Welcome to

AACL 2013

Brain Longevity Program:
Use Mind to Change Your Age

Professor Giovanni Scapagnini's Abstract

Brain Longevity Program: Use Mind to Change Your Age

Prof. Giovanni Scapagnini, MD, PhD

CONSIGLIO NAZIONALE DELLE RICERCHE
ISTITUTO DI SCIENZE NEUROLOGICHE

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The creation of Adam by Michelangelo

F.L. Meshberger, *An interpretation of Michelangelo's Creation of Adam Based on Neuroanatomy*, in: "journal of American Medical Ass.", 264, 1990, pp. 1837-41)

Brain

God

The link between brain and longevity

."Scientists have long wondered whether aging occurs independently in the body's various tissues or if it could be actively regulated by an organ in the body,"

"It's clear from our study that many aspects of aging are controlled by the hypothalamus. What's exciting is that it's possible — at least in mice — to alter signaling within the hypothalamus to slow down the aging process and increase longevity."

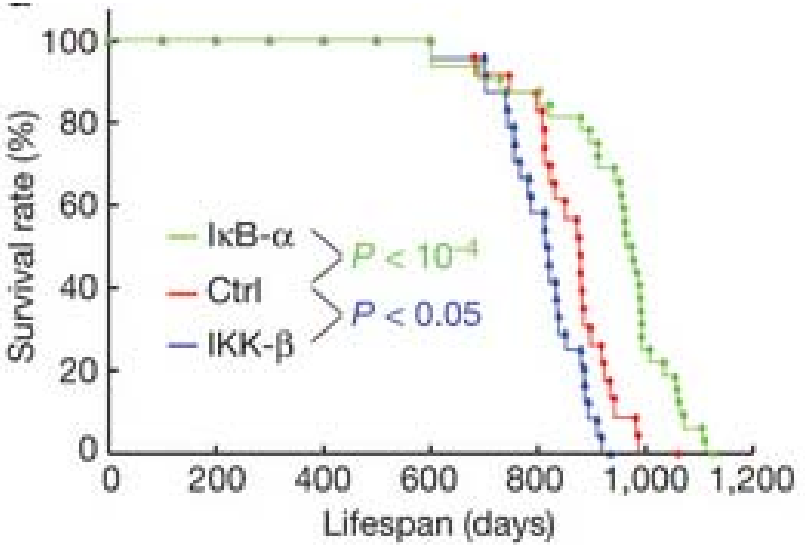
Dongsheng Cai, M.D., Ph.D, professor of molecular pharmacology at Albert Einstein College of Medicine, NY

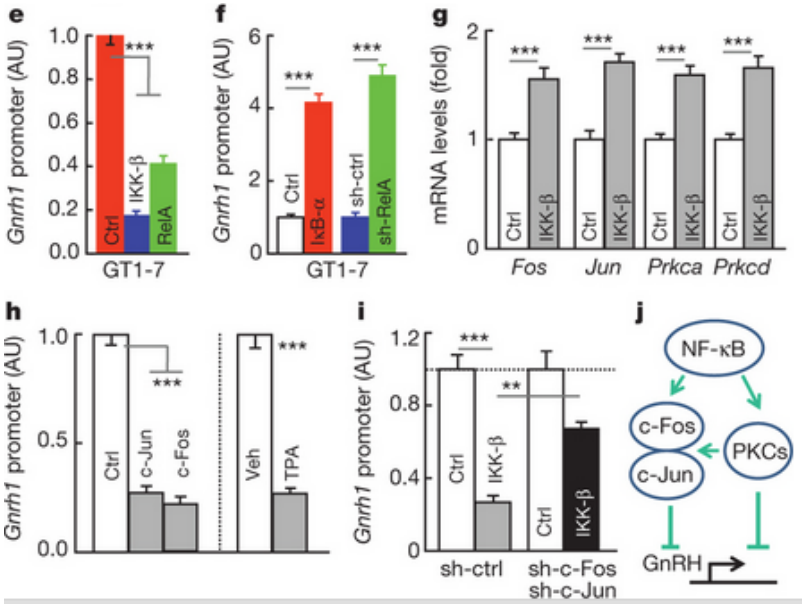
Nature. 2013 May 9;497(7448):211-6. May 1.

Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH

Guo Zhang[1,2,3*], Juxue Li[1,2,3*], Sudarshana Purkayastha[1,2,3*], Yizhe Tang[1,2,3*], Hai Zhang[1,2,3*], Ye Yin[1,2,3], Bo Li[1,2,3], Gang Liu[1,2,3] & Dongsheng Cai[1,2,3]

Ageing is a result of gradual and overall functional deteriorations across the body; however, it is unknown whether an individual tissue primarily works to mediate the ageing progress and control lifespan. Here we show that the hypothalamus is important for the development of whole-body ageing in mice, and that the underlying basis involves hypothalamic immunity mediated by IκB kinase-β (IKK-β), nuclear factor κB (NF-κB) and related microglia-neuron immune crosstalk. Several interventional models were developed showing that ageing retardation and lifespan extension are achieved in mice by preventing ageing-related hypothalamic or brain IKK-β and NF-κB activation. Mechanistic studies further revealed that IKK-β and NF-κB inhibit gonadotropin-releasing hormone (GnRH) to mediate ageing-related hypothalamic GnRH decline, and GnRH treatment amends ageing-impaired neurogenesis and decelerates ageing. In conclusion, the hypothalamus has a programmatic role in ageing development via immune-neuroendocrine integration, and immune inhibition or GnRH restoration in the hypothalamus/brain represent two potential strategies for optimizing lifespan and combating ageing-related health problems.

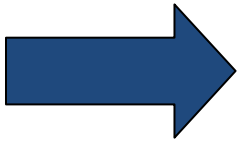




Neuroscience & Brain Health

- Has made tremendous strides in understanding the capacity for brain plasticity…

"The ability of the brain to change with learning"



Discovered a connection between brain health and life style

Gerontology Making Progress

Stages	Age
1. Young Adulthood	18-34
2. Middle Adulthood	35-54
3. Young Old	55-69
4. Middle Old	70-84
5. Old Old	85-99
6. Centenarians	100-109
7. Super-Centenarians	100+

EMBO reports

EMBO reports VOL 13 | NO 3 | 2012

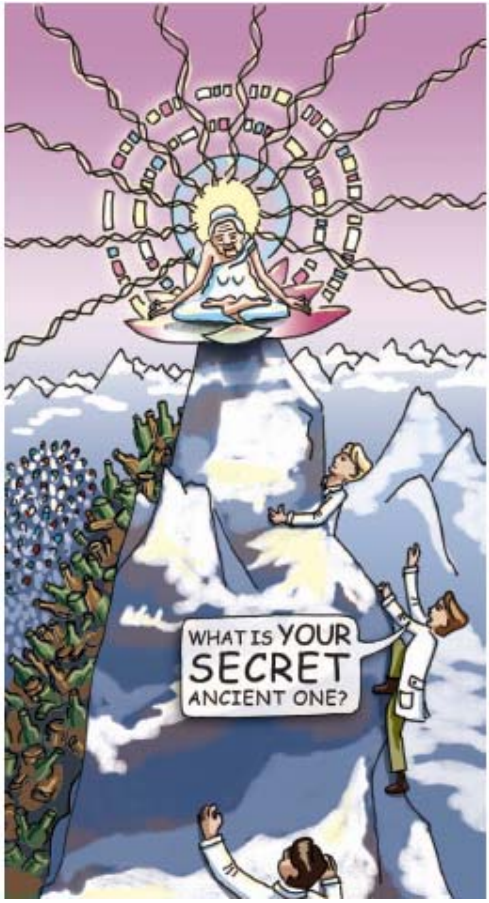
science & society

‘Positive biology’ as a new paradigm for the medical sciences

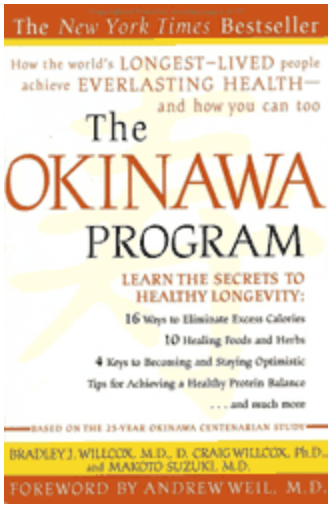
Focusing on people who live long, happy, healthy lives might hold the key to improving human well-being

Colin Farrelly

> **Eliminating all types of cancer would increase life expectancy in the USA by approximately only three years**




Sea of Japan
JAPAN
Tokyo
Pacific Ocean
Okinawa


The New York Times Bestseller
How the world's LONGEST-LIVED people achieve EVERLASTING HEALTH—and how you can too
The
OKINAWA
PROGRAM
LEARN THE SECRETS TO HEALTHY LONGEVITY:
16 Ways to Eliminate Excess Calories
10 Healing Foods and Herbs
4 Keys to Becoming and Staying Optimistic
Tips for Achieving a Healthy Protein Balance
. . . and much more
BASED ON THE 25-YEAR OKINAWA CENTENARIAN STUDY
BRADLEY J. WILLCOX, M.D., D. CRAIG WILLCOX, Ph.D., and MAKOTO SUZUKI, M.D.
FOREWORD BY ANDREW WEIL, M.D.

Interesting "Caloric Restriction (CR) Longevity" Phenotype in Older Okinawans—genetic or environmental?

Less (lifetime) chronic disease

Higher physical/cognitive function

Shorter stature

Lower BMI

Lower blood sugar

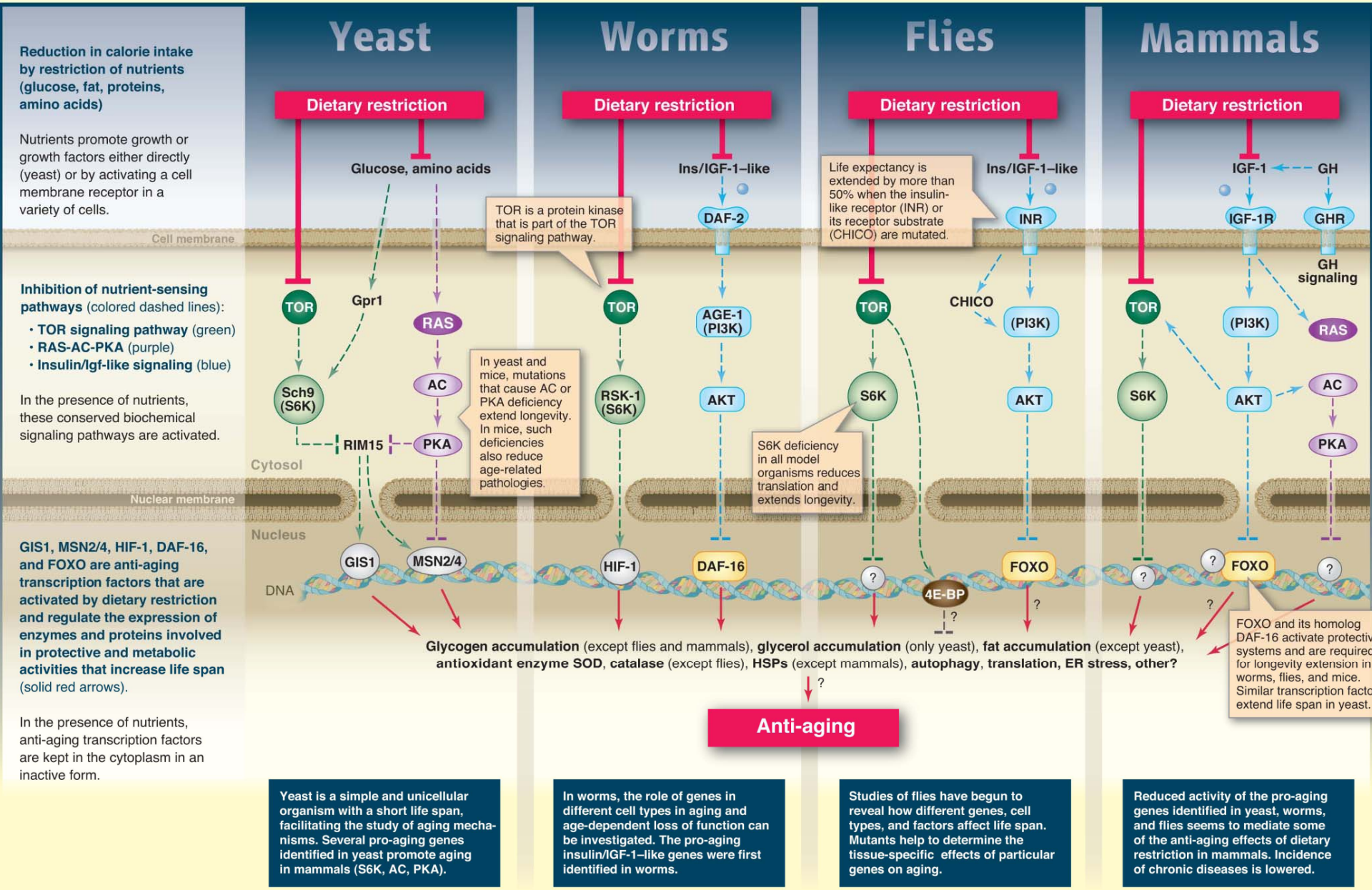
Lower % T2DM

Higher HDL

Low cancer

(Willcox et al. Ann NY Acad Sci 2007)

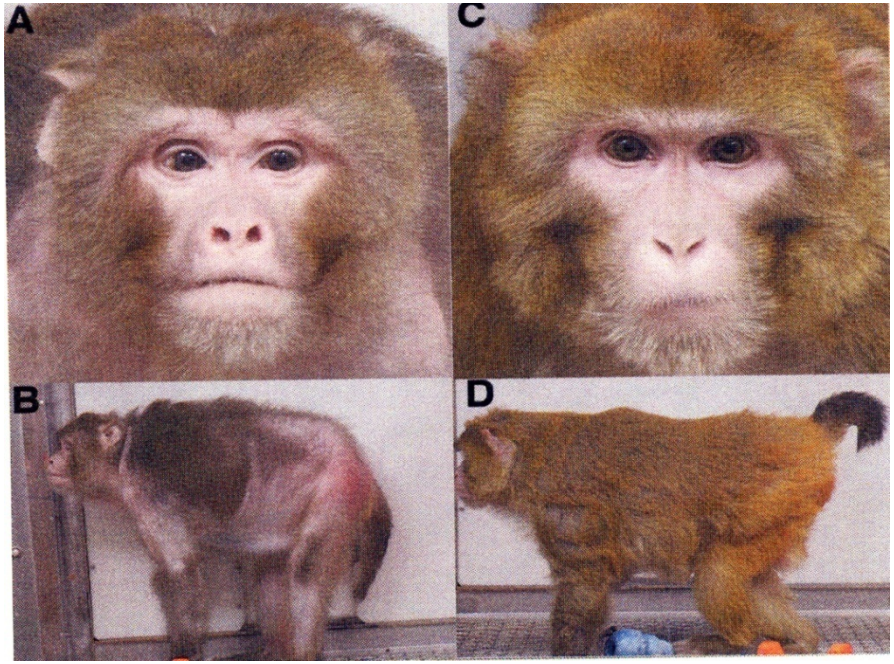
Conserved Nutrient Signaling Pathways Regulating Longevity



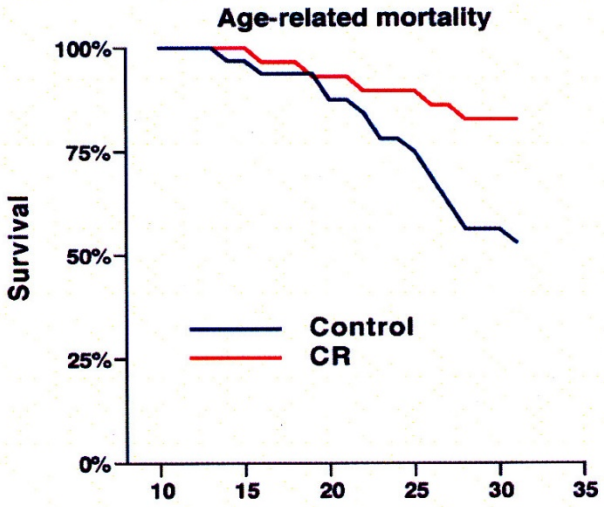
Fontana L et al. Science 2010

Caloric Restriction : Most Powerful Anti-Aging Intervention

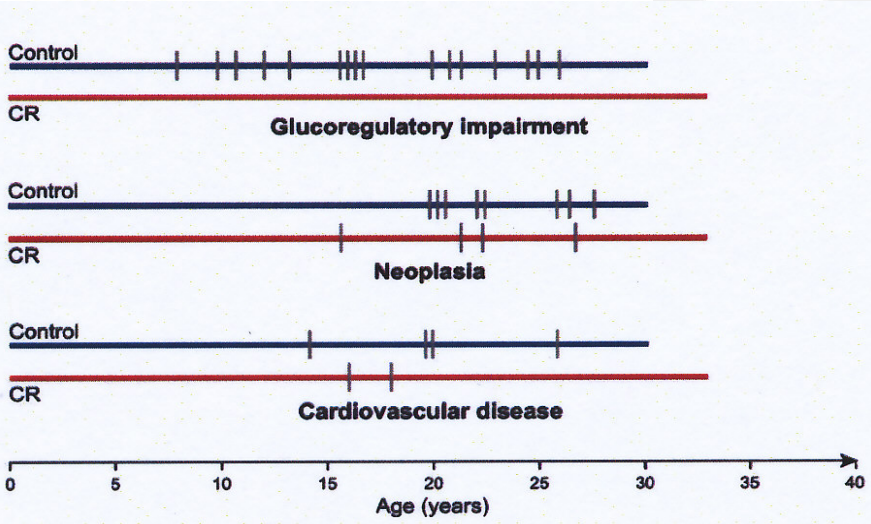
Calorie Restriction (CR) Reduces Cardiovascular and Cancer Mortality by 50% in Non-human Primates



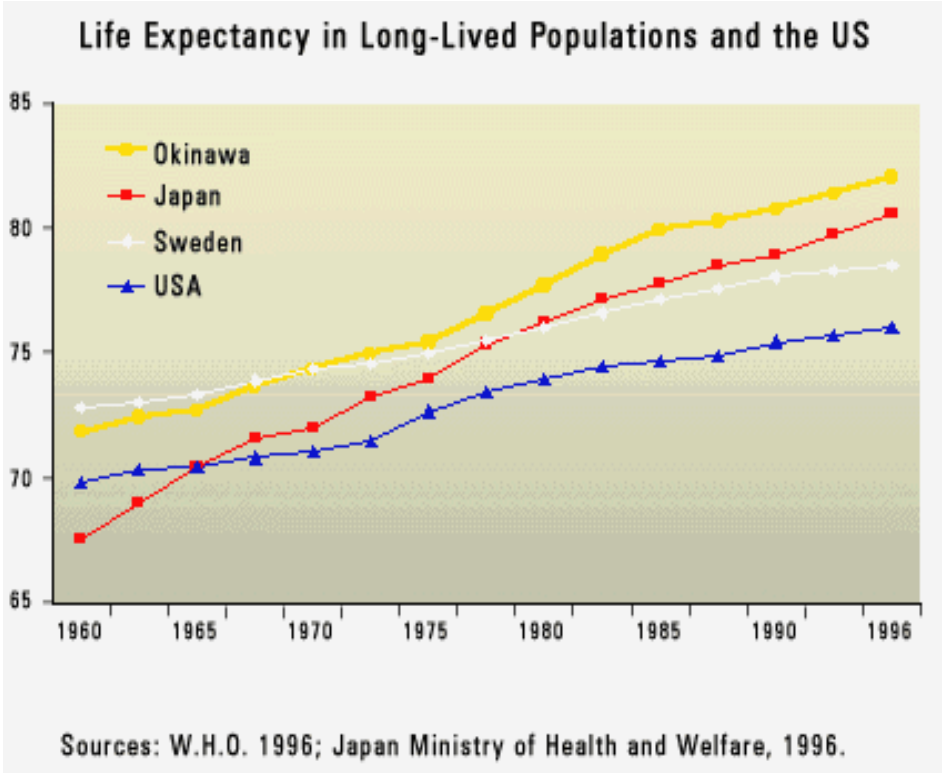
Ad libitum **CR**

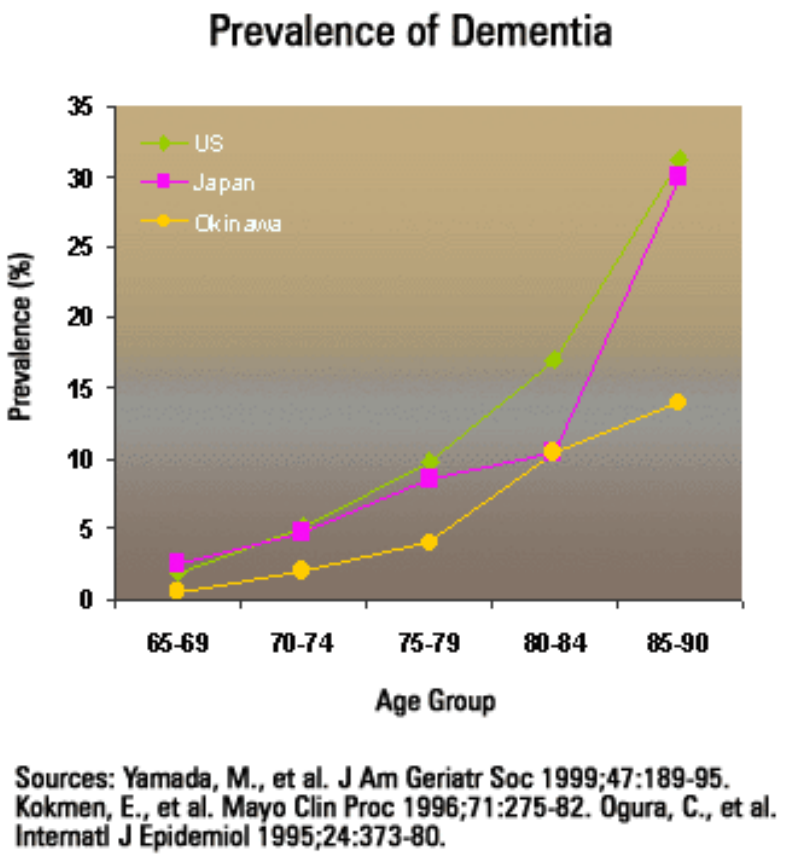


P = 0.03
HR = 3.0

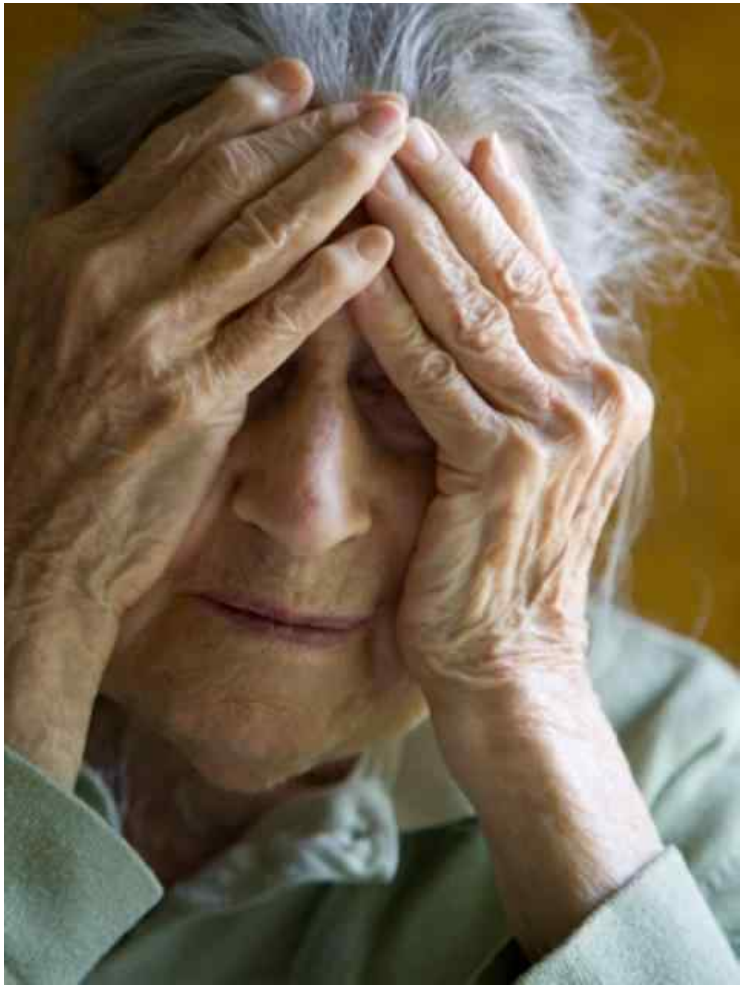


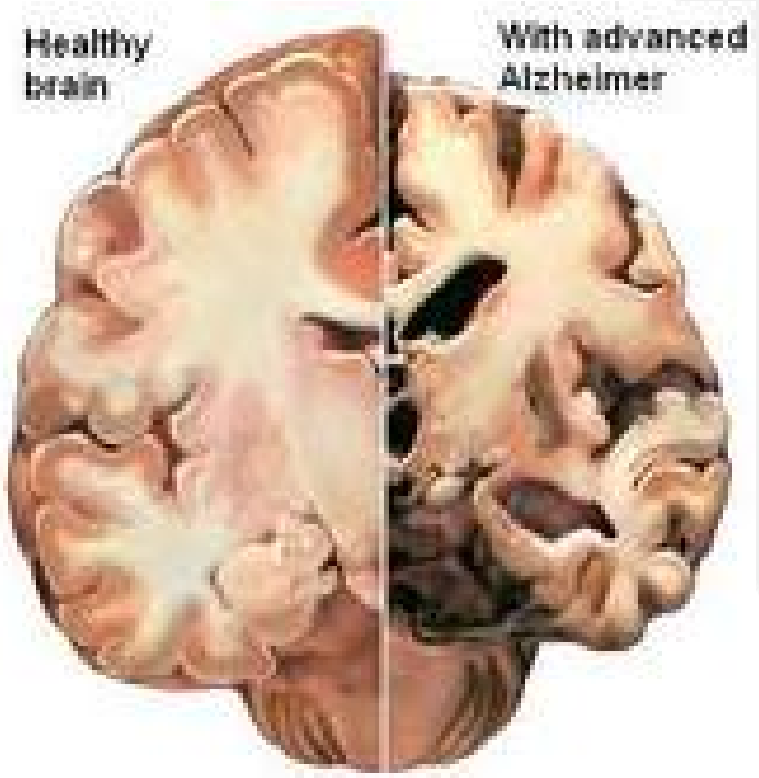
Colman et al. Science 2009





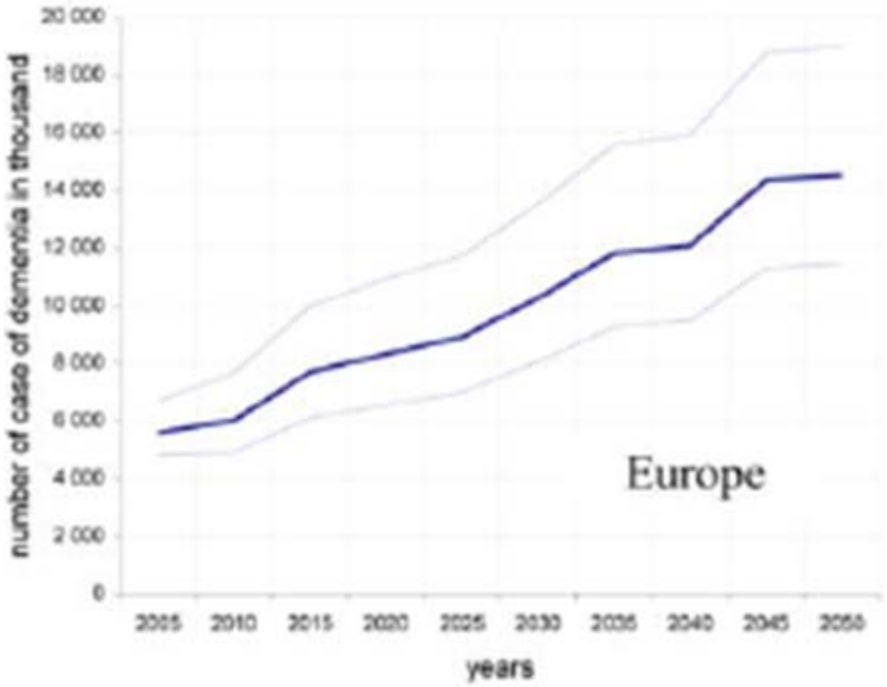
The Okinawa Centenarian Study is based on solid scientific evidences.

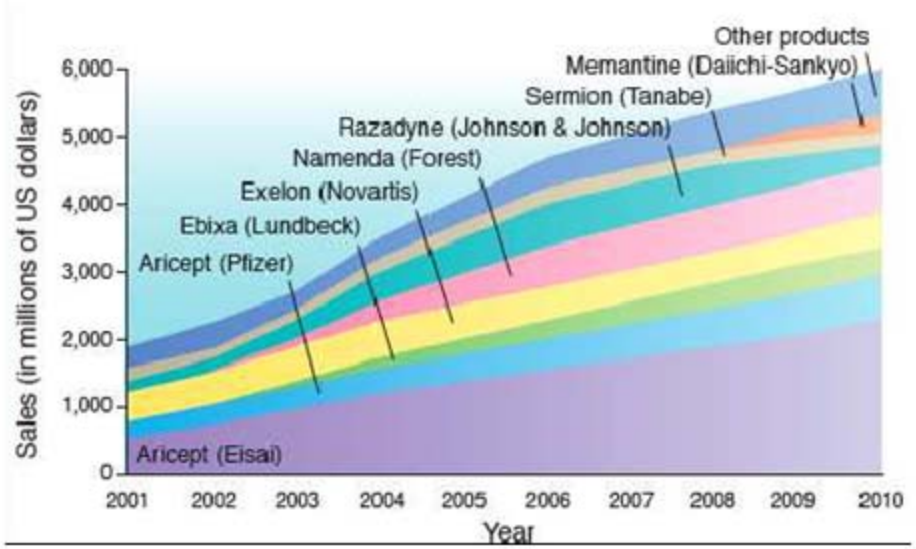



Healthy
brain
With advanced
Alzheimer

How many dementia cases in Europe? Alternative projections and scenarios 2010-2050

Centre épidémiologie et biostatistique INSERM : U897 , Université Victor Segalen - Bordeaux II , FR



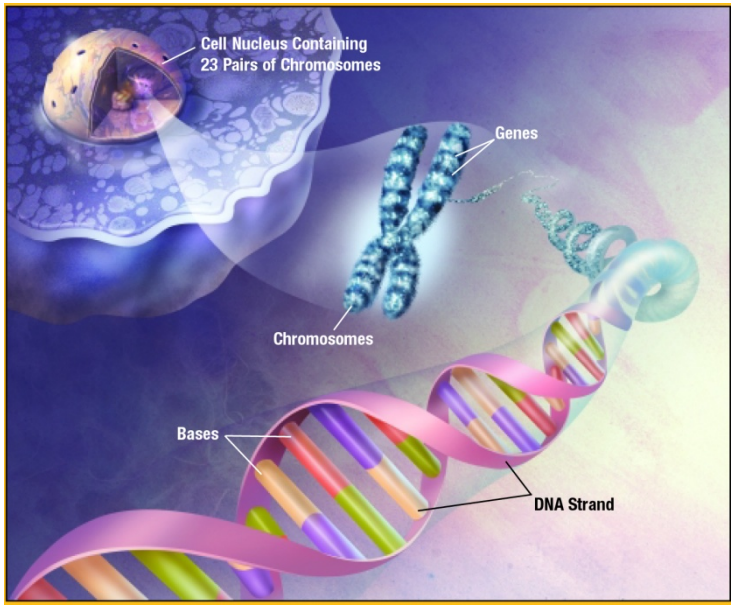


forecast of the economic burden of the dementia

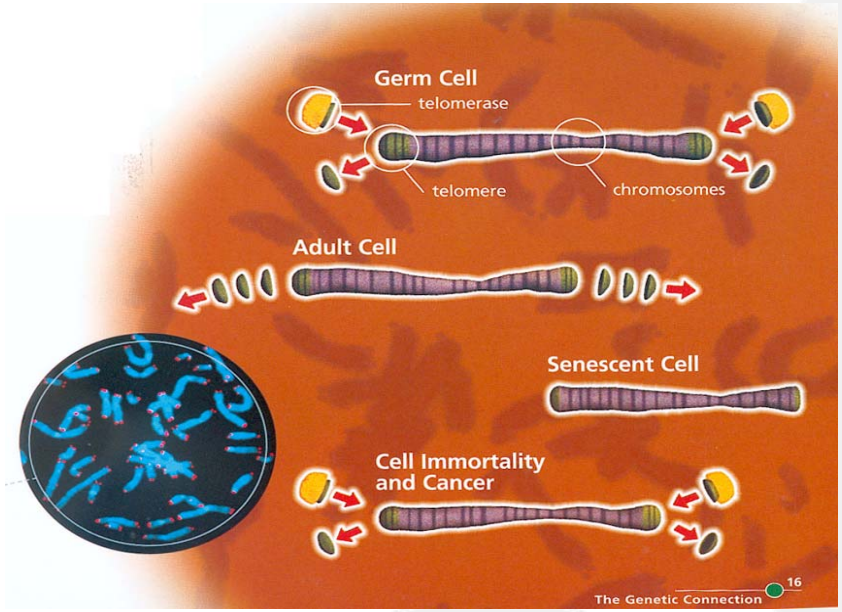
	Total cost (in billion €)	Cost divided by the total population	Cost divided by the active population
2005	16	267 €	591 €
2010	17	277 €	611 €
2015	22	347 €	780 €
2020	23	361 €	
2030	29	438 €	1 043 €
2040	36	523 €	
2050	41	592 €	1 452 €

Why do we age?

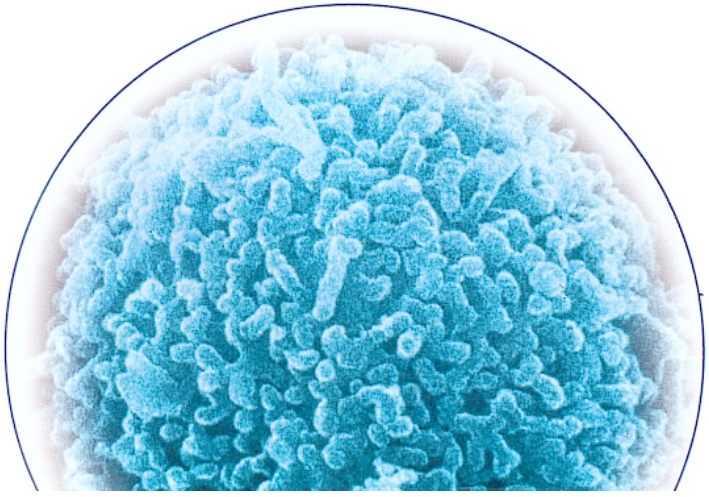
Genetic hypothesis



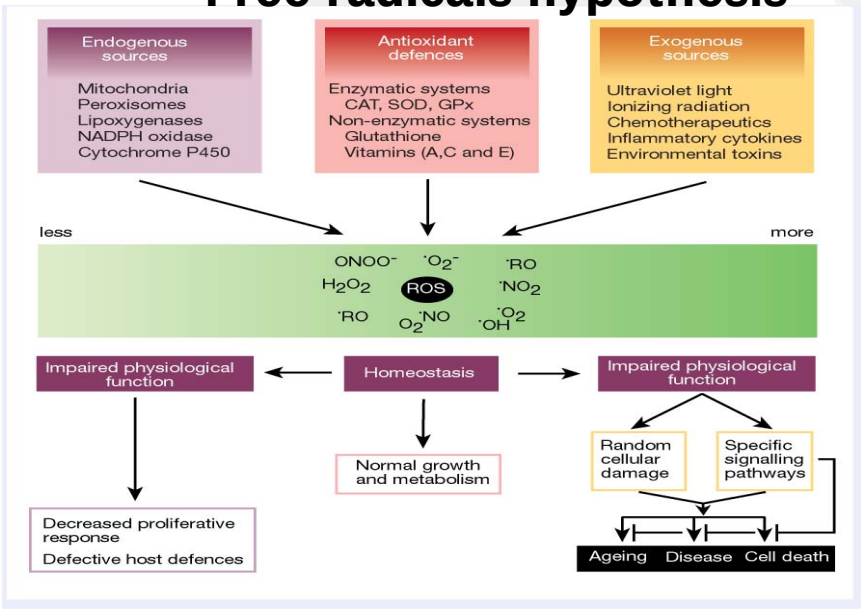
telomers



Inflammaging

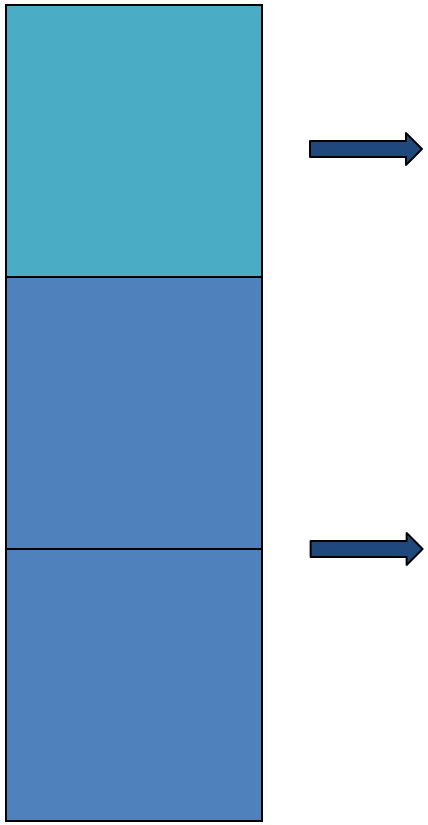


Free radicals hypothesis



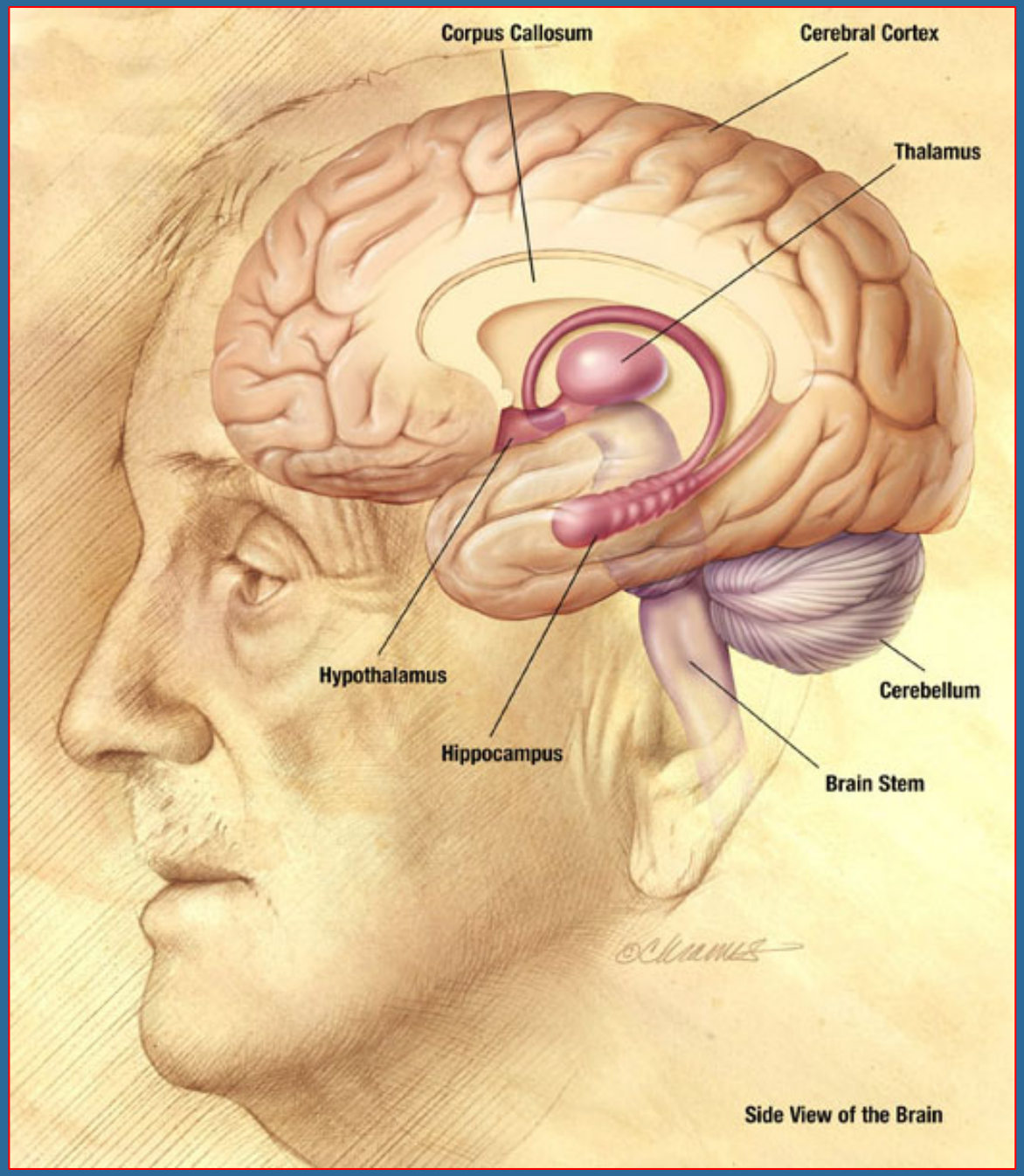
Neuroscience & Brain Health

Risk for Brain Aging



1/3 Genetics

2/3 Lifestyle Choices

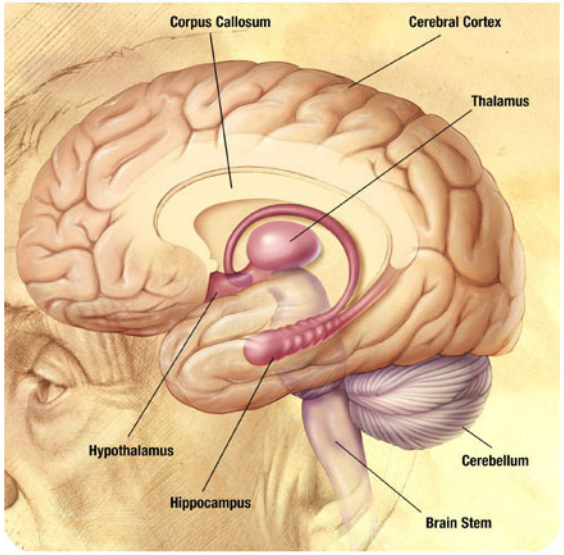


Inside the Human Brain

To understand Alzheimer's disease, it's important to know a bit about the brain…

The Brain's Vital Statistics

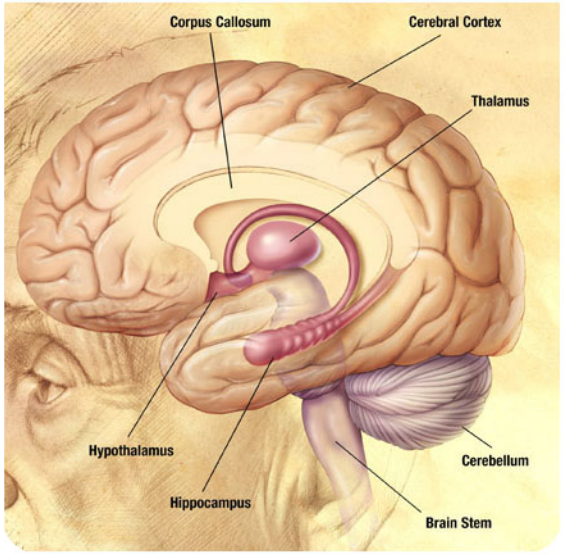
- Adult weight: about 3 pounds
- Adult size: a medium cauliflower
- Number of neurons: 100,000,000,000 (100 billion)
- Number of synapses (the gap between neurons): 100,000,000,000,000 (100 trillion)



Inside the Human Brain

The Three Main Players

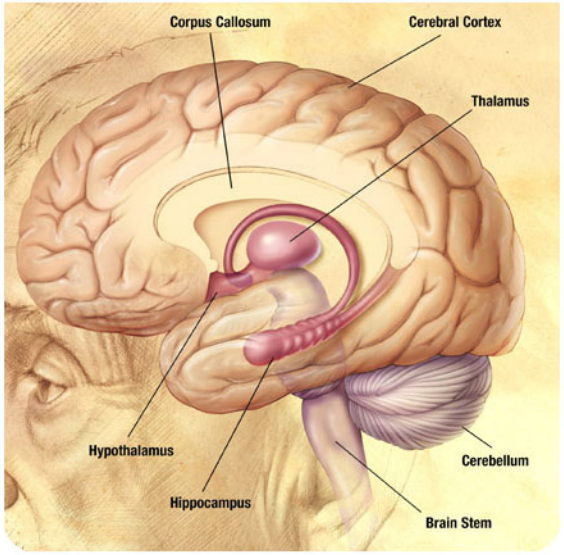
1. Cerebral Hemispheres – where sensory information received from the outside world is processed; this part of the brain controls voluntary movement and regulates conscious thought and mental activity:
   - accounts for 85% of brain's weight
   - consists of two hemispheres connected by the corpus callosum
   - is covered by an outer layer called the cerebral cortex



Inside the Human Brain

The Three Main Players

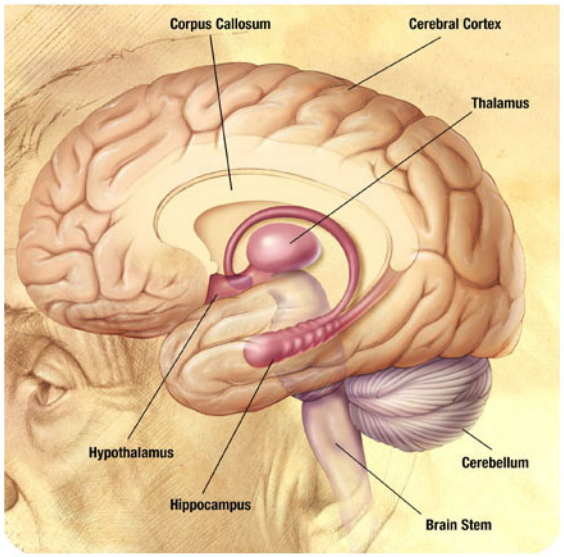
2. Cerebellum – in charge of balance and coordination:
   - takes up about 10% of brain
   - consists of two hemispheres
   - receives information from eyes, ears, and muscles and joints about body's movements and position



Inside the Human Brain

The Three Main Players

3. Brain Stem – connects the spinal cord with the brain
   - relays and receives messages to and from muscles, skin, and other organs
   - controls automatic functions such as heart rate, blood pressure, and breathing



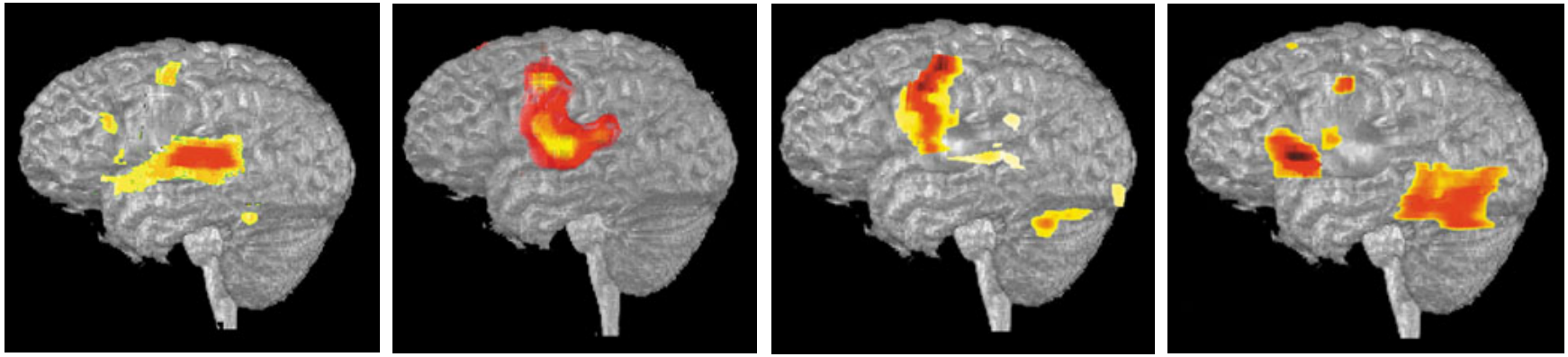
Inside the Human Brain

Other Crucial Parts

- Hippocampus: where short-term memories are converted to long-term memories
- Thalamus: receives sensory and limbic information and sends to cerebral cortex
- Hypothalamus: monitors certain activities and controls body's internal clock
- Limbic system: controls emotions and instinctive behavior (includes the hippocampus and parts of the cortex)

Inside the Human Brain

The Brain in Action



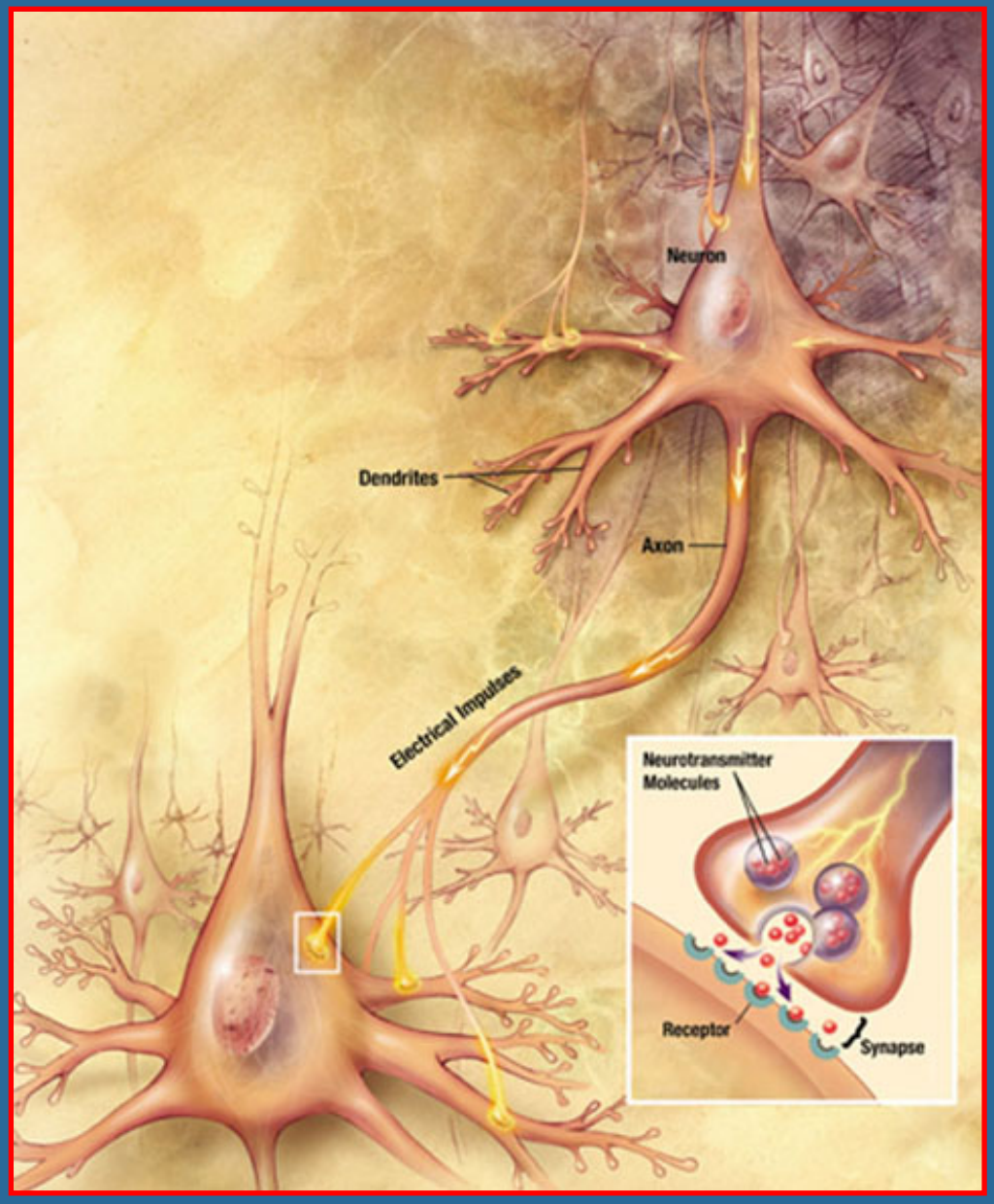
Hearing Words Speaking Words Seeing Words Thinking about Words

Different mental activities take place in different parts of the brain. Positron emission tomography (PET) scans can measure this activity. Chemicals tagged with a tracer “light up” activated regions shown in red and yellow.

