Reversal of Cognitive Decline

The Science, The Tools, and The Transformation

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Missouri Academy of Family Physicians

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Sharlin Health & Neurology
Functional Medicine

Professional Disclosures

- I am a primary investigator in several pharma-sponsored clinical trials (Novartis, Avanir, Sanofi-Genzyme, Eli Lilly, Biogen) and a paid speaker for Biohaven Pharmaceuticals, Abbvie, and Biogen.
- I have also been paid to speak by Worldlink Academy, IMMH, Age Management Medical Group, Metabolic Medical Institute of A4M, and The Cardiology Institute of America.
- I receive complimentary personal and staff certification for speaking at the annual Wahls Protocol Seminar.

“There’s nothing you can do about it.”

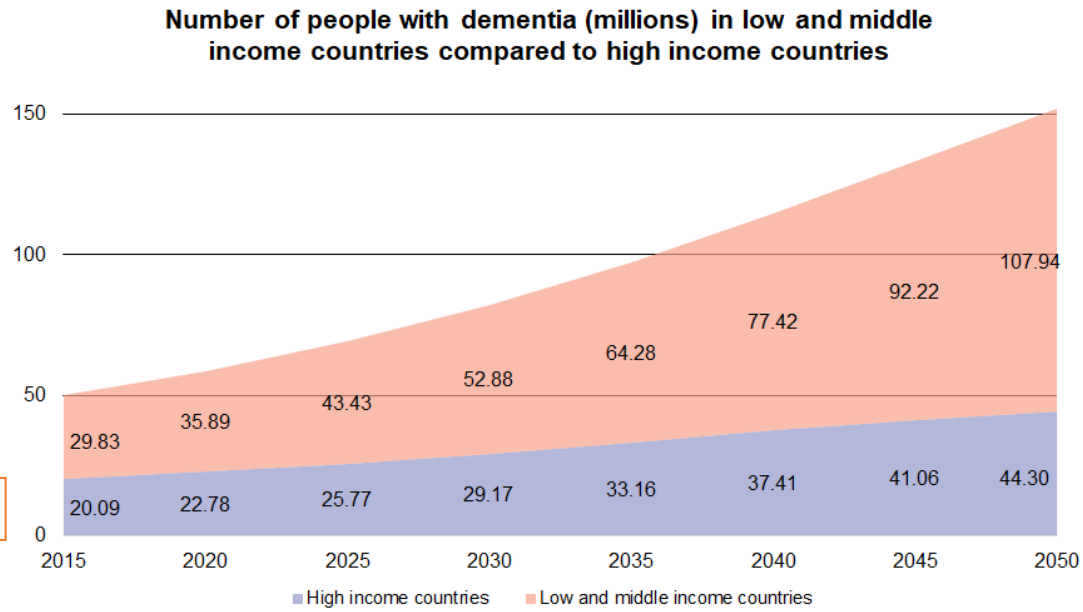
Robert's Clinical History and Findings

- 67-year-old male, small business owner, with a chief complaint of "memory loss"
- Difficulty with memory when working with clients and contracts
  - Would forget contracts he had previously discussed and names of clients he had known for years.
- Montreal Cognitive Assessment (MoCA) 19/30 - normal is 26 to 30.
  - Weakness with delayed recall (1/5 correct), sentence repetition, word fluency, visuo-spatial skills, executive functioning.
- MRI of the Brain – loss of brain volume, including the hippocampus, and iron deposits in the brain.
- CSF – findings consistent with Alzheimer's disease (low ATI and high P-tau).

Generation Alzheimer's

- An estimated 6.2 million Americans aged 65 and older are living with Alzheimer's dementia in 2021.
- More than 1 in 9 people (11.3%) age 65 and older has Alzheimer's dementia.
- A systematic review of more than 30 studies of MCI reported that 16.6% of people aged 65 and older had MCI.
- Meanwhile, studies assessing biomarkers for Alzheimer's disease with PET scans have reported that about half of people with MCI have Alzheimer's-related changes in their brains.

https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

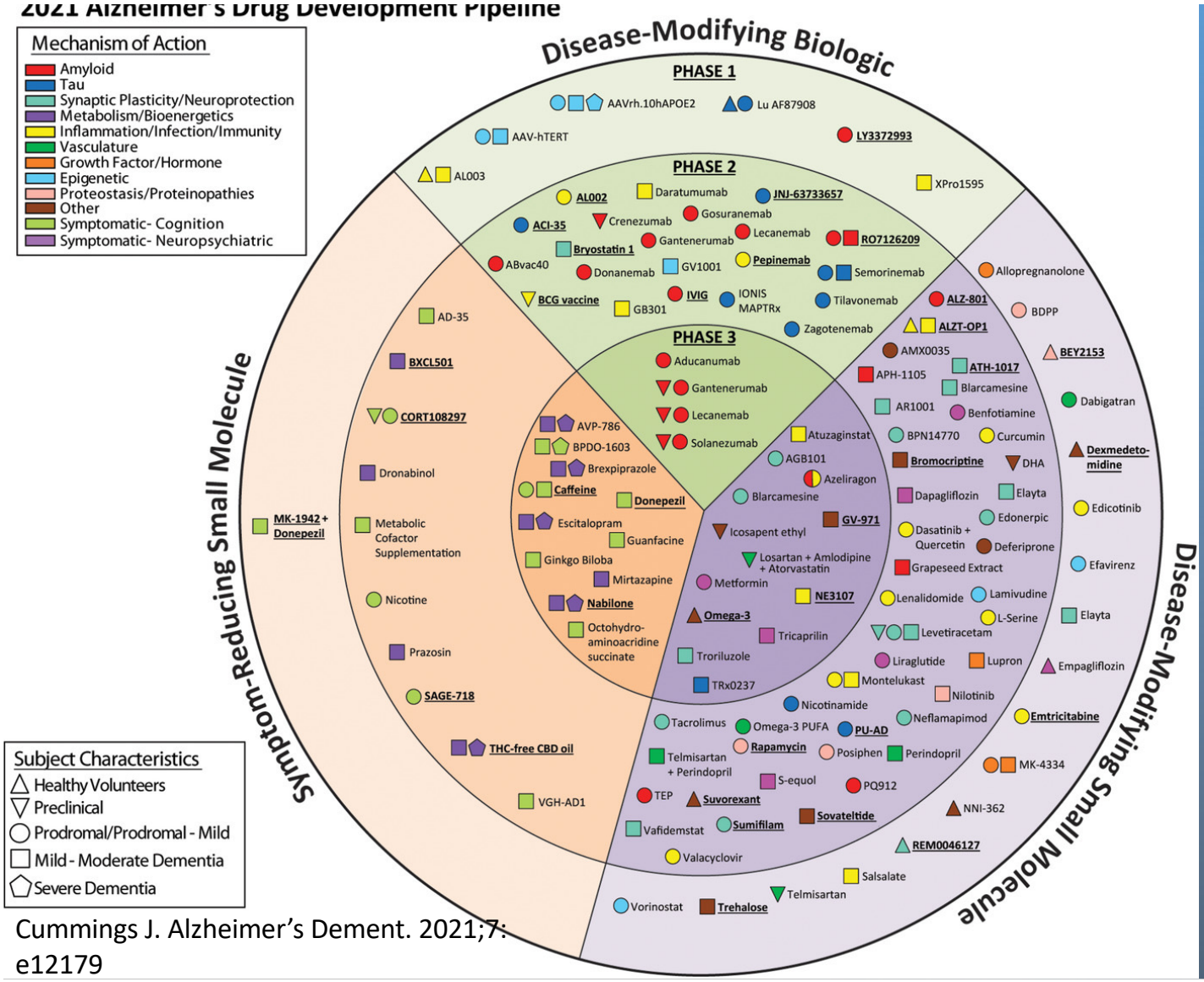


152.8 million cases by 2050

57.4 million cases (now)

World Dementia Statistics

https://alz.org/aaic/releases_2021/global-prevalence.asp



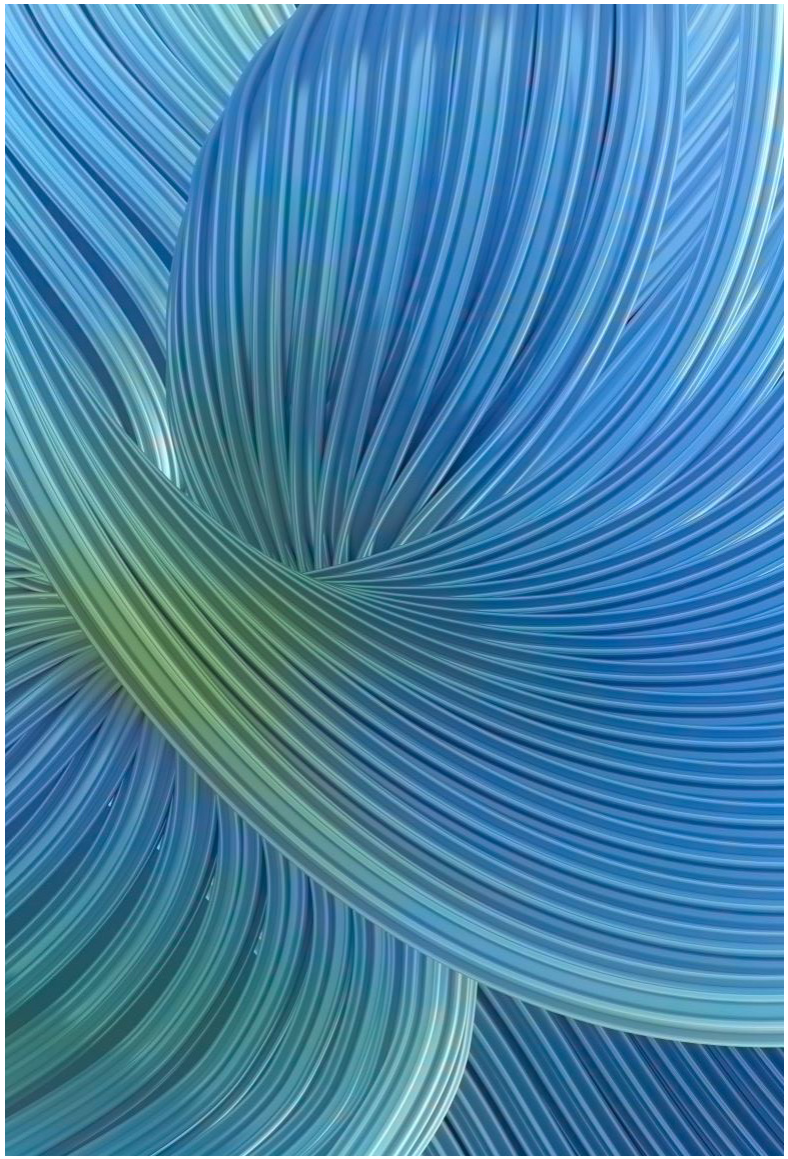
Cummings J. Alzheimer's Dement. 2021;7: e12179

"A 99.6% failure rate for clinical trials in Alzheimer's disease between 2002 and 2012."

Cummings J., et al. Alzheimer's & Dement 2017. 3(3):37-384.

"Total costs of an AD drug development program is estimated at $5.6 billion, and the process takes 13 years from preclinical studies to approval by the FDA." (Per drug)

Alzheimers Dement (NY) 2018; 4: 330–343.



Alzheimer's disease drug development pipeline: 2021

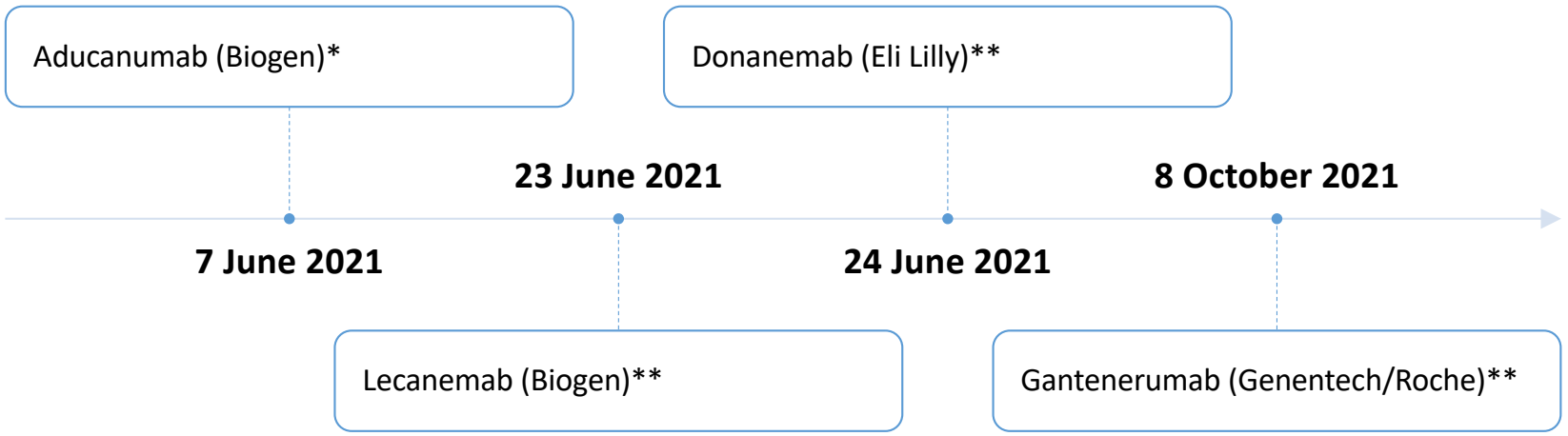
As of January 2021, there were 126 agents in 152 trials of treatments for AD. Twenty-eight agents in Phase 3 trials, 74 agents in Phase 2 trials, and 24 agents in Phase 1 trials.

DMTs are the most common agents being studied (104; 82.5% of the total number of agents in trial).

Of the DMTs, 16 (15.4%) have amyloid and 11 (10.6%) have tau as the primary target or as one of several potential effects.

Cummings J. Alzheimer's Dement. 2021;7:e12179.

FDA Grants Accelerated/Breakthrough Therapy Approval to Anti-Amyloid Therapies



*Accelerated Approval
** Breakthrough Therapy

Anti-amyloid Therapy in Clinical Trials: Aducanumab

- Aducanumab (Biogen) – Two large scale, Phase 3 double-blind, placebo-controlled trials in people with early-stage Alzheimer's disease, EMERGE and ENGAGE.
  - Collectively, about 3,300 subjects enrolled.
- Following a pre-planned futility analysis, analysis of the data from the final database lock showed that EMERGE met its primary end point, based on the pre-specified statistical analysis plan. Patients treated with high dose aducanumab showed a significant reduction of clinical decline from baseline at 78 weeks (22% versus placebo p=0.01). ENGAGE did not meet its primary endpoint. However, data from patients in ENGAGE who achieved sufficient exposure to high dose aducanumab supported the findings in EMERGE.

Haberlein SB, et al. Alzheimer's Dement. 2020;16(Suppl. 9):e047259. https://doi.org/10.1002/alz.047259

Anti-Amyloid Therapy in Clinical Trials: Donanemab

- Donanemab (Eli Lilly) - Phase 2 trial in patients with early symptomatic Alzheimers' disease (TRAILBLAZER-2). The primary outcome was a change from baseline in the score on the iADRS.
  - A total of 257 patients enrolled; 131 were assigned to receive IP and 126 to receive placebo.
  - The change from baseline score at 76 weeks suggested that donanemab slowed decline by about 32%. Additionally, data from secondary analyses showed donanemab consistently slowed cognitive and functional decline, with ranges between 20-40 percent in all secondary endpoints.

Mintun MA, et al. N Engl J Med 2021; 384:1691-1704
DOI: 10.1056/NEJMoa2100708

Anti-Amyloid Therapy in Clinical Trials: Lecanemab (BAN2401)

- Lecanemab (Esai/Biogen) - Phase 2, 18-month U.S. trial to test five different intravenous doses of BAN2401. There were 854 participants.
- The highest antibody dose of twice-monthly 10 mg/kg reduced brain amyloid accumulation by up to 93 percent while showing a drug-placebo difference in favor of active treatment (by 27% and 30% on the Alzheimer's Disease Composite score (ADCOMS), 56% and 47% on ADAS-Cog14, and 33% and 26% on CDR-SB). CSF biomarkers also were supportive of a treatment effect.

Swanson, C.J., *et al. Alz Res Therapy 2021;* 13**(**80)
https://doi.org/10.1186/s13195-021-00813-8

FDA Accelerated Approval Program

- …allows for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit.
- Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. These studies are known as phase 4 confirmatory trials. If the confirmatory trial shows that the drug provides a clinical benefit, then the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit, FDA has regulatory procedures in place that could lead to removing the drug from the market.

FDA Breakthrough Therapy

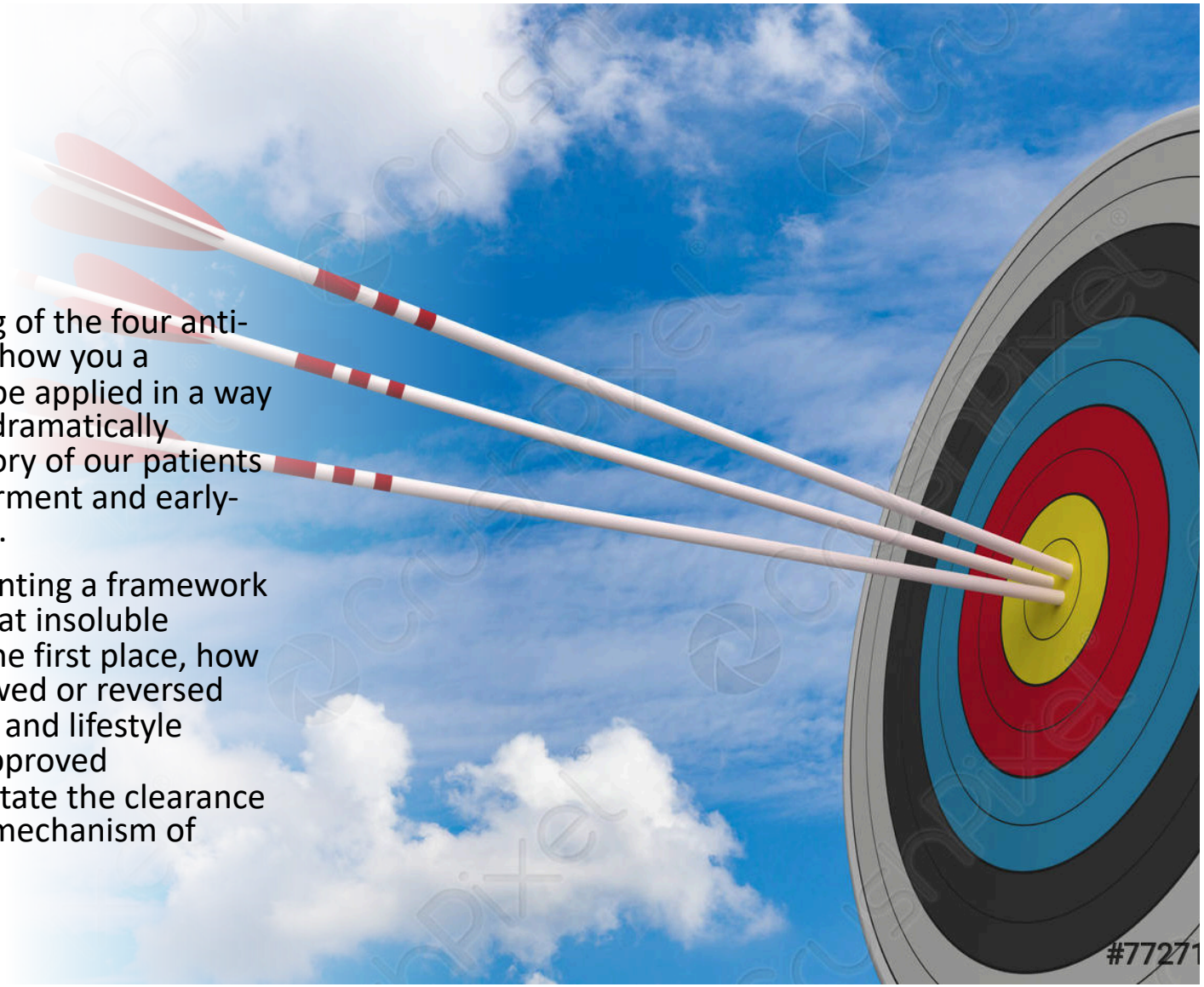
- Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.
- A breakthrough therapy designation conveys all fast-track program features, more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for rolling review and priority review.

The Amyloid Hypothesis

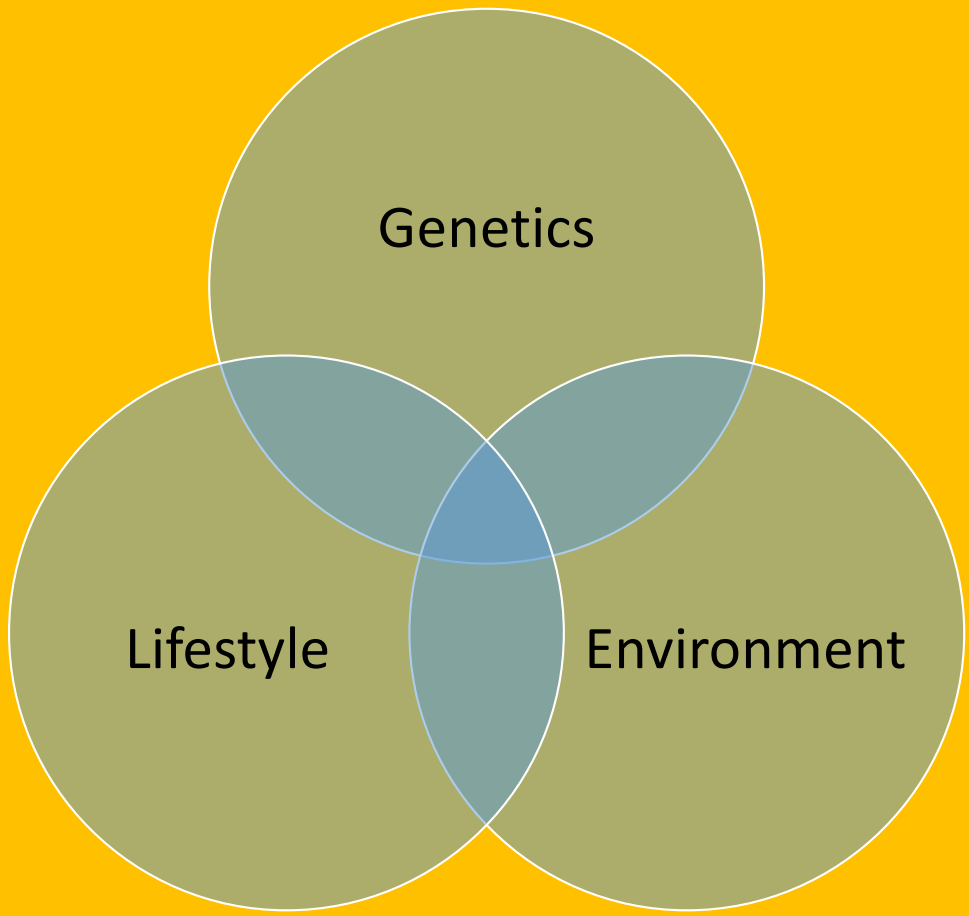
- According to the amyloid hypothesis, **accumulation of Aβ in the brain is the primary influence driving AD pathogenesis**. The rest of the disease process, including formation of neurofibrillary tangles containing tau protein, is proposed to result from an imbalance between Aβ production and Aβ clearance (amyloid “dyshomeostasis”).

My Goal for Today is

- To take our understanding of the four anti-amyloid treatments and show you a protocol where they can be applied in a way that has the potential to dramatically change the illness trajectory of our patients with mild cognitive impairment and early-stage Alzheimer's disease.
- I will accomplish by presenting a framework to understand why it is that insoluble amyloid accumulates in the first place, how this process might be slowed or reversed based on systems biology and lifestyle medicine, and how the approved treatments can then facilitate the clearance of amyloid base on their mechanism of action.



