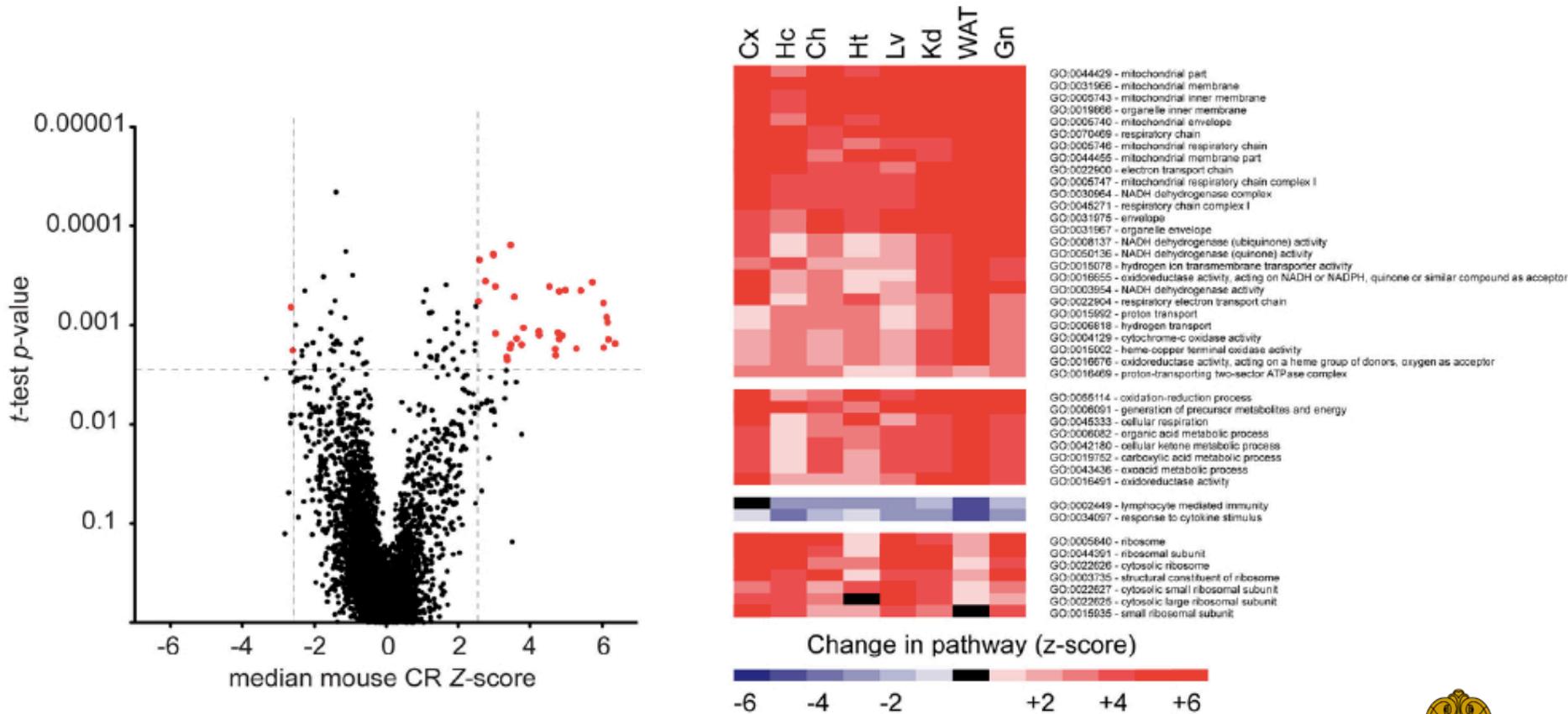
Caloric restriction extends average and maximal lifespan in mice



C3B10RF1 female mice subject to early onset CR



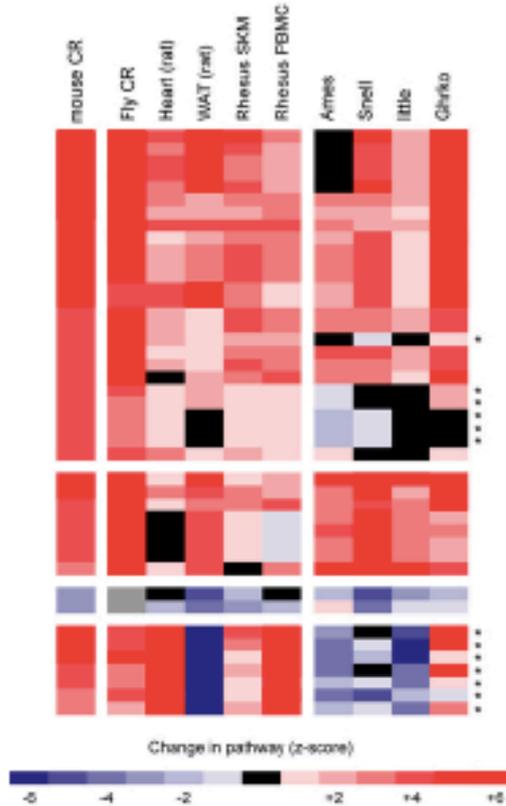
Meta-analysis reveals conserved pathways responsive to caloric restriction



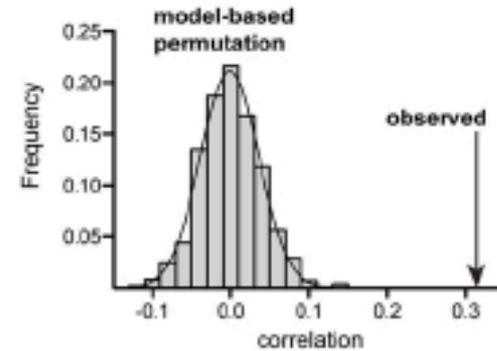
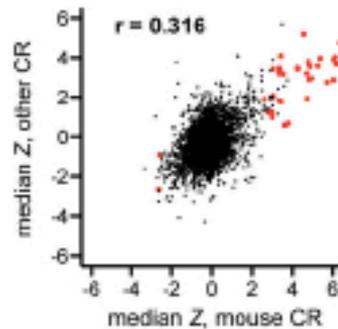
Barger *et al* in review

Transcriptional signature conserved with CR and genetic models of delayed aging

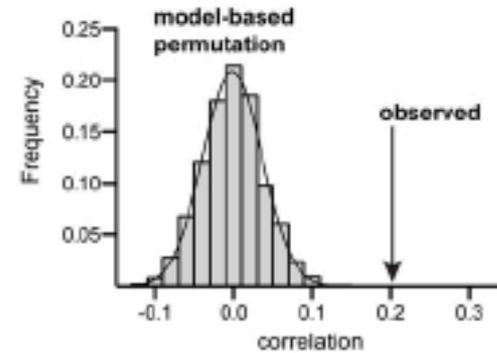
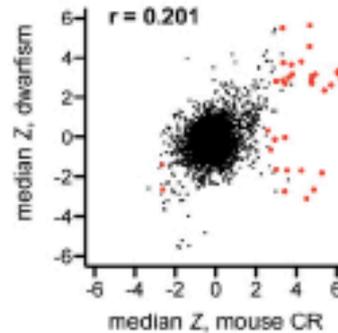
a. CR signature