Inside the Human Brain

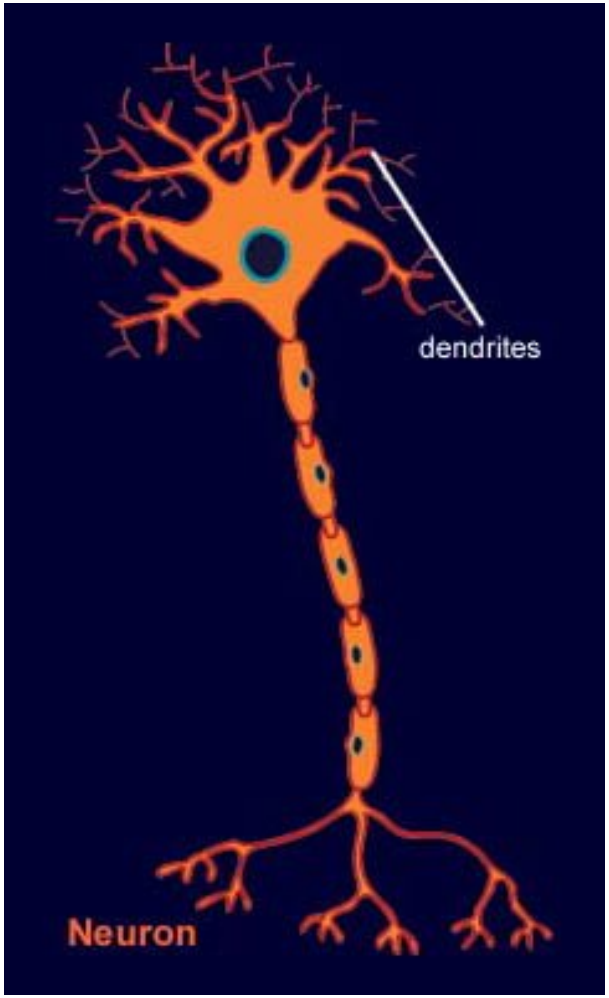
Neurons

- The brain has billions of neurons, each with an axon and many dendrites.
- To stay healthy, neurons must communicate with each other, carry out metabolism, and repair themselves.
- AD disrupts all three of these essential jobs.



Dendrites

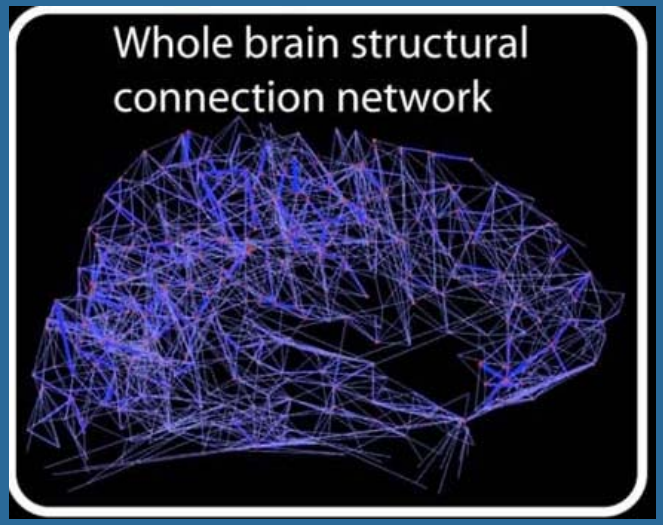
- Treelike extensions of a neuron.
- Most neurons have multiple dendrites: short & typically highly branched.
- Dendrites are specialized for receiving information
- They form synaptic contacts with the terminals of other nerve cells to allow nerve impulses (information) to be transmitted.



Brain’s plasticity = The key to adaptation

- Plastic derives from the Greek word meaning "molded" or "formed" and could be described as the tendency of the brain to shape itself according to experience

- Plasticity networks the brain, gives it cognition and memory, as well as fluidity and adaptability



Hagmann et al., 2008

Synaptic development:

# of synapses in the cerebral cortex peaks within the first few years, declines by about 1/3 between early childhood & adolescence

- **Brain size:**
  - a newborn's brain is only about one-quarter the size of an adult's;
  - about 80 percent of adult size by three years of age and 90 percent by age five
  - growth is largely due to changes in individual neurons, structured much like trees
- **Speed of neural processing:**
  - newborn's brain slower than an adult's, transmitting information less efficiently
  - increases dramatically during infancy & childhood, maximum at about age 15

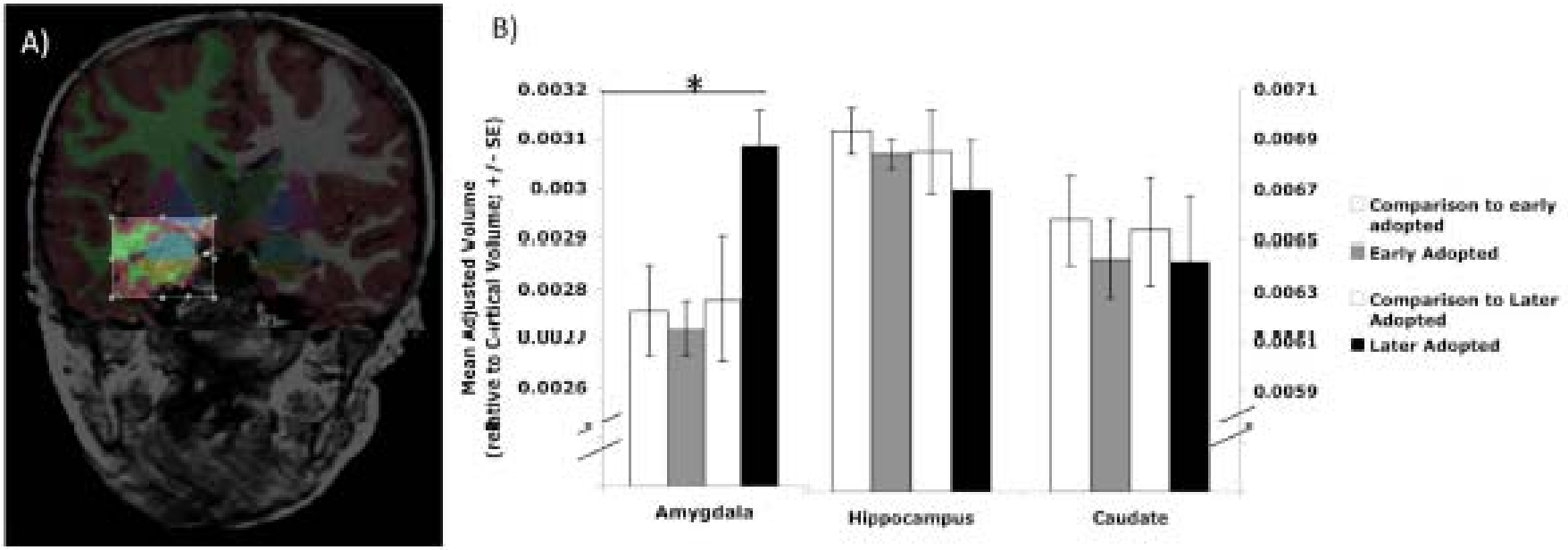
From Zero to Three, National Center for Infants, Toddlers & Families

- Does experience change the actual structure of the brain?
  - Brain development is "activity-dependent"
  - Every experience--whether it is seeing one's first rainbow, riding a bicycle, reading a book, sharing a joke--excites certain neural circuits and leaves others inactive
  - As neuroscientists sometimes say, "Cells that fire together, wire together."

Nat Neurosci. ; 15(5): 689–695. doi:10.1038/nn.3093.

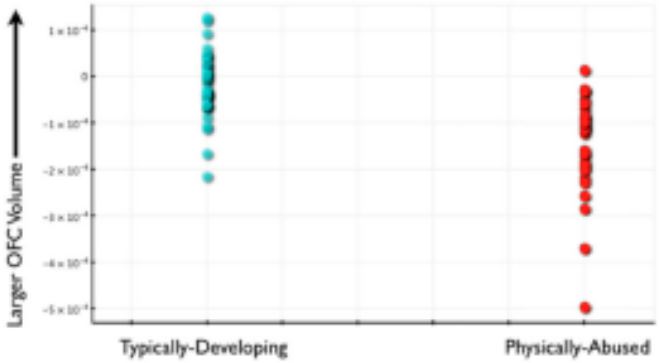
Social influences on neuroplasticity: Stress and interventions to promote well-being

Richard J. Davidson and **Bruce S. McEwen**

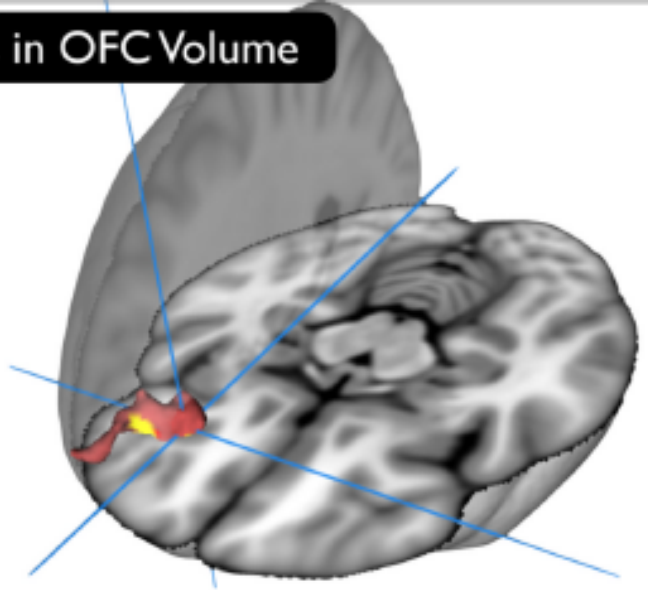


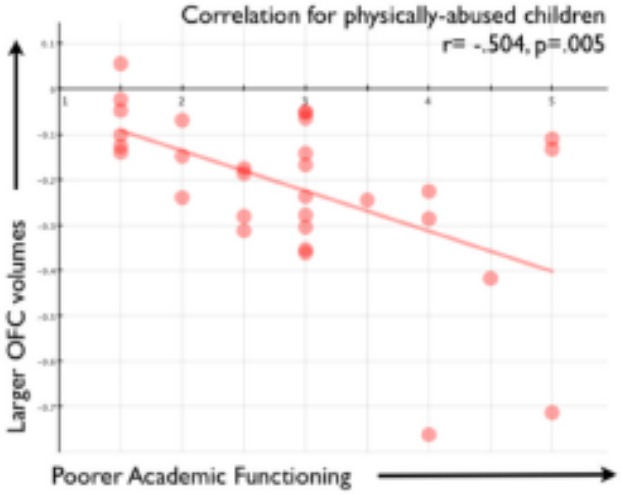
Anatomically segmented amygdala volumes are larger in later-adopted post-institutionalized children. a. Anatomical segmentation of the amygdala; b. later-adopted post-institutionalized children show larger amygdala volume compared with both early adopted children and with typically developing controls. No differences among groups were found in hippocampus or caudate. Asterisk indicates that the later adopted group exhibits significantly larger amygdala volume compared with each of the comparison groups.

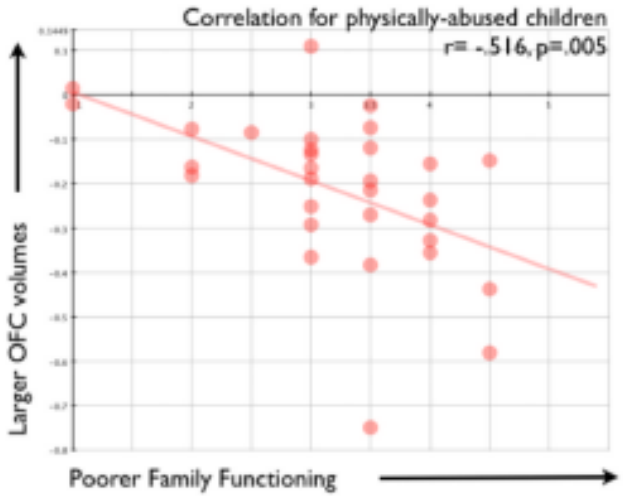
Group Differences in OFC Volume



Group Difference

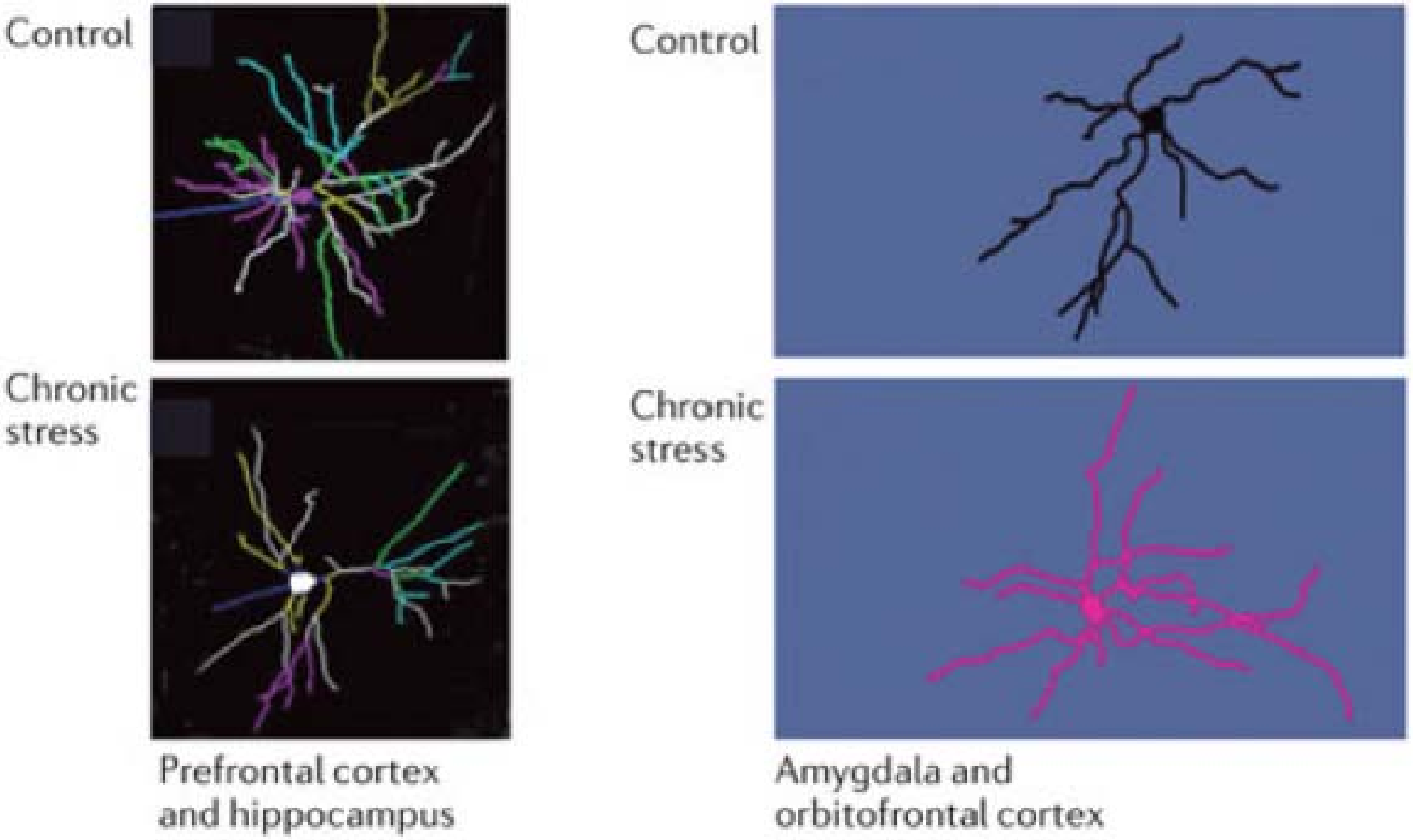




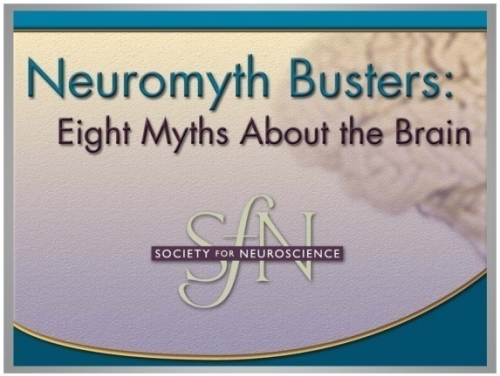


Brain - Behavior Correlations

Physically abused children show alterations in orbitofrontal volume compared with typically developing children and volume shrinkage in this region is related to measures of family stress.



Chronic stress causes neurons to shrink or grow but not necessarily to die. Representation of the chronic stress effects detected in animal models on growth or retraction of dendrites in the basolateral amygdala and orbitofrontal cortex (growth) and in the CA3 hippocampus, dentate gyrus and medial prefrontal cortex (shrinkage), as described in the text. These effects are largely reversible in young adult animals, although aging appears to compromise resilience and therefore at least in medial prefrontal cortex recovery.

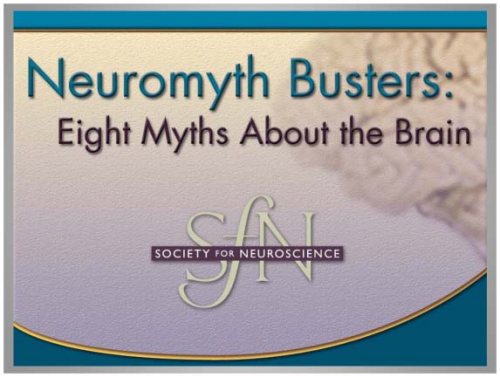


Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

1. we have 5 senses
2. "the primitive part of the brain"
3. the rational vs the emotional brain
4. the brain as a camcorder
5. new neurons doesn't appear in adult brain
6. genes vs environment effect
7. mental problems as effect of childhood traumatic memories

8. The most important myth is that consciousness dictates our decisions and actions

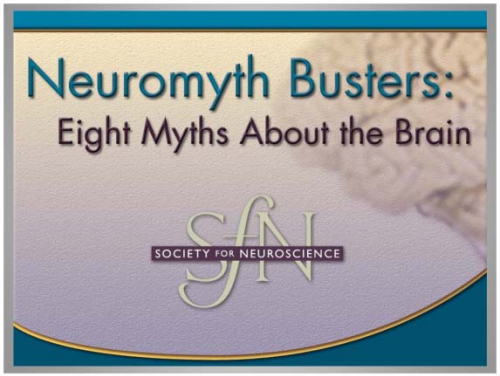


Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

1. we have 5 senses

Actualy we have 13 (discovered until now): sight (ophthalmoception), hearing (audioception), taste (gustaoception), smell (olfacoception or olfacception), touch (tactioception) , feromonal sense, blue light sense, temperature (thermoception), kinesthetic sense (proprioception), pain (nociception), balance (equilibrioception), visceral sense (the perception of internal organs), chemical sense (e.g. the different chemoreceptors for detecting salt and carbon dioxide concentrations in the blood)

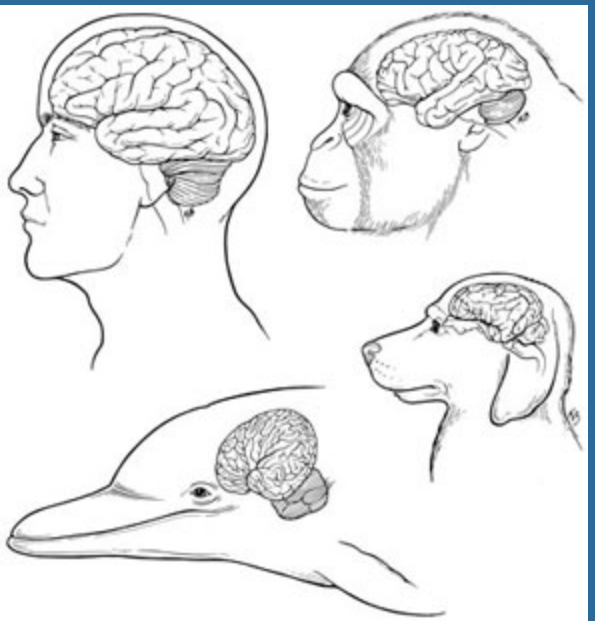


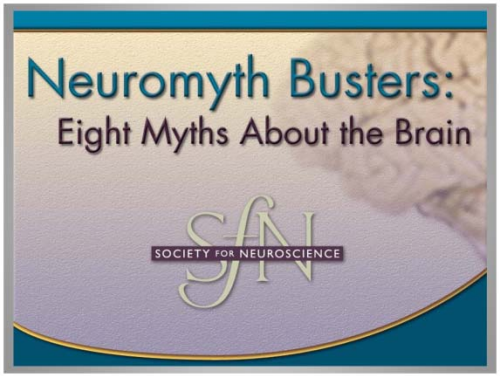
Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

2. "the primitive part of the brain"

Human brain is similar in its organization and functions with all the mammals brain. Only some parts are more evolved but these parts exist also in mammals brain.



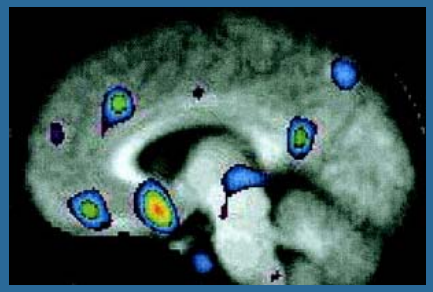
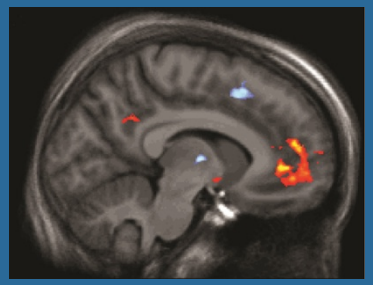
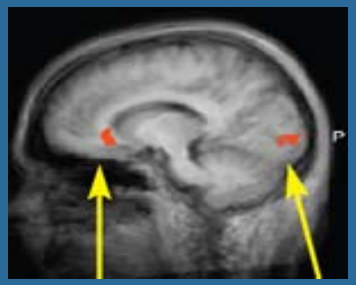
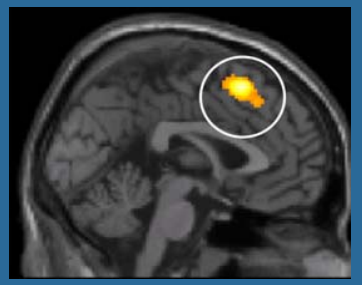
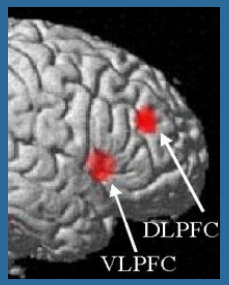


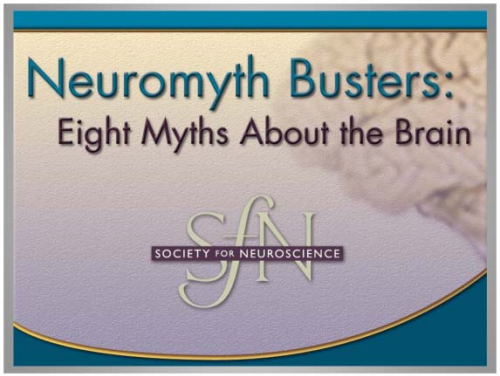
Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

3. the rational/the emotional brain

Emotions appear almost in all parts of the brain. Differences consist only in timing and type of context/action.



Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

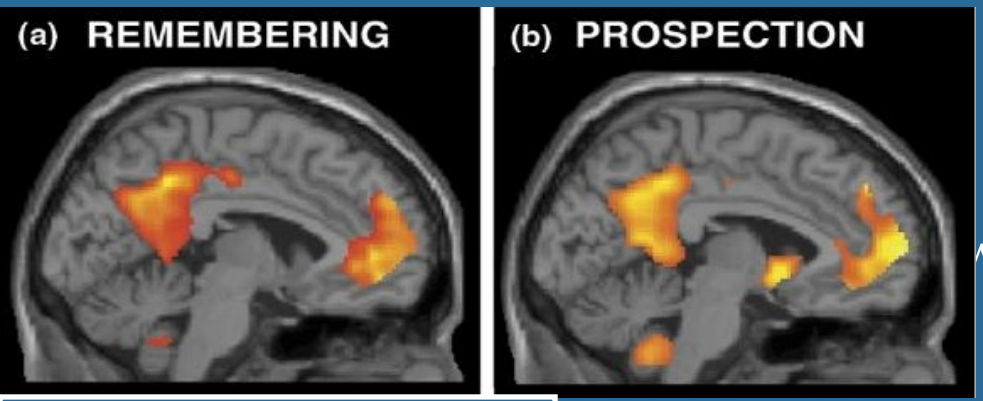
4. the brain as a camcorder

The memories are not "replayed from the tape" when they are remembered.

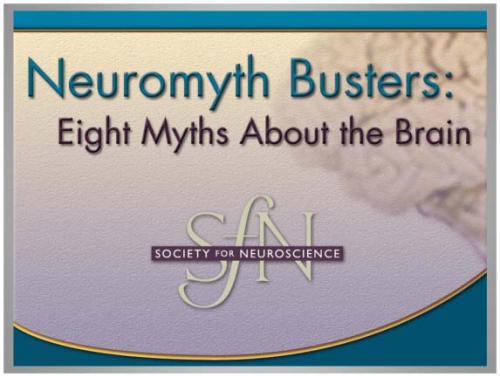
The information stored in the brain is actually reconstructed and updated every time when we remember.

Every time when we do this that memory could become a new memory incorporating new information related with it.

We can learn only things related what we already know



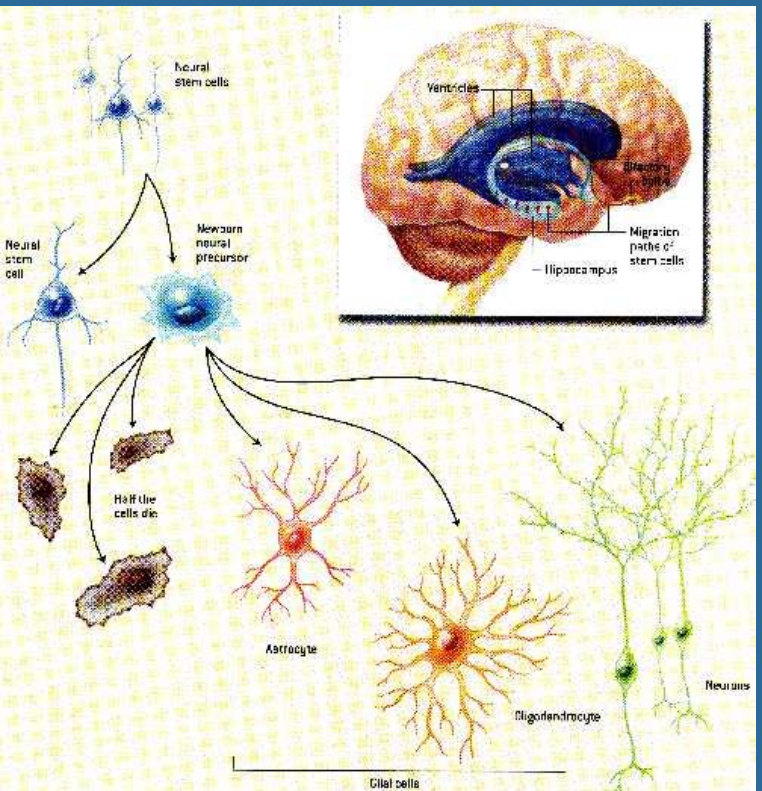
Schacter & Addis, 2007



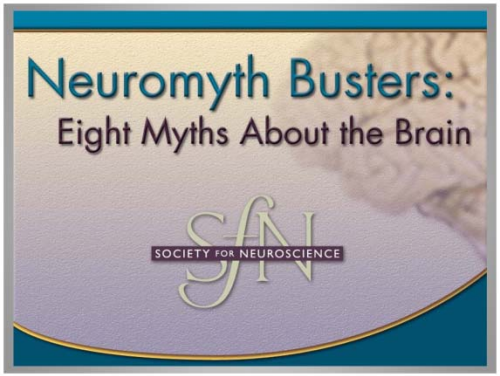
Neuromyths

= common misconceptions about brain mechanisms, which are taken for granted in today's society

5. new neurons doesn't appear in adult brain



The brain generates new neurons during the entire life. These new neurons are essential for learning and coping with stress.

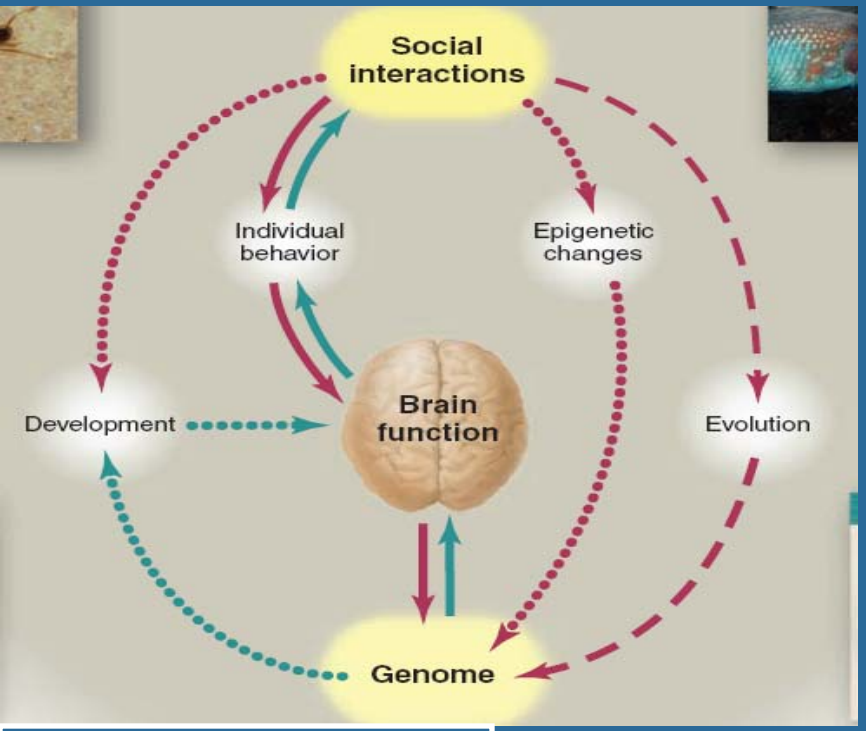


Neuromyths

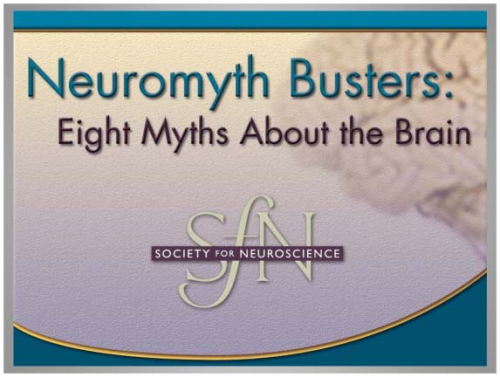
= common misconceptions about brain mechanisms, which are taken for granted in today's society

6. genes vs environment effect

The environment acts upon our brain by modifying the brain's genes activity (some genes are turned on some are turned off). Learning and stress are actually examples of genetic effects– or more precisely "epigenetic effects".



Robinson et al. 2008



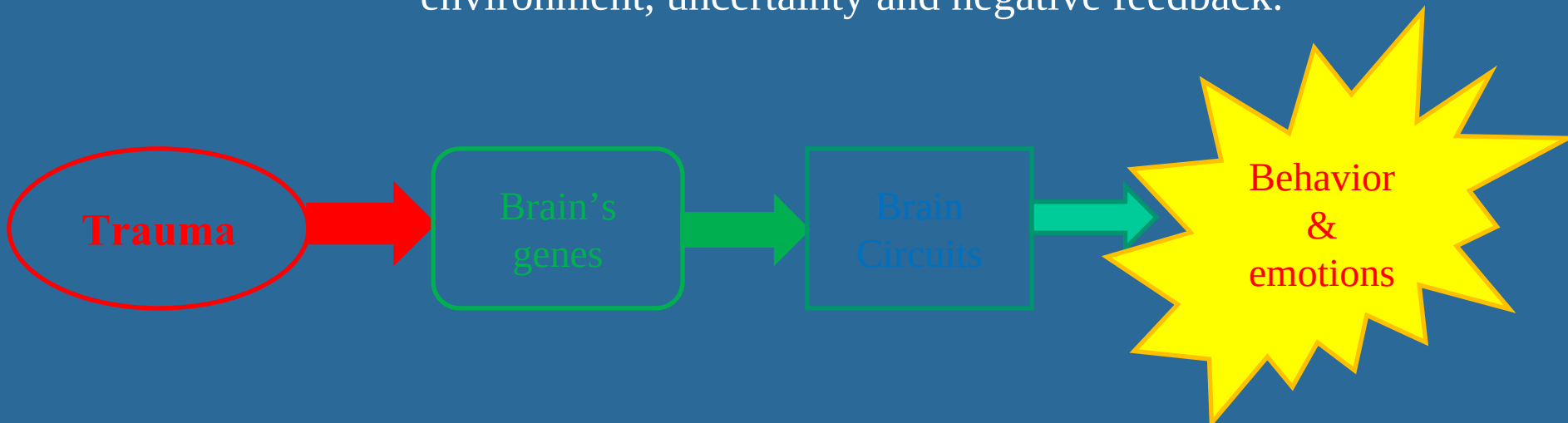
Neuromyths

= common misconceptions about brain mechanisms,

which are taken for granted in today's society

7. mental problems as effect of childhood traumatic memories

Adult mental problems are frequently rooted in childhood traumatic events but in most of the cases not the memory of the event is the cause of the problem. Traumatic events exert epigenetic effects upon the brain's genes responsible for the circuits involved in adapting to novelty, fast changing environment, uncertainty and negative feedback.



“The tiger and the monkey” metaphor describing the relationship between unconscious and conscious mind – after Dennis Overbye (2007)

Dragos Cirneci

Have we Made Conceptual Progress on Cognitive Aging Over the Past 50 years?

THEN:

1) Old = Senile

2) Aging = extensive cell loss

3) Brain aging = passive deterioration

4) Unknown genetic risks for cognitive aging

5) Several lifestyle risks for cognitive aging

NOW:

1) AD is not inevitable

2) Minimal/selective cell loss

3) Brain aging = continual adaptation

4) Many complex and interacting factors for longevity & cognition

5) Many lifestyle factors interact to modulate cognitive aging

NOW:

1) AD is not inevitable
   - but memory does change
   - centenarians/supercenentarians can be dementia free
   - you do not “die of aging”, aging is not a disease
2) Minimal/selective cell loss
3) Brain aging = continual adaptation
4) Many complex and interacting factors for longevity & cognition
5) Many lifestyle factors interact to modulate cognitive aging

NOW:

1) AD is not inevitable

2) Minimal/selective cell loss

while there is cell loss, larger changes occur in:

- molecular cascades, synapse #s, plasticity
- actual neural circuits recruited and used

3) Brain aging = continual adaptation

4) Many complex and interacting factors for longevity & cognition

5) Many lifestyle factors interact to modulate cognitive aging

NOW:

1) AD is not inevitable

2) Minimal/selective cell loss

3) Brain aging = continual adaptation

rearrangement of function (compensation?) at molecular, cellular, network and behavioral levels

4) Many complex and interacting factors for longevity & cognition

5) Many lifestyle factors interact to modulate cognitive aging

NOW:

1) AD is not inevitable

2) Minimal/selective cell loss

3) Brain aging = continual adaptation

4) Many complex and interacting factors for longevity and cognition – among them:

- KIBRA
- APOE
- COMT
- BDNF
- Insulin
- HDL
- Epigenetic regulatory factors

5) Many lifestyle factors interact to modulate cognitive aging

NOW:

1) AD is not inevitable

2) Minimal/selective cell loss

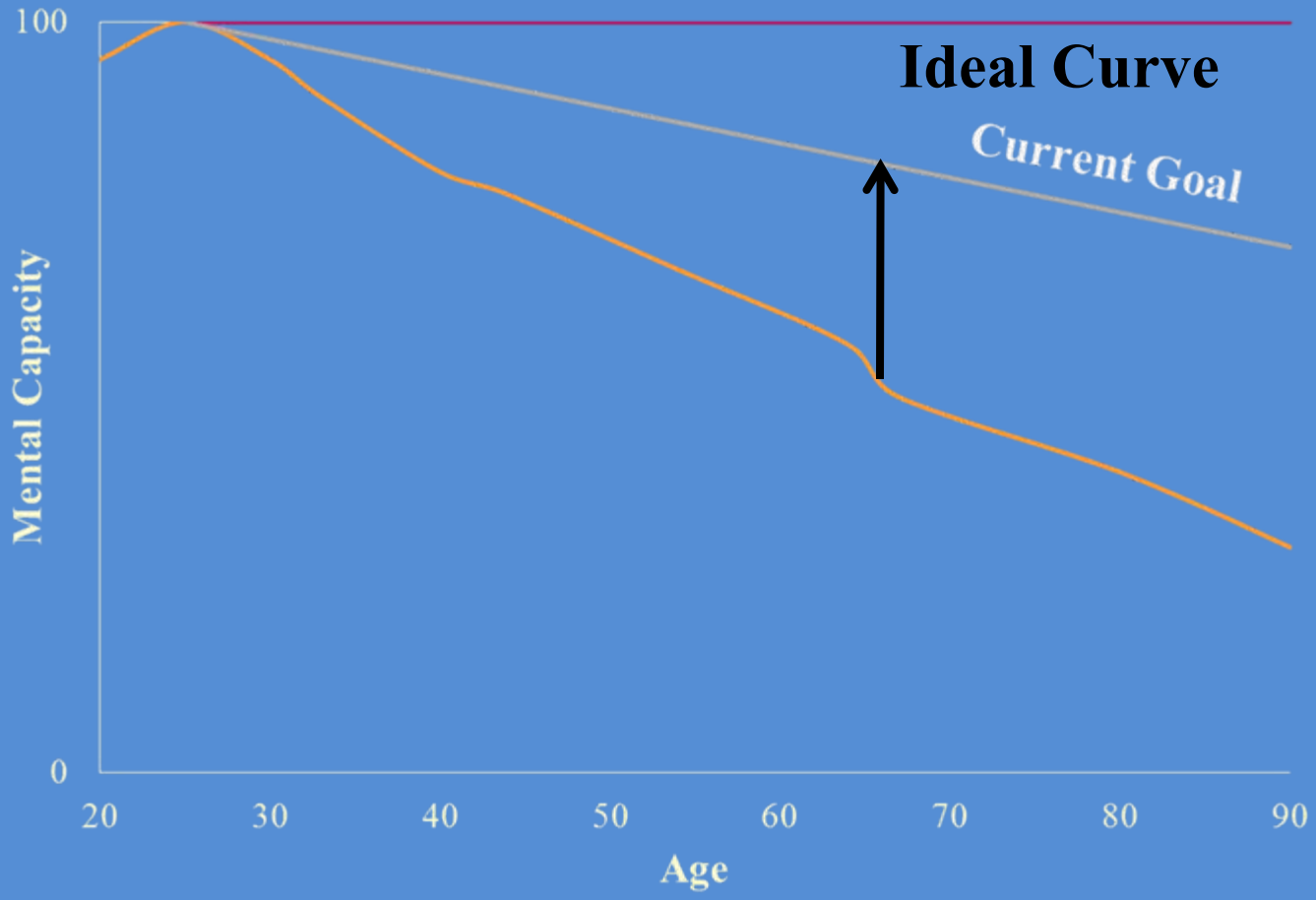
3) Brain aging = continual adaptation

4) Many complex and interacting factors for longevity and cognition

5) Many lifestyle and biomarkers interact to modulate cognitive aging, among them:

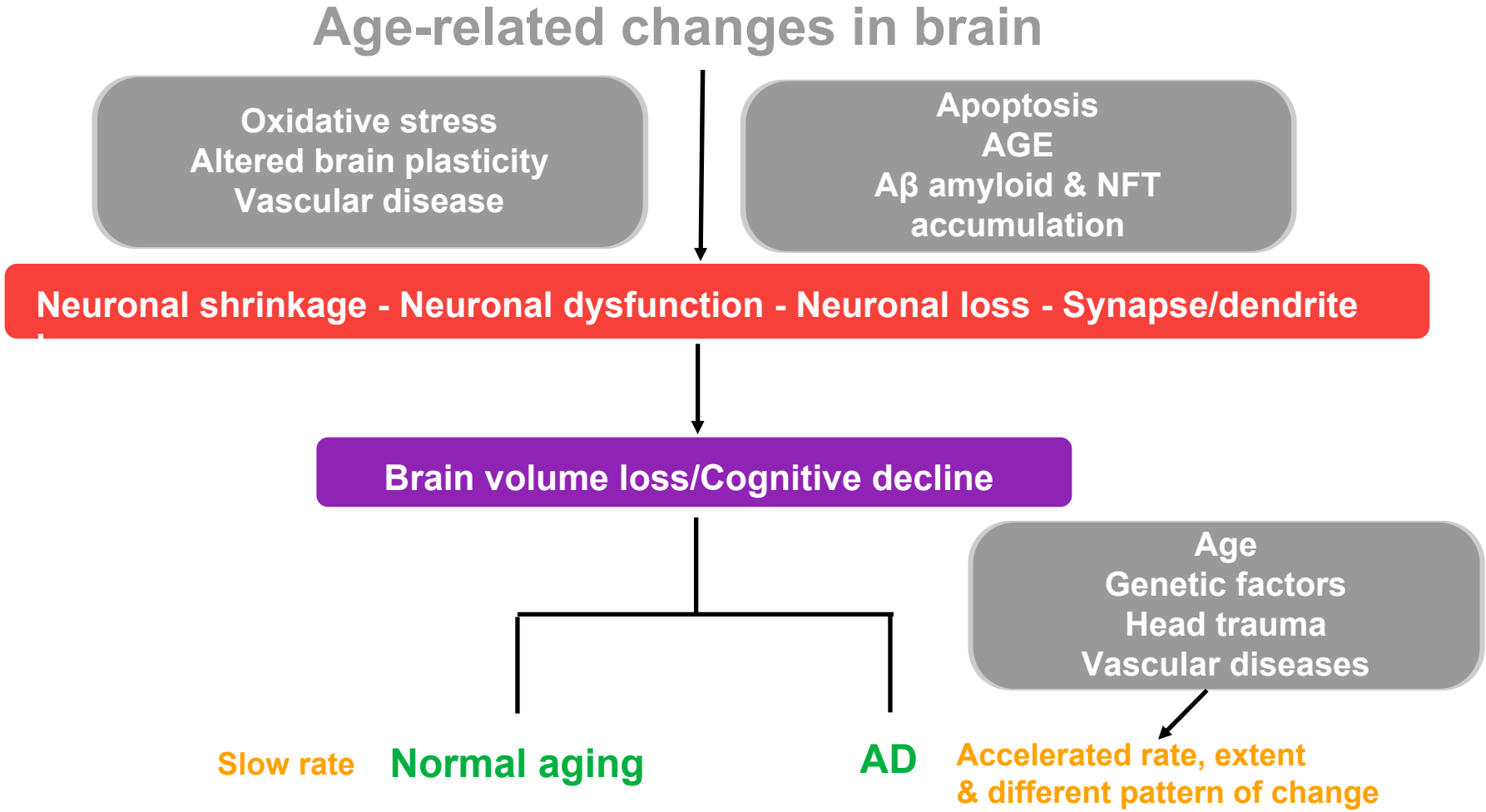
- exercise
- stress
- vascular state
- metabolic syndrome factors
- inflammation

Mind the Gap



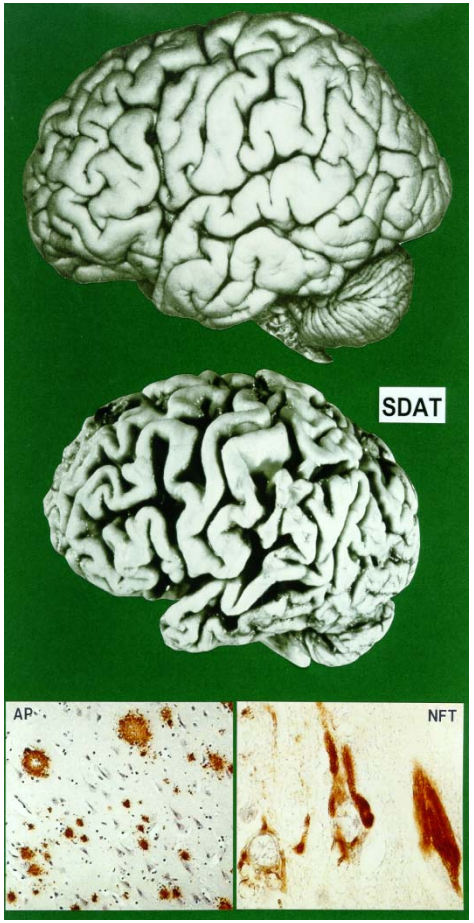
Chapman, Anand, Bartz 2010

Common Neurobiological changes in the Aging Brain and Alzheimer's Disease (AD)



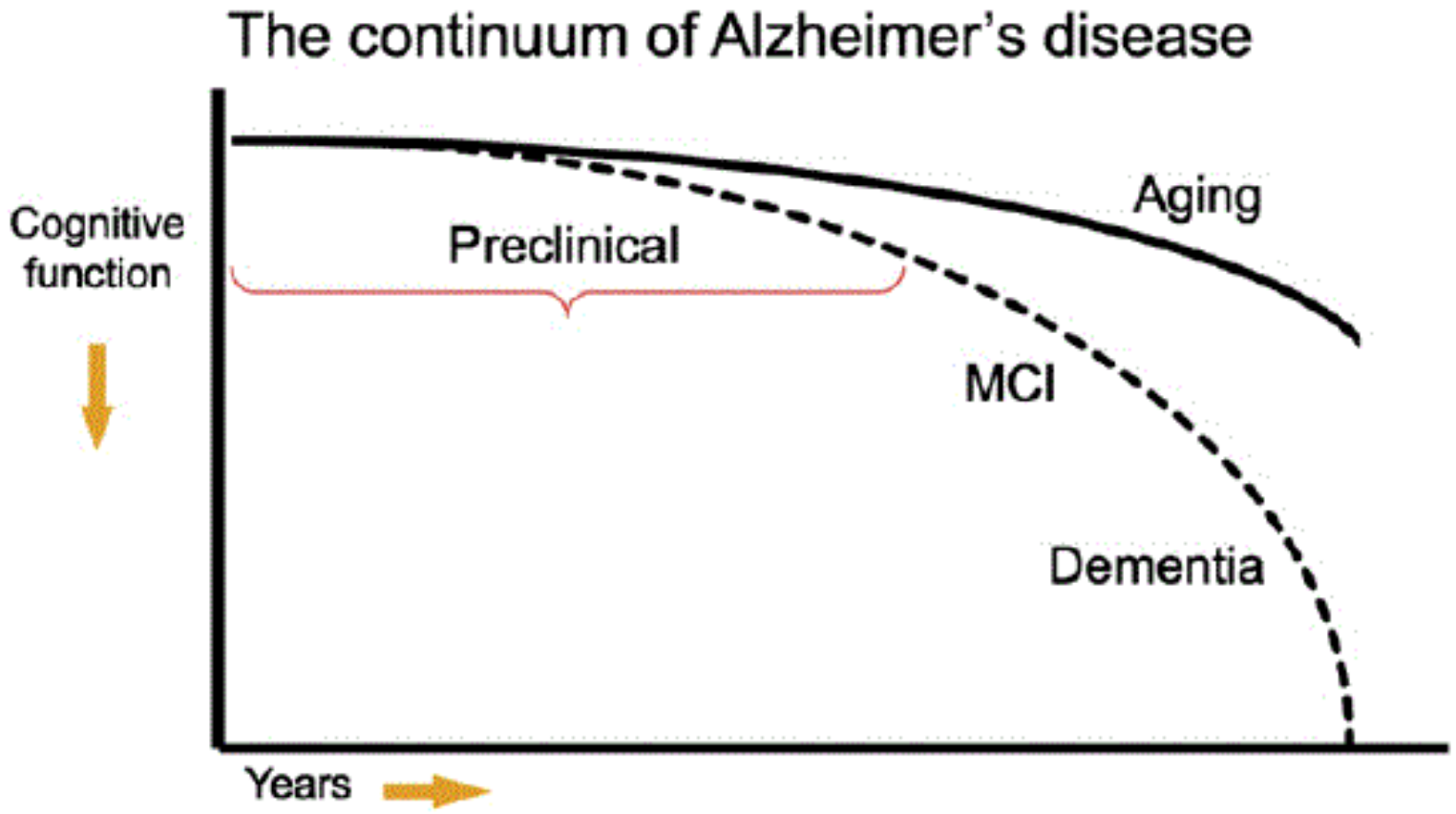
Role of Aβ Amyloid in Cognitive Decline in the Aging Brain and AD

- Accumulation of Aβ increases with aging and AD[1,2]
- Aβ distribution in aging brain is similar to that of AD[3]
- Association between Aβ accumulation and depletion of cholinergic neurons and impaired memory in non-demented individuals[4,5]



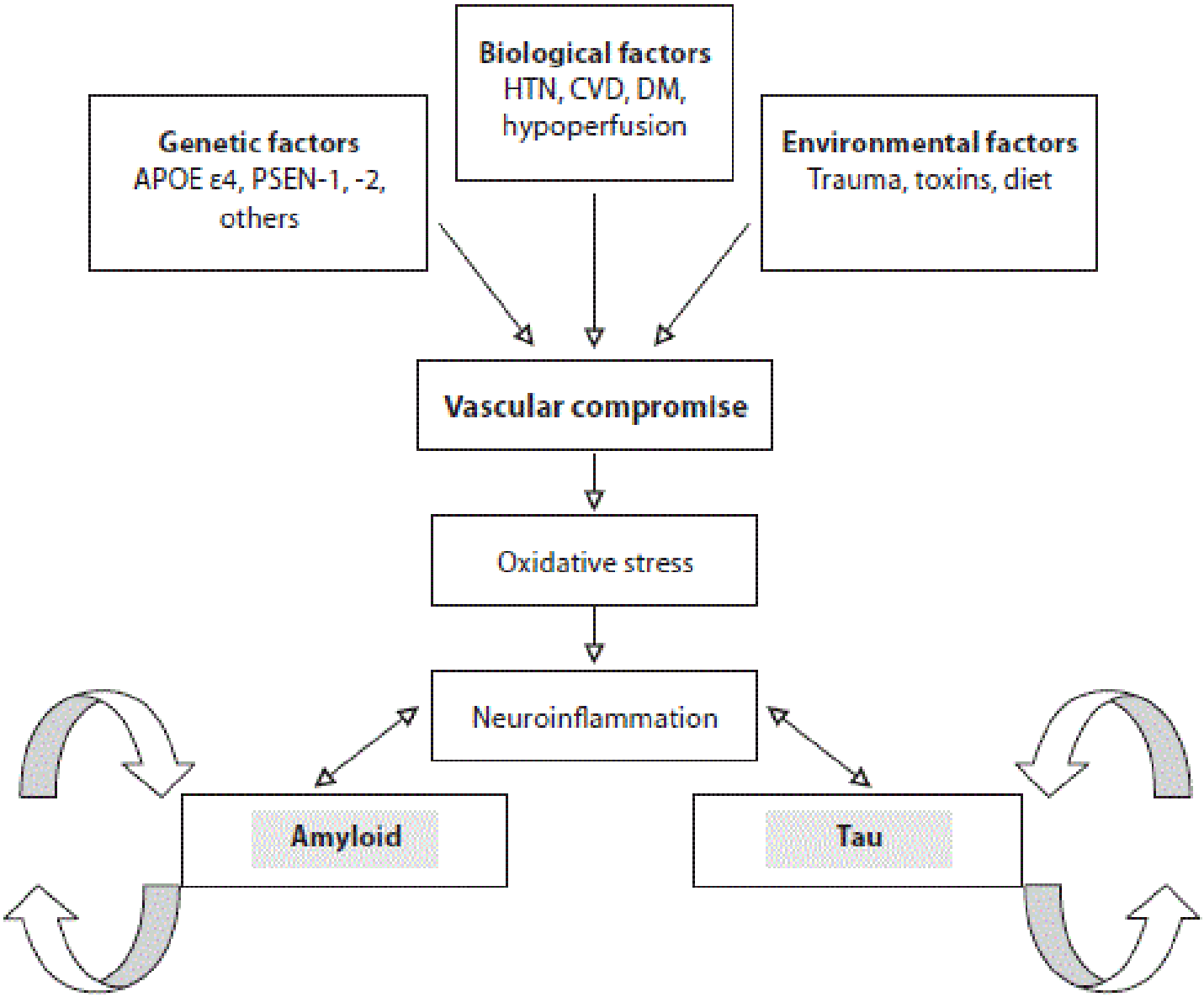
[1] Davis et al. J. Neuropathol. Exp. Neuro. 1999; 58; 376-88.
[2] Schmitt et al. Neurology 2000; 55; 370-76.
[3] Arriagada et al Neurology 2002: 42: 1681-88.
[4] Beach et al. Acta Neuropathol. (Berl) 1997; 93: 146-53.
[5] Pike et al. Brain 2007; 130: 2837-44

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup



Common Mediators of Neurodegeneraton

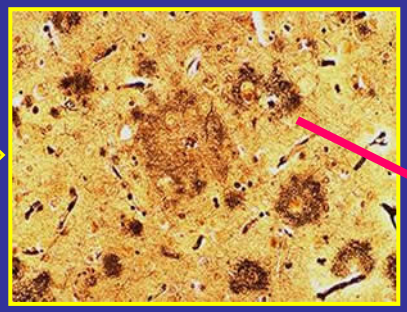
- Reactive species and oxidative/nitrative damage-which offending species?
- Mitochondrial dysfunction
- Proteosomal dysfunction
- Abnormal protein aggregates
- Inflammation


Biological factors
HTN, CVD, DM, hypoperfusion
Genetic factors
APOE ε4, PSEN-1, -2, others
Environmental factors
Trauma, toxins, diet
Vascular compromise
Oxidative stress
Neuroinflammation
Amyloid
Tau

NEURO-PATHOLOGICAL HALLMARKS OF AD

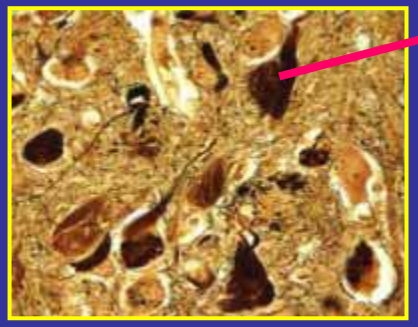
1. Amyloid plaques

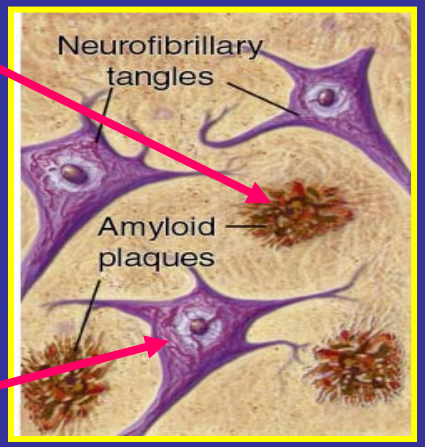
Consist of a core of amyloid-β peptide deposits, dystrophic neurites, activated microglia and reactive astrocytes



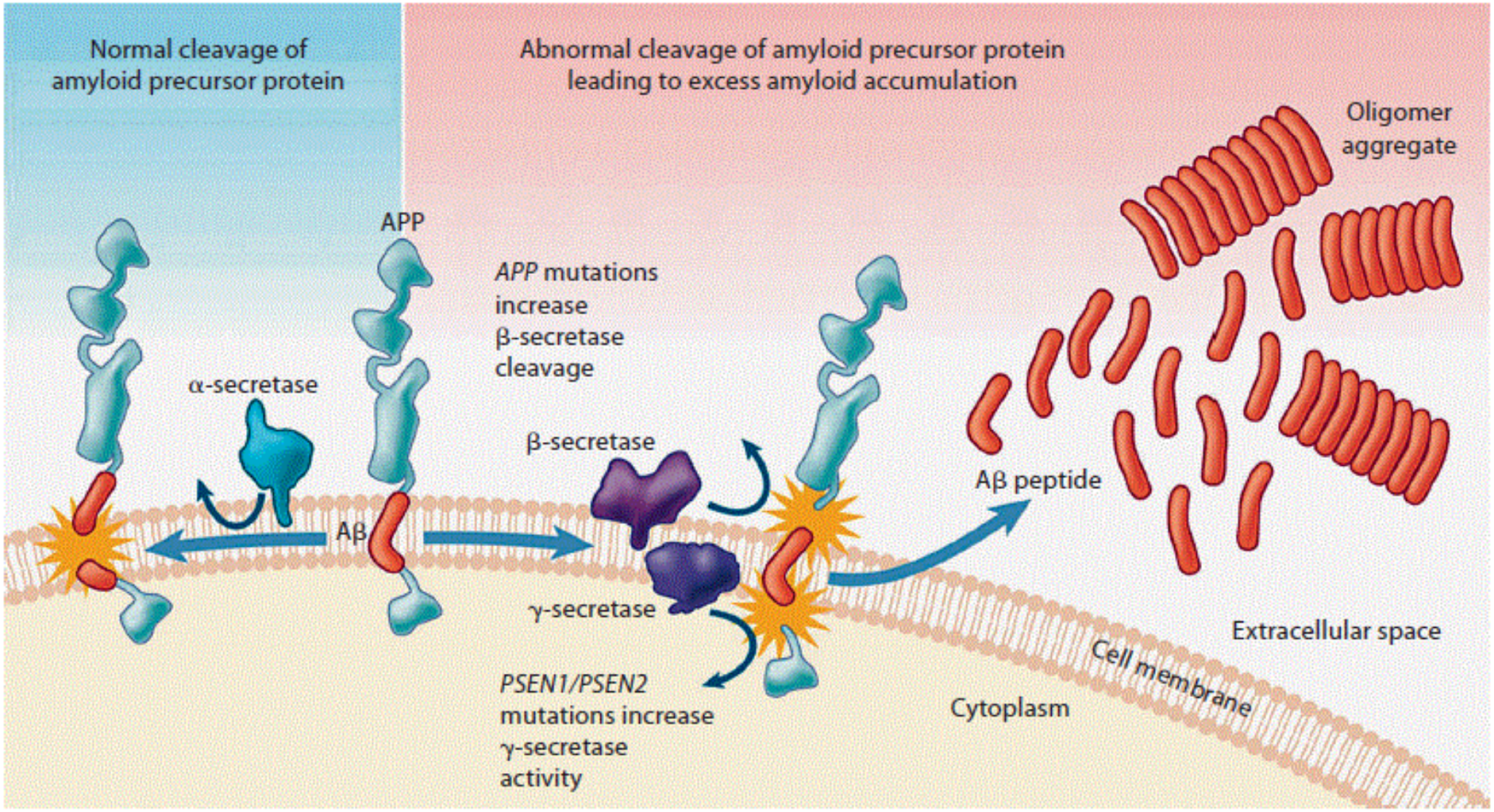
2. Neurofibrillary tangles

Are formed by neuronal intracellular deposition of Tau protein and results in the collapse of microtubules

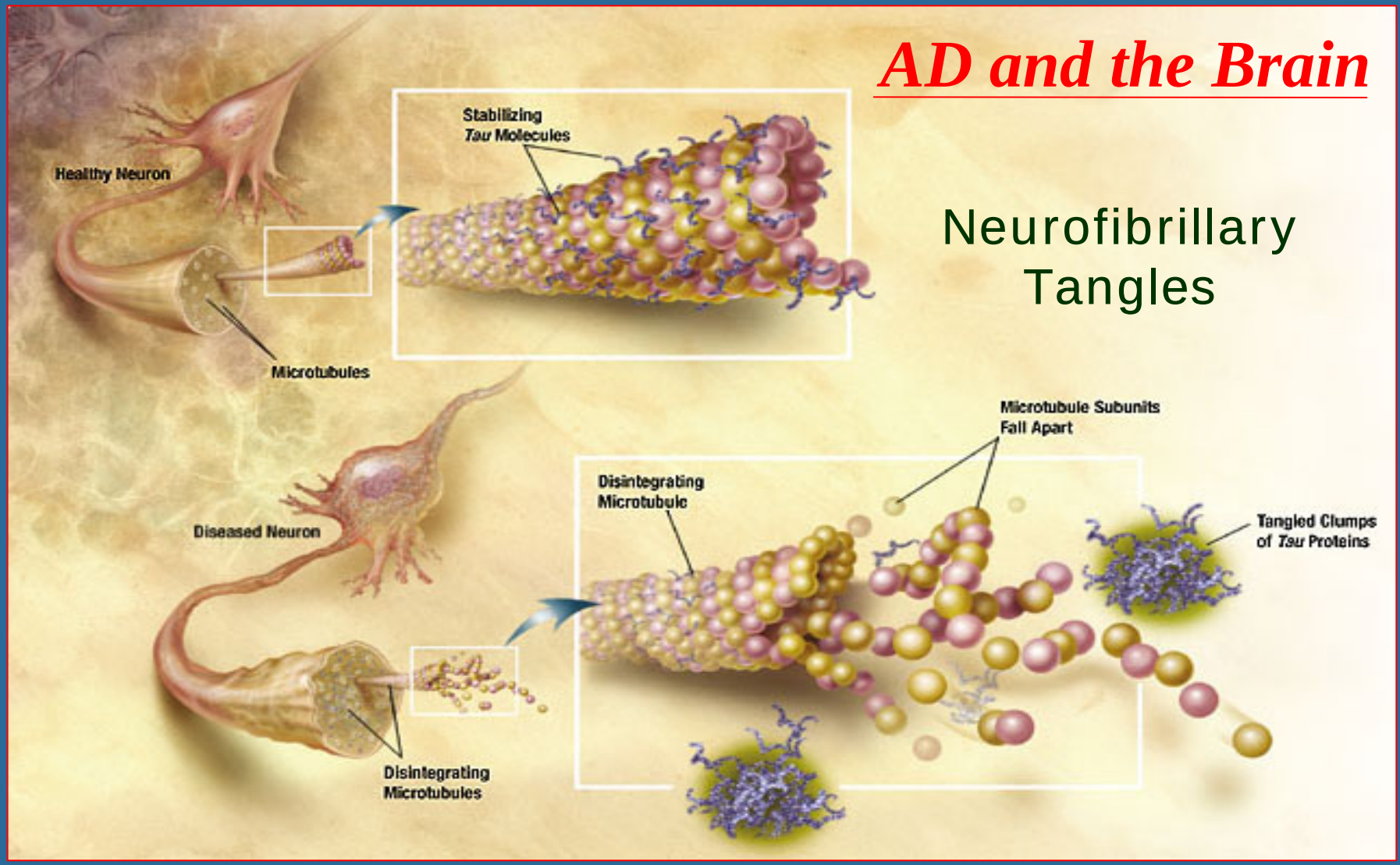




3. Neuronal degeneration

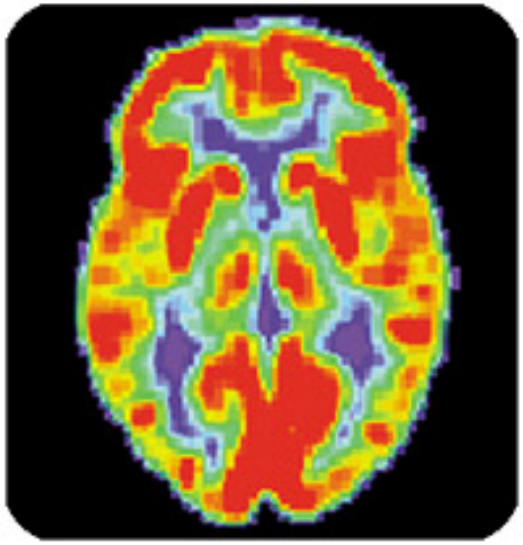

Normal cleavage of amyloid precursor protein
Abnormal cleavage of amyloid precursor protein leading to excess amyloid accumulation
Oligomer aggregate
APP
α-secretase
Aβ
APP mutations increase β-secretase cleavage
β-secretase
γ-secretase
PSEN1/PSEN2 mutations increase γ-secretase activity
Aβ peptide
Extracellular space
Cell membrane
Cytoplasm

AD and the Brain



Neurons have an internal support structure partly made up of microtubules. A protein called *tau* helps stabilize microtubules. In AD, *tau* changes, causing microtubules to collapse, and *tau* proteins clump together to form neurofibrillary tangles.

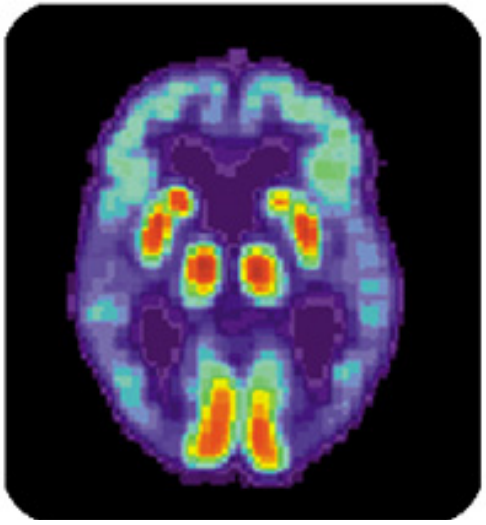
AD and the Brain



Pet Scan of
Normal Brain

The Changing Brain in Alzheimer's Disease

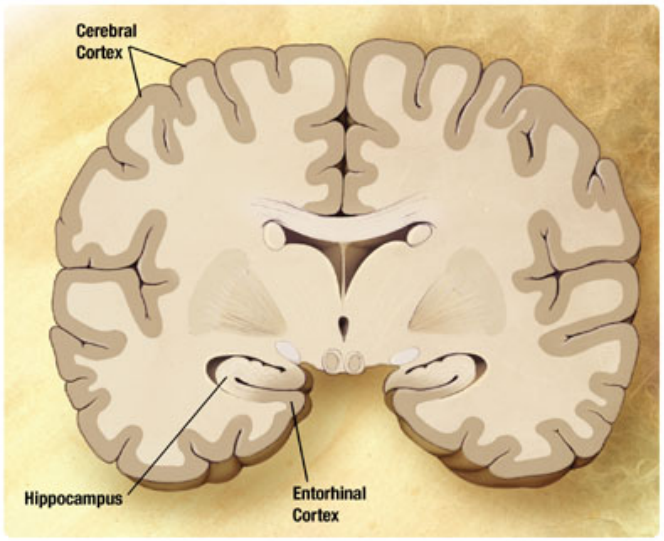
No one knows what causes AD to begin, but we do know a lot about what happens in the brain once AD takes hold.

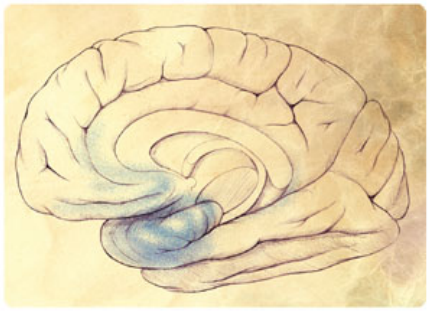


Pet Scan of Alzheimer's
Disease Brain

AD and the Brain

Preclinical AD

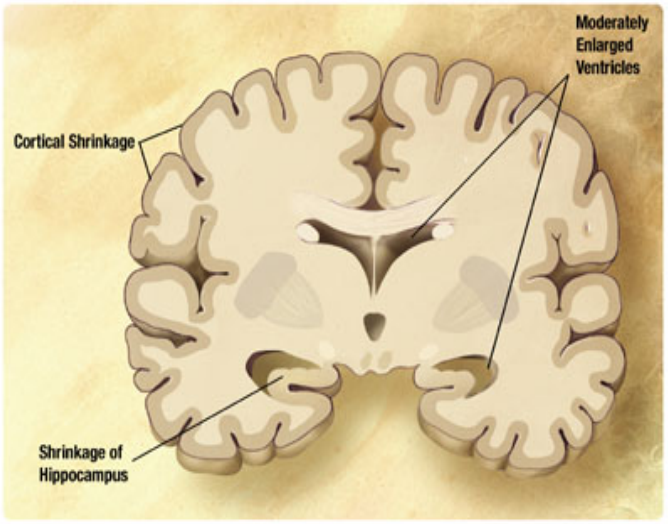


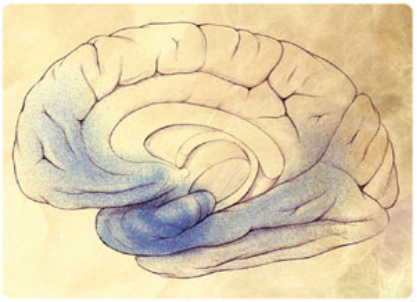


- Signs of AD are first noticed in the entorhinal cortex, then proceed to the hippocampus.
- Affected regions begin to shrink as nerve cells die.
- Changes can begin 10-20 years before symptoms appear.
- Memory loss is the first sign of AD.

AD and the Brain

Mild to Moderate AD

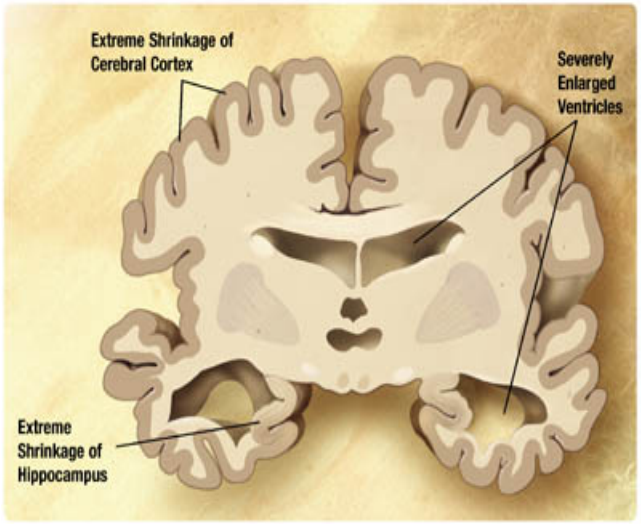


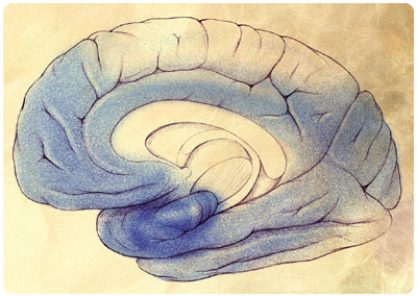


- AD spreads through the brain. The cerebral cortex begins to shrink as more and more neurons stop working and die.
- *Mild AD signs* can include memory loss, confusion, trouble handling money, poor judgment, mood changes, and increased anxiety.
- *Moderate AD signs* can include increased memory loss and confusion, problems recognizing people, difficulty with language and thoughts, restlessness, agitation, wandering, and repetitive statements.

AD and the Brain

Severe AD



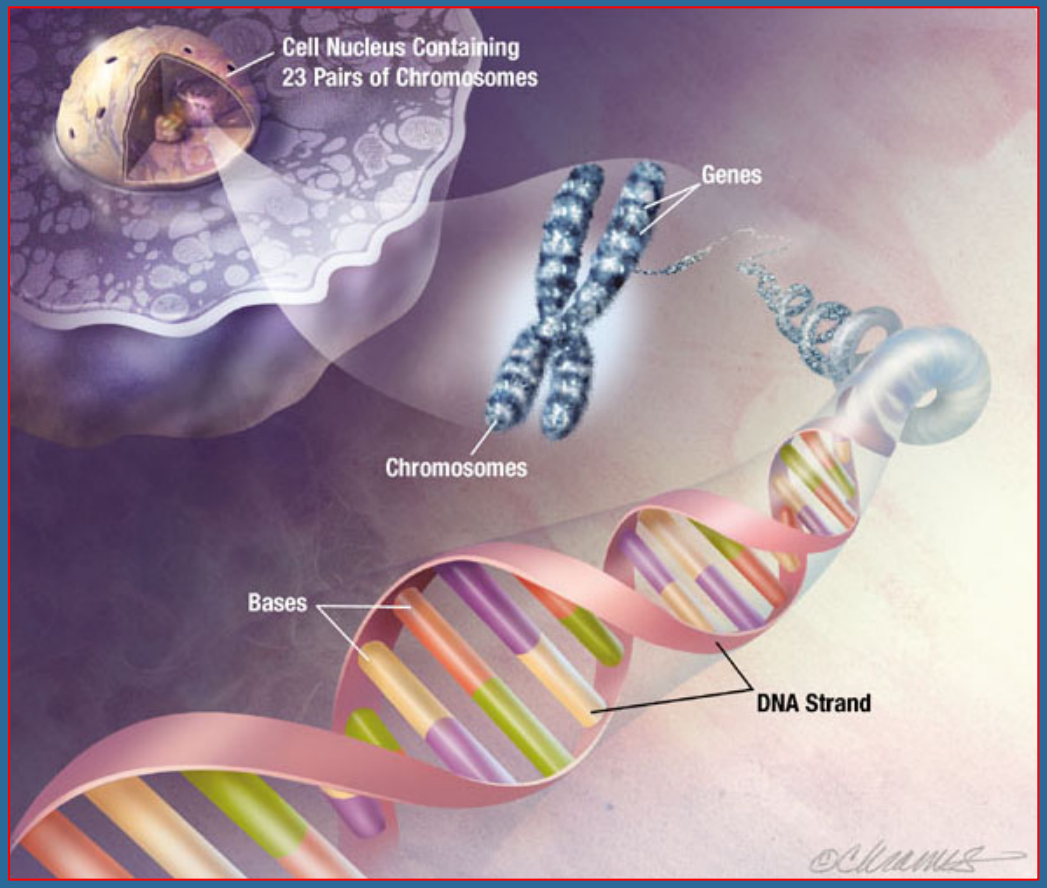


- In severe AD, extreme shrinkage occurs in the brain. Patients are completely dependent on others for care.
- Symptoms can include weight loss, seizures, skin infections, groaning, moaning, or grunting, increased sleeping, loss of bladder and bowel control.
- Death usually occurs from aspiration pneumonia or other infections. Caregivers can turn to a hospice for help and palliative care.

AD Research: the Search for Causes

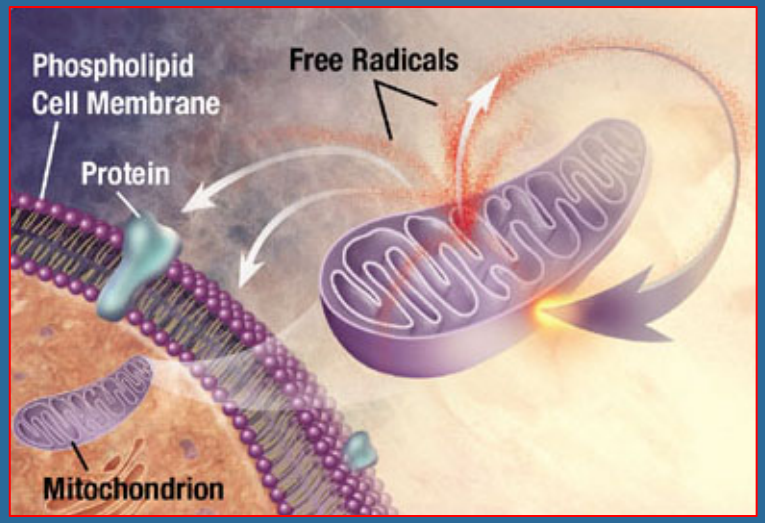
Genetic Studies

The two main types of AD are early-onset and late-onset:



- Early-onset AD is rare, usually affecting people aged 30 to 60 and usually running in families. Researchers have identified mutations in three genes that cause early-onset AD.
- Late-onset AD is more common. It usually affects people over age 65. Researchers have identified a gene that produces a protein called apolipoprotein E (ApoE). Scientists believe this protein is involved in the formation of beta-amyloid plaques.

AD Research: the Search for Causes



Studies at the Cellular and Molecular Level

- Oxidative damage from free radical molecules can injure neurons.

- Homocysteine, an amino acid, is a risk factor for heart disease. A study shows that an elevated level of homocysteine is associated with increased risk of AD.
- Scientists are also looking at inflammation in certain regions of the brain and strokes as risk factors for AD.

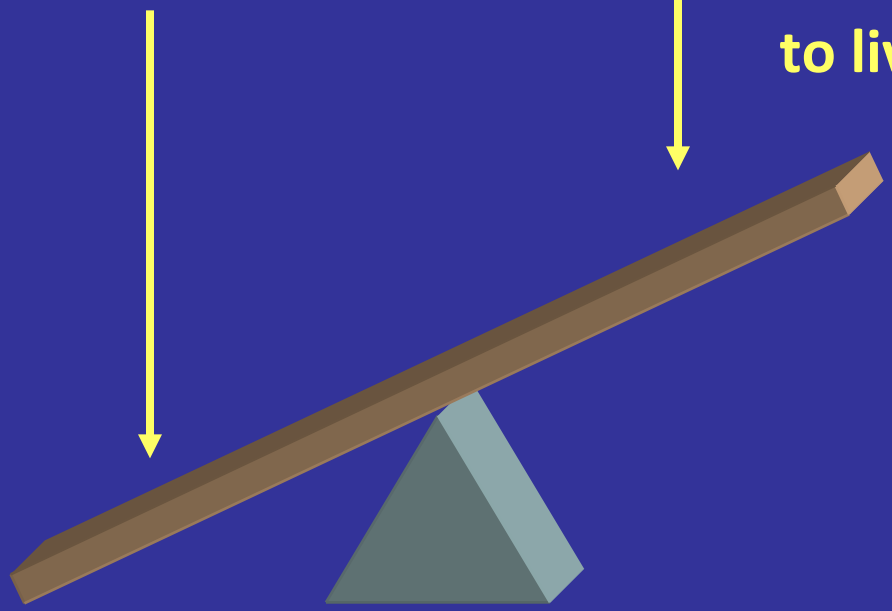
Brain is poised for oxidative damage

Rich in PUFA (polyunsaturated fatty acids)

High use of oxygen

Areas rich in iron

Low antioxidant Capacity (Catalase, GSH and SOD less than 1/5 compared to liver)



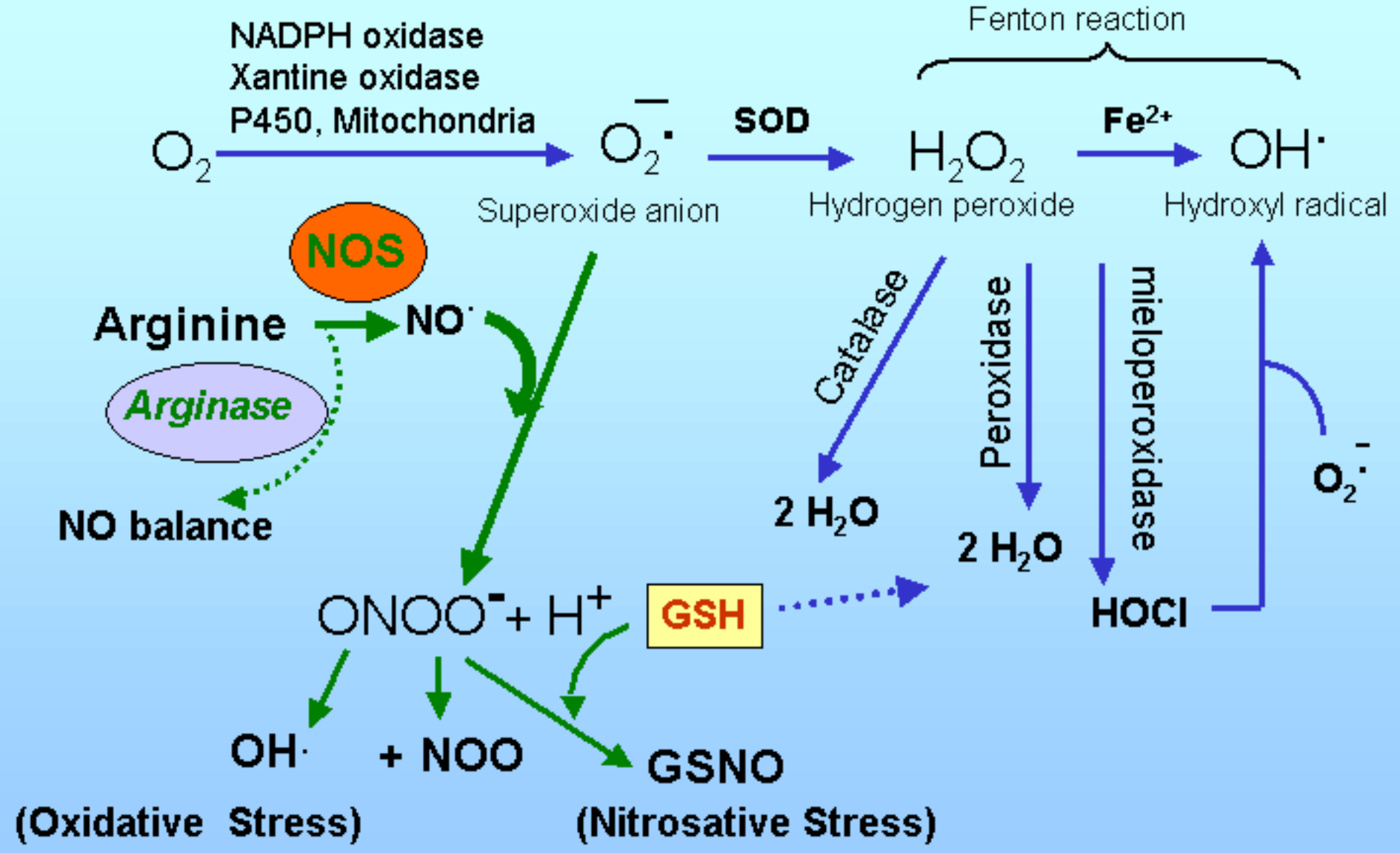
The Brain is Uniquely Vulnerable to Oxidative Damage

- Intolerance for blood flow interruptions
- Limited regeneration-although neurogenesis and gliogenesis can be stimulated
- Circuit-based functions-small deficits have huge impact
- Aging sensitive
- Ca-dependent processes
- PUFAs

The Brain is Uniquely Vulnerable to Oxidative Damage

- Multiple sources of ROS generation (e.g. MAO, Aconitase, a-KGDH, Nox(s), Complex I, P450s, neurotrophic factor withdrawal
- Redox active metal-rich (catalytic iron)
- Autooxidation of monoamines
- Glutamate excitotoxicity
- Limited antioxidant and repair capacity (low catalase, mitochondria lack catalase)
- Resident immune cells (microglia) produce ROS and cytokines

GENERATION AND METABOLISM OF MAJOR ROS



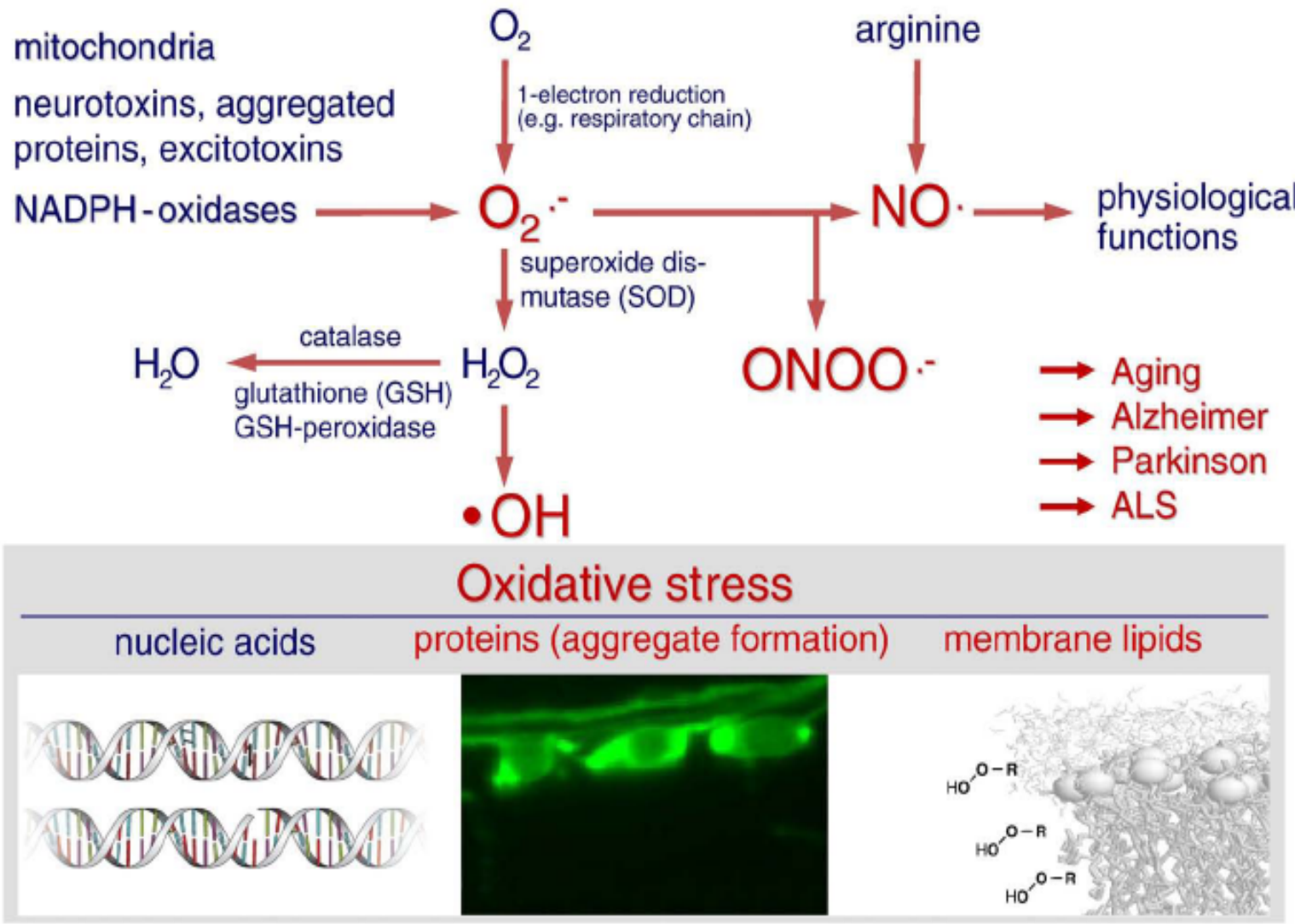
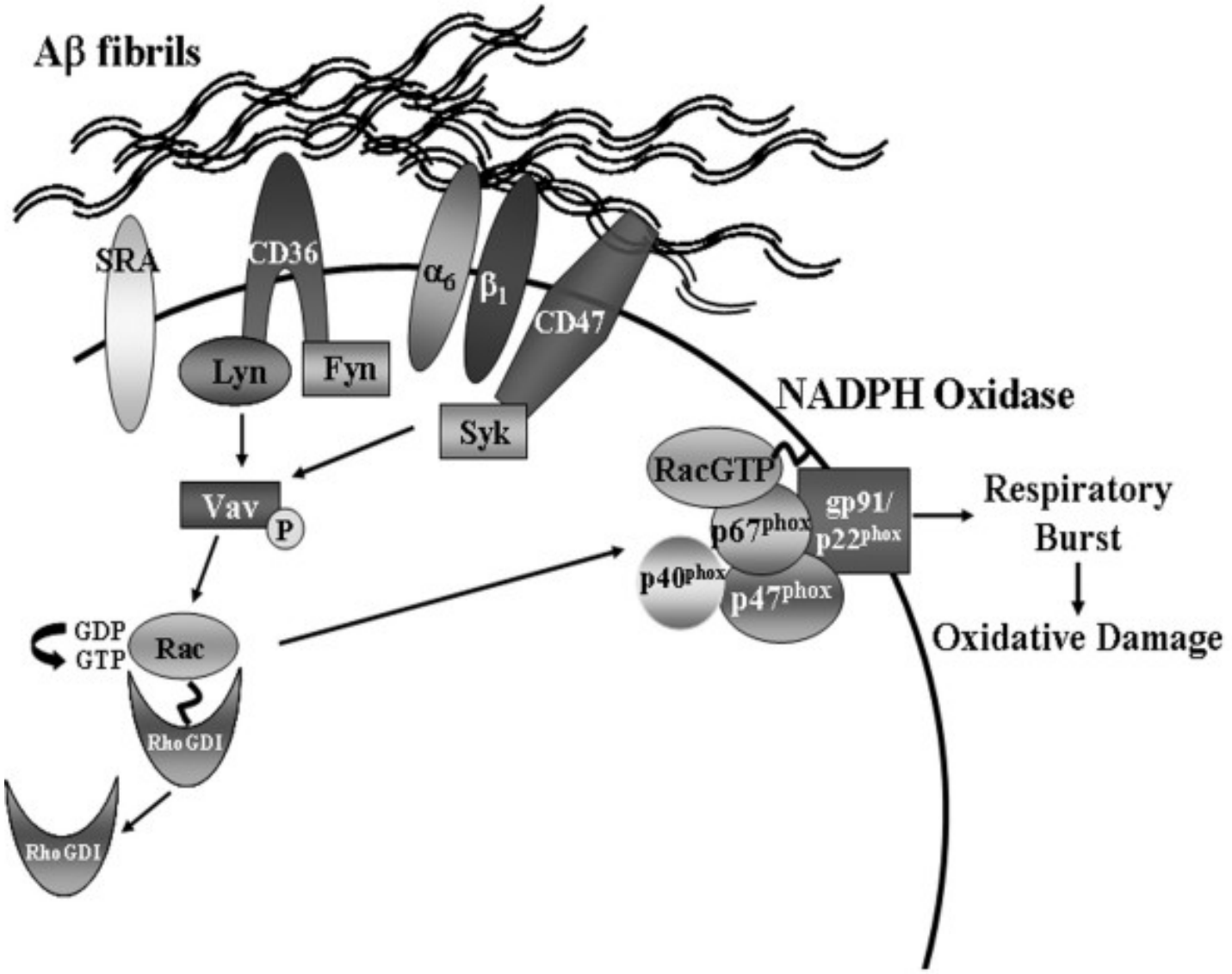


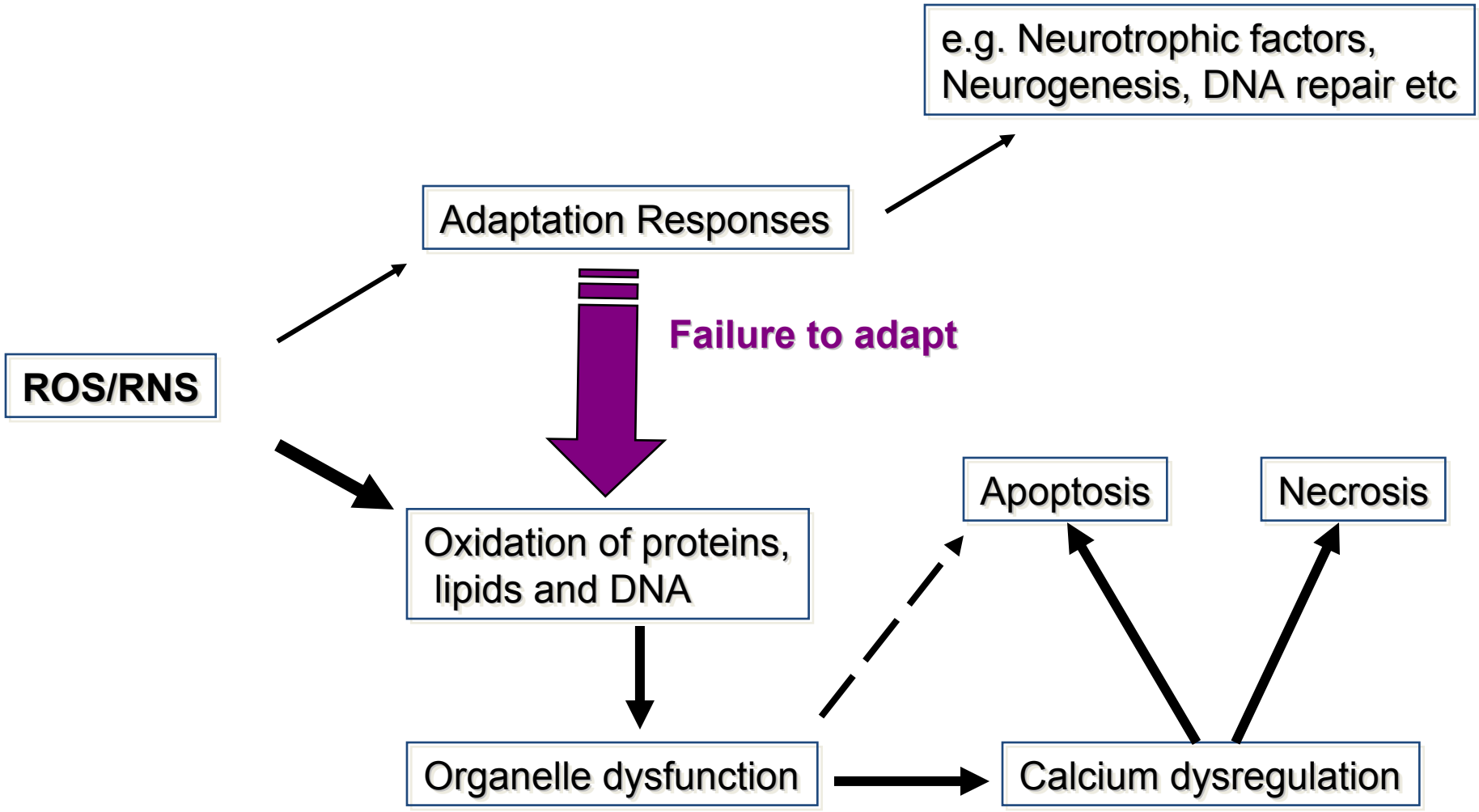
Fig. 1. Free oxygen and nitrogen radicals as driving force for aging and neurodegeneration. The free radical theory of aging and neurodegeneration summarizes the role of the accumulation of oxygen and nitrogen radicals in pathology. Basically all macromolecules can be attacked and oxidized by free radicals, leading to structural changes and molecule dysfunction. During neurodegeneration the oxidation of membrane lipid compounds and of proteins is especially well described, the latter is frequently leading to protein misfiling and aggregation.