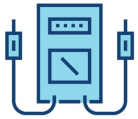
"Scientists believe that for most people, Alzheimer's disease is caused by **a combination of genetic, lifestyle and environmental factors that affect the brain over time**. Less than 1% of the time, Alzheimer's is caused by specific genetic changes that virtually guarantee a person will develop the disease."



https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447

1

THE
SCIENCE



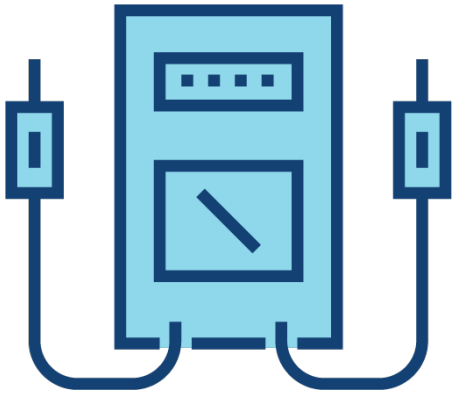
2

THE
TOOLS

3

THE
TRANSFORMATION

1 THE SCIENCE



Mild cognitive impairment (MCI)

MCI defines the state between normal aging and dementia and is defined by three key features:[1]

1. **Cognitive complaint,** decline, or impairment: reported by the patient, an informant, or clinician[1]
2. **Objective evidence** of attention, executive function, visuospatial function, and episodic **memory impairment**[1]
3. **Performs ADLs independently. However, cognitive difficulty may have a mild but detectable impact on more complex activities, either self-reported or corroborated by informant**[1,2]

- ✓ MCI can be caused by multiple underlying neurodegenerative pathologies[3]
- ✓ **Current DSM-5 nomenclature refers to MCI as mild neurocognitive disorder**[4]

Some patients with MCI remain stable for many years and may even revert to normal cognition. Other patients progress to dementia; indeed, there is significant heterogeneity in the MCI population[5,6]

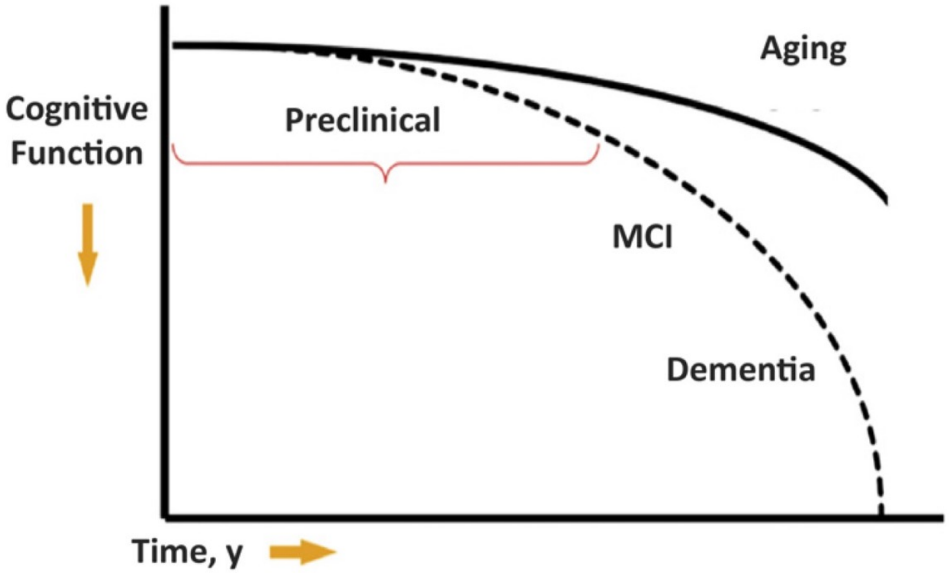
AD, Alzheimer's disease; ADL, activities of daily living; DSM, Diagnostic and Statistical Manual of Mental Disorders; MCI, mild cognitive impairment

1. Alberts MS, et al. Alzheimers Dement 2011;7:270–279; 2. Mlinac ME, Feng MC. Arch Clin Neuropsychol 2016;31:506–516; 3. Dugger BN, et al. BMC Neurol 2015;15:146; 4. Hugo J et al. Clin Geriatr Med 2014;30:421–442; 5. Sugarman MA, et al. J Alzheimers Dis 2018;62:1841–1855; 6. Ganguli M, et al. J Am Geriatr Soc 2019;67:232–238

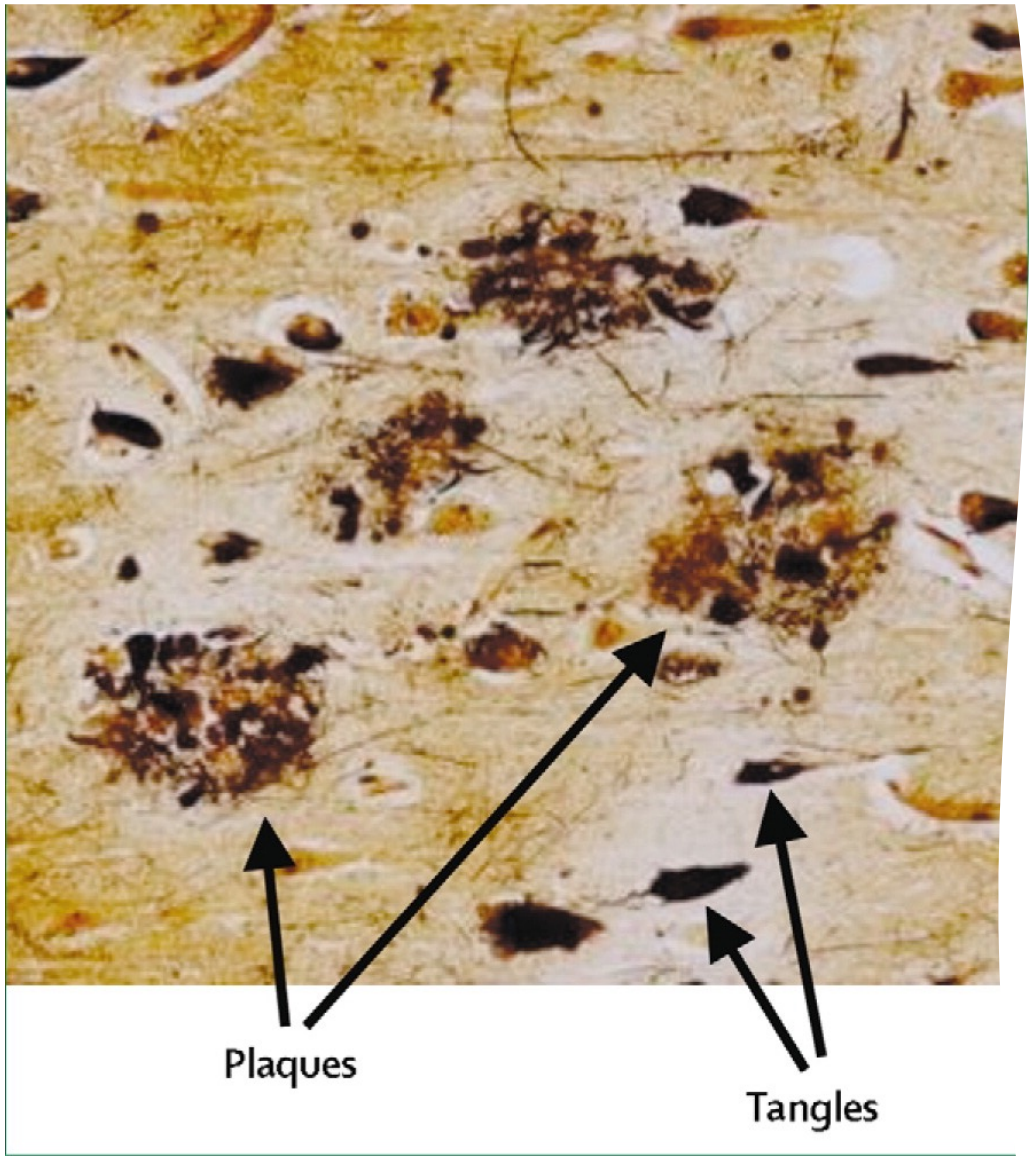
Clinical Diagnostic Criteria for PROBABLE Alzheimer's Disease (1984)

- Dementia
- Deficits in two or more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65; and
- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive decline in memory and cognition

The Continuum of AD

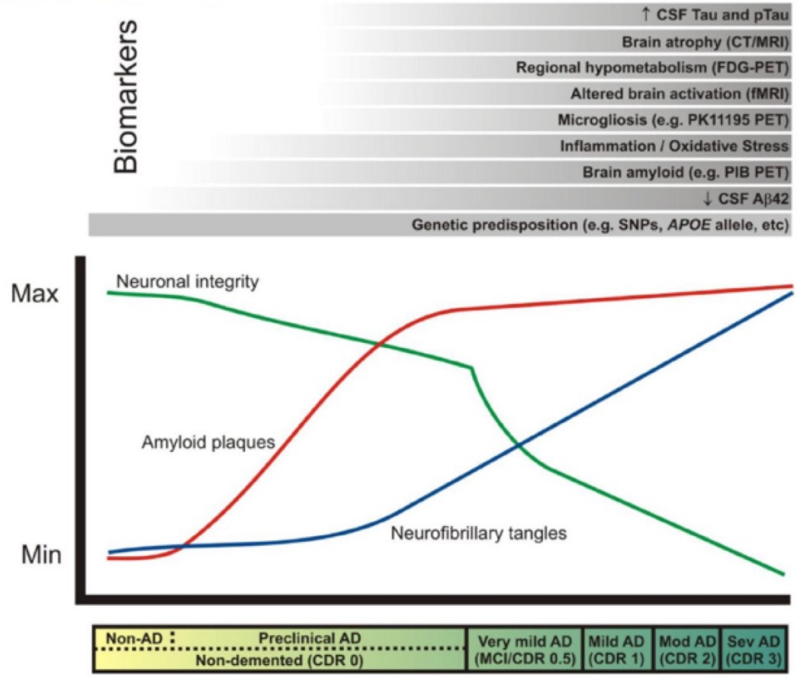


5 Sperling RA, et al. *Alzheimers Dement*. 2011;7:280-292. With permission from Elsevier.



- **Plaques (amyloid beta 42) and Tangles (Tau protein)**

Hypothetical Time Course of AD Biomarker Changes in Relation to Pathological and Clinical Stages



NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease (2018)

"The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined *in vivo* by biomarkers and by postmortem examination, not by clinical symptoms."

Jack, Clifford R., et al. Alzheimer's & Dementia 2018;14(4):535-562.

Crdenas-Aguayo, et al. Neurochemistry 2014. https://doi.org/10.5772/57398

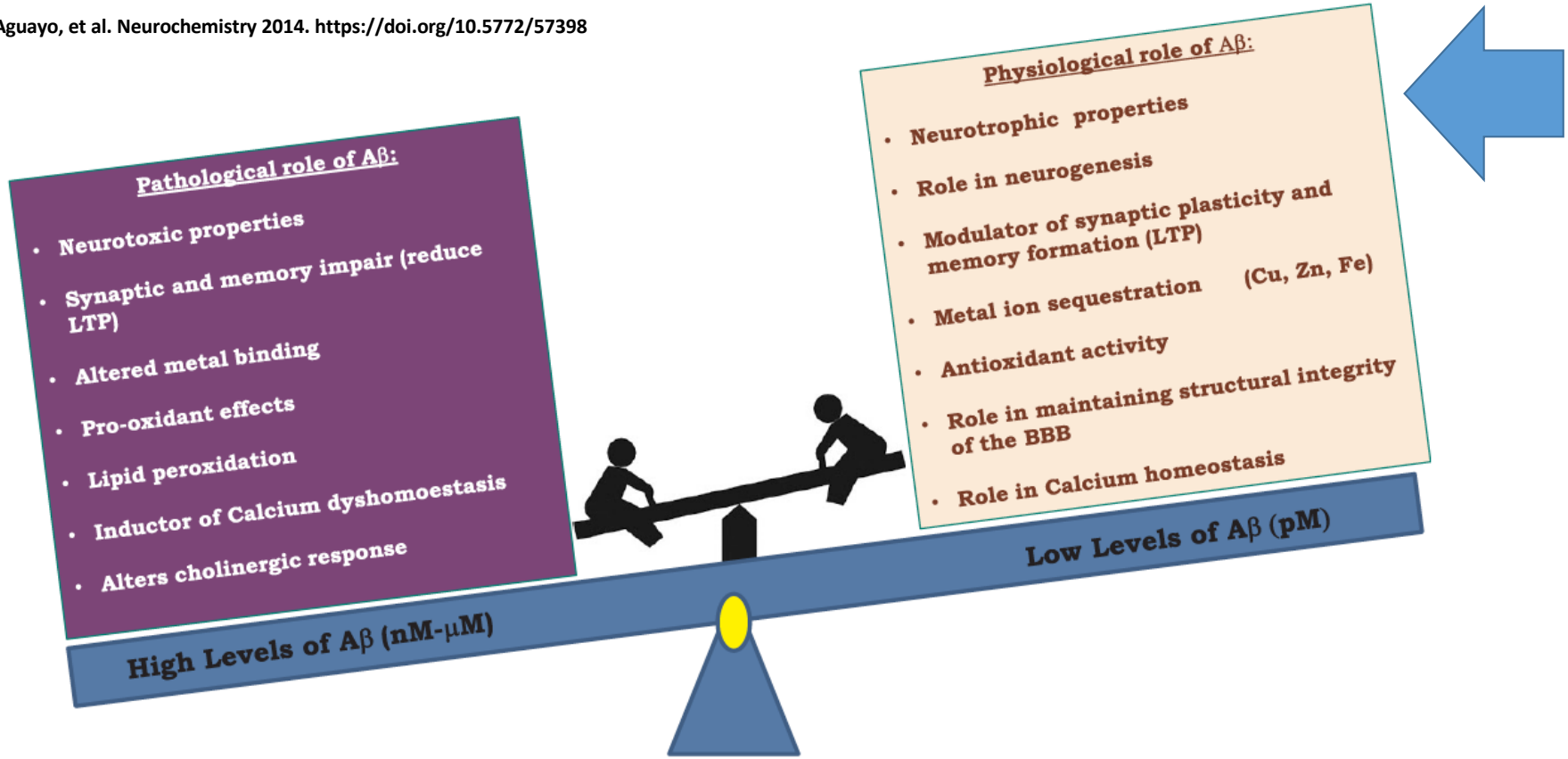
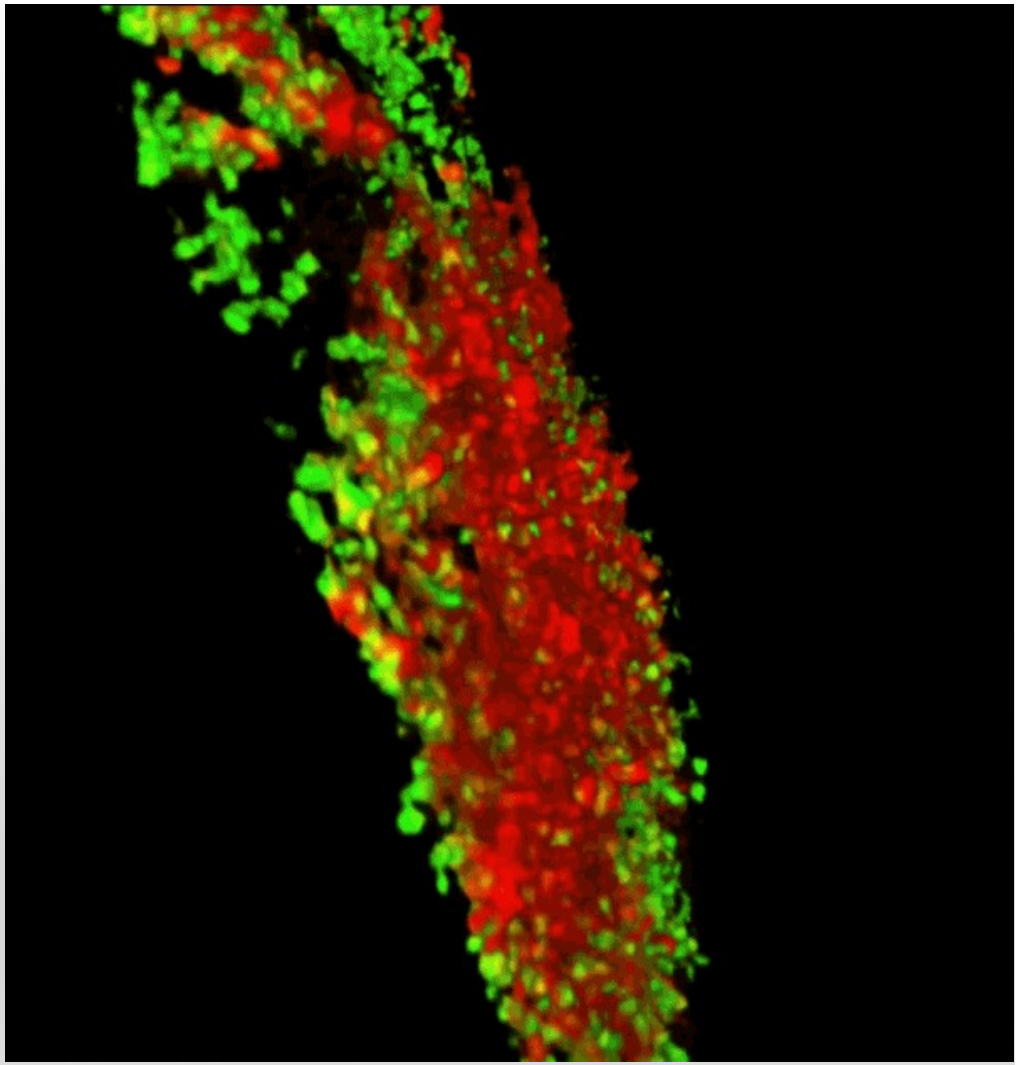


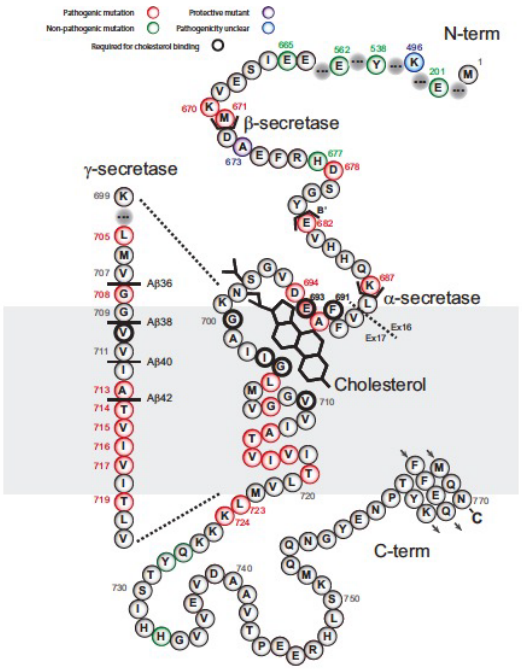
Figure 2. Balance between physiological and pathological effects of Aβ. Like a seesaw in a park, the levels of Aβ change due to environmental factors or genetic background. In normal healthy conditions, Aβ is at lower concentration (pM), and exerts its physiological functions, but in disease conditions the levels of Aβ are elevated (nM to μM) and it switches it functions to pathological effects.

Amyloid as an Anti-Microbial Peptide*

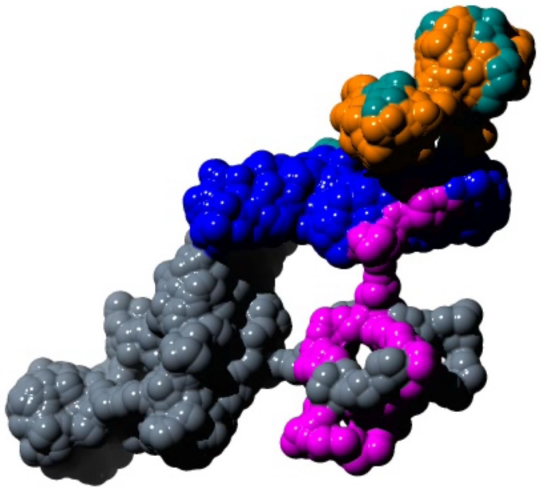
- Harvard-MGH Researchers Robert Moir and Rudolf Tanzi demonstrated that mice genetically modified to produce human amyloid injected with Salmonella formed plaques and lived 30 hours longer than control mice.
- Similar response different microbes, including the yeast *Candida albicans*, and bacteria like *Escherichia coli* and several different strains of *Streptococcus*.
- 100 times more lethal than penicillin.
- Rotating 3-D image of a slice of a brain amyloid plaque that formed in a genetically modified mouse in response to bacterial encephalitis. Credit: Robert Moir



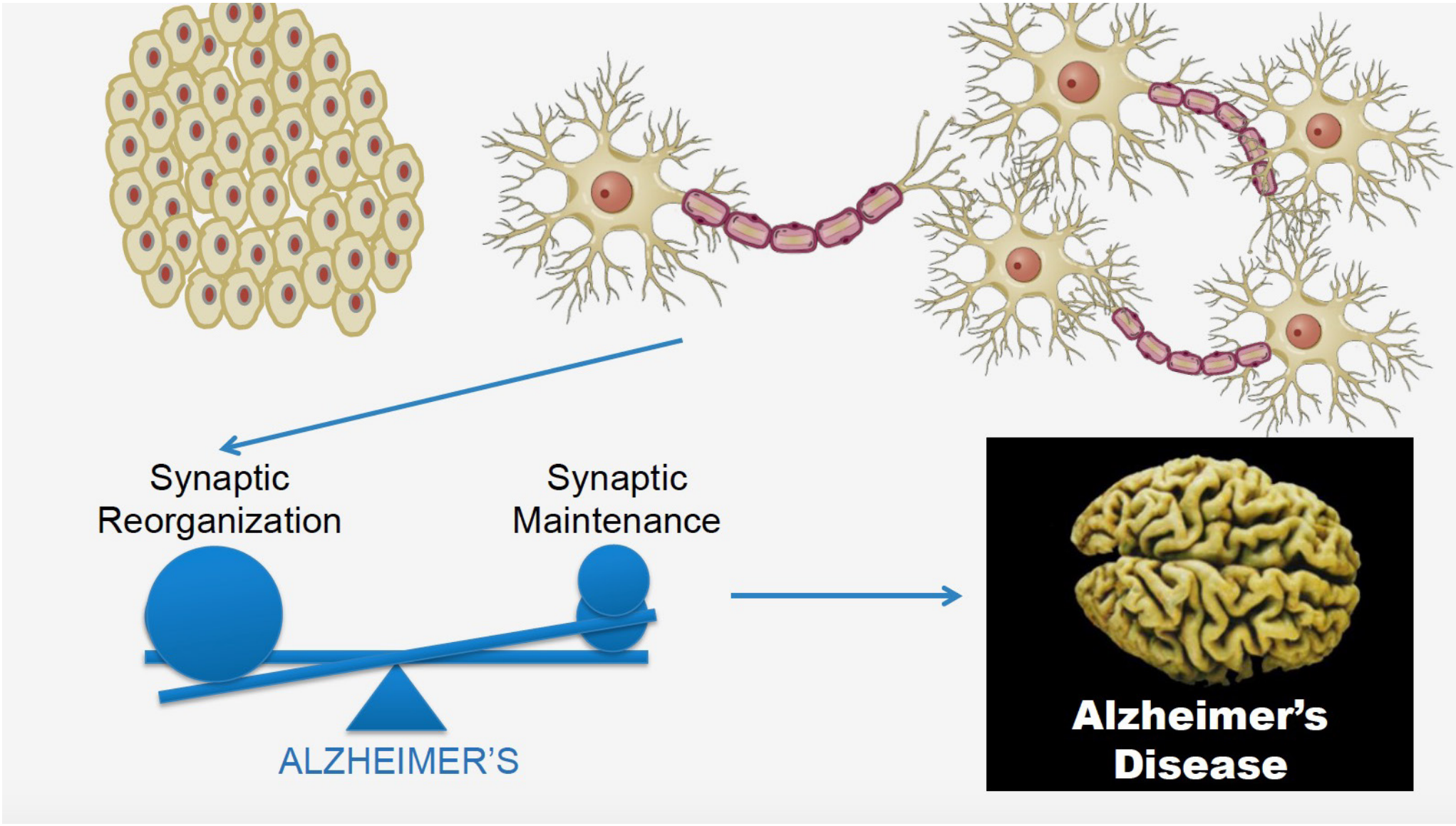
*http://www.sciencemag.org/news/2016/05/alzheimer-s-protein-may-help-brain-fight-infection.



