Alzheimer's: Diagnosis and Treatment Update

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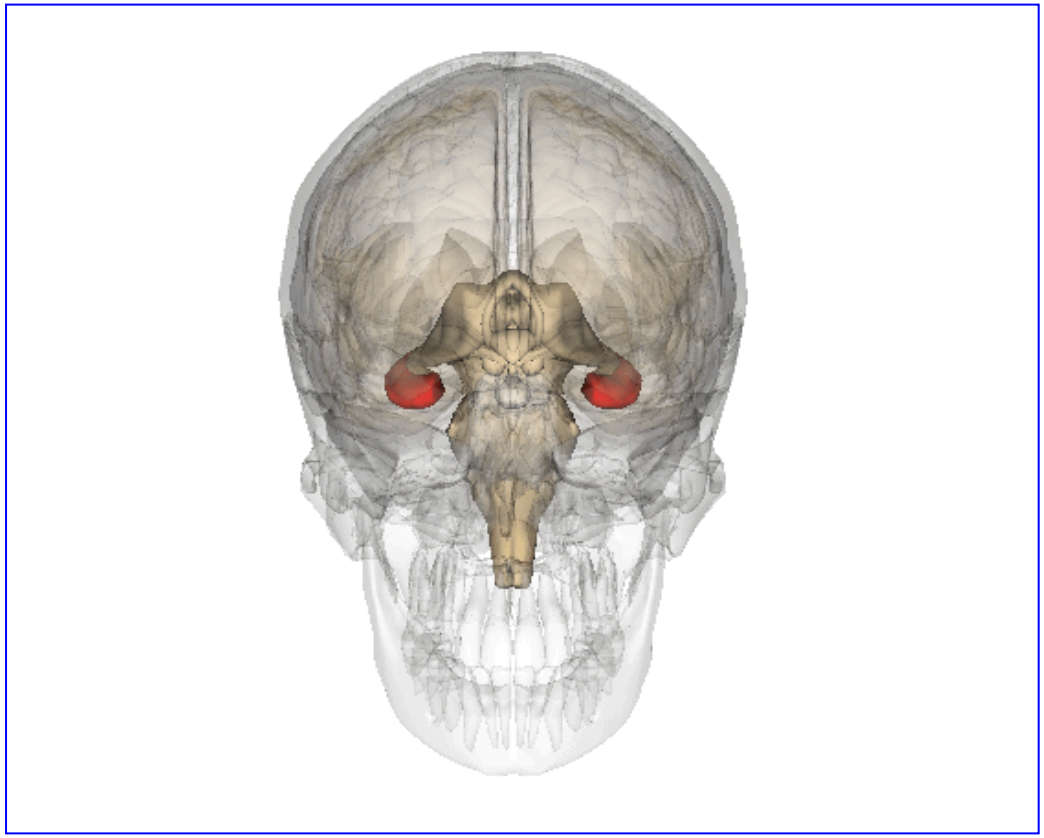
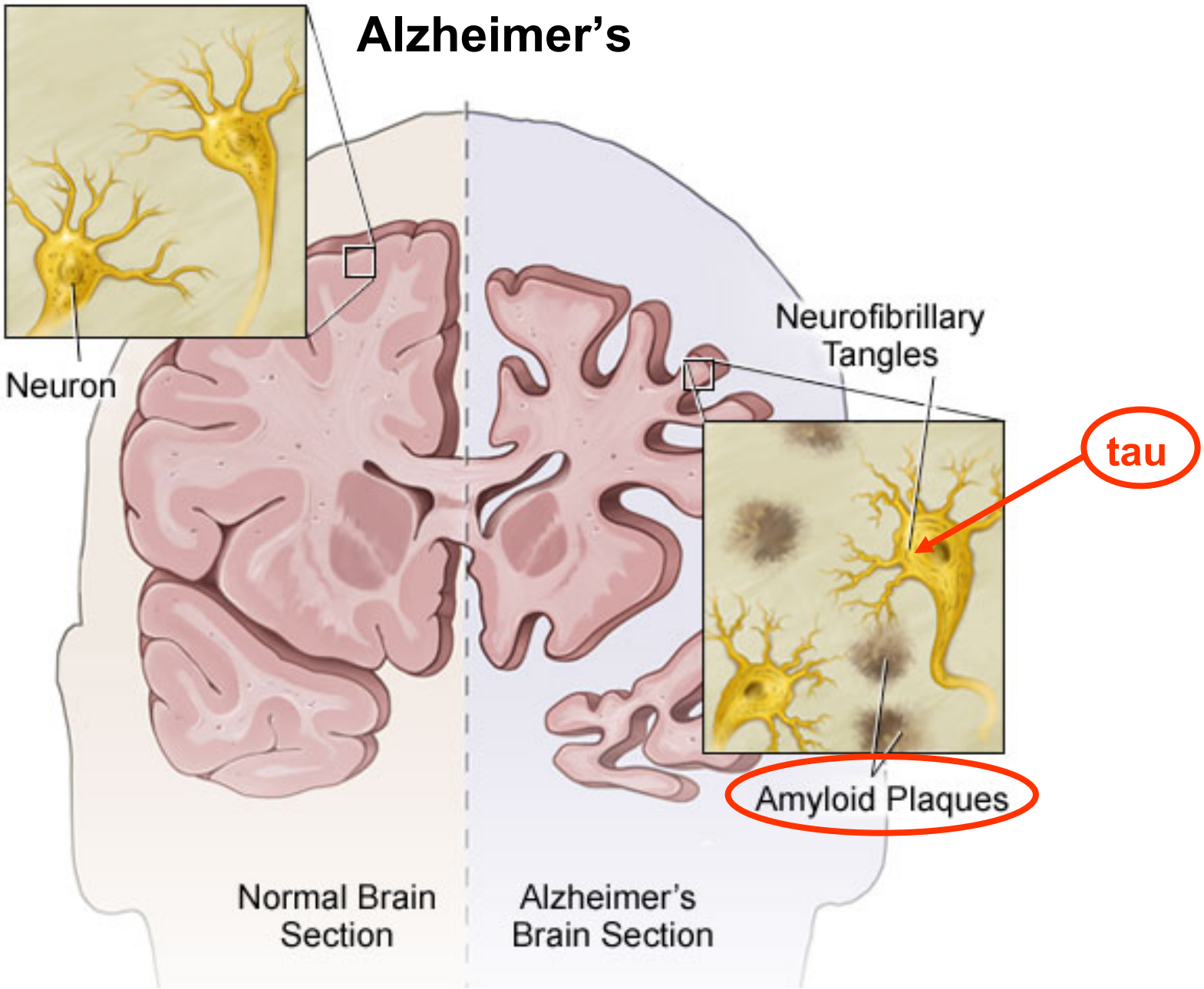
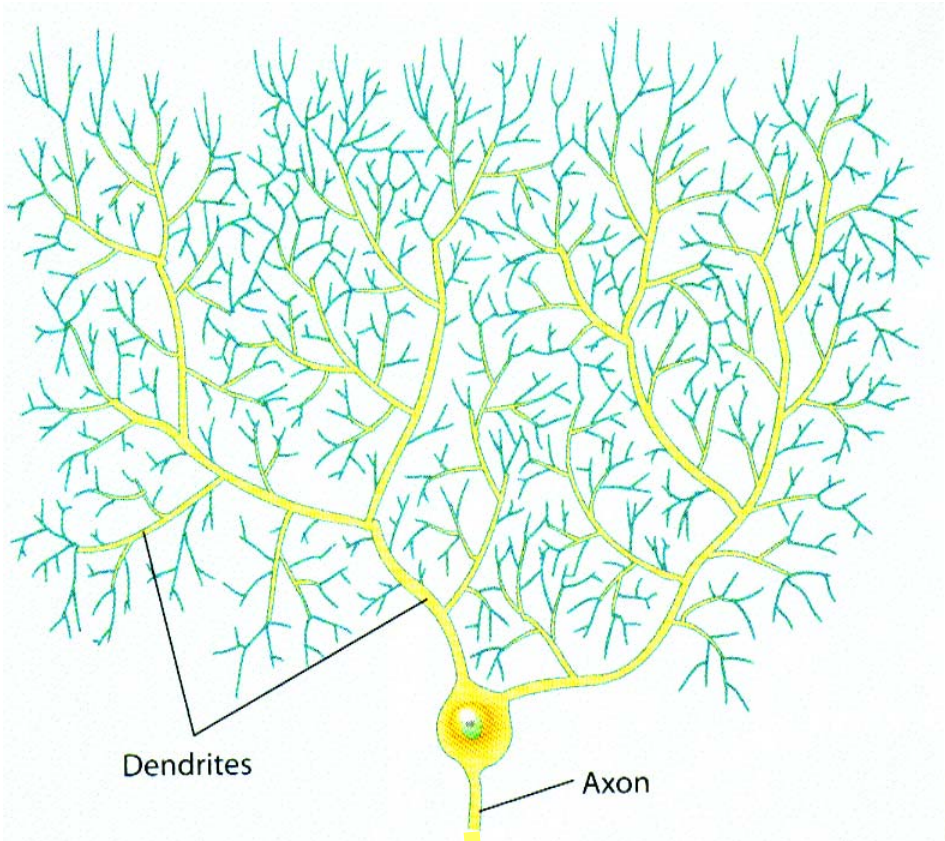
Dept of Neurology and Neurological Sciences

May 18, 2011

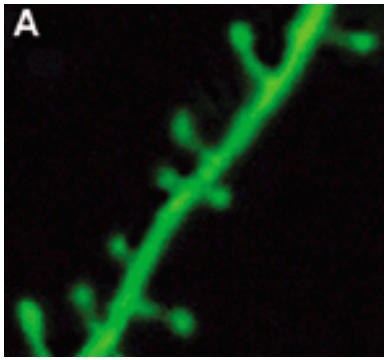


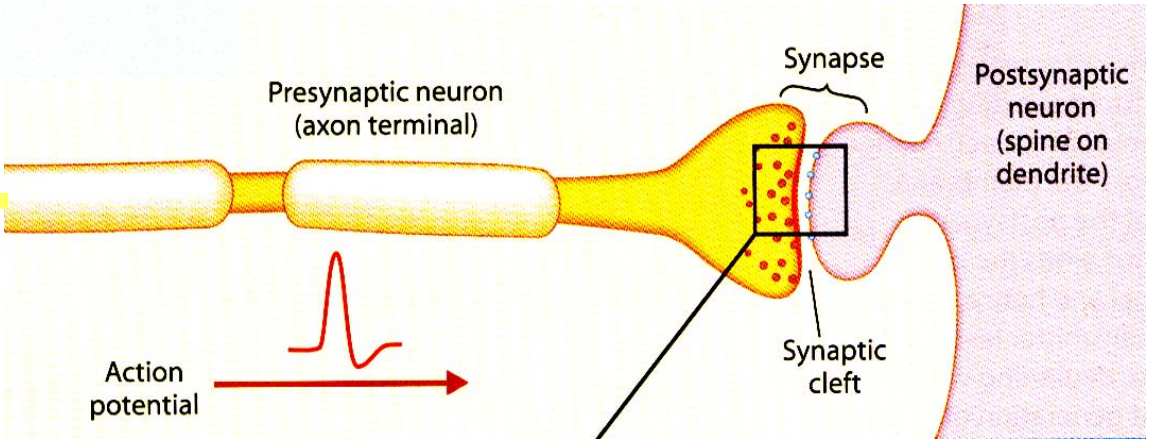
Alzheimer's


Neuron
Neurofibrillary Tangles
tau
Amyloid Plaques
Normal Brain Section
Alzheimer's Brain Section