Kern A et al. Biochim Biophys Acta. 2009

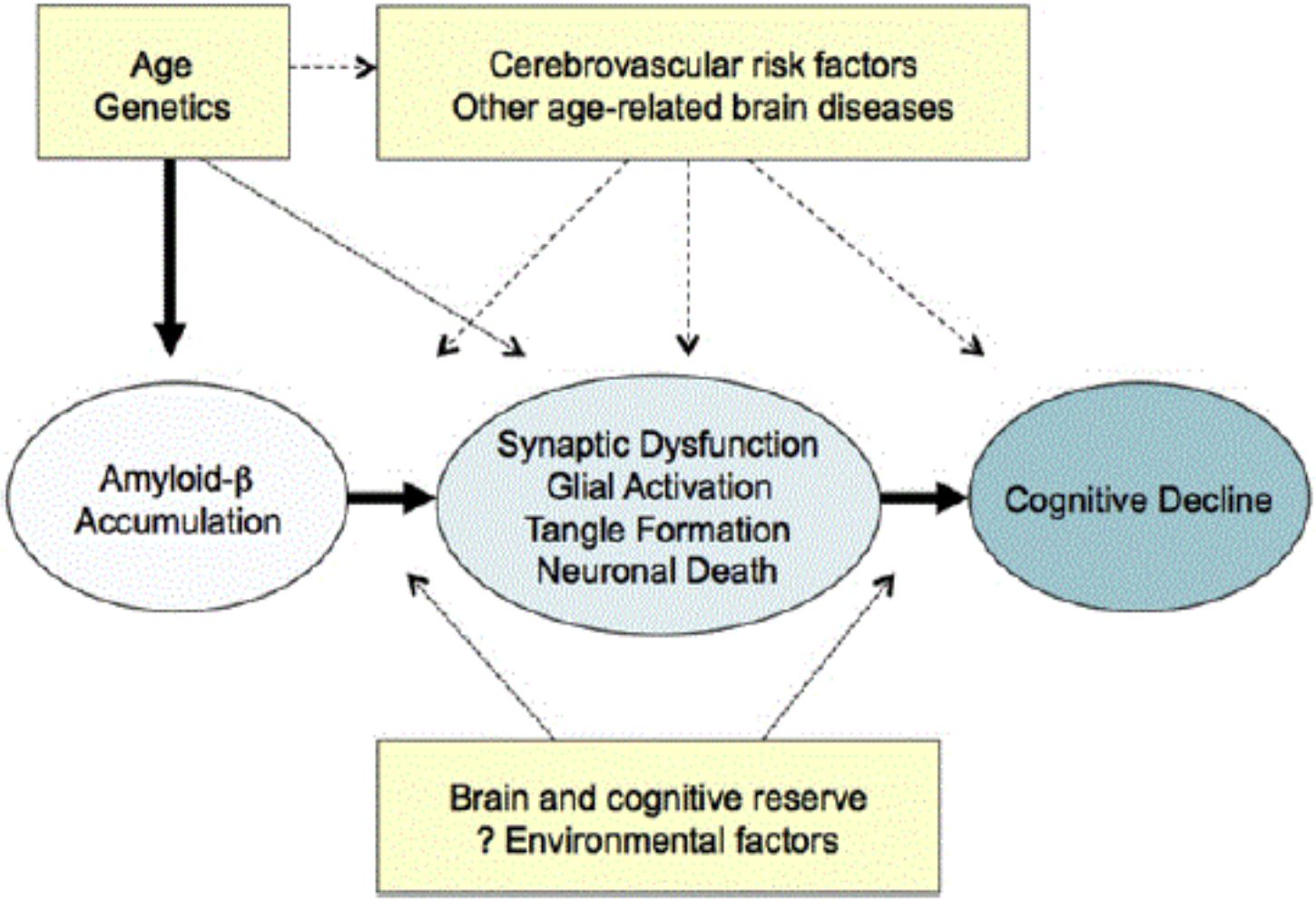


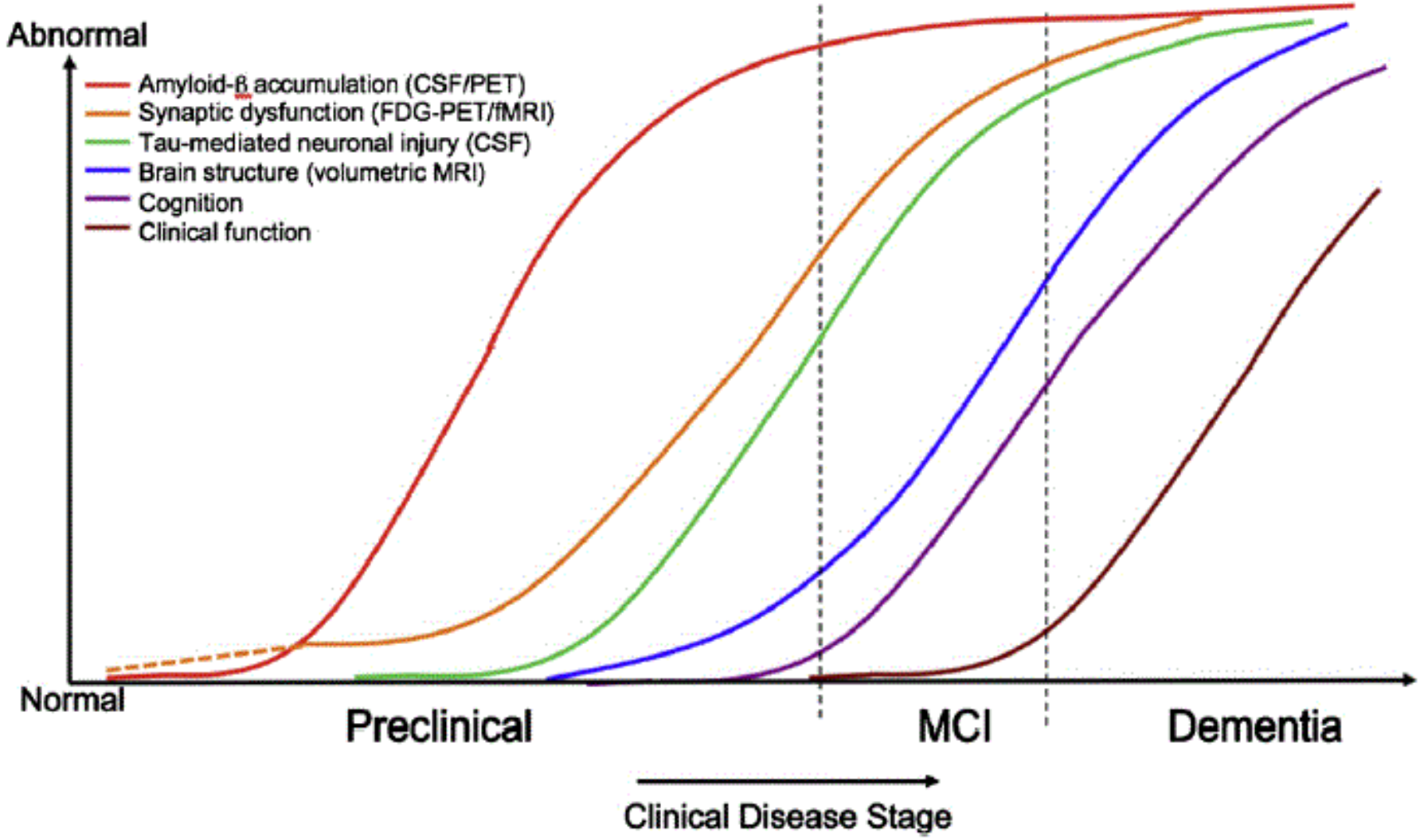
Lambeth JD. Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. Free Radic Biol Med. 2007, 43(3):332-47.

Oxidative Stress Response



Hypothetical model of AD pathophysiological cascade




Abnormal
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
MCI
Dementia
Clinical Disease Stage

BioMed Central

Immunity & Ageing 2011, 8:7
http://www.immunityageing.com/content/8/1/7

IMMUNITY & AGEING

REVIEW Open Access

The "Alzheimer's disease signature": potential perspectives for novel biomarkers.

Sergio Davinelli[1], Mariano Intrieri[1], Claudio Russo[1], Alfonso Di Costanzo[1], Davide Zella[2], Paolo Bosco[3], Giovanni Scapagnini[1]

[1]Department of Health Sciences, University of Molise, Campobasso, Italy
[2]Department of Biochemistry and Molecular Biology, University of Maryland, Baltimore, MD, USA
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The authors review potential biomarker candidates from the latest research, which could hold the key to the Alzheimer's disease signature, providing a way of diagnosing the disease and its progressive stages.

Published: 20 September 2011

Schematic Overview of Major Alzheimer's Disease (AD) Gene

Familial Genes	Locus	Functions
APP	21q21.3	APP gene encodes a membrane protein cleaved by secretase. Mutations in App locus causes autosomal dominant early onset AD and cerebroarterial amyloidosis.
PS1	14q24.2	PS1 is involved in APP processing and mutations can interfere the production of Aβ42 and to form plaques. Numerous alternatively spliced transcript variants encoding different isoforms have been identified for this gene.
PS2	1q42.13	Regulate APP processing as a part of the α-secretase complex. Familial mutations can change the production of Aβ42.
Risk Genes		
APOE	19q13.32	ApoE regulates the normal catabolism of triglyceride-rich lipoprotein constituents. APOE binds Aβ and it is involved in Aβ clearance. Subjects carrying the E4 allele have an increased amyloid burden.
TAU	17q21.31	The transcript undergoes complex alternative splicing and tau exists as six splice isoforms. The mutations can alter microtubule binding efficacy.
DYRK1A	21q22.13	DYRK1A is localized in the critical region of chromosome 21 and is involved in tau and APP phosphorylation. Firstly the activity is upregulated by Aβ and APP phosphorylation result in increased amyloidogenic processing with BACE interaction.
GSK3β	3q13.33	The overexpression of this gene may be relevant for AD. GSK-3 phosphorylates tau and presenilin-1, which are involved in the development of AD. The phosphorylation of tau leads to tangle formation and APP cleavage products can activate GSK3β resulting increased tau phosphorylation.

Genes in genomic location are in according to Ensembl cytogenetic band

LETTERS

nature genetics

Common variants at *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33* and *CD2AP* are associated with Alzheimer's disease

We sought to identify new susceptibility loci for Alzheimer's disease through a staged association study (GERAD+) and by testing suggestive loci reported by the Alzheimer's Disease Genetic Consortium (ADGC) in a companion paper. We undertook a combined analysis of four genome-wide association datasets (stage 1) and identified ten newly associated variants with $P \leq 1 \times 10{-}5$. We tested these variants for association in an independent sample (stage 2). Three SNPs at two loci replicated and showed evidence for association in a further sample (stage 3). Meta-analyses of all data provided compelling evidence that ABCA7 (rs3764650, meta $P = 4.5 \times 10{-}17$; including ADGC data, meta $P = 5.0 \times 10{-}21$) and the MS4A gene cluster (rs610932, meta $P = 1.8 \times 10{-}14$; including ADGC data, meta $P = 1.2 \times 10{-}16$) are new Alzheimer's disease susceptibility loci. We also found independent evidence for association for three loci reported by the ADGC, which, when combined, showed genome-wide significance: CD2AP (GERAD+, $P = 8.0 \times 10{-}4$; including ADGC data, meta $P = 8.6 \times 10{-}9$), CD33 (GERAD+, $P = 2.2 \times 10{-}4$; including ADGC data, meta $P = 1.6 \times 10{-}9$) and EPHA1 (GERAD+, $P = 3.4 \times 10{-}4$; including ADGC data, meta $P = 6.0 \times 10{-}10$).

Nat Genet. 2011 May;43(5):429-35.

Schematic Overview of Major Alzheimer's Disease (AD) Gene

New GWAS Genes	Locus	Functions
CLU	8p21.1	Clusterin is a chaperone molecule involved in clearence, aggregation and fibrillization of Aβ. It is associated with the progression of AD.
PICALM	11q14.2	Phosphatidylinositol binding clathrin assembly protein is associated with an increased risk of developing AD. PICALM plays a role in synaptic trasmission and may be involved in Aβ clearence. The protein is present in endosomes connected with AD.
CR1	1q32.2	This gene is a member of the receptors of complement activation (RCA) family, precisely the complement C3b protein, a key inflammatory protein activated in AD .
BIN1	2q14.3	This gene encodes several isoforms of a nucleocytoplasmic adaptor protein involved in endocytosis. BIN1 could have an effect on Aβ production and/or the clearance of Aβ.
ABCA7	19p13.3	This gene is a member of the superfamily of ATP-binding cassette (ABC) transporters and is highly expressed in brain, particularly in the microglia. ABCA7 inhibit β-amyloid secretion in cultured cells overexpressing APP.
MS4A	11q12.2	The genes in the MS4A cluster are locolized on chromosome 11 and encode proteins with at least 4 potential transmembrane domains but do not have specific function yet.
CD2AP	6p12.3	C2AP encodes a scaffolding molecule that regulates the actin cytoskeleton and is involved in the regulation of receptor-mediated endocytosis.
EPHA1	7q35	EPHA1 is a member of the ephrin receptor subfamily of the protein-tyrosine kinase family. It is implicated in synaptic development and plasticity but also axon guidance. Other functions have been proposed.
CD33	19q13.41	CD33 molecule belongs to the family of sialic acid-binding, immunoglobulinlike lectins. CD33 regulate the functions in the adaptive and innate immune systems both involved into the inflammatory reactions observed in the brains of AD patients.

Genes in genomic location are in according to Ensembl cytogenetic band

Genome-Wide Association Study (GWAS)

Main Pathway and Biomarkers AD-related

Pathwway	Biomarker	Potential association with AD
Signal trasduction	GSK3β	GSK3β integrates a variety of intracellular and extracellular pathways and appears to be increased in the AD brain . GSK3β is regulated by phosphorylation and is the major tau kinases.
	CDK5	Cdk5 plays a role in processes of neural development, synaptic signalling, learning and can influence tau phosphorylation indirectly via regulation of GSK3β.
	ERK2	The phosphorylation of tau by ERK2 induces tau to acquire biochemical properties of AD. ERK2 was detected in neurofibrillary tangles.
	DYRK1A	Dyrk1A is abnormally expressed in AD and recently it has been found to be associated with neurofibrillary tangles in sporadic AD.
	PKC	PKC has been implicated in memory mechanisms and is also involved in the processing of APP. The activators of PKC lead to increased processing of APP by the α-secretase pathway.
	VLP-1	Visinin-like protein 1 concentration is significantly altered in the CSF of AD patients and ia is associated with fibrillar tangles in AD brains.
Oxidative stress	F2-isoprostanes	Incresed levels of F2-isoprostanes are found in AD plasma and CSF.
Inflammation	Interleukins	Interleukins are consistently detected in the brains of AD and polymorphisms are implicated in AD. The activity in AD contributes to synaptic dysfunction and loss, and later, neuronal death.
	TNF-α	TNF-α has a central role in AD pathogenesis. The levels are increased in CSF and correlated with clinical deterioration.
	C-reactive protein	C-reactive protein has been found to be associated with AD in histopathological and longitudinal studies. It is associated with increased risk of AD.
	α-1-antichymotrypsin	α-1-antichymotrypsin participates in the inflammatory cascade of AD and enhances the formation of amyloid-fibrils.

Main Pathway and Biomarkers AD-related

Pathwway	Biomarker	Potential association with AD
Inflammation	**α2-macroglobulin**	α2-macroglobulin has an important role in AD etiopathology. The main ability is to mediate the clearance and degradation of Aβ.
	Homocysteine	Hyperhomocysteinaemia is a risk factor for AD and mental decline.
	ICAM-1	ICAM-1 is expressed on cerebrovascular endothelium and neuritic plaques in brain of AD patients and seems to be implicated in the process of neuro-degeneration.
	VCAM-1	Abnormal levels of VCAM-1 levels have been found in individuals with AD as well as other cell adhesion molecules.
Lipid metabolism	**Total cholesterol**	High concentration of serum cholesterol is associated with increased risk of incident AD.
	APOE	APOE E2, E3, and E4 alleles alter the likelihood of developing AD and cerebral amyloid angiopathy.

BRAIN RESEARCH REVIEWS 59 (2008) 155–163

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BRAIN RESEARCH REVIEWS

Review

Association between the interleukin-1β polymorphisms and Alzheimer's disease: A systematic review and meta-analysis

Danilo Di Bona[a,b,c], Antonella Plaia[d], Sonya Vasto[b,c], Luca Cavallone[e], Francesco Lescai[f], Claudio Franceschi[f], Federico Licastro[f], Giuseppina Colonna-Romano[c], Domenico Lio[c], Giuseppina Candore[c], Calogero Caruso[b,c,*]

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[b]Unità Operativa di Immunoematologia e Medicina Trasfusionale, Italy
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[d]Dipartimento di Scienze Statistiche e Matematiche, "S. Vianelli", Università di Palermo, Italy
[e]Molecular Biology Unit, McGill University, Montreal, Canada

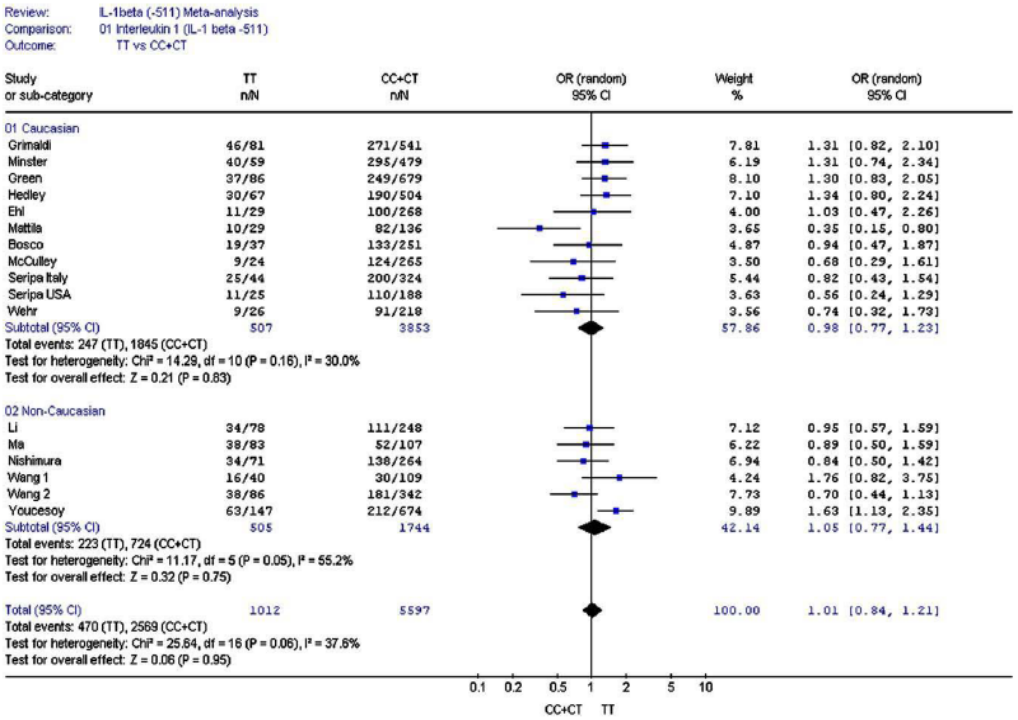

Fig. 2 – Meta-analysis of 17 case-control studies (11 Caucasian and 6 non-Caucasian) of the IL-1β –511 polymorphism and the risk for AD using the random effects model. The odds ratio (OD) and 95% confidence interval (C.I.) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

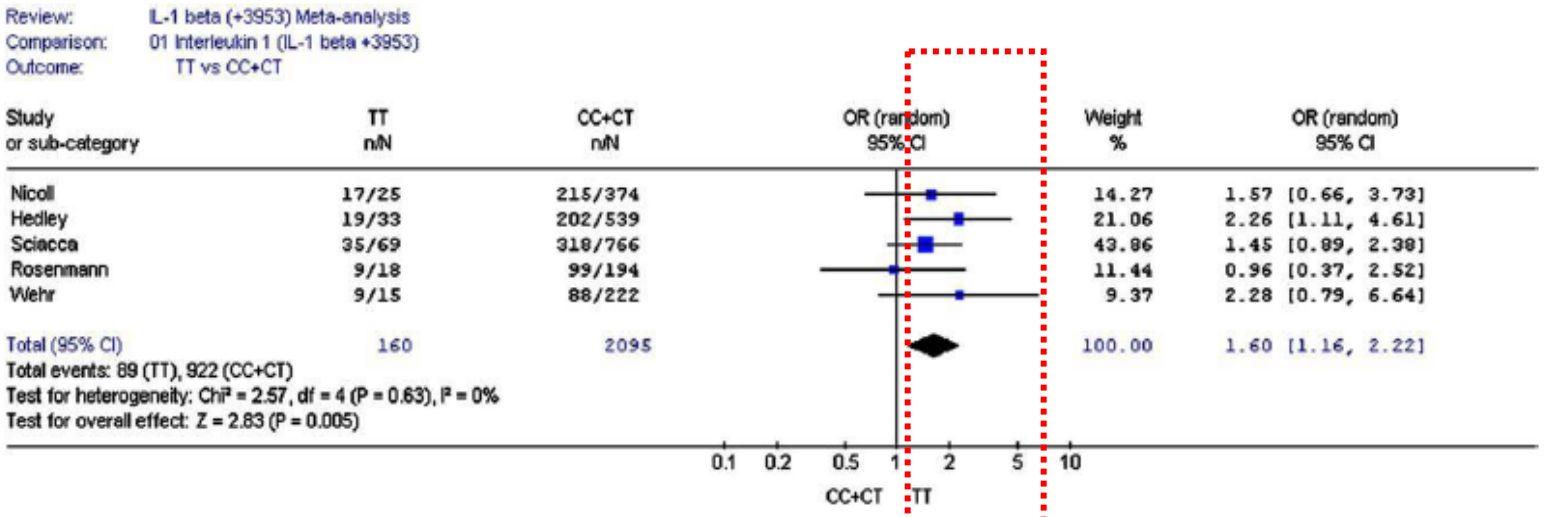

Fig. 1 – Meta-analysis of 5 case-control studies of the IL-1β +3953 polymorphism and the risk for AD using the random effects model. The odds ratio (OD) and 95% confidence interval (C.I.) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

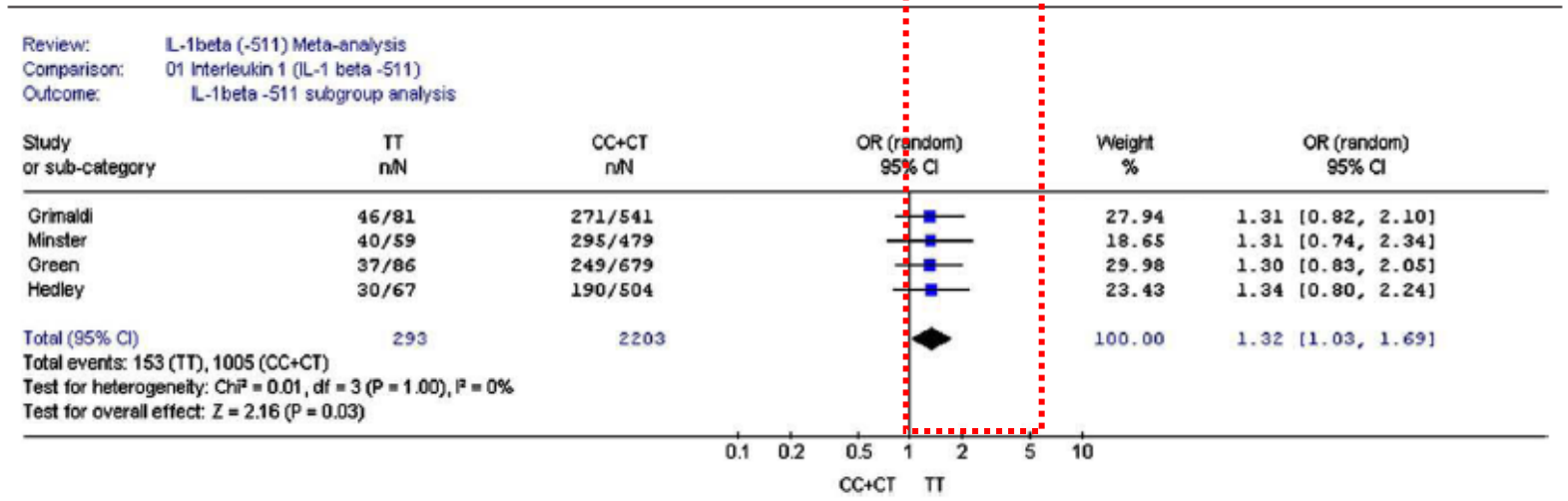

Fig. 3 – Meta-analysis (using a random effects model) of the four Caucasian case-control studies, with a statistical power >0.18, of the IL-1β –511 polymorphism and the risk for AD. The odds ratio (OD) and 95% confidence interval (C.I.) for the effect of the TT genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

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BRAIN RESEARCH REVIEWS

Review

Systematic review by meta-analyses on the possible role of TNF-α polymorphisms in association with Alzheimer's disease

Danilo Di Bona[a,b], *Giuseppina Candore*[a], *Claudio Franceschi*[c], *Federico Licastro*[c], *Giuseppina Colonna-Romano*[a], *Calogero Cammà*[d], *Domenico Lio*[a], *Calogero Caruso*[a,b,*]

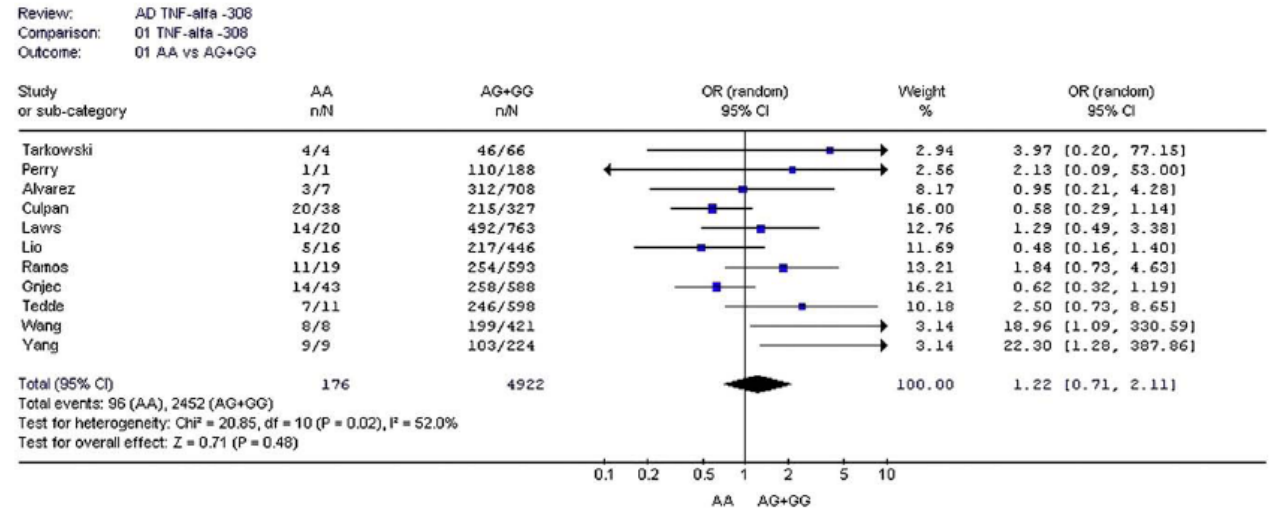


Fig. 1 – Meta-analysis of 11 case-control studies of the TNF-α –308 polymorphism and the risk for AD using the random-effects model. The odds ratio (OD) and 95% confidence interval (CI) for the effect of AA genotype for the risk of AD are plotted on the graph. Studies are arranged chronologically based on the year of publication.

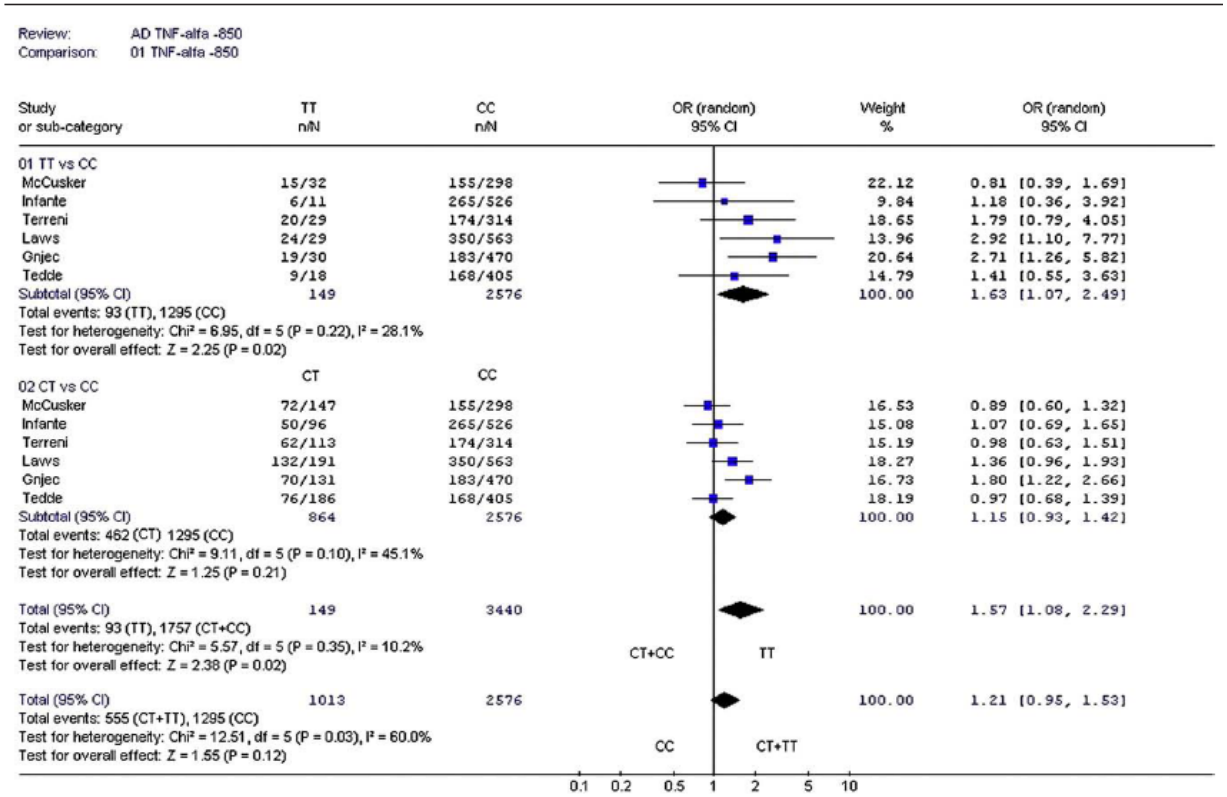


Fig. 2 – Meta-analysis of 6 case-control studies of the TNF-α –850 polymorphism and the risk for AD using the random-effects model. The genotype effect for TT and CT vs. CC genotypes (comparison 01 and 02, respectively) were estimated for each study. The pooled ORs for CT/CC vs. TT and for CC vs. CT/TT were also calculated. The odds ratio (OD) and 95% confidence interval (CI) for all comparisons are plotted on the graph. Studies are arranged chronologically based on the year of publication.

Table 3 – Random-effects meta-analyses using genotypic contrasts for –863, –238 and –1031 TNF-α SNPs.

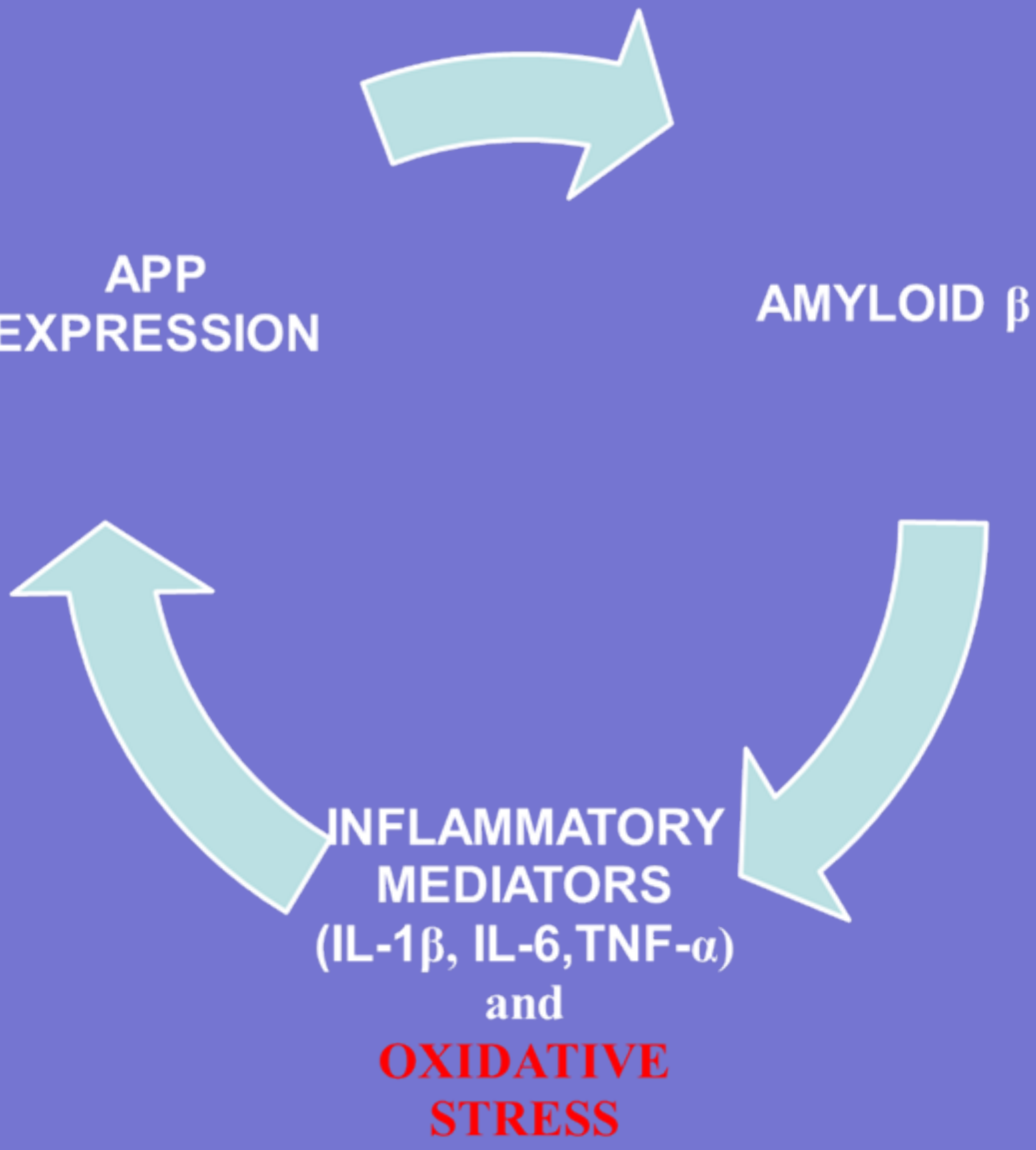
SNP	Studies (*n*)	Ethnicity	Participants (*n*)	Genotypic summary OR (95% CI)	*p*-value	Heterogeneity *p*-value; I^2
–863	4	1 Europe 1 USA 2 Asia (China, Taiwan)	1657	CC vs. AC+AA: 1.26 (0.86–1.85),	$p=0.24$	$p=0.04$, 64%
–238	4	2 Europe 1 USA (African Americans) 1 USA/Europe	1878	GG vs. AG+AA: 0.78 (0.57–1.08),	$p=0.14$	$p=0.32$, 14.4%
–1031	3	3 Asia (China, Taiwan, Japan)	771	TT vs. CT+CC: 0.62 (0.36–1.09),	$p=0.10$	$p=0.05$, 65.8%

Meta-analyses of other cytokine SNPs involved in AD

Gene	Studies(n)	SNP	Genotype	Participants (n)	OR (95%C.I.)	Heterogeneity
IL-1α	17	-889	TT vs CT+CC	7407	1.25 (0.98-1.60)	P = 0.008; I^2 = 50.9%
IL-6	12	-174	GG vs CG+GG	5274	1.01 (0.77-1.33)	P = 0.00001; I^2 = 78.3%
TGF-β	6	-509	TT vs CT+CC	9321	1.00 (0.78-1.28)	P = 0.09; I^2 = 46.9%
	4	+10	CC vs CT+TT	6682	0.98 (0.61-1.57)	P = 0.02; I^2 = 69.9%
IL-10	9	-1082	GG vs AG+AA	3069	0.84 (0.65-1.09)	P = 0.04; I^2 = 49.9%
	7	-819	TT vs CT+CC	2334	1.26 (0.69-2.31)	P = 0.001; I^2 = 72.1%
	8	-592	AA vs AC+CC	2886	0.95 (0.66-1.38)	P = 0.06; I^2 = 48.1%

Manuscript in preparation

VICIOUS CYCLE



Fassbender K. Et al 2000

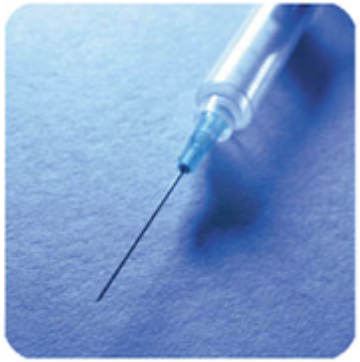
AD Research: the Search for Treatments

Drugs used to treat mild to moderate AD symptoms include:

- Aricept
- Exelon
- Reminyl

An additional drug, Namenda, has been approved to treat symptoms of moderate to severe AD. These drugs can help improve some patients' abilities to carry out activities up to a year or so, but they do not stop or reverse AD.

Scientists are also studying agents that someday may be useful in preventing AD. For example, they have experimented with a vaccine against AD. Although the first clinical trial was stopped due to side effects in some participants, valuable information was gathered.