b. Mouse CR vs other CR

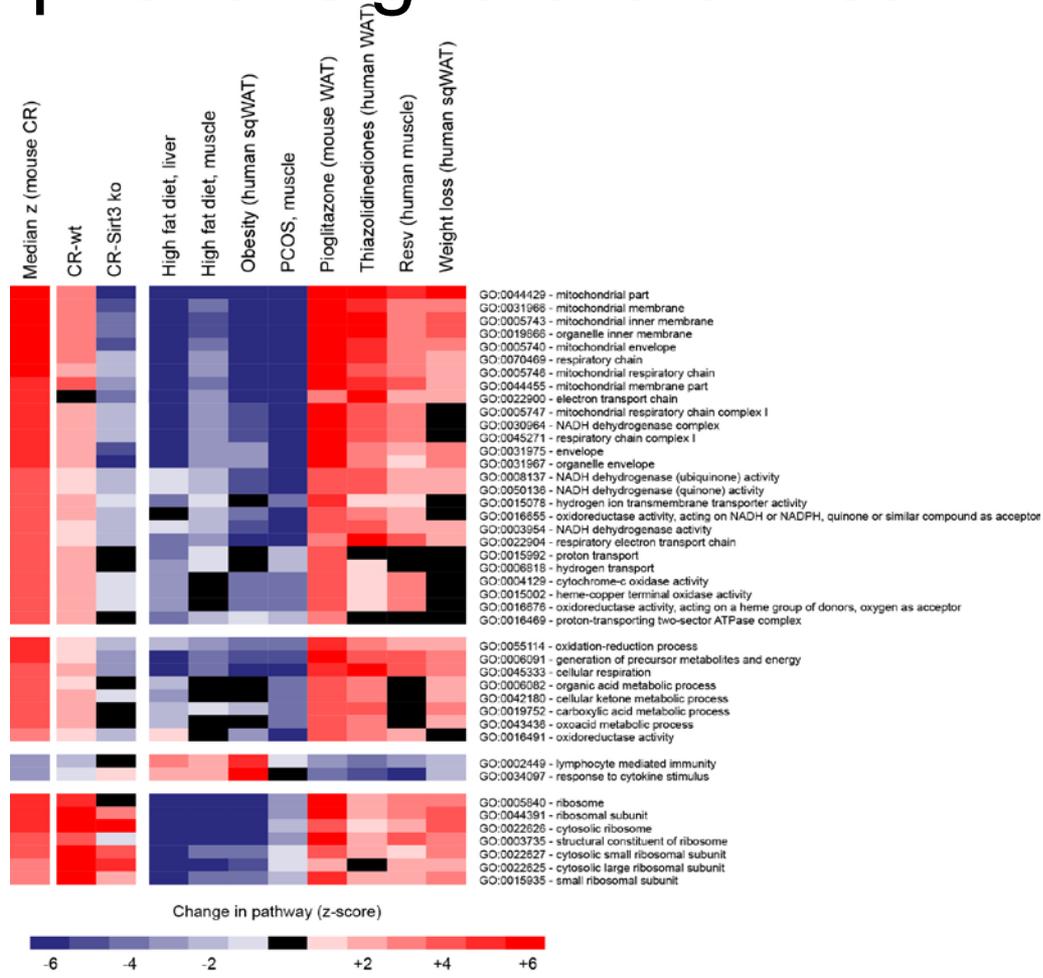


c. Mouse CR vs dwarf mouse





Transcriptional signature of health status





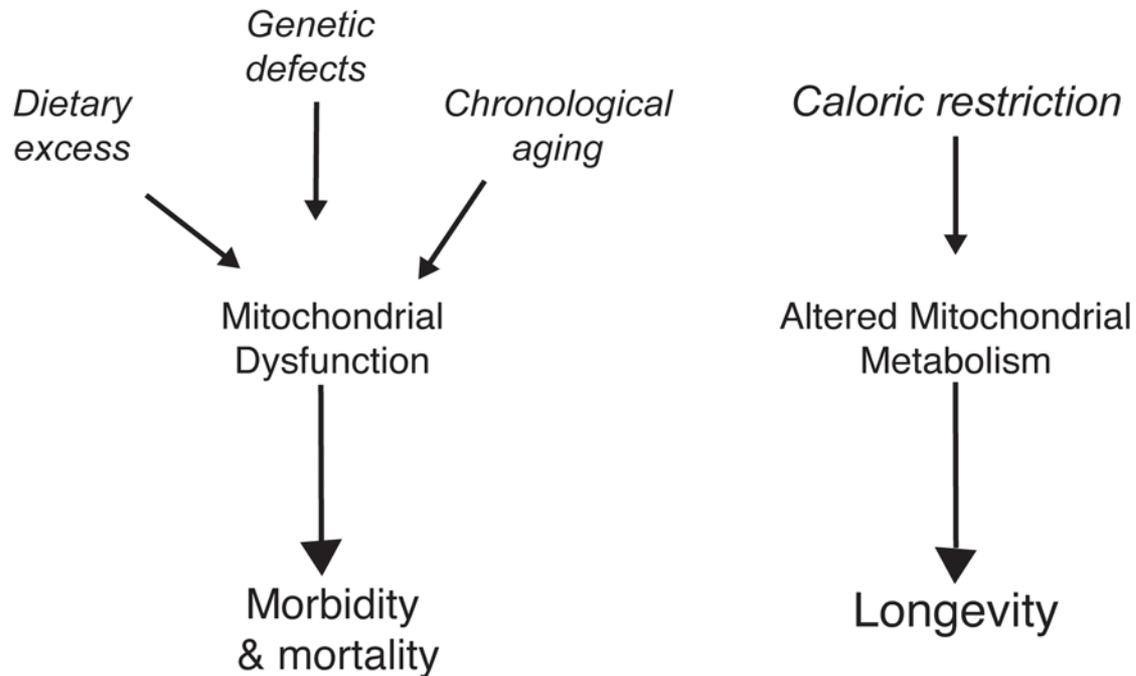
Insights from CR apply to
health not just to aging



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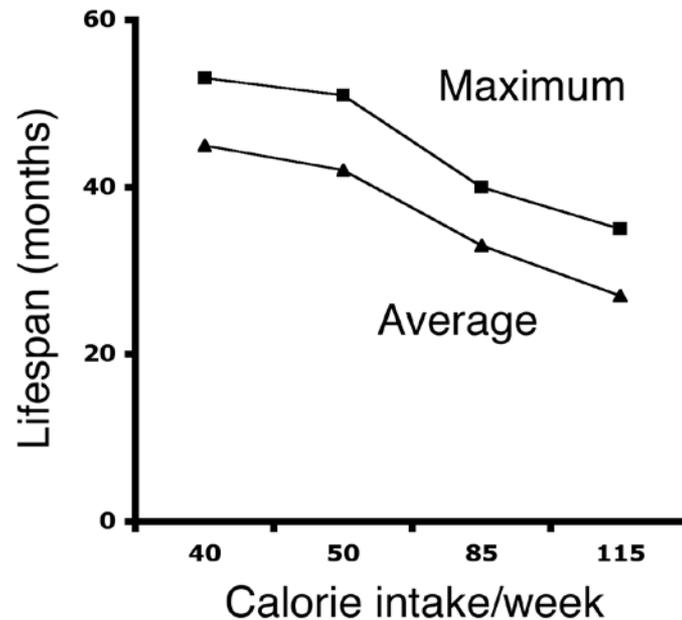


Mitochondrial function influences morbidity and survival





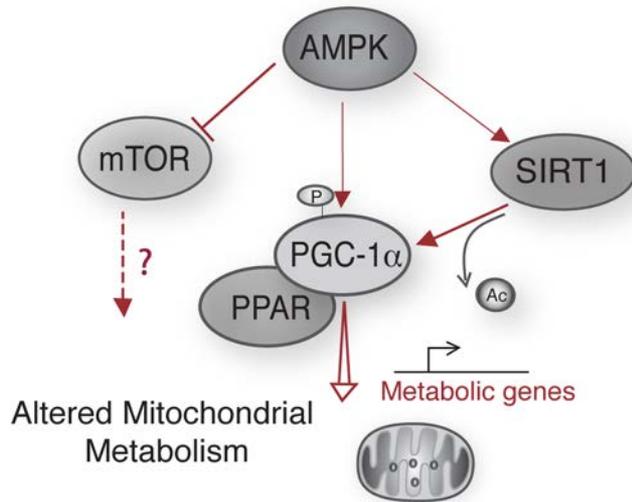
Inverse linear relationship between calorie intake and lifespan in mice



Nutrient sensitive metabolic regulators?



Aging, diet, and disease vulnerability, a central role for metabolic integrity



	Energy metabolism	Insulin sensitivity	Adiposity	Disease vulnerability
<i>Aging</i>	↓	↓	↑	↑
<i>Caloric restriction</i>	↑	↑	↓	↓
<i>Dietary excess</i>	?	↓	↑↑	↑

Metabolic indicator	amino acids	NAD	AMP	fatty acids
Metabolic regulator	mTOR	sirtuins	AMPK	PPARs



Metabolic reprogramming by CR

Hypothesis: CR induces a state of altered energy metabolism that underlies it's ability to slow aging

Fundamental questions:

- i) what are the mechanisms of CR, studies in mice, flies, worms, and yeast
- ii) are CR insights translatable to human health, studies in NHPs
- iii) can we identify CR mimetics, small molecule screens, pharmaceuticals nutraceuticals, ITP





Nonhuman primates
have a lot to offer



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Why the monkey model matters

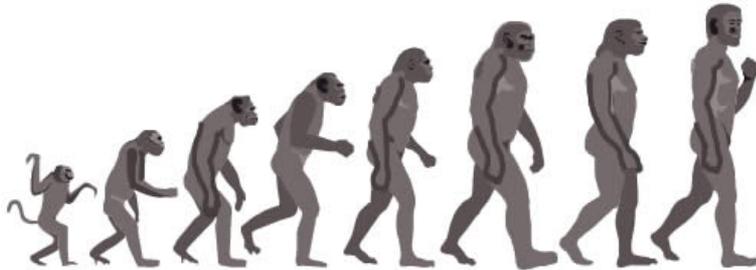


Table 3 - Body composition of adult Rhesus monkeys.

AGE	N	LTM (kg)	FTM (kg)	% FTM (%)
FEMALES				
YA	7	5.05±0.11	0.95±0.44	13.3±5.3
MA	7	5.55±0.14	2.38±0.22	29.7±1.7
OA	7	4.50±0.31	1.75±0.45	18.5±4.7
MALES				
YA	7	7.57±0.32	0.73±0.17	8.4±1.6
MA	7	7.56±0.35	1.24±0.41	18.0±4.1
OA	6	6.20±0.43	1.43±0.50	16.4±4.2
ANOVA p-values				
Sex		0.001	NS	0.057
Age		0.001	0.009	0.007

Values are means ± SEM. Age: YA=6-9 years; MA=15-19 years; OA=26-30 years. LTM, FTM: lean and fat tissue weight; BMC, BMD: bone mineral content and density, respectively. There were no significant interactions.