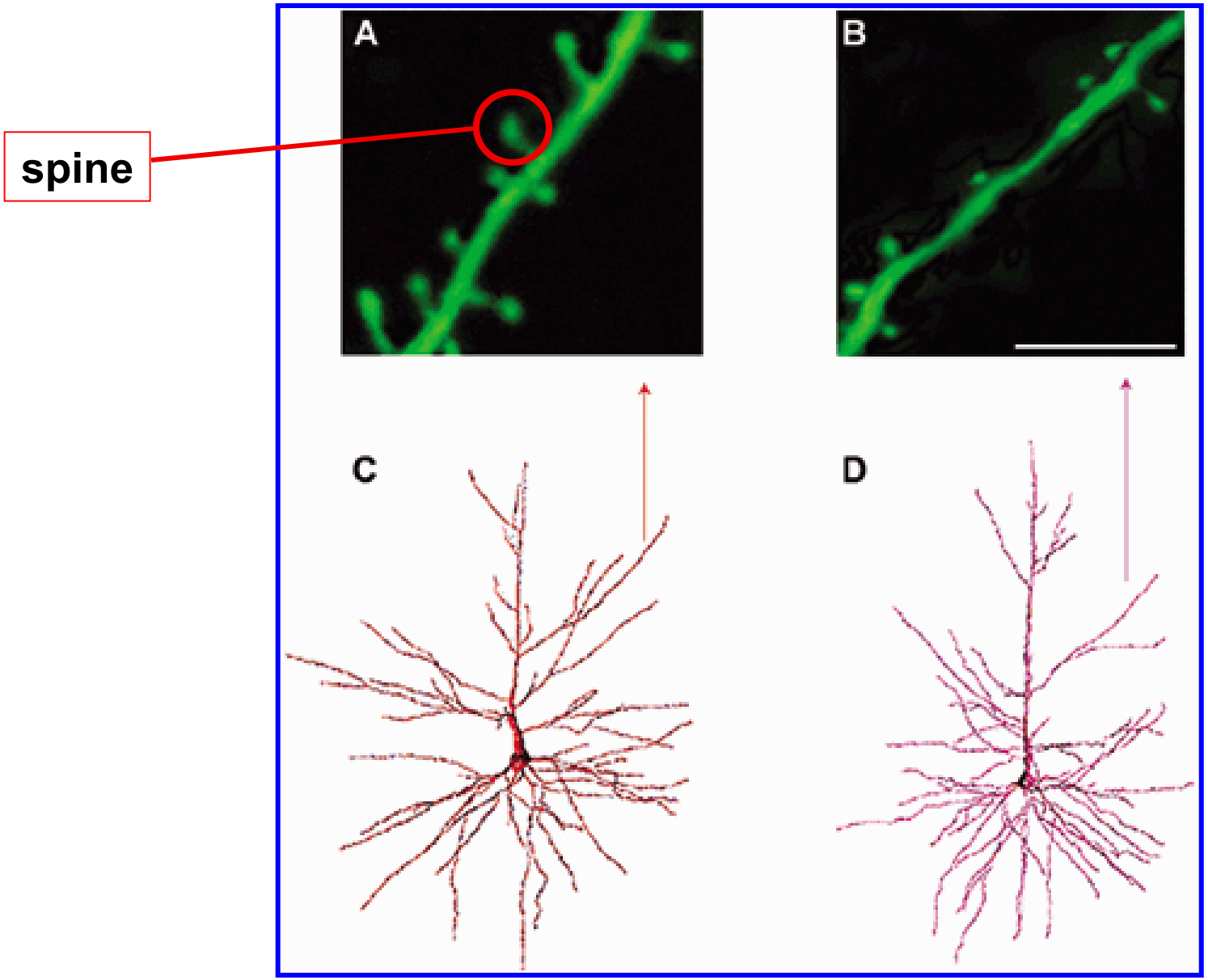
100 B (10^{11}) neurons
100 T (10^{14}) synapses



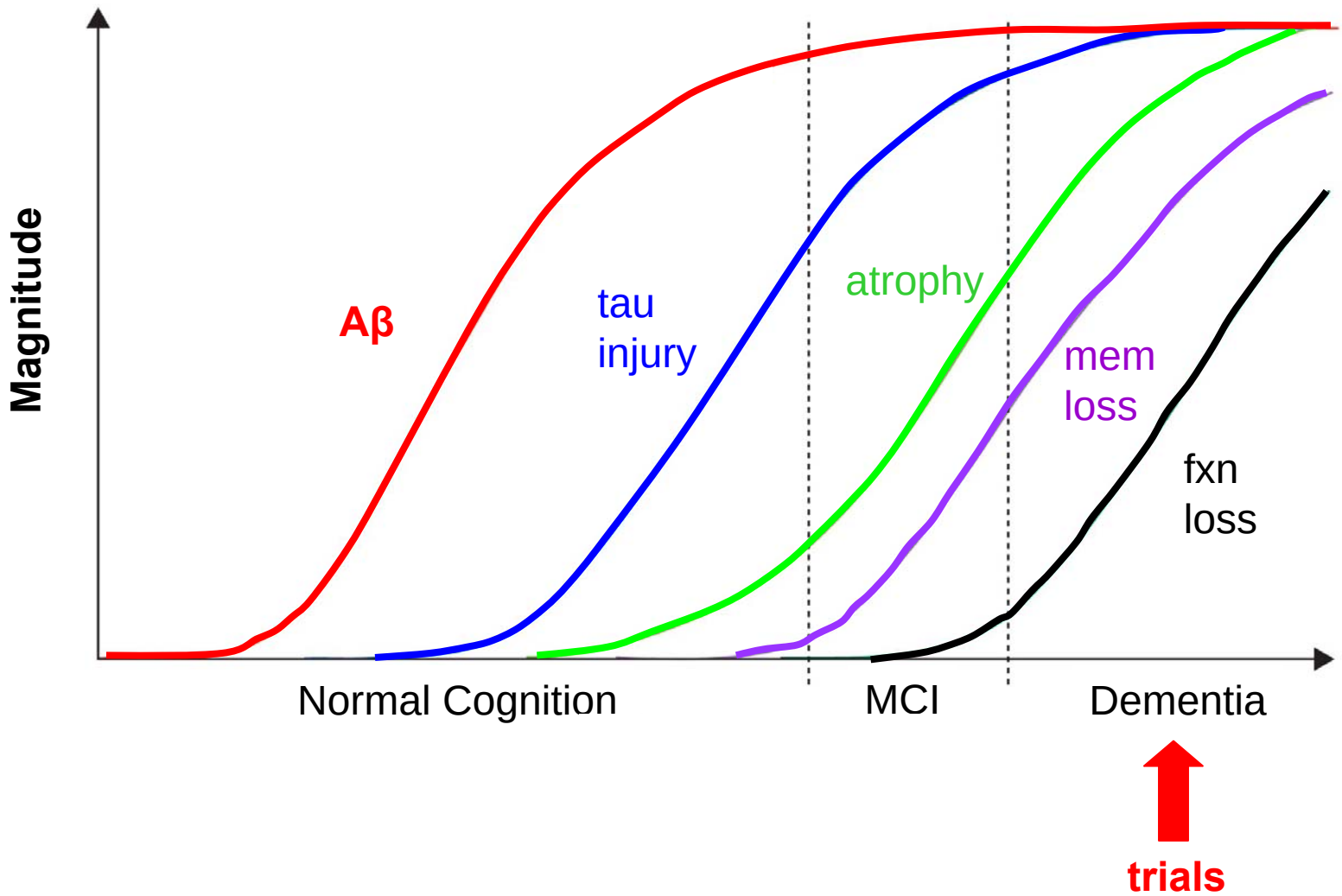


Modified from Gazzaniga et al, 2009

Loss of Spines

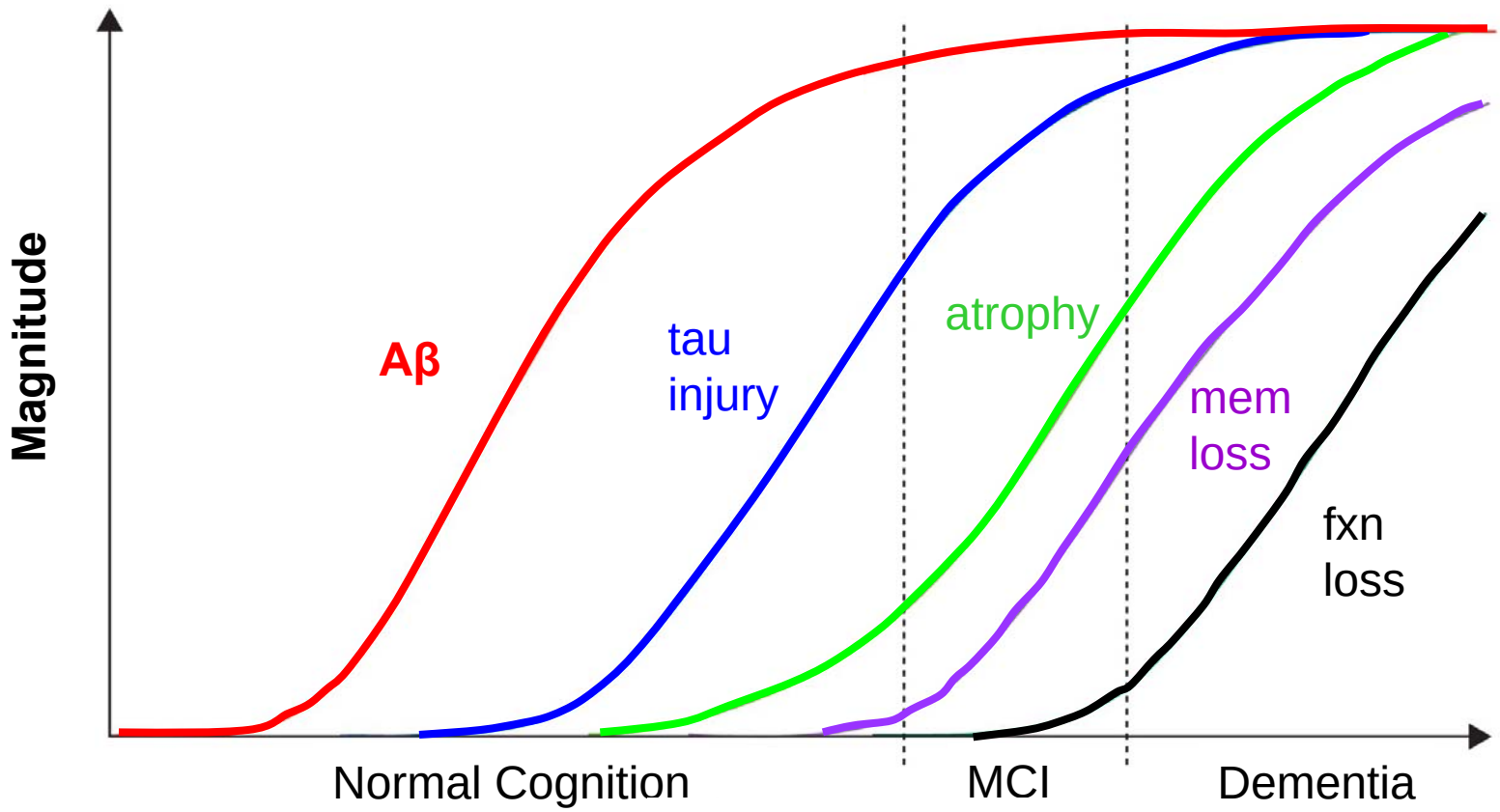


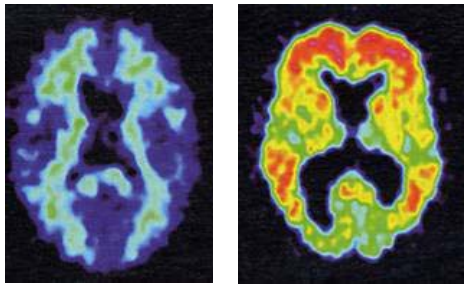
Alzheimer's starts well before sxs



Modified from Jack et al
Lancet Neurology 2010

Alzheimer's starts well before sxs





trials

Modified from Jack et al
Lancet Neurology 2010

Alzheimer's Genetics

Sporadic AD (95%): onset > 65 yo
Familial/single gene AD (5%) onset 40-50s

Sporadic: Many genes + environment

ApoE gene: (ApoE2) / ApoE3 / ApoE4

No family hx:	One parent with AD:
Lifetime risk 15%	E3/E3: 30%
- E4 9%	E3/E4: 45%
+ E4 30%	E4/E4: 60%