AD Research: the Search for New Treatments

Researchers also are looking at other treatments, including:

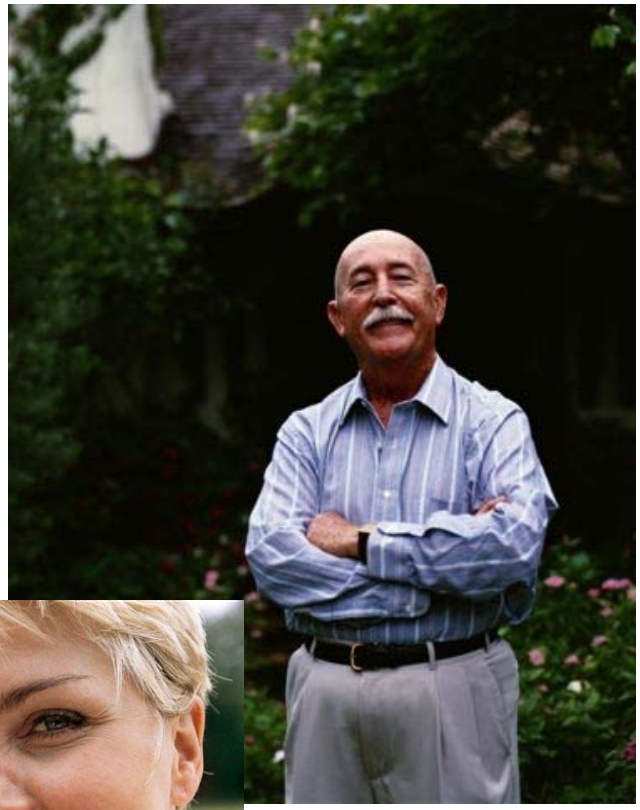
- cholesterol-lowering drugs called statins
- anti-oxidants (vitamins) and folic acid
- anti-inflammatory drugs
- substances that prevent formation of beta-amyloid plaques
- nerve growth factor to keep neurons healthy

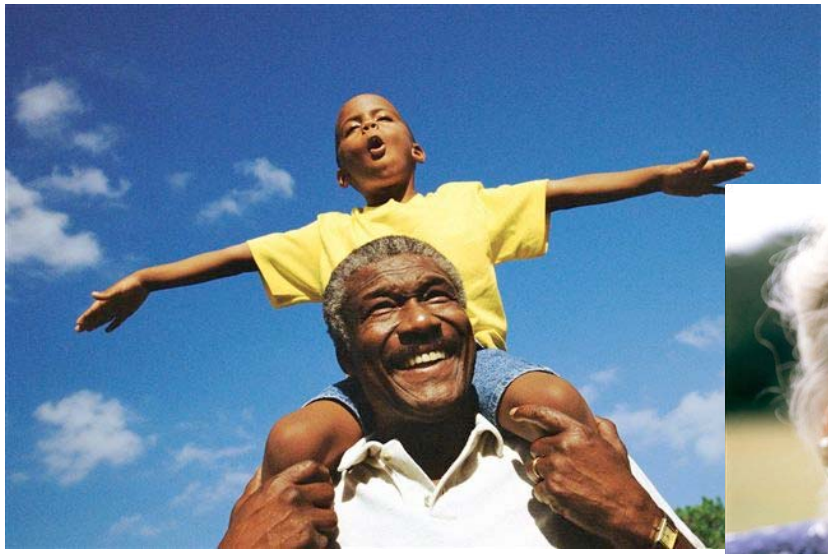
- **The Gerontologist: Promoting Cognitive Health in Diverse Populations of Older Adults.**

The Gerontologist Volume 49 Issue S1
June 2009

Cognitive Ability = Quality of Life

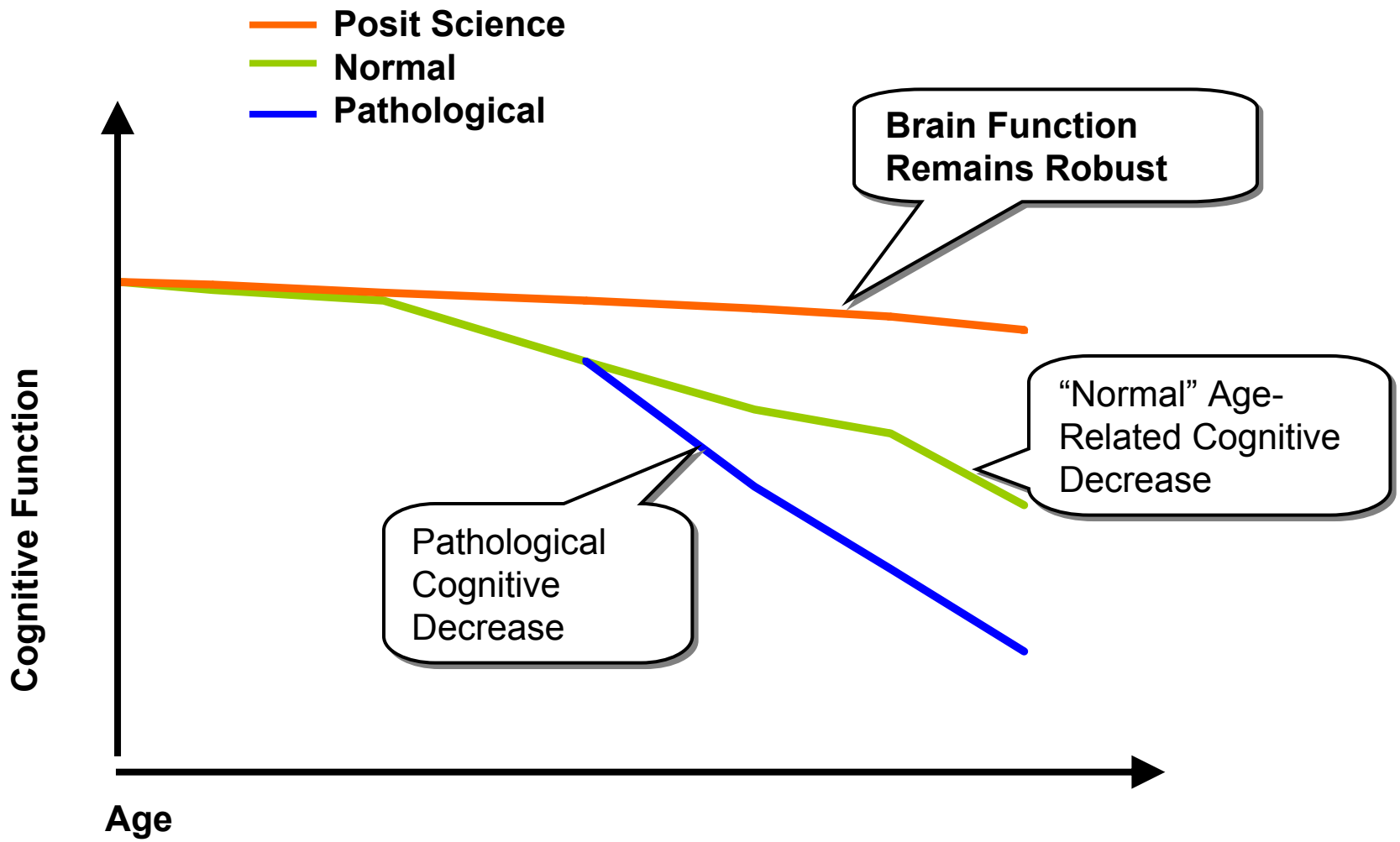
- Staying Sharp
- Staying Vital
- Maintaining Independence



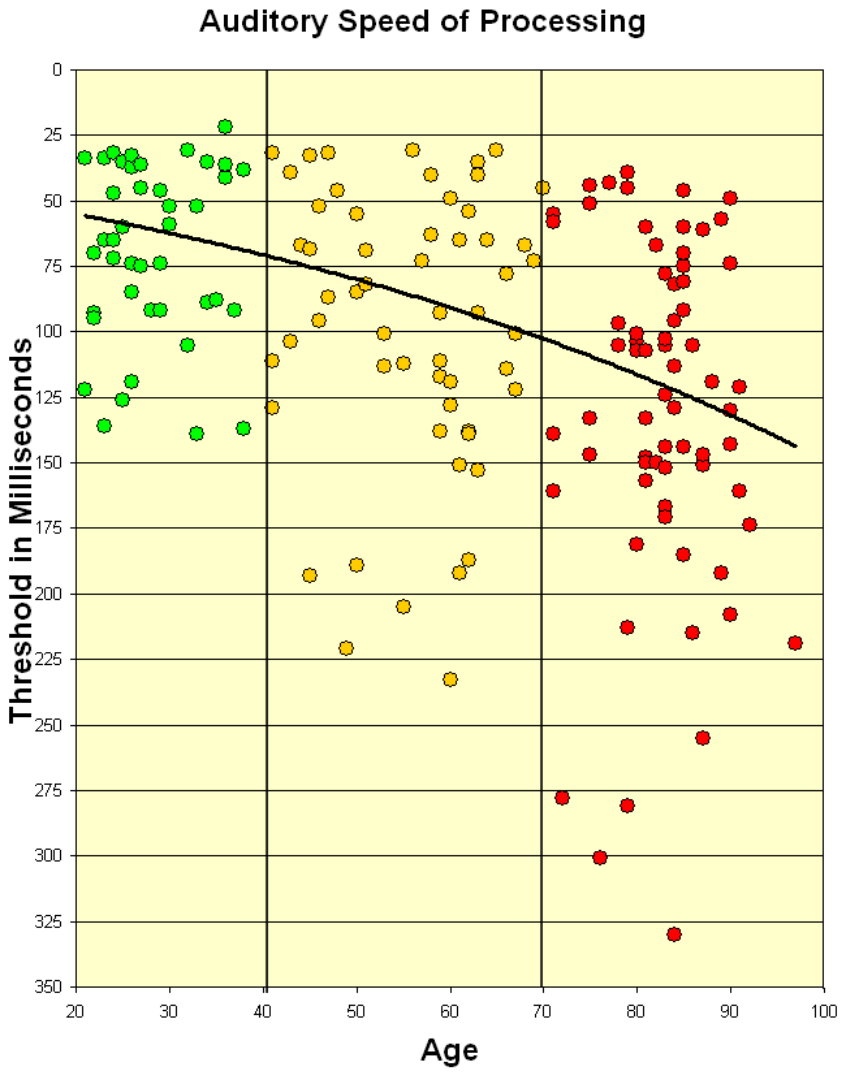


Source: Posit Science Qualitative Study 9/04

Brainspan Should Match Lifespan



The Brain Changes *Functionally* With Age – Encoding and Processing Speed

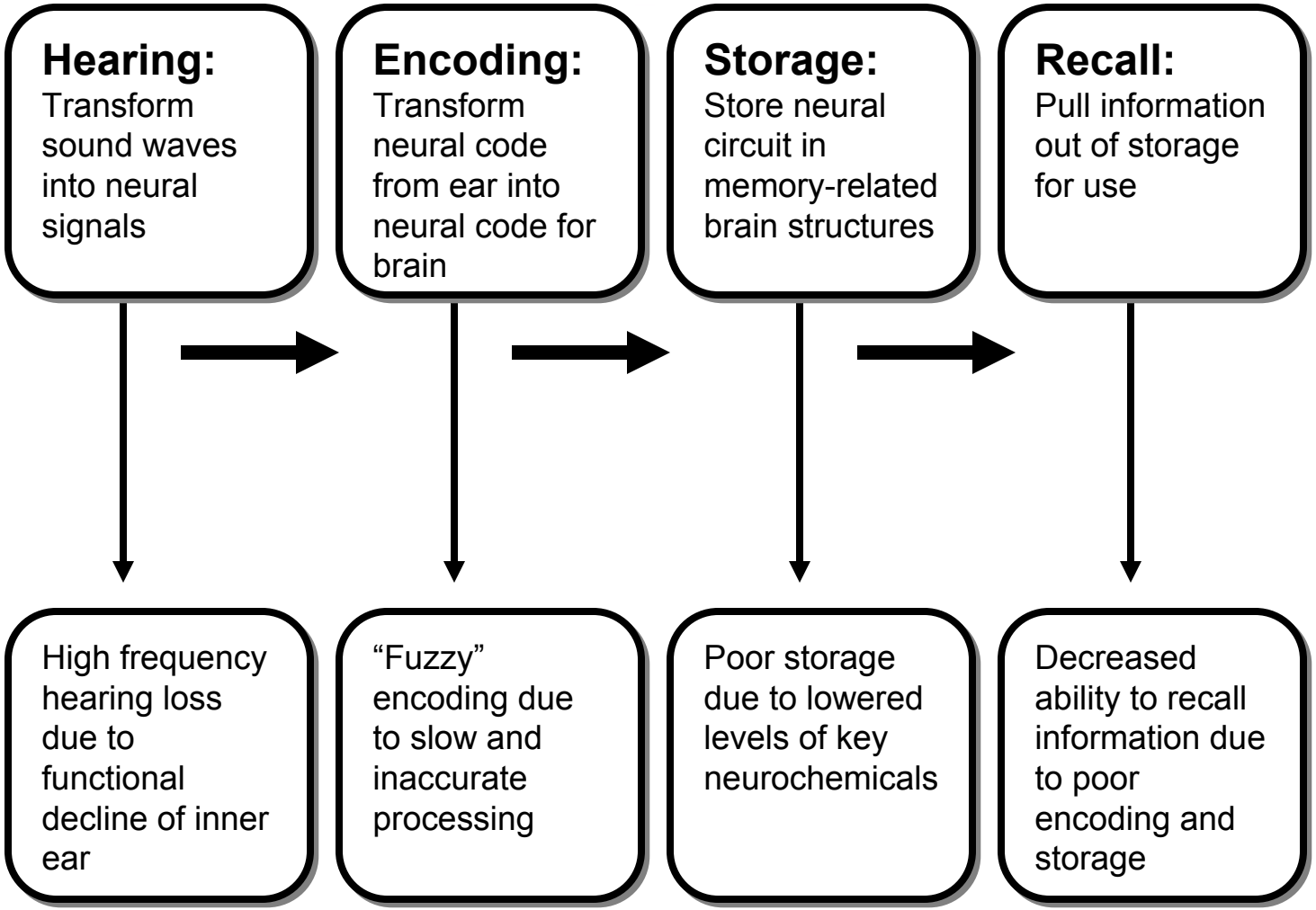


At age 75, it takes us more than twice as long to process information than when we were age 20

And this is why we all need to work on keeping our brain sharp…

How do we remember?

A science perspective



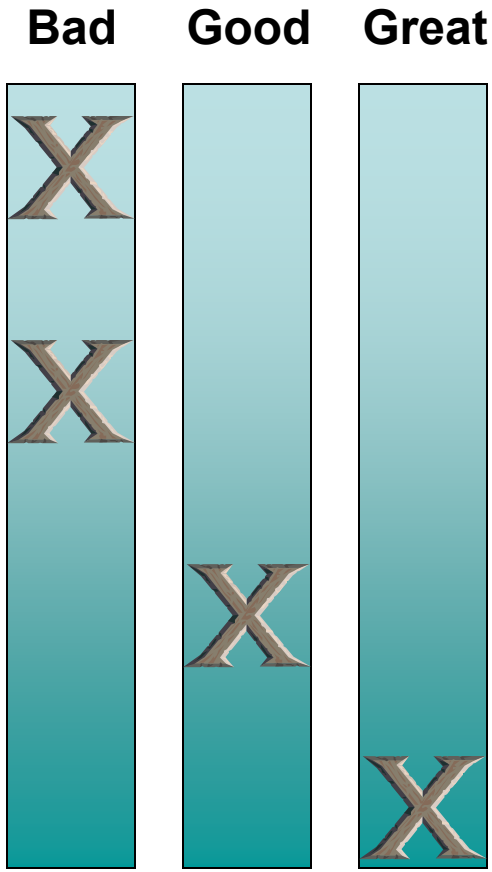
What Do People Do About Cognitive Decline?

Do nothing

Compensate

Crosswords, etc

Targeted Exercise



We have control over important causes of brain function decline

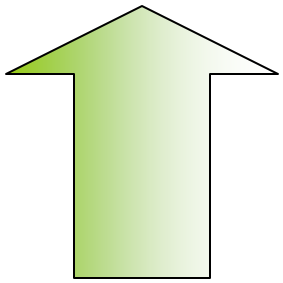
Aging Machinery	Noisy Processing	Chemical Changes	Negative Behavior
Loss of hearing in the ear Shrinkage of brain	"Fuzzy" input reduces accuracy and slows brain processing functions	Lower levels of memory-enabling chemicals released	"Do Nothing" and compensatory Habits lead to under use

"Negative Plasticity"

Within **our control**

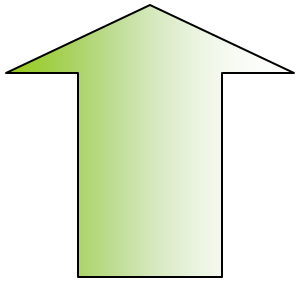
Characteristics of Activities that Prevent and Reverse Brain Function Change

Noisy Processing



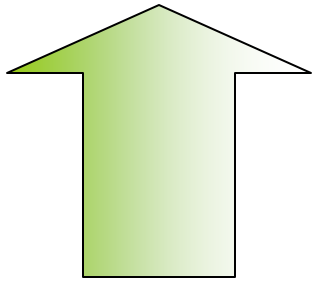
- Appropriately challenging
- Repetitive and intensive

Chemical Changes



- Frequently Rewarding
- Attentionally demanding
- Surprising

Negative Behavior



- New
- Demanding
- Confronting

Increase cognitive reserve?

Many Lifestyle Changes May Help With Brain Fitness

- Regular Exercise
- Sleep
- Stress Relief
- Socialization
- Diet

…The <u>Real Power</u> is in targeting the root causes of brain function change

Nutrients acts as dietary signals

Nutritional factors

↓

Transcription factors

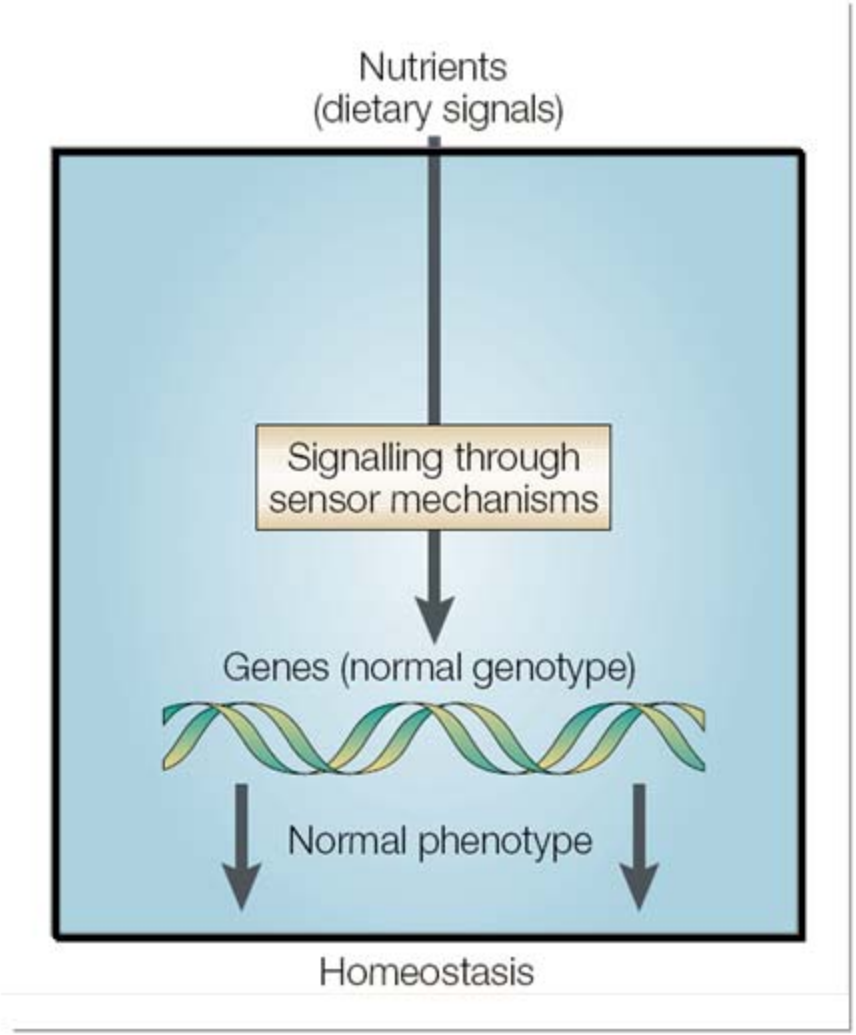
↓

Gene transcription

Energy homeostasis

Cell proliferation

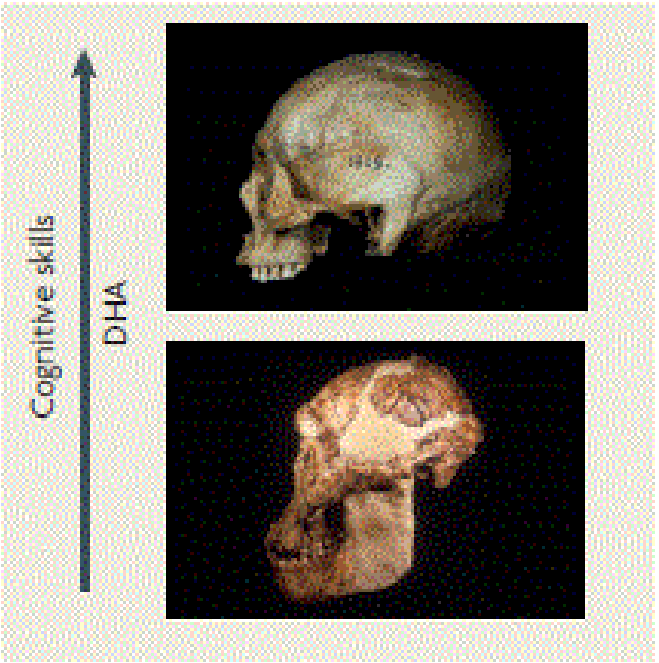
Nutrient absorption



Published in final edited form as:
Nat Rev Neurosci. 2008 July ; 9(7): 568–578. doi:10.1038/nrn2421.

Brain foods: the effects of nutrients on brain function

Fernando Gómez-Pinilla
Departments of Neurosurgery and Physiological Science, University of California at Los Angeles School of Medicine, Los Angeles 90095, California, USA



Crawford MA, et al. Evidence for the unique function of docosahexaenoic acid during the evolution of the modern hominid brain. Lipids 1999;34 (Suppl):39–47.

Mediterranean Diet, Alzheimer Disease, and Vascular Mediation

Nikolaos Scarmeas, Yaakov Stern, Richard Mayeux, Jose A. Luchsinger. Arch Neurol. 2006;63:1709-1717

Higher adherence to the MeDi is associated with a reduced risk for AD. The association does not seem to be mediated by vascular comorbidity. This could be the result of other biological mechanisms (oxidative or inflammatory) being implicated.

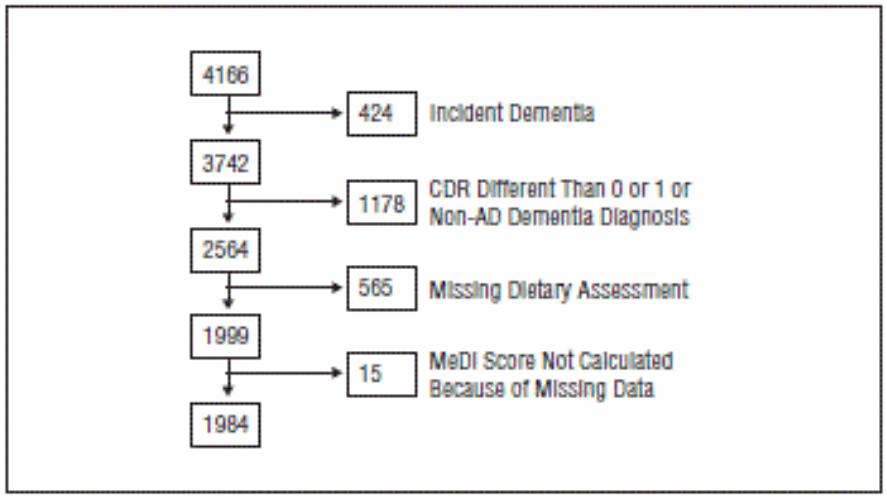


Figure 1. Flowchart describing sample size. AD indicates Alzheimer disease; CDR, Clinical Dementia Rating; MeDi, Mediterranean diet.

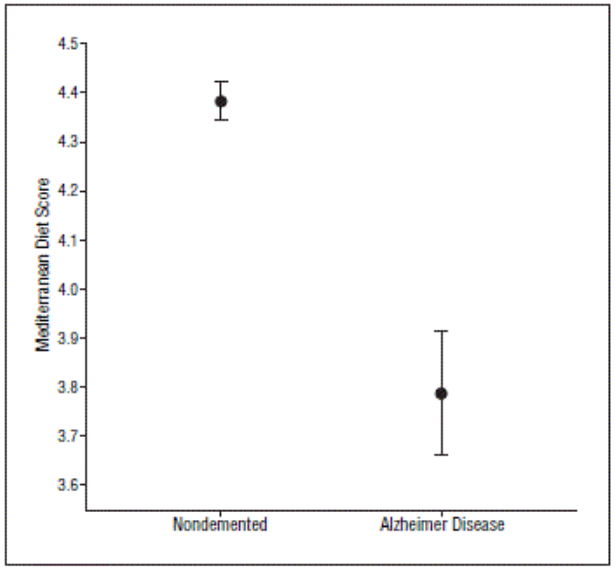


Figure 2. Means and standard errors of Mediterranean diet score for subjects with Alzheimer disease and nondemented subjects.

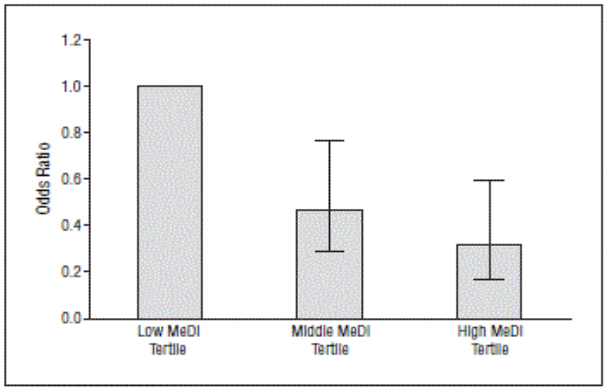


Figure 3. Odds ratios and 95% confidence intervals (bars) for subjects with Alzheimer disease vs nondemented subjects, for each Mediterranean diet (MeDi) adherence tertile based on logistic regression models that adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, comorbidity index, and body mass index (calculated as weight in kilograms divided by height in meters squared).

Physical Activity, Diet, and Risk of Alzheimer Disease

Nikolaos Scarmeas, Jose A. Luchsinger, Nicole Schupf, Adam M. Brickman, Stephanie Cosentino, Ming X. Tang and **Yaakov Stern.**

JAMA. 2009 August 12; 302(6): 627–637.

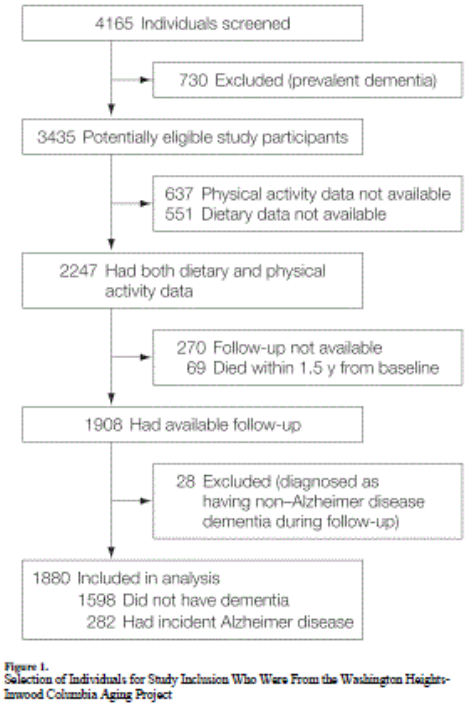
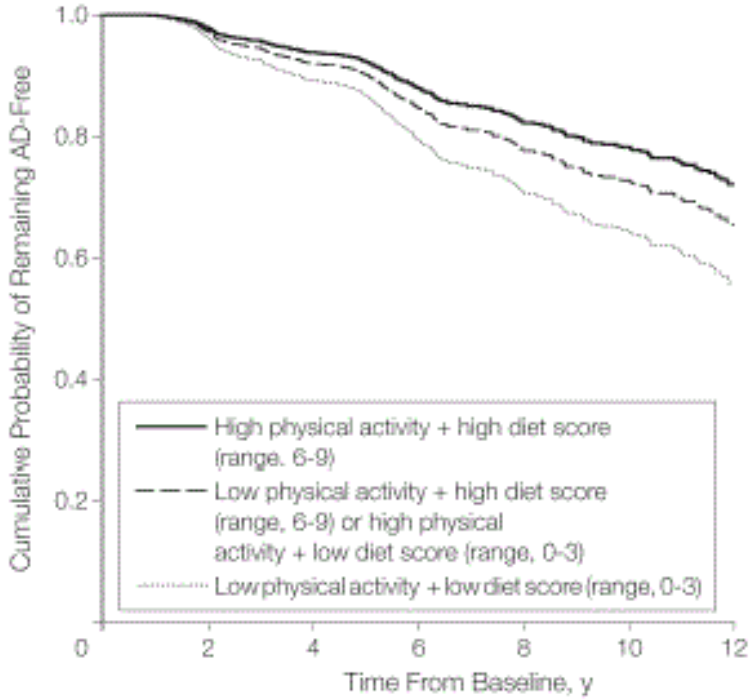


Figure 1.
Selection of Individuals for Study Inclusion Who Were From the Washington Heights-Inwood Columbia Aging Project



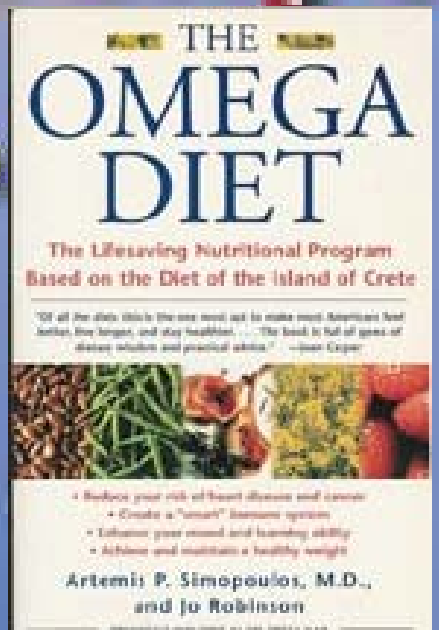
In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.

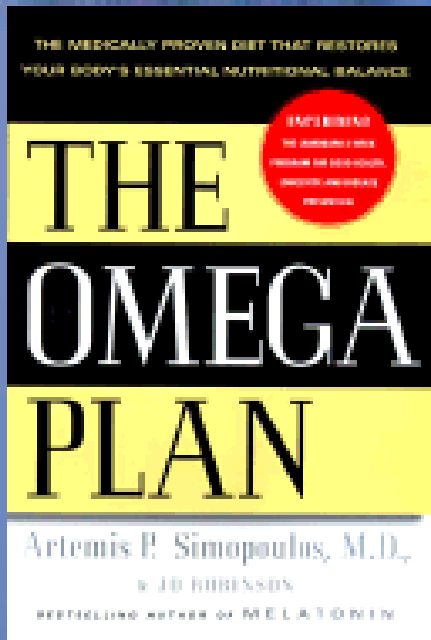
Evolutionary Aspects of Diet: Omega-6/Omega-3 Fatty Acid Ratio

Dr. Artemis P. Simopoulos

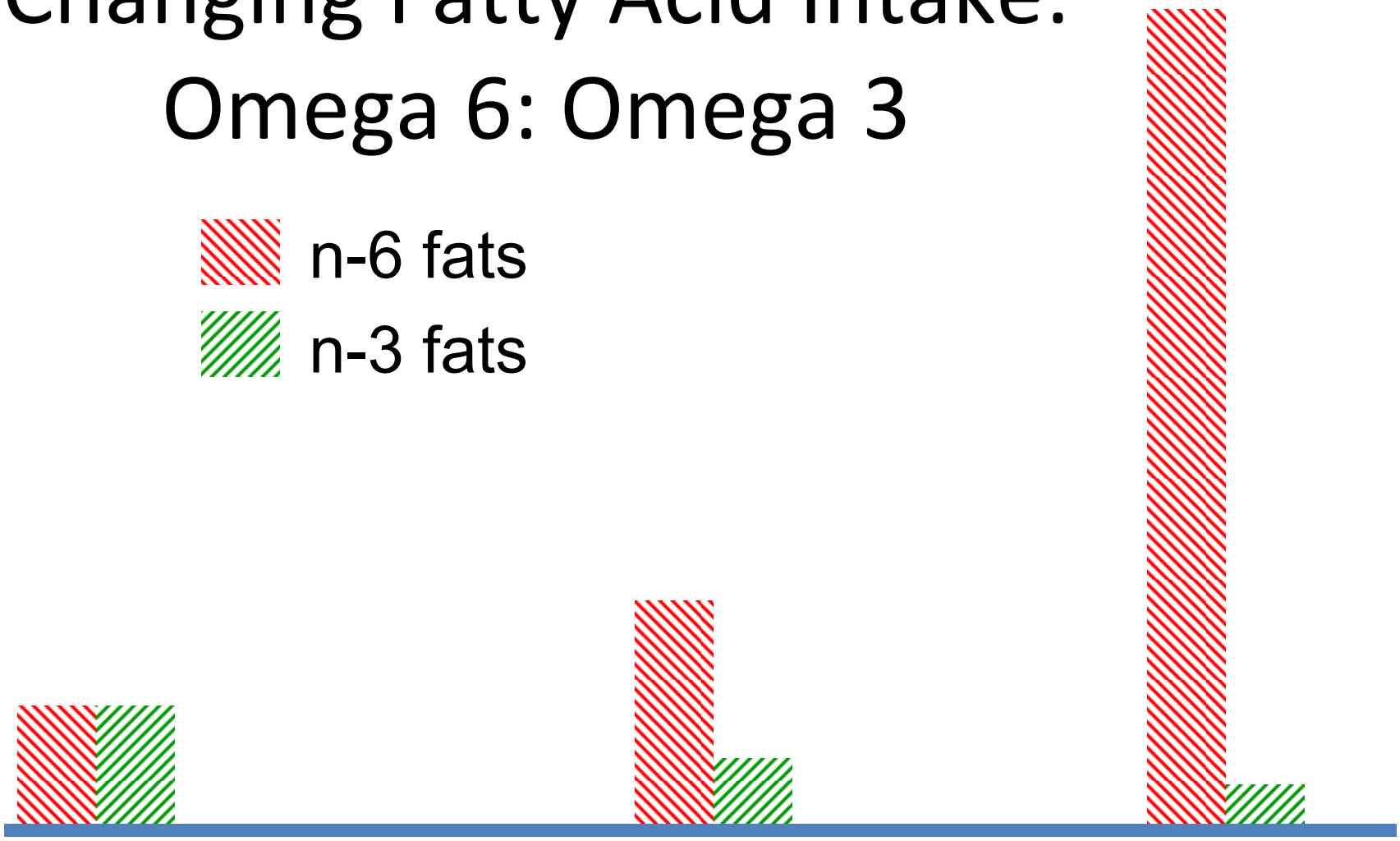
President and Founder
The Center for Genetics, Nutrition and Health,

Washington, DC





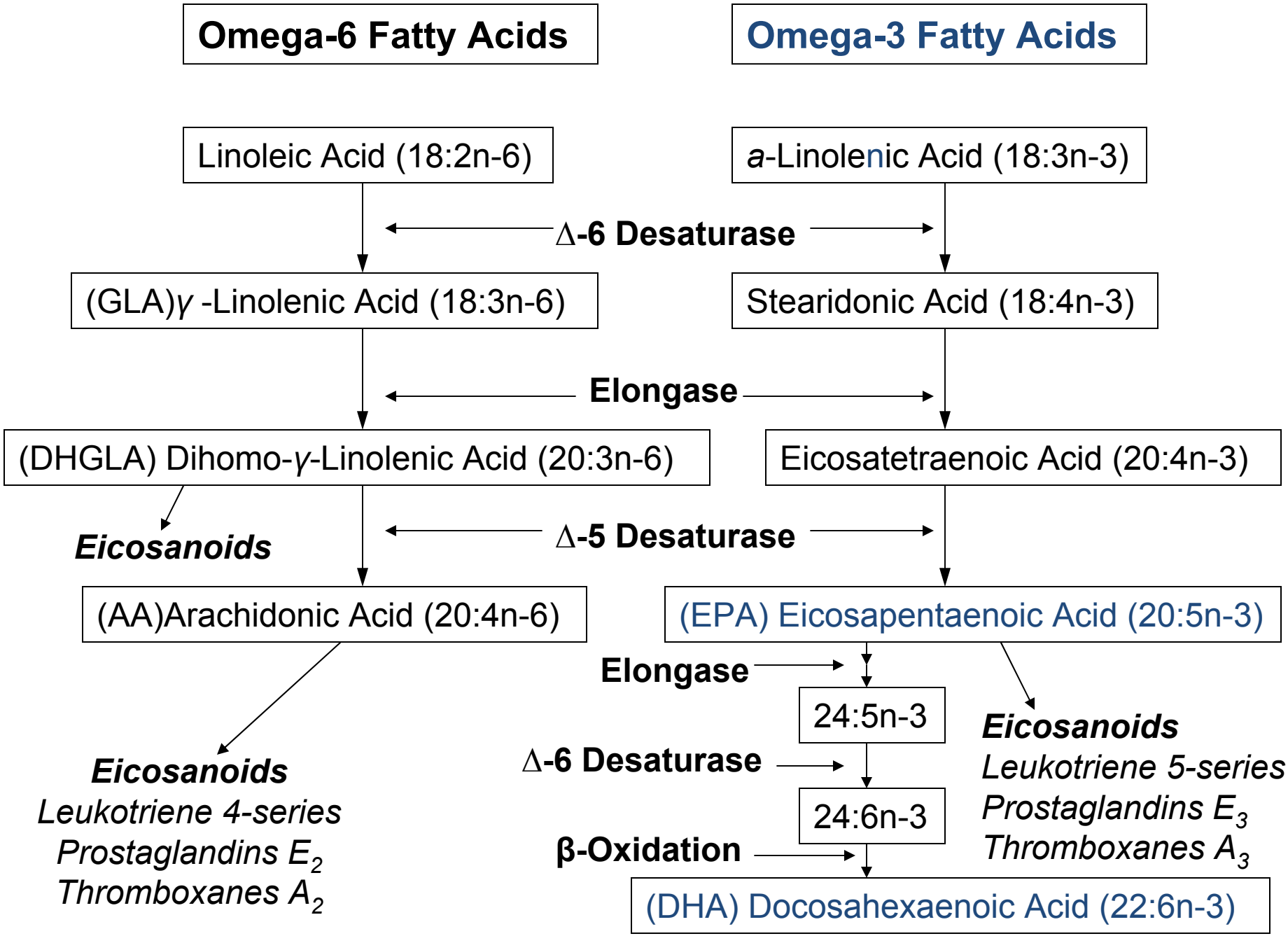
Changing Fatty Acid Intake: Omega 6: Omega 3



- Prehistoric
- 1:1

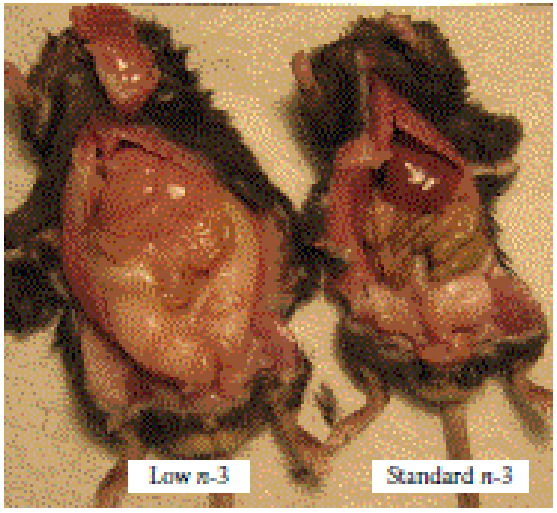
~ 1900
4:1

~ 2000
25:1

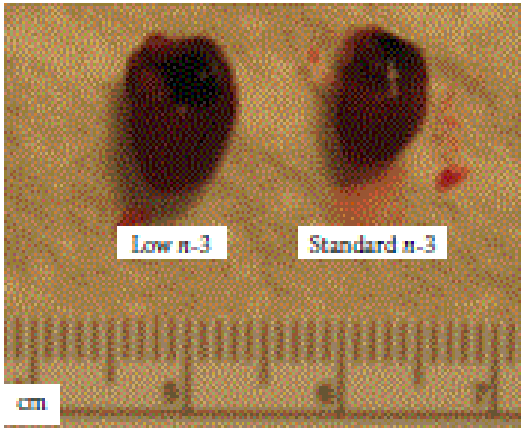

Omega-6 Fatty Acids
Omega-3 Fatty Acids
Linoleic Acid (18:2n-6)
a-Linolenic Acid (18:3n-3)
Δ-6 Desaturase
(GLA)γ -Linolenic Acid (18:3n-6)
Stearidonic Acid (18:4n-3)
Elongase
(DHGLA) Dihomo-γ-Linolenic Acid (20:3n-6)
Eicosatetraenoic Acid (20:4n-3)
Eicosanoids
Δ-5 Desaturase
(AA)Arachidonic Acid (20:4n-6)
(EPA) Eicosapentaenoic Acid (20:5n-3)
Elongase
24:5n-3
Eicosanoids
Leukotriene 4-series
Prostaglandins E2
Thromboxanes A2
Δ-6 Desaturase
24:6n-3
Eicosanoids
Leukotriene 5-series
Prostaglandins E3
Thromboxanes A3
β-Oxidation
(DHA) Docosahexaenoic Acid (22:6n-3)

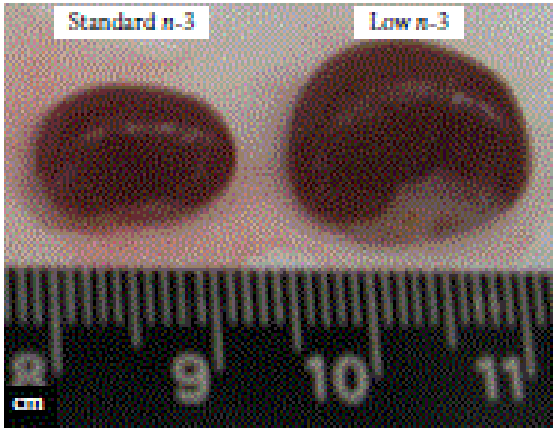
Hanbauer I, Rivero-Covelo I, Maloku E, Baca A, Hu Q, Hibbeln JR, Davis JM.
The Decrease of n-3 Fatty Acid Energy Percentage in an Equicaloric Diet Fed to B6C3Fe Mice for Three Generations Elicits Obesity.
Cardiovasc Psychiatry Neurol. 2009;2009:867041.

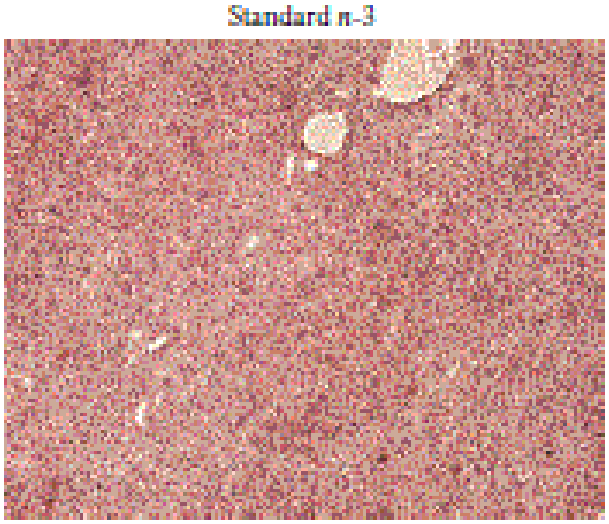
(a)



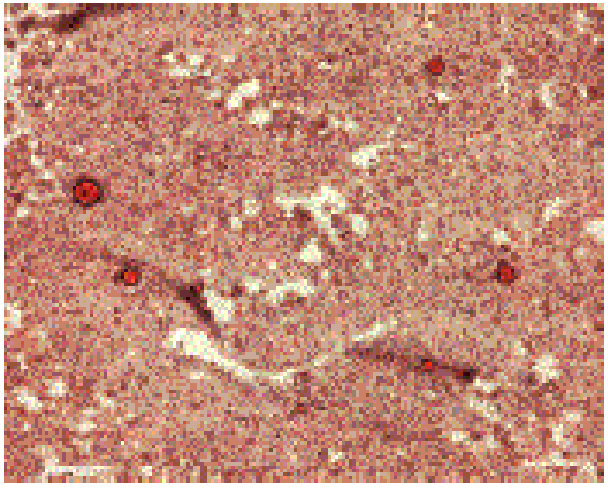
(b)





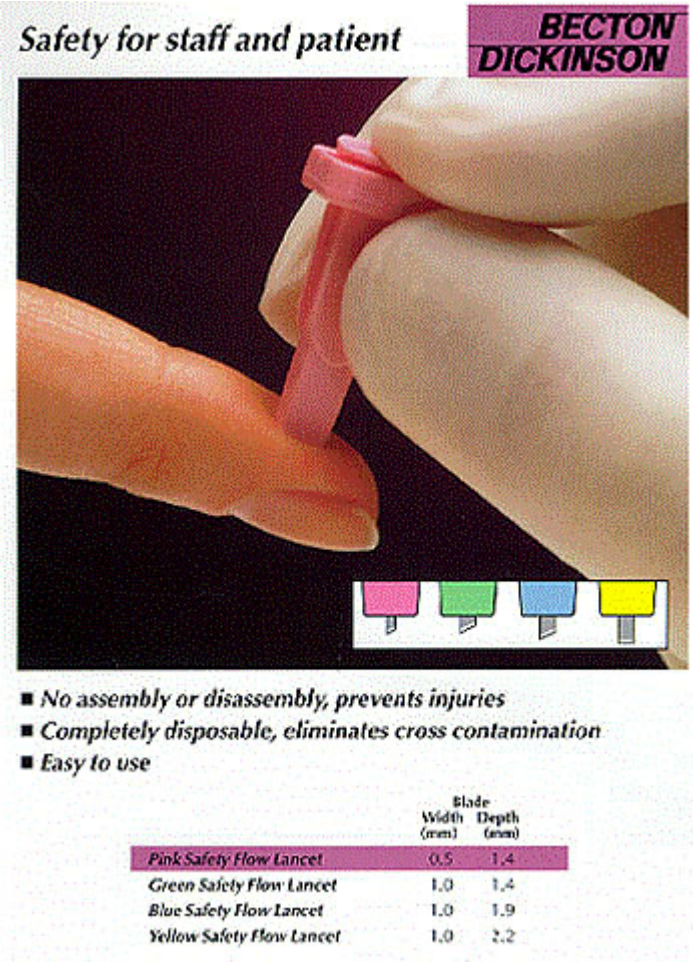


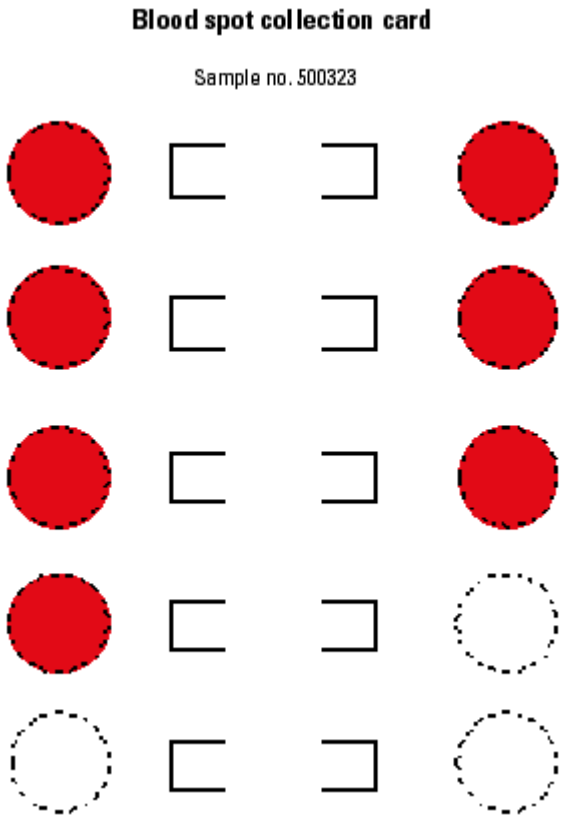
(a)

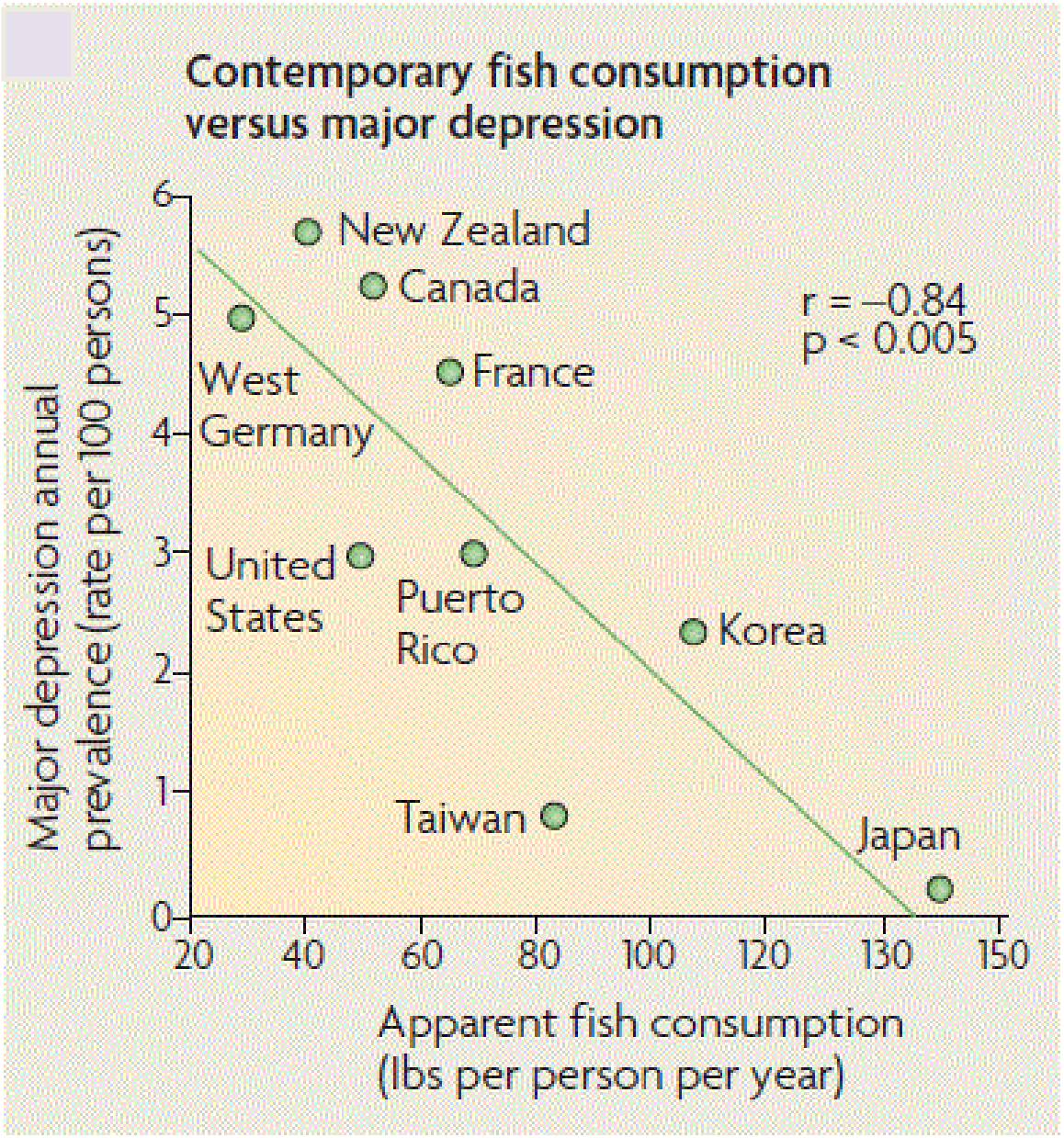


(b)