APP—candidate mediator of plasticity balance



Amyloid Precursor Protein


Synaptic
Reorganization
Synaptic
Maintenance
ALZHEIMER'S
Alzheimer's
Disease

C. Crdenas-Aguayo, M. del, et al. Neurochemistry 2014 https://doi.org/10.5772/57398

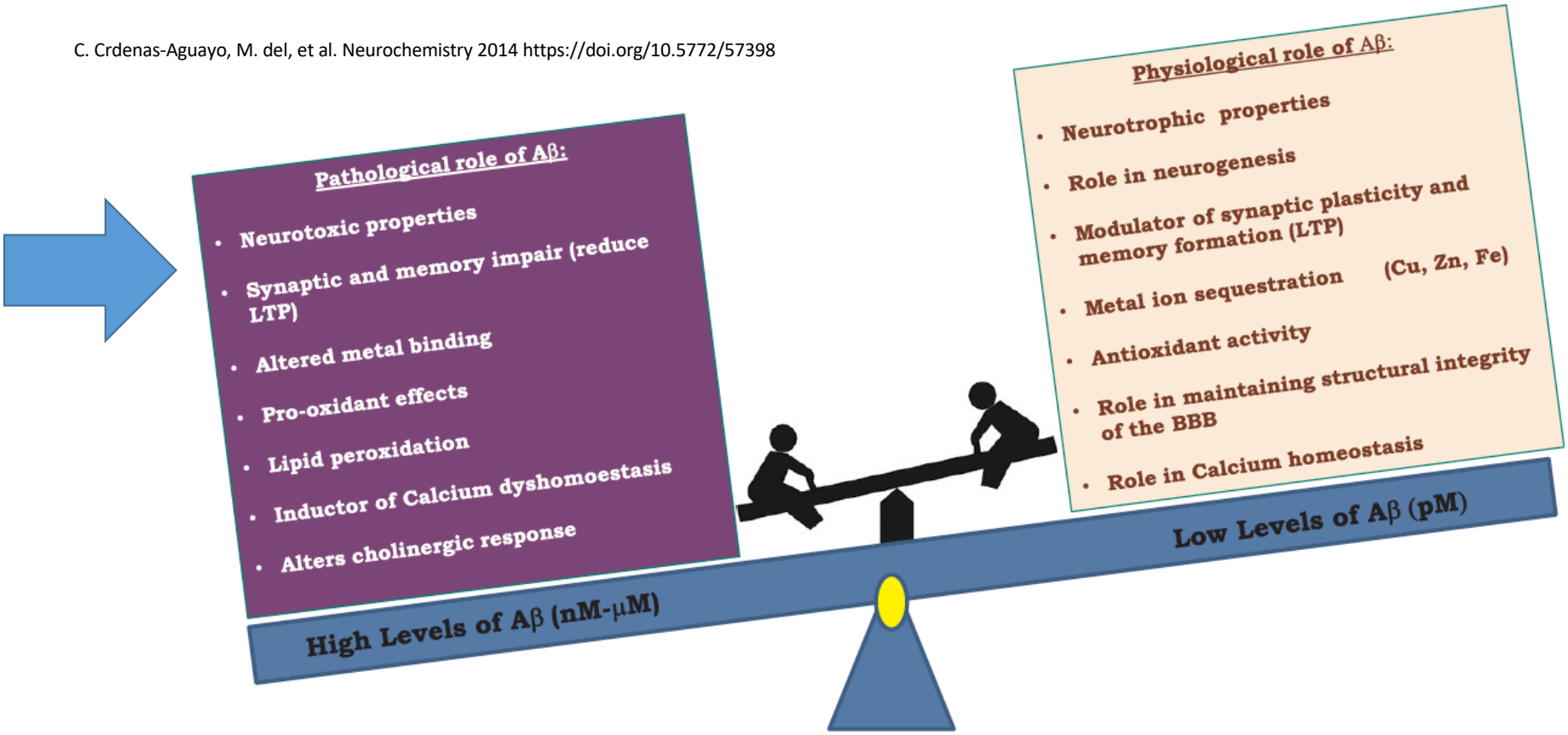
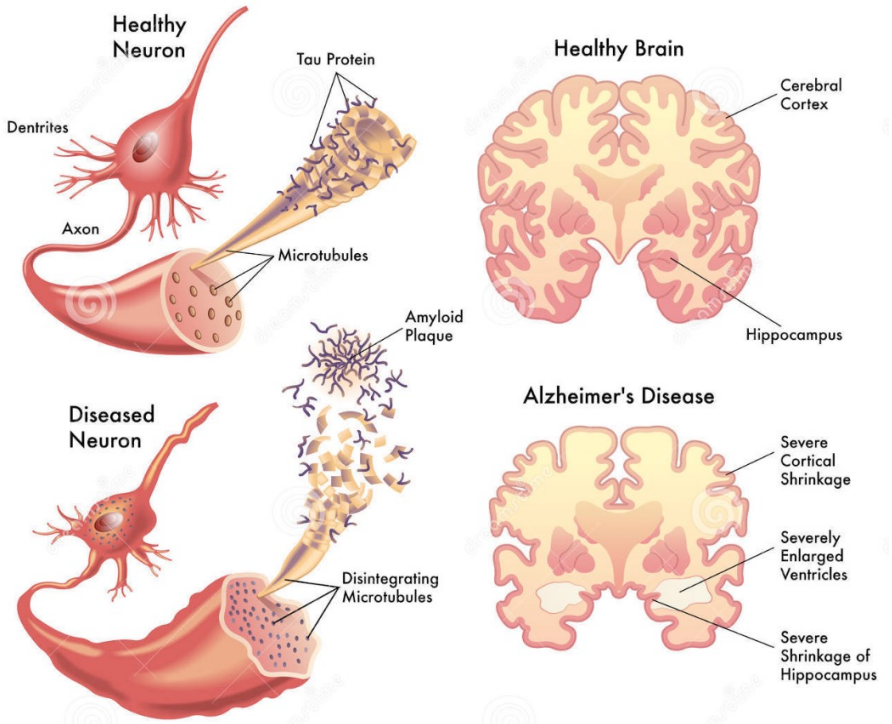


Figure 2. Balance between physiological and pathological effects of Aβ. Like a seesaw in a park, the levels of Aβ change due to environmental factors or genetic background. In normal healthy conditions, Aβ is at lower concentration (pM), and exerts its physiological functions, but in disease conditions the levels of Aβ are elevated (nM to μM) and it switches it functions to pathological effects.

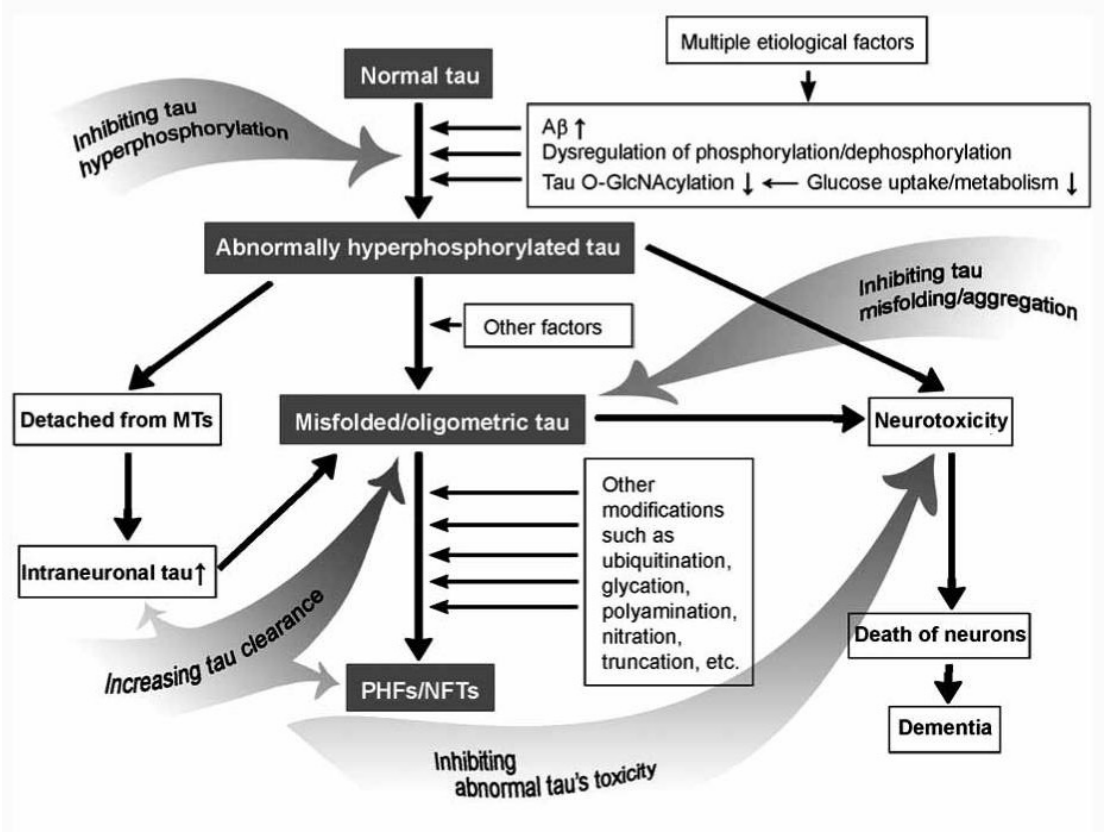
Tau Protein

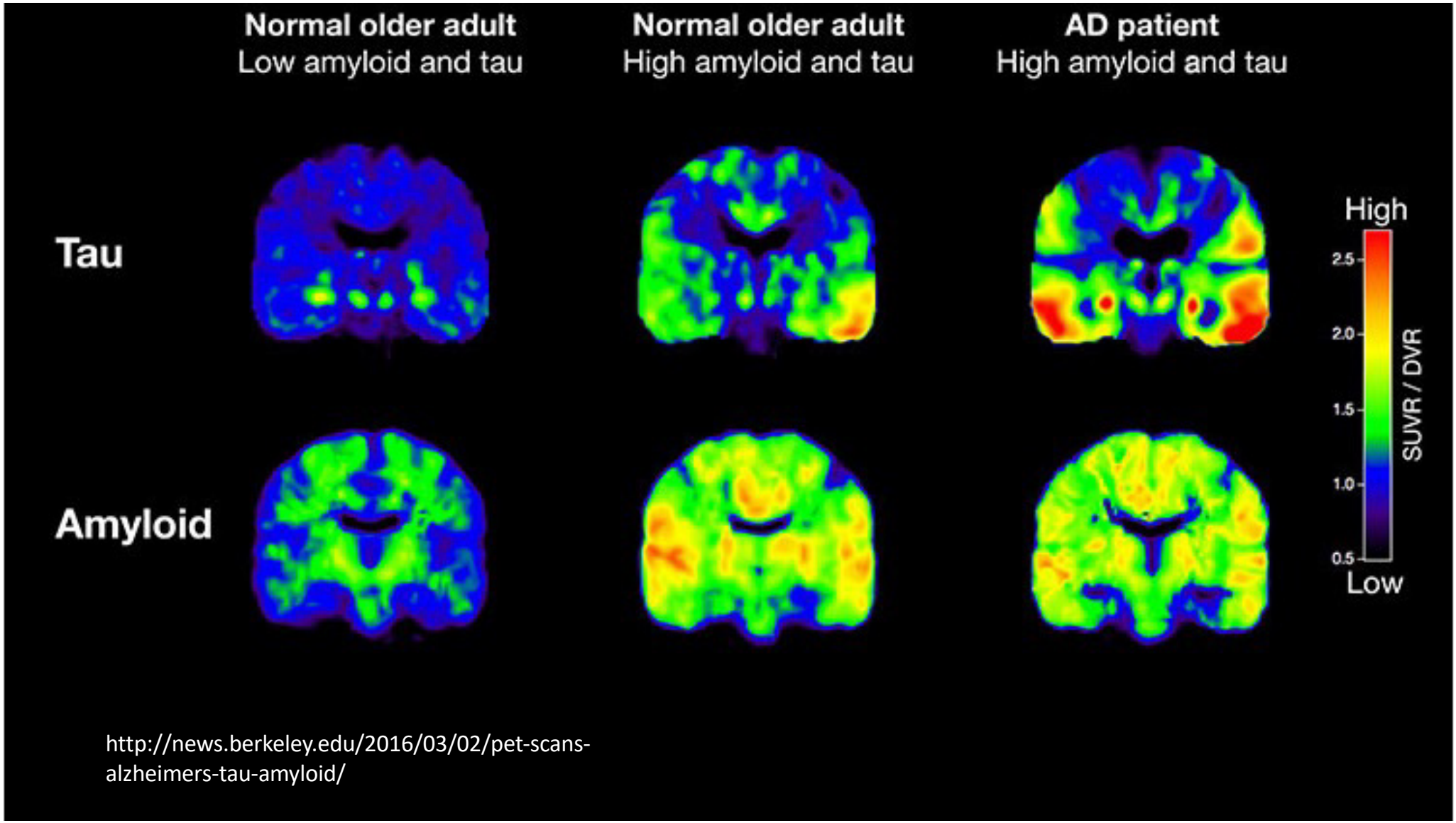
- A Microtubule-Associated Protein (MAP)
- Found mostly in axons of neurons
- Like the “ties” along the railroad tracks Modulates the stability of axonal microtubules
- **Hyperphosphorylation** of tau reduces the affinity of tau for the binding domains on the microtubule assembly contributing to the formation of “tangles.”



Hyperphosphorylation of microtubule-associated protein tau

Gong CX. Curr Med Chem 2008;15(23): 2321–2328



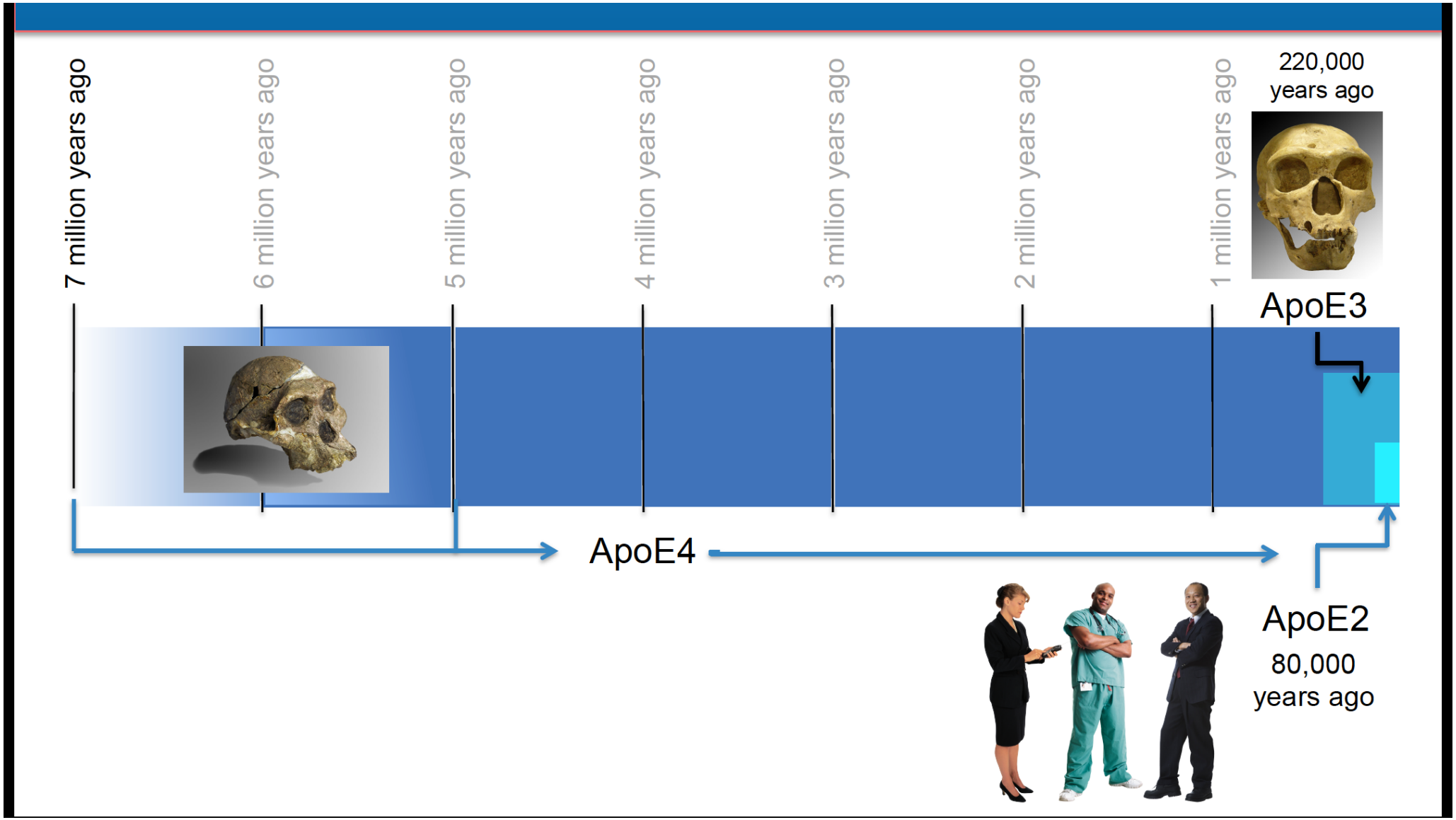


http://news.berkeley.edu/2016/03/02/pet-scans-alzheimers-tau-amyloid/

Inflammation: Acute or Chronic?

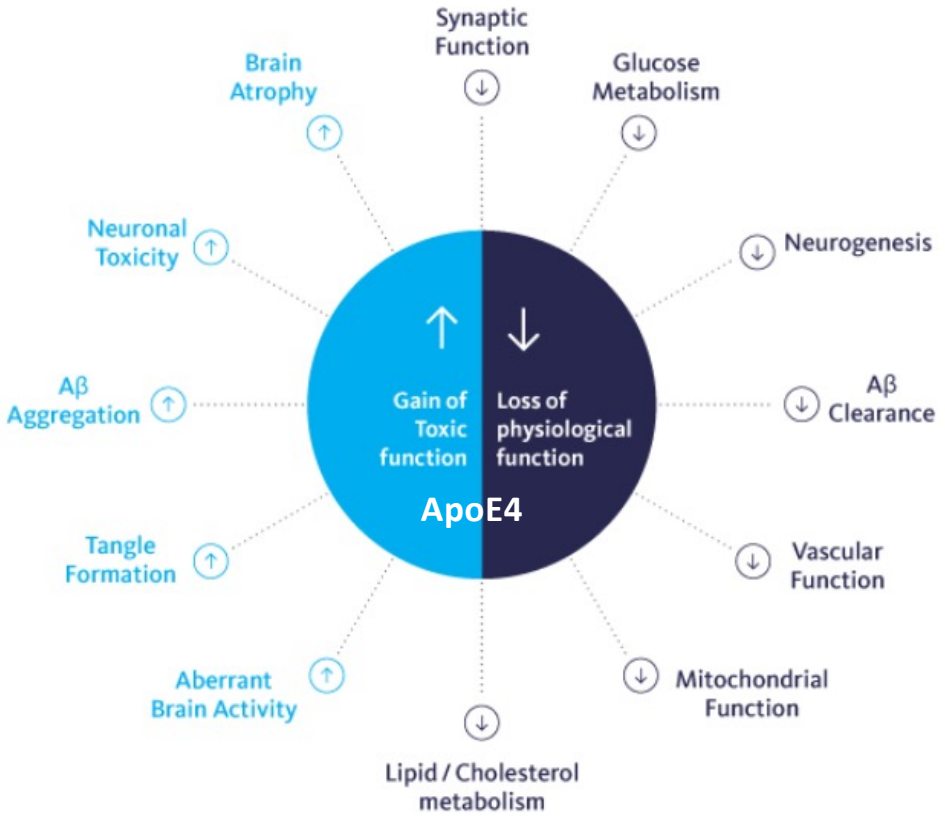
"Acute inflammation in the brain is a well-established defense against infection, toxins, and injury, but when a disruption in the equilibrium of anti-inflammatory and pro-inflammatory signaling occurs, as seen in AD, it results in chronic inflammation (neuroinflammation)….[A] substantial body of research has now demonstrated that a persistent immune response in the brain is not only associated with neurodegeneration, but it also facilitates and exacerbates both Aβ and NFT pathologies. Furthermore, it has been suggested that the inflammatory response may provide a link between the initial Aβ pathology and the later development of NFT."

Kinney JW, et al. *Alzheimers Dement (N Y)*. 2018;4:575-590. doi:10.1016/j.trci.2018.06.014


7 million years ago
6 million years ago
5 million years ago
4 million years ago
3 million years ago
2 million years ago
1 million years ago
220,000 years ago
ApoE3
ApoE4
ApoE2
80,000 years ago

ApoE4

- Apolipoproteins transport cholesterol and phospholipids to nerve cells.
- ApoE = apoliporotein epsilon.
  - Genotypes ApoE2, ApoE3, ApoE4
  - ApoE4 confers an increased risk of Late Onset Alzheimer's Disease, onset after 65.
  - ApoE4 found in 20-30% of the population
  - ApoE2 protective
  - ApoE3 neutral risk



Liu CC, et al. Nat Rev Neurol 2013;9(2):106-118.