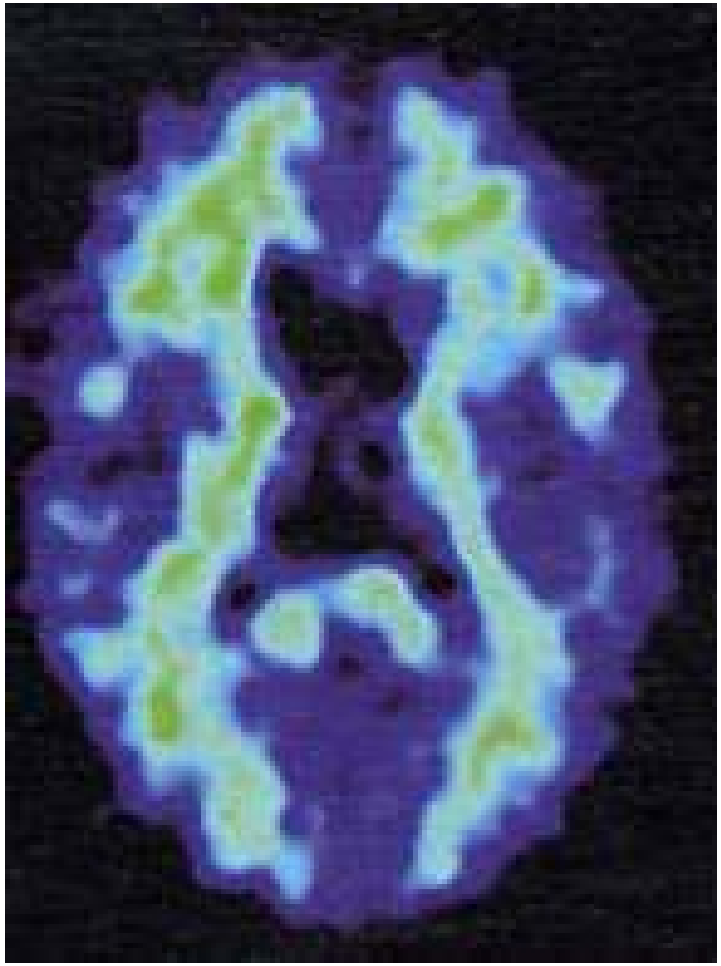
23andMe

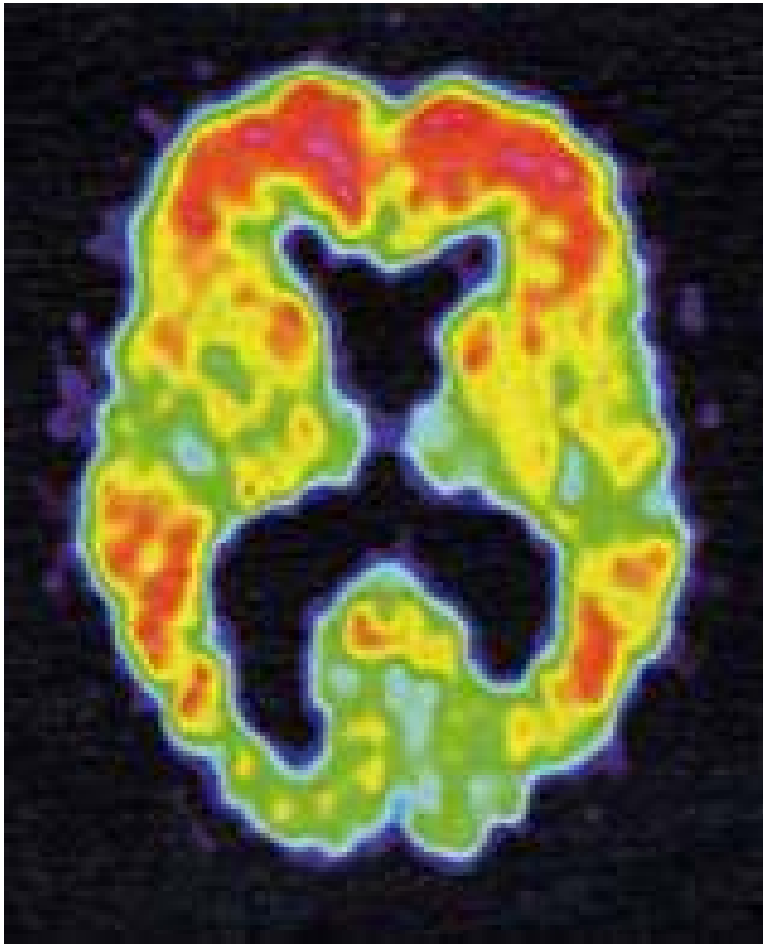
Navigenics™

+ E4: 6X more long-term disability insur.

Conventional MRI scan

Amyloid Plaque Imaging

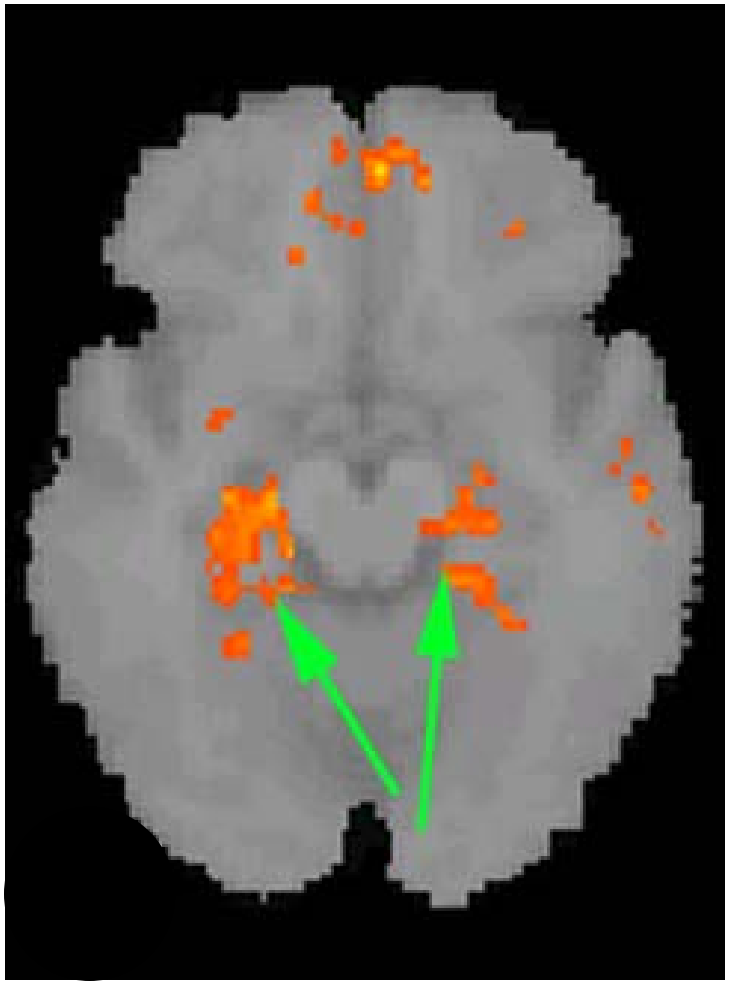




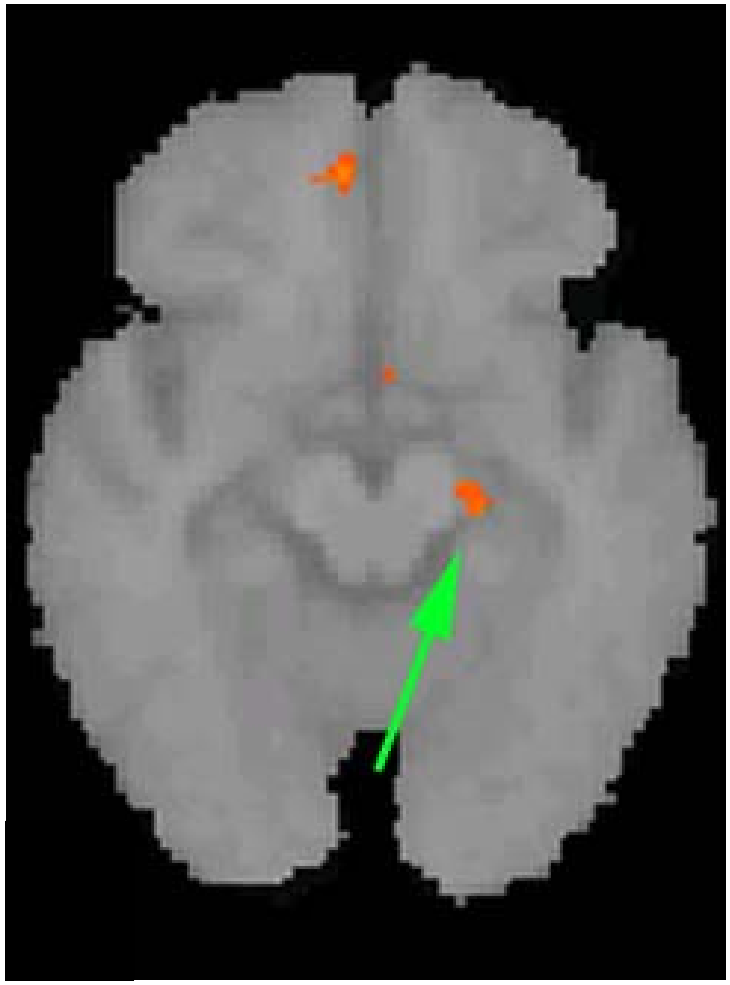
1/3 of normal elderly
2/3 of Mild Cog Impairment

