

Taking the pulse of aging: early predictors of brain and cognitive decline and risk factors for dementia

Monica Fabiani

OLLI Class
September 23, 2020

I ILLINOIS

Beckman Institute for Advanced
Science & Technology

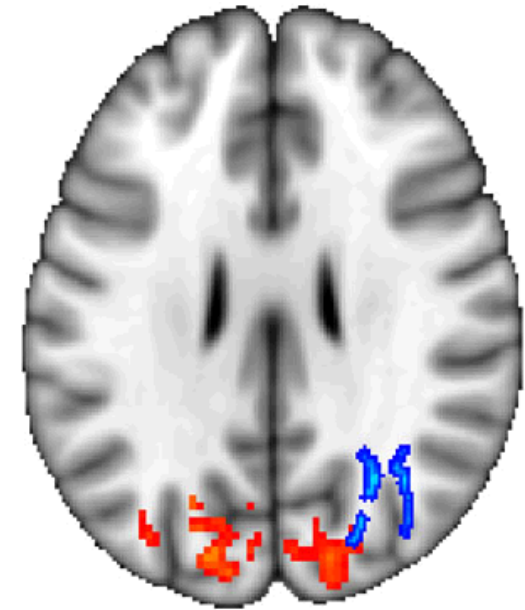


Outline

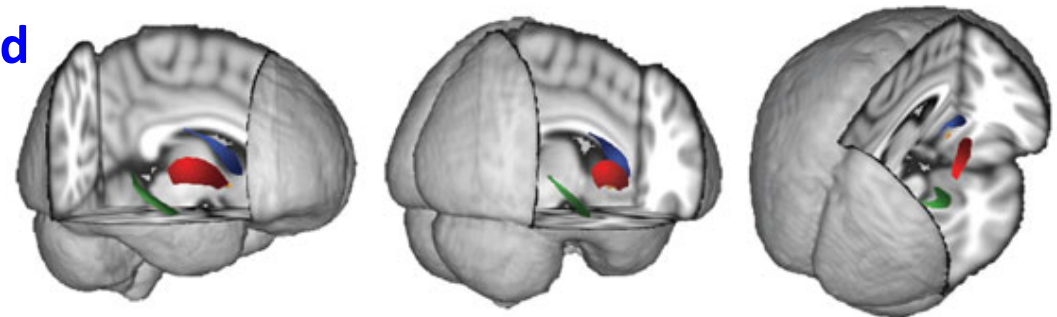
- A lifetime perspective
- A brief history Alzheimer's Disease (AD) and some definitions
- Risk factors for AD
- Cerebrovascular contributions
 - Brief overview of methods
 - Main results and conclusions

A lifespan perspective

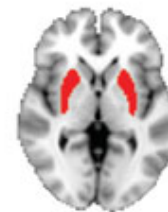
- The brain changes constantly, **even in adults**
 - Changes can result from
 - » Development and **maturation**
 - » **Learning, memory** and other processes
 - » Use (and abuse)
 - » Life-style factors such as...
 - **Nutrition, education, and fitness (e.g., exercise)**
 - » Chronic inflammation and disease states
 - Dementia, Parkinson's, etc.



Scholz et al. (2009) *Nat. Neuroscience*



■ Nucleus Accumbens



■ Putamen



■ Caudate Nucleus

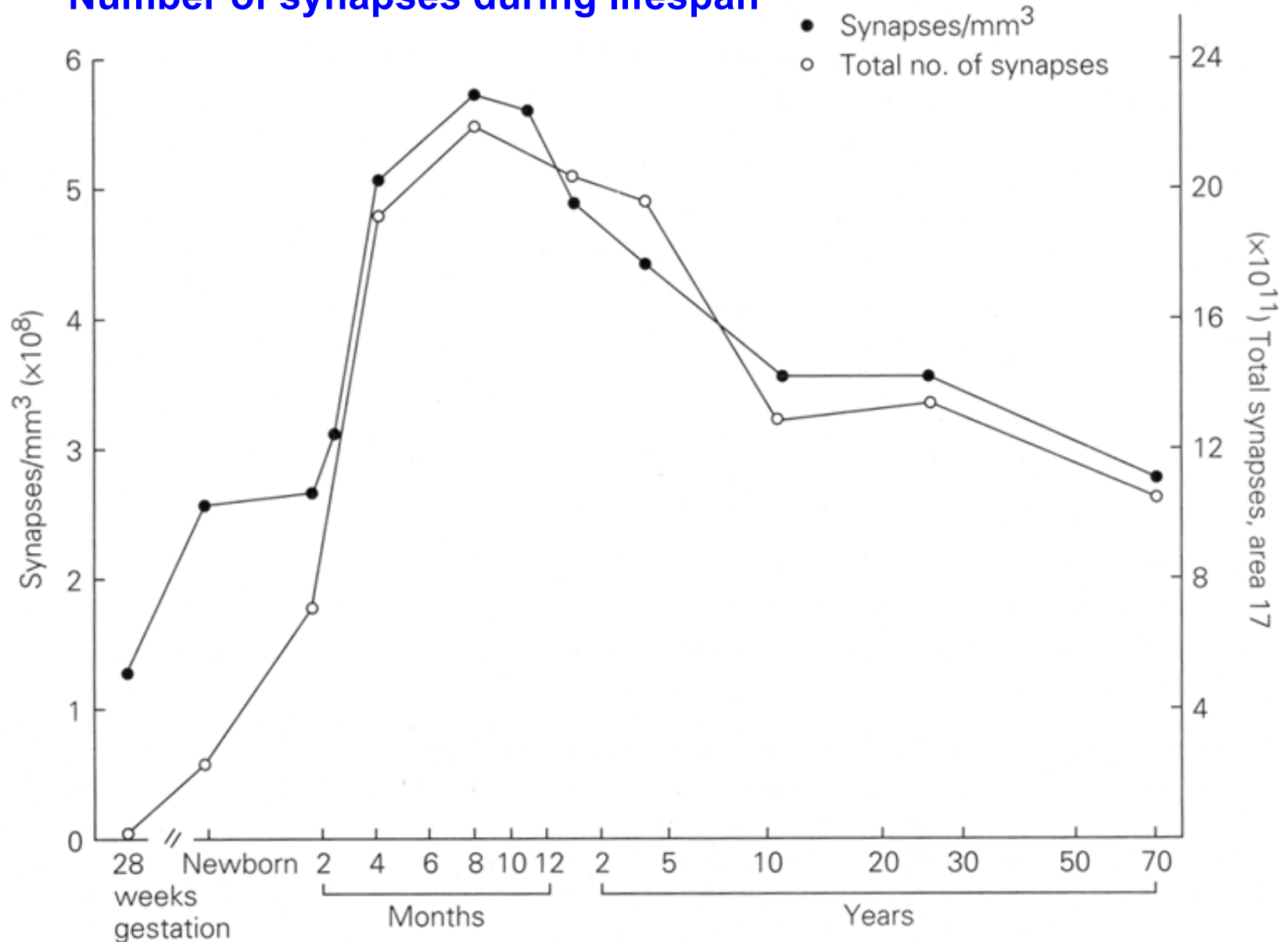


■ Hippocampus

Erickson et al. (2010)
Cerebral Cortex

The human brain is plastic and dynamic

Number of synapses during lifespan



Lifestyle factors are key!

- Lifestyle factors (such as **exercise** and **nutrition**) help promote a healthy cognitive, brain and bodily aging
 - This has been emphasized since the ancient Romans!



Satire X of the Roman poet Juvenal (2nd century AD)

Latin

Orandum est ut sit **mens sana in corpore sano**.
Fortem posce animum mortis terrore carentem,
qui spatium vitae extremum inter munera ponat
naturae, qui ferre queat quoscumque labores,
nesciat irasci, cupiat nihil et potiores
Herculis aerumnas credat saevosque labores
et venere et cenis et pluma Sardanapalli.
monstro quod ipse tibi possis dare; semita certe
tranquillae per virtutem patet unica vitae.

English

You should pray for **a healthy mind in a healthy body**.
Ask for a stout heart that has no fear of death,
and deems length of days the least of Nature's gifts
that can endure any kind of toil,
that knows neither wrath nor desire and thinks
the woes and hard labors of Hercules better than
the loves and banquets and downy cushions of
Sardanapalus.
What I recommend to you, you can give to yourself;
For assuredly, the only road to a life of peace is virtue.

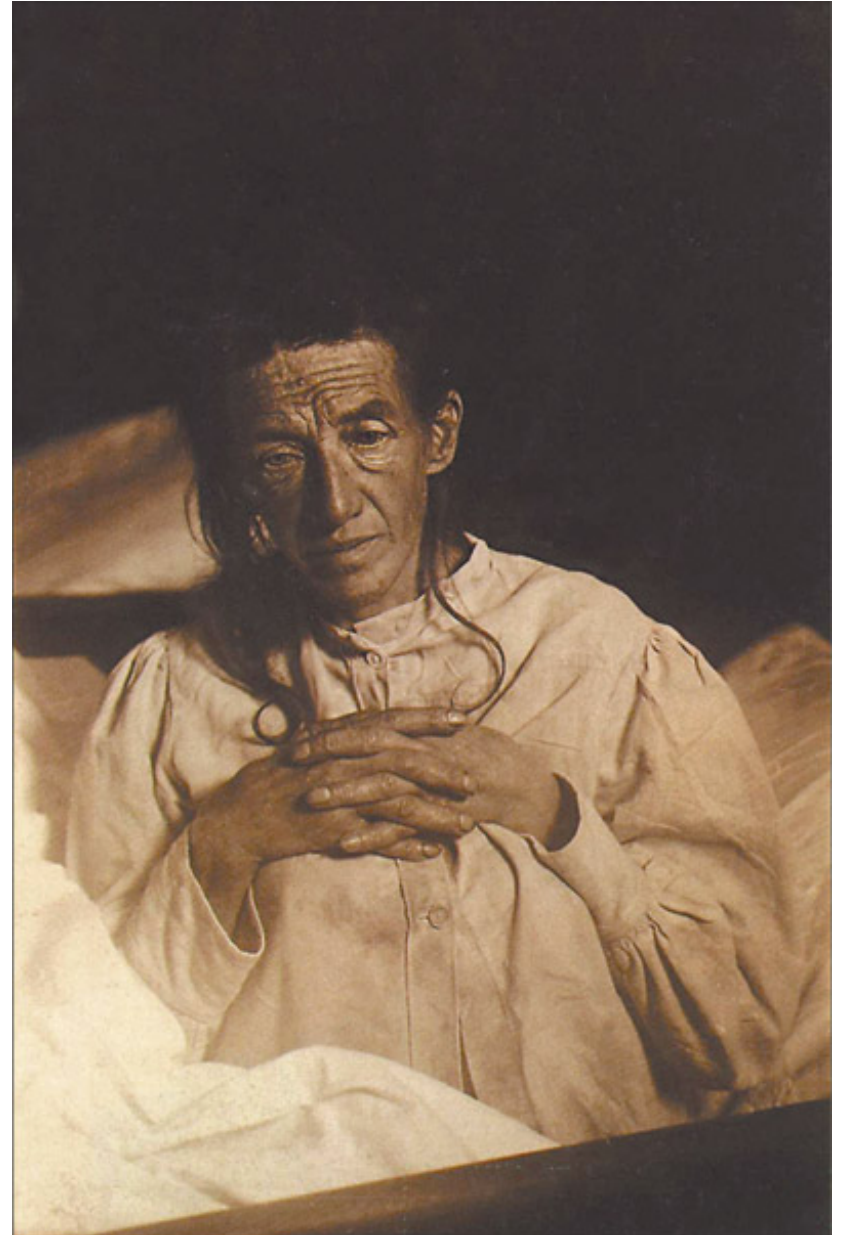
Outline

- A lifetime perspective
- A brief history Alzheimer's Disease (AD) and some definitions
- Risk factors for AD
- Cerebrovascular contributions
 - Brief overview of methods
 - Main results and conclusions

Alois Alzheimer
(1864-1915)



Auguste Deter
(1850-1906)

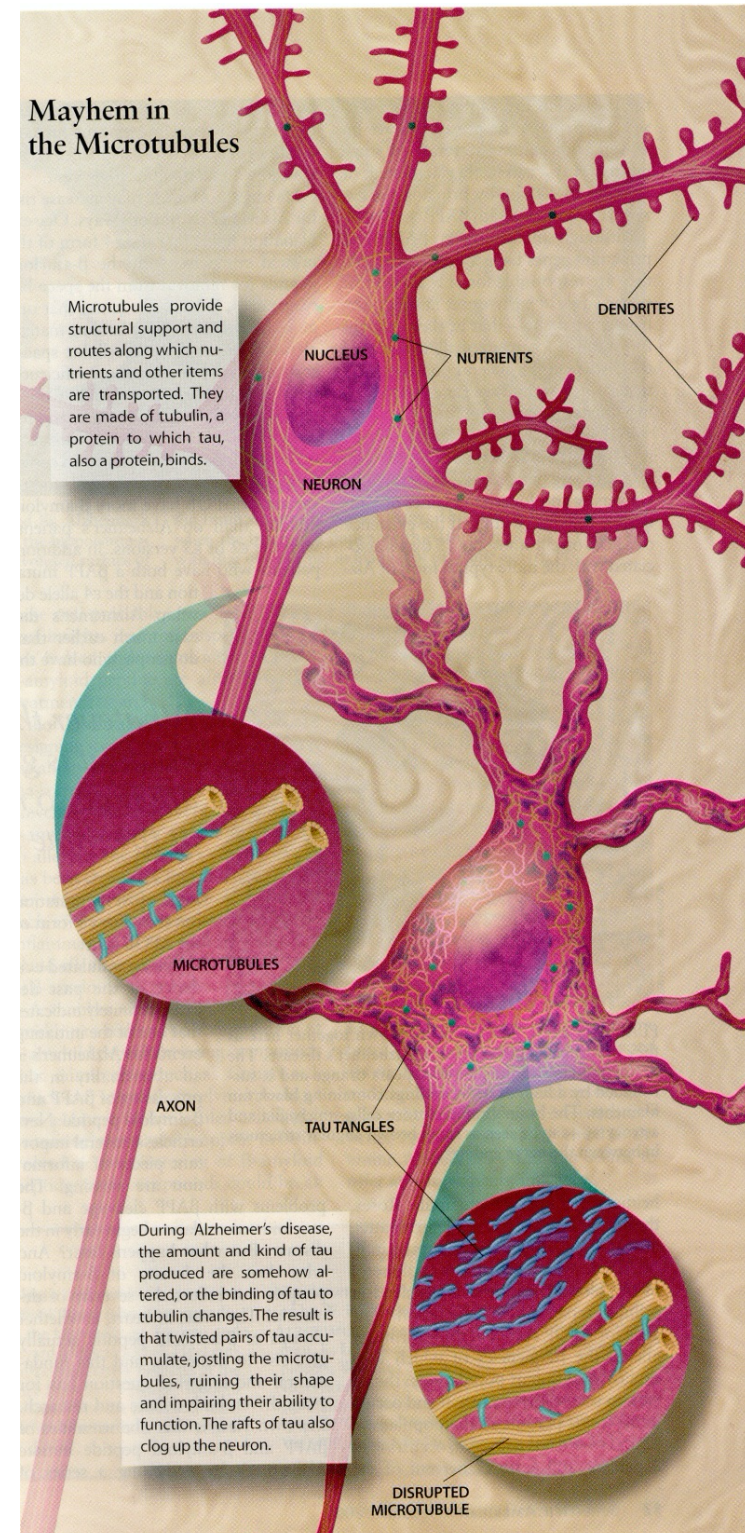


Neurofibrillary tangles



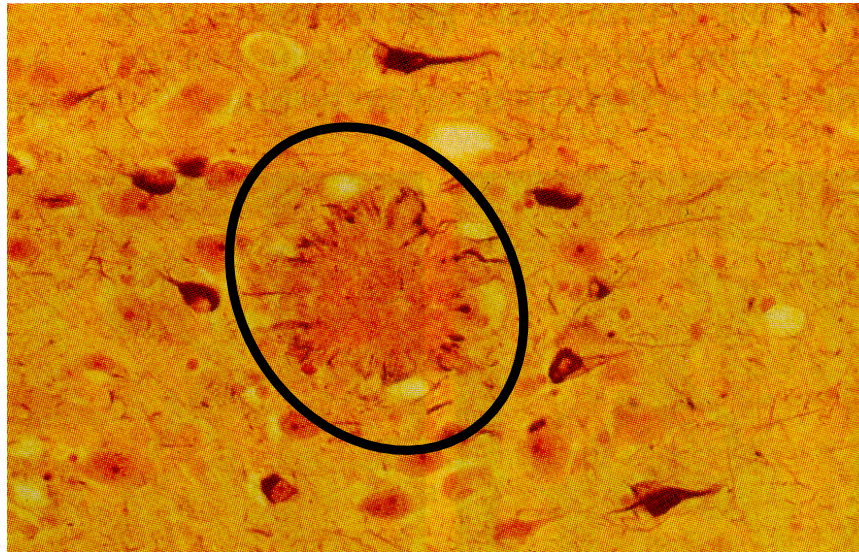
Section of hippocampus from AD patient (silver stain)