Table 2 - Indices of adiposity and tissue distribution.

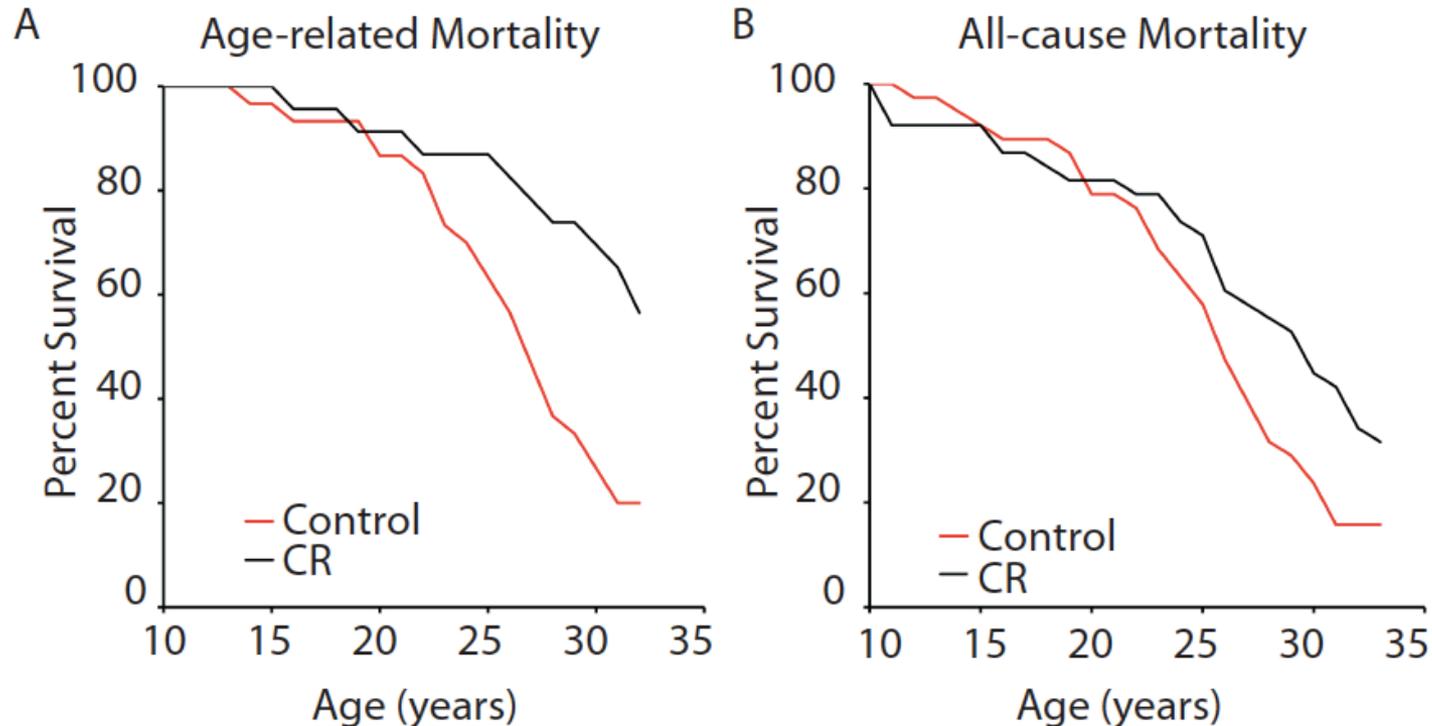
AGE	N	BMI (kg/m ²)	BULGE	SAG
FEMALES				
YA	7	29.55±2.27	0.72±0.06	0.88±0.03
MA	7	36.54±1.23	0.90±0.01	0.96±0.02
OA	7	28.35±2.62	0.90±0.07	1.01±0.05
MALES				
YA	7	32.59±0.92	0.65±0.01	0.81±0.02
MA	7	37.41±1.46	0.77±0.04	0.88±0.03
OA	6	33.50±3.40	0.86±0.07	0.97±0.04
ANOVA p-values				
Sex		NS	NS	0.02
Age		0.007	0.001	0.0002

Values are means±SEM. Age: YA=6-9 years; MA=15-19 years; OA=26-30 years. BMI: body mass index (BW/CR²); BULGE, SAG: ABCIR/CR and ABCIR/CHCIR, respectively. There were no significant age*sex interactions.

Hudson et al 1996 Aging Clin. Exp. Res. 8:197

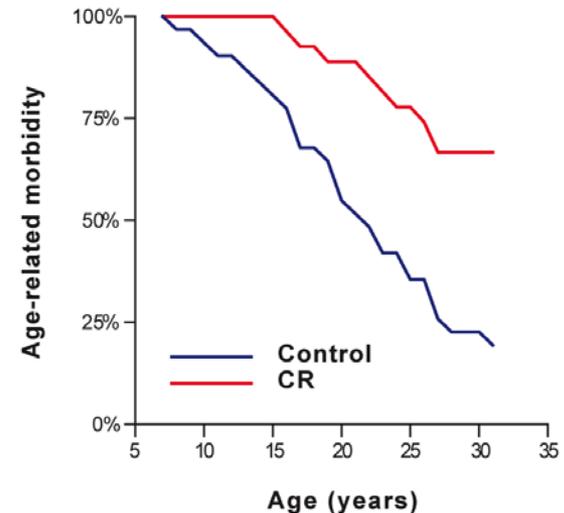
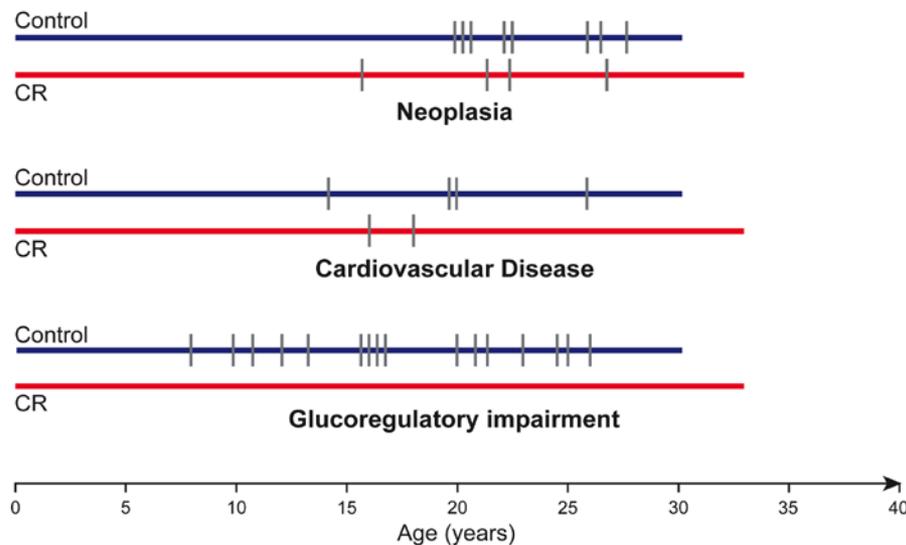


Adult onset CR lowers the incidence of age-related death in monkeys



Of the original 76 animals, 63% of the control animals died of age-related causes compared to 26% of the CR group (HR 2.4, $p < 0.001$).

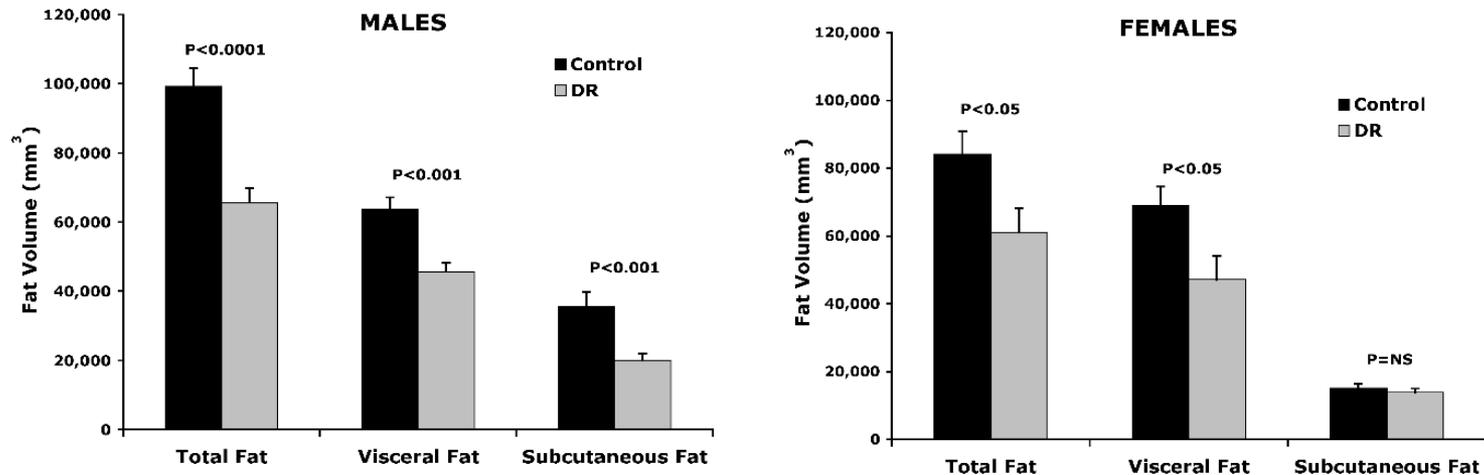
CR delays the onset of age-related disease in monkeys



Age-associated disease was detected at 3 times the rate in Control animals compared to CR animals.