Stanford Resting State fMRI

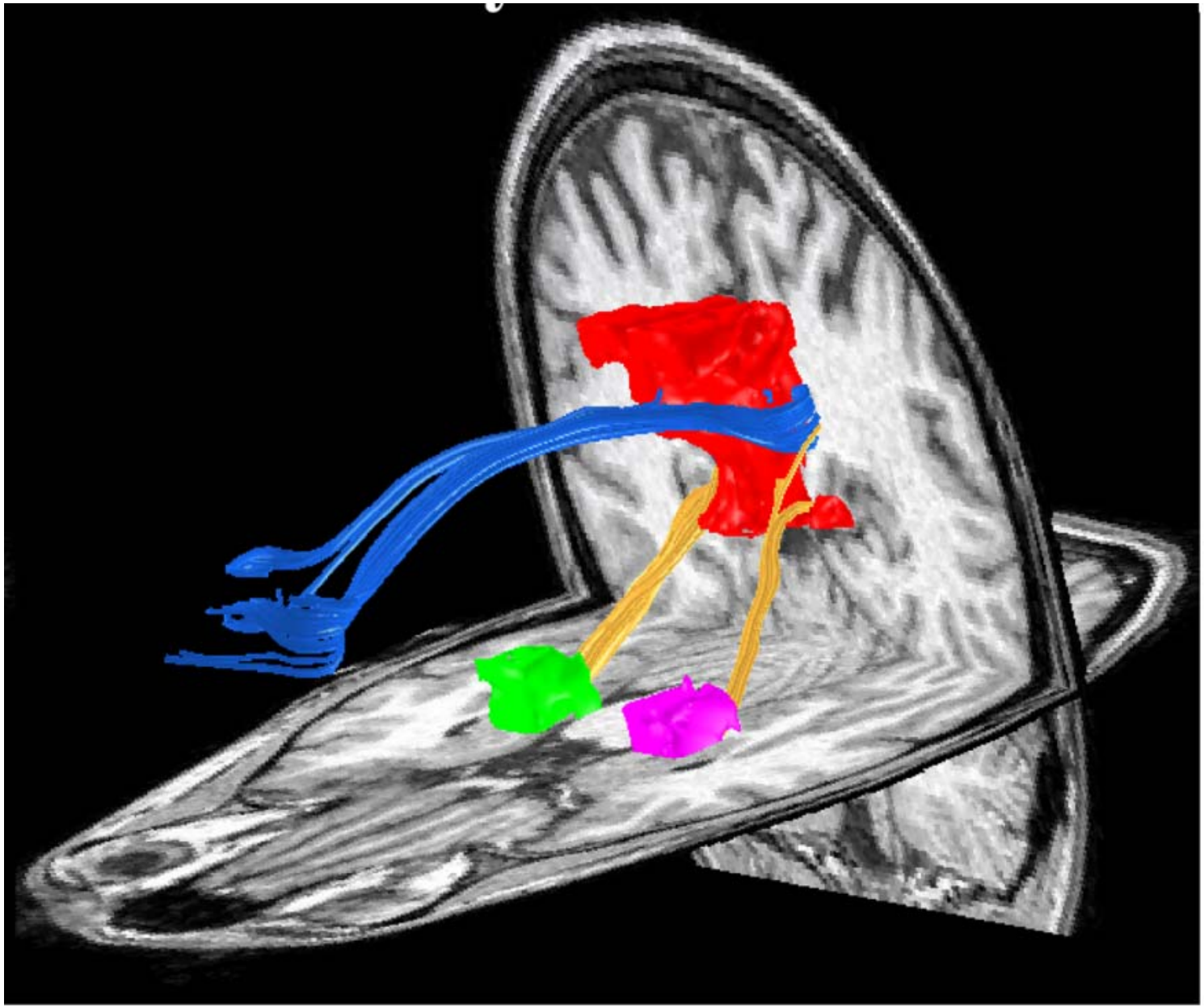
Healthy elderly



Early Alzheimer's

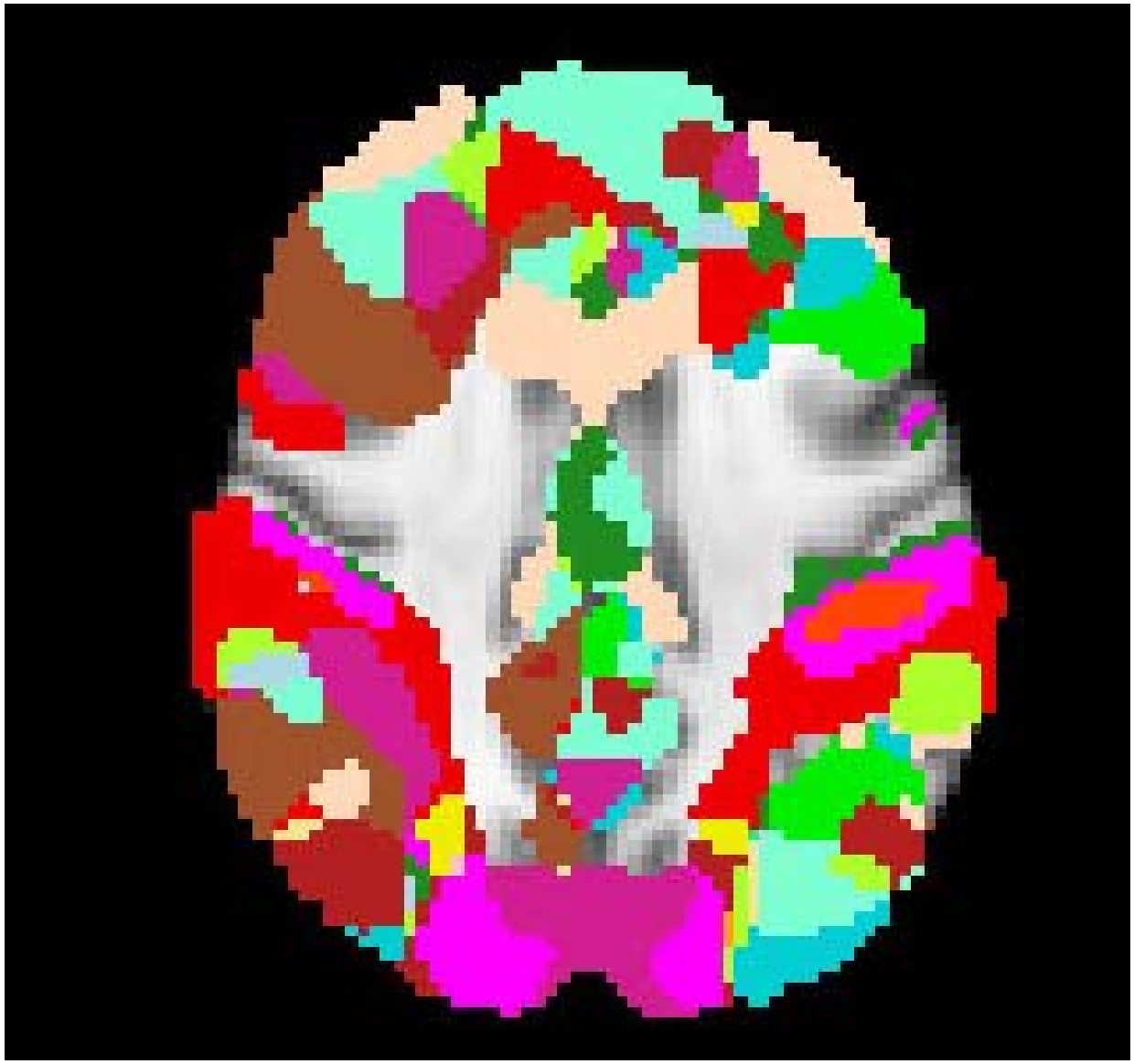


Drs. Michael Greicius and Vinod Menon - Stanford



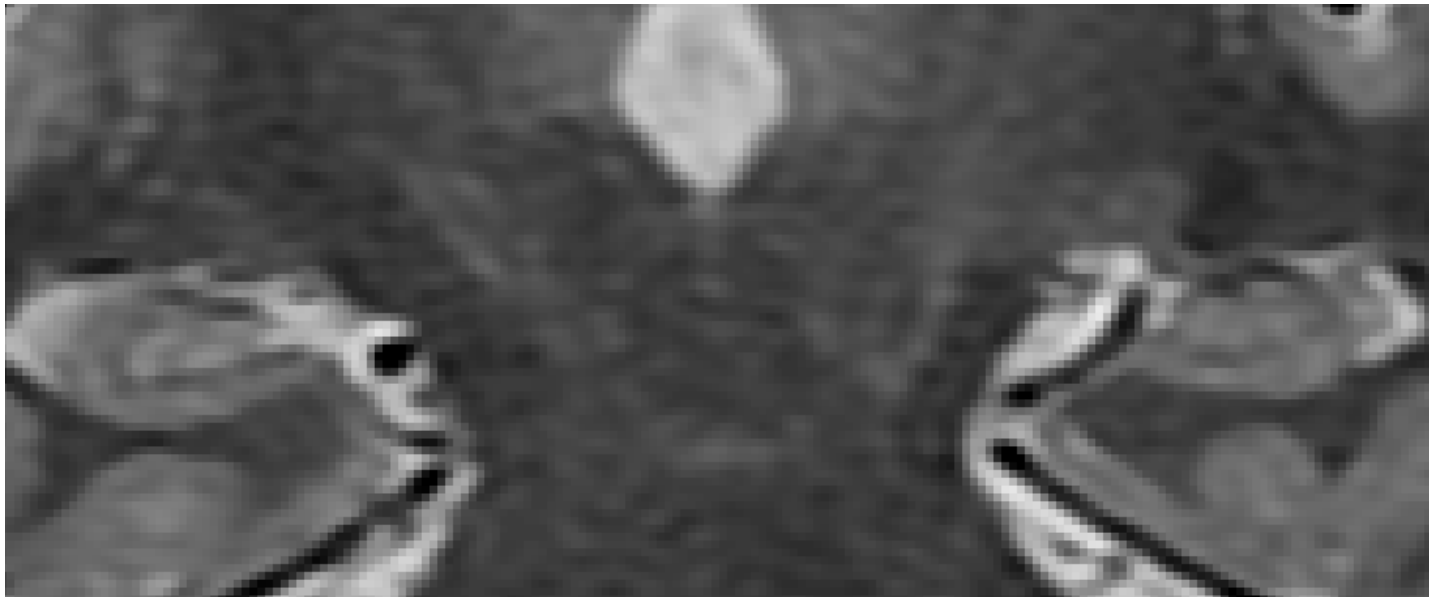
Drs. Michael Greicius and Vinod Menon - Stanford