- Microtubules are part of the neuron's support system and are bound by the tau protein
- During AD there are alteration in the quantity and type of tau produced

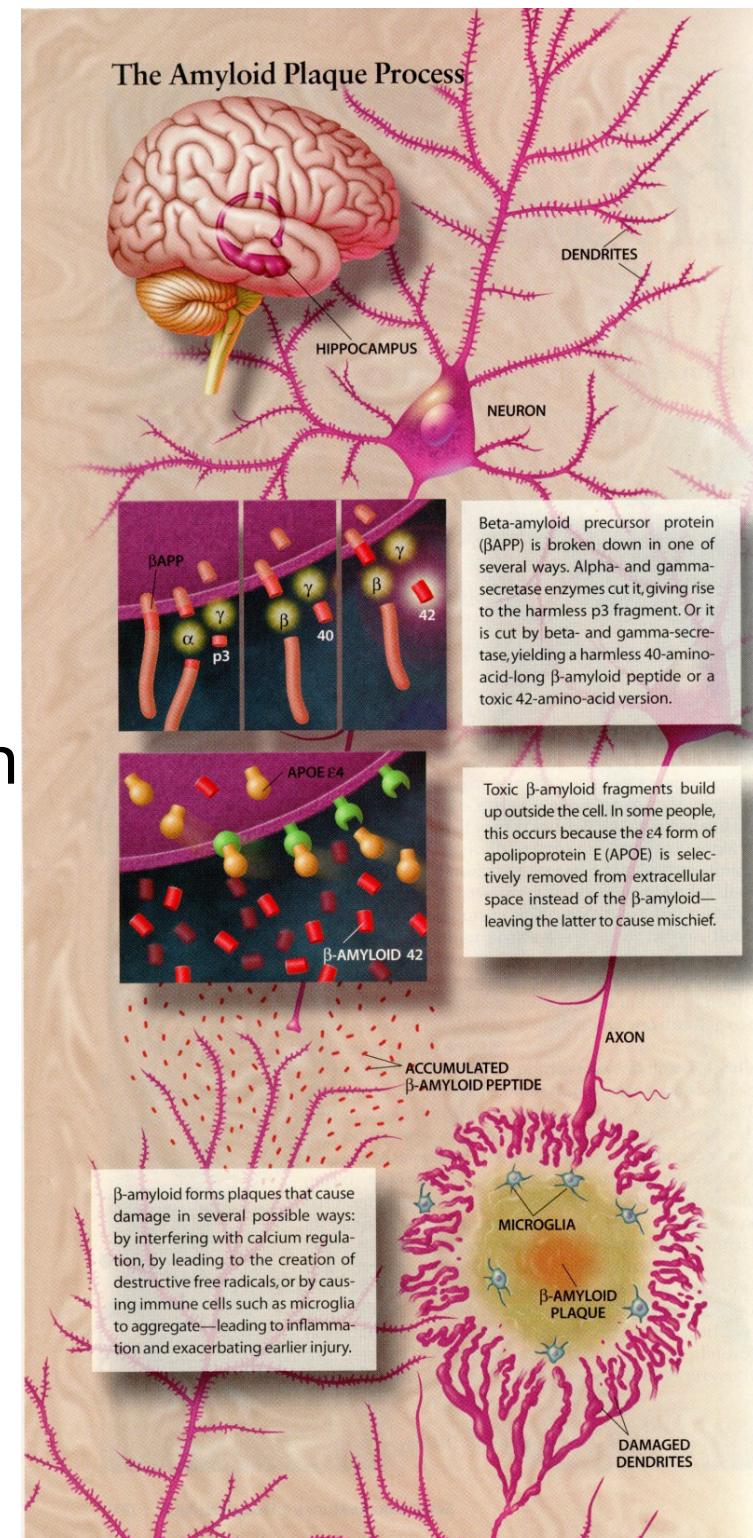


Amyloid plaques

Cortex of AD patient



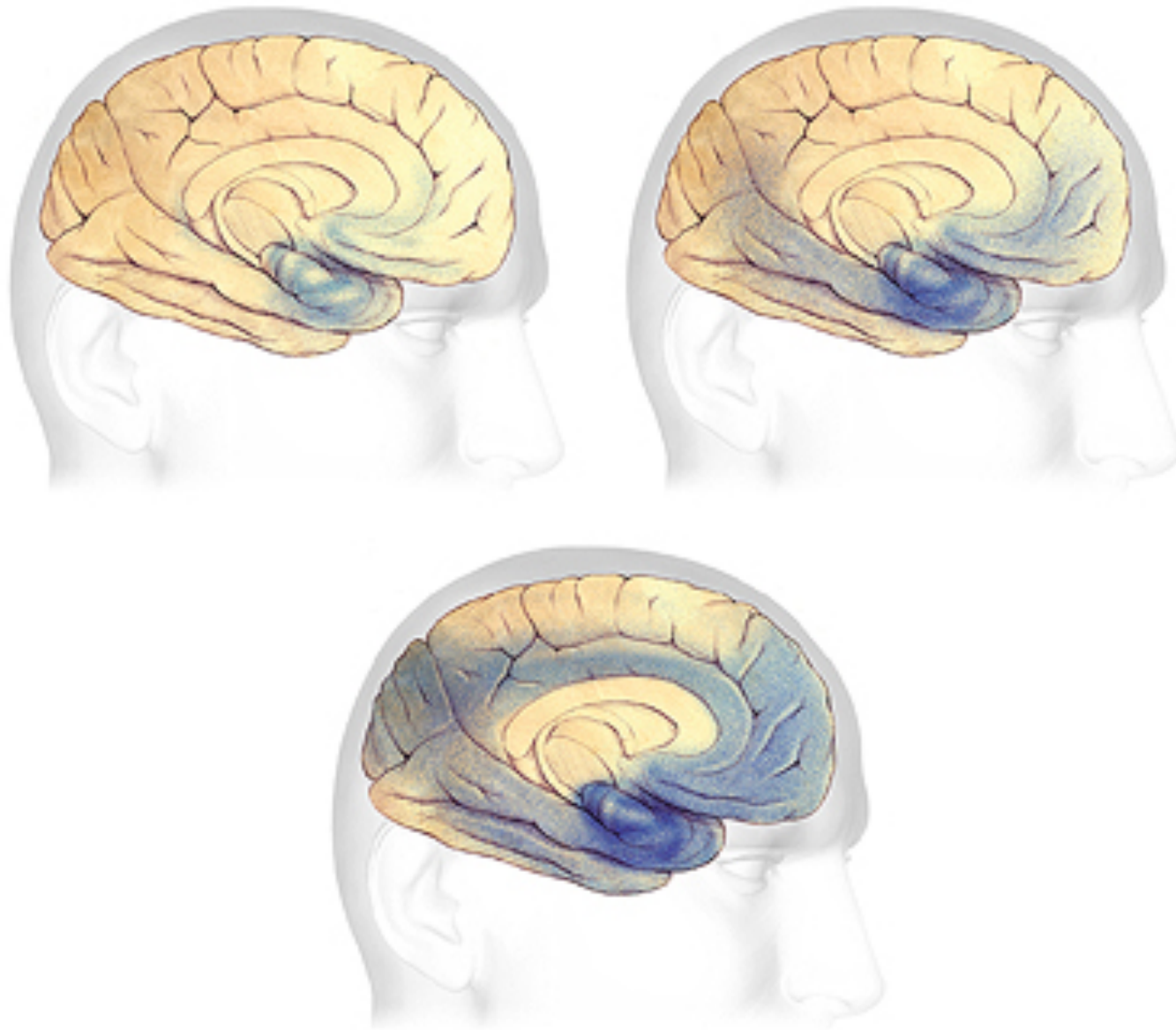
- Amyloid-beta precursor protein plays an essential role in neural growth and repair, but it can break down into toxic fragments
- Beta-amyloid plaques
 - Typically surrounded by neurons containing neurofibrillary tangles
 - Believed to cause vascular damage and neuronal cell loss
 - Found in the brain of the average healthy older individual

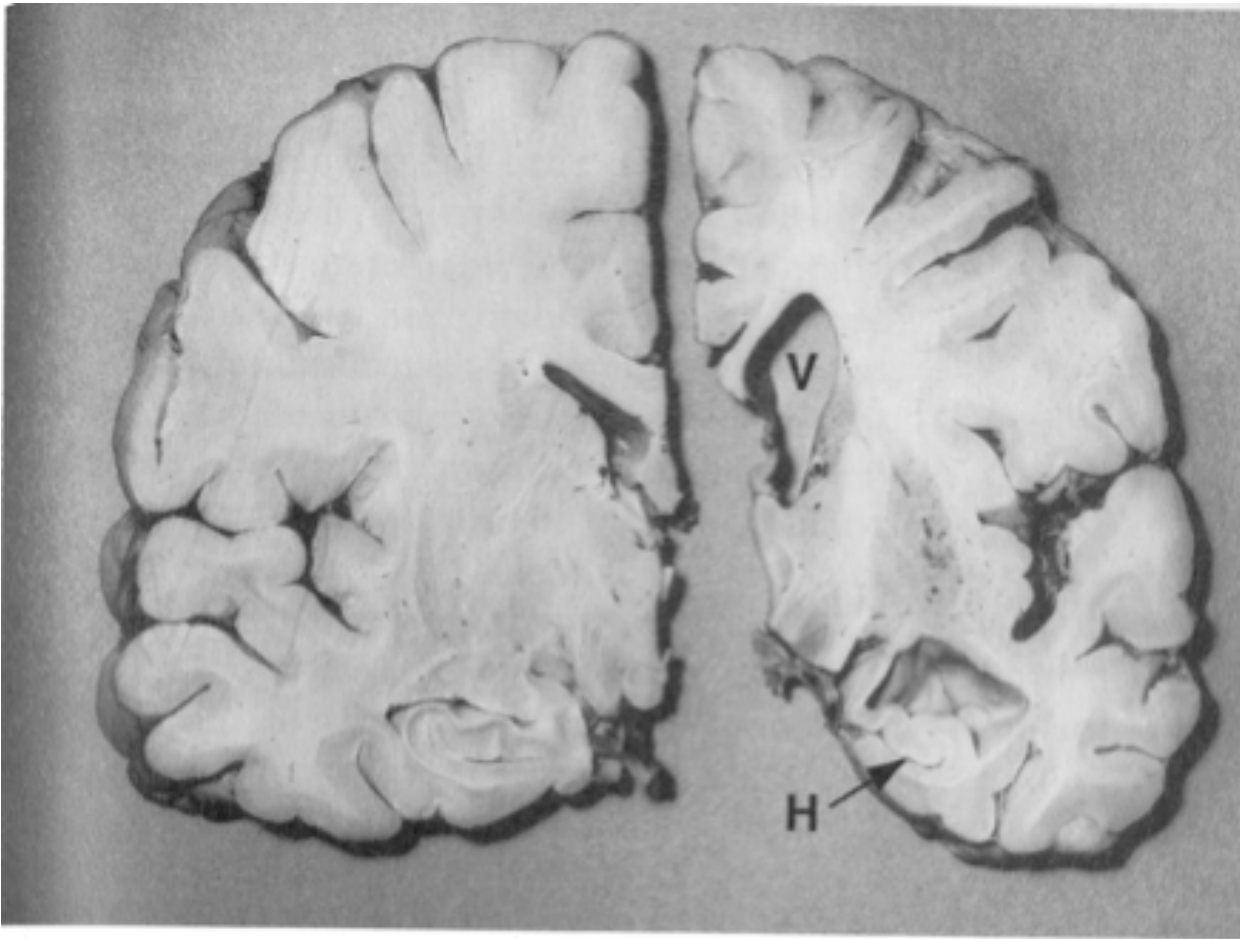


Early classifications of dementia

- **Alzheimer's disease** (rare)
 - Early onset
 - Hereditary
- **Senile dementia** (common)
 - Late onset
 - Attributed to age-related wear and tear
 - Closely linked to arteriosclerosis

Alzheimer's Disease progression through the brain





**H= hippocampus; V= ventricle
75 year old AD patient, 5 years
after onset of AD**

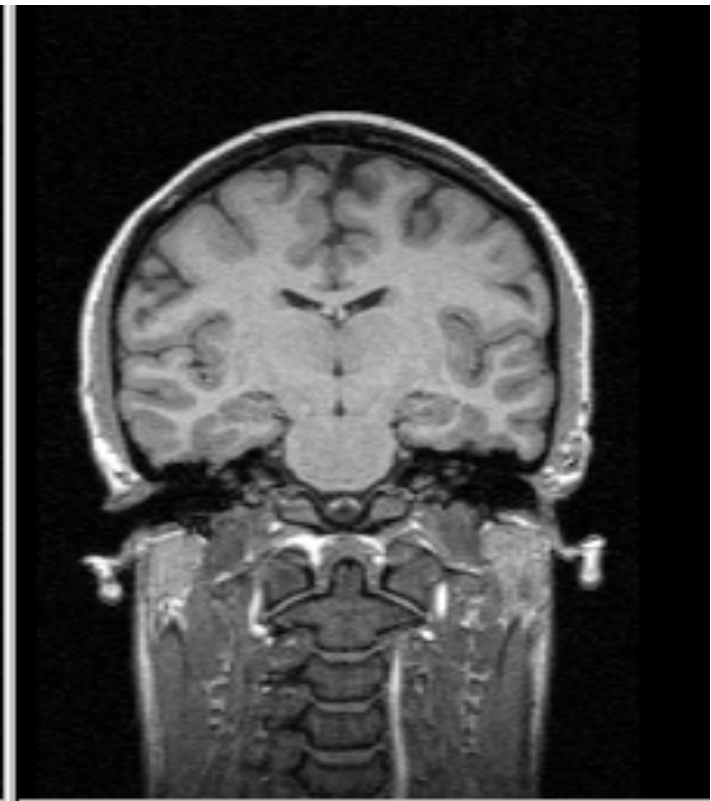
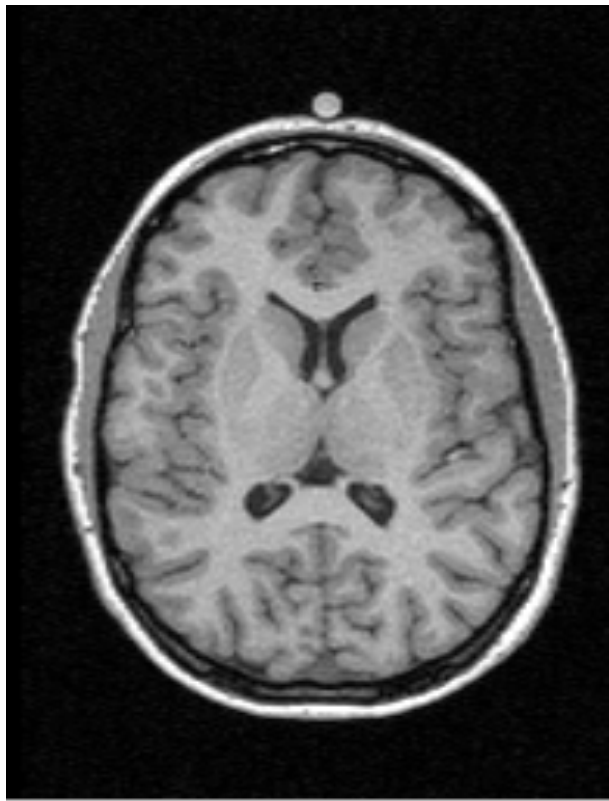
**Compared to a normal
hemisphere**