CR reduces adiposity in a depot and gender specific manner

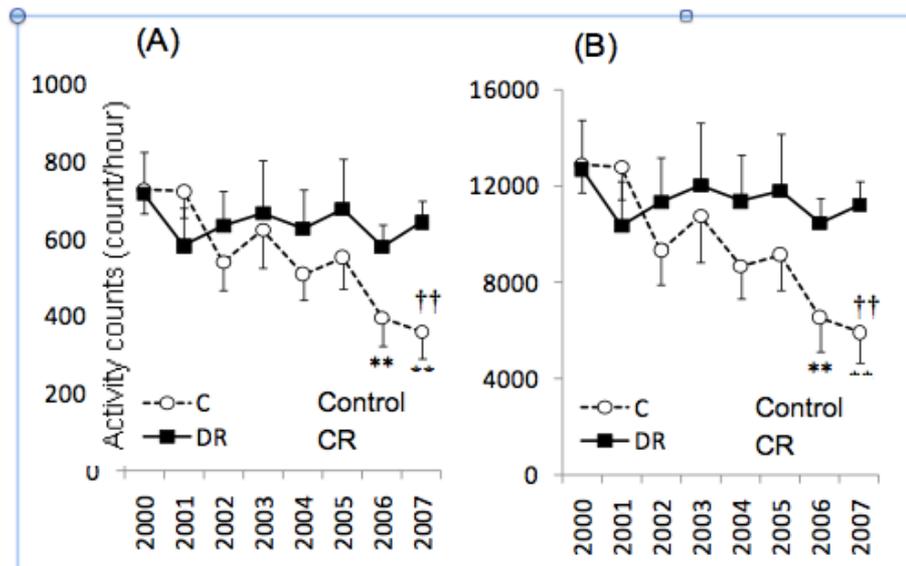


MRI detection of abdominal adiposity

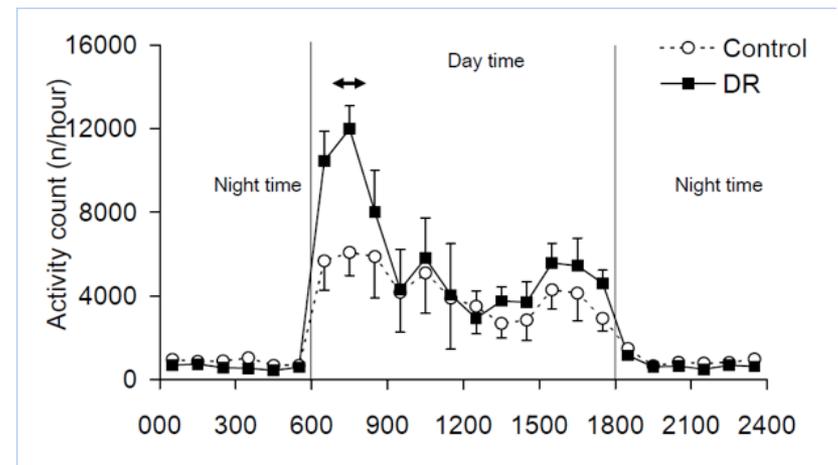


CR prevents the age associated decline in physical activity

Longitudinal data



24 hour data

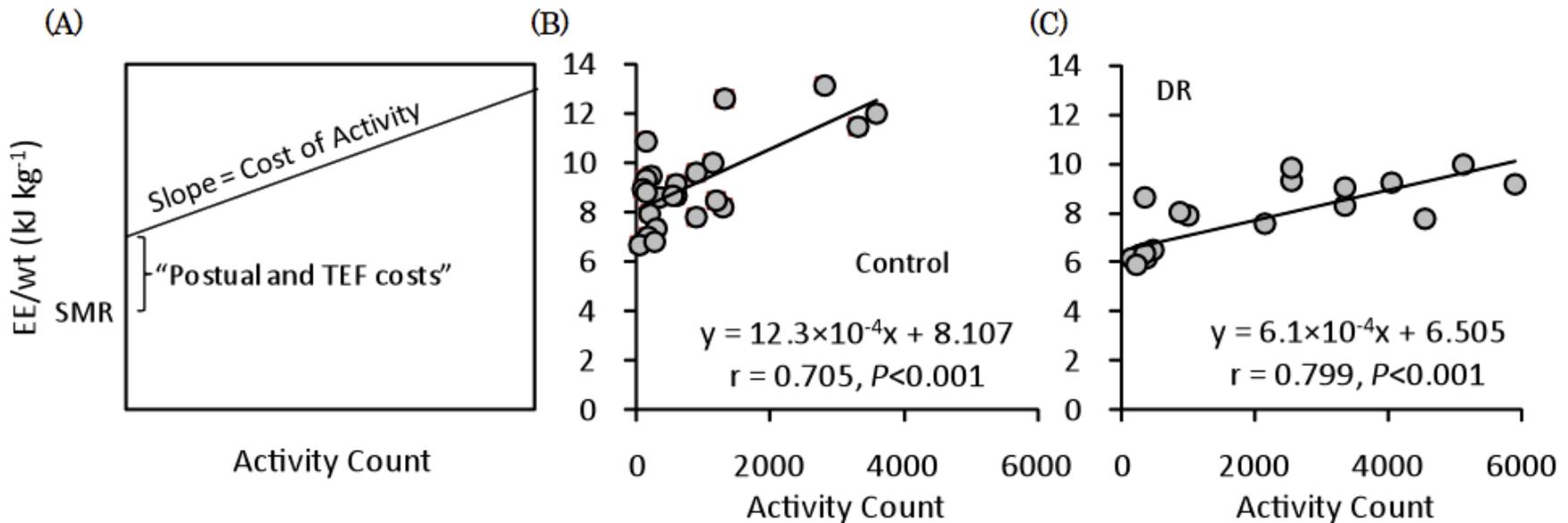


Metabolic chamber



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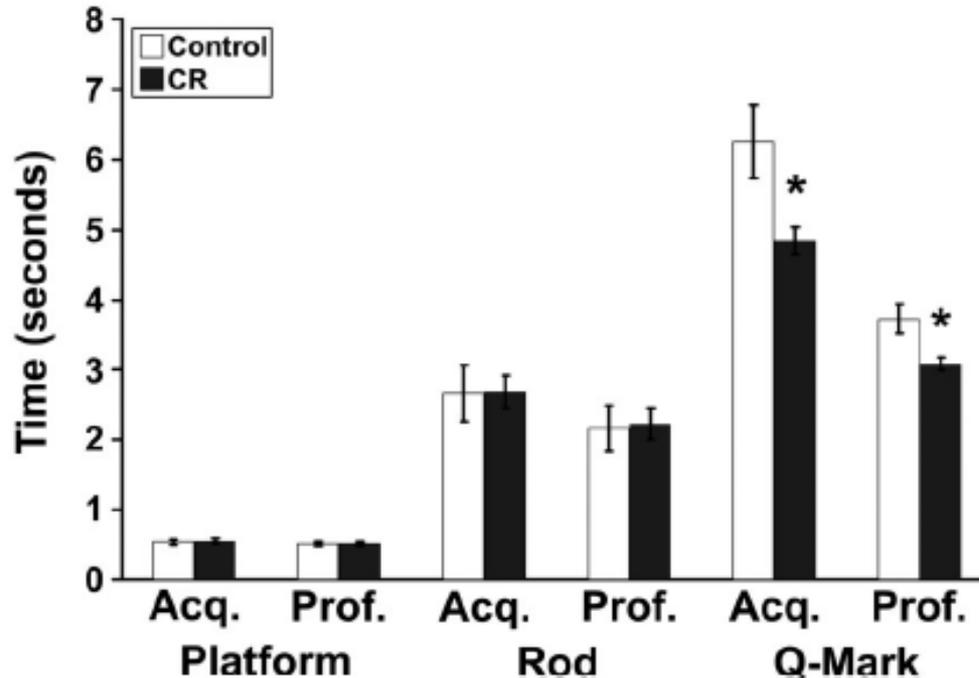
CR prevents the age associated decline in physical activity and decreases the metabolic cost of movement





CR enhances learning and execution in motor function tests

Fine Motor Performance During Different mMAP Tasks



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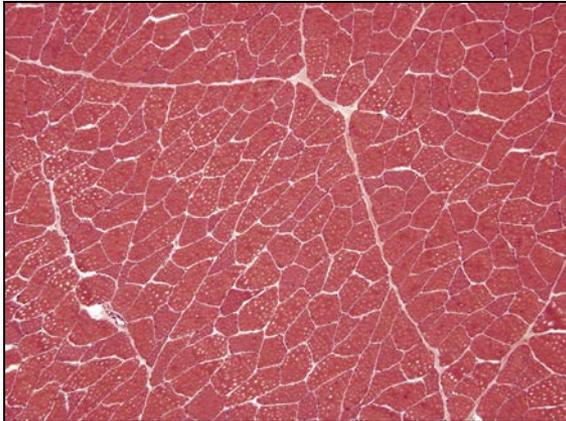