Connectivity Maps

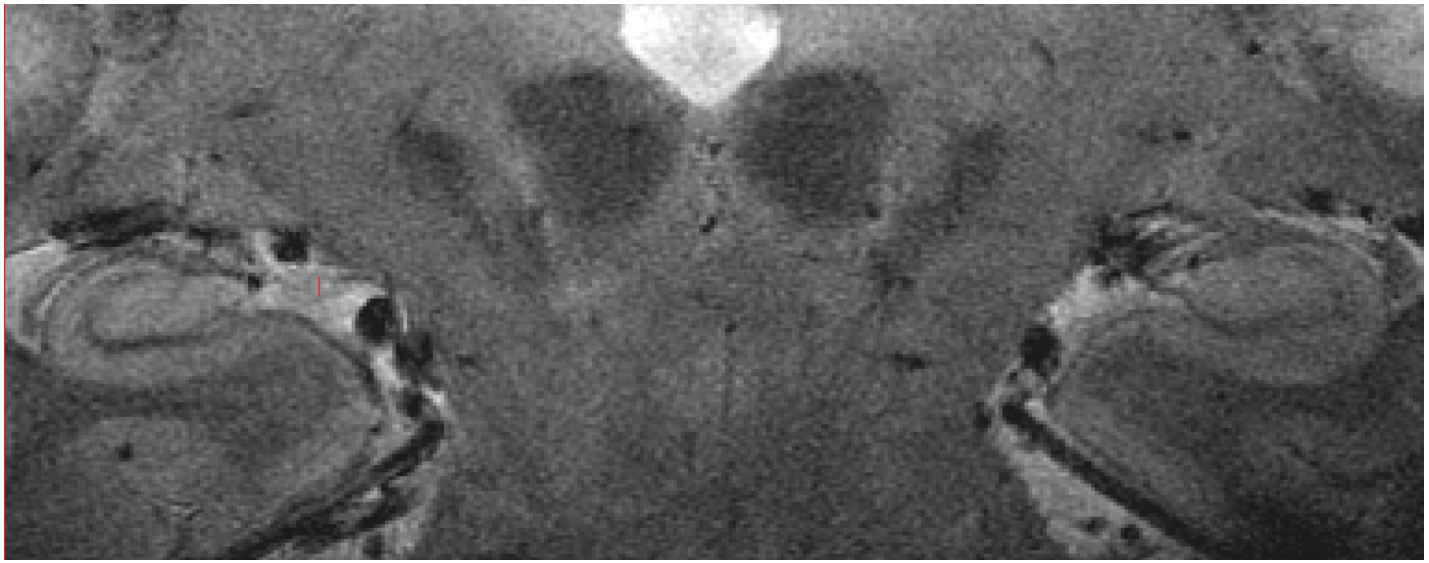


Conventional MRI scan

3T

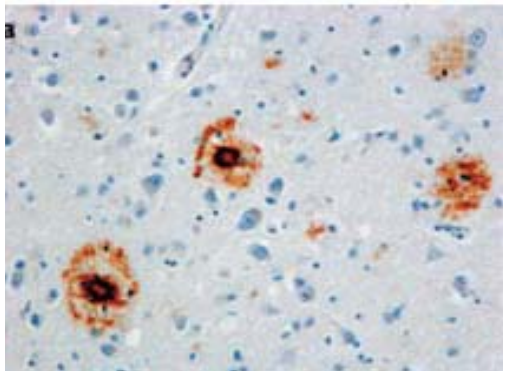


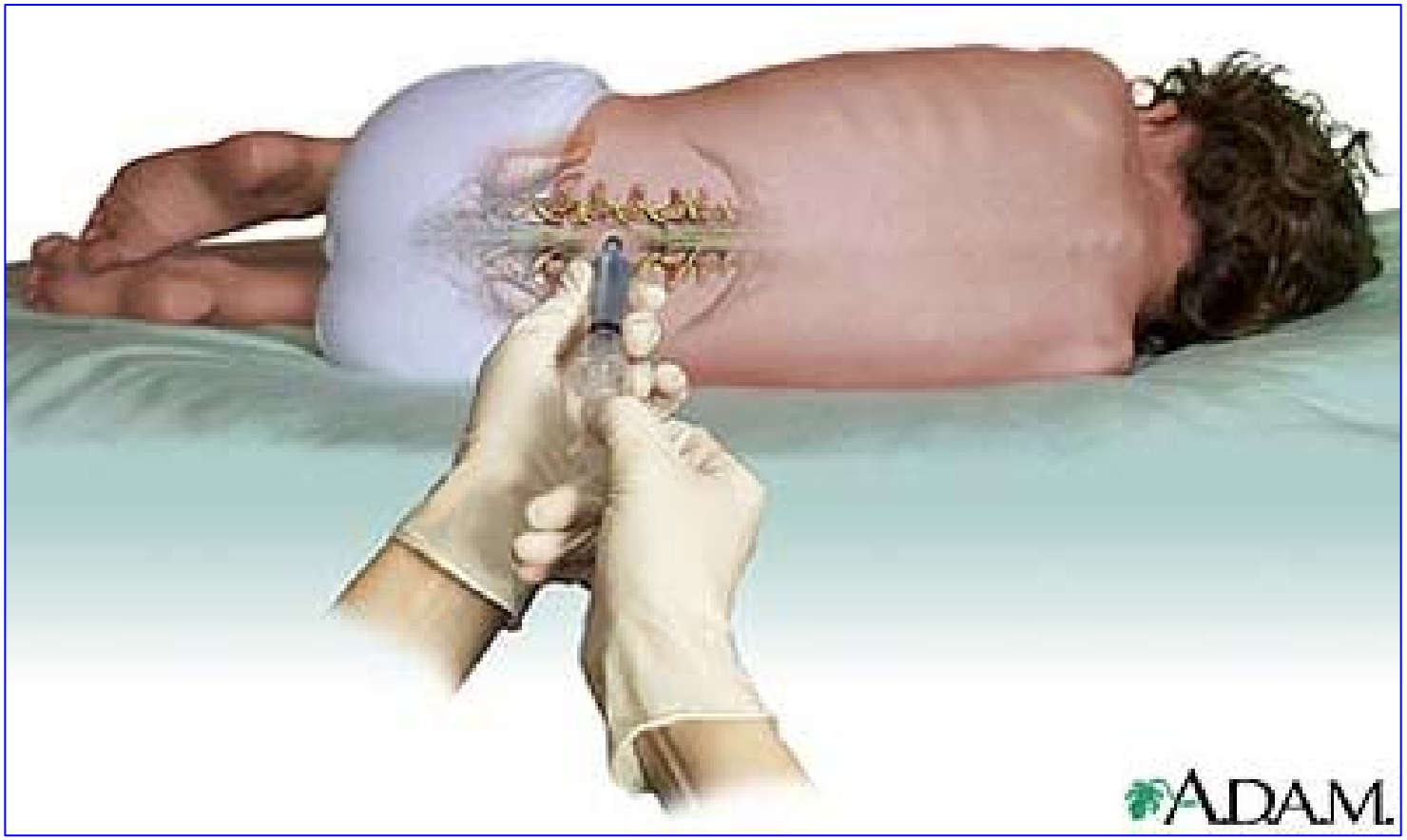
7T



Geoff Kerchner - Stanford

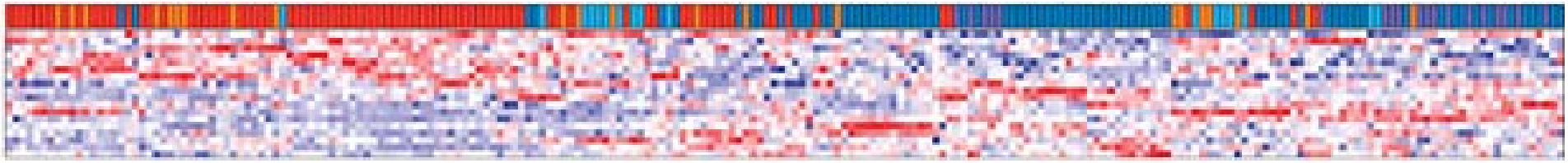
Spinal tap for Alzheimer's
Prediction or diagnosis?





Proteomics to predict or dx Alzheimer's

AD
MCI to AD
NL/other dementia



Tony Wyss-Coray (Stanford)

Exercise and the Brain

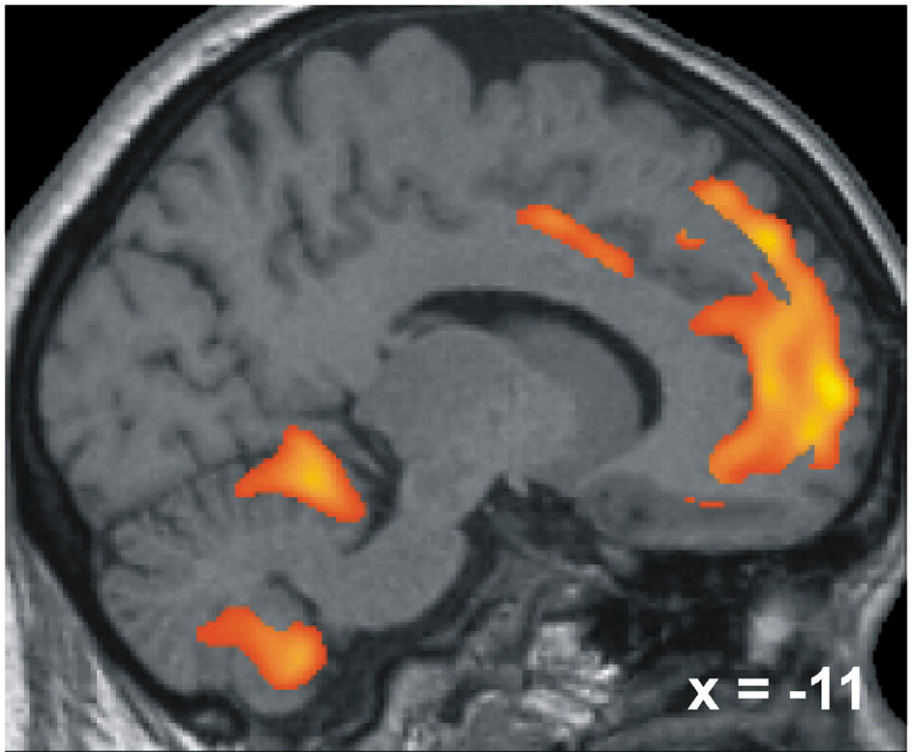
Photo by Marketa Ebert

Audrey Lary set 5 new records in 2009 Age:75

National Senior Games Association

Physical activity level: memory function and brain volume

kcal/week 0-7000 (cycling to work, stairs, gardening):
- **15 word recall**
- **MRI grey matter analysis**



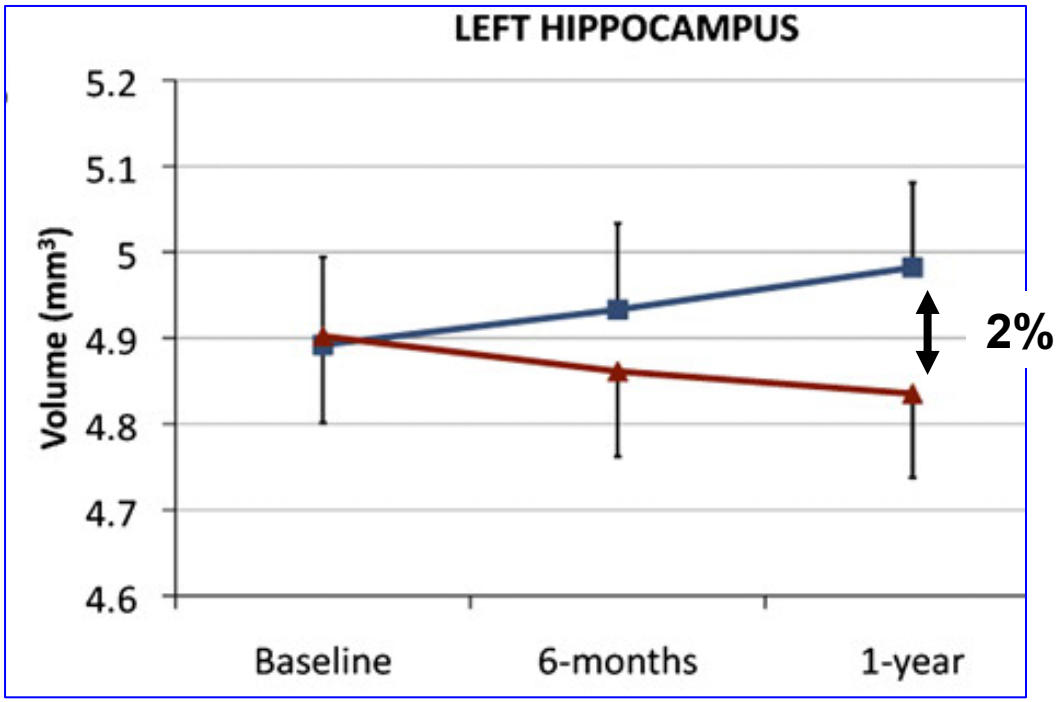
Floel et al, 2010

Exercise – Reversal of Hippocampus Age-related Atrophy

10 ⟶ 40 min/day walk 1 year

Hippocampus

1-2%/yr atrophy



Erickson et al PNAS 2011

Diet and Supplements

Mediterranean diet:
low animal, high grains, high vegetable, high ω3 FA

→ **40% dementia risk reduction**

Martek MIDAS Study: Omega-3 FA

- >55 age-associated memory impairment (> 1 SD below age mean)
- DHA 900 mg/day
- 24 weeks, memory and executive function