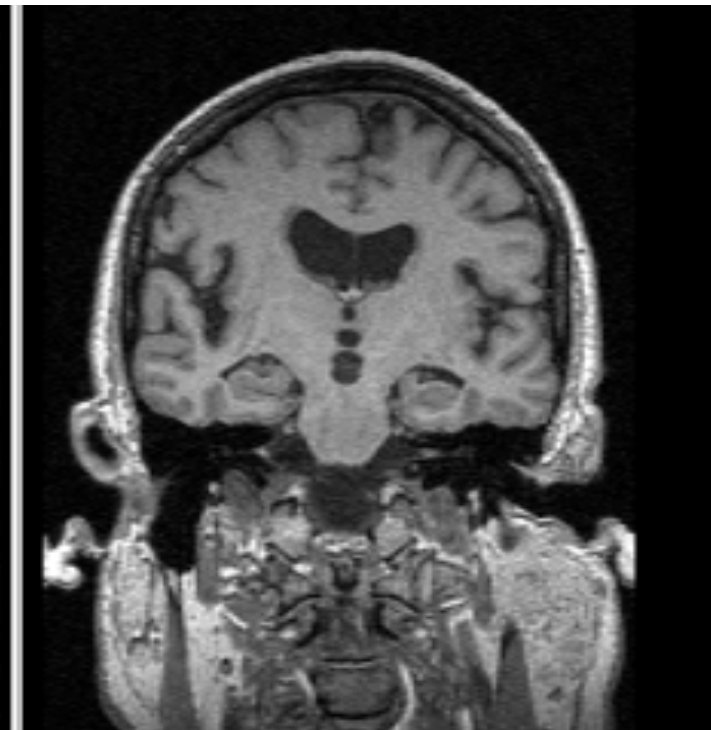
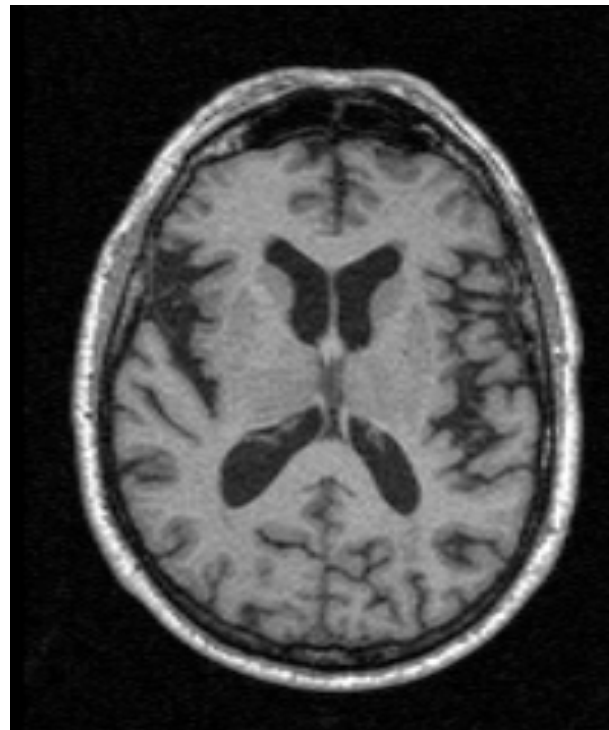
However, things are not so simple!

Brain aging

- The brain of a normal young adult
 - mid 20' s

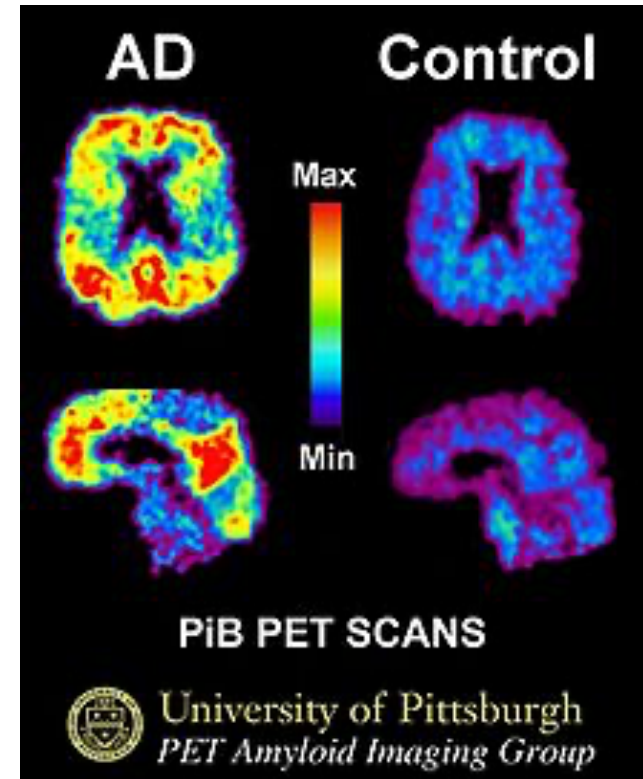


- The brain of a normal older adult
 - late 70' s



(Senile) Dementia of the Alzheimer's type (SDAT or DAT) or Alzheimer's Disease (AD)

- Hallmark changes in the brains of AD patients are microscopic
 - Therefore AD could only be definitively diagnosed at autopsy
 - New measures have changed that and show that **cognitively intact people also display some of these same signs!**
- Characteristics
 - Most common form of dementia
 - Progressive, degenerative, fatal
 - A person can live 3-20+ years after onset
 - **Lack of a dose response between a-beta and cognitive decline!**
- Typical and atypical presentations, progressions, and subtypes
 - Acknowledged in 2011
 - See Dickerson et al., 2017, *CNS Spectr.*



Outline

- A lifetime perspective
- A brief history Alzheimer's Disease (AD) and some definitions
- **Risk factors for AD**
- **Cerebrovascular contributions**
 - Brief overview of methods
 - Main results and conclusions

Searching for the cause(s)

- **Early-onset AD**

- Rare!
- Autosomal dominant gene
- Mutations in the presenilin proteins (PSEN1; PSEN2) or the amyloid precursor protein (APP).
- The majority of these cases carry mutant presenilin genes

- **Late-onset AD**

- More common
- Some **genetic influences**
- Links with **diabetes**
- Beta-amyloid cascade hypothesis, leading to **inflammation**
- **Blood brain barrier (BBB) dysfunction**
 - Links with bacteria (e.g., those involved in gum disease)

- **Vascular hypothesis**

Genetic influences

- The APOE protein combines with lipids to form lipoproteins. Lipoproteins are responsible for **packaging cholesterol and other lipids** and carrying them through the bloodstream. Apolipoprotein E (APOE) gene variants:
 - APOE3 (most common, no influence)
 - **APOE4** (less common, increased risk)
 - APOE2 (most rare, may decrease risk)
- Other genes:
 - **Cholesterol and cholesterol cycle**
 - **ABCA7**: linked to how the body uses cholesterol.
 - Clearance of amyloid-beta
 - **CLU**: imbalance between production and clearance of amyloid-beta
 - Inflammation
 - **CR1**: deficiency may contribute to chronic brain inflammation
 - **TREM2**: regulation of the brain's response to inflammation (rare variants).



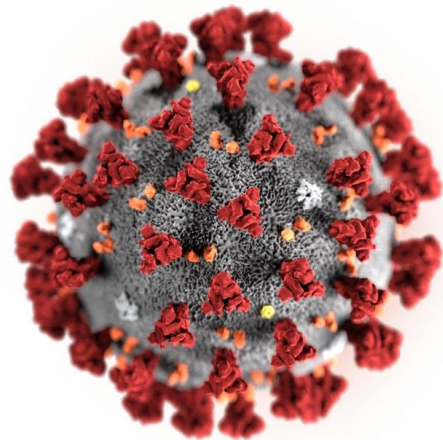
Links with diabetes

- Insulin is designed to go up after food ingestions to allow sugars (glucose) to be absorbed by cells. The insulin response is supposed to be phasic (short duration).
- Certain types of diets over-exert the insulin system, wearing the system out. For example:
 - High fats, high carbs; and especially simple sugars
- This leads to pre-diabetes and eventually full-fledged diabetes, which in turn leads to:
 - Starving of cells, including the **vascular endothelium**
 - **Small vessel disease, peripherally and centrally**
 - Nerve damage
 - Increased risk of local inflammation
 - Impaired immune response

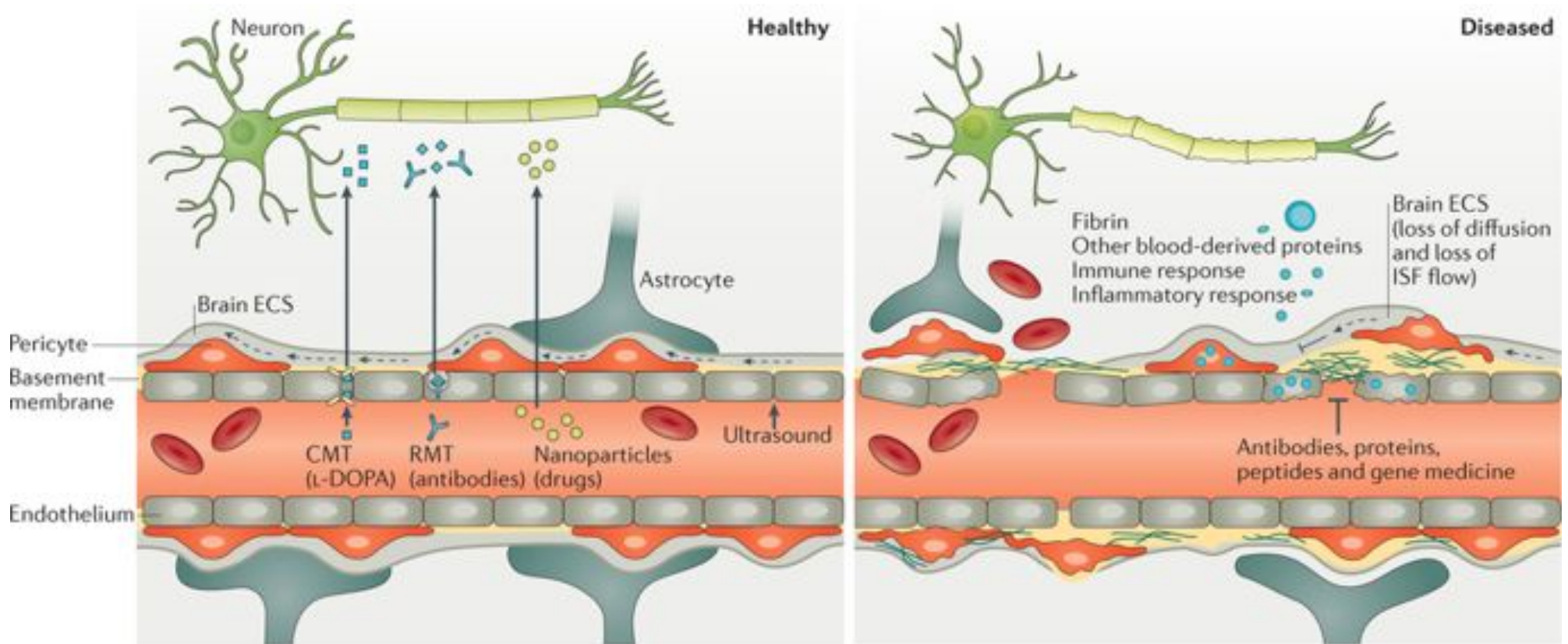


Immune system and inflammation

- Chronic Stress
 - Persistent blood pressure increase
 - **Damage to endothelium** (inner part of arterial wall)
 - **Damage to blood brain barrier** (BBB)
 - Local inflammation
 - Diminished global immune response
 - Shortening of telomeres
 - Increased oxidative processes due to local hyperaemia and metabolism



Dysfunction of BBB



Nature Reviews | Neurology

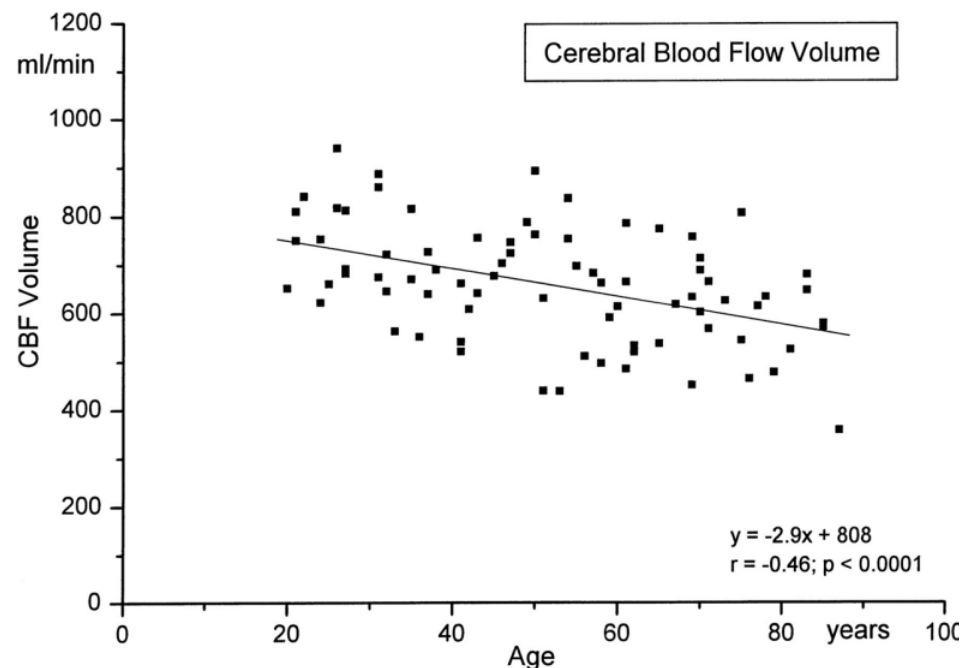
- Bacterial infections (e.g., bacterial related to gum disease)
 - <https://www.sciencemag.org/news/2019/01/gum-disease-causing-bacteria-could-spur-alzheimer-s>
- Inflammation

Outline

- A lifetime perspective
- A brief history Alzheimer's Disease (AD) and some definitions
- Risk factors for AD
- **Cerebrovascular contributions**
 - Brief overview of methods
 - Main results and conclusions