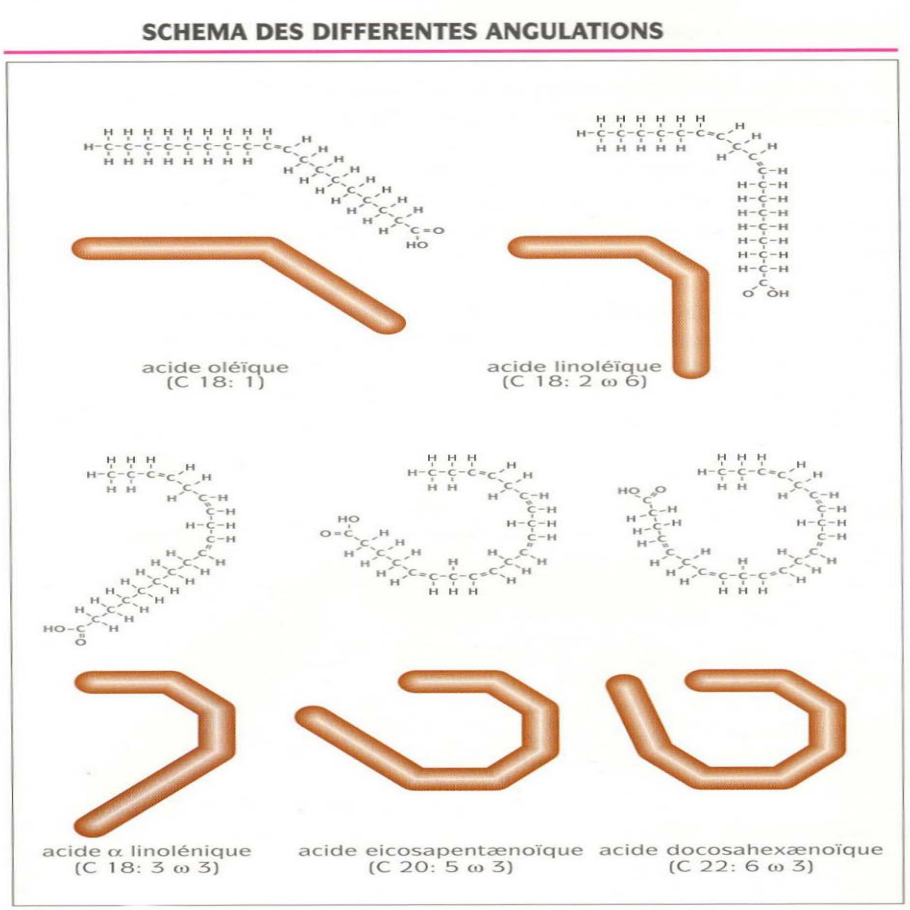
Procedure to assay total blood fatty acid composition





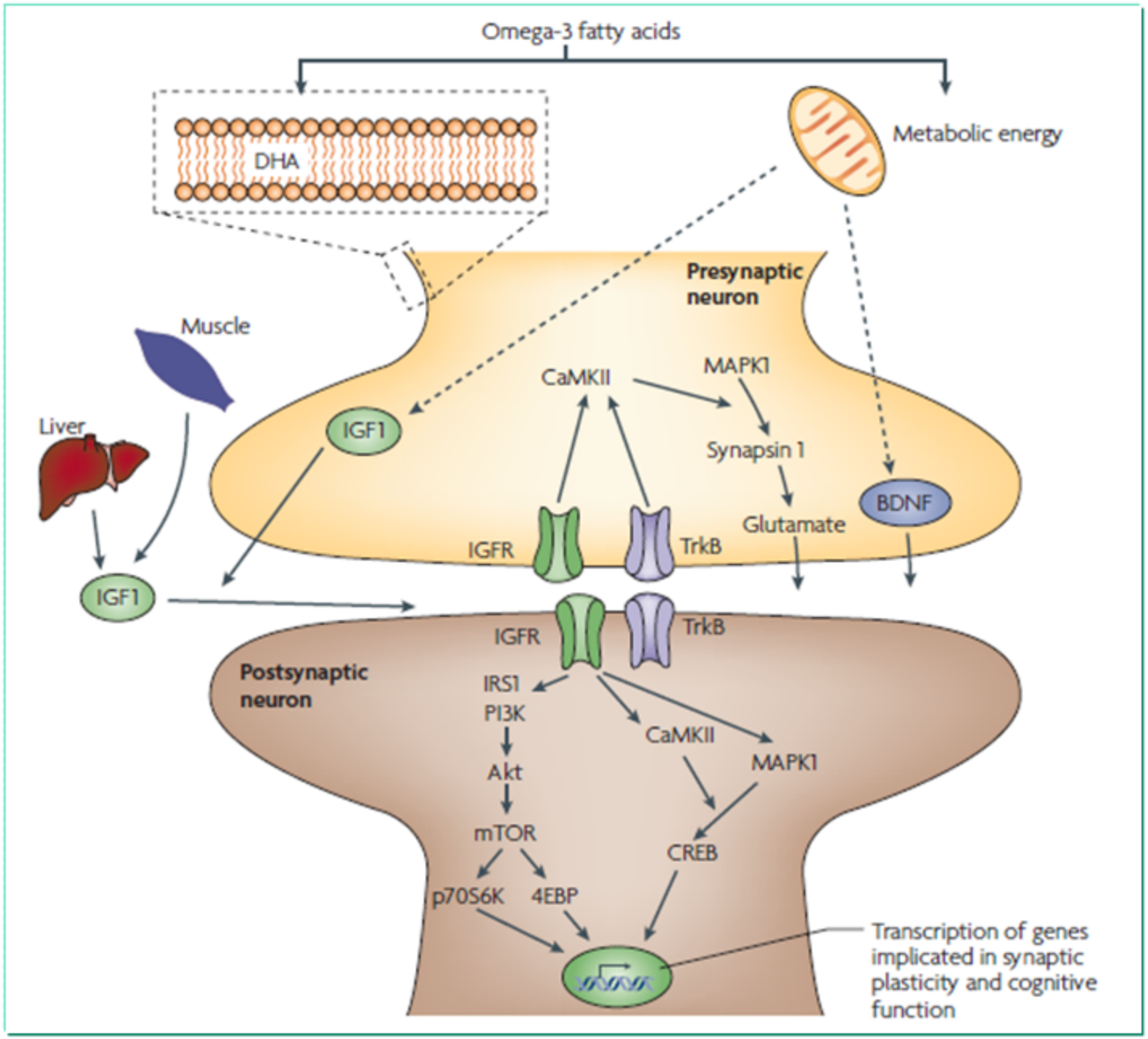

Contemporary fish consumption versus major depression
Major depression annual prevalence (rate per 100 persons)
6
5
4
3
2
1
0
New Zealand
Canada
West Germany
France
United States
Puerto Rico
Korea
Taiwan
Japan
r = –0.84
p < 0.005
20
40
60
80
100
120
130
150
Apparent fish consumption (lbs per person per year)

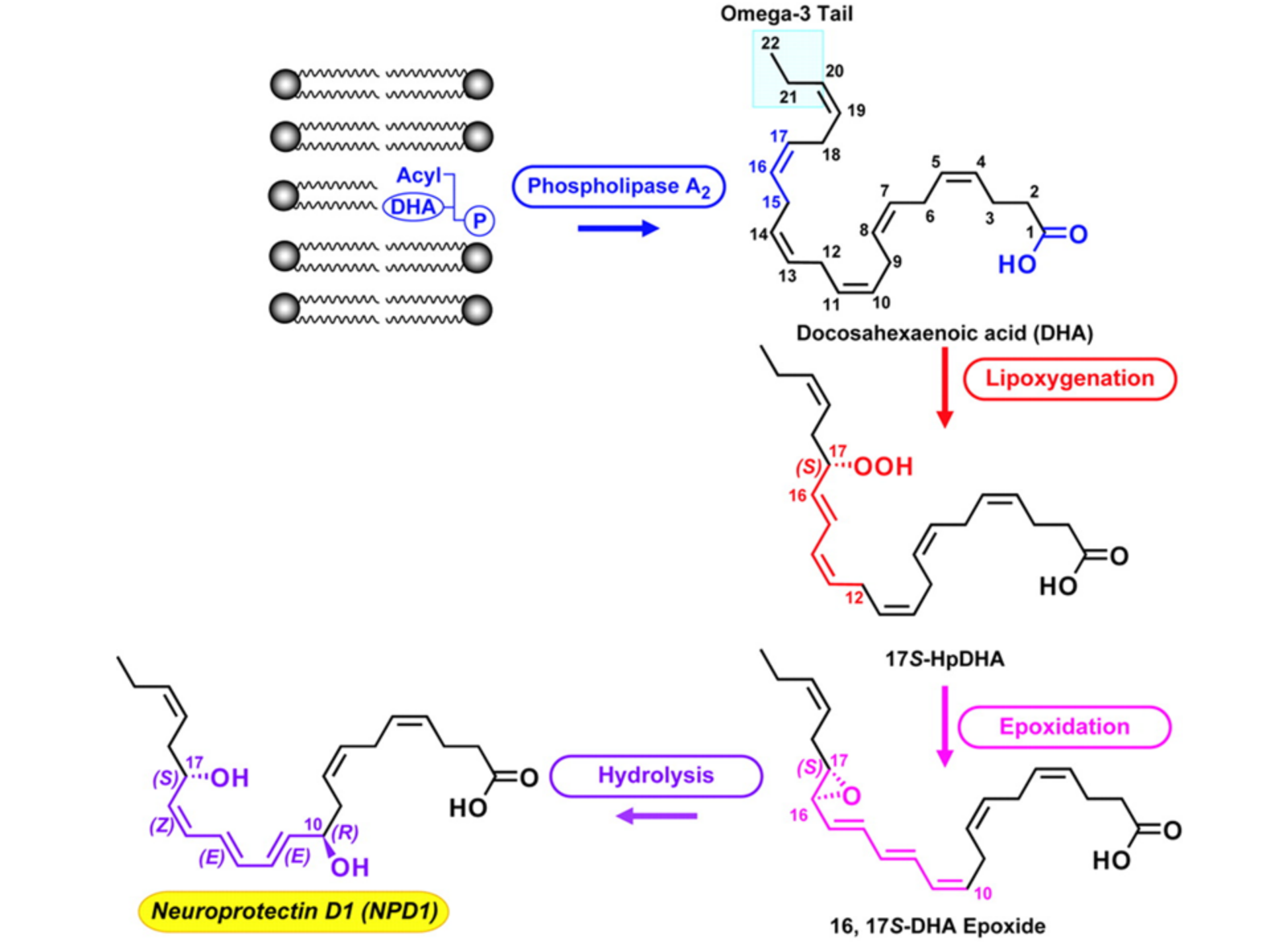
Gregory A Jicha & William R Markesbery



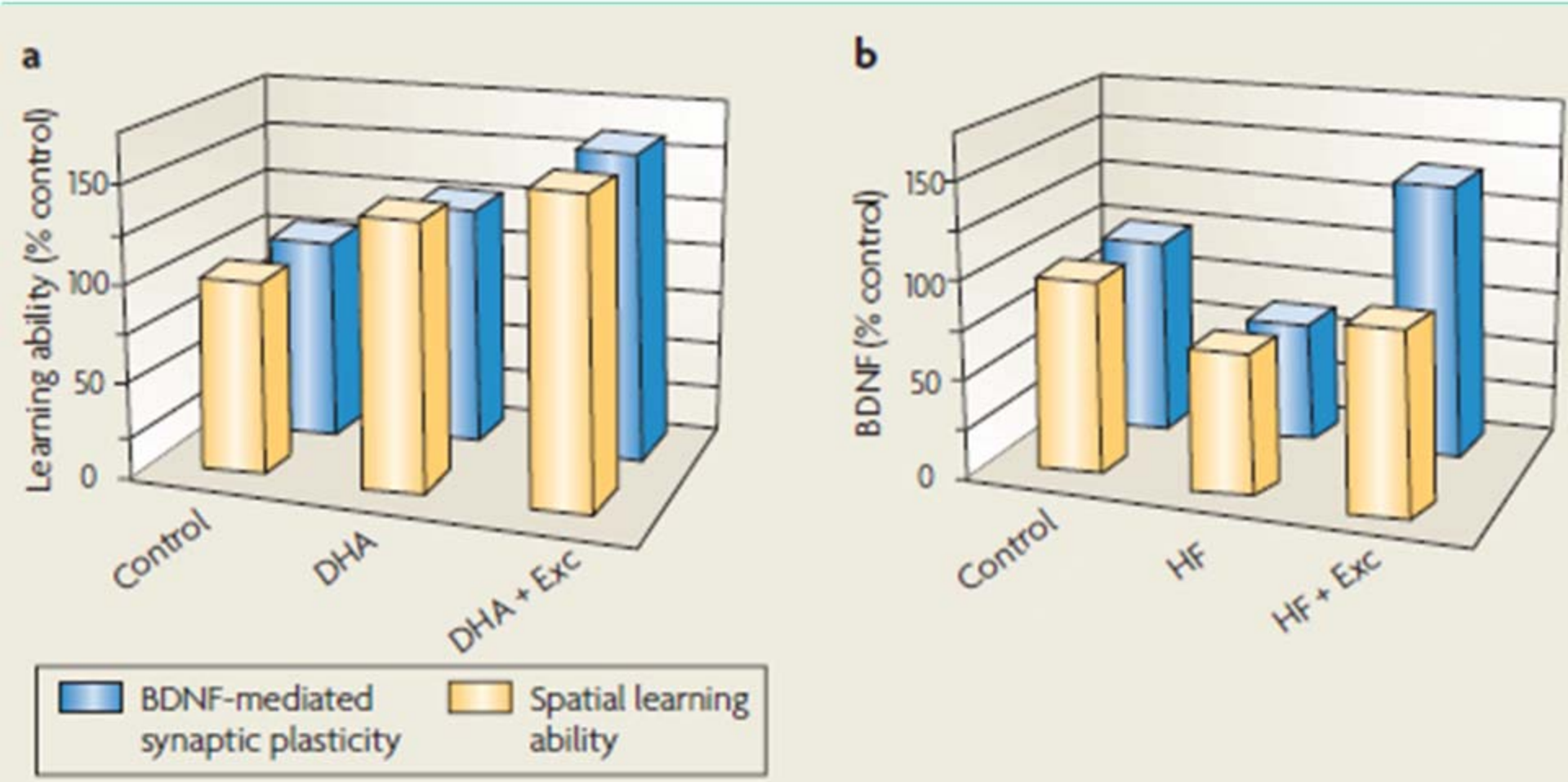
Clinical Interventions in Aging 2010:5 45–61

Dietary omega-3 fatty acids can affect synaptic plasticity and cognition.



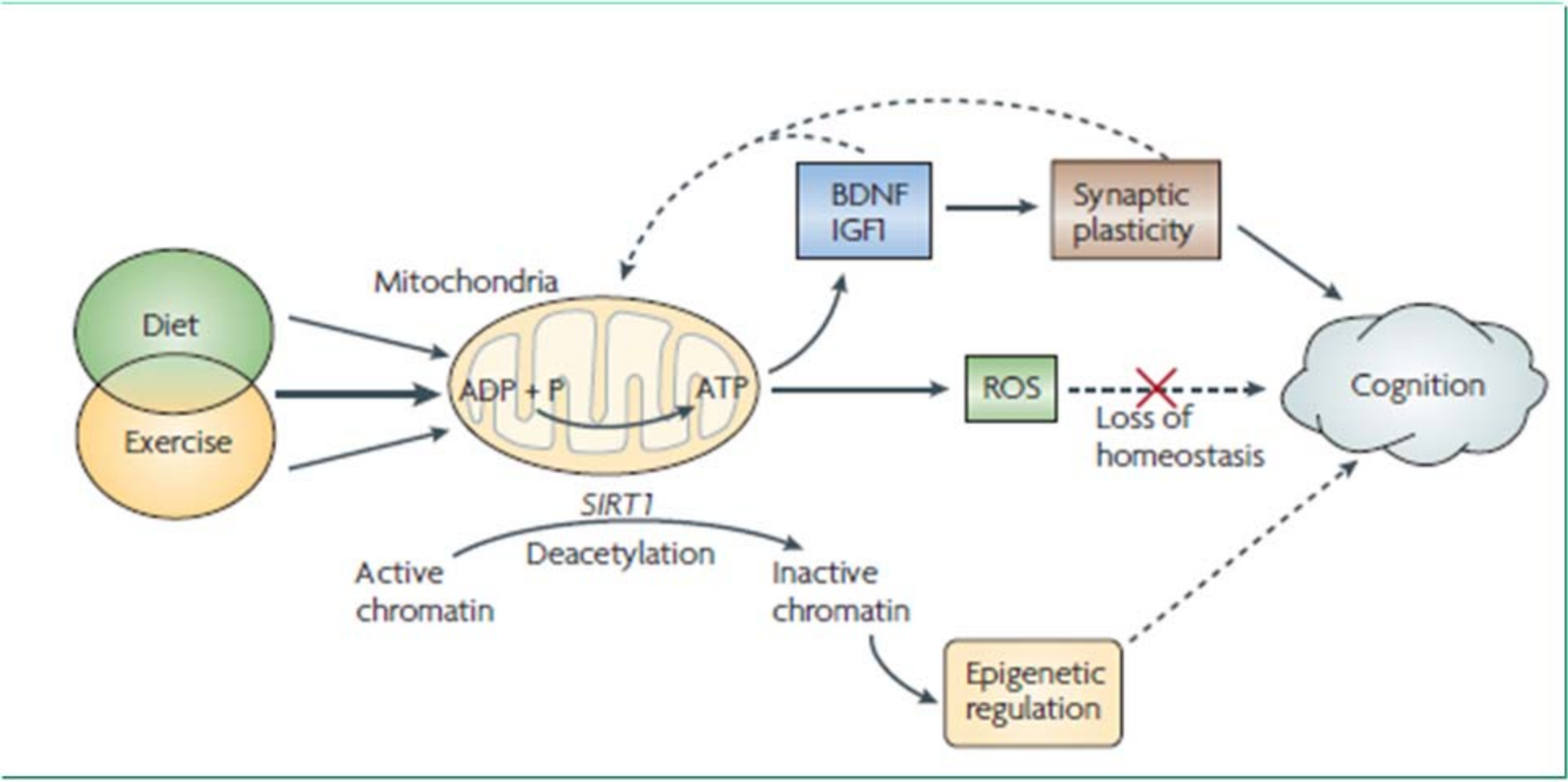

Omega-3 Tail
Acyl
DHA
P
Phospholipase A2
Docosahexaenoic acid (DHA)
Lipoxygenation
17S-HpDHA
Epoxidation
16, 17S-DHA Epoxide
Hydrolysis
Neuroprotectin D1 (NPD1)

Additive effects of diet and exercise on synaptic plasticity and cognitionc



Fernando Gómez-Pinilla. **Brain foods: the effects of nutrients on brain function**
Nature Neuroscience 2008

Diet, exercise and cognition.

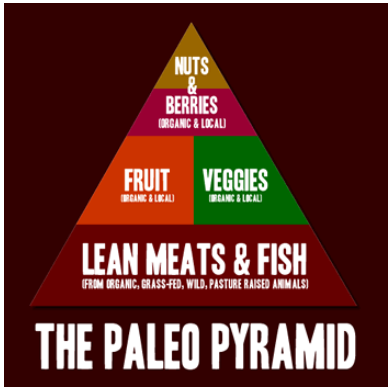


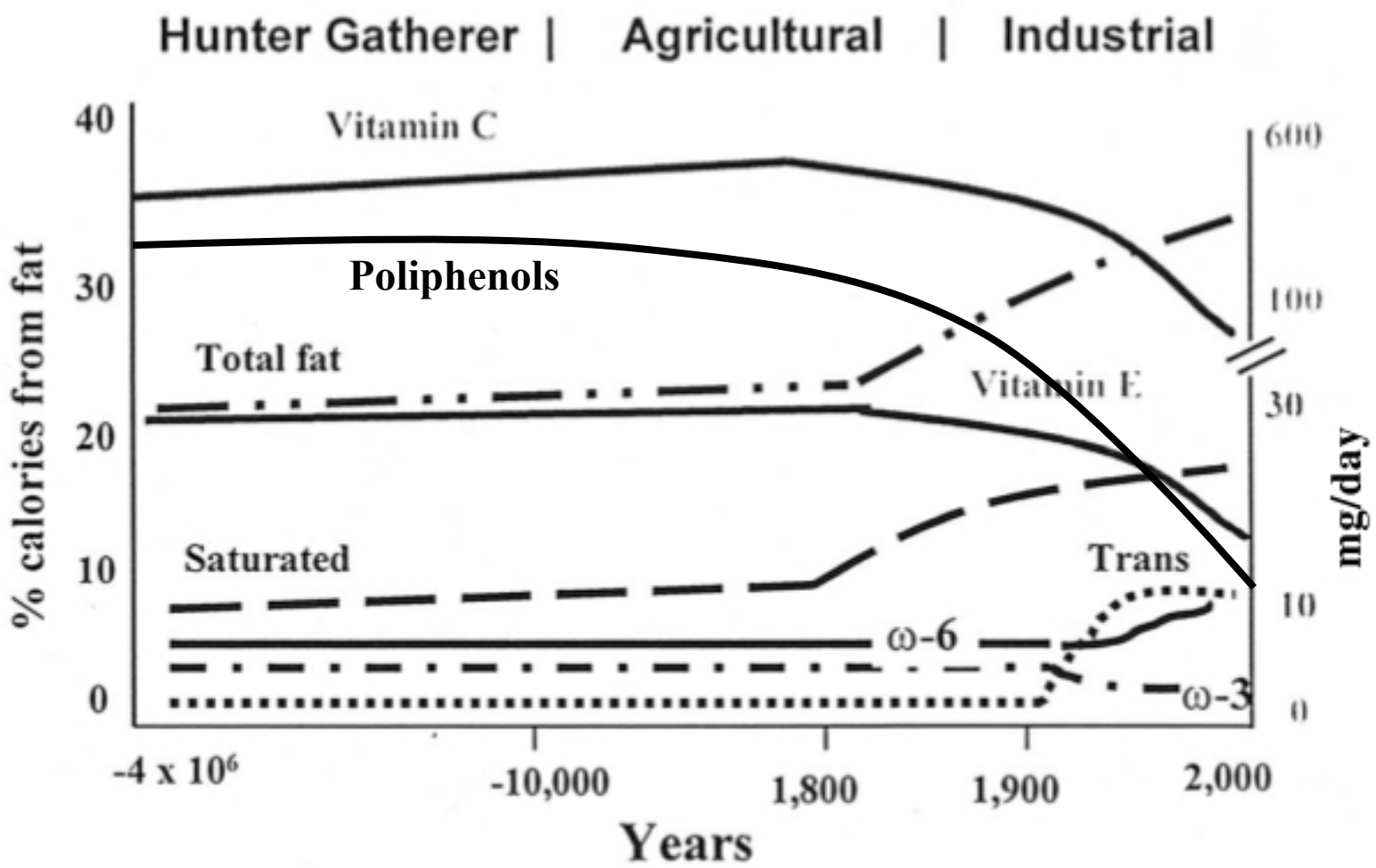
Fernando Gómez-Pinilla. Brain foods: the effects of nutrients on brain function
Nature Neuroscience 2008

Commentary on ‘‘A roadmap for the prevention of dementia II. Leon Thal Symposium 2008.’’ The Multidomain Alzheimer Preventive Trial (MAPT): A new approach to the prevention of Alzheimer’s disease

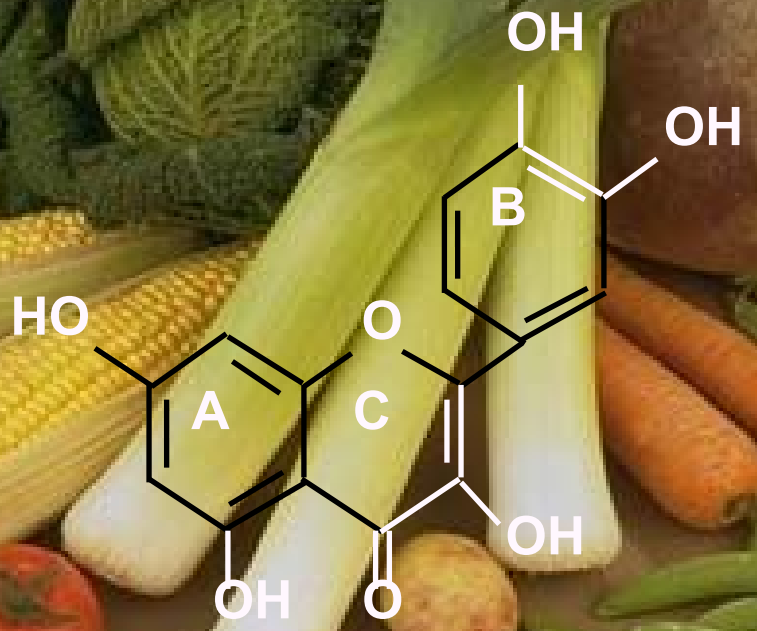
Sophie Gillette-Guyonneta, Sandrine Andrieua, Thierry Dantoinee, Jean-Francois Dartiguesf, Jacques Touchong, B. Vellasa, MAPT Study Group

Alzheimer’s & Dementia
5 (2009) 114–121

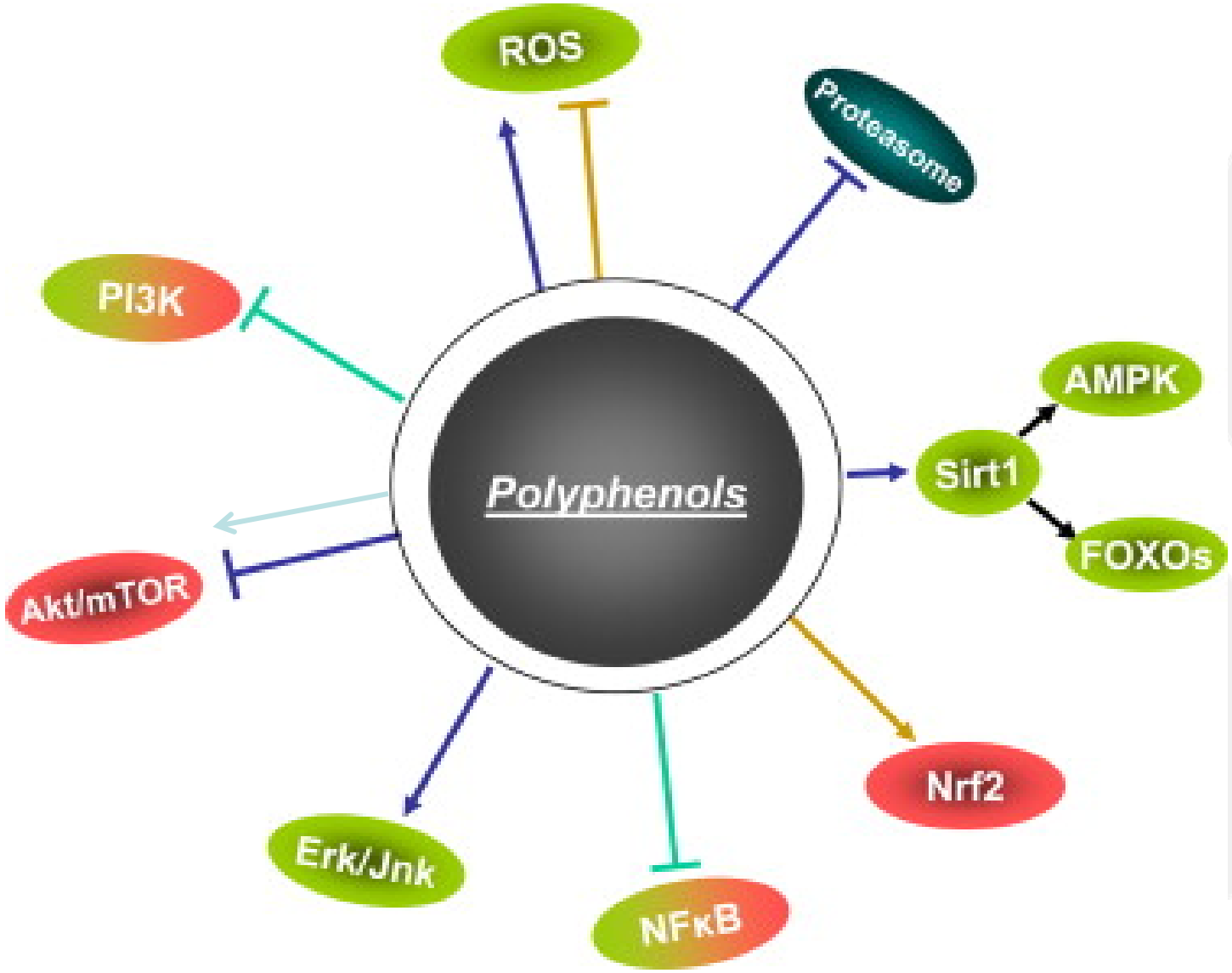

NUTS & BERRIES
(ORGANIC & LOCAL)
FRUIT
(ORGANIC & LOCAL)
VEGGIES
(ORGANIC & LOCAL)
LEAN MEATS & FISH
(FROM ORGANIC, GRASS-FED, WILD, PASTURE RAISED ANIMALS)
THE PALEO PYRAMID


Hunter Gatherer | Agricultural | Industrial
Vitamin C
Poliphenols
Total fat
Vitamin E
Saturated
Trans
ω-6
ω-3
% calories from fat
mg/day
40
30
20
10
0
600
100
30
10
0
-4 x 10⁶
-10,000
1,800
1,900
2,000
Years

POLIFENOLI



Major pathways activated by polyphenols



Classification of Antioxidants

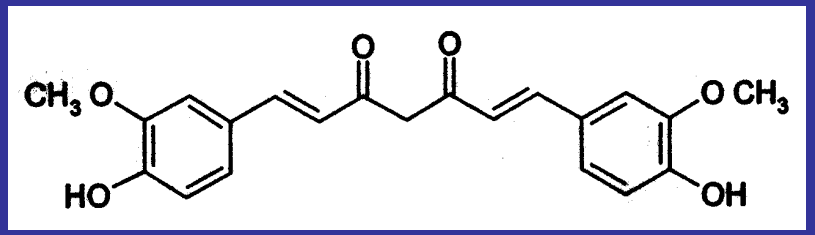
- Direct Antioxidants
  - Free radical scavengers (SOD/$O_2^{-\cdot}$)
  - Non radical scavengers (Catalase/H_2O_2)
- Indirect Antioxidants
  - Inhibitors of cellular sources of oxidants (chelators/metals, apocynin/Nox)
  - Inducers of cellular antioxidants (sulforaphane/Nrf2 targets-GSH)

Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V.

Curcumin activates defensive genes and protects neurons against oxidative stress.

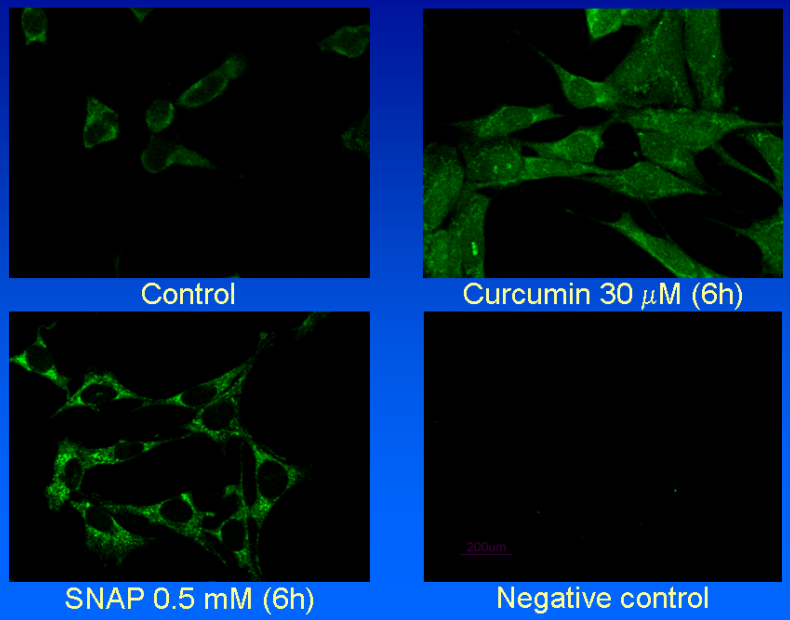
Antioxid Redox Signal. 2006 Mar-Apr;8(3-4):395-403.

Institute of Neurological Sciences, National Research Council (CNR), Catania, Italy.,
Blanchette Rockefeller Neurosciences Institute, West Virginia University, Rockville, Maryland.

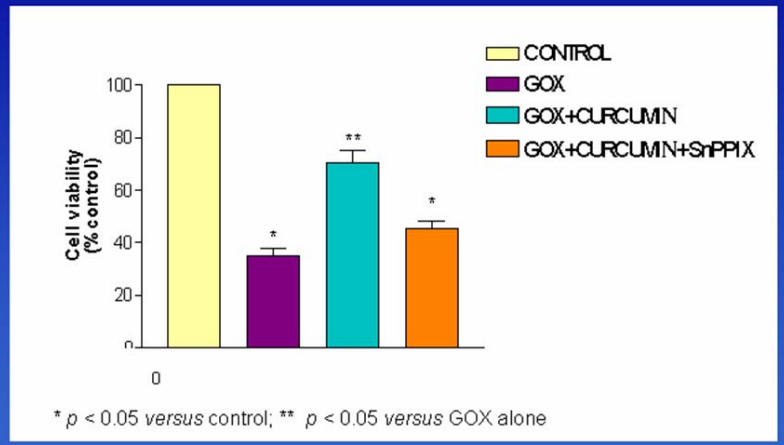


CURCUMIN

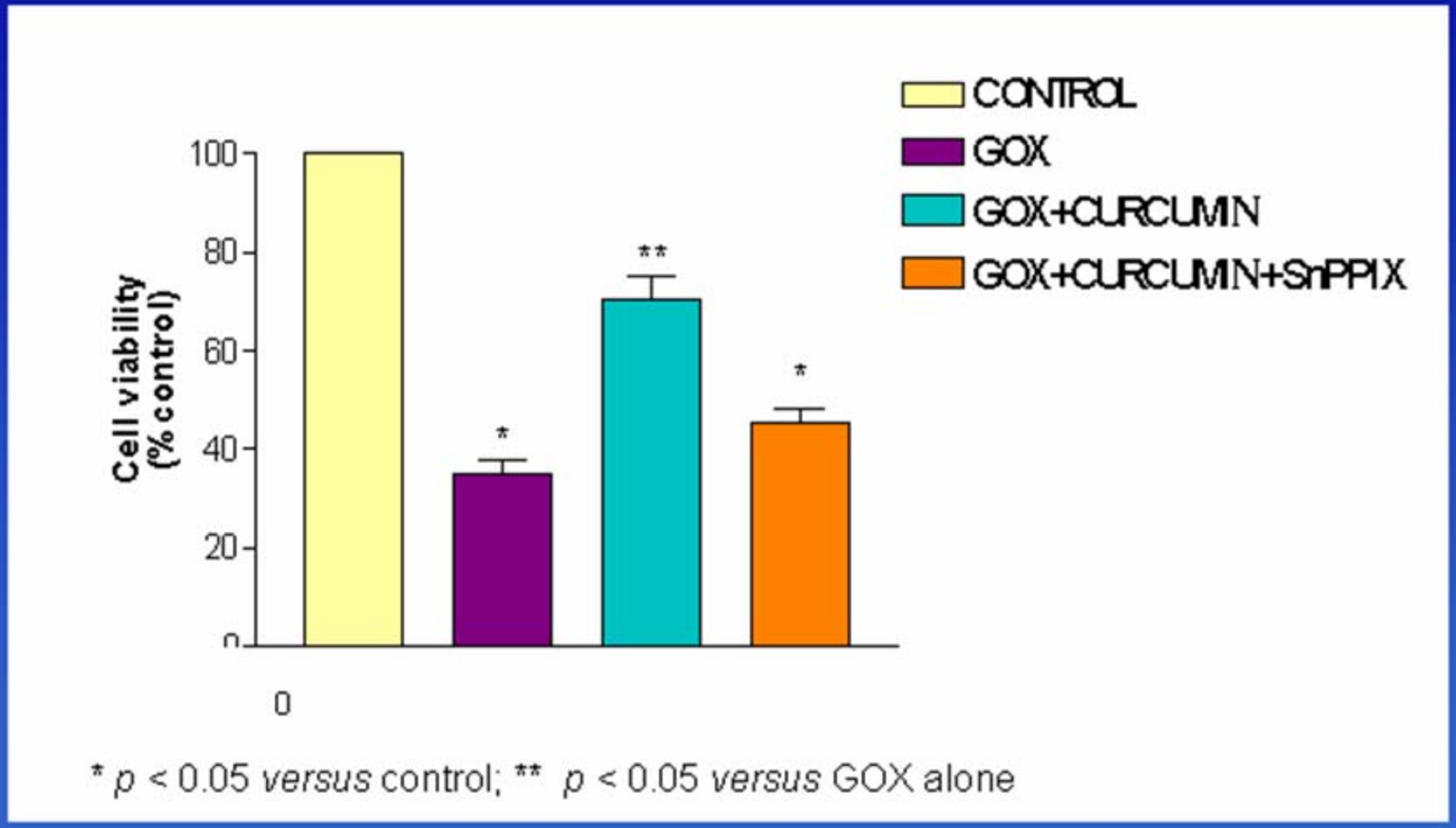
Effect of curcumin and SNAP on HO-1 protein expression in astrocytes



Effect of curcumin on glucose oxidase (GOX) mediated cellular injury in cortical neurons

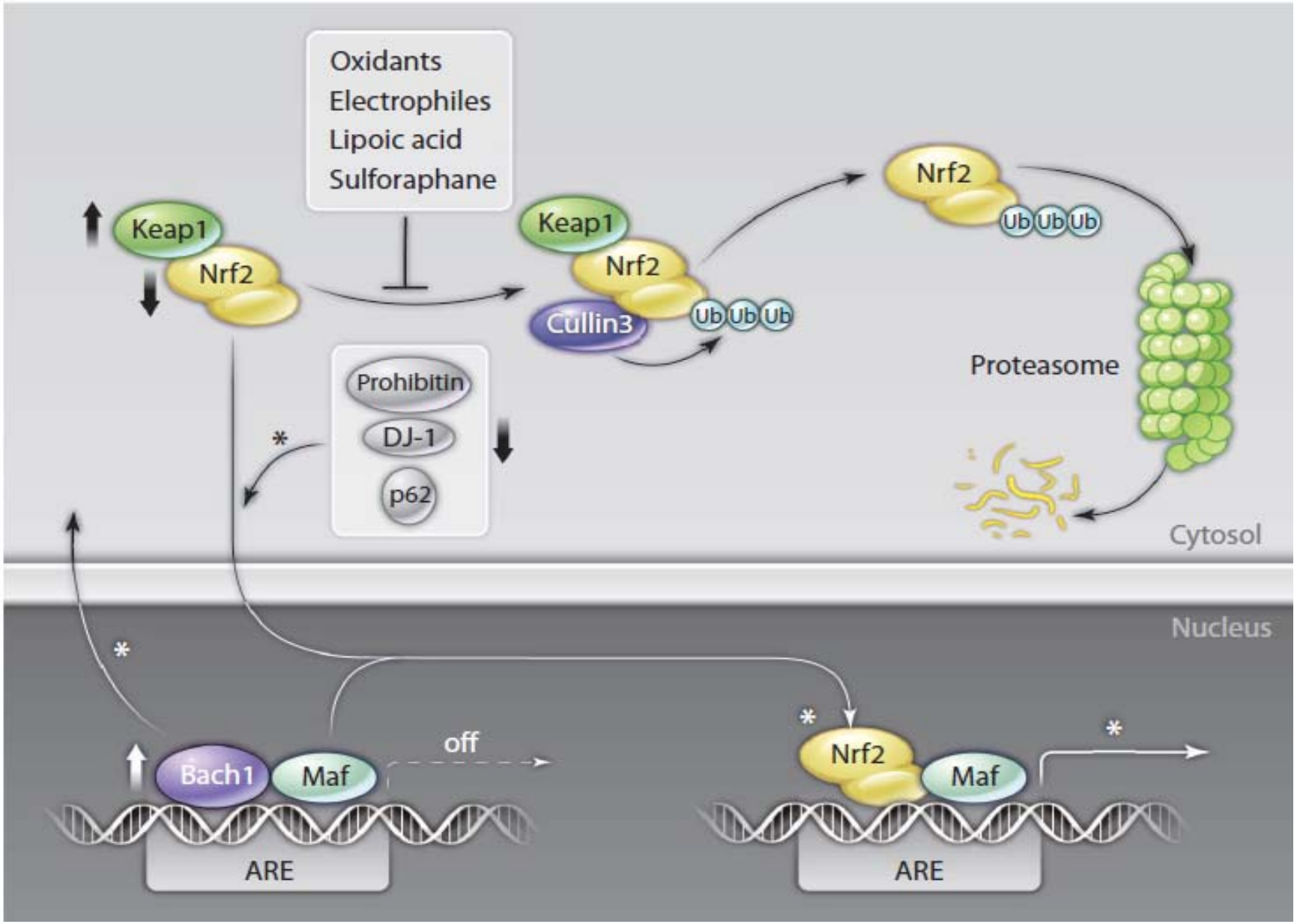


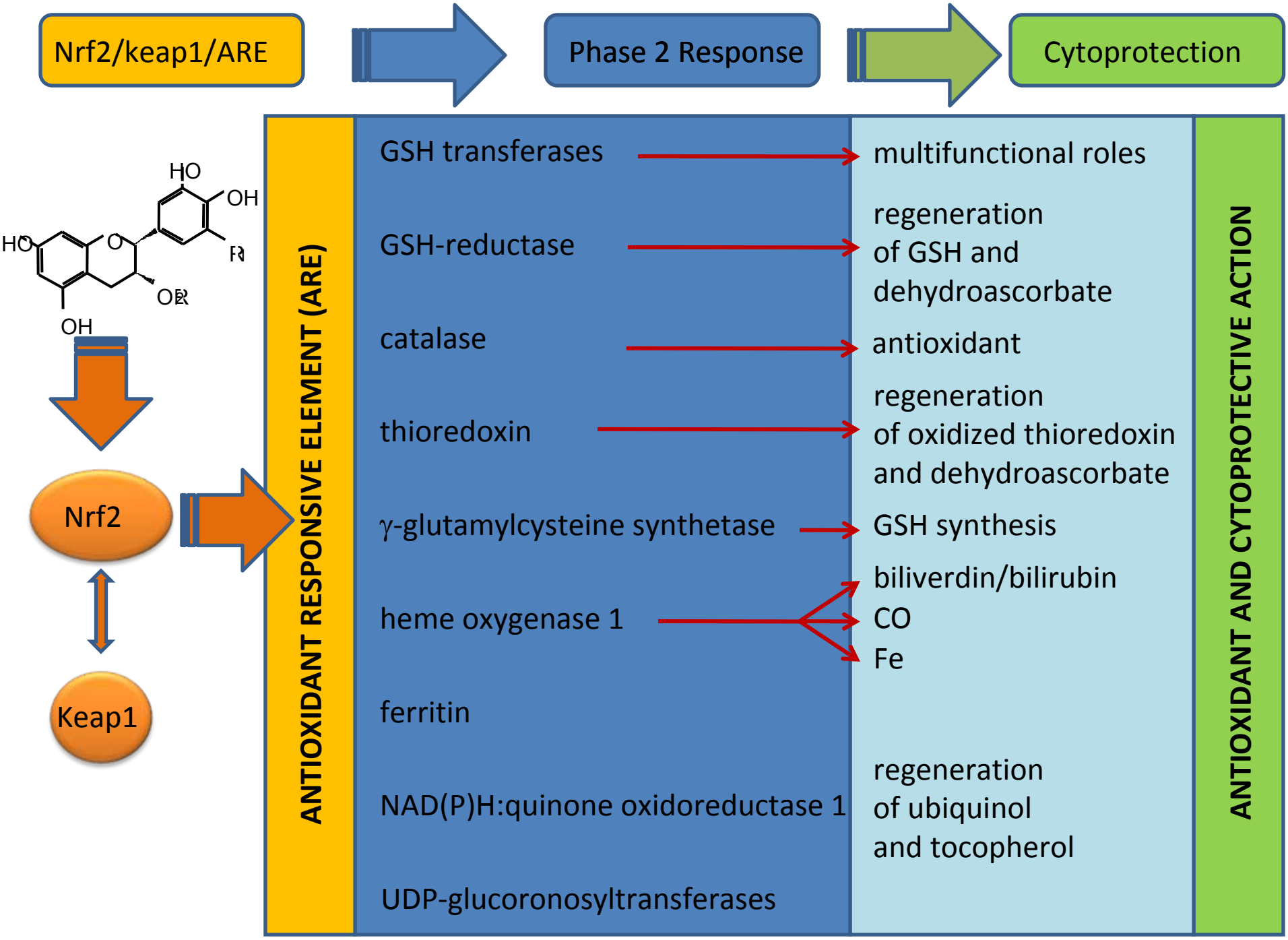
Effect of curcumin on glucose oxidase (GOX) mediated cellular injury in cortical neurons



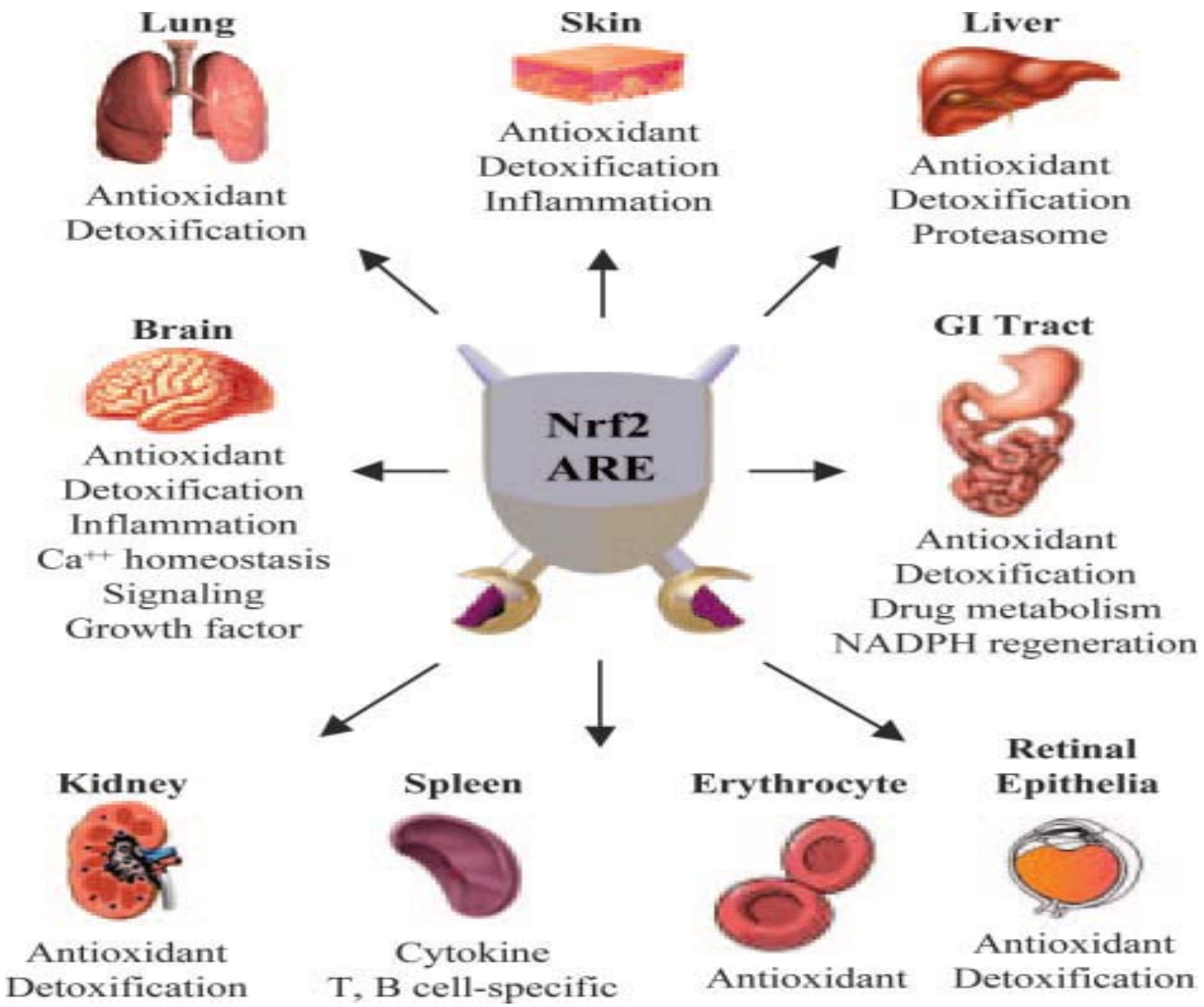
Scapagnini G. et al. Antioxid Redox Signal. 2006

The Keap1-Nrf2-ARE signaling pathway




Nrf2/keap1/ARE
Phase 2 Response
Cytoprotection
HO
OH
HO
O
OH
OH
Nrf2
Keap1
ANTIOXIDANT RESPONSIVE ELEMENT (ARE)
GSH transferases
multifunctional roles
GSH-reductase
regeneration of GSH and dehydroascorbate
catalase
antioxidant
thioredoxin
regeneration of oxidized thioredoxin and dehydroascorbate
γ-glutamylcysteine synthetase
GSH synthesis
heme oxygenase 1
biliverdin/bilirubin
CO
Fe
ferritin
NAD(P)H:quinone oxidoreductase 1
regeneration of ubiquinol and tocopherol
UDP-glucoronosyltransferases
ANTIOXIDANT AND CYTOPROTECTIVE ACTION

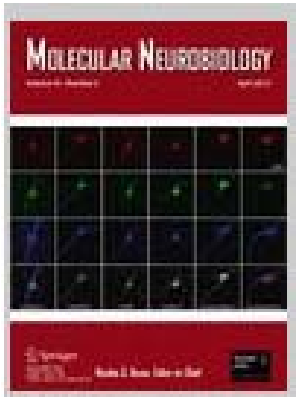
Multi-organ protection by the Nrf2 pathway



Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders.