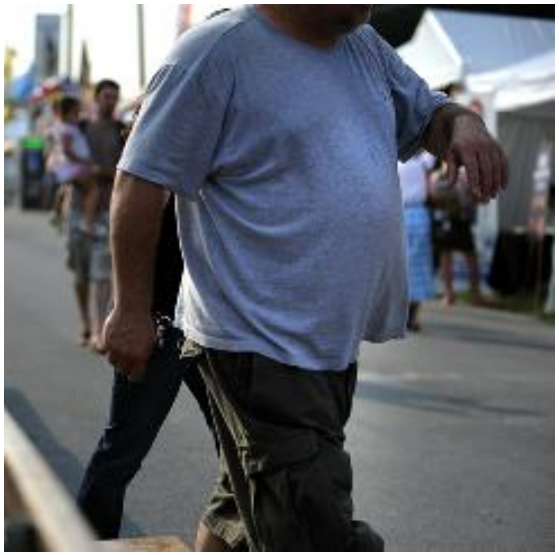
Improvement in visual-spatial learning

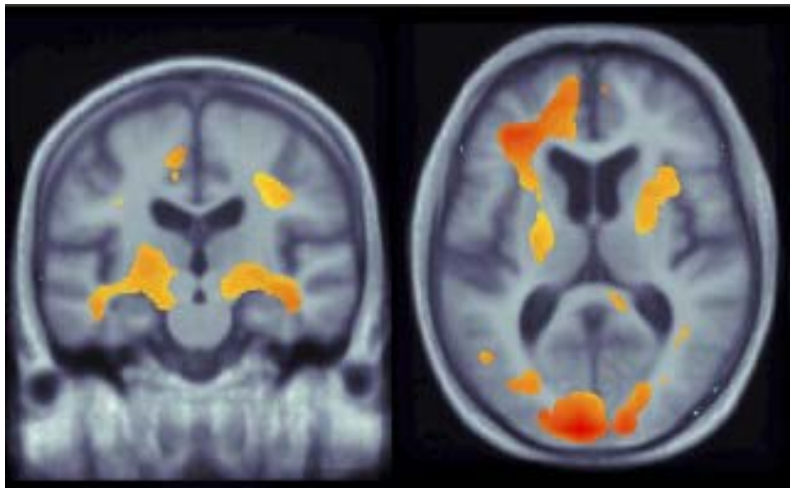
NIA-Martek: Omega-3 FA in mild-mod AD

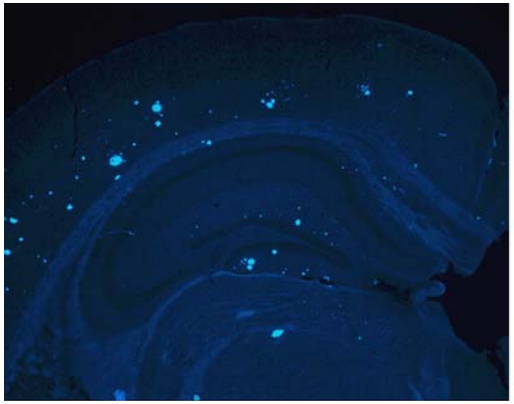
- Mild-mod AD
- DHA 1000 mg twice/day X 18 months

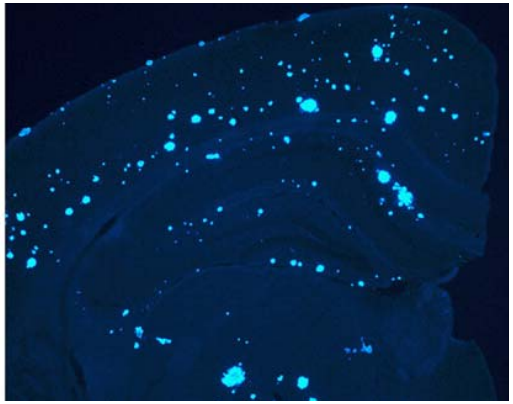
No improvement in cognitive function (ADAScog) unless no ApoE4

Brain atrophy with higher BMI



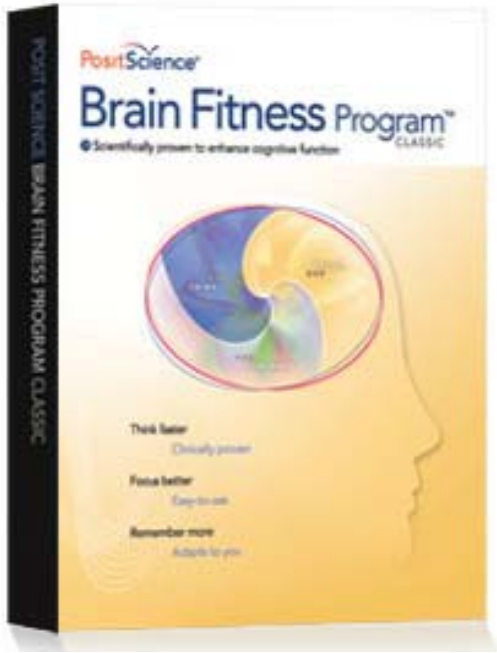


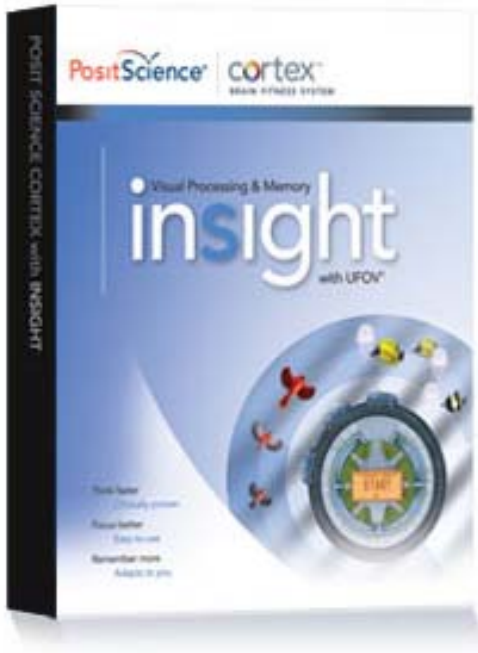


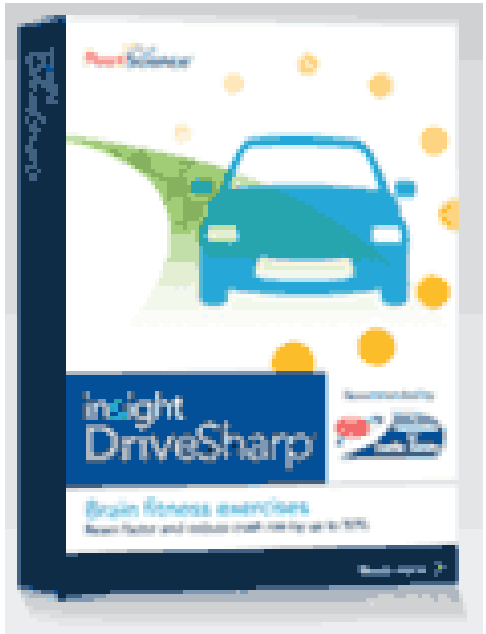


Ho et al, 2010; Fitz et al, 2010

Cognitive Exercise







Posit
Nintendo
Mattel
Hasbro

FDA Approved Therapies

Cholinesterase Inhibitors

- Donepezil (Aricept)
- Galantamine (Reminyl, Razadyne)
- Rivastigmine (Exelon)

NMDA Receptor Antagonist

- Memantine (Namenda)

Caprylic triglyceride (Axona)
FDA- "medical food"

AD Clinical Trials

Clinical Trials.gov

(May 2011):

Current AD listings: 923
Interventional: 789
Recruiting: 197

Alzheimer's Trials

35% Existing AD drugs

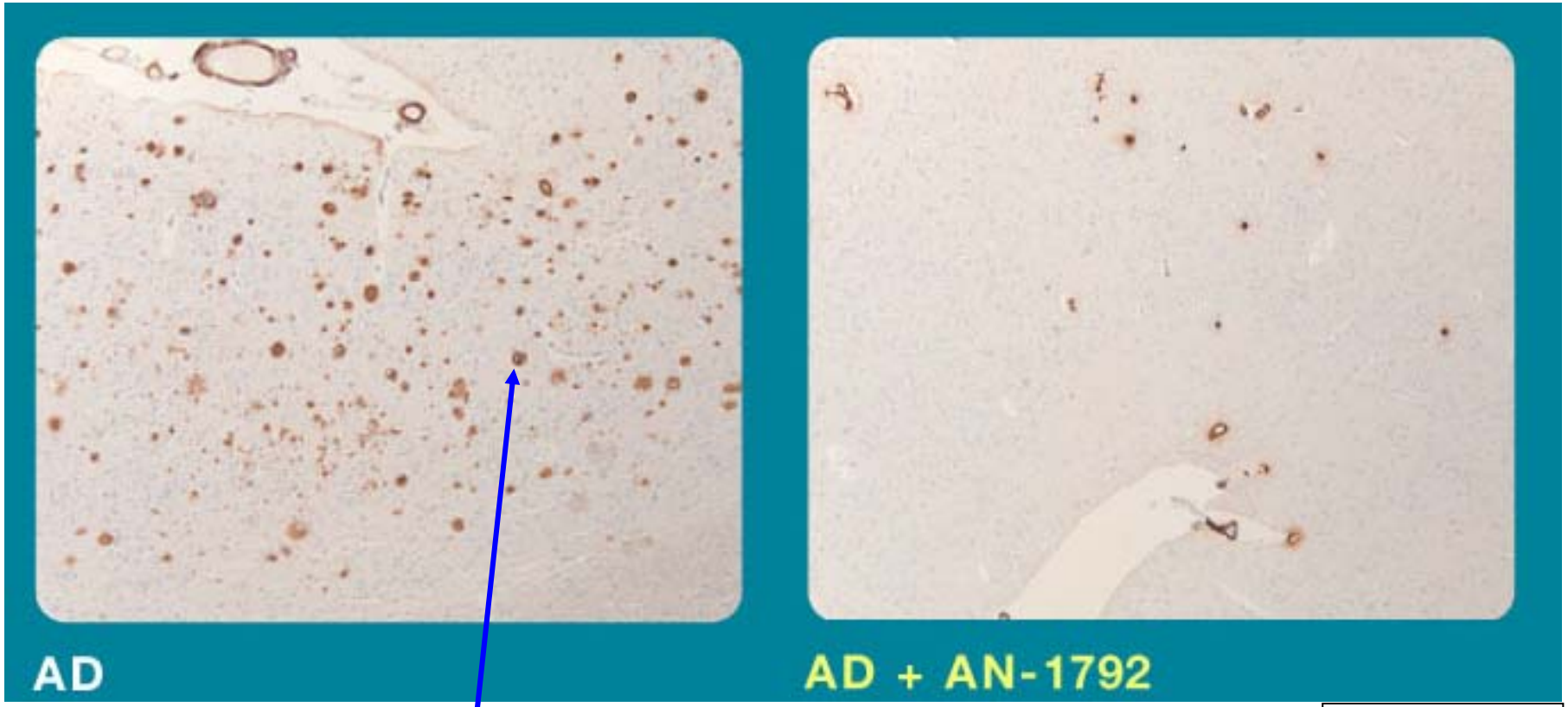
I 25% Lowering amyloid beta
- Antibodies
- Enzyme inhibition

II 20% Neurotransmitter receptors
- Intranasal insulin, cognitive enhancers, neurotransmitters (nicotinic)

III 15% Protecting neurons
Growth factor, inflammatory, anti-oxidants

Analysis by Dr. F. Longo - Stanford

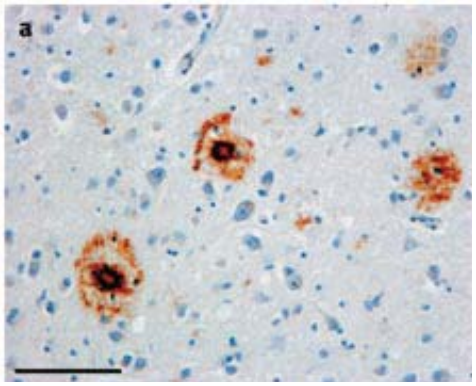
Amyloid Immunization - Elan



J Nicoll, UK

Amyloid plaques

I. Lowering Amyloid Beta



Bapineuzumab (antibody)
Solanezumab (antibody)
PF-04360365 (antibody)
GSK933776A (antibody)
MABT5102A (antibody)

IVIG (antibody)

ACC-001 (immunization)
CAD-106 (immunization)
V950 (immunization)

LY450139 (γ-secretase inhib)
BMS-708163 (γ-secretase inhib)
GSI-136, 953 (γ-secretase inhib)
NIC5-15 (γ-secretase inhib)
E2212 (γ-secretase inhib)