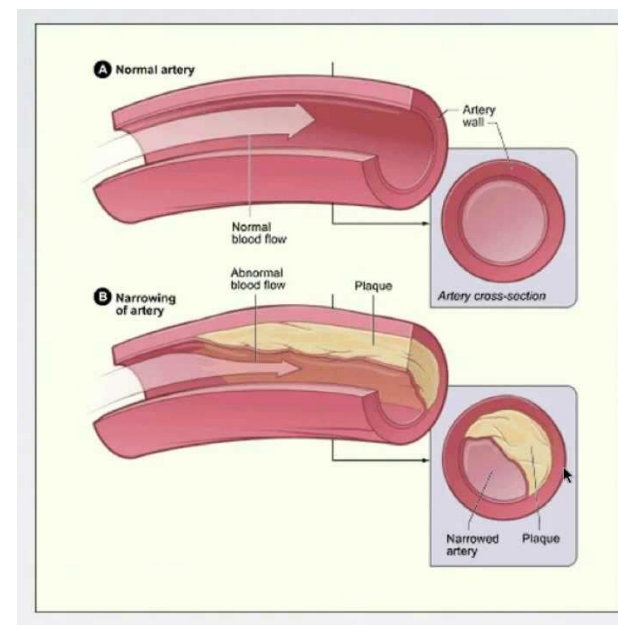
Cerebrovascular function and aging

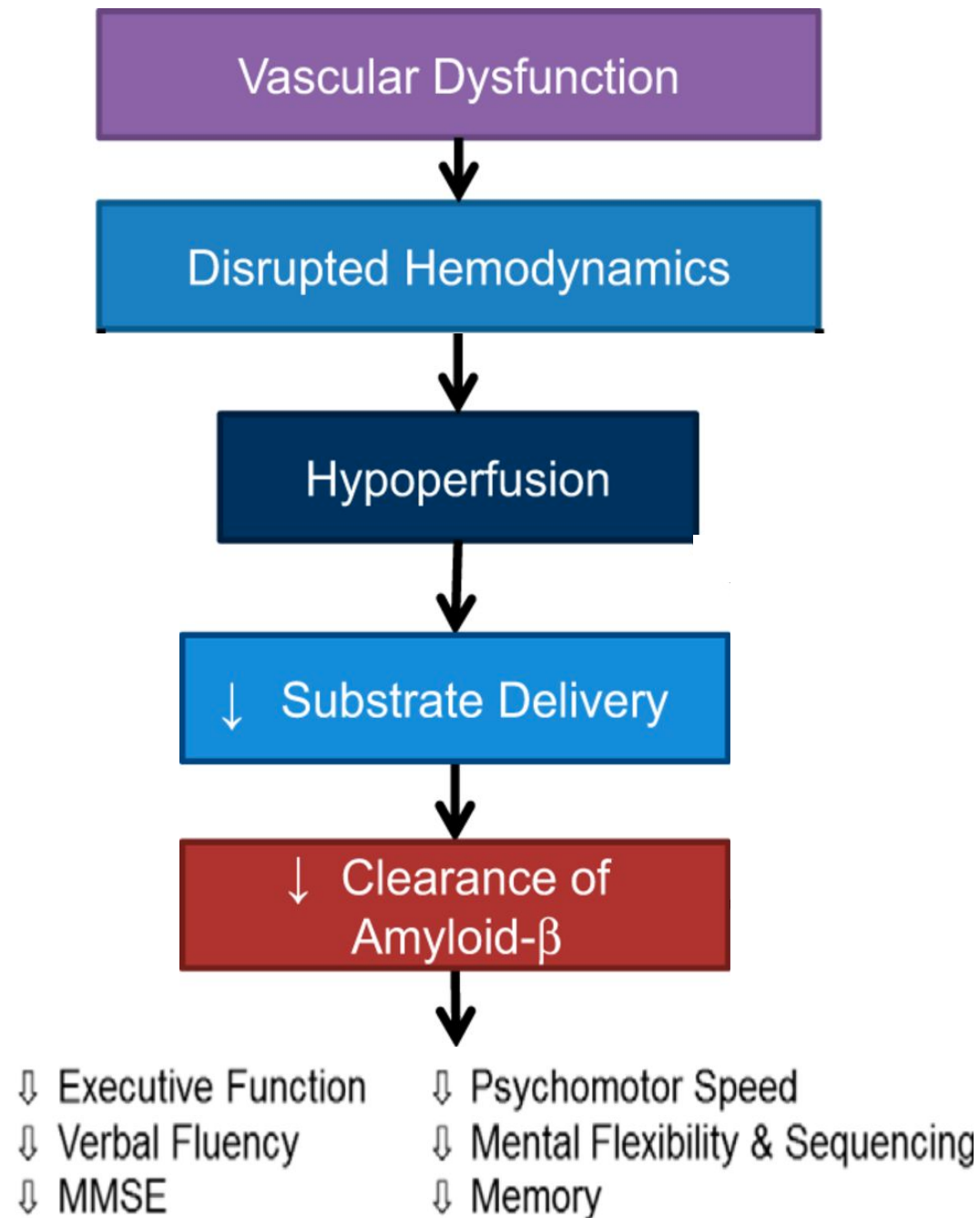
- Blood flow and tissue perfusion in the brain decrease with aging due to:
 - Arteriosclerosis and plaque formation
 - e.g., Boreham et al. (2004)
 - Hypertension and increased peripheral resistance
 - e.g., Jennings & Heim (2012)
 - Decreased cardiovascular reactivity
 - Tan et al. (2016)



Scheel P et al. Stroke 2000;31:147-150

American Heart



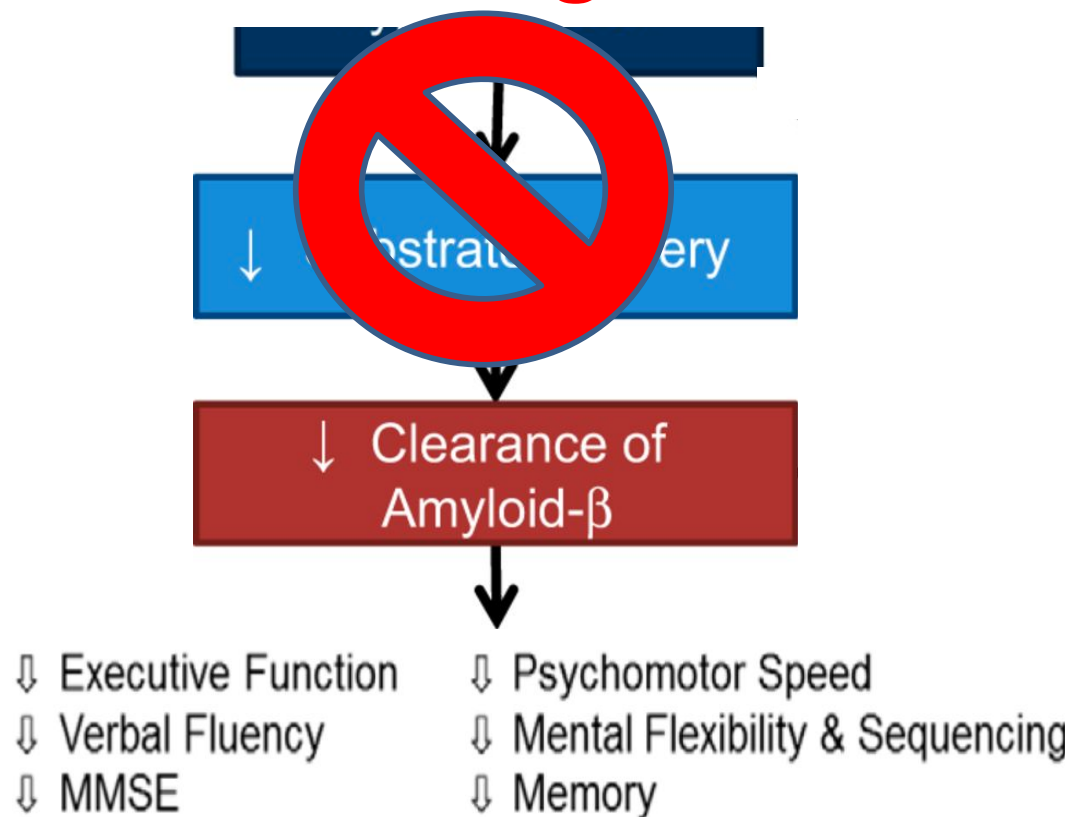


Modified from de la Torre, *Cardiovasc Psychiatry Neurol* (2012)
See also Barnes, *Adv Physiol Educ* (2015)

NIA grant R01AG059878
NIA grant RF1AG062666

Vascular Dysfunction

Exercise
Good nutrition
Controlling stress



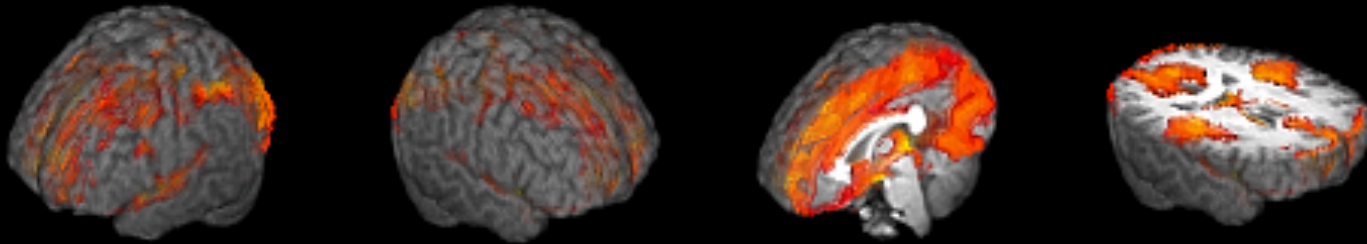
Modified from de la Torre, *Cardiovasc Psychiatry Neurol* (2012)
See also Barnes, *Adv Physiol Educ* (2015)

NIA grant R01AG059878
NIA grant RF1AG062666

Aging and fitness

- Cardiorespiratory fitness (CRF) can counteract some of the negative effects of aging by:
 - Increase in trophic factors (e.g., BDNF)
 - e.g., Falkenberg et al. (1992)
 - Spine, dendrite and neuronal growth
 - e.g., Greenough et al. (1973); Jessberger & Gage (2008)
 - **Angiogenesis**
 - e.g., Isaacs et al. (1992); Swain et al. (2003)
 - **Preserving arterial elasticity**
 - e.g., Ferreira et al., 2006; Fabiani et al. 2014; Tan et al., 2017
 - Preserving/improving cognitive function
 - Preventing brain tissue loss
 - e.g., Colcombe & Kramer (2003); Gordon et al. (2008);
 - See Heijnen, Hommel, Kibele, & Colzato (2016) for a review of additional factors in this cascade.