Risk of Alzheimer's Disease by ApoE Genotype

	APOE4		
	Non-carrier	Heterozygous	Homozygous
AD frequency	20%	47%	91%
Mean age of clinical onset	84-yr	76-yr	68-yr

ApoE Genotype	Odds Ratio	Ethnicity
E3/E3	1.0	
E2/E4	2.6	
E3/E4	3.2	
E4/E4	14.9	Caucasian
E2/E2	0.6	
E2/E3	0.6	
E4/E4	5.7	African American
E4/E4	2.2	Hispanic
E4/E4	33.1	Japanese

Liu CC, et al. Nat Rev Neurol 2013;9(2):106–118

Direct Transcriptional Effects of Apolipoprotein E4

Direct Transcriptional Effects of Apolipoprotein E

Veena Theendakara,[1] Clare A. Peters-Libeu,[1] Patricia Spilman,[1,2] Karen S. Poksay,[1] Dale E. Bredesen,[1,2]* and Rammohan V. Rao[1]*

[1]Buck Institute for Research on Aging, Novato, California 94945, and [2]Easton Laboratories for Neurodegenerative Disease Research, University of California Los Angeles, Los Angeles, California 90025

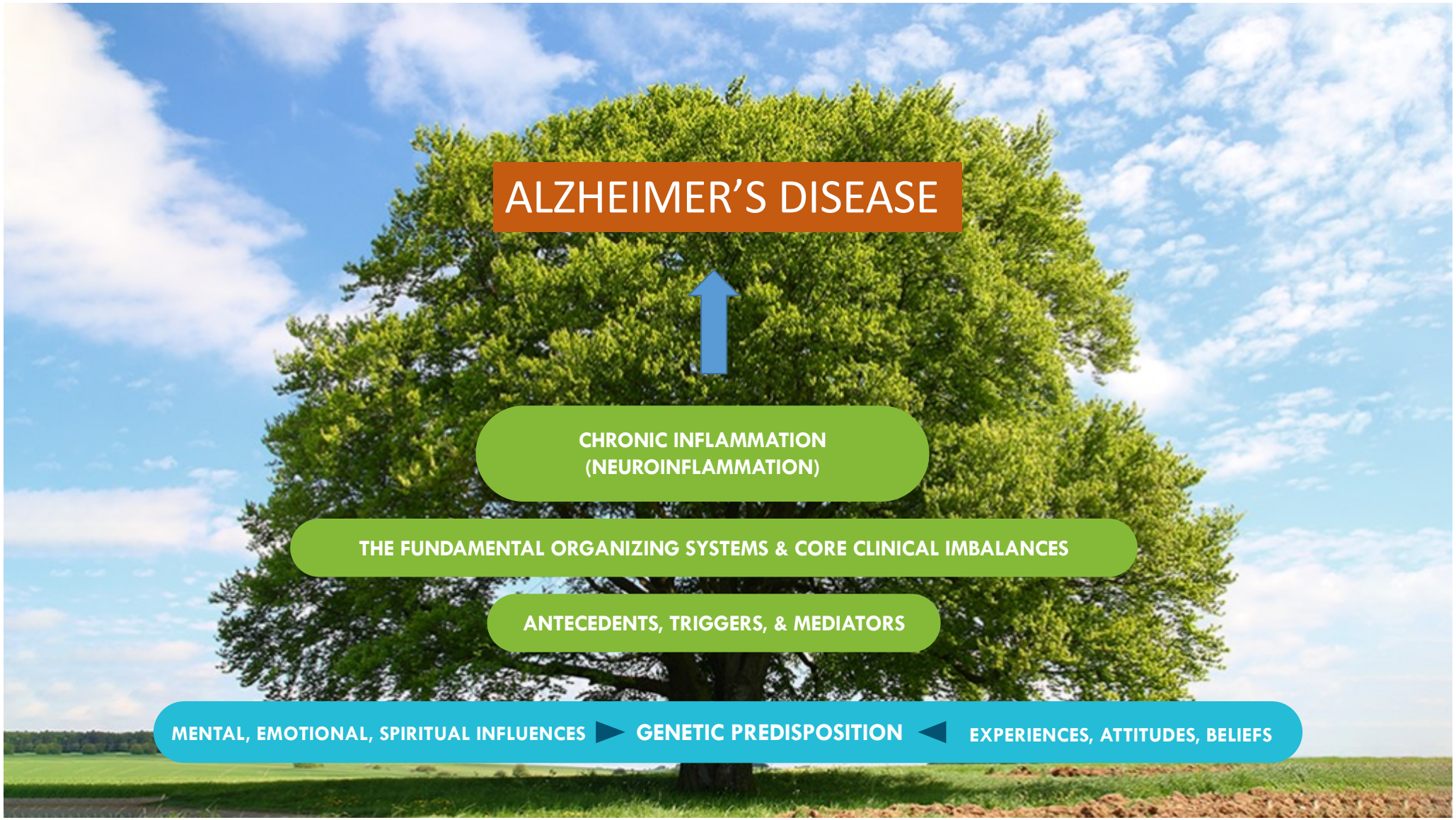
A major unanswered question in biology and medicine is the mechanism by which the product of the apolipoprotein E ε4 allele, the

This study shows for the first time that apolipoprotein E4 binds DNA with high affinity and that its binding sites include 1700 promoter regions that include genes associated with neurotrophins, programmed cell death, synaptic function, sirtuins and aging, and insulin resistance, all processes that have been implicated in Alzheimer's disease pathogenesis.

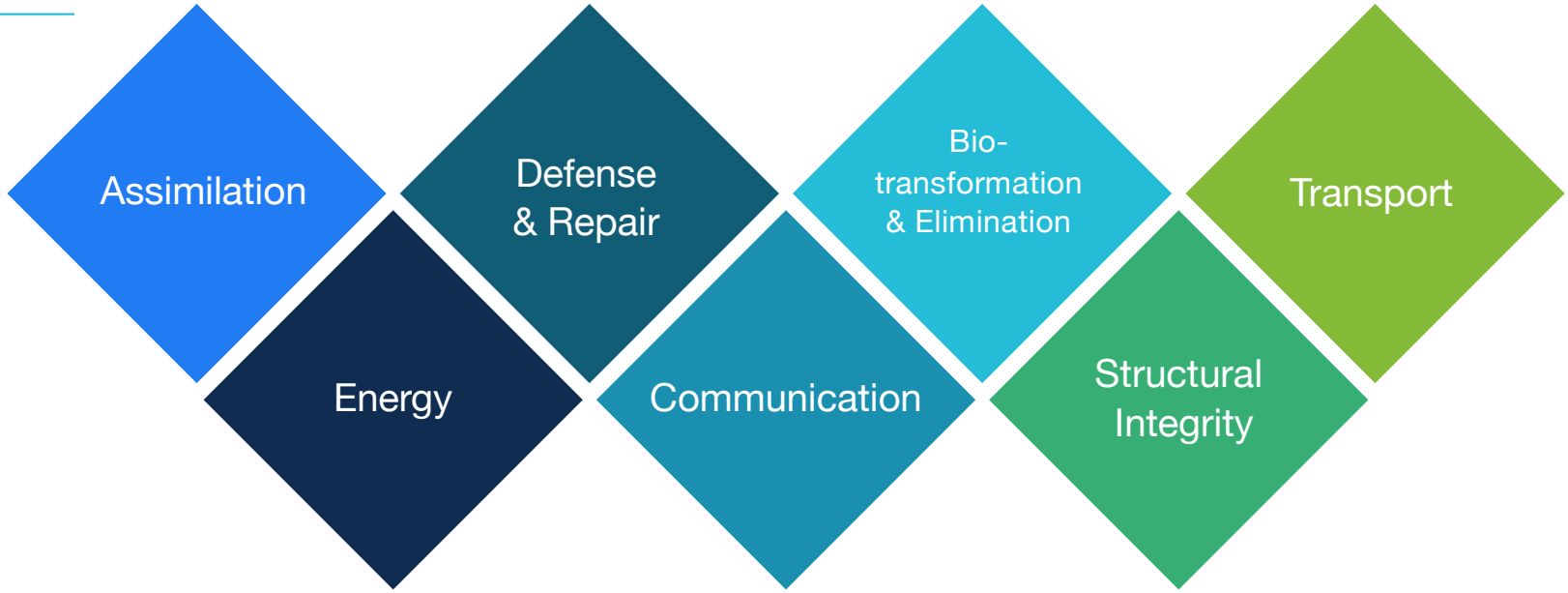
indicate that the ApoE4 DNA binding sites include ~1700 gene promoter regions. The genes associated with these promoters provide new insight into the mechanism by which AD risk is conferred by ApoE4, because they include genes associated with trophic support, programmed cell death, microtubule disassembly, synaptic function, aging, and insulin resistance, all processes that have been implicated in AD pathogenesis.

Key words: activity-dependent neuroprotective protein; Alzheimer's disease; amyloid precursor protein; apolipoprotein E; MAP kinase-activating death domain; sirtuin

Theendakara V, et al. J Neurosci 2016;36(3):685-700


ALZHEIMER'S DISEASE
CHRONIC INFLAMMATION
(NEUROINFLAMMATION)
THE FUNDAMENTAL ORGANIZING SYSTEMS & CORE CLINICAL IMBALANCES
ANTECEDENTS, TRIGGERS, & MEDIATORS
MENTAL, EMOTIONAL, SPIRITUAL INFLUENCES
GENETIC PREDISPOSITION
EXPERIENCES, ATTITUDES, BELIEFS

THE SEVEN FUNCTIONAL BIOLOGICAL SYSTEMS:



Assimilation

- Making food part of the cell
- Ingestion, digestion, absorption, and assimilation
- Requires adequate intake of nutrients, adequate breakdown of nutrients (masticatory, enzymatic and chemical such as HCl and bile), hormones, microbial balance and diversity (“microbiome”), gut barrier and immune function, transporter function.
- Inadequate nutrient intake, inadequate chewing, hypochlorhydria, intrinsic factor deficiency, pancreatic enzyme deficiency, SIBO/dysbiolsis.
- Alzheimer’s: decreased Firmicutes, increased Bacteriodetes, and decreased Bifidobacterium compared to controls.*
- In Alzheimer's models there are a variety of negative effects of an altered microbiome as demonstrated in studies using germ-free mice, as well as a positive or beneficial effects following probiotic treatment.**

*Vogt NM, et al. Scientific Reports. October 2017;7:e13537.

**Jiang C, et al. Journal of Alzheimer’s disease 2017;58(1):1-15.

Defense & Repair

- Represented by the coordinated efforts of white blood cells (humoral and cellular immunity), cytokines, bioactive molecules (omega 3 & 6 fatty acids),etc.
- Key role in protection and repair of damaged tissue
- Major presence in the gut
- Able to distinguish self from non-self
- Aberrations in Defense & Repair are associated with chronic infections and autoimmunity
    - Lipopolysaccharides (LPS) enter the blood through a compromised gut barrier and act as a major driver of inflammation.
    - Have been found to cause build up of amyloid beta-42 in Alzheimer's susceptible brains.*
- Alzheimer's-infection associations: HSV-1, Chlamydia pneumonia, Helicobacter pylori, and Borrelia burgdorferi.

*Lee JW, et al. Journal of Neuroinflammation 2008;5;37.

Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections—a Nationwide, Population-Based Cohort Study in Taiwan

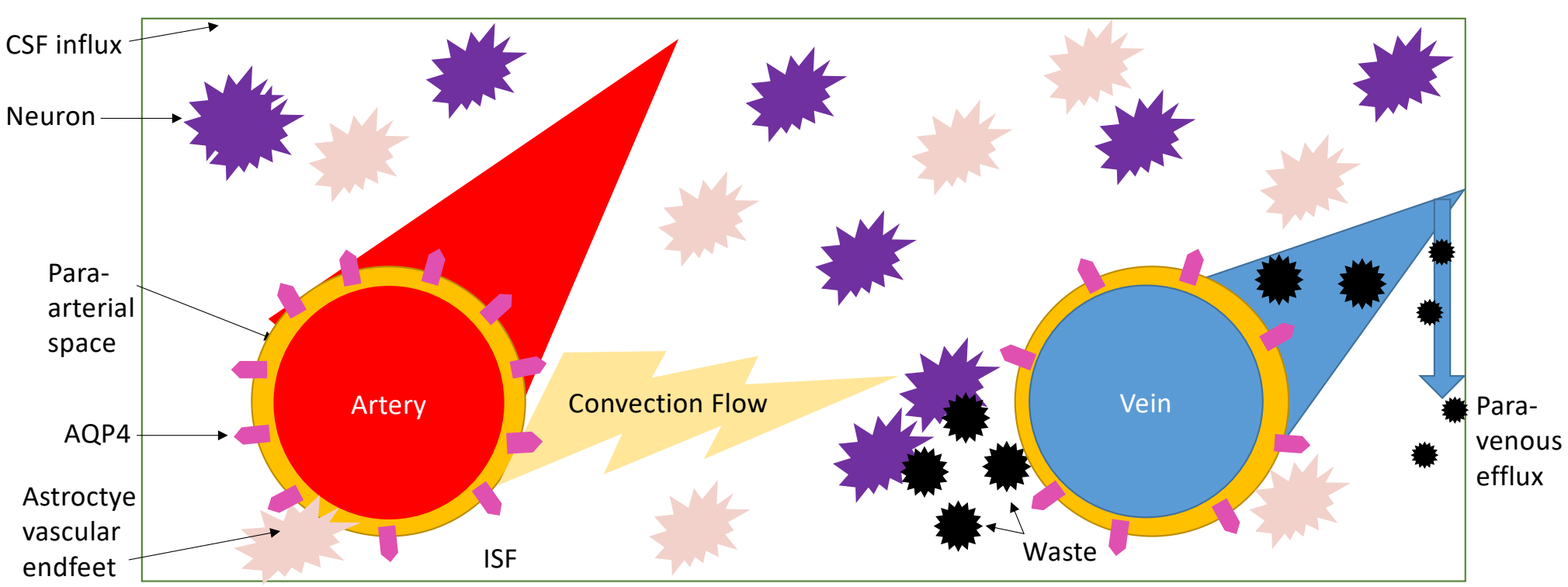
Nian-Sheng Tzeng [1,2] · Chi-Hsiang Chung [3,4,5] · Fu-Huang Lin [4] · Chien-Ping Chiang [6] · Chin-Bin Yeh [1,7] · San-Yuan Huang [1,7] · Ru-Band Lu [1,8,9,10,11,12] · Hsin-An Chang [1,2] · Yu-Chen Kao [1,13] · Hui-Wen Yeh [1] · Wei-Shan Chiang [1,14] · Yu-Ching Chou [4] · Chang-Huei Tsao [5] · Yung-Fu Wu [5] · Wu-Chien Chien [4,5]

 Neurotherapeutics 2018 https://doi.org/10.1007/s13311-018-0611-x

Abstract

This retrospective cohort study is to investigate the association between herpes simplex virus (HSV) infections and dementia, and the effects of anti-herpetic medications on the risk involved, using Taiwan's National Health Insurance Research Database (NHIRD). We enrolled a total of 33,448 subjects, and identified 8362 with newly diagnosed HSV infections and 25,086 randomly selected sex- and age-matched controls without HSV infections in a ratio of 1:3, selected from January 1, to December 31, 2000. A multivariable Cox proportio[illegible] analysis revealed [illegible] the HSV-infected [illegible] developing dementia. A risk reduction of dementia development in patients affected by HSV infections was found upon treatment with anti-herpetic medications (adjusted HR = 0.092 [95% CI 0.079-0.108], $P < 0.001$). The usage of anti-herpetic medications in the treatment of HSV infections was associated with a decreased risk of dementia. These findings could be a signal to clinicians caring for patients with HSV infections. Further research is, therefore, necessary to explore the underlying mechanism(s) of these associations.

An adjusted hazard ratio of 2.564 for the development of dementia (Alzheimer's, Vascular, and All types) in the HSV-infected cohort.

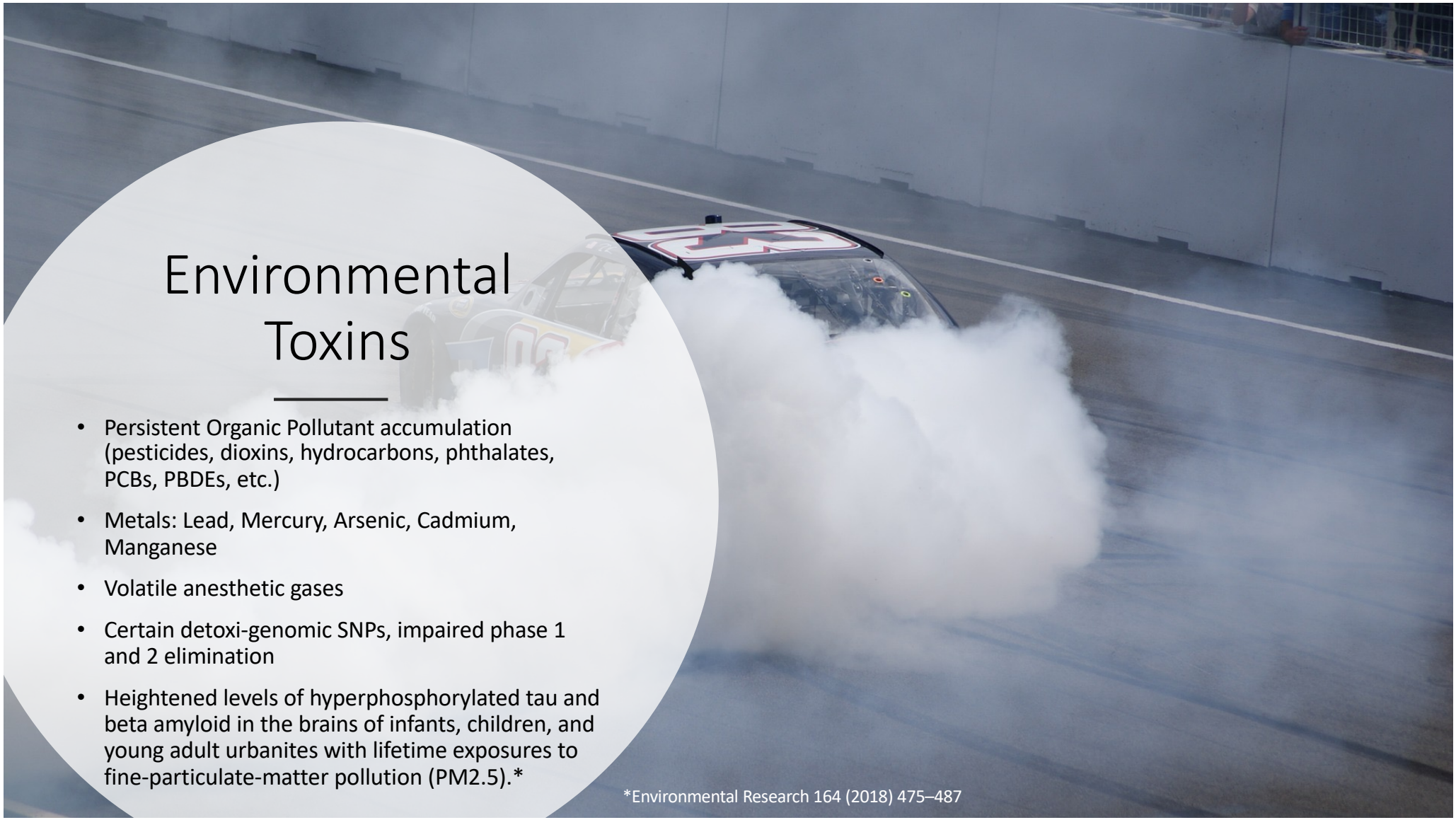


Biotransformation & Elimination, Transport Systems

- The Glymphatic System
- Toxins
- Vascular disease

The Glymphatic System

- Waste clearance system from the brain
- “Glymphatic” comes from the glial cells (support cells for neurons), including microglia, astrocytes, oligodendrocytes, and ependyma.
- Promotes elimination of soluble proteins and metabolites from the CNS and helps distribute non-waste compounds such as glucose, lipids, amino acids, and neurotransmitters.
- Primarily active during sleep.
- Impairment of the glymphatic system implicated in Alzheimer’s disease (Nat Rev Neurol 2015;11(8):457-470.)
- Mouse model: Acute and chronic sleep deprivation stimulated astrocytic phagocytosis of presynaptic elements of large synapses and microglial activation. “Microglial priming may predispose the brain to further damage.” (Bellesi M, et al. The Journal of Neuroscience 2017; 37(21):5263–5273)



Environmental Toxins

- Persistent Organic Pollutant accumulation (pesticides, dioxins, hydrocarbons, phthalates, PCBs, PBDEs, etc.)
- Metals: Lead, Mercury, Arsenic, Cadmium, Manganese
- Volatile anesthetic gases
- Certain detoxi-genomic SNPs, impaired phase 1 and 2 elimination
- Heightened levels of hyperphosphorylated tau and beta amyloid in the brains of infants, children, and young adult urbanites with lifetime exposures to fine-particulate-matter pollution (PM2.5).*

*Environmental Research 164 (2018) 475–487

"Transport"

Covert Vascular Brain Injury Markers on MRI

- **Meta-analysis: 16,000 community-dwelling older persons from 94 prospective, longitudinal cohort studies. Extensive white matter hyperintensity burden associated with:**
  - **Dementia (HR 1.84)**
  - **Alzheimer's disease (HR 1.50)**
  - **Stroke (HR 2.40)**
  - **Death (HR 2.00)**

Debette S. Jama Neurology 2018;
DOI:10:1001/jamaneurol.2018.3122

Mild Moderate Severe

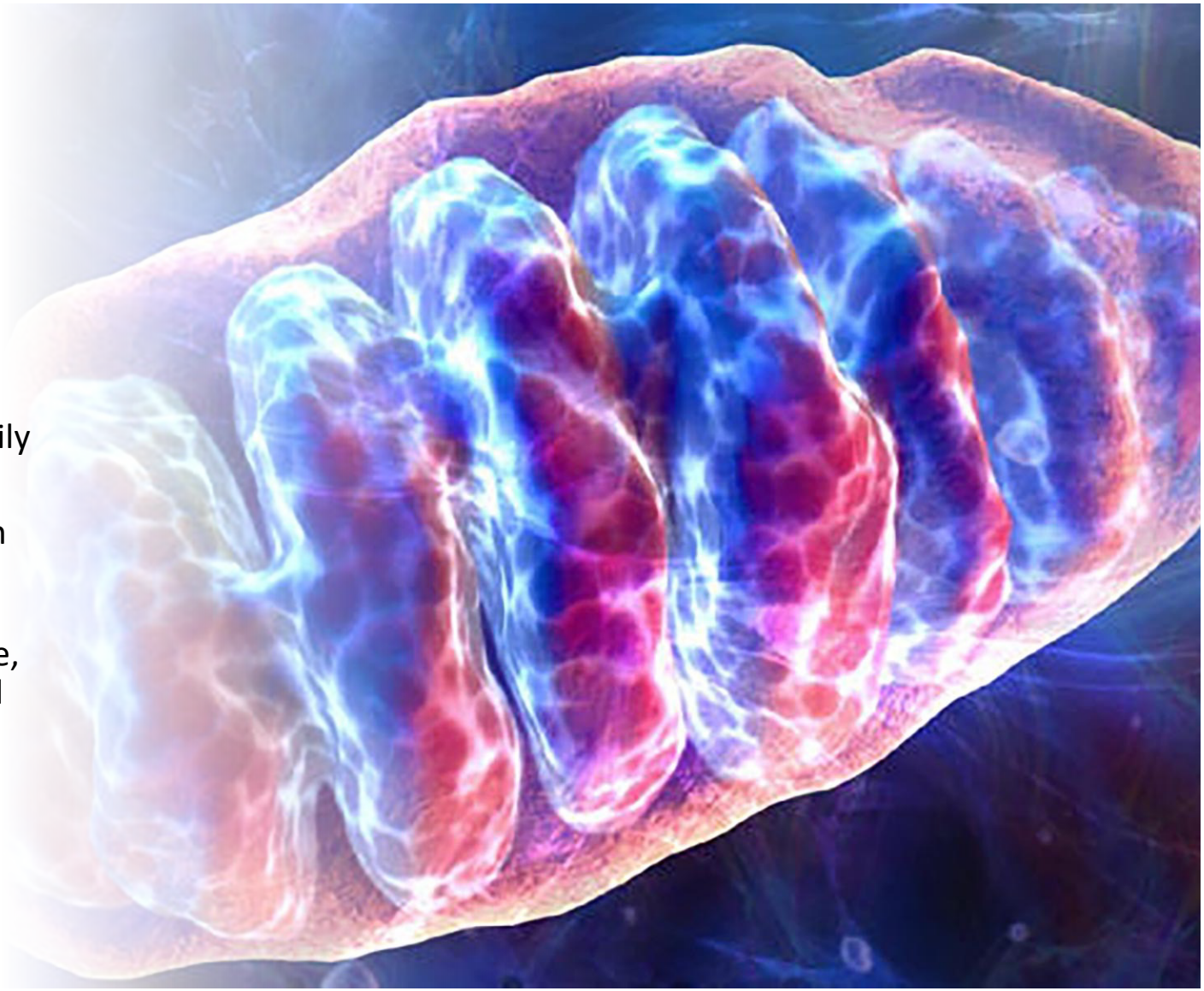
Risk Factors and Biomarkers of Vascular Disease

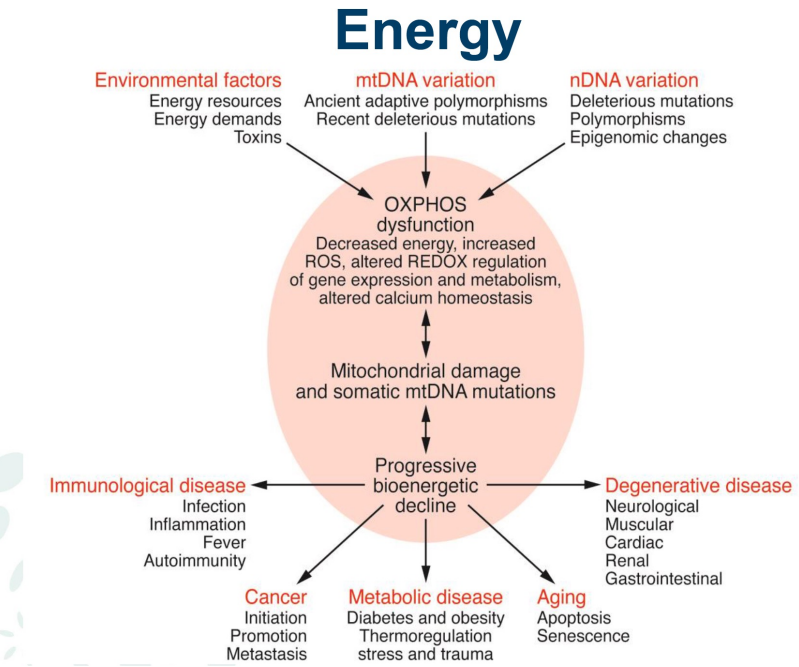
- Prediabetes/insulin resistance
- Hypertension
- Dyslipidemia
- Abdominal obesity
- Cigarette smoking
- Obstructive Sleep Apnea
- Sedentary lifestyle
- Family history of CVD

- Impaired eccentric contraction, poor elasticity index, high remaining blood volume, Wave forms IV – VII, abnormal HRV.
- Increased intimal medial thickness; calcified, mixed, or soft plaque; stenosis greater than or equal to 50%.