CTS-2116 (β-secretase inhib)
E2609 (β-secretase inhib)

ST101 (lowers Aβ + other activities)
PAZ-417 (lowers Aβ)
3APS (binds Aβ)
Posiphen (phenserine, lowers Aβ)
PPI-1019 APAN (inhibit Aβ aggregation)

Analysis by Dr. F. Longo - Stanford

II. Neurotransmitter receptors

Cholinergic receptor: Varenicline, ABT-089, GSK239512, EVP-6124
DNXB-A, AZD3480, AZD1446, ZT-1-huperzine derivative

Locezotan (5-HT1A)
SR57746A (xaliproden, 5-HT1A)
GSK239512 (H3)
ABT-288 (H3)
PRX-03140 (5-HT4)
SB-742457 (5HT6)
SAM-531 (5HT6)
PRX-03140 (5-HT4)

LY451395 (AMPA)
CX516 (AMPA)
SGS742 (GABA)
AFQ056 (mGluR5)
Neramexane (NMDA)
Atomoxetine (strattera, NERI)
PF-04447943 (PDE9A inhib)
NS2330 Tesofensine (monamine uptake)
ORM-12742 (alpha adrenoceptor)

Analysis by Dr. F. Longo - Stanford

III. Protecting Neurons

Roziglitazone, metformin (insulin)
Intranasal insulin
Extendin-4, Liraglutide (GLP1 agonists)
Ladostigil (ACI/MAO-B/growth factors)
SR57667B (growth factor induction, ~xaliproden)
CERE-110 (NGF gene therapy)
TH9507 (GH releasing factor)

Bryostatin (PKC activator)
PF-04494700 (neuroprotective-RAGE)
Rasagiline (MAO-B/PKC)
Resveratrol (gene expression)
Trx0014 (Rember) (microtubules)
Acitretin (Soriatane, retinoid)
Tamibarotene (retinoid)
Mesenchymal stem cells (trophic?)
Dimebon (neuroprotective/cholinergic)

Estrogen/progesterone
Testosterone gel
Leupride

SK-PC-B70M (anti-oxidant)
Epigallocatechin-gallate (inflam-ox)
T-817MA (anti-oxidant, trophic)
Thalidomide (immunomodulation)
Curcumin (Longvida) (inflam-ox)
Etanercept (TGFα/inflammation)
HF0220 (anti-inflam/prostaglandins
Indomethacin (anti-inflammatory
IFβ-1a (inflam modulation)
Omega-3 FA (inflam-ox)

Analysis by Dr. F. Longo - Stanford

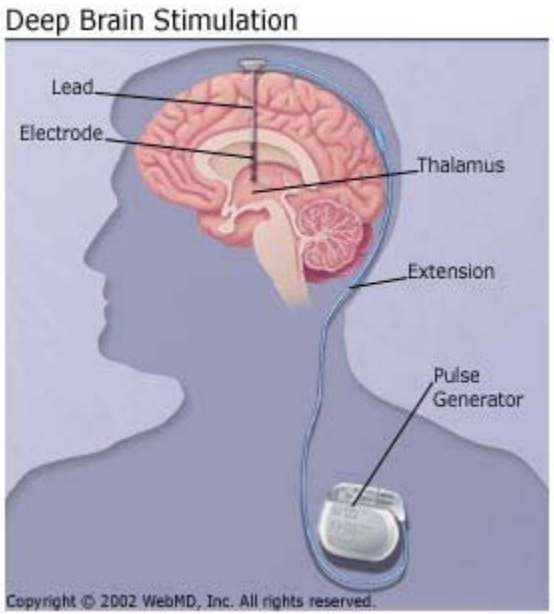
“Interventional” “San Francisco”

9 Studies:

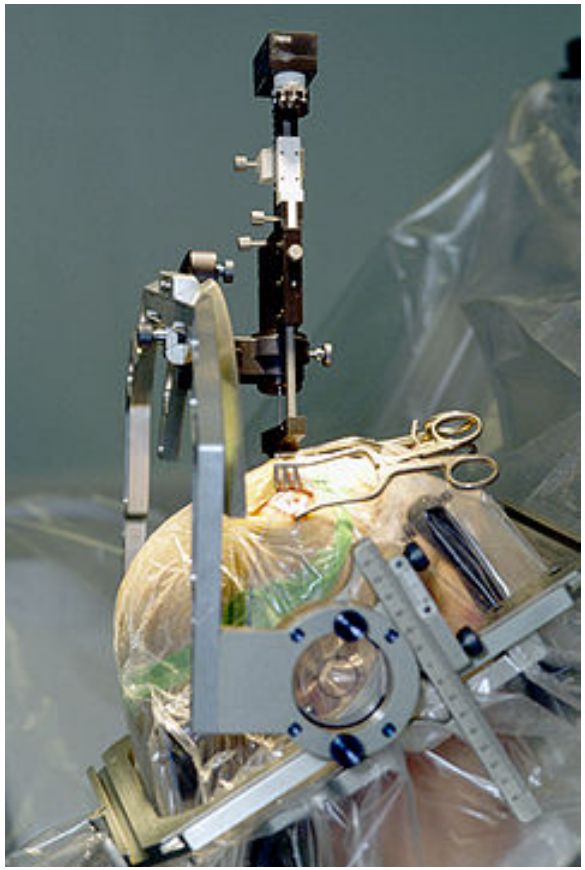
- rivastigmine
- donepezil
- ACC-001
- solanezumab
- bapineuzumab

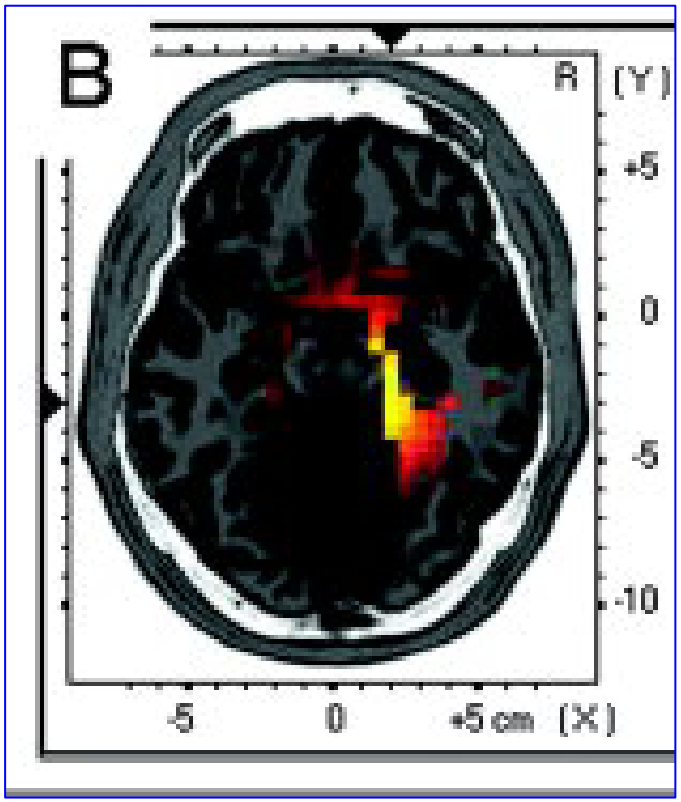
Analysis by Dr. F. Longo - Stanford

Deep brain stimulation for Alzheimer's?