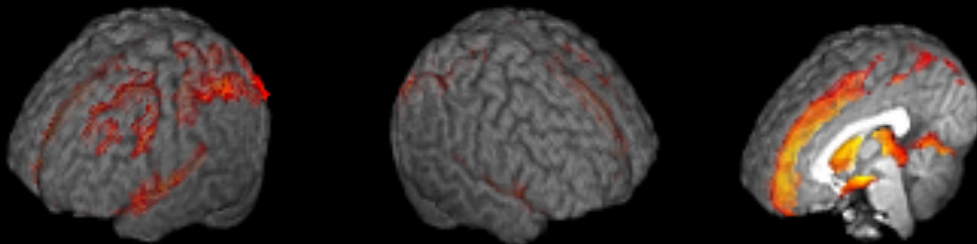
Brain Aging



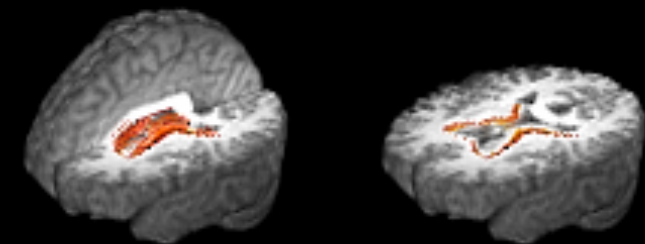
Grey matter: Y > O

N=60

Z-score 2.3  8.4

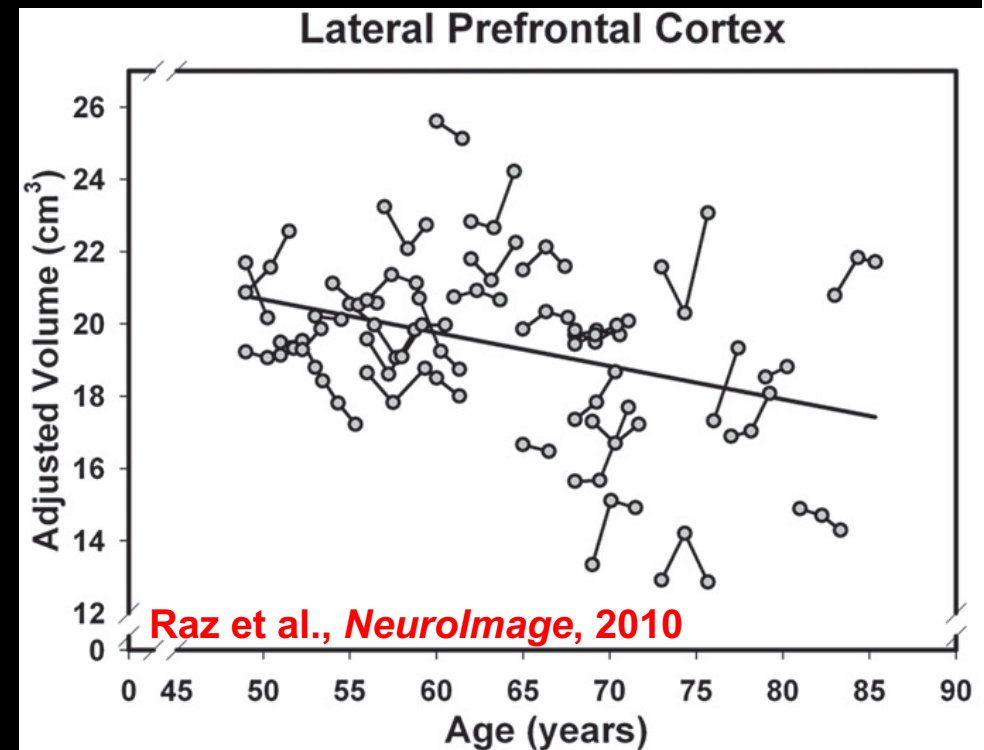


CSF: O > Y



White matter: Y > O

Gordon et al., *Psychophysiology*, 2008

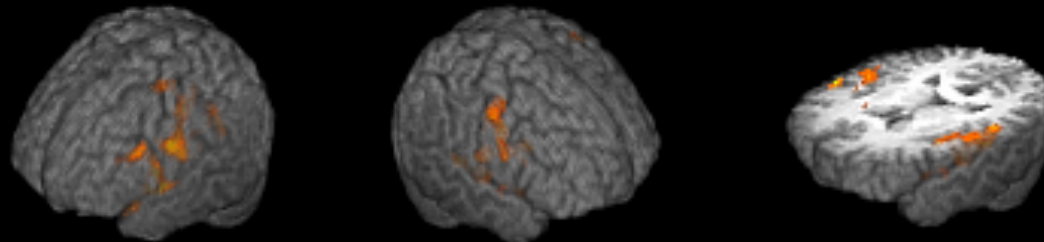


Effects of Fitness and Education in Older Adults

Fitness with age, education and gender removed

Grey matter

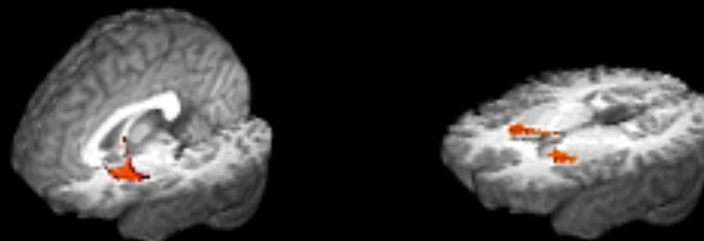
HF>LF



Education with age, fitness and gender removed

White matter

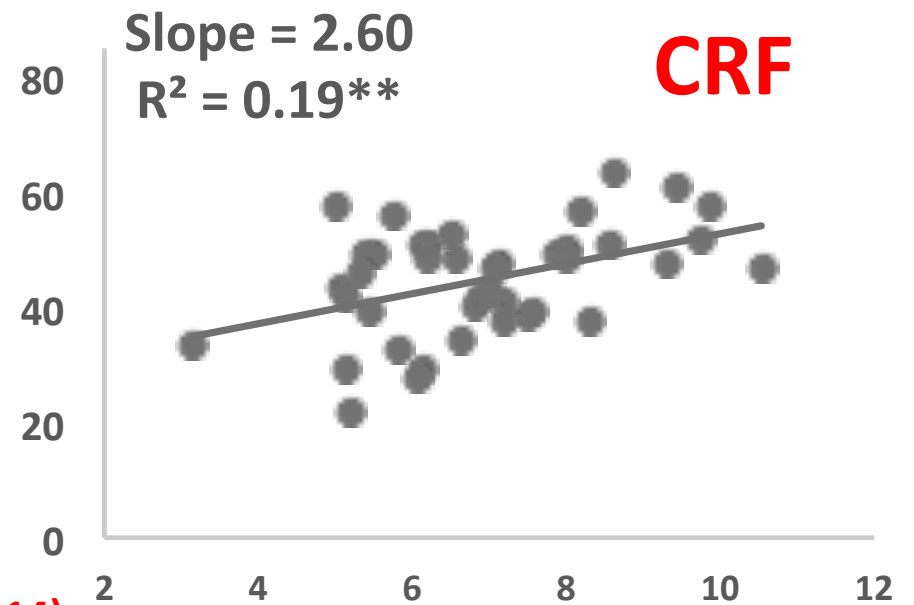
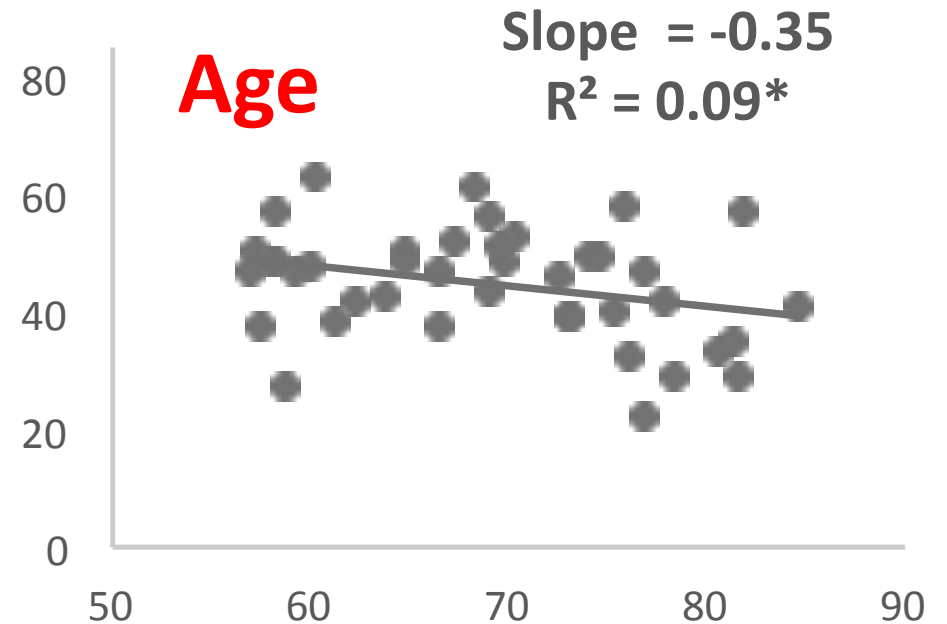
HE>LE



Cerebral blood flow in gray matter



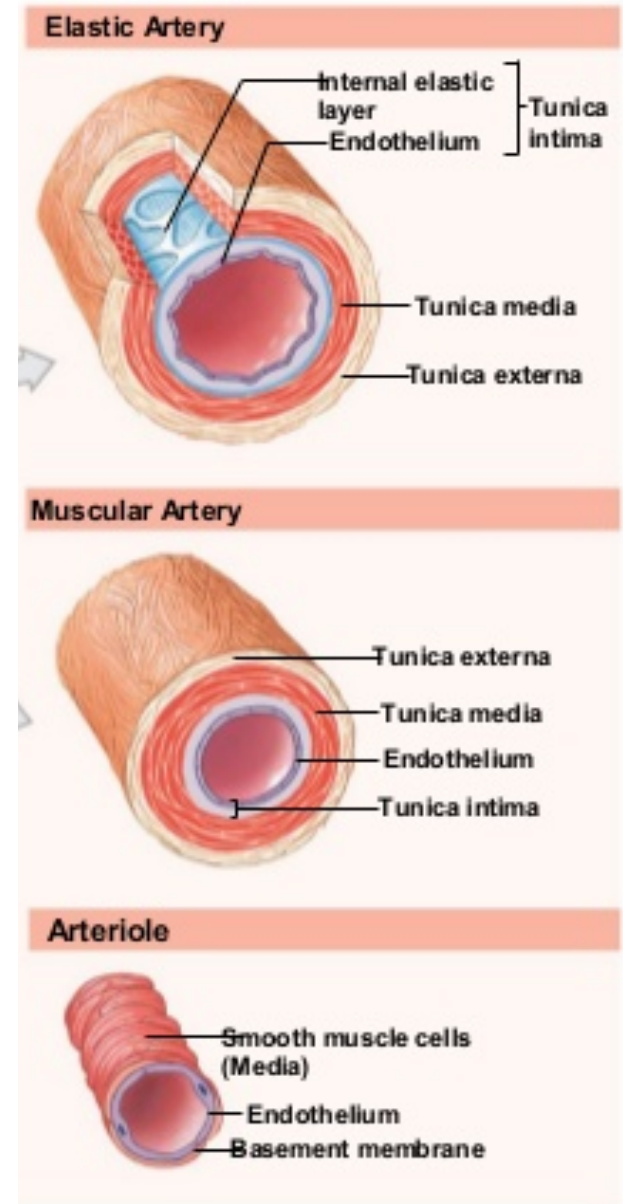
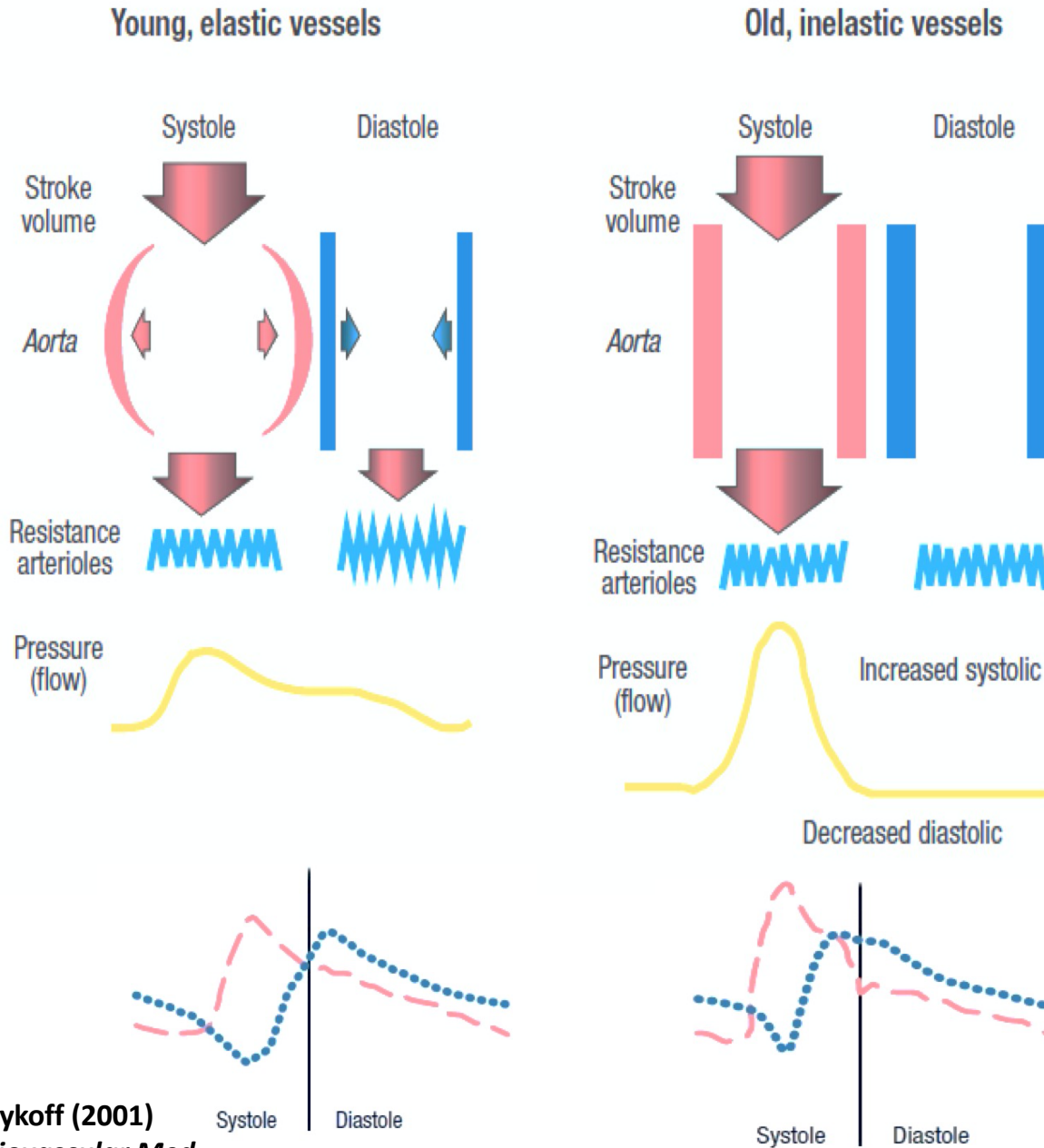
Global CBF
(mL/100g tissue/min)