Energy

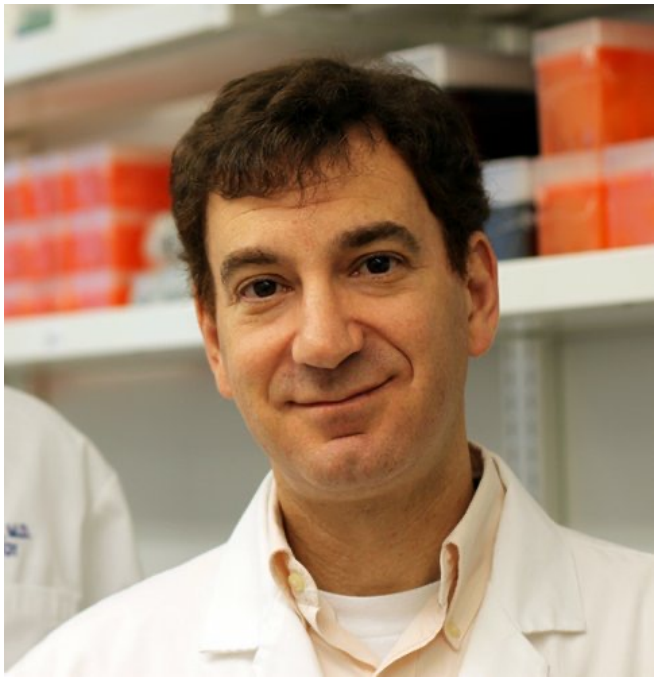
- Mitochondria
- Generation of ATP, primarily from glucose and fat
- Oxidative phosphorylation requires several nutrient cofactors: magnesium, manganese, iron, carnitine, lipoic acid, B1, B2, B3, and glutathione.

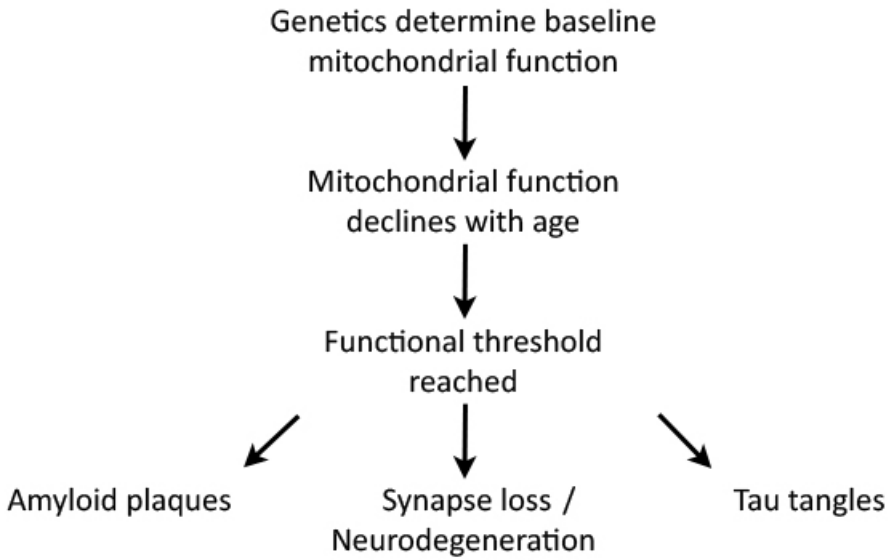




A Mitochondrial Bioenergetic Etiology of Disease

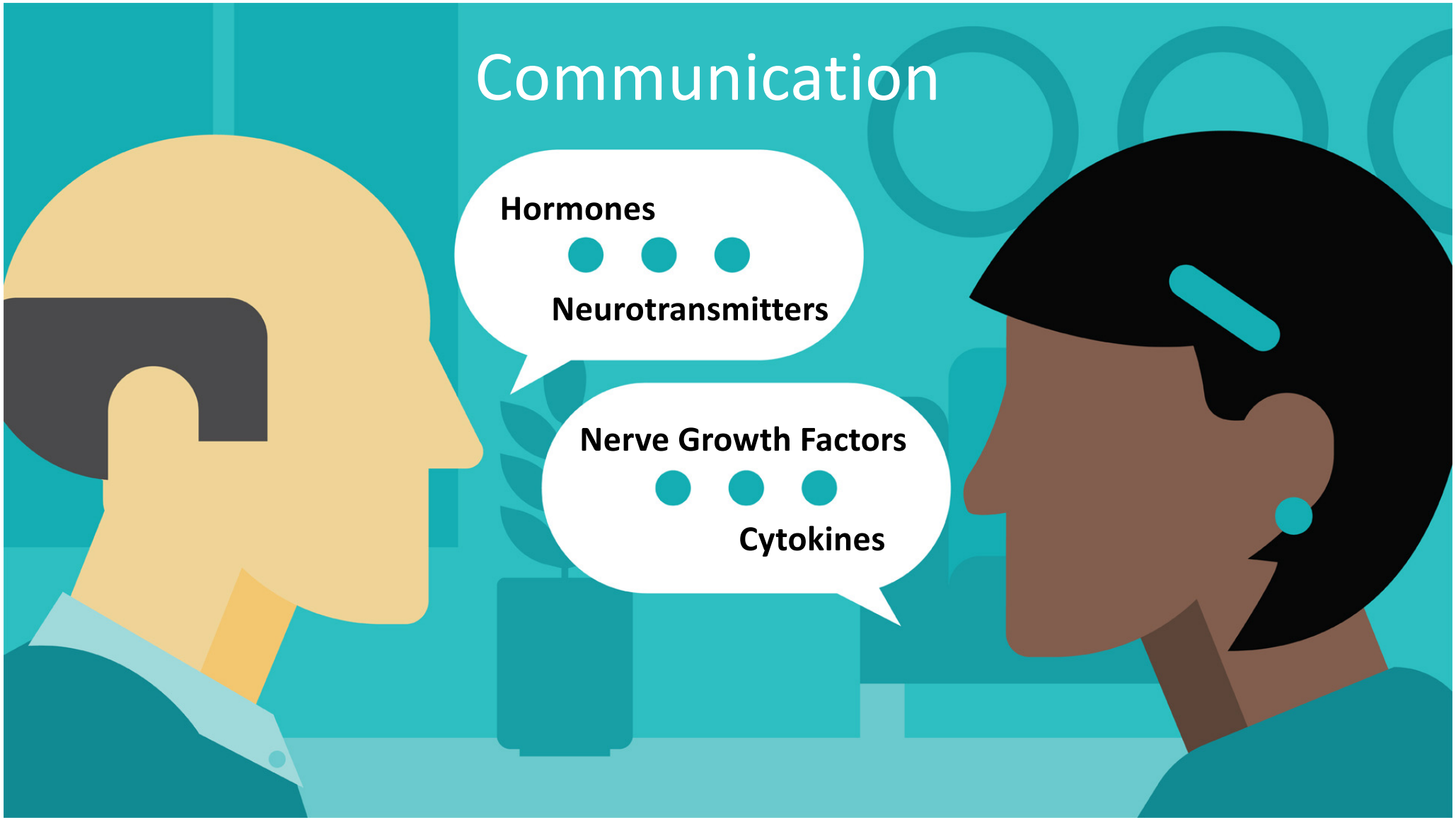
Wallace DC. J Clin Invest 2013; 123(4):1405-12.

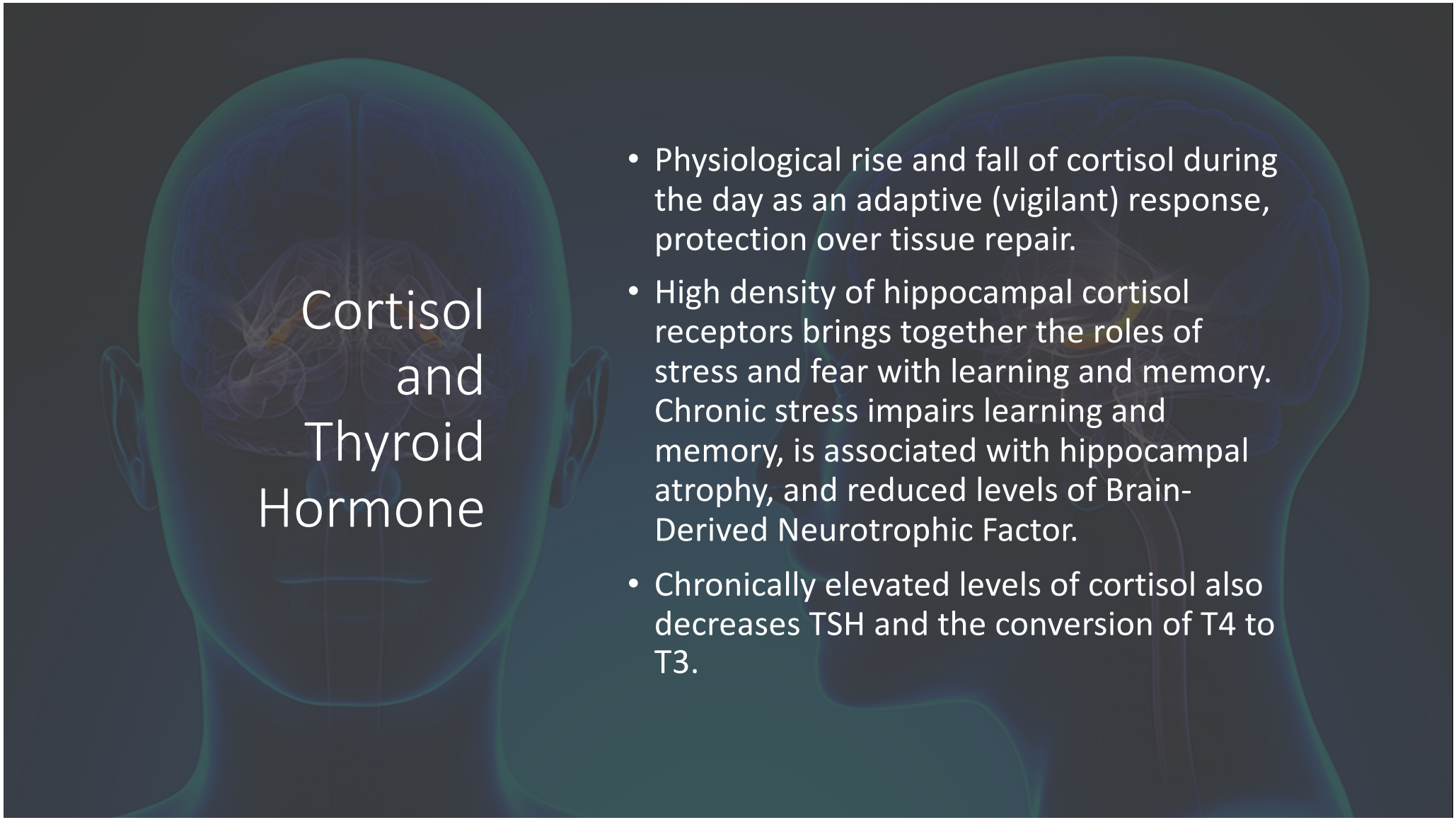




The Mitochondrial "Cascade" Hypothesis

Russell Swerdlow, M.D., University of Kansas Alzheimer's Disease Center & Landon Center on Aging


Communication
Hormones
Neurotransmitters
Nerve Growth Factors
Cytokines

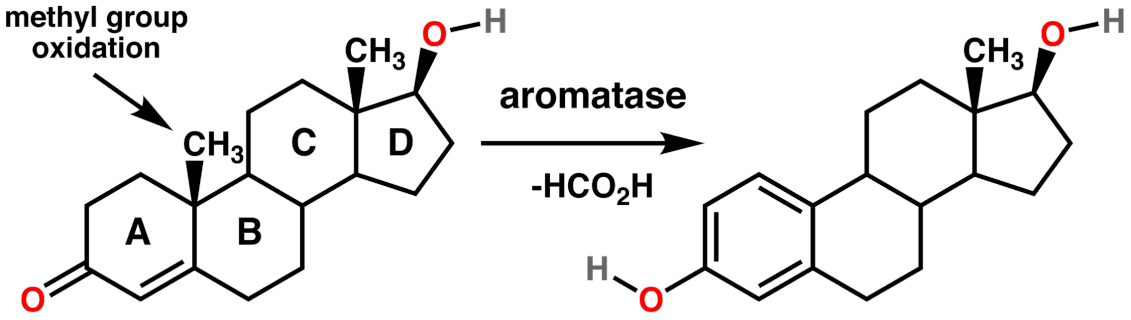


Cortisol and Thyroid Hormone

- Physiological rise and fall of cortisol during the day as an adaptive (vigilant) response, protection over tissue repair.
- High density of hippocampal cortisol receptors brings together the roles of stress and fear with learning and memory. Chronic stress impairs learning and memory, is associated with hippocampal atrophy, and reduced levels of Brain-Derived Neurotrophic Factor.
- Chronically elevated levels of cortisol also decreases TSH and the conversion of T4 to T3.

- Affects the excitability of neurons and glia
- Through its action on GABA receptors promotes a calming, anti-anxiety effect
- Counters the excitatory effect of cortisol
- Promotes tissue repair by stimulating the formation of myelin.

Testosterone and Estrogen



testosterone estradiol

- Testosterone affects memory, attention, and spatial awareness. In lab models T reduces beta amyloid and P-tau levels. T appears to be lower in ApoE4 positive men (*Neurology* Jan 2004, 62 (2) 170-171).
- Estrogen involved in learning, memory, motor control, pain perception, and has a positive effect on DNA repair mechanisms (antiaging and neuroprotective).
- Evidence from The Cache County Study on Memory and Aging found that women who used any form of hormone replacement therapy within five years of menopause had a **30% reduced risk of Alzheimer's disease**.[1] The Mayo Clinic Cohort Study of Oopherectomy and Aging showed that **women whose ovaries were surgically removed before the age of 45 had a 5-fold increased risk of mortality from neurological disease, including cognitive impairment and dementia**.[2]

1. Zandi PP, et al. *JAMA* 2002;288(17):2123-2129.
2. Rivera CM, et al. *Neuroepidemiology* 2009;33:32-40.

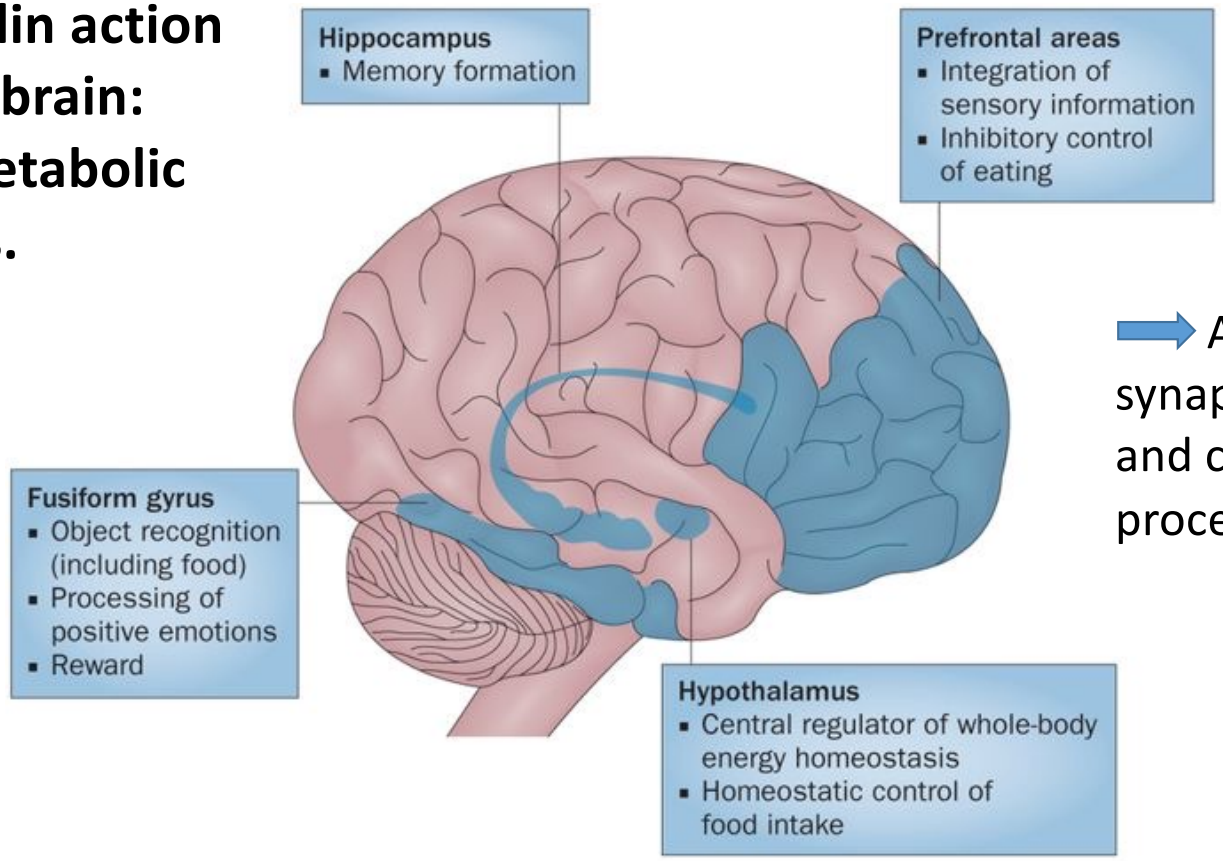
Risk of incident dementia associated with diabetes and APOE ε4: the HAAS

AD§	
Diabetes only	1.6 (0.9–2.8)
APOE ε4 only	2.0 (0.9–4.0)
Diabetes/ε4	4.4 (1.9–10.0)
ε4 × diabetes interaction term $P > 0.2$‡	
AD without CVD	
Diabetes only	1.1 (0.5–2.4)
APOE ε4 only	1.7 (0.7–4.2)
Diabetes/ε4	5.5 (2.2–13.7)
ε4 × diabetes interaction term $P = 0.114$‡	

CVD = cerebrovascular disease

Pella R, et al. Diabetes 2002;51(4):1256-1262

Impaired insulin action in the human brain: causes and metabolic consequences.



➡ Alterations in synaptic activity and cognitive processing.

*Martin, H., et al. Nature Reviews Endocrinology 2015;*11: 701–711.

Neurotransmitters

Synthesis requires an adequate supply of the amino acids tyrosine, tryptophan, glutamic acid, the vitamin choline, and B-vitamins such as folate and B12.

The availability of choline – found in meat, poultry, fish, and eggs – affects the synthesis of acetylcholine in the nerve cells of the hippocampus.

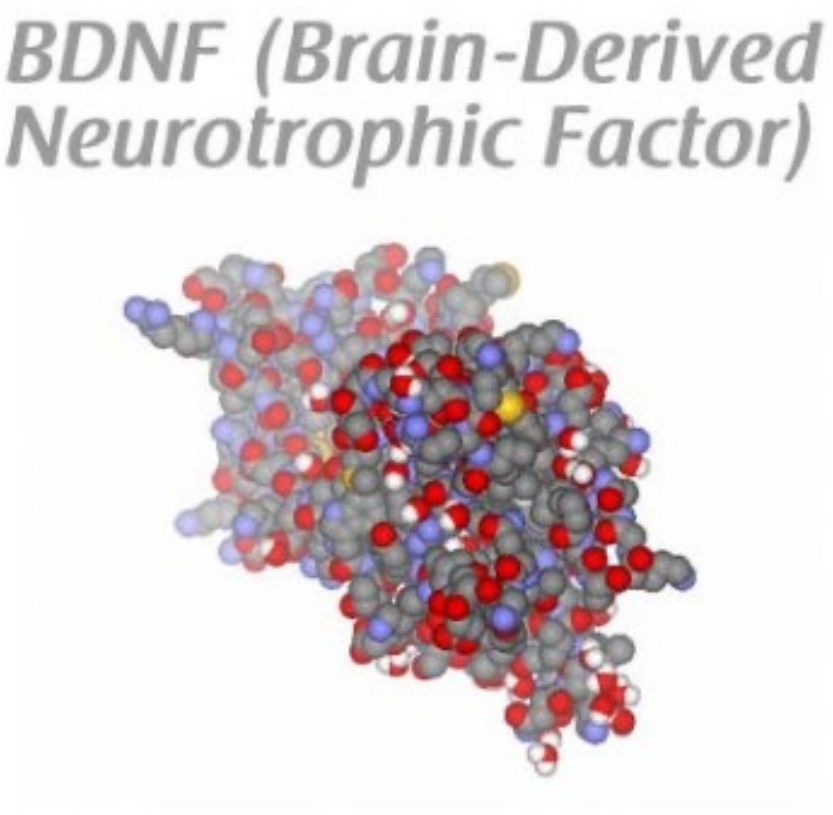
Glutamate also plays a major role in memory and learning. Excessive glutaminergic stimulation may be excitotoxic and contribute to the risk of AD.

GABA, serotonin, norepinephrine, and acetylcholine each play a role in sleep.