Scapagnini G, Vasto S, Abraham NG, Caruso C, Zella D, Galvano F.

Mol Neurobiol. 2011 Oct;44(2):192-201.



Received: 30 November 2010 / Accepted: 4 April 2011

Abstract In recent years, there has been a growing interest, supported by a large number of experimental and epidemiological studies, for the beneficial effects of some phenolic substances, contained in commonly used spices and herbs, in preventing various age-related pathologic conditions, ranging from cancer to neurodegenerative diseases. Although the exact mechanisms by which polyphenols promote these effects remain to be elucidated, several reports have shown their ability to stimulate a general xenobiotic response in the target cells, activating multiple defense genes. Data from our and other laboratories have previously demonstrated that curcumin, the yellow pigment of curry, strongly induces heme-oxygenase-1 (HO-1) expression and activity in different brain cells via the activation of *heterodimers of NF-E2-related factors 2* (Nrf2)/antioxidant responsive element (ARE) pathway. Many studies clearly demonstrate that activation ofNrf2 target genes, and particularly HO-1, in astrocytes and neurons is strongly protective against inflammation, oxidative damage, and cell death. In the central nervous system, the HO system has been reported to be very active, and its modulation seems to play a crucial role in the pathogenesis of neurodegenerative disorders. Recent and unpublished data from our group revealed that low concentrations of epigallocatechin-3-gallate, the major green tea catechin, induces HO-1 by ARE/Nrf2 pathway in hippocampal neurons, and by this induction, it is able to protect neurons against different models of oxidative damages. Furthermore, we have demonstrated that other phenolics, such as caffeic acid phenethyl ester and ethyl ferulate, are also able to protect neurons via HO-1 induction. These studies identify a novel class of compounds that could be used for therapeutic purposes as preventive agents against cognitive decline.

G. Scapagnini (✉)
Department of Health Sciences, University of Molise, Campobasso, Italy
e-mail: gscapag@gmail.com

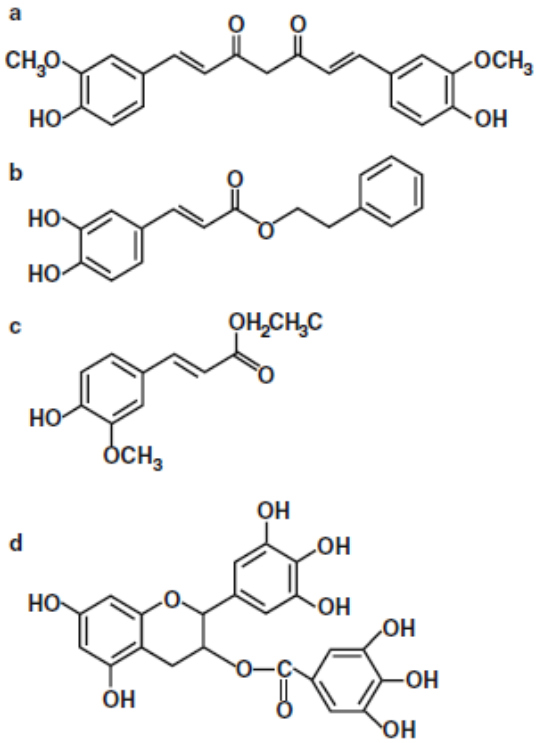


Fig. 1 The chemical structures of curcumin (**a**), CAPE (**b**), EFE (**c**), (−)-EGCG (**d**)

THE JOURNAL OF BIOLOGICAL CHEMISTRY

THE JOURNAL OF BIOLOGICAL CHEMISTRY

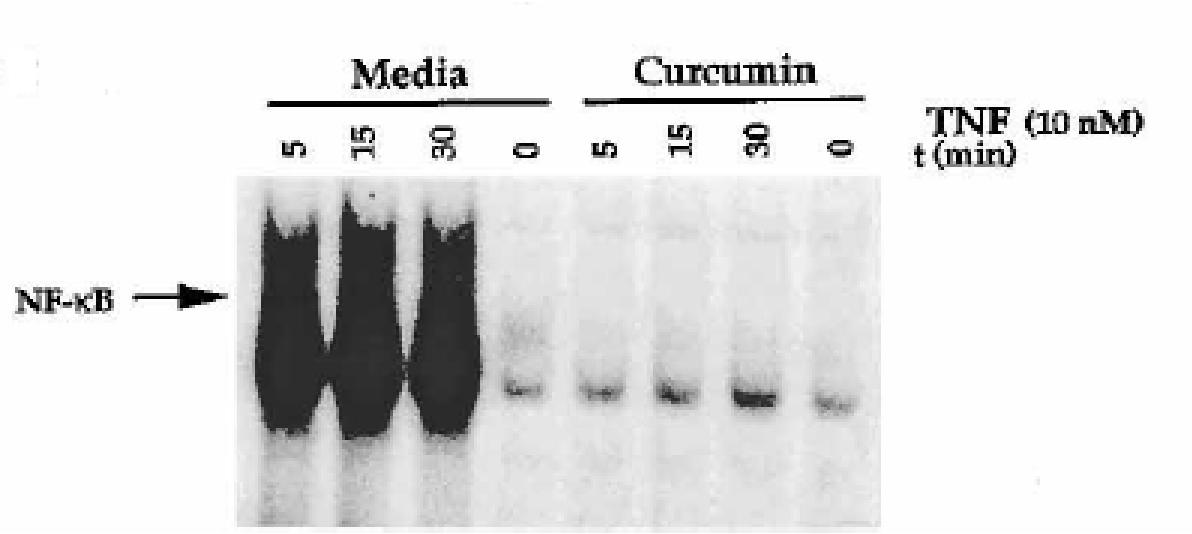
Vol. 270, No. 42, Issue of October 20, pp. 24995–25000, 1995
Printed in U.S.A.

Activation of Transcription Factor NF-κB Is Suppressed by Curcumin (Diferulolylmethane)*

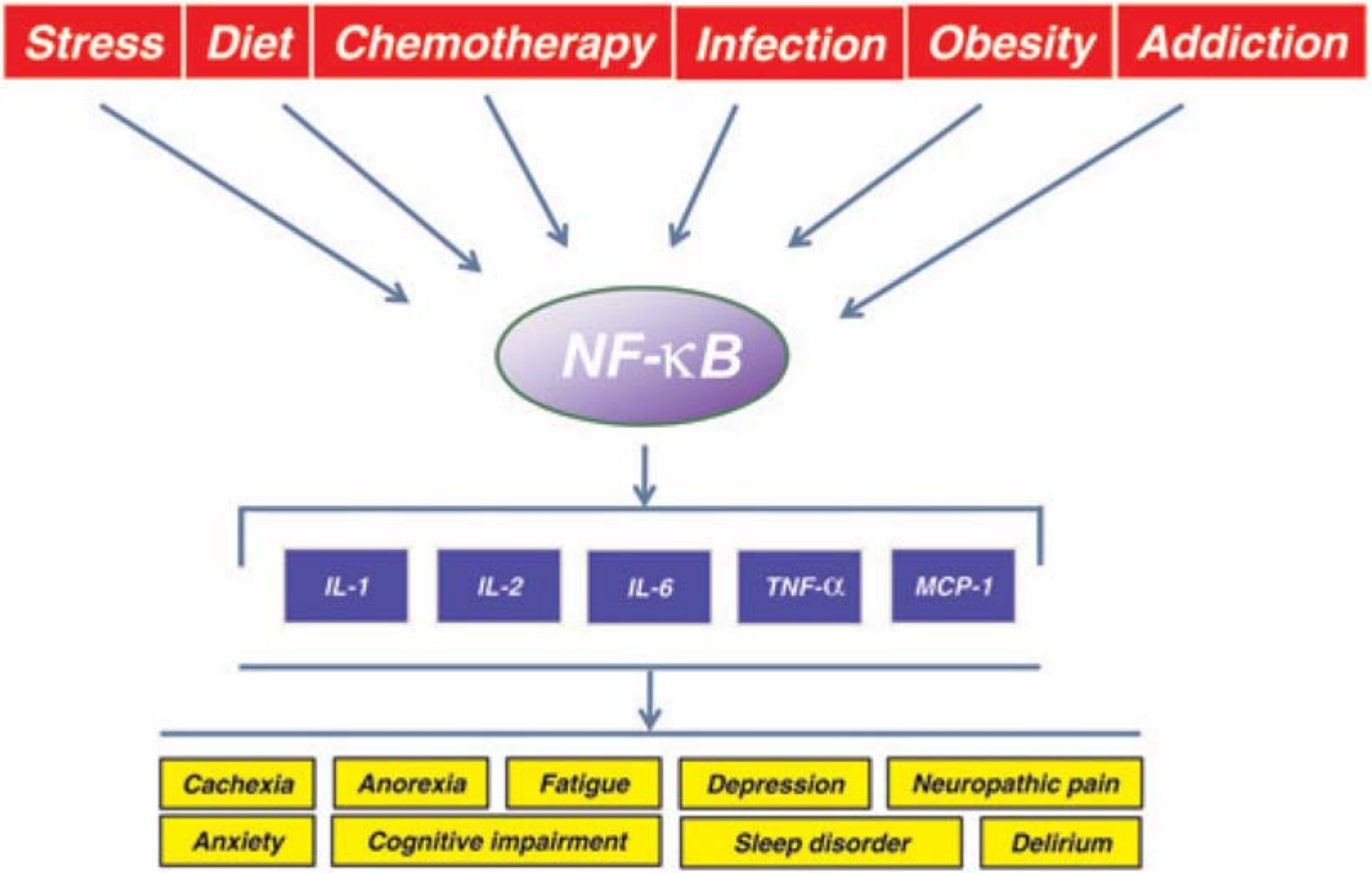
(Received for publication, July 13, 1995, and in revised form, August 11, 1995)

Sanjaya Singh and Bharat B. Aggarwal‡

From the Cytokine Research Laboratory, Department of Molecular Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

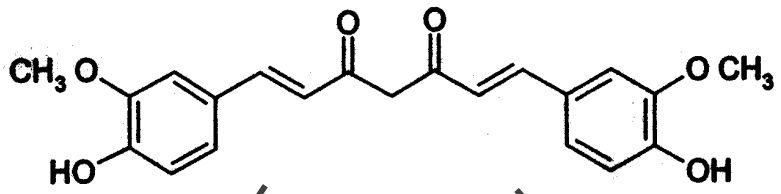


Regulation of inflammatory cytokines through activation of NF-κB



Inflammation

Inflammation



Oxidative Stress

Curcumin

Oxidative Stress

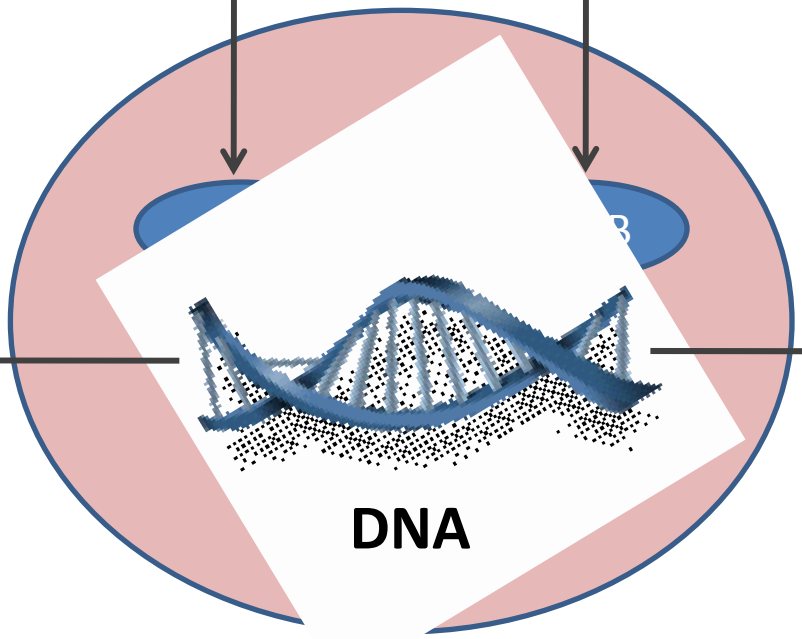
Keap1 Nrf2

NFkB IkB

Defensive Response

Detox enzymes type II

HO-1



Inflammatory Response

Cytokines

NOS

COX

Epidemiological studies showed that in India, where curcumin is widely used in daily diet, there is a reduced age-adjusted prevalence of AD (in patients between 70 and 79 years of age is 4.4 fold less than that of the United States), as well as a lower prevalence of Parkinson's disease.

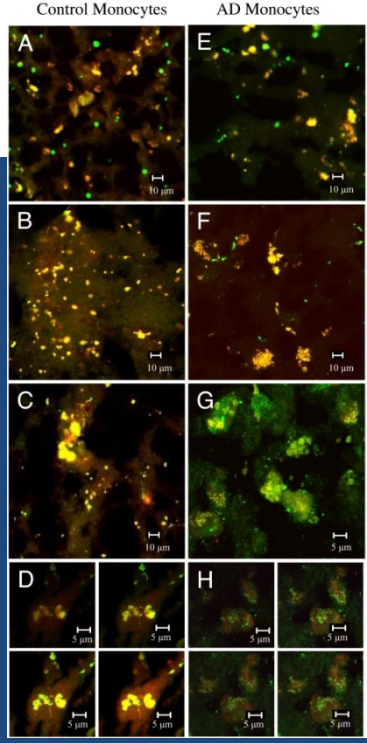
Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, DeKosky ST, and Ganguli M. **Incidence of Alzheimer's disease in a rural community in India: the Indo-US study.** *Neurology* 57: 985-989, 2001.

Muthane U, Yasha TC, and Shankar SK. **Low numbers and no loss of melanized nigral neurons with increasing age in normal human brains from India.** *Ann Neurol* 43: 283-287, 1998.

Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. **Curry consumption and cognitive function in the elderly.** *Am J Epidemiol* 164(9):898-9, 2006

PNAS

Proceedings of the National Academy of Sciences of the United States of America



Proc Natl Acad Sci U S A. 2007 July 31; 104(31): 12849–12854.

Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin

Fiala M. et al.

Department of Medicine, Greater Los Angeles Veteran's Affairs Medical Center

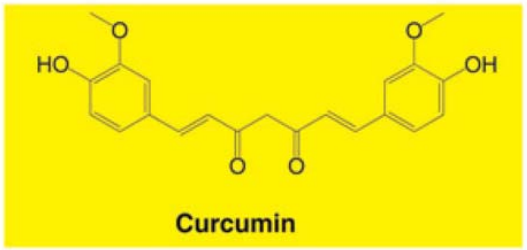
J Clin Psychopharmacol. 2008 Feb;28(1):110-3.

Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease.

Baum L. et al

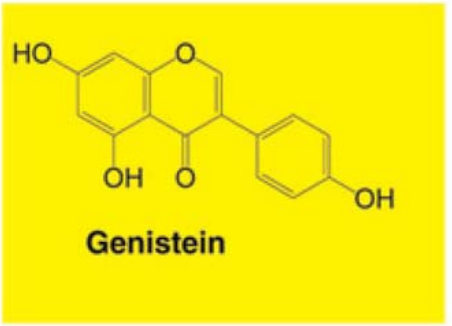
Low bioavailability

Turmeric
(*Curcuma longa*)



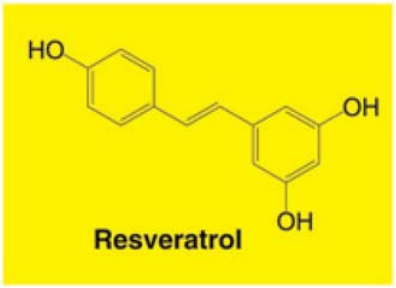
Curcumin

Soybean
(*Glycine max*)



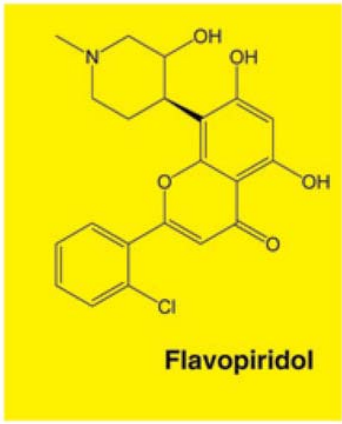
Genistein

Grape
(*Vitis vinifera*)



Resveratrol

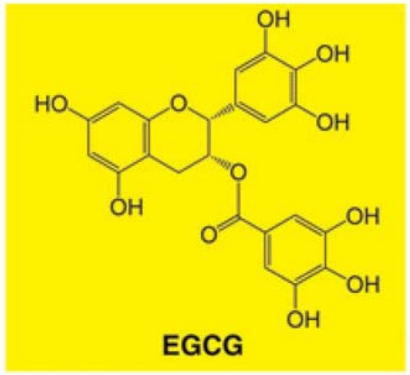
Dysoxylum binectariferum



Flavopiridol

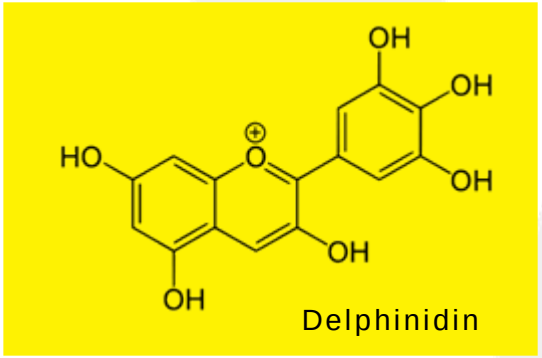
Goo bioavailability

Green Tea
(*Camellia sinensis*)



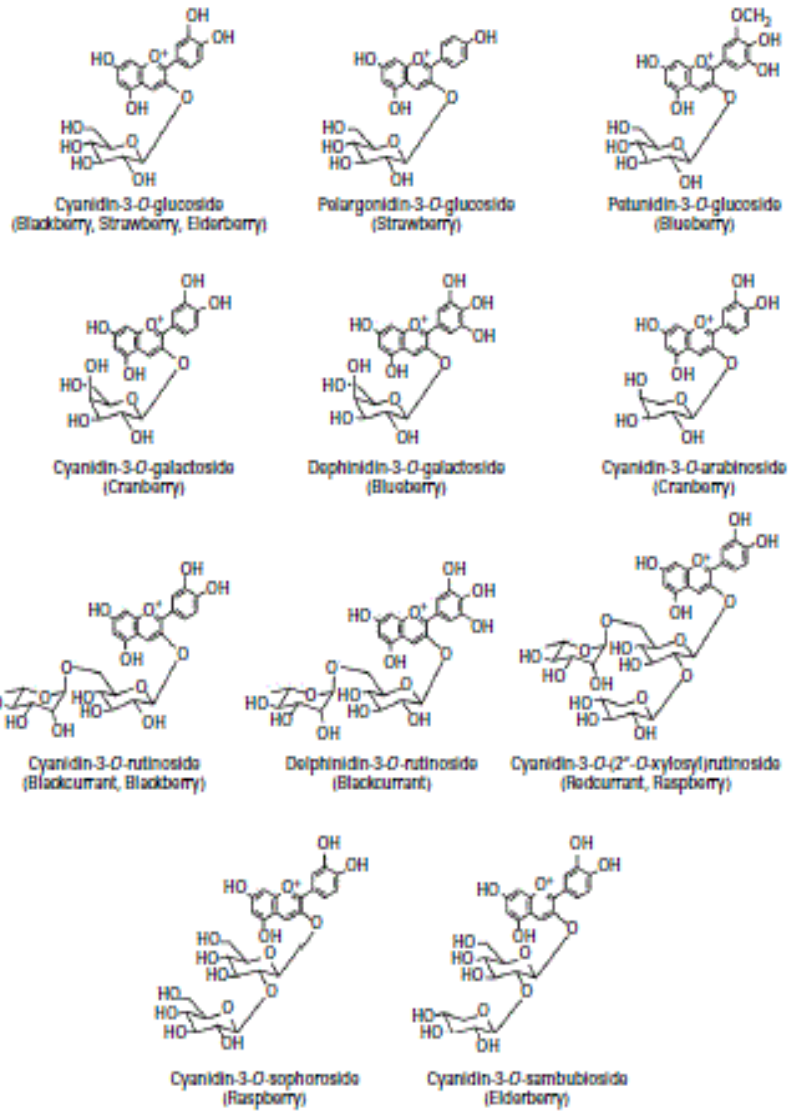
EGCG

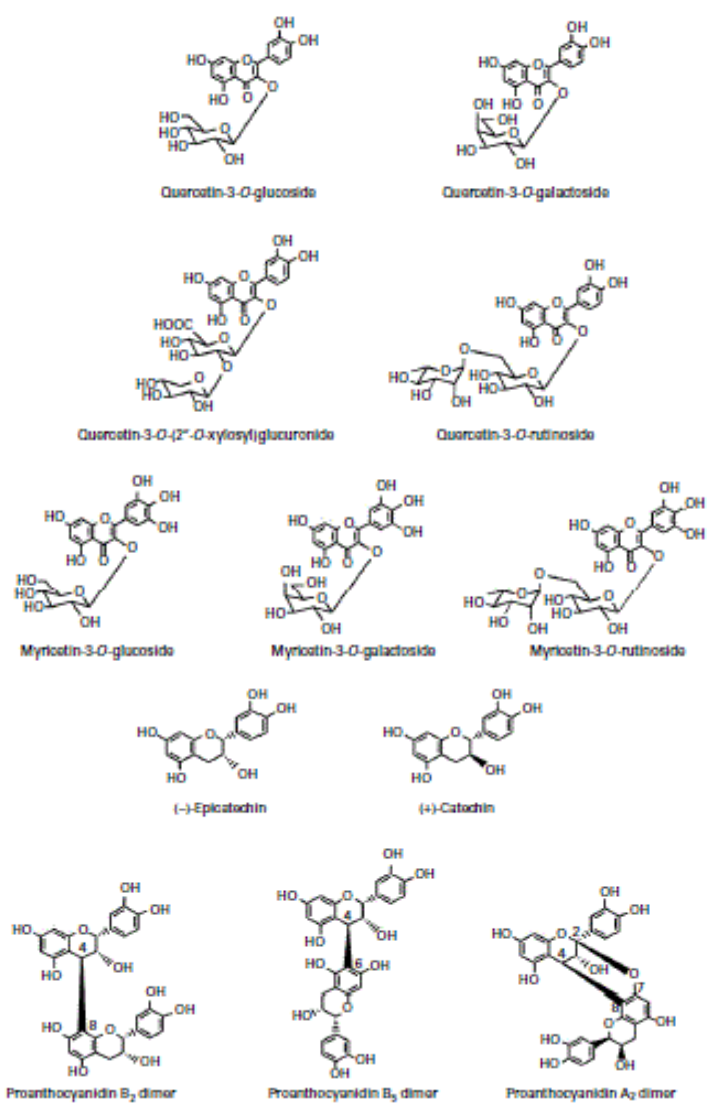
Maqui
(Aristotelia chilensis)



Delphinidin

Berry's anthocyanins





Literature Review

- James Joseph (2007-2009)
- Tested and still testing fruit polyphenols and their effects on aging and the brain
- Tested effects of bilberries, blackberries, blueberries, and other berry fruits

Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, et al. (1999) Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci 19: 8114–8121.

Bickford PC, Gould T, Briederick L, Chadman K, Pollock A, et al. (2000) Antioxidant-rich diets improve cerebellar physiology and motor learning in aged rats. Brain Res 866: 211–217.

Joseph JA, Denisova NA, Arendash G, Gordon M, Diamond D, et al. (2003) Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. Nutr Neurosci 6: 153–162.

Ramassamy C (2006) Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. Eur J Pharmacol 545: 51–64. Review.

Lau FC, Bielinski DF, Joseph JA (2007) Inhibitory effects of blueberry extract on the production of inflammatory mediators in lipopolysaccharide-activated BV2 microglia. J Neurosci Res 85: 1010–1017.

Sweeney MI, Kalt W, MacKinnon SL, Ashby J, Gottschall-Pass KT (2002) Feeding rats diets enriched in lowbush blueberries for six weeks decreases ischemia-induced brain damage. Nutr Neurosci 5: 427–431.

Duffy KB, Spangler EL, Devan BD, Guo Z, Bowker JL, et al. (2008) A blueberry-enriched diet provides cellular protection against oxidative stress and attenuates a kainate-induced learning impairment in rats. Neurobiol Aging 29: 1680–1689.

Shukitt-Hale B, Lau FC, Carey AN, Galli RL, Spangler EL, et al. (2008) Blueberry polyphenols prevent kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. Nutrit Neurosci 11: 172–182.

Calorie Restriction (without nutritional deficiency) extends life in all species tested

THE EFFECT OF RETARDED GROWTH UPON THE LENGTH OF LIFE SPAN AND UPON THE ULTIMATE BODY SIZE [1]

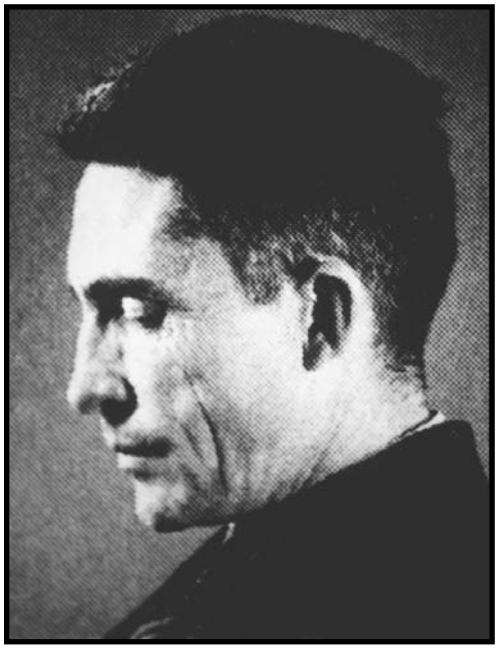
C. M. McCAY, MARY F. CROWELL AND L. A. MAYNARD
Animal Nutrition Laboratory, Cornell University, Ithaca

ONE FIGURE

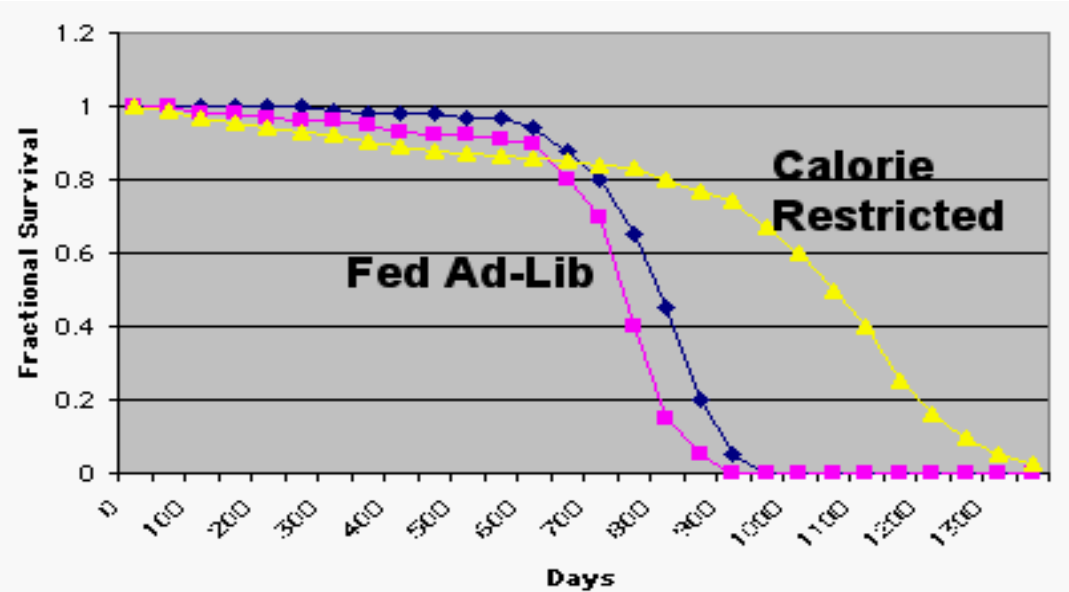
(Received for publication January 18, 1935)

In a preliminary report, the literature concerning the effect of retarded growth upon the life span was reviewed (McCay and Crowell, '34). In this report was also included a summary in the nature of a progress report dealing with a study employing rats to determine the effect of retarding growth upon the total length of life.

The present summary represents a complete, final report of this experiment employing white rats and covering a period of nearly 4 years. The object of this study was to determine the effect of retarding growth upon the total length of life and to measure the effects of retarded growth upon the ultimate size of the animal's body. In the present study, growth was retarded by limiting the calories.



Eakin F & Witten M Experimental Gerontology 1995, 30: 33-64
McCay CM et al. J. Nutrition 1935, 10: 63-79

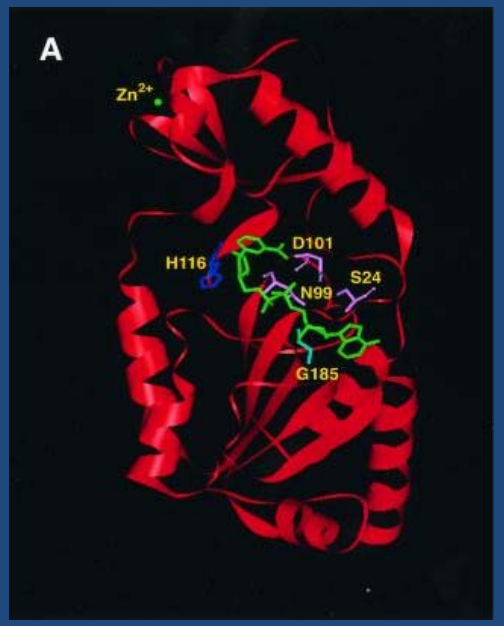


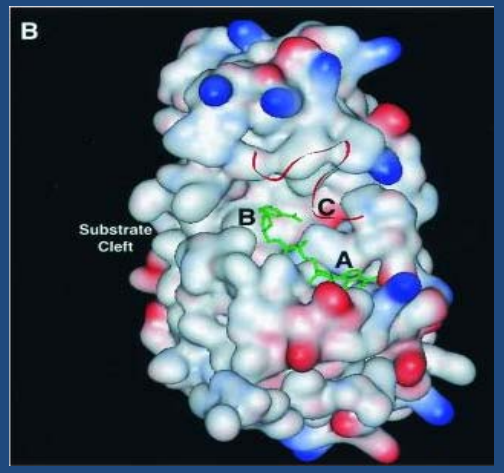
Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, Sinclair DA.

Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan.

Nature. 2003 Sep 11;425(6954):191-6.

- Caloric restriction has been proven to extend the lifespan of a number of species, including mammals
- In yeast, a caloric restriction stimulates the activity of an enzyme referred to as Sir2
- Administering resveratrol to yeast increased Sir2 activity in the absence of caloric restriction and extended the replicative lifespan of yeast by 70%$

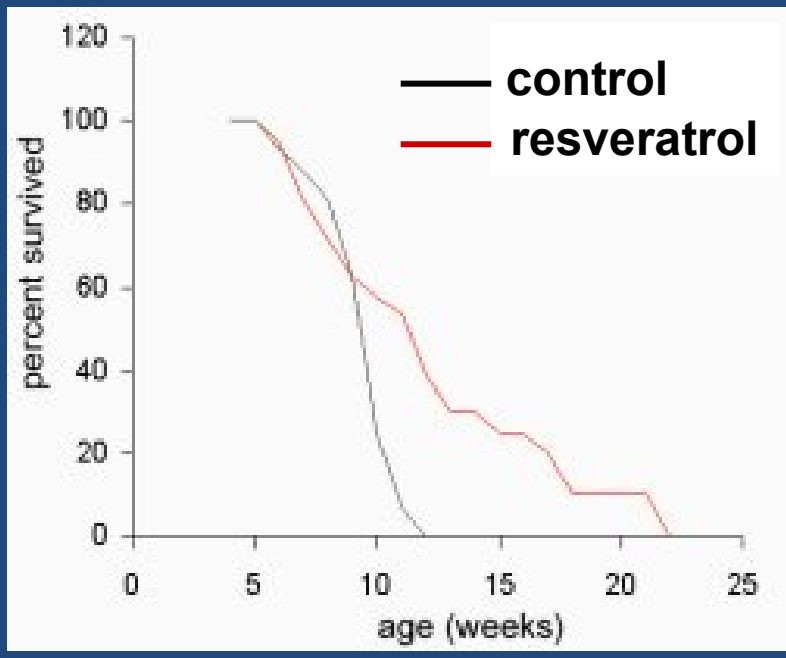




Valenzano DR, Cellerino A.

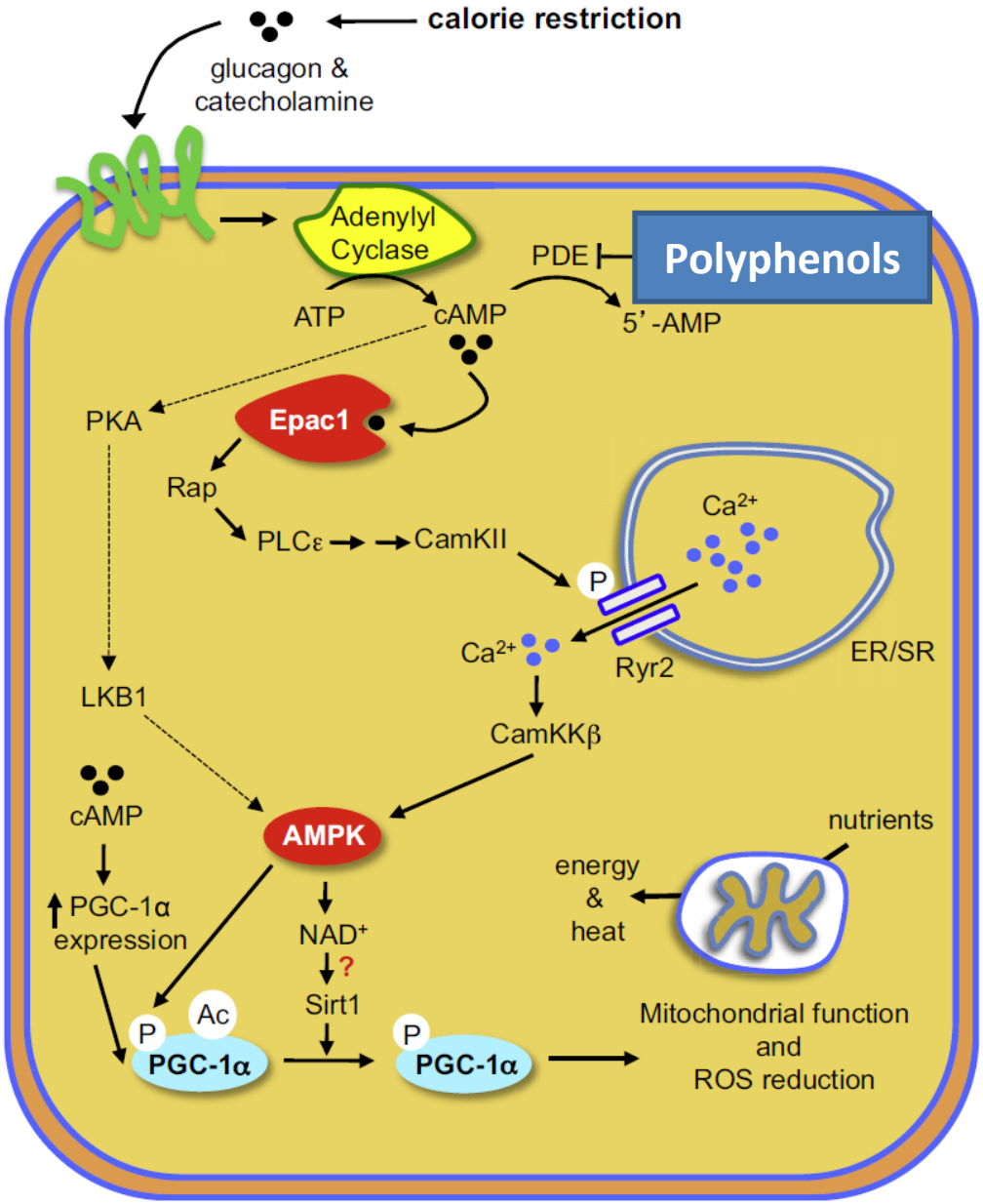
Resveratrol and the pharmacology of aging: a new vertebrate model to validate an old molecule.

Cell Cycle. 2006 May;5(10):1027-32.

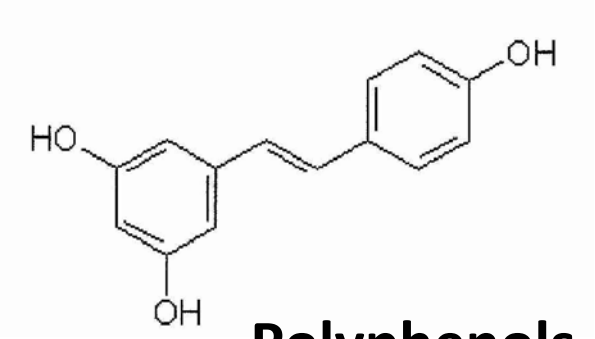


Resveratrol treatment prolonged lifespan and delayed the onset of age-related dysfunctions in this fish.