* $p < .05$

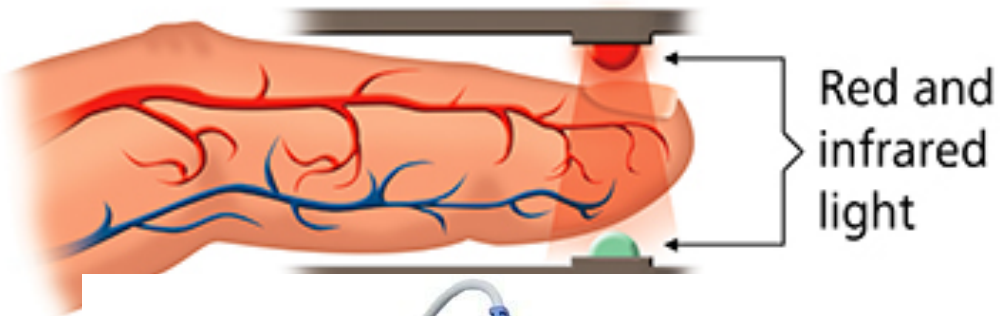
** $p < .01$

Measuring arterial elasticity

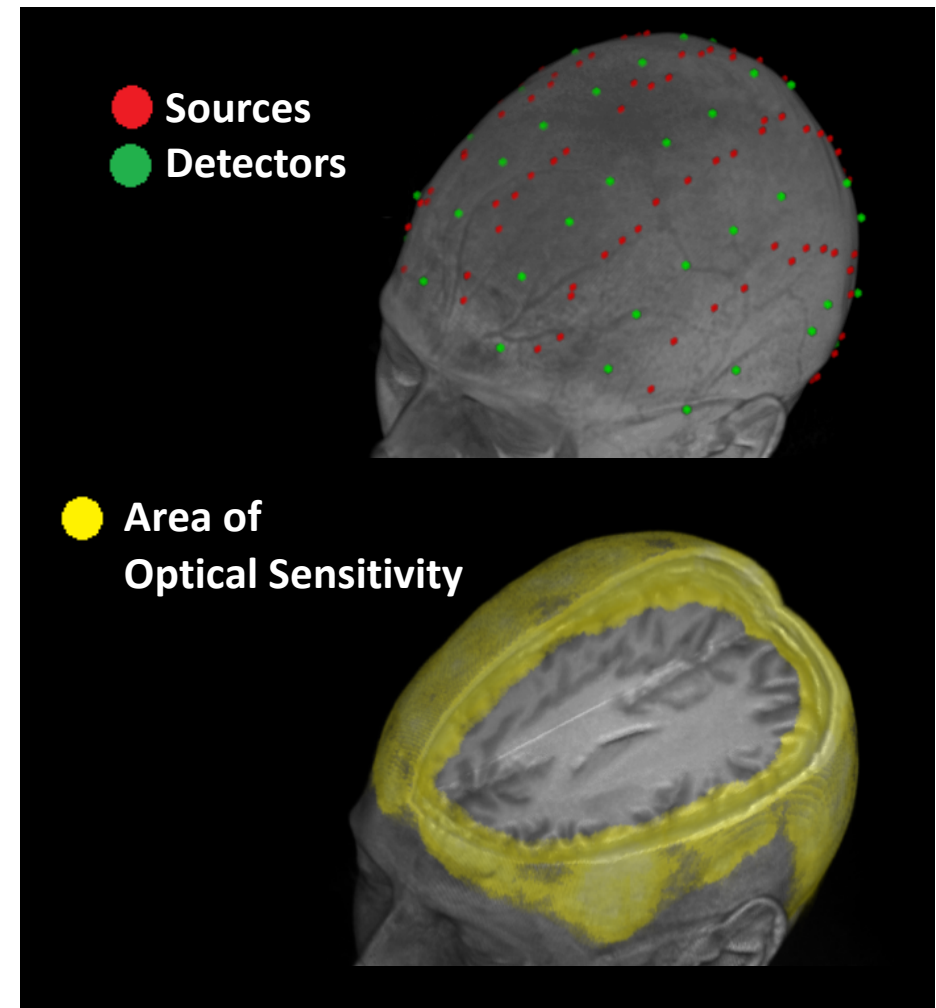


Measuring the arterial pulse **optically**

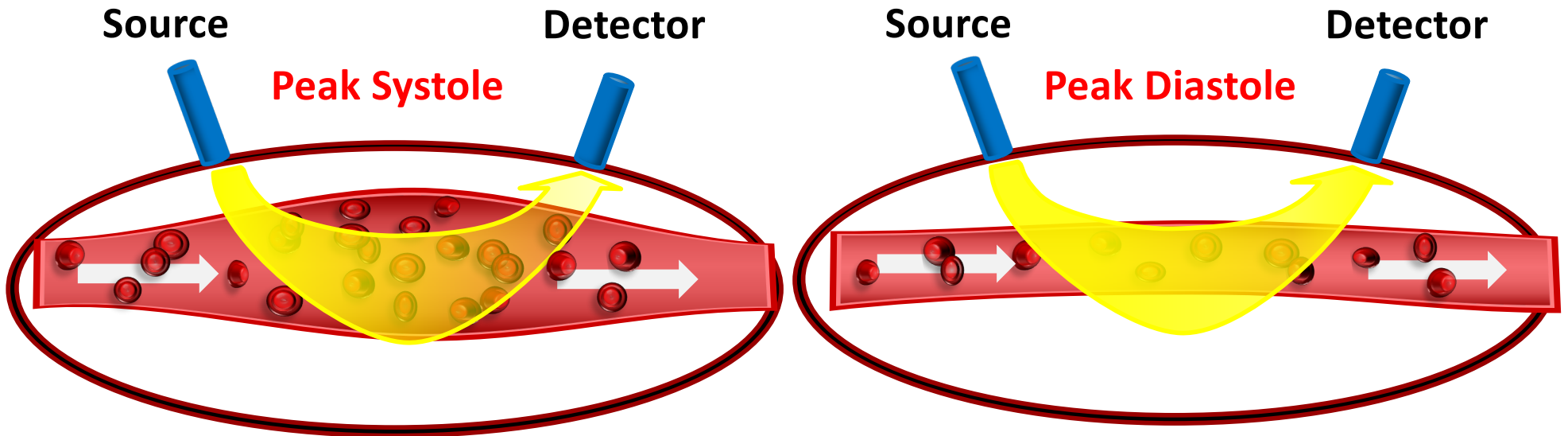
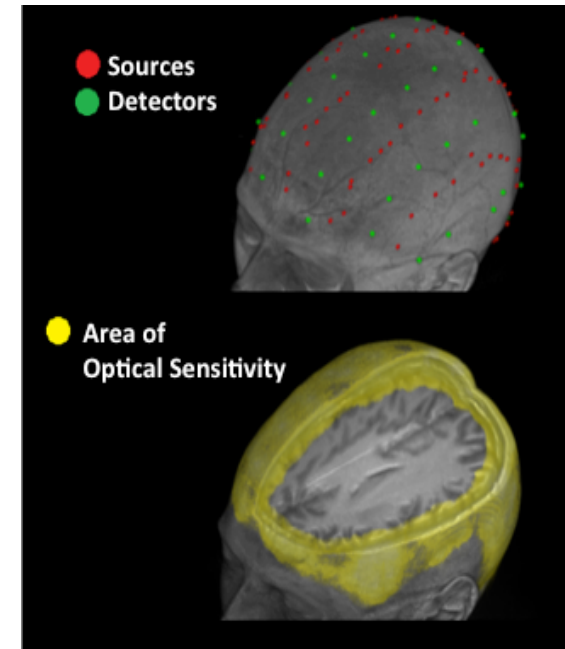
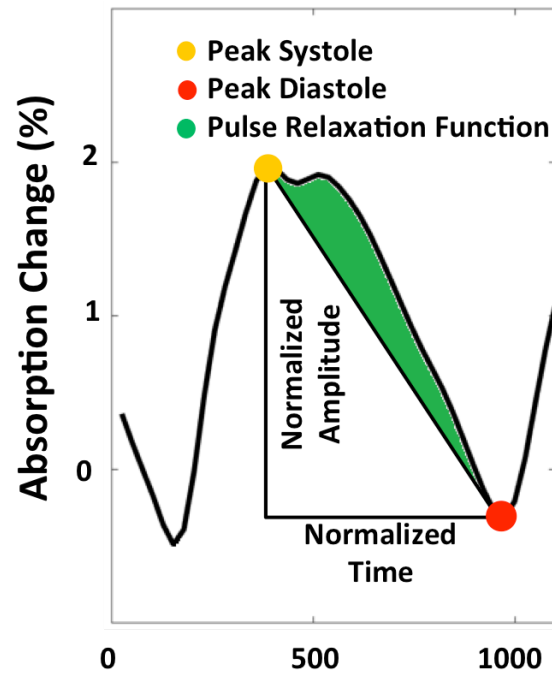
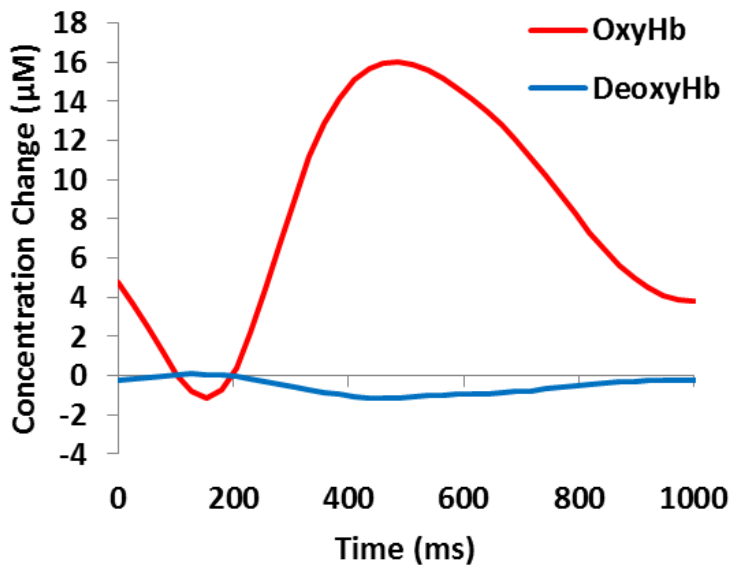
Pulse oximetry



Pulse-DOT in the brain



PATENT: G. Gratton, M. Fabiani, K.A. Low, E. L. Maclin. *Non-invasive optical imaging for measuring pulse and arterial elasticity in the brain.* US Patent No.: US 9,167,970 B2; Date of Patent: Oct. 27, 2015

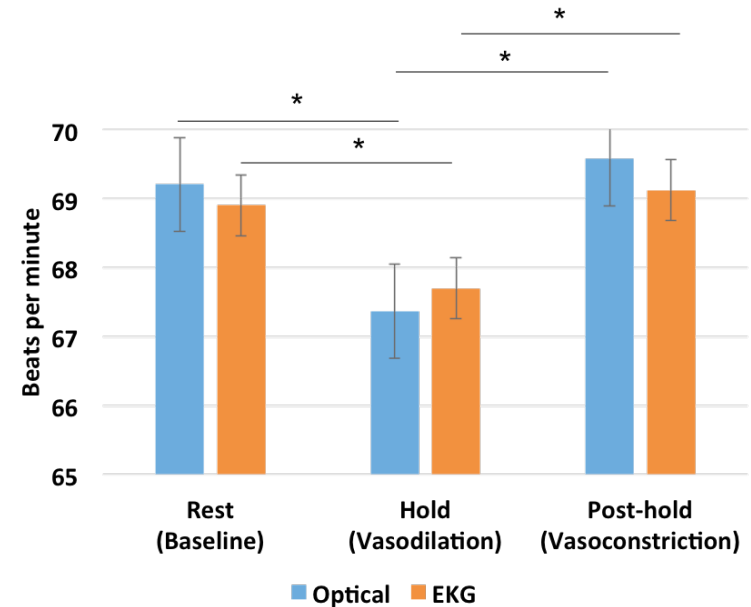


Maximum absorption = minimum AC light at systole;
vice-versa at diastole

Cerebrovascular reactivity during breath holding

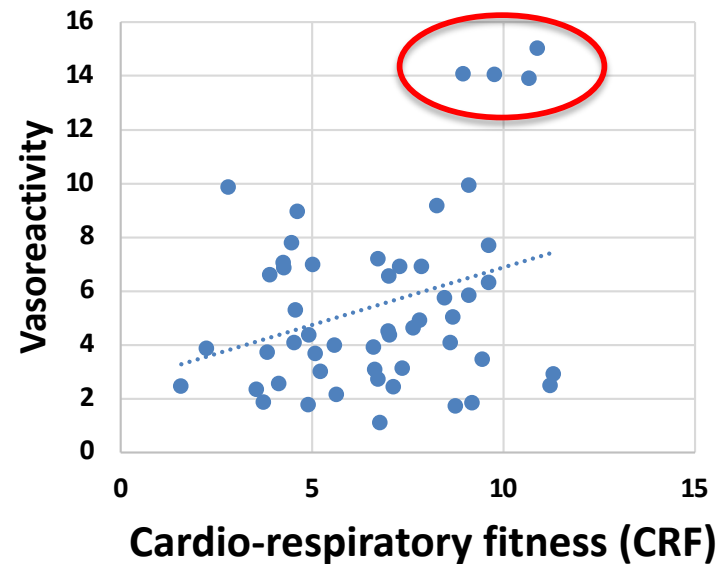
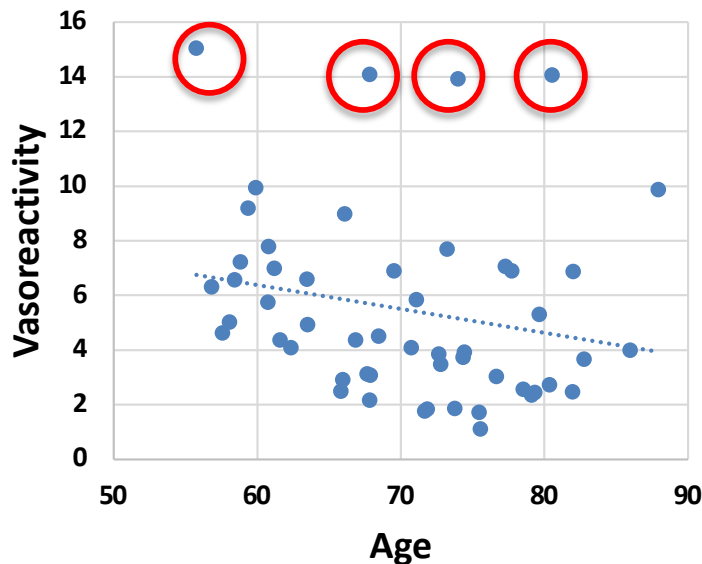
■ **Breath-holding** is a way to induce **hypercapnia**

- Induces vagal activation
- Increases blood CO₂
- Induces vasodilation and a drop in BP
- Increases cerebral perfusion and delivery of oxy-hemoglobin
- Compensatory blood flow due to hypercapnia is typically larger than compensatory blood flow due to neural activation

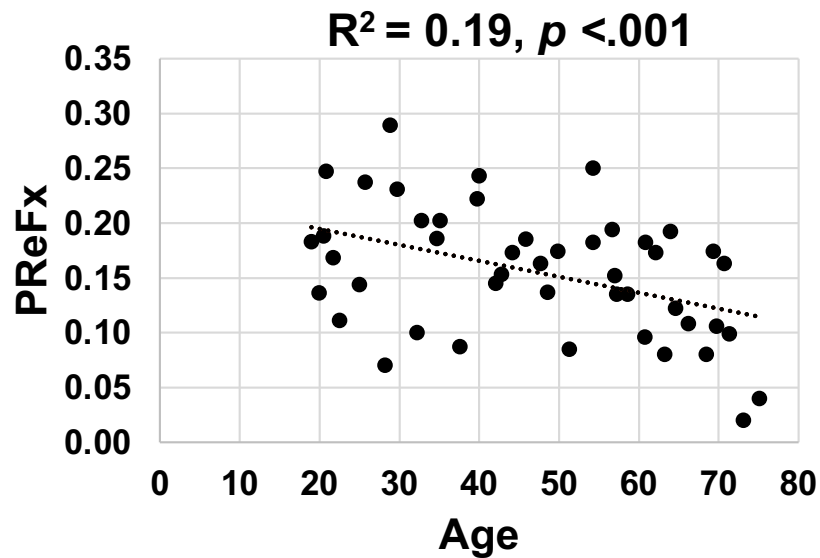


* $p < .05$

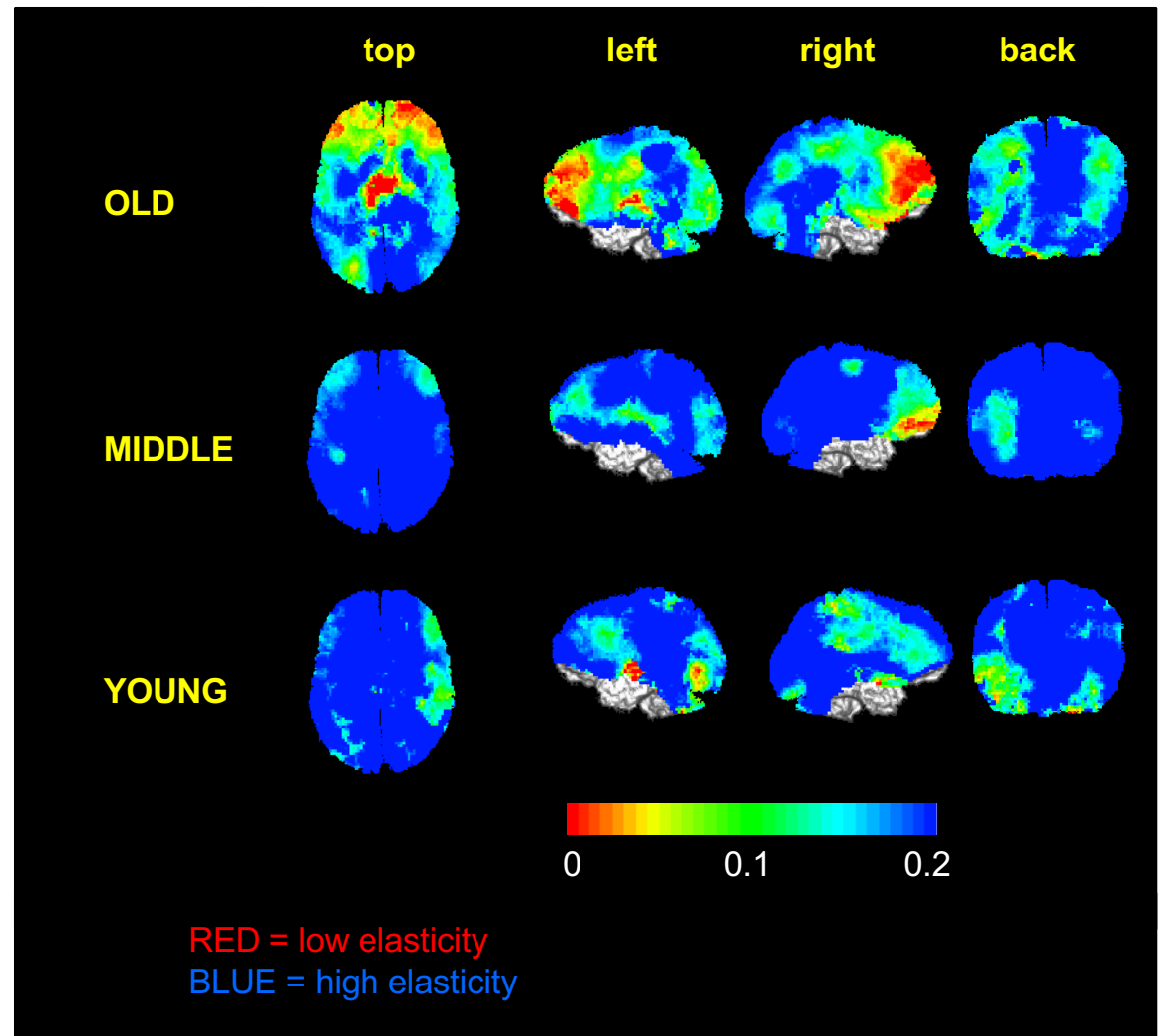
Vasoreactivity: SD in brain pulse pressure across the 3 periods