CR delays or prevents multiple age-related disease and disorders

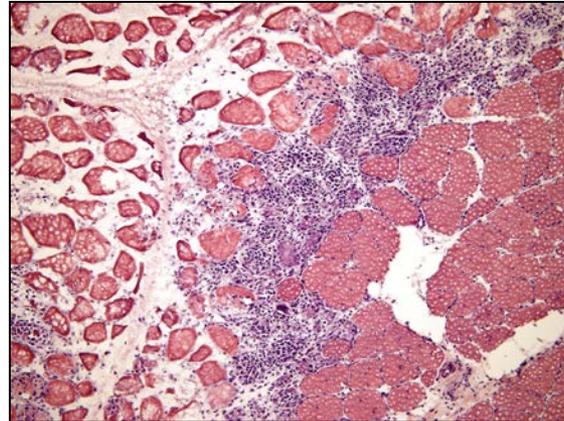


Age induced changes in morphology and composition in skeletal muscle

middle age



Extreme old age

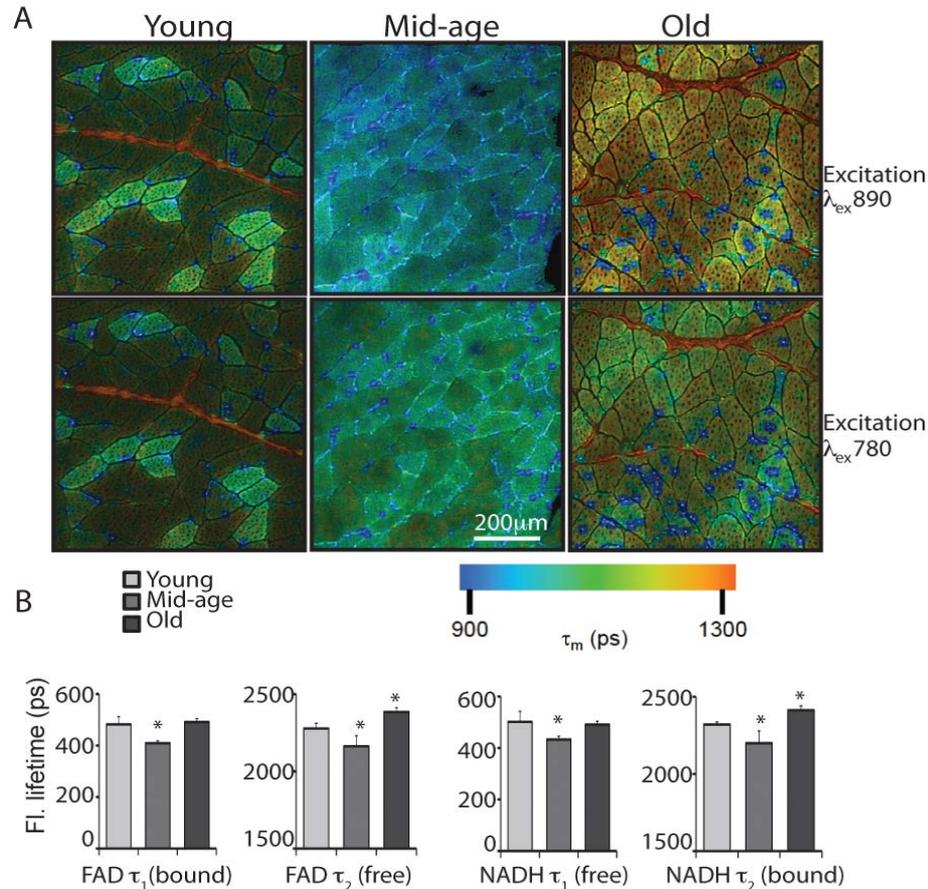


Phenotypes of sarcopenia

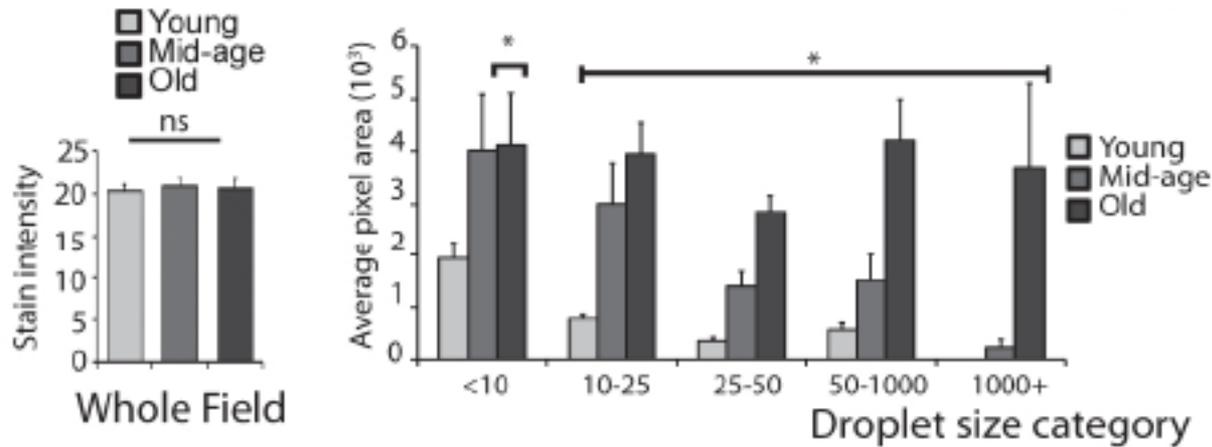
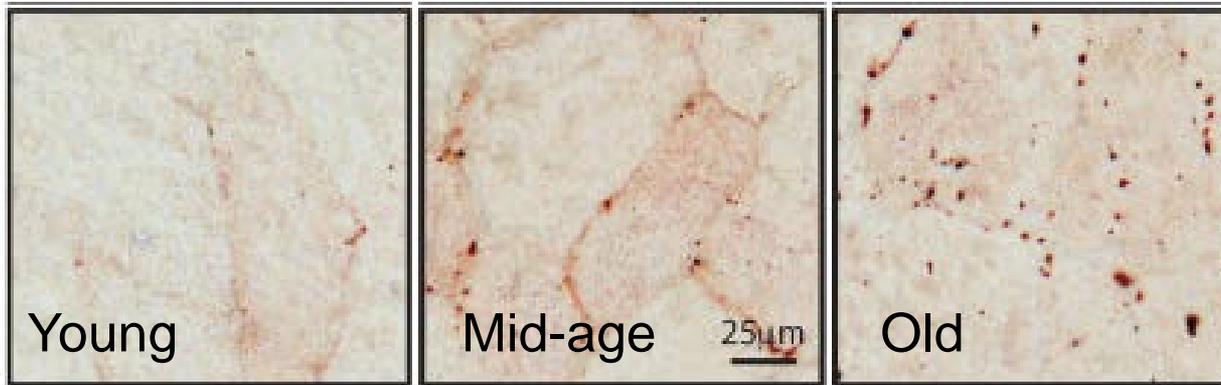
- Fiber loss
- Fiber atrophy
- Adiposity
- Inflammation