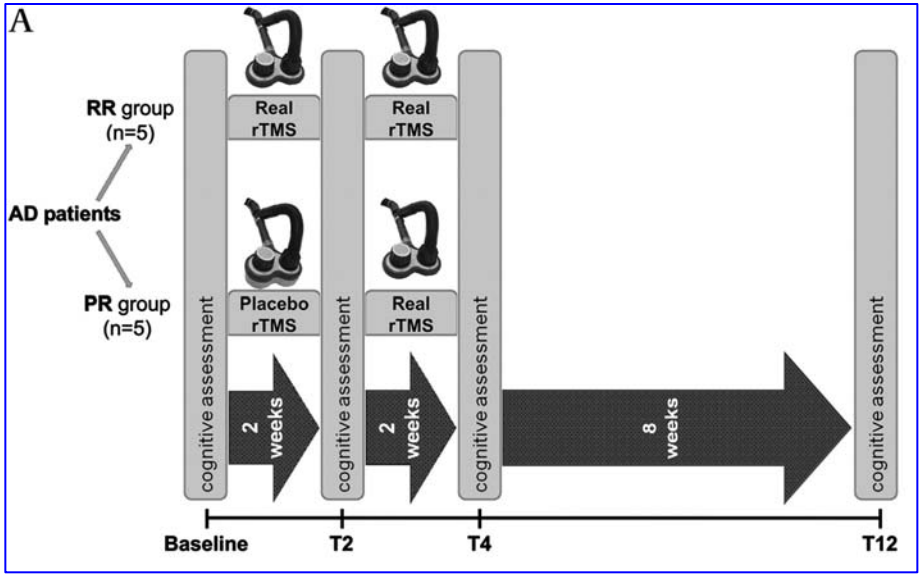
Hypothalamic stimulation

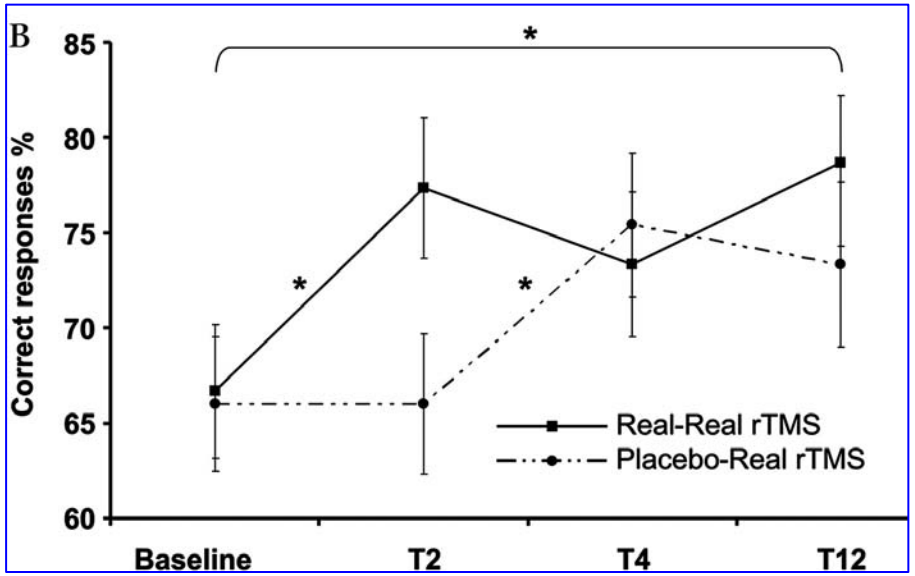




Hamani et al, 2007

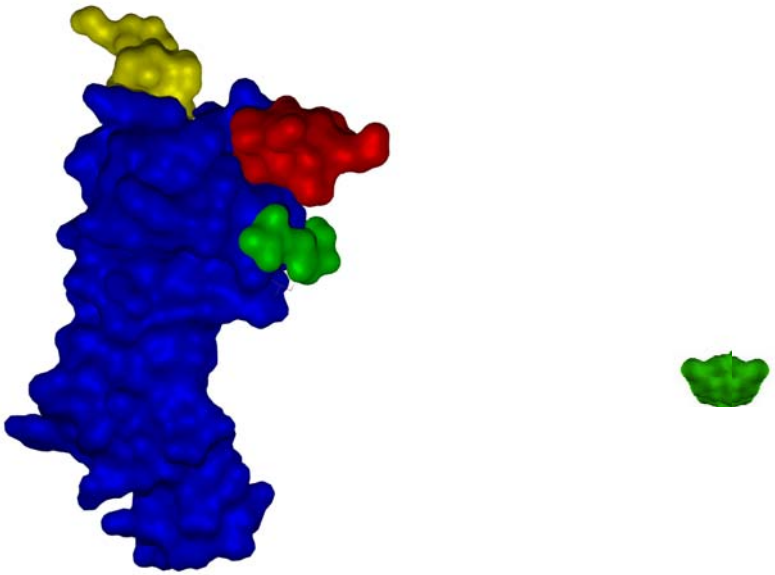
rTMS in AD improves language fxn

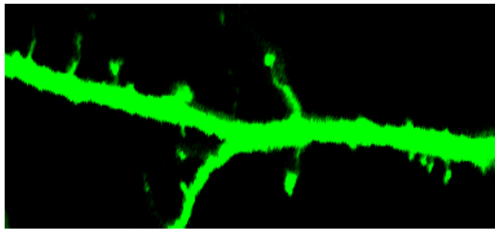


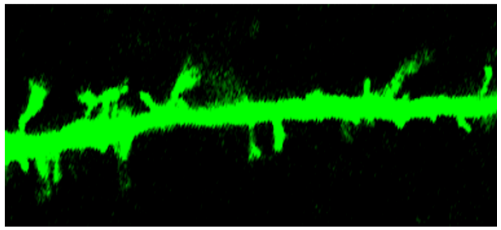


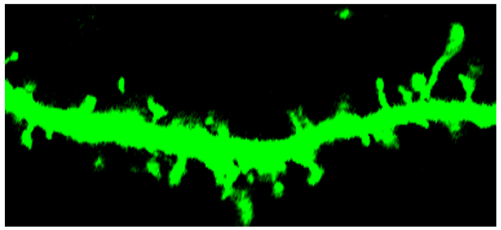
Cotelli et al 2009 JNNP

BDNF Protein: ↓aging ↑exercise







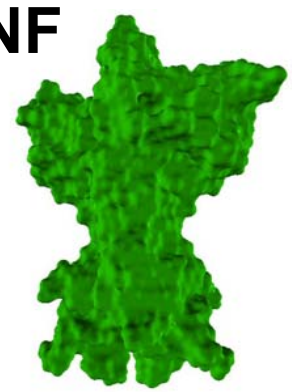


Longo Lab - Stanford

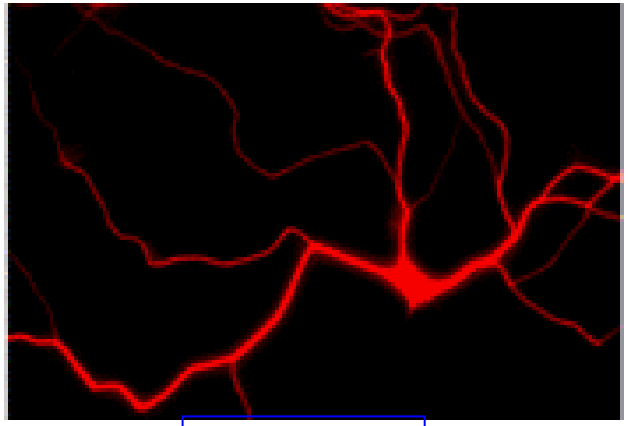
BDNF Protein: ↓aging ↑exercise

No BDNF

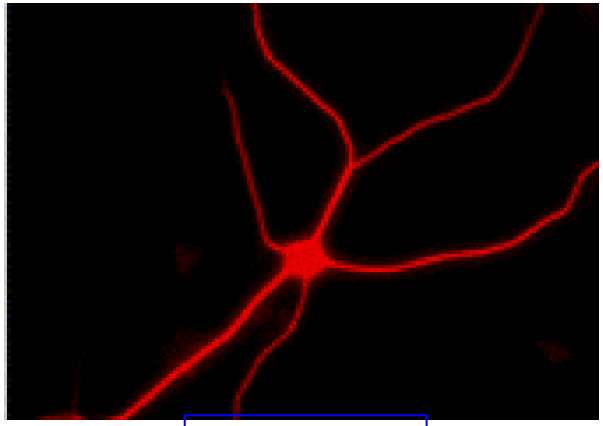
BDNF



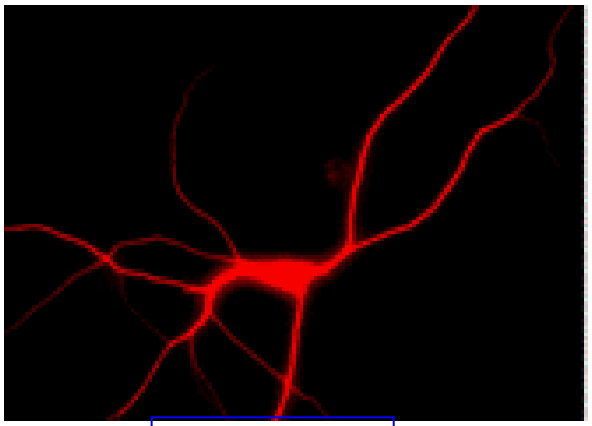
BDNF Mimetic



amyloid



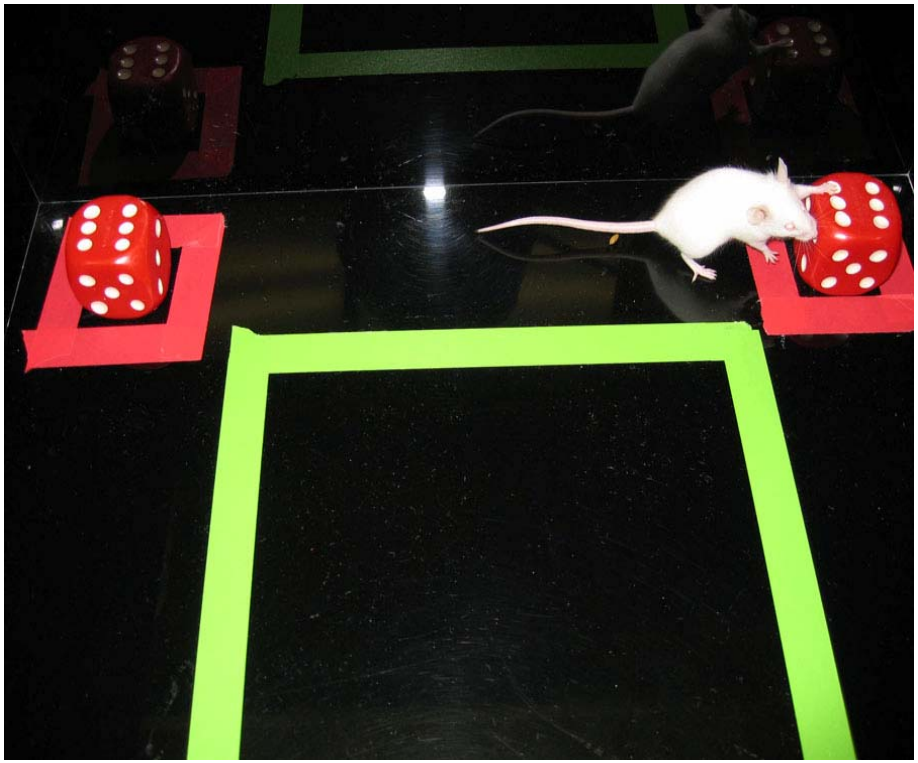
amyloid

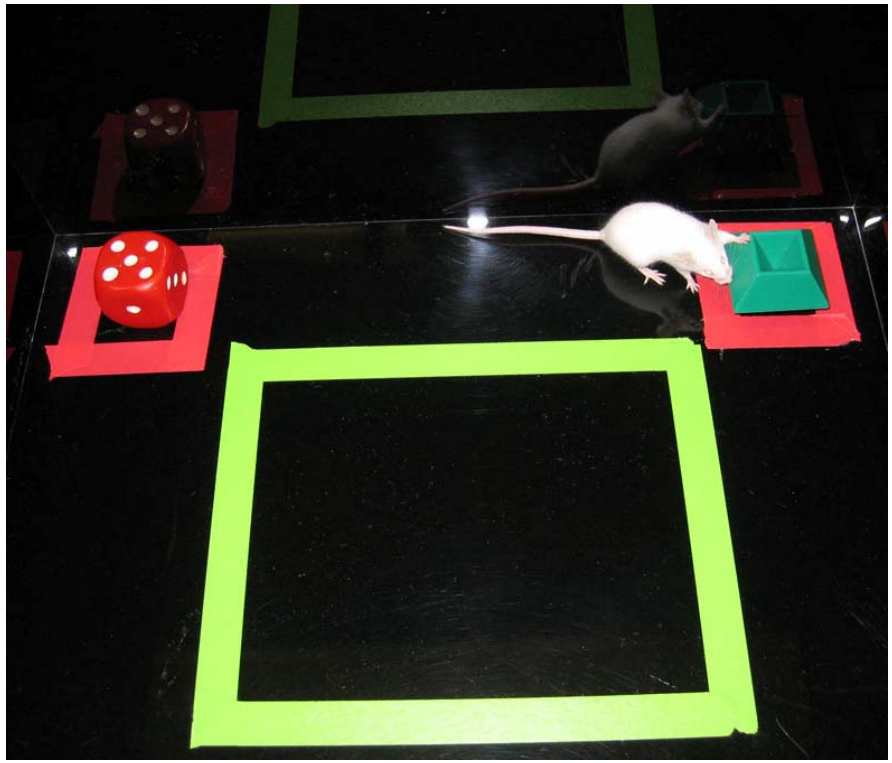


amyloid

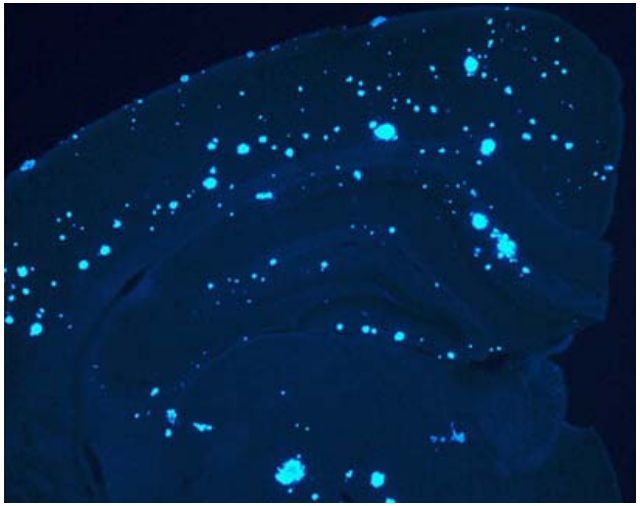
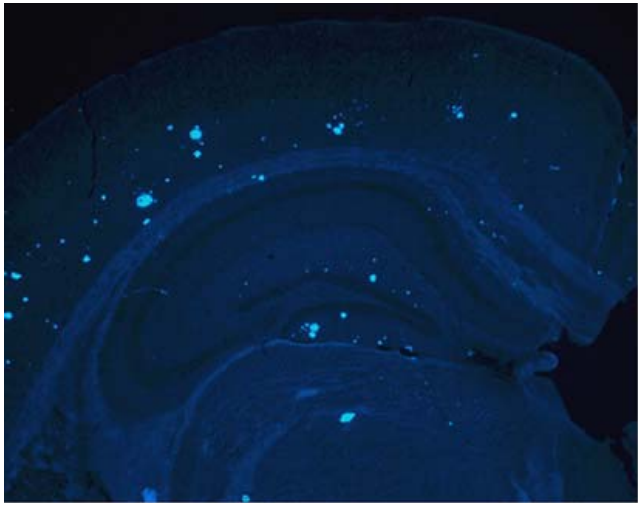
Longo Lab - Stanford

Testing Alzheimer's Therapies





Drs. Tony Wyss-Coray and Frank Longo

Therapies

- Drugs
- Physical exercise
- Diet/nutraceuticals
- Cognitive exercise
- TMS
- DBS