Dopamine, serotonin, and norepinephrine involved in attentiveness

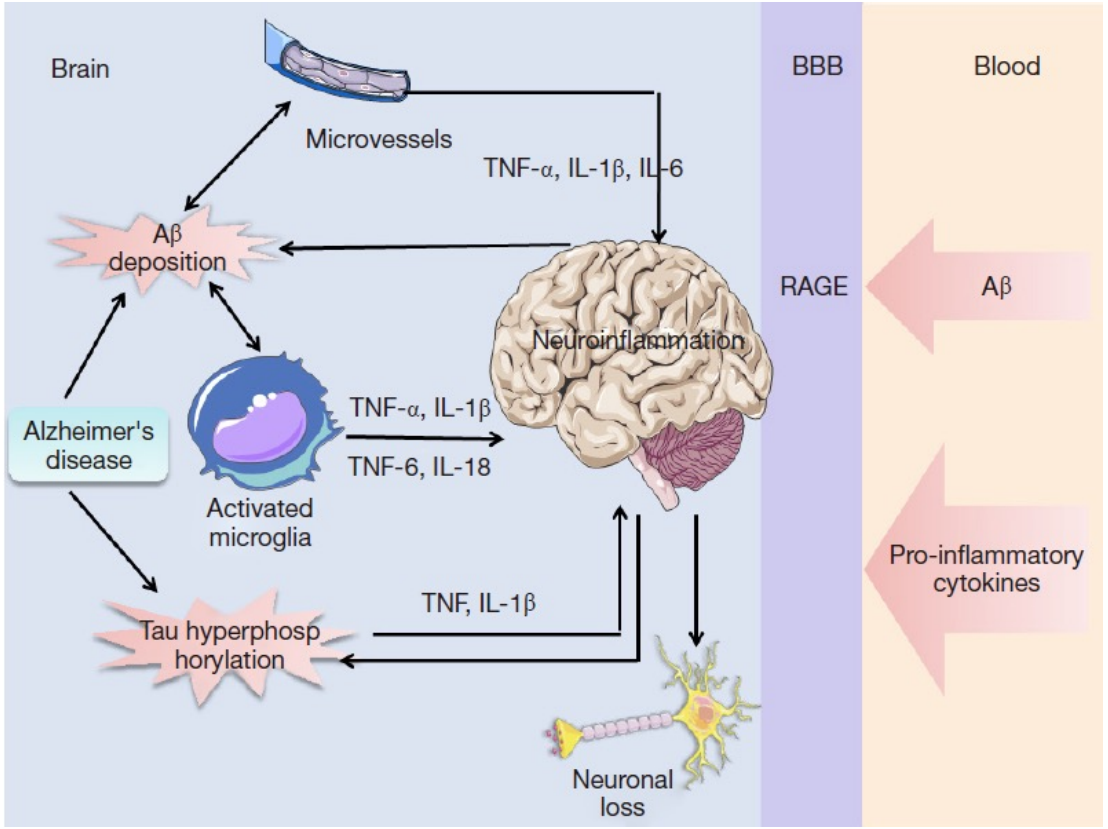
Brain-derived Neurotrophic Factor (BDNF)

- Most widely distributed neurotrophin in the CNS
- Supports neuron survival
- Supports growth and differentiation of new neurons and synapses
- Active in areas vital to learning, memory, higher thinking – e.g., hippocampus
- Reduced expression in human brains closely associated with the pathogenesis of AD

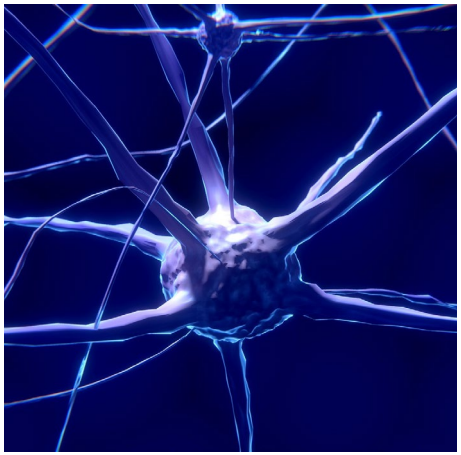


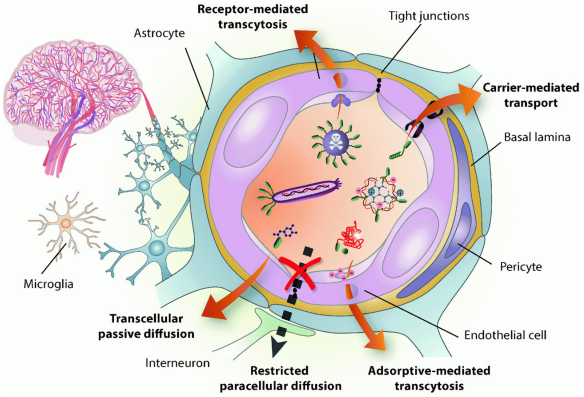
Cytokines

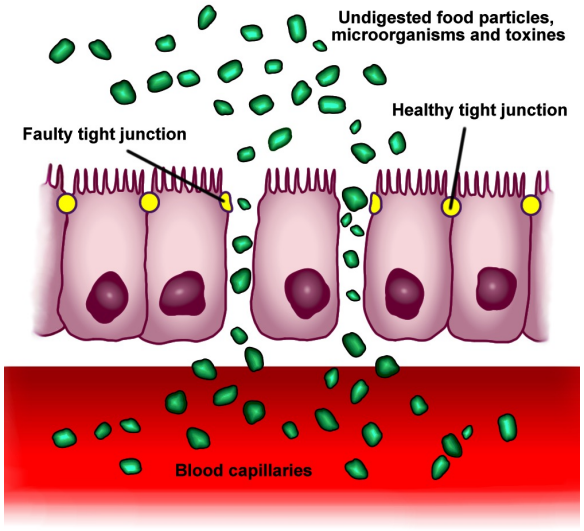
- Broad category of proteins involved in cell signaling - immunomodulating agents.
- Interleukin-1beta, Interleukin-6, Tumor Necrosis Factor-alpha, Interleukin-8, Transforming Growth Factor-beta, Macrophage Inflammatory Protein-1alpha – all upregulated in AD.
- Roles include pro-apoptosis, decreased long-term potentiation, synaptic loss, increased Abeta 42 synthesis, decreased Abeta 42 clearance, increased tau hyperphosphorylation



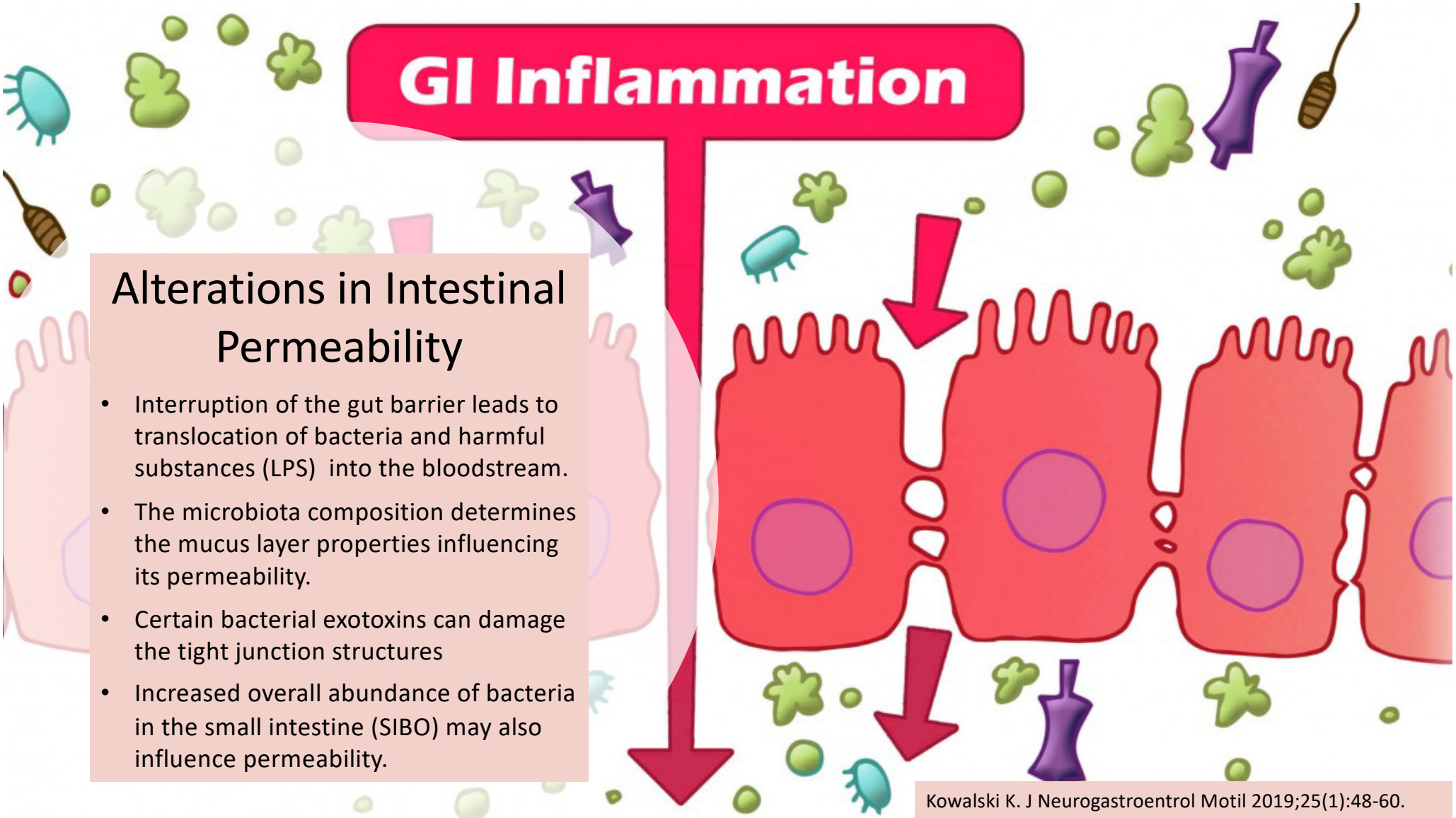
Wang WY, et al. Ann Transl Med 2015;3(10)136







Structural Integrity

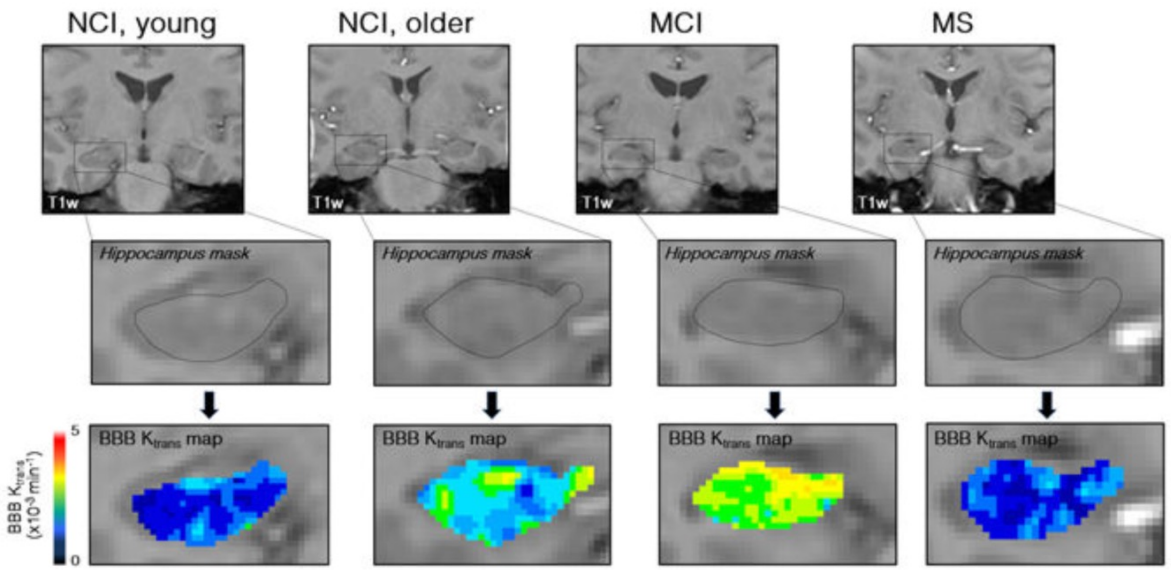


Alterations in Intestinal Permeability

- Interruption of the gut barrier leads to translocation of bacteria and harmful substances (LPS) into the bloodstream.
- The microbiota composition determines the mucus layer properties influencing its permeability.
- Certain bacterial exotoxins can damage the tight junction structures
- Increased overall abundance of bacteria in the small intestine (SIBO) may also influence permeability.

Kowalski K. J Neurogastroentrol Motil 2019;25(1):48-60.

Alterations in Blood-Brain Barrier Permeability



- Blood-brain barrier breakdown during normal aging occurs initially in the hippocampus but is more pronounced in MCI compared to age-matched neurologically intact controls.
- Leads to tissue accumulation of potentially neurotoxic blood-derived products that normally do not enter the brain but can damage neurons when vessels become leaky.
- Vascular leakage over time associated with excessive microglial stimulation and increased neuroinflammatory signaling, leading to increased amyloid beta 42 production, tau phosphorylation, hippocampal and cortical atrophy.

Montagne A. *Neuron*. 2015;85(2): 296–302.

- Sleep
- Movement
- Food
- Stress Resilience
- Connection
- Meaning/Purpose in Life

THE VALUE OF SLEEP

THE BENEFITS OF MOVEMENT

THE POWER OF FOOD

Food as Medicine

- The Washington Heights–Inwood Columbia Aging Project (WHICAP) was the first to report a beneficial effect of the Mediterranean diet on incidence of AD.
  - Over 2000 individuals older than 65 years of age followed for an average of 4 years.
  - A higher adherence to the Mediterranean diet was significantly associated with a lower risk of development of AD, even after adjustment for age, sex, ethnicity, education, *ApoE* genotype, caloric intake, smoking, comorbidity index and BMI.
  - Compared with individuals in the lowest tertile of the Mediterranean diet score (score 0–3; indicating a low adherence to the Mediterranean diet), those in the middle score tertile (score 4–5) had 21% less risk for development of AD and those in the highest tertile (score 6–9; indicating a high adherence to the Mediterranean diet) had 40% less risk for development of AD
- Among individuals who had MCI at baseline, adherence to the Mediterranean diet had a significantly reduced risk of developing AD over time.
  - Subjects in the middle tertile had 45% less risk (HR = 0.55; 95% CI, 0.34-0.90; *P* = .01) of developing AD and those in the highest tertile had 48% less risk (HR = 0.52; 95% CI, 0.30-0.91; *P* = .02) of developing AD (trend HR = 0.71; 95% CI, 0.53-0.95; *P* for trend = .02).

Thaipisuttikul P, et al. *Clin Pract (Lond)*. 2012;9(2):199-209. doi:10.2217/cpr.12.3

The Effect of Nutrients on Brain Function: The Perfect Diet?

- Nutrient dense: All essential vitamins, minerals, amino acids.
- Anti-inflammatory: High in mono- and polyunsaturated fats > saturated fat, low O6:O3 ratio, low carbohydrate, moderate protein
- Antioxidant rich: Vitamins, phytonutrients (e.g., alpha lipoic acid, vitamin E, polyphenols…)
- Methylation support: Folate, etc.
- Detoxification support: Cruciferous vegetables, garlic (alliums), parsley and other greens.
- Plant-based, but omnivorous: B12, creatine, carnosine, D3, DHA, heme-iron, taurine, choline
- Fiber-rich, supports gut microbiome
- Consumed mindfully and in the company of others

STRESS RESILIENCE

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

The relationship between stress and Alzheimer's disease

Nicholas J. Justice*

Institute of Molecular Medicine, University of Texas Health Sciences Center, Houston, TX, 77030, USA

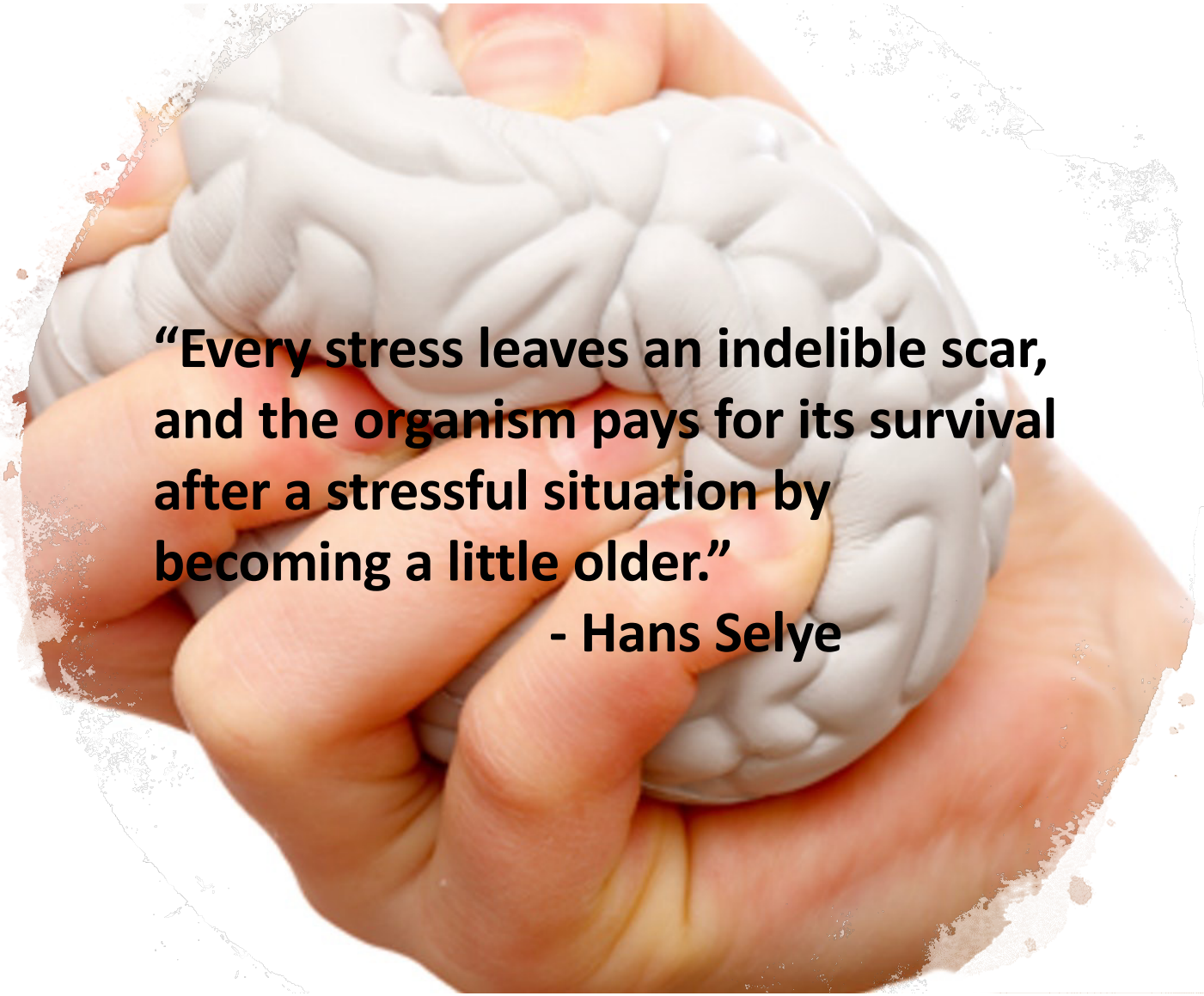
ARTICLE INFO

Keywords:
Alzheimer's disease
Stress
Cortisol
Corticosteroids
CRF
CRH

ABSTRACT

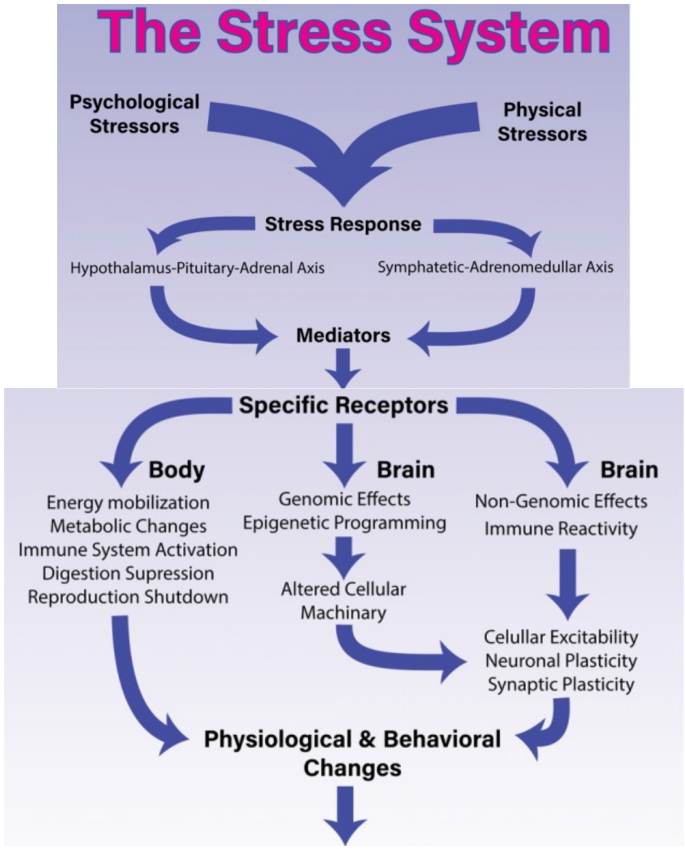
Stress is critically involved in the development and progression of disease. From the stress of undergoing treatments to facing your own mortality, the physiological processes that stress drives have a serious detrimental effect on the ability to heal, cope and maintain a positive quality of life. This is becoming increasingly clear in the case of neurodegenerative diseases. Neurodegenerative diseases involve the devastating loss of cognitive and motor function which is stressful in itself, but can also disrupt neural circuits that mediate stress responses. Disrupting these circuits produces aberrant emotional and aggressive behavior that causes long-term care to be especially difficult. In addition, added stress drives progression of the disease and can exacerbate symptoms. In this review, I describe how neural and endocrine pathways activated by stress interact with ongoing neurodegenerative disease from both a clinical and experimental perspective.

https://doi.org/10.1016/j.ynstr.2018.04.002


“Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older.”
- Hans Selye

Many Paths to the Mountain Top

- Meditation
- Patterned Breathing
- Yoga
- Tai Chi
- Reiki
- Music/sound
- Flow
- LED/Alternating Current Electricity



Godoy LD, et al. Front Behav Neurosci 2018; 12: 127

STRONG RELATIONSHIPS

Association of Higher Cortical Amyloid Burden with Loneliness in Cognitively Normal Adults