Metabolic imaging reveals impact of age on intracellular redox metabolism



Aging increases droplet size of intracellular lipid stores



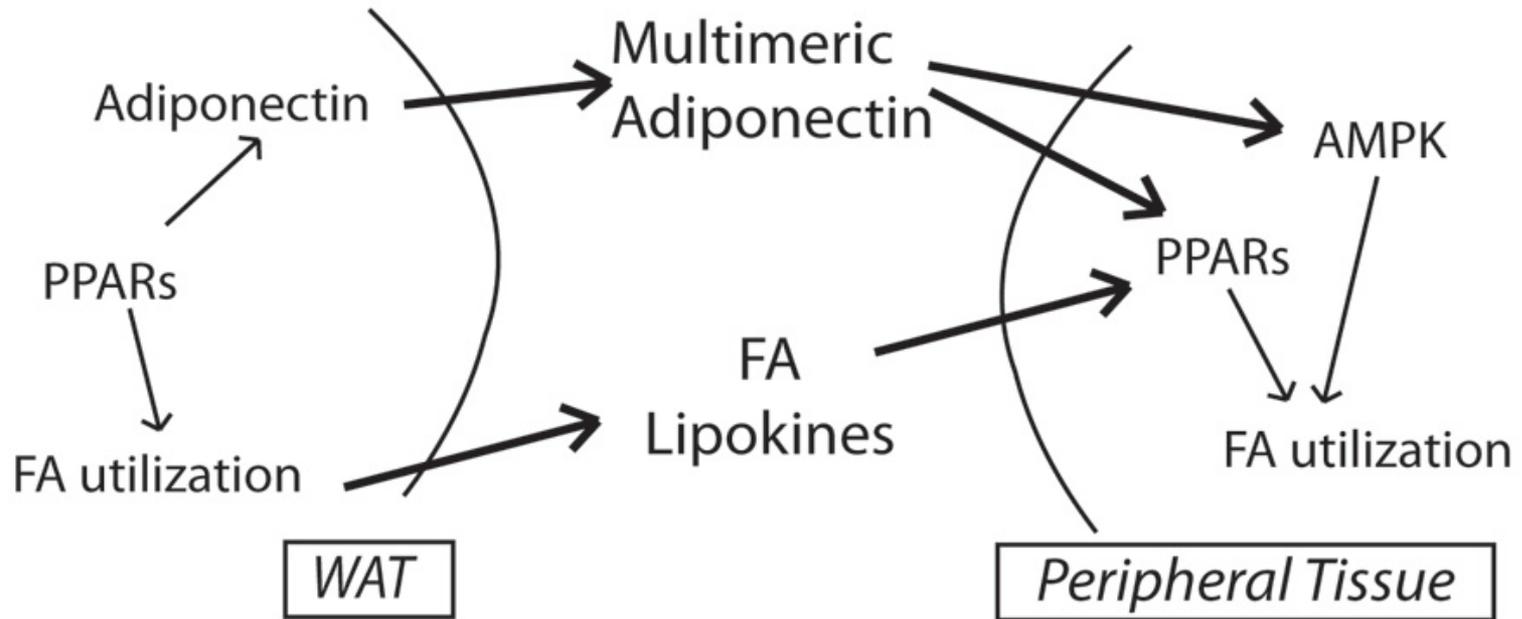


The Fat's where its At

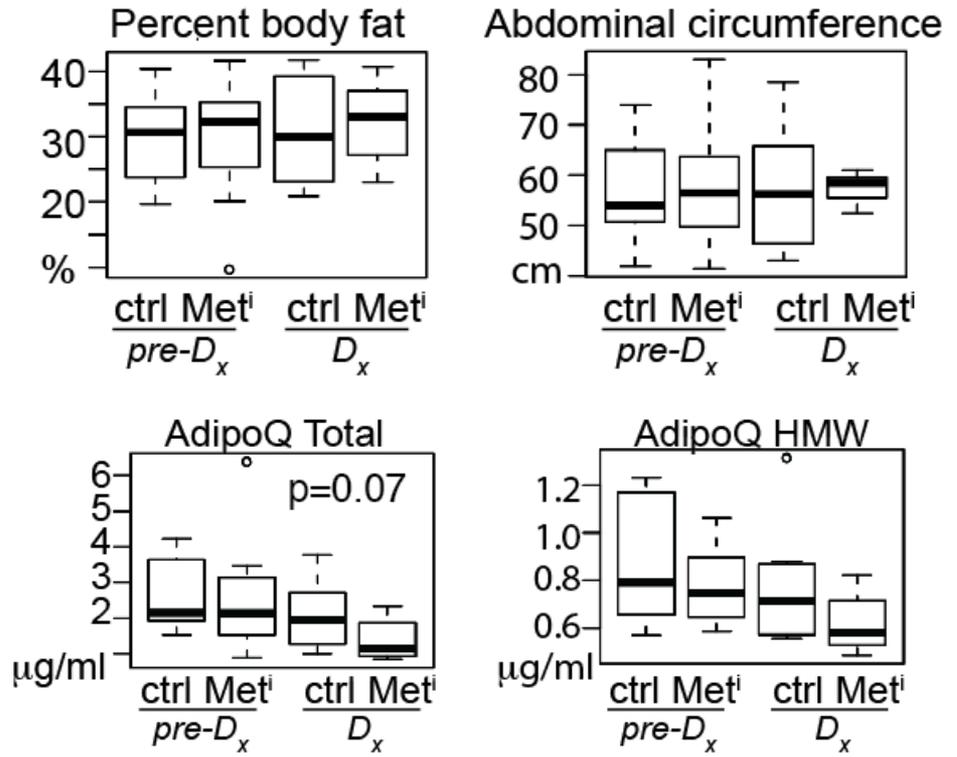
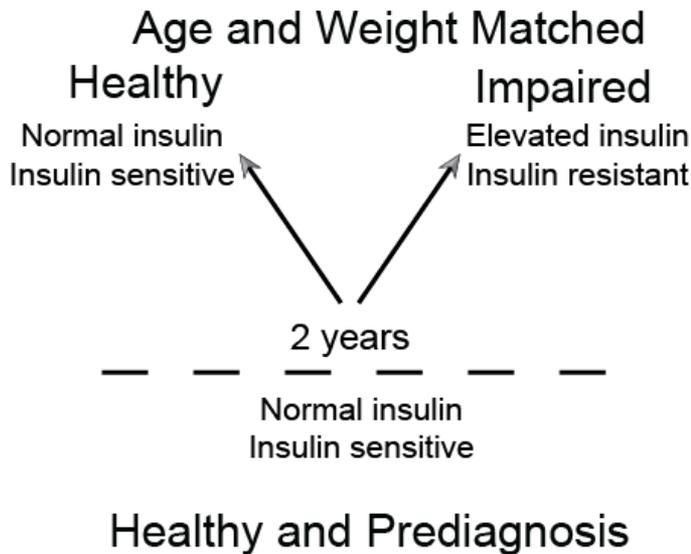


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WAT derived Systemic Signaling