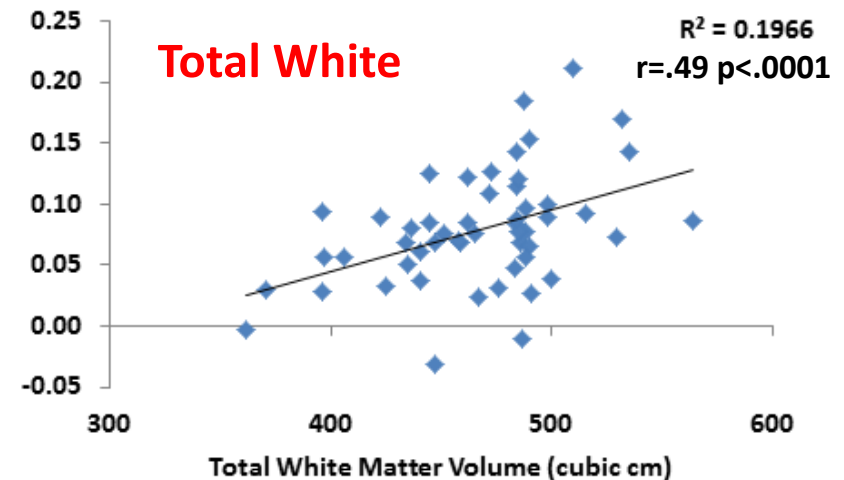
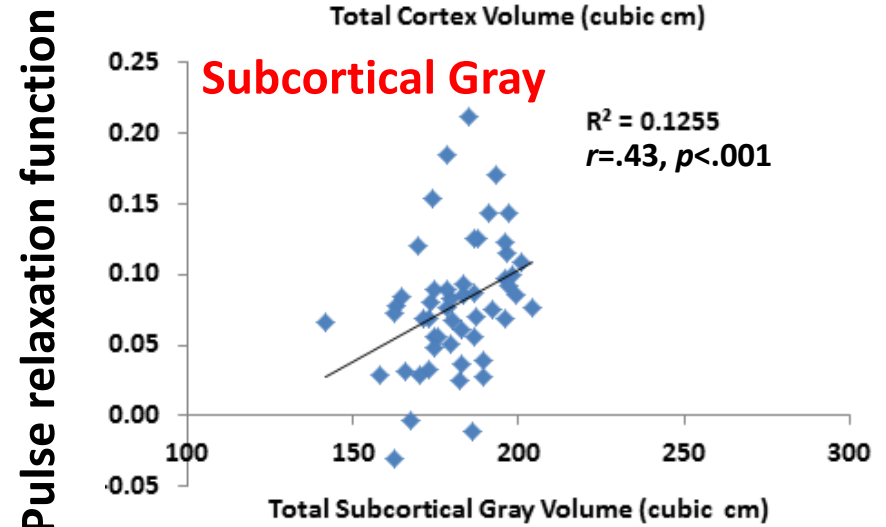
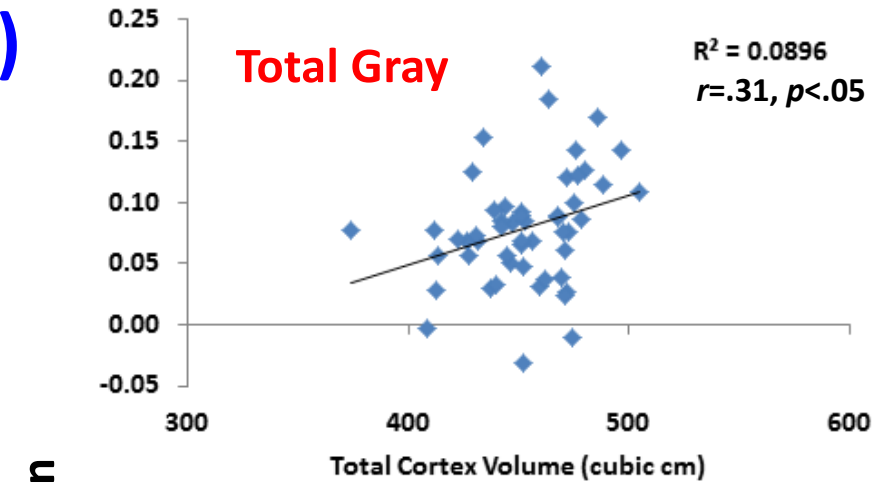
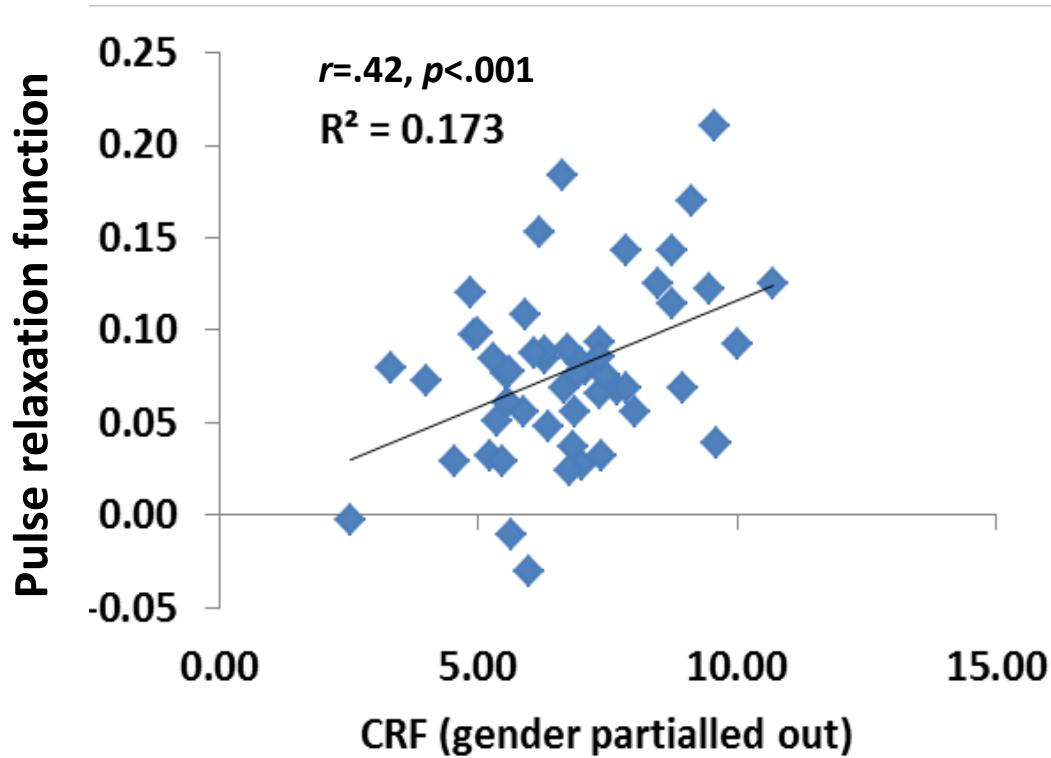
Pulse relaxation function (PReFx) and Age



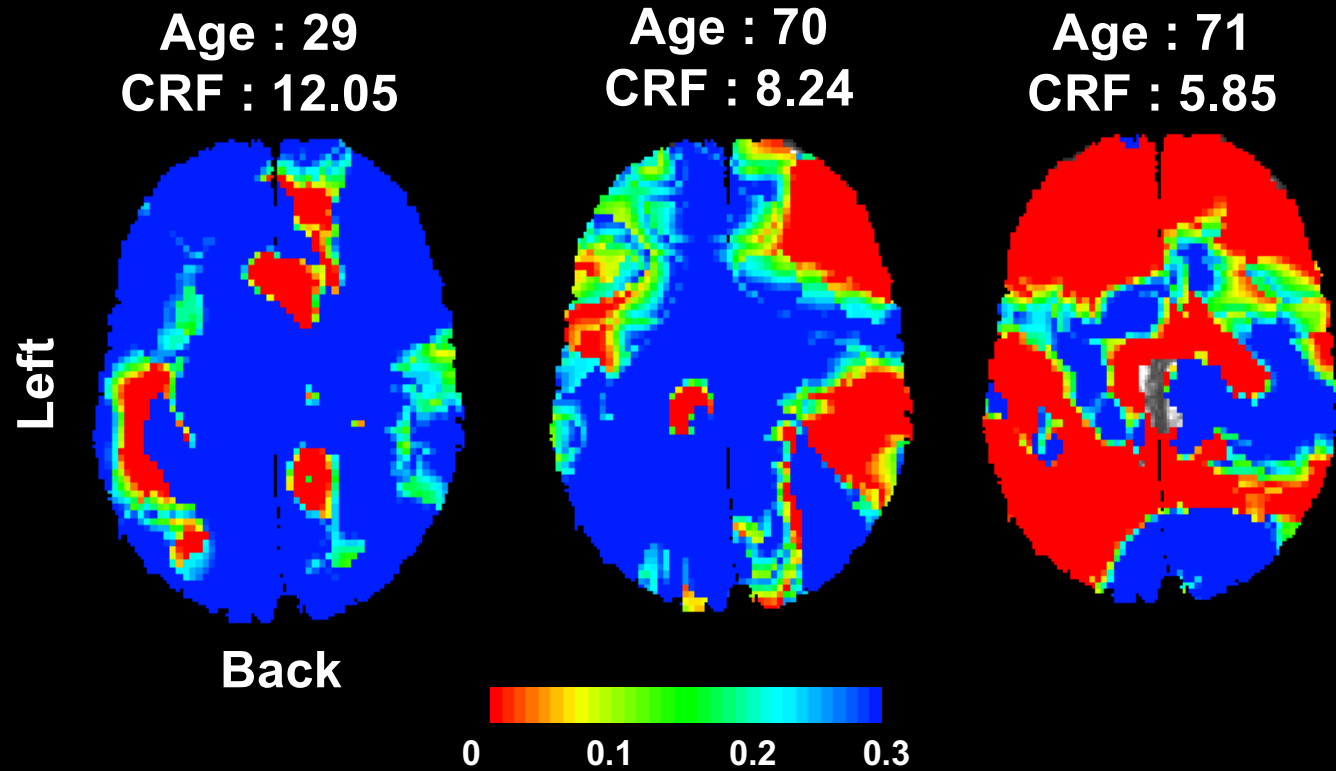
Tan et al., *PlosOne*, 2017



Pulse Relaxation Function (PReFx) cardiorespiratory fitness, and brain anatomy



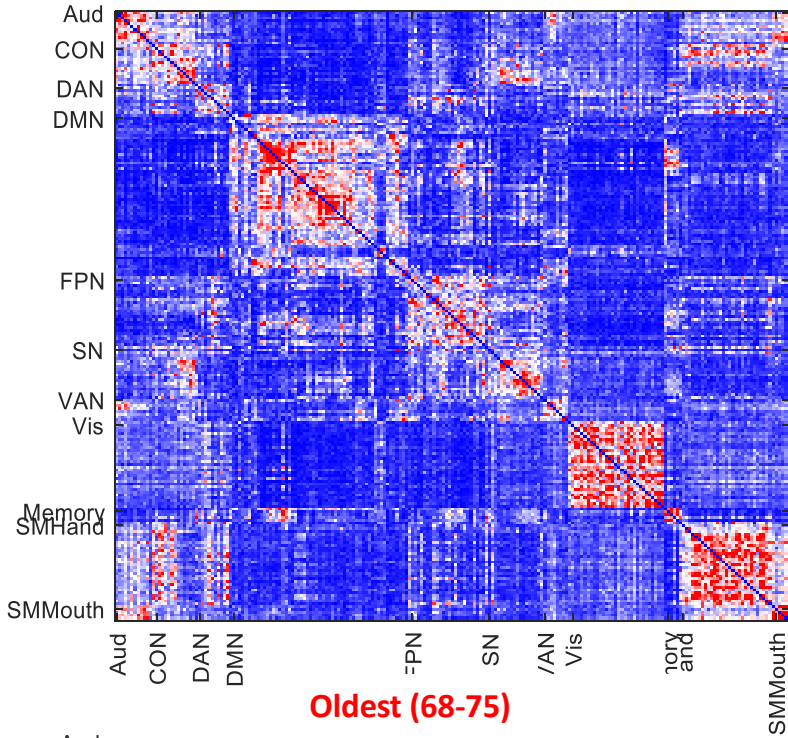
Individual PReFx maps



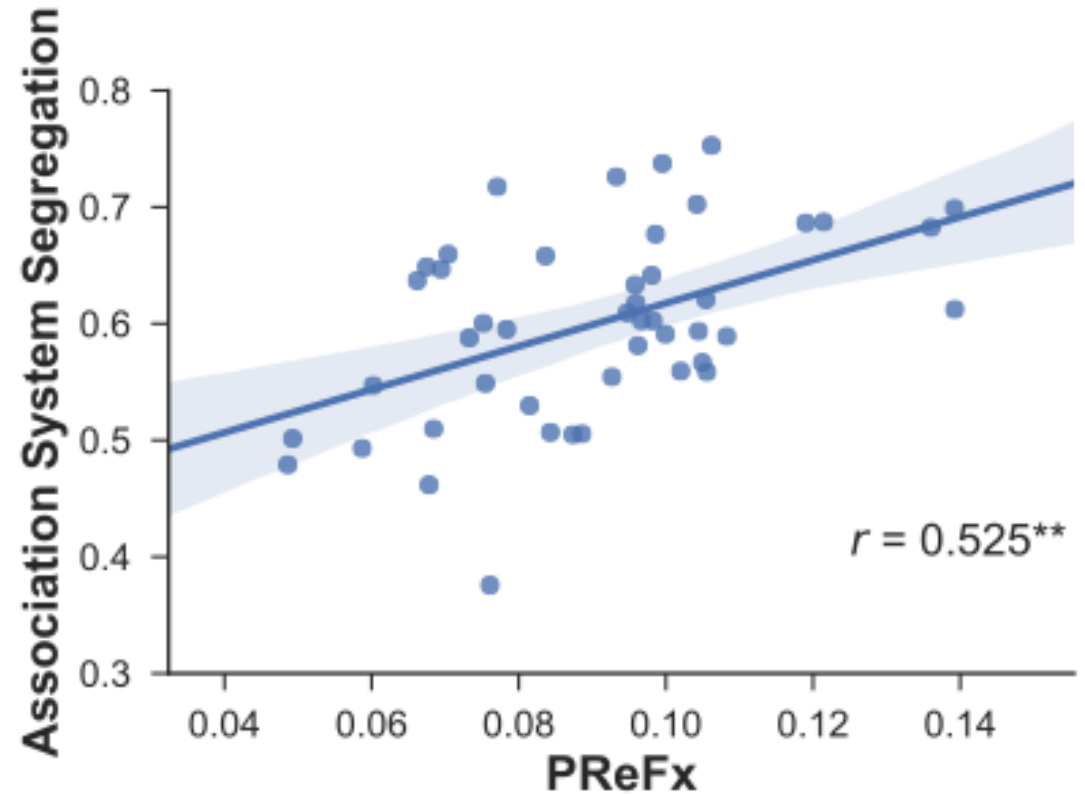
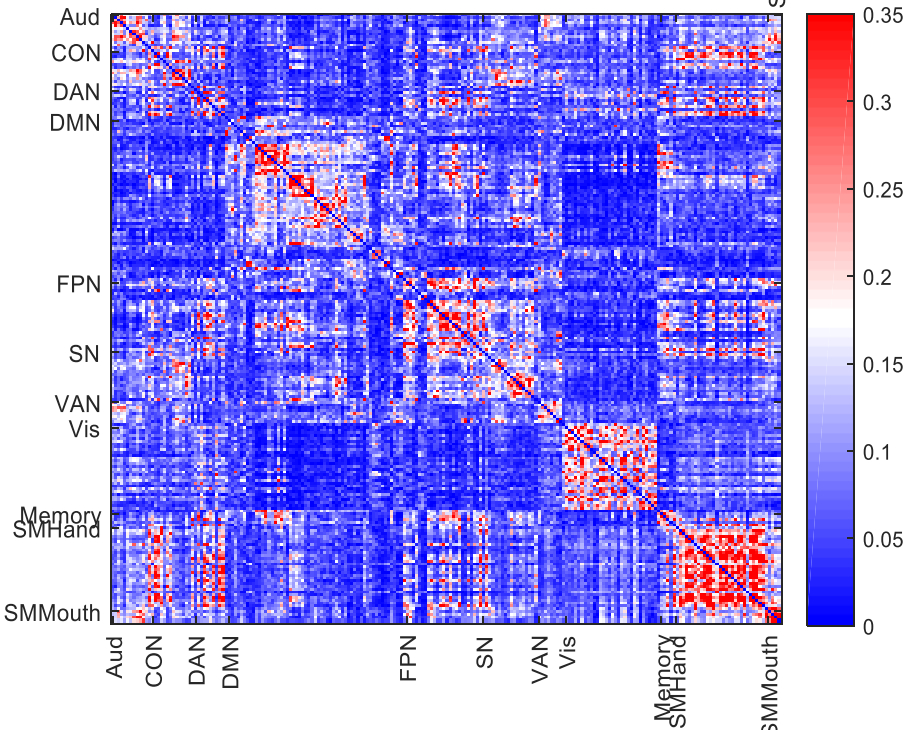
RED = low elasticity
BLUE = high elasticity