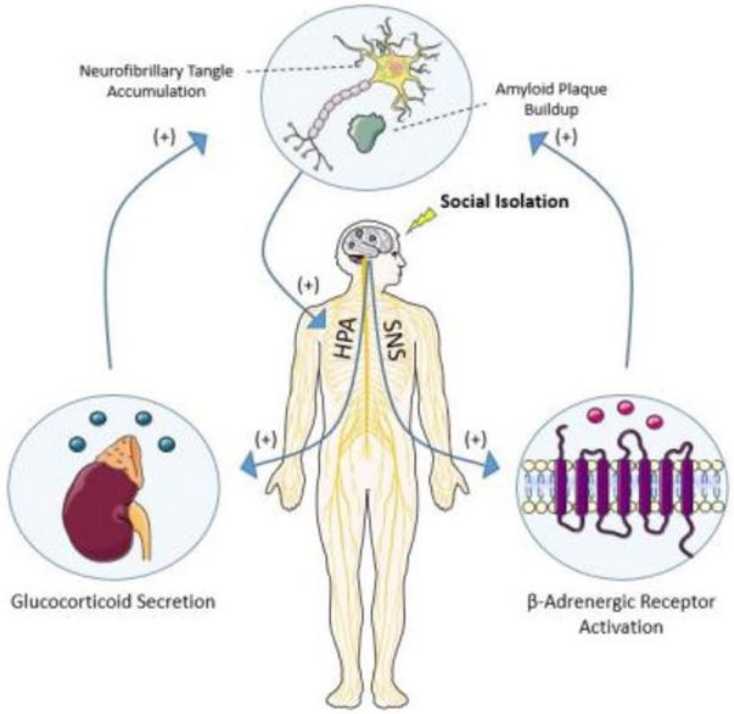
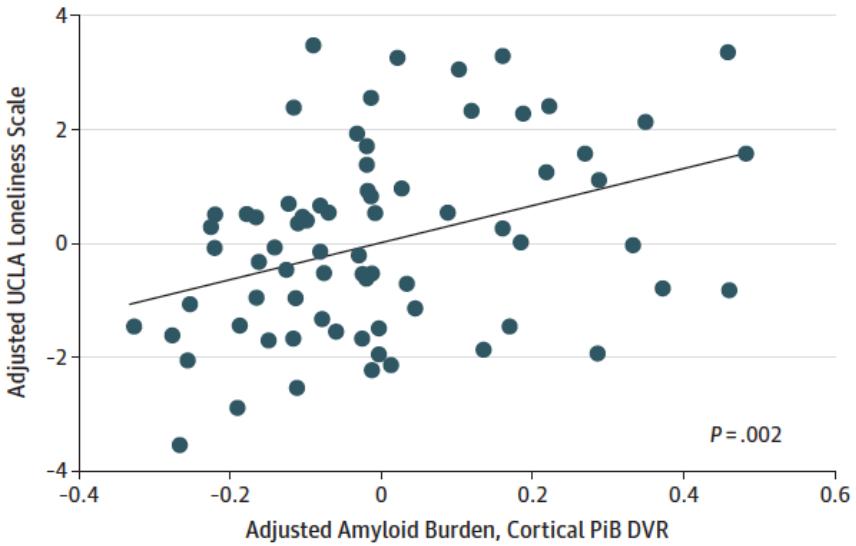
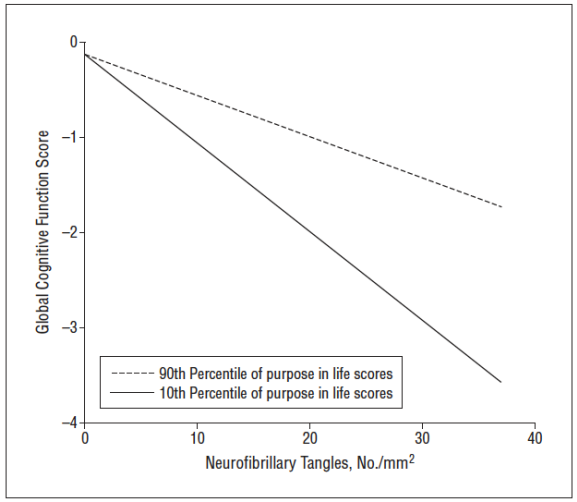
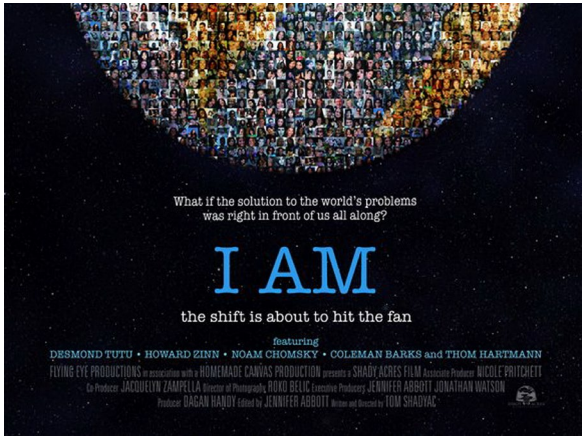


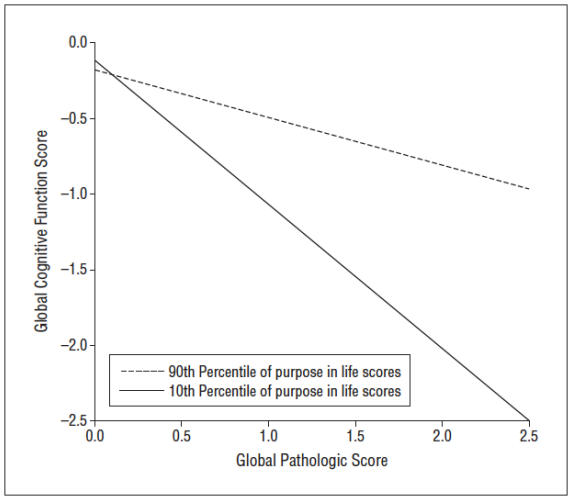
Figure. Cross-sectional Relation of Cortical Amyloid Burden and Loneliness



Donovan NJ, et al. JAMA Psychiatry 2016;73(12):1230-37.
Friedler MS, et al. Acta Neuropathol 2015;129(4):493-509.





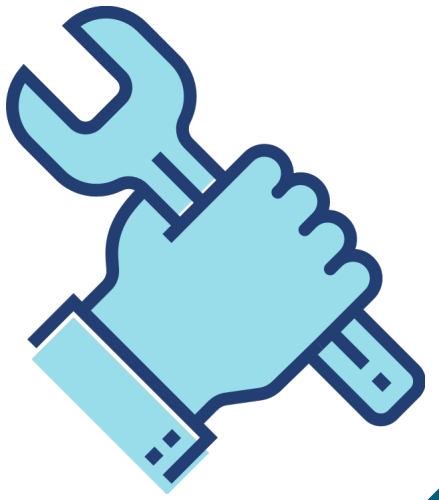


Effect of Purpose in Life on the Relation Between Alzheimer Disease Pathologic Changes on Cognitive Function in Advanced Age: 246 Older Persons from the Rush Memory and Aging Project

Boyle PA, et al. Arch Gen Psychiatry 2012; 69(5):499-506.

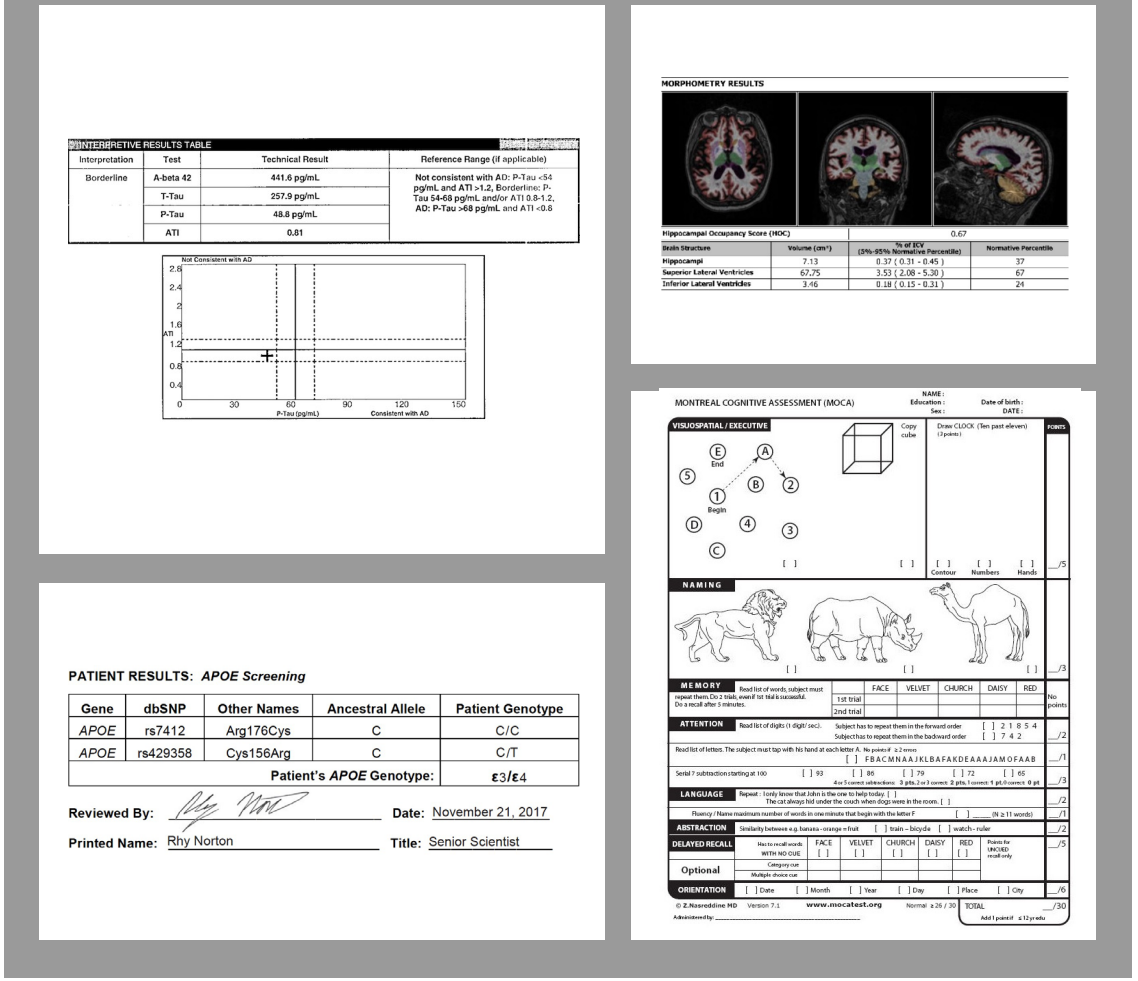
2

THE TOOLS



Neurological History and Physical Examination Dementia Differential Diagnosis

- Alzheimer's Disease
- Lewy Body Dementia
- Features of other neurodegenerative conditions
- Vascular Dementia (ischemic)
- B12/Folate Deficiency
- Hypothyroidism
- Wernicke Korsakoff Syndrome
- Hypoxic
- Autoimmune, including GCA
- Paraneoplastic
- Renal/Hepatic Encephalopathy
- Hydrocephalus, incl. NPH
- Polypharmacy
- Psychiatric
- Infectious – HIV, PML, CJD, Syphilis, TB, Fungal
- Demyelinating d/o's
- Traumatic, incl. CTE



INTERPRETIVE RESULTS TABLE

Interpretation	Test	Technical Result	Reference Range (if applicable)
Borderline	A-beta 42	441.6 pg/mL	Not consistent with AD: P-Tau <54 pg/mL and ATI >1.2, Borderline: P-Tau 54-68 pg/mL and/or ATI 0.8-1.2, AD: P-Tau >68 pg/mL and ATI <0.8
	T-Tau	257.9 pg/mL	
	P-Tau	48.8 pg/mL	
	ATI	0.81	

MORPHOMETRY RESULTS

Hippocampal Occupancy Score (HOC)		0.67	
Brain Structure	Volume (cm³)	% of ECV (5%-95% Normative Percentile)	Normative Percentile
Hippocampi	7.13	0.37 (0.31 - 0.45)	37
Superior Lateral Ventricles	67.75	3.53 (2.08 - 5.30)	67
Inferior Lateral Ventricles	3.46	0.18 (0.15 - 0.31)	24

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube; Draw CLOCK (Ten past eleven) (3 points) — POINTS — /5

NAMING — /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. FACE | VELVET | CHURCH | DAISY | RED — 1st trial, 2nd trial — No points

ATTENTION — Read list of digits (1 digit/ sec). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 — /2

Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors. [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65. 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt — /3

LANGUAGE — Repeat : I only know that John is the one to help today [ ] The cat always hid under the couch when dogs were in the room. [ ] — /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) — /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — /2

DELAYED RECALL — Has to recall words WITH NO CUE: FACE [ ] | VELVET [ ] | CHURCH [ ] | DAISY [ ] | RED [ ] — Points for UNCUED recall only — /5

Optional — Category cue; Multiple choice cue

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — /6

© Z.Nasreddine MD Version 7.1 www.mocatest.org — Normal ≥ 26 / 30 — TOTAL — /30 — Add 1 point if ≤ 12 yr edu

Administered By: _____

PATIENT RESULTS: ***APOE Screening***

Gene	dbSNP	Other Names	Ancestral Allele	Patient Genotype
APOE	rs7412	Arg176Cys	C	C/C
APOE	rs429358	Cys156Arg	C	C/T
			Patient's *APOE* Genotype:	**ε3/ε4**

Reviewed By: _____ **Date:** November 21, 2017

Printed Name: Rhy Norton **Title:** Senior Scientist

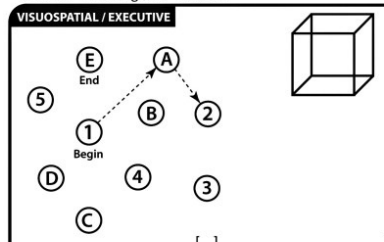
Diagnostic Testing

- MoCA/MMSE, NPI-Q, FAQ, Neuropsychological Testing.
- Standard blood work: B12, folate, Comprehensive Metabolic Panel, ESR, TSH with reflex Free T4.
- MRI Brain w/ 3D Volumetric Analysis
- FDG-, amyloid-, and tau-PET
- Lumbar Puncture
  - 42/40, Amyloid 42, Tau, P-Tau
- Genetic Testing: ApoE, PSN1, PSN2

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

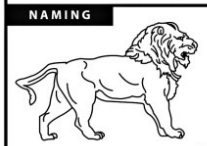
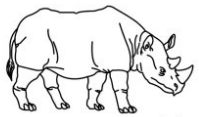
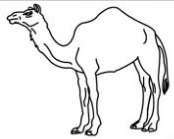


Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL — **Optional**

Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Category cue						
Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

www.mocatest.org
Normal ≥ 26 / 30
TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Functional Activities Questionnaire

Administration

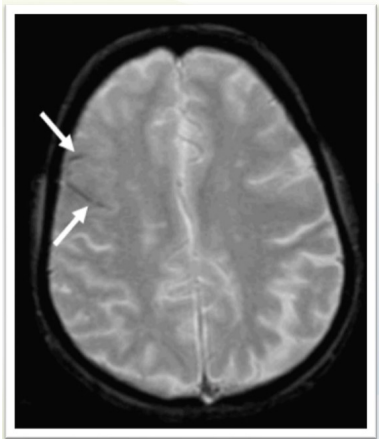
Ask informant to rate patient's ability using the following scoring system:

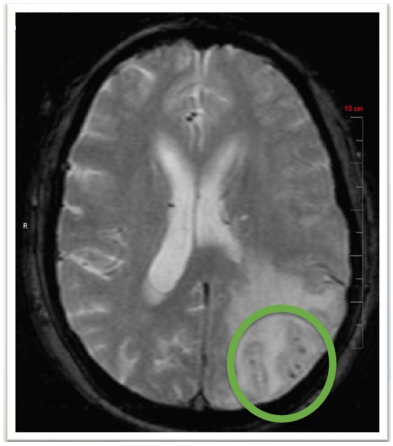
- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0
- Never did [the activity] but could do now = 0
- Never did and would have difficulty now = 1

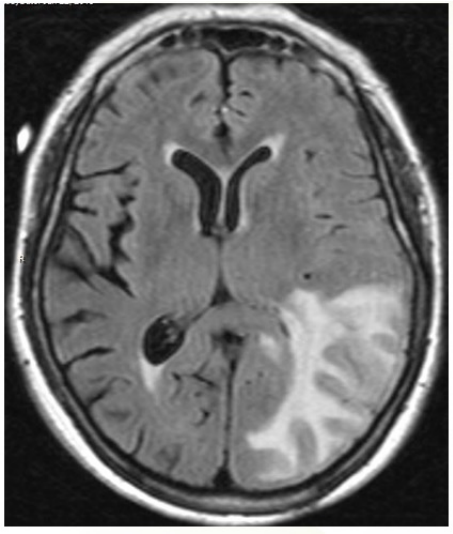
Writing checks, paying bills, balancing checkbook	
Assembling tax records, business affairs, or papers	
Shopping alone for clothes, household necessities, or groceries	
Playing a game of skill, working on a hobby	
Heating water, making a cup of coffee, turning off stove after use	
Preparing a balanced meal	
Keeping track of current events	
Paying attention to, understanding, discussing TV, book, magazine	
Remembering appointments, family occasions, holidays, medications	
Traveling out of neighborhood, driving, arranging to take buses	
TOTAL SCORE:	

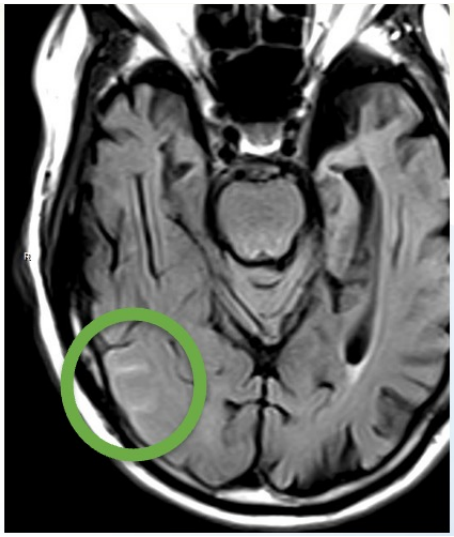
npiTEST

The Neuropsychiatric Inventory Questionnaire:
Background and Administration









Structural Neuroimaging for AD Diagnosis and Treatment

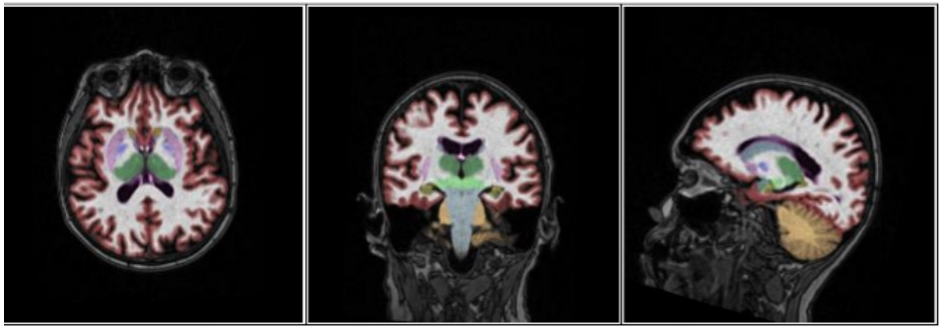
- **MRI** and **CT** have high sensitivity in detecting structural abnormalities and large pathological events (e.g., tumors, hydrocephalus, stroke), but low sensitivity to detect AD or to distinguish one type of dementia from another.
    - **However, MRI is still preferred and required for newer structural imaging technology and for monitoring treatment with anti-amyloid antibodies.**
- From the clinical application of anti-amyloid therapy have emerged the recognition of novel imaging abnormalities collectively called **ARIA** or Amyloid-Related Imaging Abnormalities. Patients who may be candidates for anti-amyloid therapies must be screened for ARIA at baseline and will require repeat MRIs during their course of treatment with a protocol in place for managing patients with these findings.
    - **ARIA-E**, identified on FLAIR sequences, located in the parenchyma (vasogenic edema) or leptomeninges (sulcal effusions/exudates), consist of proteinaceous fluid.
    - **ARIA-H**, identified on GRE/T2* sequences, located in the parenchyma where they consist of microhemorrhages (typically defined as < 10 mm) and macro-hemorrhages (>/= 10 mm), and in the leptomeninges, where they consist of superficial hemosiderin deposits.

ARIA-Related Complications: Most Asymptomatic or Mild

- In total, 454 of the 1105 patients treated with high-dose aducanumab in the 2 trials experienced ARIA. Of those, 76% of patients (n = 344) were asymptomatic while 24% (n = 110) reported symptoms—the majority of which were mild (65%; n = 72) or moderate (16%) in nature. In total, 5 patients (4%) experienced severe symptoms.
- ARIA-E events were typically seen early in treatment, with 50% occurring prior the seventh dose and 90% occurring before the twelfth dose. ApoE4 carriers were approximately twice as likely to experience ARIA-E compared to noncarriers.
- The most frequently reported symptom of ARIA was headache (13% of participants with ARIA), while other frequent symptoms included confusion (5%), dizziness (4%), visual disturbance (2%), and nausea (2%).

https://www.neurologylive.com/view/aria-most-often-asymptomatic-aducanumab-alzheimer-disease

ORPHOMETRY RESULTS

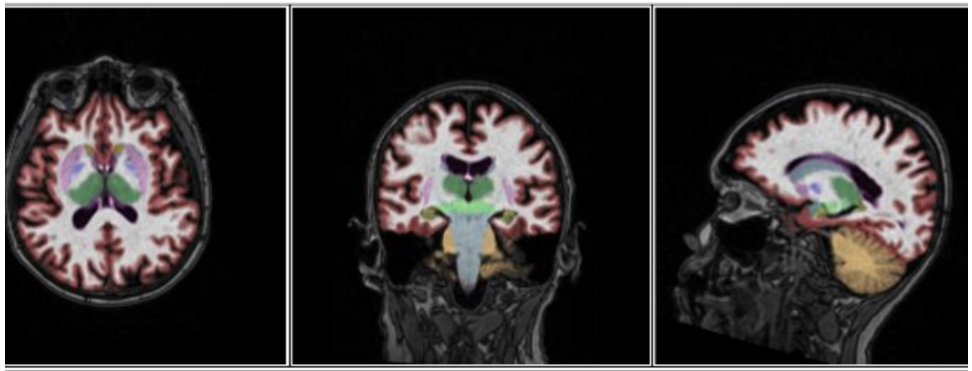


Intracranial Volume (ICV) (cm^3)	ICV Percentile
1430.61	35

otal Volumes	Percentiles		
	Left	Right	Total
erebral White Matter	97	98	98
ortical Gray Matter	9	7	8
entricles	51	62	56
ubcortical Structures			
erebellar White Matter	85	73	80
erebellar Gray Matter	71	52	62
rainstem	-	-	65
halamus	89	60	78
entral Diencephalon	53	76	65
asal Ganglia			
utamen	21	20	20
audate	44	63	54
ucleus Accumbens	20	12	13
allidum	10	19	13
ingulate	73	25	49
nterior Cingulate	72	60	68
osterior Cingulate	37	33	34
sthmus Cingulate	79	6	40

Cortical Brain Regions	Percentiles		
	Left	Right	Total
Frontal Lobes	1	1	1
Superior Frontal	4	3	3
Middle Frontal	1	1	1
Inferior Frontal	6	2	2
Lateral Orbitofrontal	6	6	4
Medial Orbitofrontal	13	11	11
Paracentral	28	43	33
Primary Motor	5	16	8
Parietal Lobes	61	52	57
Primary Sensory	37	71	54
Medial Parietal	78	21	55
Superior Parietal	16	12	11
Inferior Parietal	65	89	83
Supramarginal	92	60	86
Occipital Lobes	17	11	13
Medial Occipital	26	6	13
Lateral Occipital	22	28	20
Temporal Lobes	17	17	17
Transverse Temporal + Superior Temporal	78	32	58
Posterior Superior Temporal Sulcus	81	93	92
Middle Temporal	4	6	4
Inferior Temporal	10	26	14
Fusiform	76	83	81
Parahippocampal	57	73	67
Entorhinal Cortex	4	8	3
Temporal Pole	6	3	3
Amygdala	11	6	7
Hippocampus	52	43	47

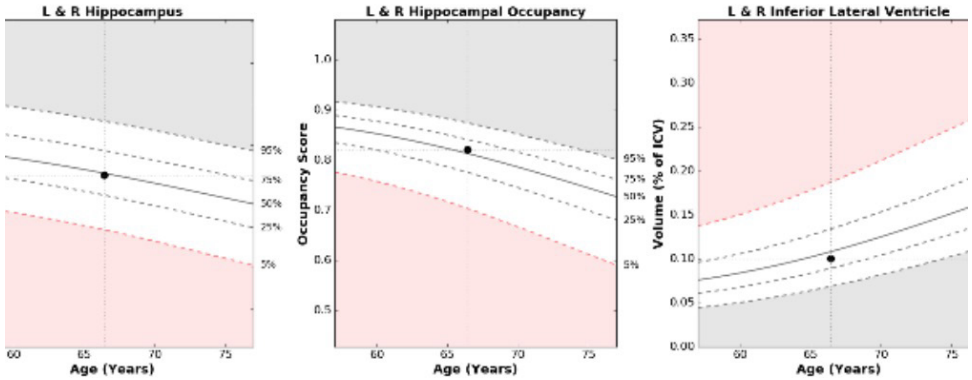
OMETRY RESULTS



mpal Occupancy Score (HOC)	0.82

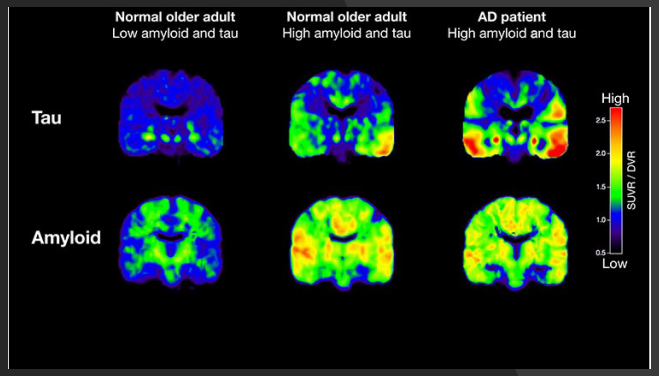
ucture	Volume (cm^3)	% of ICV (5%-95% Normative Percentile)	Normative Percentile
mpi	6.62	0.46 (0.40 - 0.53)	47
Lateral Ventricles	28.55	2.00 (0.96 - 3.59)	57
Lateral Ventricles	1.44	0.10 (0.07 - 0.19)	40

ATCHED REFERENCE CHARTS



PET Scan for Alzheimer’s Disease

- Fluorodeoxyglucose-PET has a sensitivity of > 90% for identifying cortical hypometabolism, but its specificity for Alzheimer’s disease is only about 75%.
- The US Food and Drug Administration (FDA) has approved a three agents for imaging β-amyloid in the setting of Alzheimer’s disease, florbetaben F18 injection (*Neuraceq*, Piramal Imaging), florbetapir (*Amyvid*, Eli Lilly) and flutemetamol (*Vizamyl*, GE Healthcare).
    - *As with these other imaging agents, a positive amyloid PET scan does not establish a diagnosis of AD or any other cognitive disorder, but a negative scan indicating sparse to no amyloid plaques is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD.*
- In 2020, the FDA also approved Flortaucipir (*Tauvid,* Eli Lilly) for PET imaging of adult patients with cognitive impairments undergoing evaluation for Alzheimer's disease (AD) based on tau pathology.