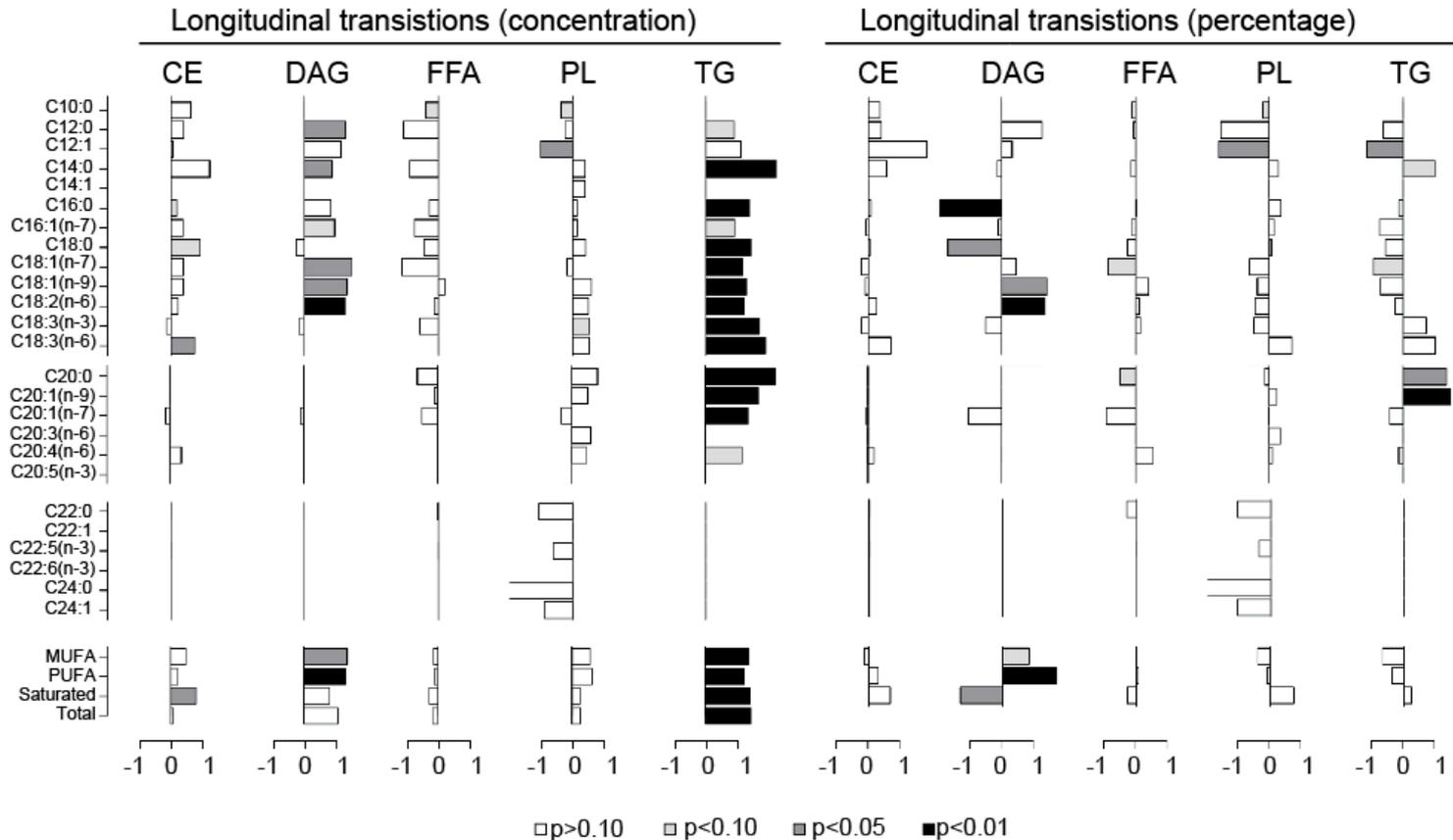


Adiposity and metabolic disease



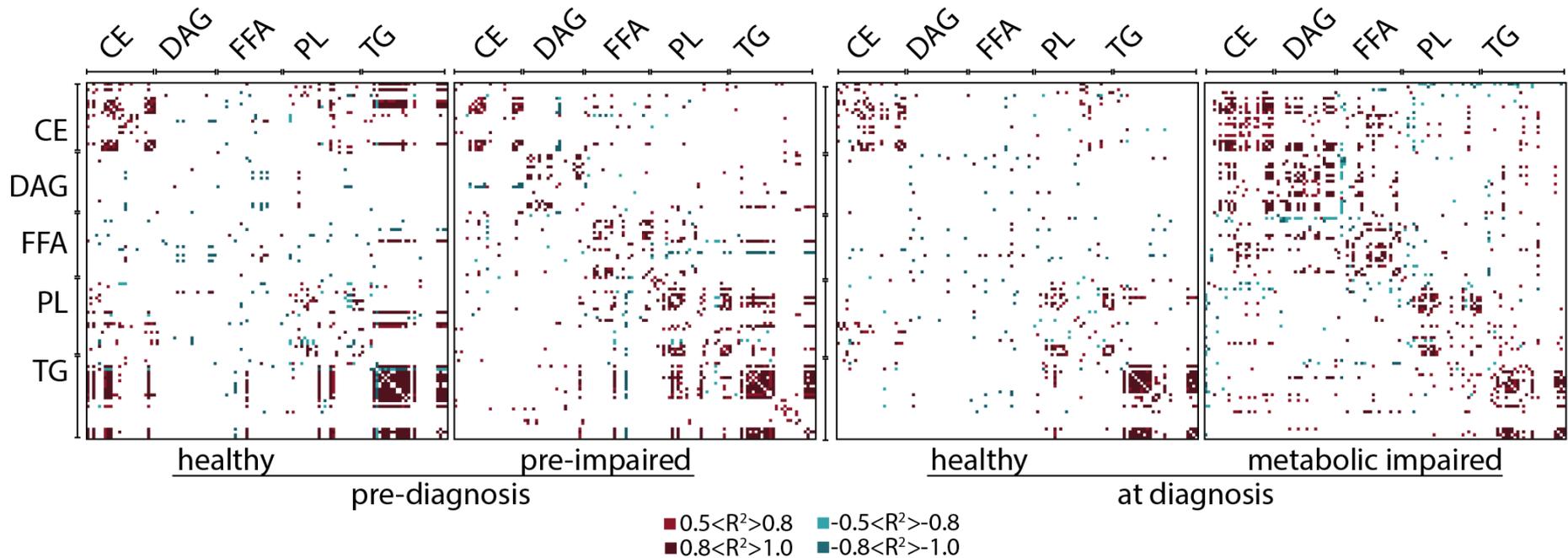


Changes in lipid metabolism and onset of metabolic disease





Lipid profiling reveals late and early effects in the progression to metabolic impairment

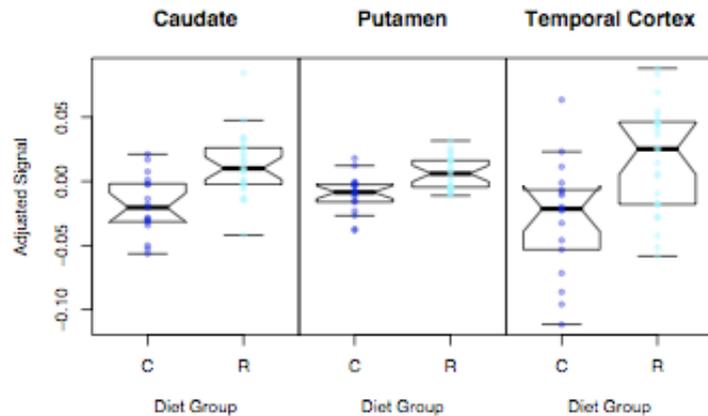
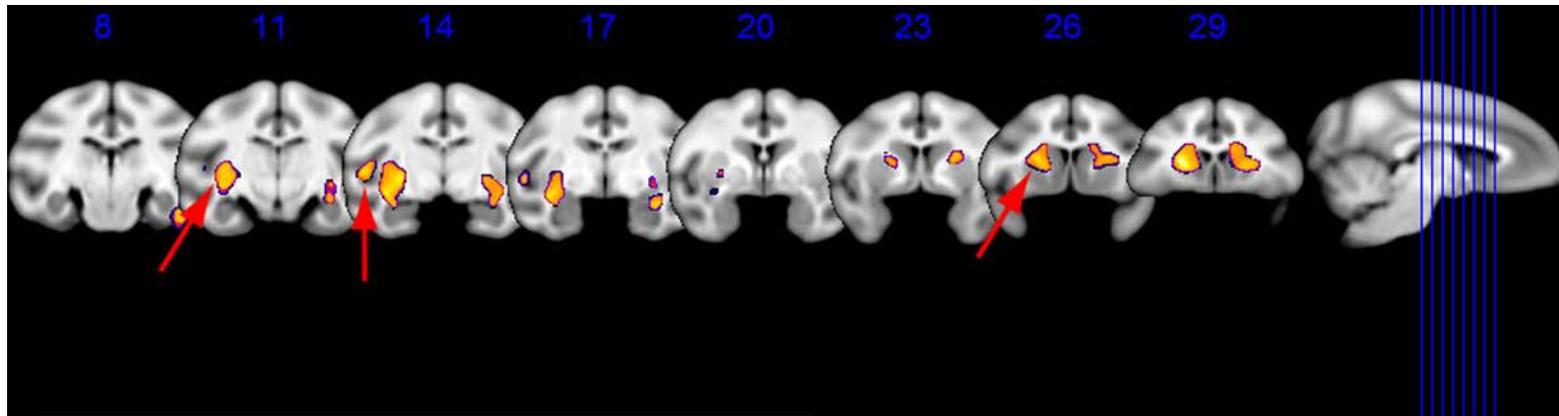