PReFx and function: Network segregation

Youngest (18-25)

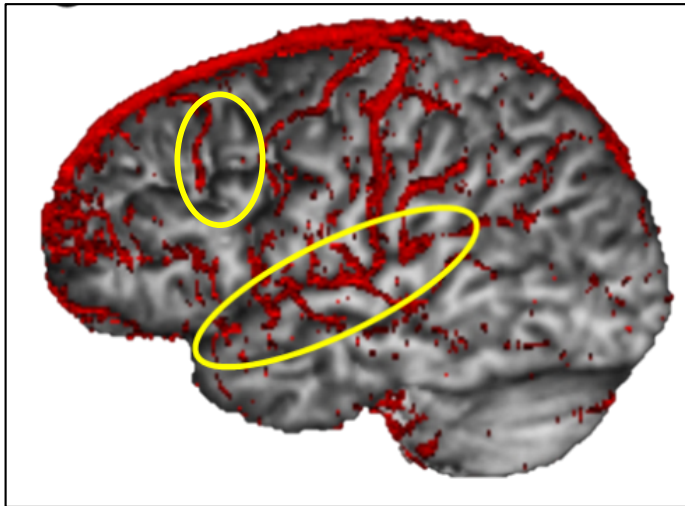


Oldest (68-75)

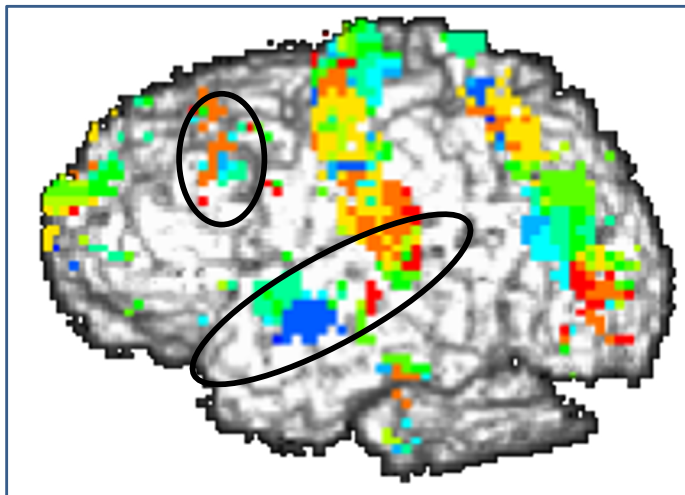


Kong et al., *Network Neuroscience*, 2020

Arterial elasticity and cognition

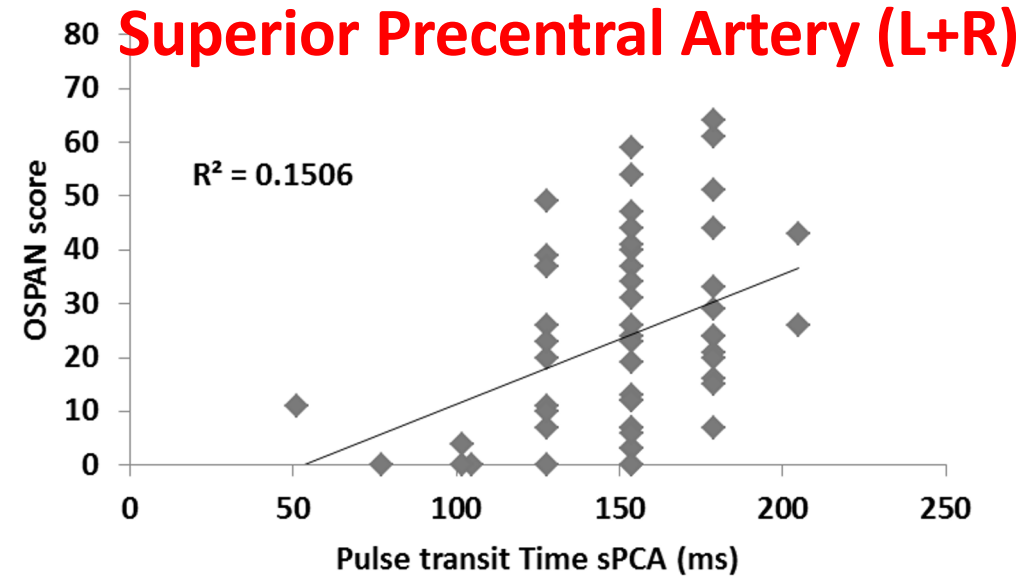
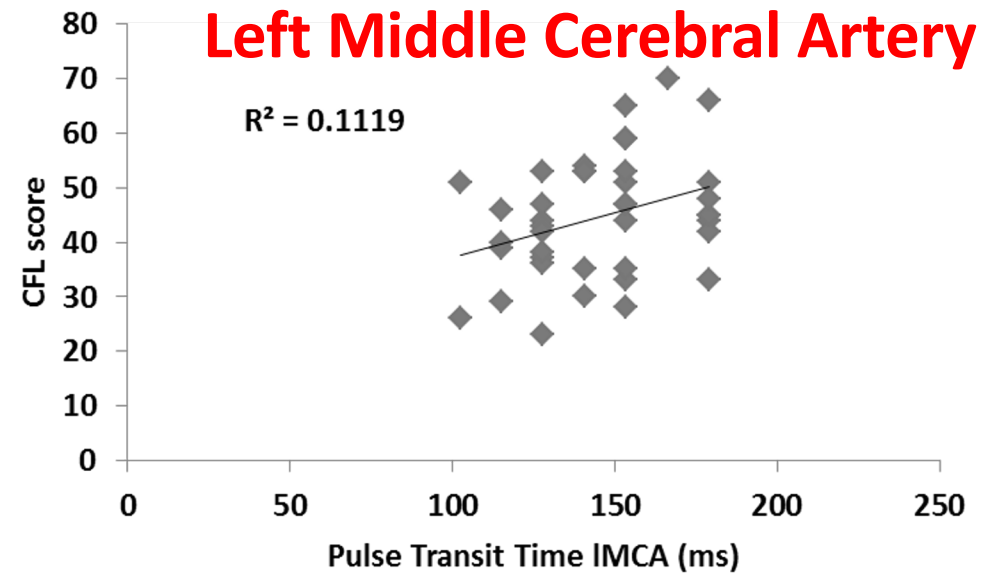


MRI arteriogram



333 ms 589

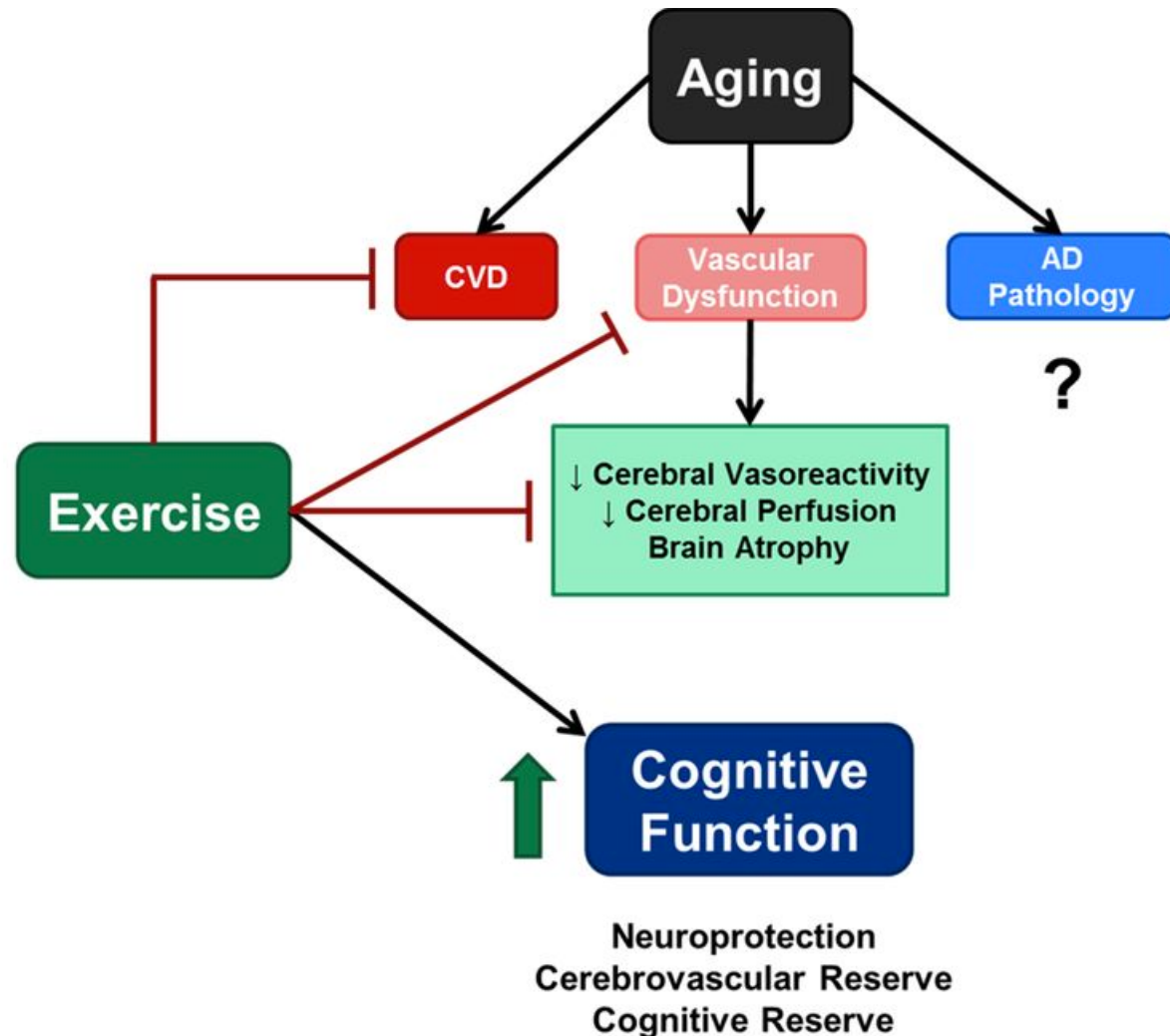
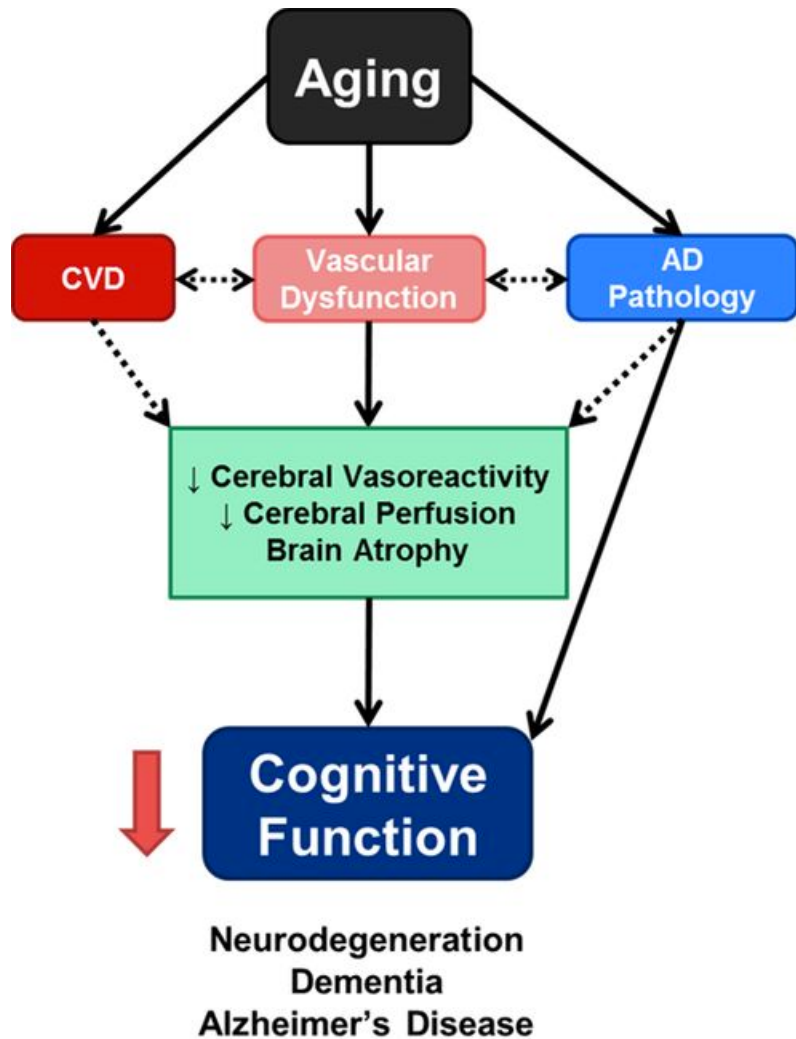
Pulse transit time



Summary and conclusions -1

- Cerebral pulse parameters measured regionally from the brain with diffuse optical methods (pulse-DOT) can be used to estimate the status of the cerebrovascular system
 - Relationships with brain volume, function and cognition **are evident in the early 50's**
 - Could be used to **predict and help prevent** cerebrovascular accidents and tissue loss and therefore protect from cognitive decline
 - Could open avenues for **individualized precision-medicine interventions**

Summary and conclusions -2



CVD=cerebrovascular disease

A Summary and conclusions - 3

3,000,000  10% reduction

The best prescription for a healthy, dementia-free aging is what the ancient Romans knew all along...

Mens sana in corpore sano!

Nutrition

Exercise

Smoking cessation

Stress reduction

Reduction of inflammation

Continuing education

Diabetes m.

Midlife hypert.

Midlife c.

Depre.

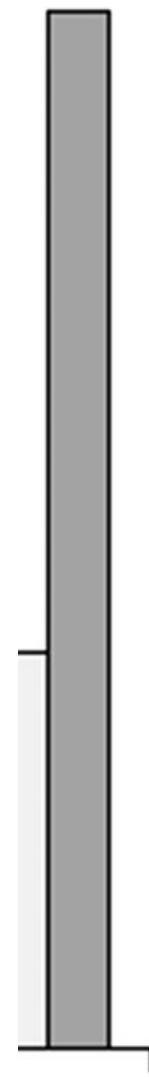
Physical in.

St.

Cognitive in.

Combined

Number of AD cases prevented worldwide



The best prescription for a healthy, dementia-free aging is what the ancient Romans knew all along...

Mens sana in corpore sano!

Nutrition

Exercise

Smoking cessation

Stress reduction

Reduction of inflammation

Continuing education



Thanks to the support of:

NIA grant R01AG035927

NIMH grant R56MH097973

NIA grant RC1AG035927

NIA grant R01AG059878

NIA grant RF1AG062666

I ILLINOIS

Beckman Institute for Advanced
Science & Technology

THANKS FOR YOUR ATTENTION! QUESTIONS?

Useful URLs

- **National Institute for Aging (NIA)** <http://www.nia.nih.gov/>
 - Accurate information on ongoing aging research
- **Studies:**
 - New England Centenarian Study www.bumc.bu.edu/centenarian
- **Alzheimer's dementia:**
 - <http://www.alz.org/index.asp>
- **Documentaries:**
 - Parkinson's <http://video.pbs.org/video/1082086931/>
 - Alzheimer's <http://www.hbo.com/alzheimers/momentum-in-science.html>

If you are interested in volunteering for our studies, please contact me at mfabiani@Illinois.edu