What About CSF Testing for Alzheimer's Disease?

- CSF testing is desirable because it directly measures changes occurring in the CNS
- CSF testing can measure Aβ, tau, and p-tau
- AD participants have reduced Aβ42 (< 200 pg/dL), increased tau, and increased p-tau
- CSF testing for NTP has not been accurate or reliable and may reflect leakage from blood (FDA denied approval)
- Other CSF biomarkers being validated
- Less expensive than amyloid PET

BETA AMYLOID 42/40 RATIO,
CSF

ABETA 42	1238		pg/mL
ABETA 40	12451		pg/mL
ABETA 42/40 RATIO		**0.10 L**	

>0.25	Low Risk
0.20 to 0.25	Average Risk
<0.20	High Risk

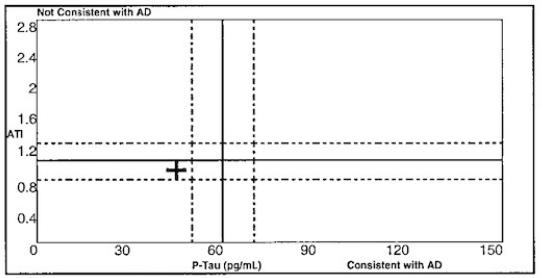
This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

ADmark Phospho-Tau / Total-Tau / A Beta 42 CSF Analysis and Interp.

This test detected borderline levels of A-beta 42, T-tau and/or P-tau proteins in the cerebrospinal fluid (CSF).

INTERPRETIVE RESULTS TABLE

Interpretation	Test	Technical Result	Reference Range (if applicable)
Borderline	A-beta 42	441.6 pg/mL	Not consistent with AD: P-Tau <54 pg/mL and ATI >1.2, Borderline: P-Tau 54-68 pg/mL and/or ATI 0.8-1.2, AD: P-Tau >68 pg/mL and ATI <0.8
	T-Tau	257.9 pg/mL	
	P-Tau	48.8 pg/mL	
	ATI	0.81	



CSF Analysis: Quest Abeta 42/40 Ratio vs. Athena Diagnostics ADMark (ATI/P-Tau)

Labs to Investigate Using a Systems Biology Approach

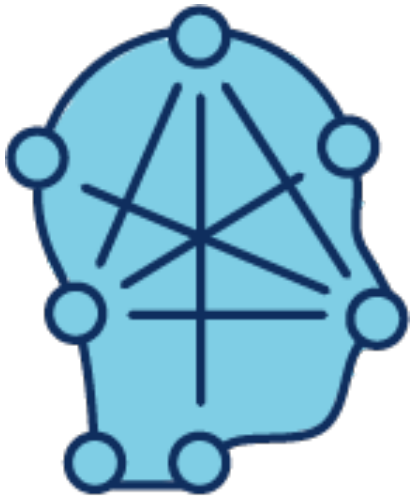
- ApoE genetic status
- Methylation: MTHFR, homocysteine, B12 (and MMA), folate, B6, choline.
- Anti-inflammatory Markers and Antioxidants: HS-CRP, Vitamins C, D, and E, CoQ, Omega Fatty Acid Profile, A/G ratio,, Oxidized LDL, Glutathione, Cu:Zn ratio.
- Glycemic control: fasting glucose and insulin, hemoglobin A1c
- Hormones: Estradiol, Progesterone, Testosterone, 4-point salivary cortisol with DHEA-S, TSH, Free T3, Free T4, Reverse T3, TPO antibodies.
- Toxins: RBC Mercury, Lead, Arsenic, Cadmium, Herpes Simplex Virus antibodies, Tickborne illness.
- Trace Minerals: RBC Magnesium, Serum Copper, Serum Zinc, Selenium, Potassium, Calcium, iodine.

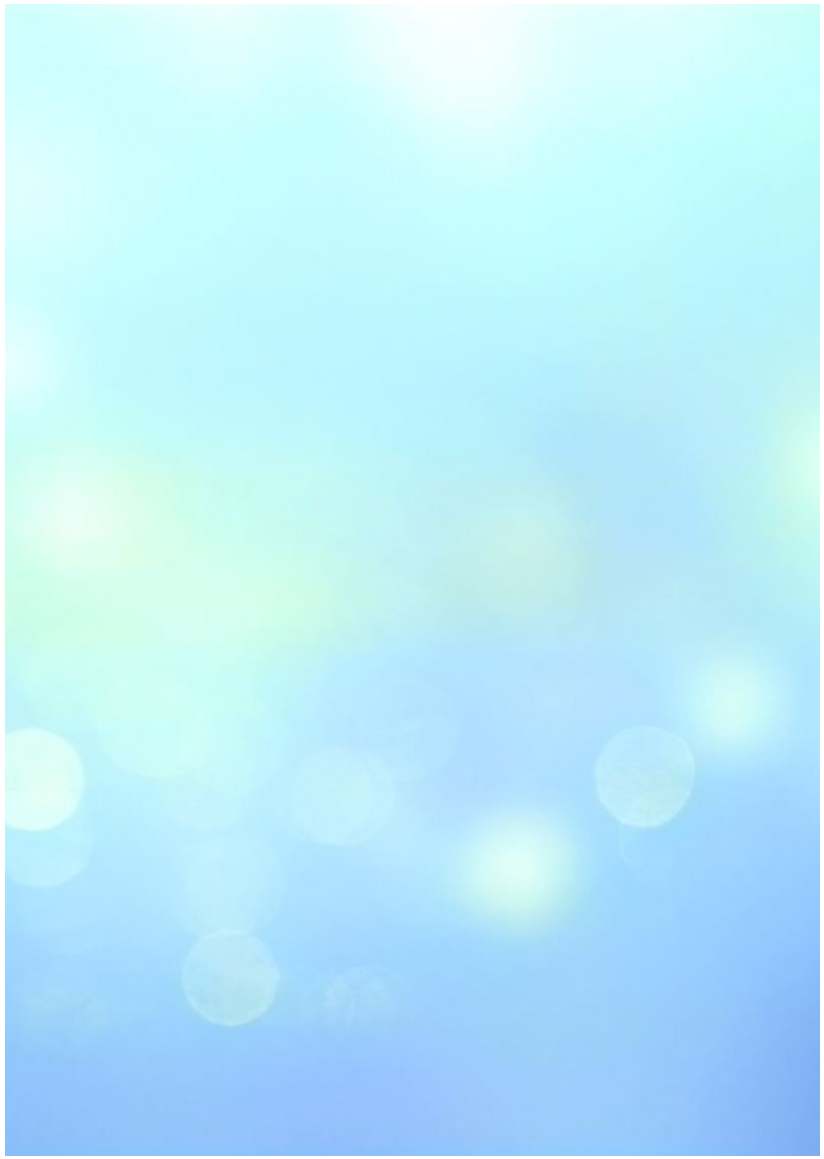
Nutraceuticals and Medicinal Foods

- My suggestion is to use targeted supplementation – decide what is most important for your patients based on what you have measured in their labs, then track.

3

THE TRANSFORMATION



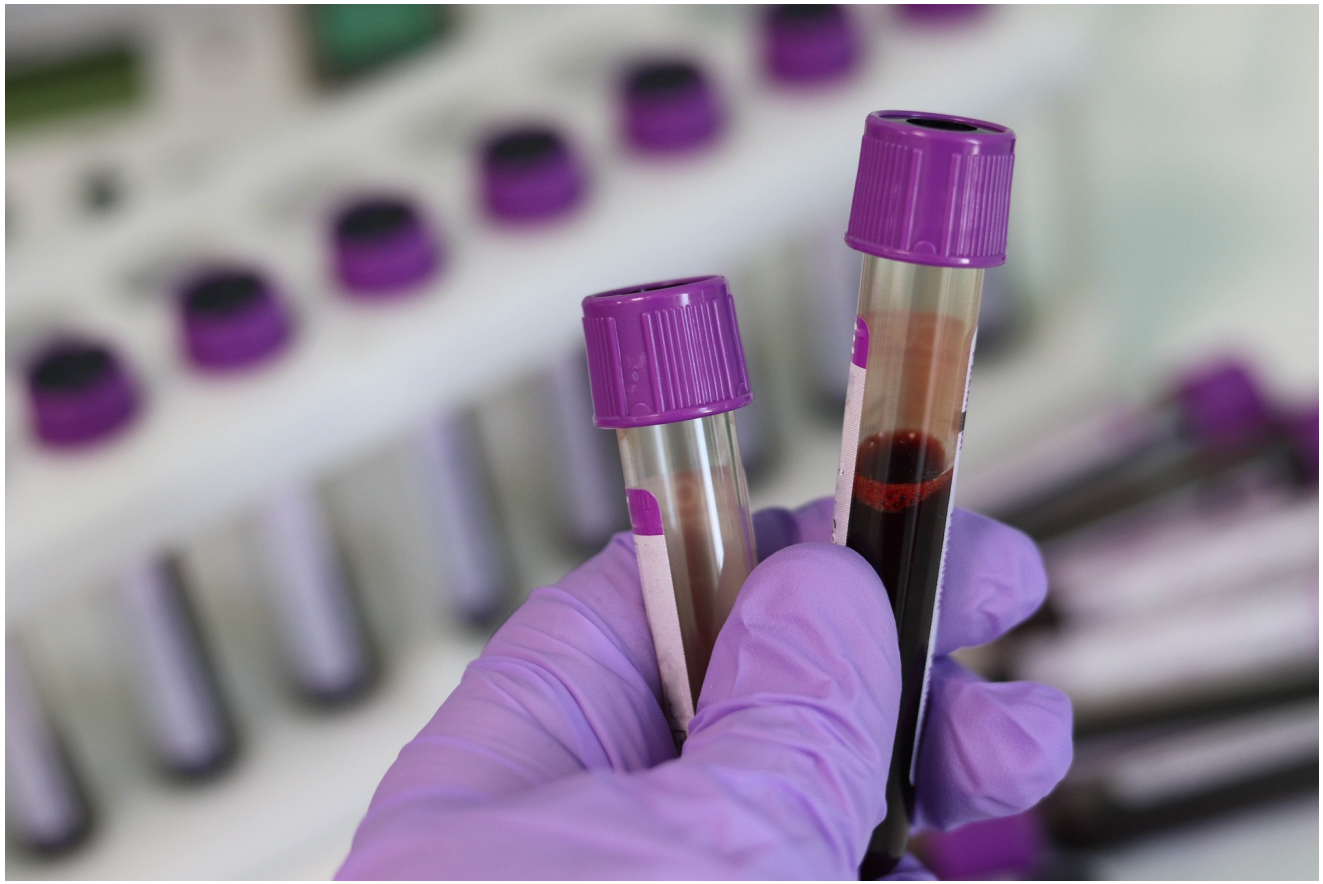


Clues in Robert's History

- Bottle fed as an infant
- Repeated antibiotic use
- Concussion
- History of prior cigarette smoking
- Use of benzodiazepine sleeping pills
- Pro-inflammatory diet
- Overweight (Visceral Adipose Tissue)
- Sedentary lifestyle
- Hypertension
- Chronic anxiety

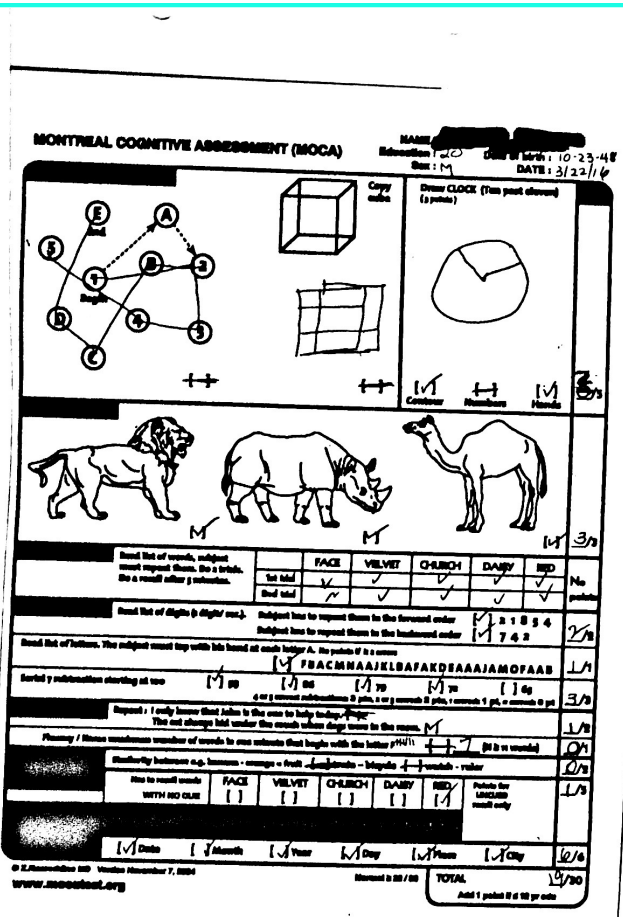
Laboratory Testing

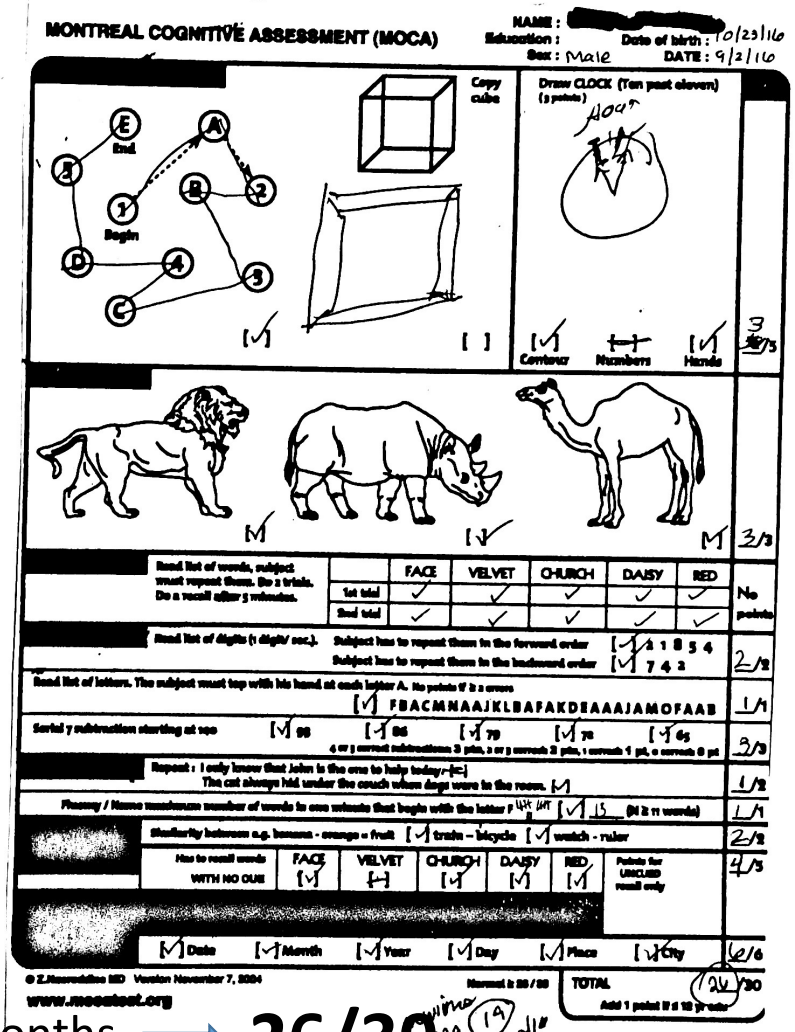
- Increased Homocysteine
- Increased High-Sensitivity C-Reactive Protein
- Low Vitamin D
- Low Zinc
- Low Thyroid Hormone
- Low Magnesium
- High Omega 6:3 Fatty Acid Profile



THIS IS Robert

Businessman, husband, father,
Alzheimer's Sufferer





19/30 → 6 months → **26/30**

Journal of
Alzheimer's Disease & Parkinsonism

Bredesen et al., J Alzheimers Dis Parkinsonism 2018, 8:5
DOI: 10.4172/2161-0460.1000450

Case Report Open Access

Reversal of Cognitive Decline: 100 Patients

Dale E Bredesen[1*], Kenneth Sharlin[2], David Jenkins[3], Miki Okuno[3], Wes Youngberg[4], Sharon Hausman Cohen[5], Anne Stefani[5], Ronald L Brown[6], Seth Conger[6], Craig Tanio[7], Ann Hathaway[8], Mikhail Kogan[9], David Hagedorn[10], Edwin Amos[11], Amylee Amos[12], Nathaniel Bergman[13], Carol Diamond[14], Jean Lawrence[15], Ilene Naomi Rusk[16], Patricia Henry[16] and Mary Braud[16]

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[9]GW Center for Integrative Medicine, George Washington University, Washington, DC, USA
[10]Coastal Integrative Medicine, Jacksonville, NC, USA
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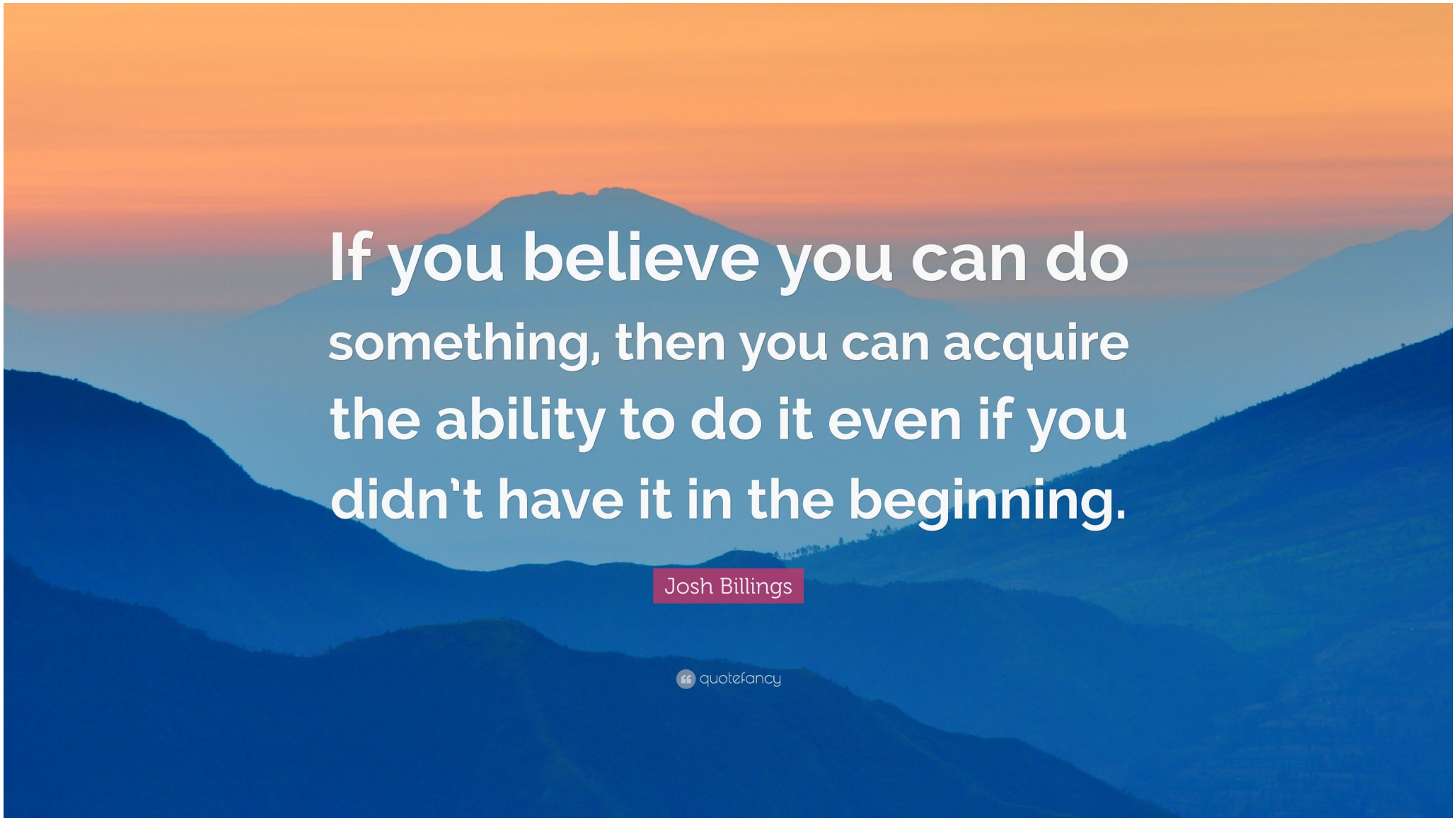
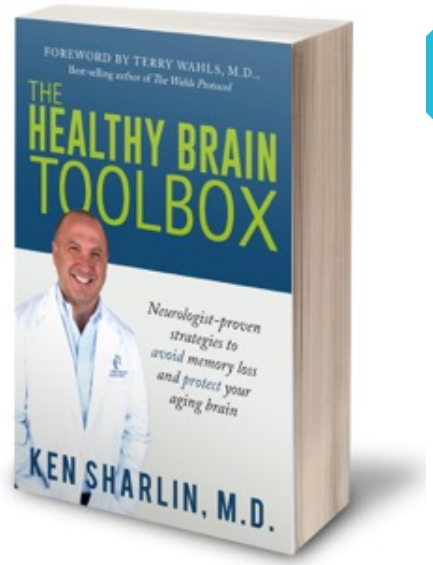
[12]Amos Institute, Los Angeles, CA, USA
[13]Center for Functional Medicine, Cleveland Clinic, Cleveland, OH, USA
[14]Mount Sinai Hospital, New York, NY, USA
[15]Lawrence Health and Wellness, Toccoa, GA, USA
[16]Brain and Behavior Clinic, Boulder, CO, USA

Abstract

The first examples of reversal of cognitive decline in Alzheimer's disease and the pre-Alzheimer's disease conditions MCI (Mild Cognitive Impairment) and SCI (Subjective Cognitive Impairment) have recently been published.


If you believe you can do something, then you can acquire the ability to do it even if you didn't have it in the beginning.
Josh Billings
quotefancy

CONNECT
WITH ME



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THANK YOU