Where and What really matter



CR protects against brain aging

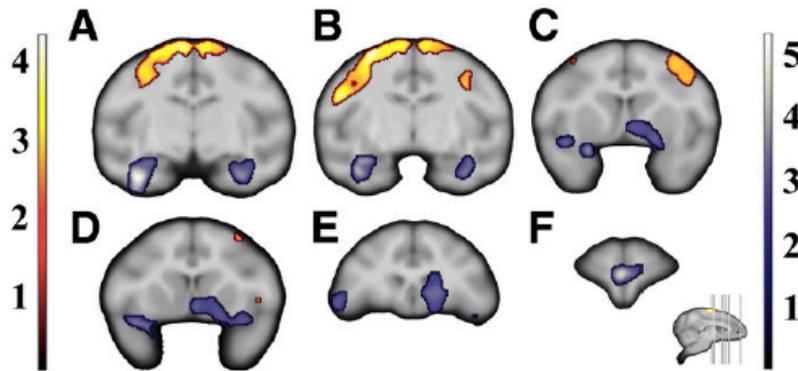


Gray matter regions

- Putamen
- Insula
- Caudate

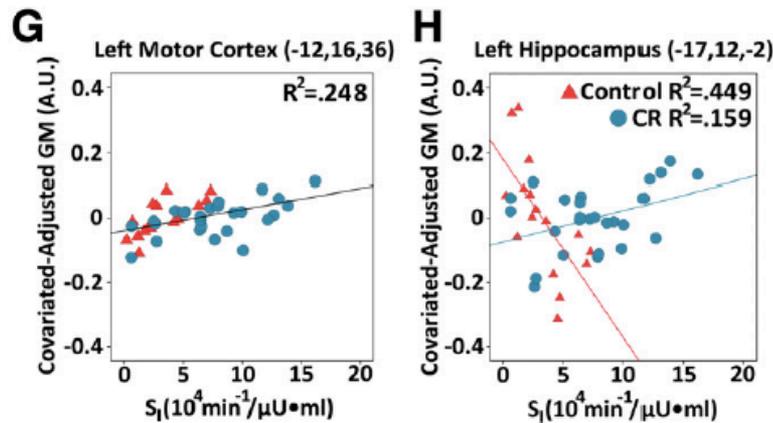
Cognitive & motor functions

Influence of insulin on GM



Motor & somatosensory

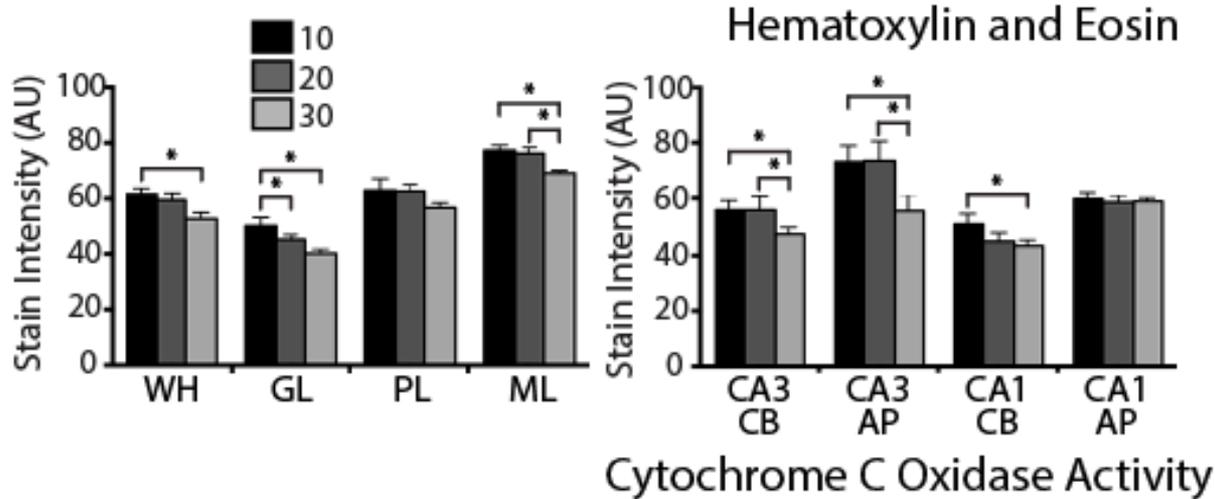
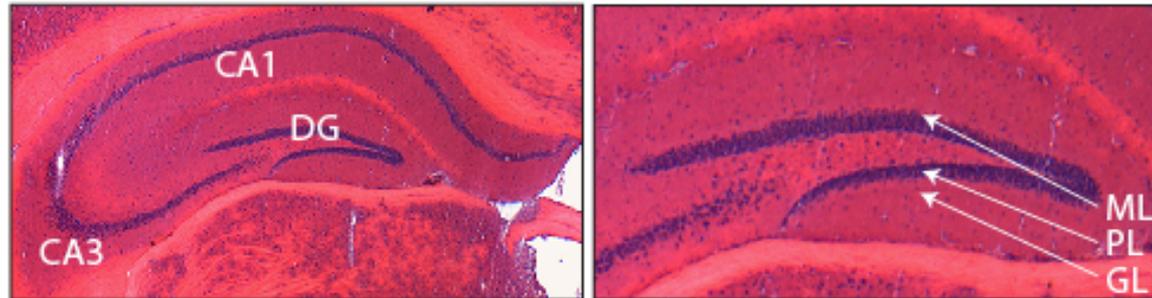
Hippocampus



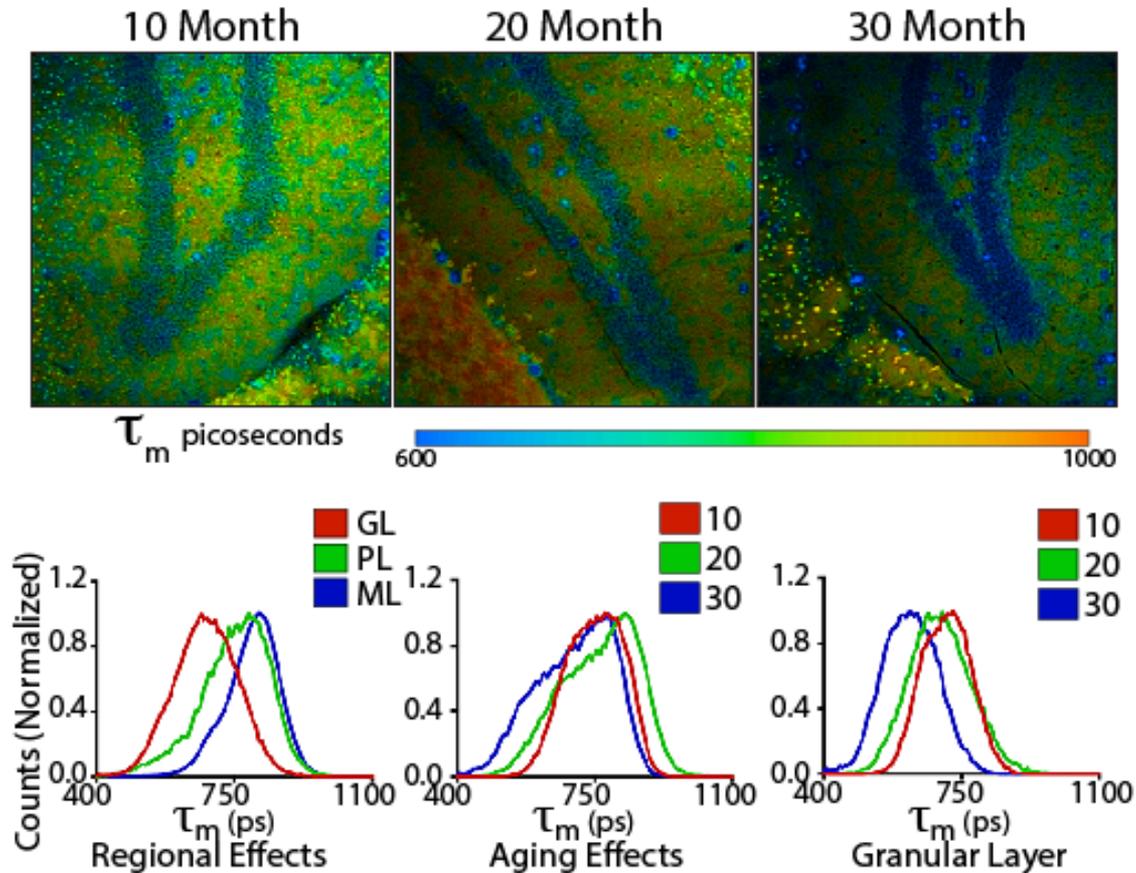
Insulin's effects are region
And diet specific



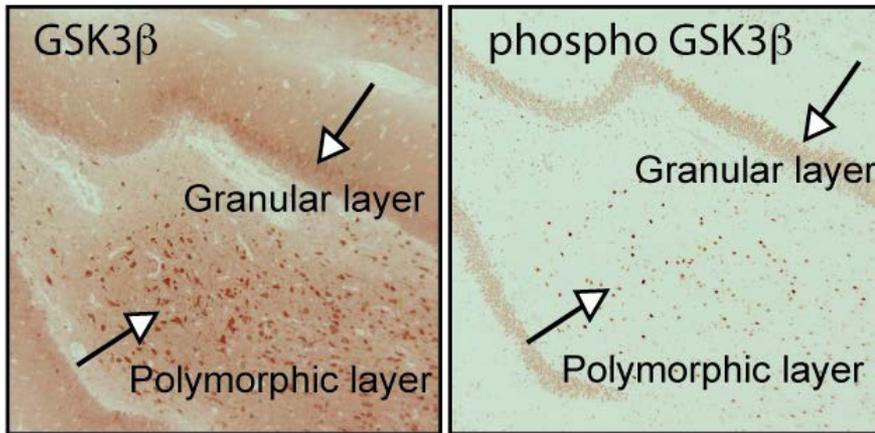
Mitochondrial metabolism in the aging Hippocampus



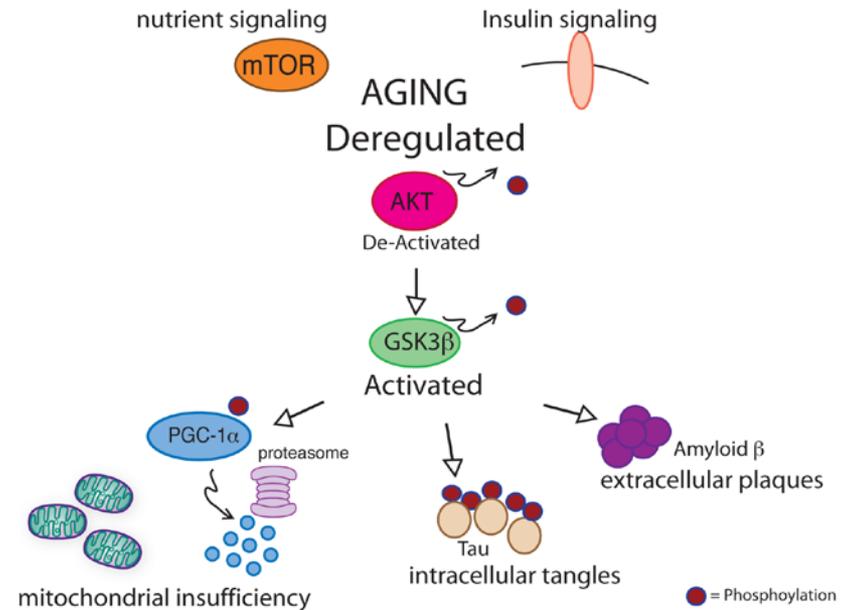
Brain region specific changes in metabolism



Metabolic links to development and progression of neurodegenerative disease



Dentate gyrus from 25 year old rhesus monkey





Insights from CR apply to
health not just to aging

Nonhuman primates have a lot to offer

The Fat's where its At

Where and What really matter

CR research points to a key role for
metabolism in aging & delayed aging





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