Proposed model of how polyphenols mimics Calories Restriction



Sun-Jun Park et al., Cell, 148; 421, 2012



Polyphenols

Insulin

Sirtuin activation

AMPK

FOXO

Apoptosis

PGC-1α

mitochondrial biogenesis

Metabolic diseases

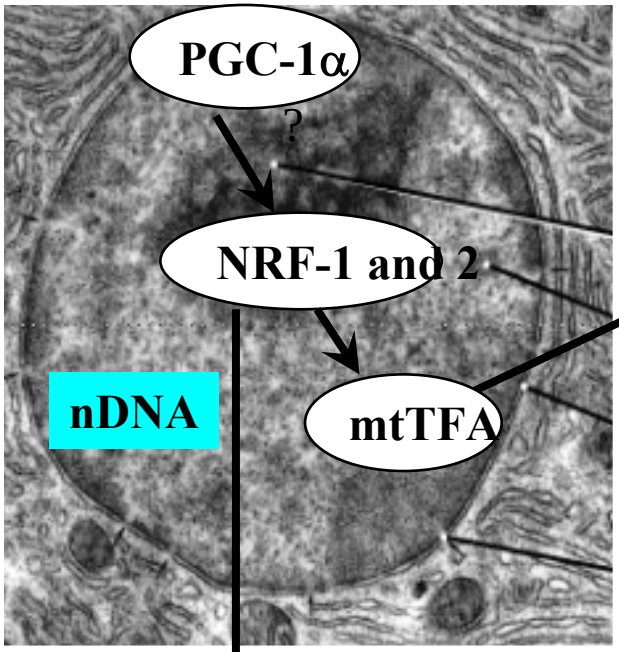
CVD

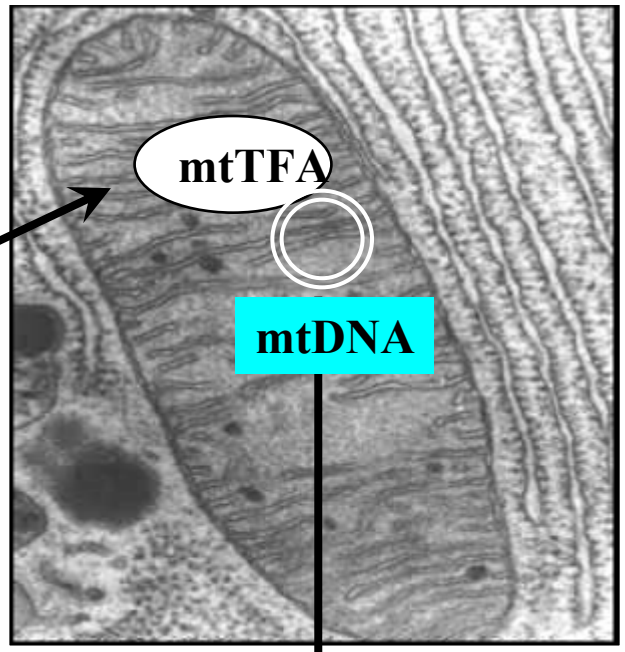
Neurodegenerative disorders

Mitochondrial biogenesis

Nucleus

Mitochondria





Transcription

Krebs cycle enzymes
Transporters
OXPHOS mRNAs
(**COXVb**)
More than 300 proteins

Replication

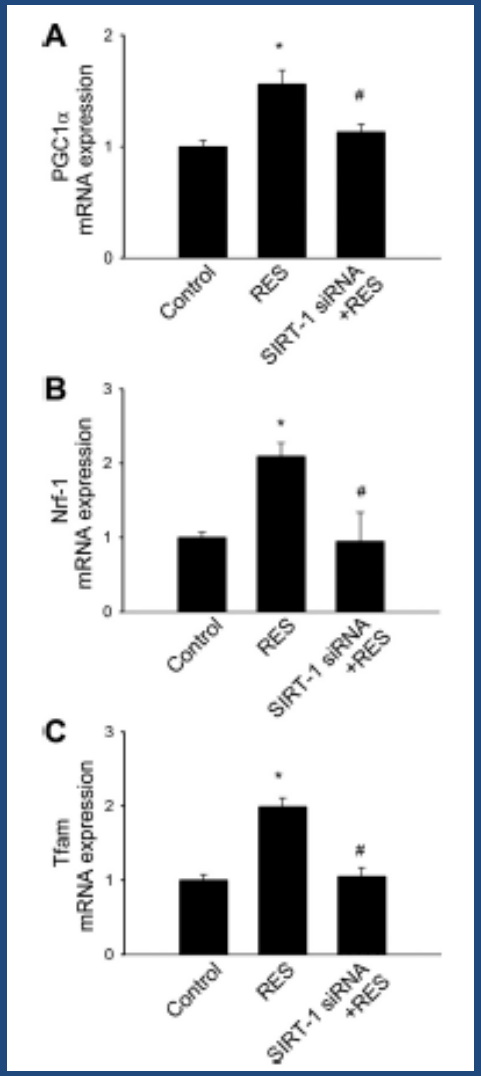
Transcription

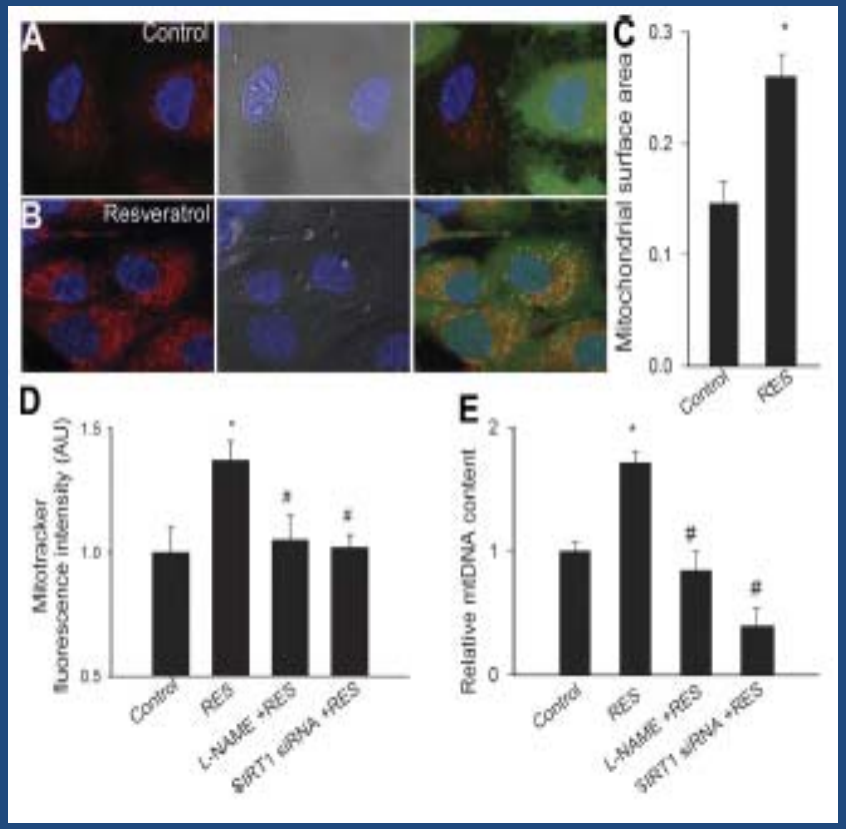
2 rRNAs (12S rRNA)
13 OXPHOS mRNAs (**COXI**)

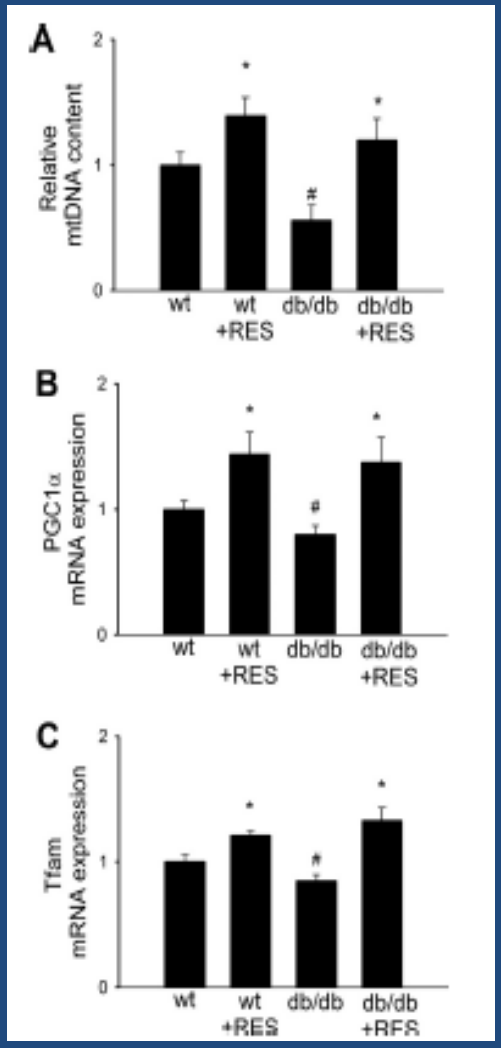
PGC-1α - peroxisome proliferator-activated receptor gamma co-activator

Resveratrol induces mitochondrial biogenesis in endothelial cells

Csiszar A et al. *Am J Physiol Heart Circ Physiol 2009*

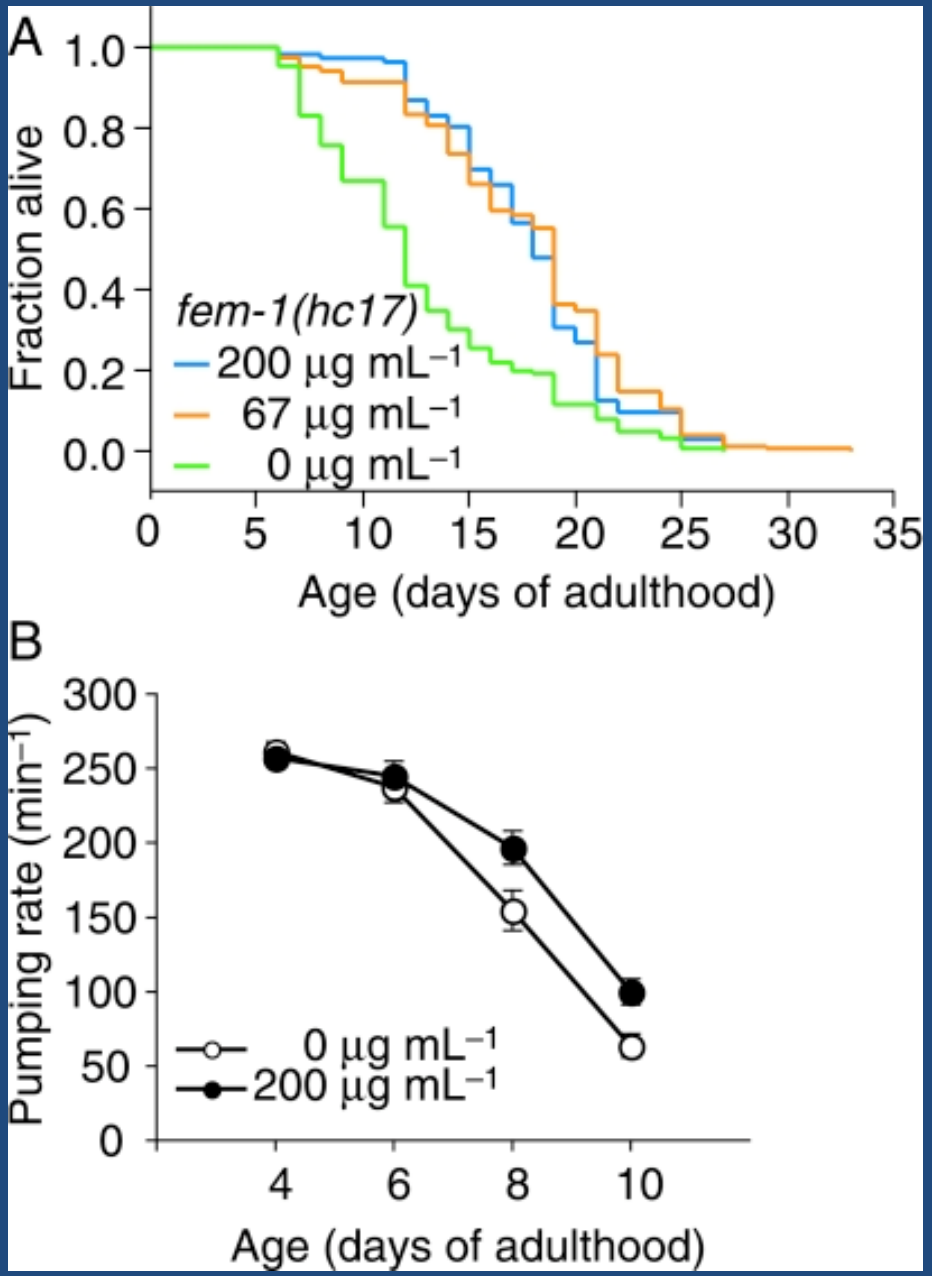






Literature Review

Fig. 3 Blueberry polyphenols extend lifespan and slow aging in *Caenorhabditis elegans*.



Wilson et. al. 2006


Isla Alejandro
Selkirk


Santiago

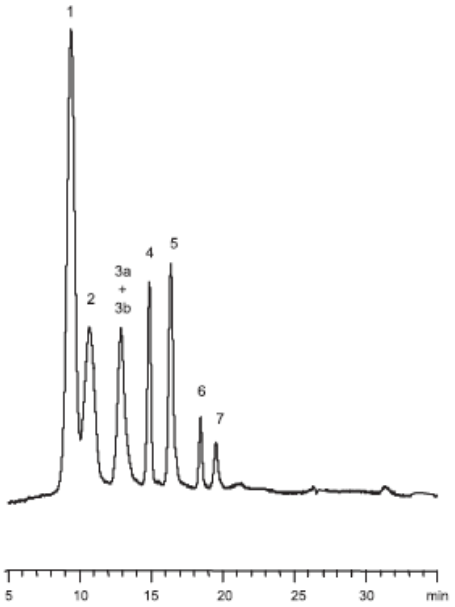

BIENVENIDO
AERODROMO
ROBINSON-CRUSOE
V.REGION
Dirección de Aeropuertos

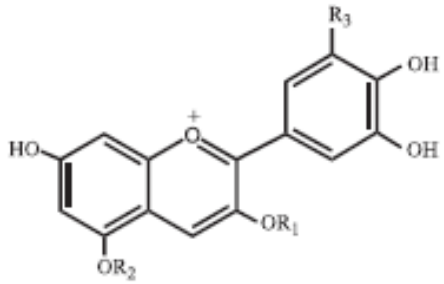
Maqui Berry

(Aristotelia chilensis)

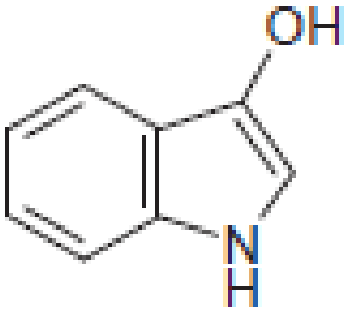
- **Maqui is a deeply purpled berry** from the Patagonia region, that stretches from Cemtral/Southern Chile to Antarctica, one of the cleanest place on this planet.
- **Extraordinary high concentration of anthocyanins,** contain high content of phenolic compounds and anthocyanins that exhibits high antioxidant activity.

Anthocyanins in berries of Maqui (Aristotelia chilensis (Mol.) Stuntz).
Escribano-Bailón MT et al Phytochem Anal. 2006 Jan-Feb;17(1):8-14.





Peak number	R1	R2	R3	Proposed identity
1	Xyl-Glc	Glc	OH	Delphinidin 3-sambubioside-5-glucoside
2	Glc	Glc	OH	Delphinidin 3,5-diglucoside
3a	Xyl-Glc	Glc	H	Cyanidin 3-sambubioside-5-glucoside
3b	Glc	Glc	H	Cyanidin 3,5-diglucoside
4	Xyl-Glc	H	OH	Delphinidin 3-sambubioside
5	Glc	H	OH	Delphinidin 3-glucoside
6	Xyl-Glc	H	H	Cyanidin 3-sambubioside
7	Glc	H	H	Cyanidin 3-glucoside



3-Hydroxyindole

Antioxidant Activity of an Unusual 3-Hydroxyindole Derivative Isolated from Fruits of *Aristotelia chilensis* (Molina) Stuntz
Céspedes CL et al. Z. Naturforsch. **64 c**, 759 – 762 (2009);

J Agric Food Chem. 2002 Dec 18;50(26):7542-7.

Juice and phenolic fractions of the berry Aristotelia chilensis inhibit LDL oxidation in vitro and protect human endothelial cells against oxidative stress.

Miranda-Rottmann S, Aspillaga AA, Pérez DD, Vasquez L, Martinez AL, Leighton F.

Programa Bases Moleculares de las Enfermedades Crónicas, Facultad de Ciencias Biológicas, Pontifica Universidad Católica de Chile, Santiago, Chile.

Food Chem. 2013 Aug 15;139(1-4):129-37. doi: 10.1016/j.foodchem.2013.01.036. Epub 2013 Jan 29.

Maqui berry (Aristotelia chilensis) and the constituent delphinidin glycoside inhibit photoreceptor cell death induced by visible light.

Tanaka J, Kadekaru T, Ogawa K, Hitoe S, Shimoda H, Hara H.

Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan.

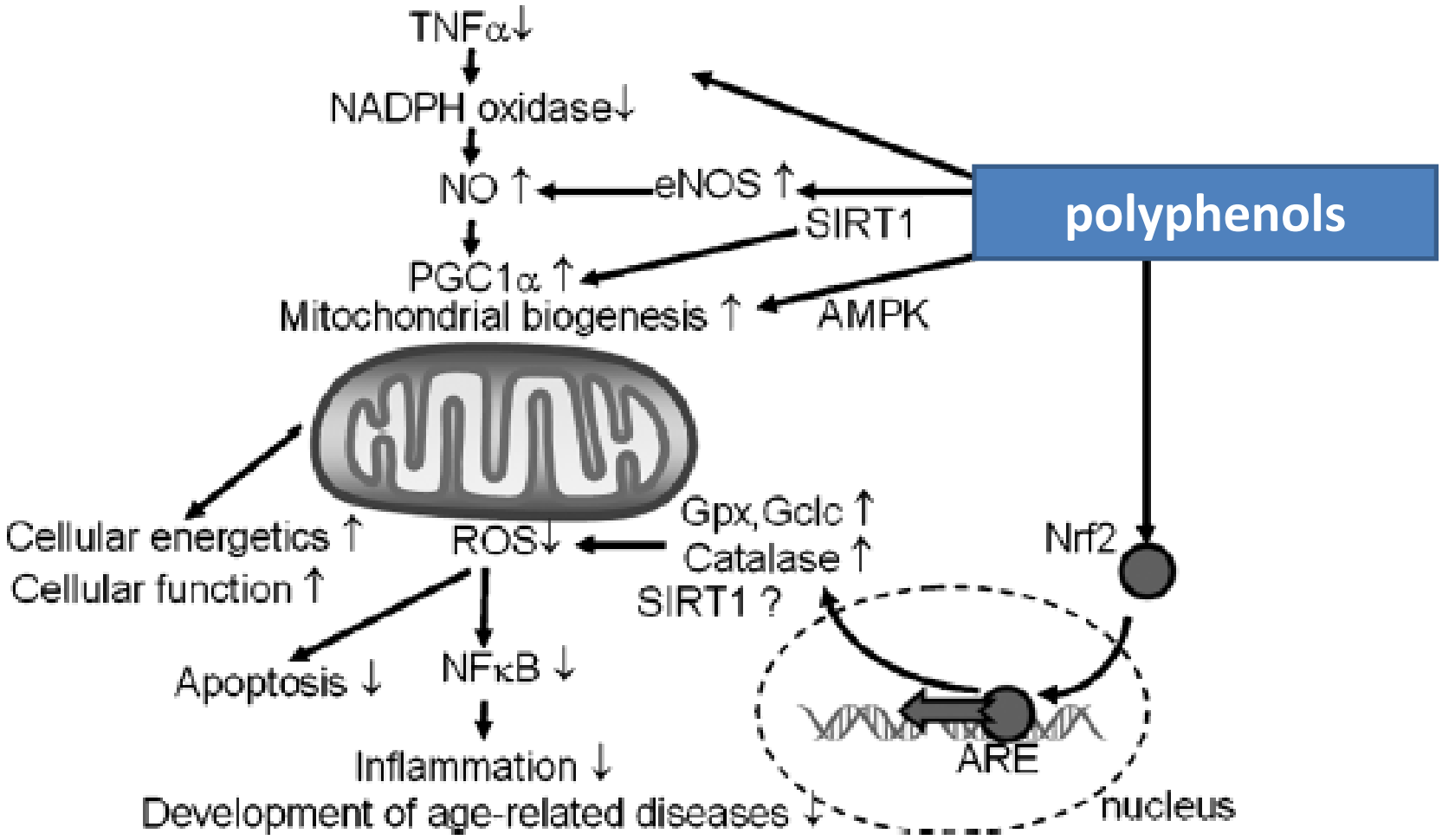
J Alzheimers Dis. 2012;31(4):879-89. doi: 10.3233/JAD-2012-120229.

Synaptic silencing and plasma membrane dyshomeostasis induced by amyloid-β peptide are prevented by Aristotelia chilensis enriched extract.

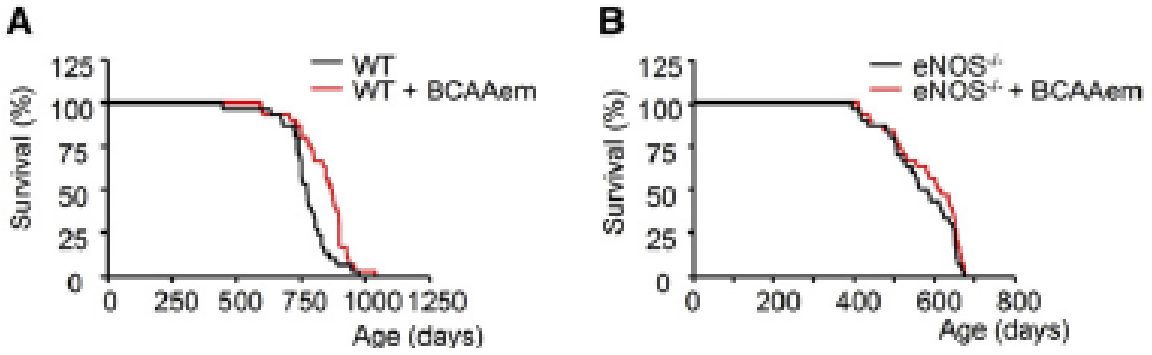
Fuentealba J, Dibarrart A, Saez-Orellana F, Fuentes-Fuentes MC, Oyanedel CN, Guzmán J, Perez C, Becerra J, Aquayo LG.

Laboratorio de Screening de Compuestos Neuroactivos, Universidad de Concepción, Concepción, Chile. jorgefuentealba@udec.cl

Proposed mechanisms by which polyphenols confers mitochondrial protection in aging.

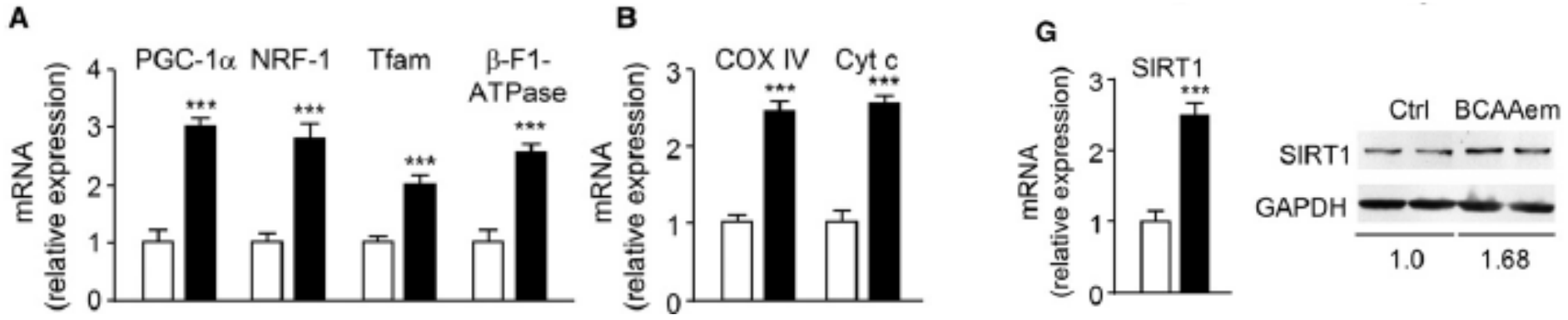


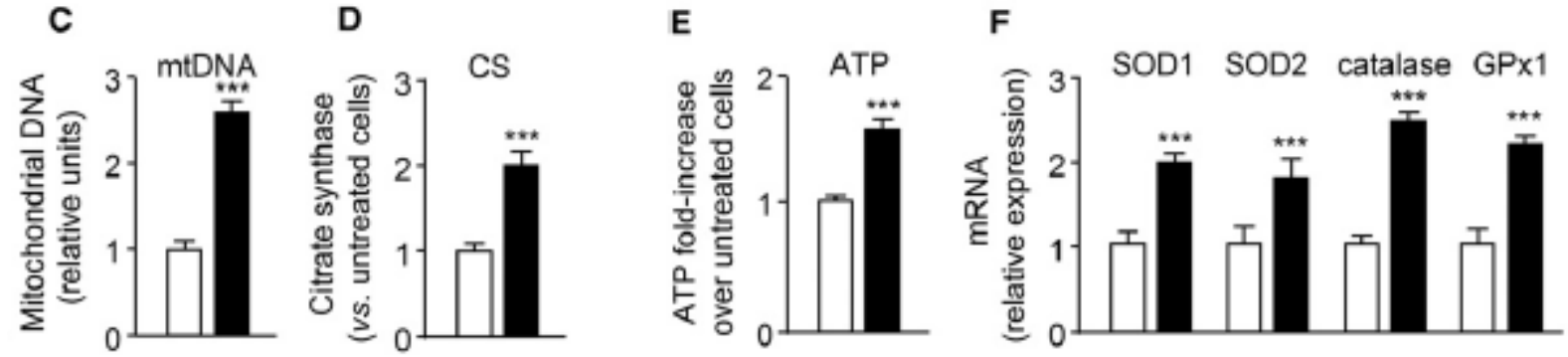
Branched-Chain Amino Acid Supplementation Promotes Survival and Supports Cardiac and Skeletal Muscle Mitochondrial Biogenesis inMiddle-Aged Mice. D'Antona G et al. 2010



Cell Metabolism

Article





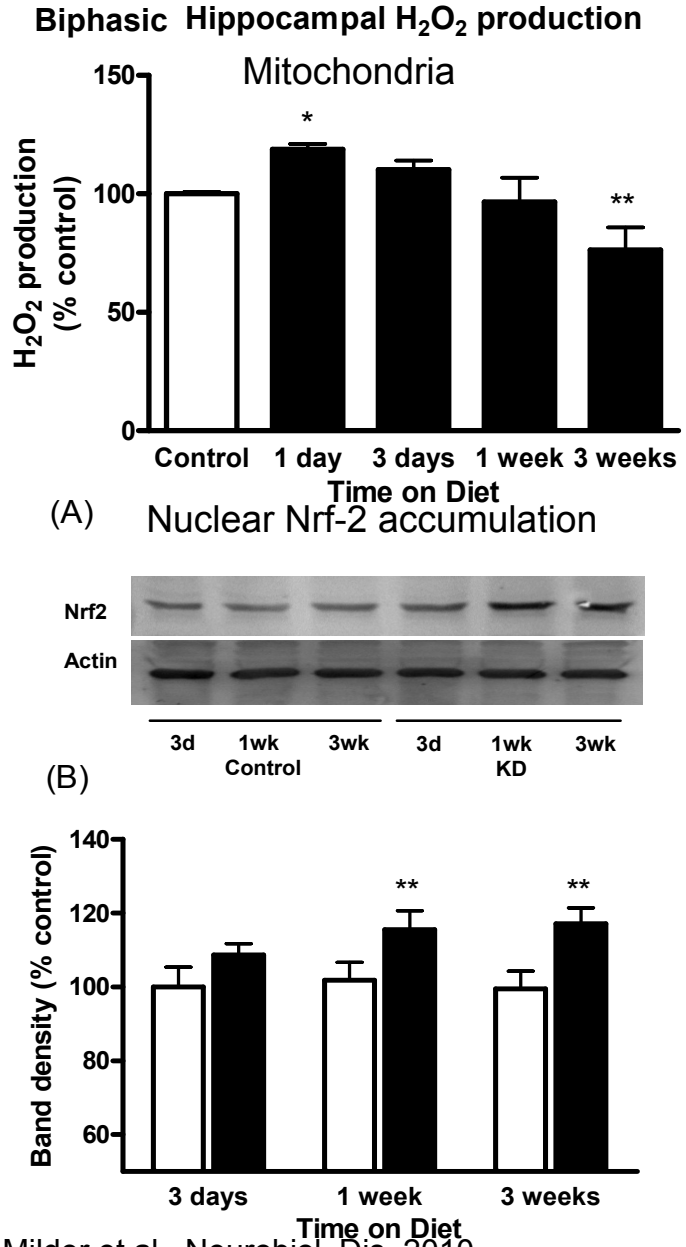
The Ketogenic Diet (KD)

- Mimics fasting state – switches from metabolism of glucose to metabolism of ketones
- Clinically-used treatment for intractable seizures in children and adolescents
- High fat – low carbohydrate (4:1, fat:non-fat)
- Efficacy appears to be independent of seizure type
- Mechanism of action unknown but attributed to ketone bodies , glycolysis and mitochondrial metabolism
- Research direction: clinic to bench

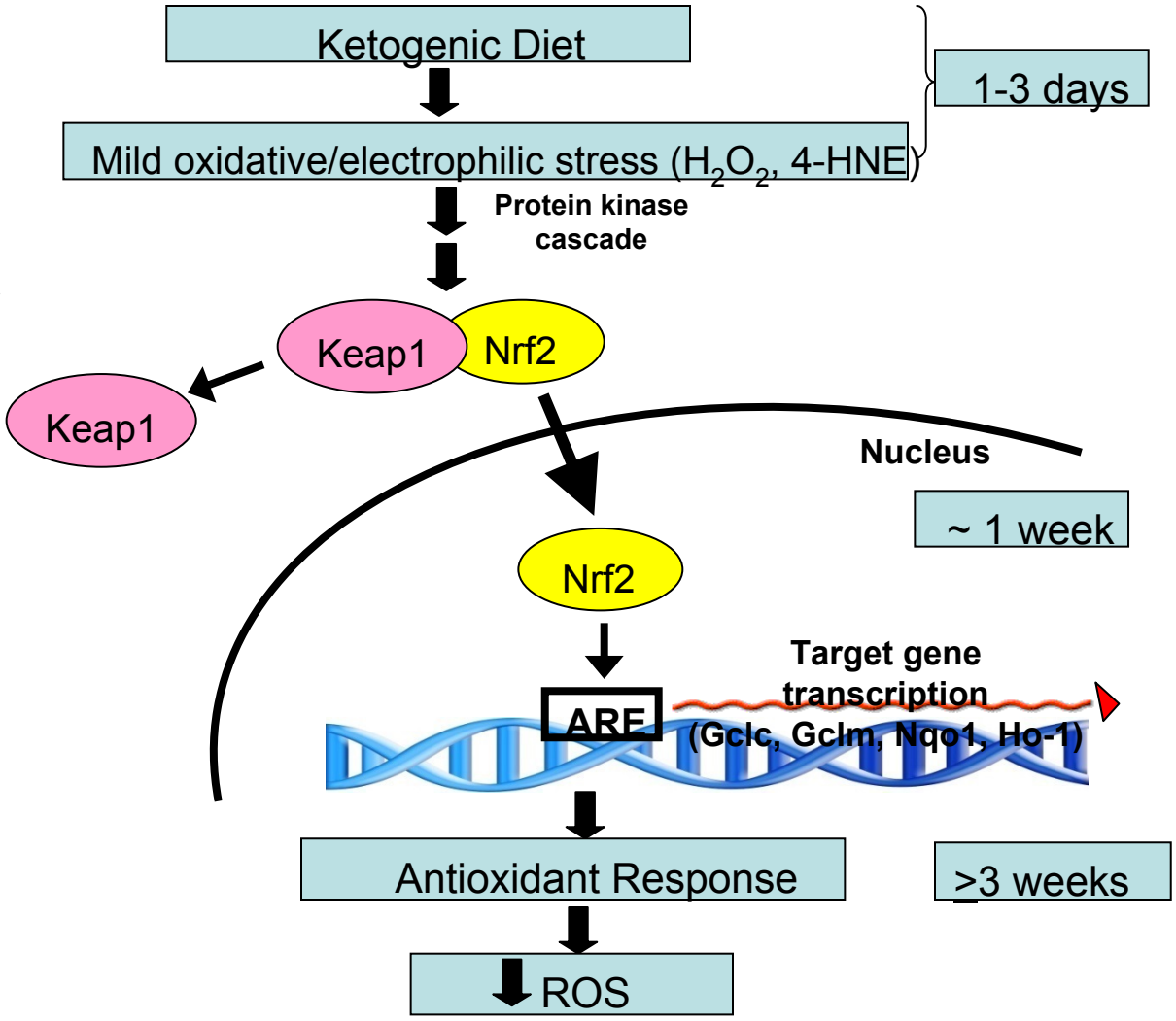
Mitochondrial effects of the ketogenic diet

- Increased mitochondrial biogenesis in KD (Bough et al, Ann Neurol, 60:223-235, 2006)
- Upregulation of uncoupling proteins (UCPs) (Sullivan et al, Ann Neurol, 55:576-580, 2004)
- Increased mitochondrial glutathione and increased γ-GCL activity (Jarrett et al., J. Neurochem 2009)

Activation of the Nrf-2 Adaptive response in the ketogenic diet



Milder et al., Neurobiol. Dis. 2010

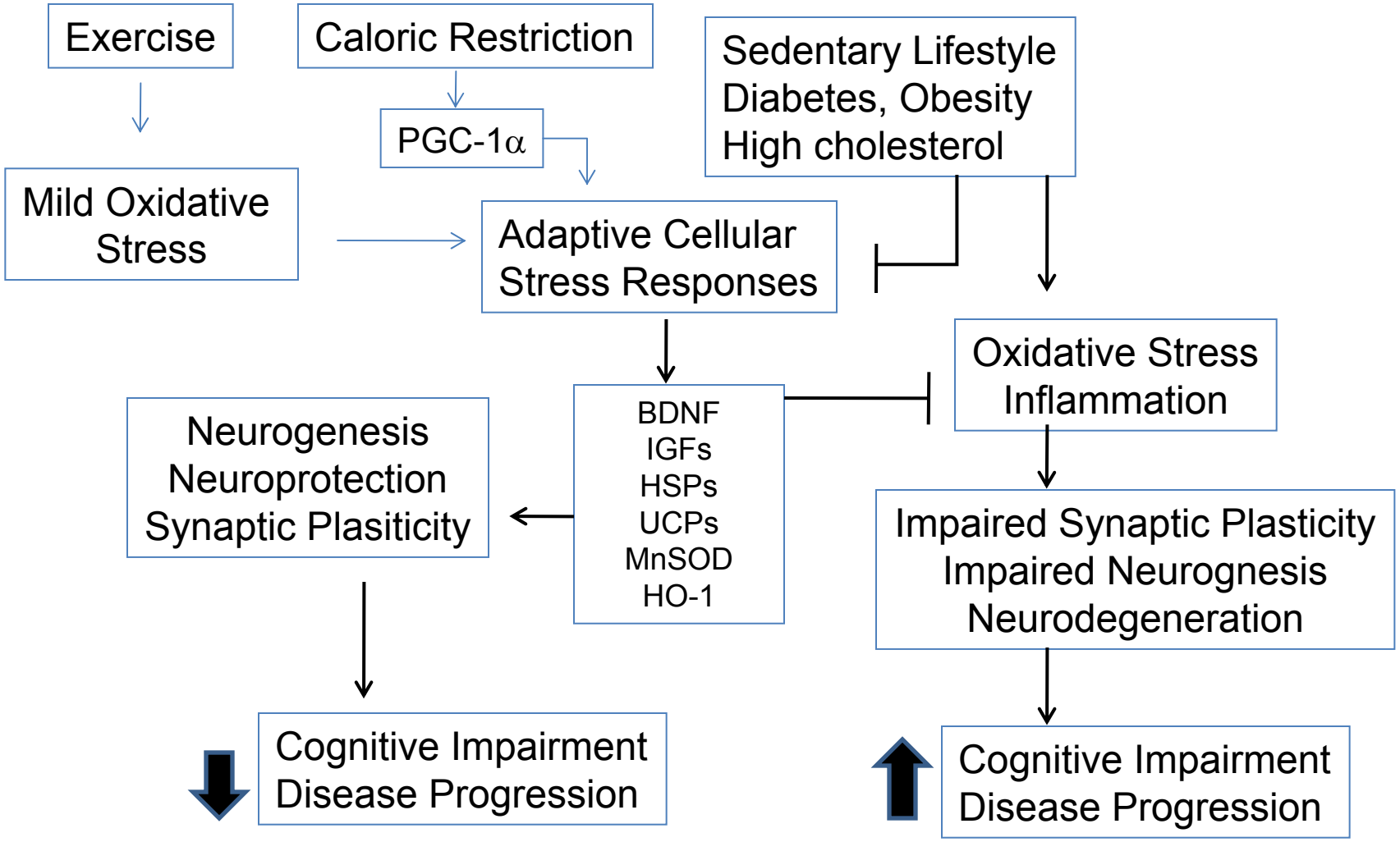


Milder and Patel, Epilepsy Res. 2011

Metabolic Regulation of Cognitive Dysfunction: Non-Pharmacological Approaches Indirectly Targeting Reactive Species

- Diabetes aggravates and energetic challenges attenuate CNS inflammation
- Exercise and caloric restriction ameliorate and diabetes exacerbates Alzheimer's disease models
- Cognitive impairment associated with trauma or ischemia can be modified by caloric intake and exercise

Regulation of Cognitive Function by metabolic factors, oxidative stress and inflammation



Adapted from: Stranahan and Mattson, 2011

International Journal of General Medicine

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REVIEW

Effectiveness of exercise on cognitive impairment and Alzheimer's disease

Balsamo S et al

Structured physical exercise (strength and cardiorespiratory exercise) appears to be a promising non-pharmacological strategy for preventing cognitive decline. Individuals with mild or moderate dementia should be more physically active to prevent major losses of physical fitness and function.

Exercise as a paradigm for hormesis

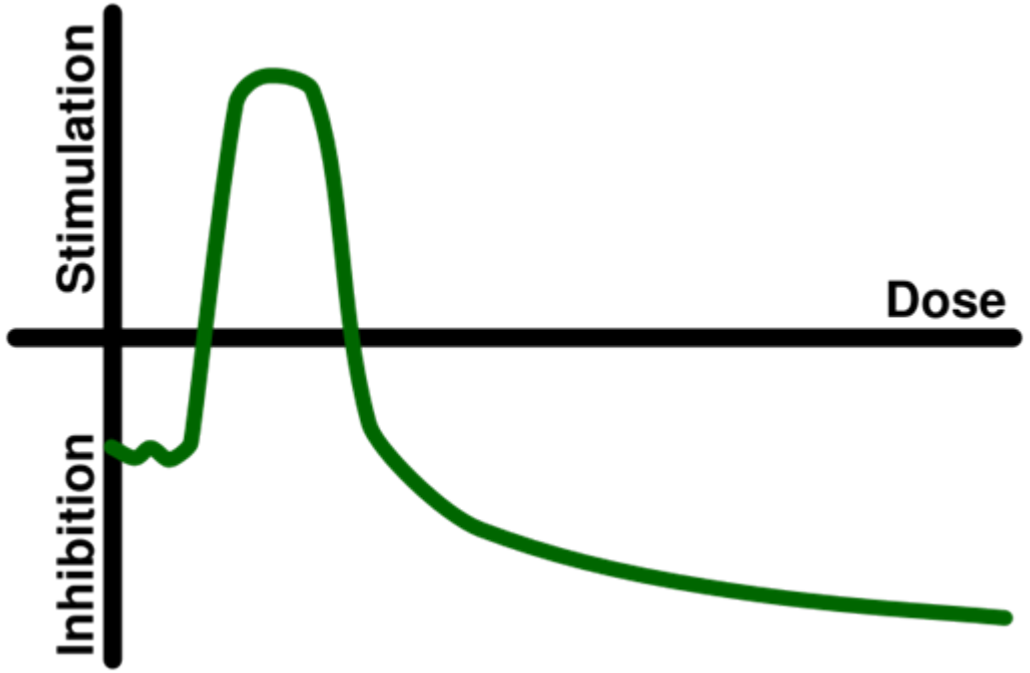
- Biochemically, exercise is damaging.

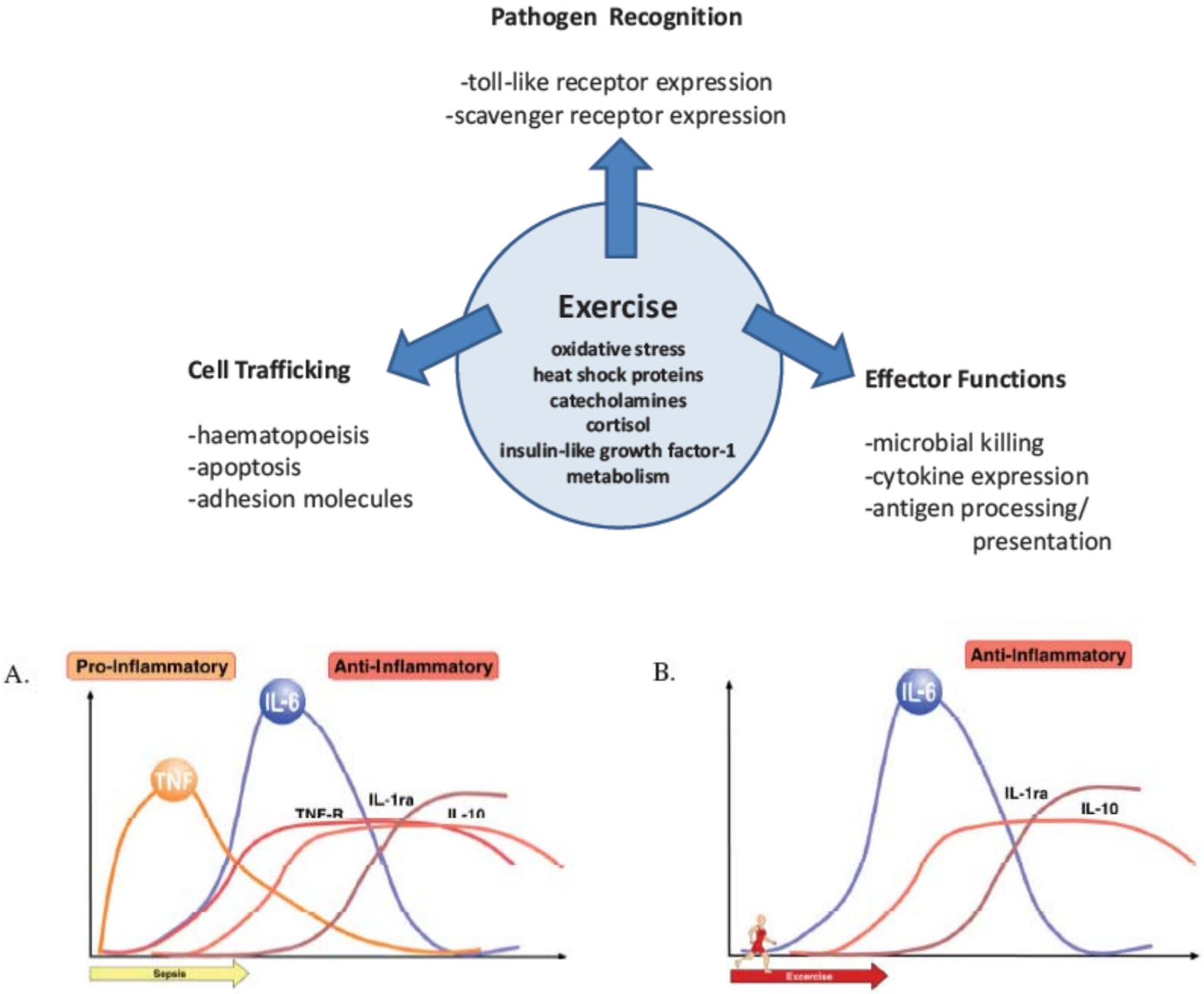
- But, biologically, it is generally good -

HORMETICALLY

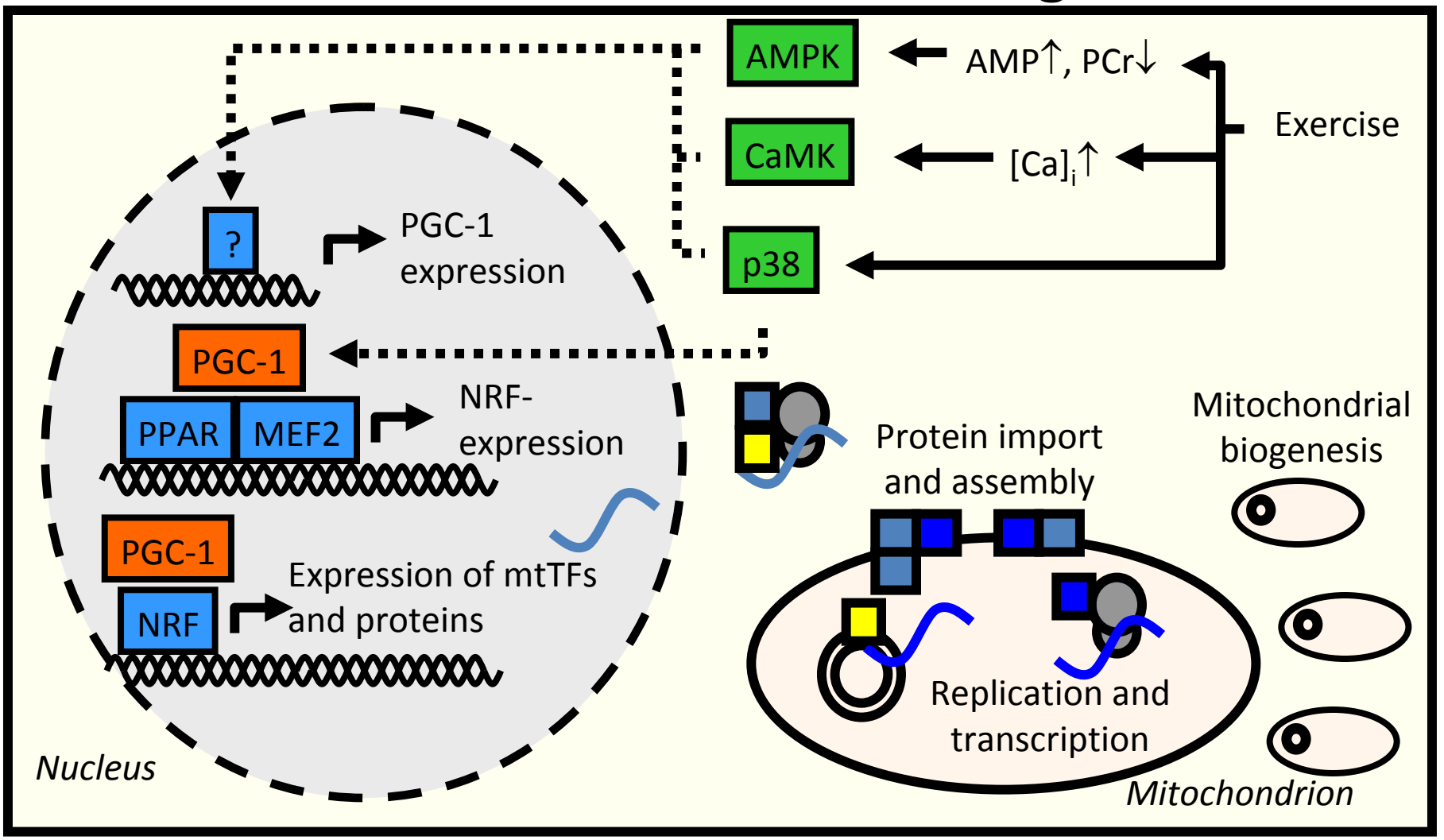
HORMESIS


PARACELSVS AVREOLVS PHILIPP. THEOPHRAST.


Stimulation
Inhibition
Dose


Pathogen Recognition
-toll-like receptor expression
-scavenger receptor expression
Exercise
oxidative stress
heat shock proteins
catecholamines
cortisol
insulin-like growth factor-1
metabolism
Cell Trafficking
-haematopoeisis
-apoptosis
-adhesion molecules
Effector Functions
-microbial killing
-cytokine expression
-antigen processing/
presentation
A.
Pro-Inflammatory
Anti-Inflammatory
IL-6
TNF
IL-1ra
TNF-R
IL-10
Sepsis
B.
Anti-Inflammatory
IL-6
IL-1ra
IL-10
Exercise

Exercise-induced mitochondrial biogenesis

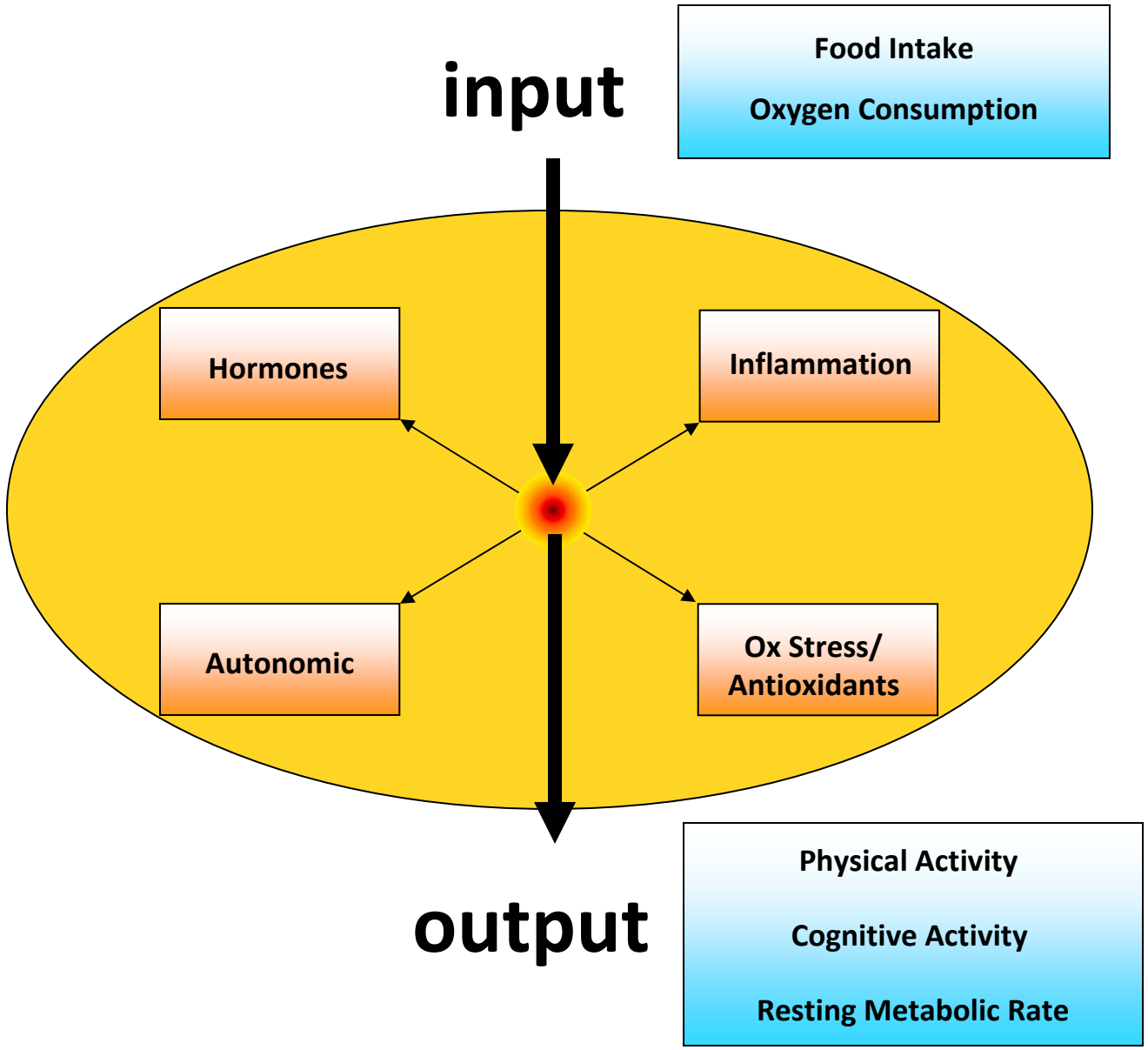


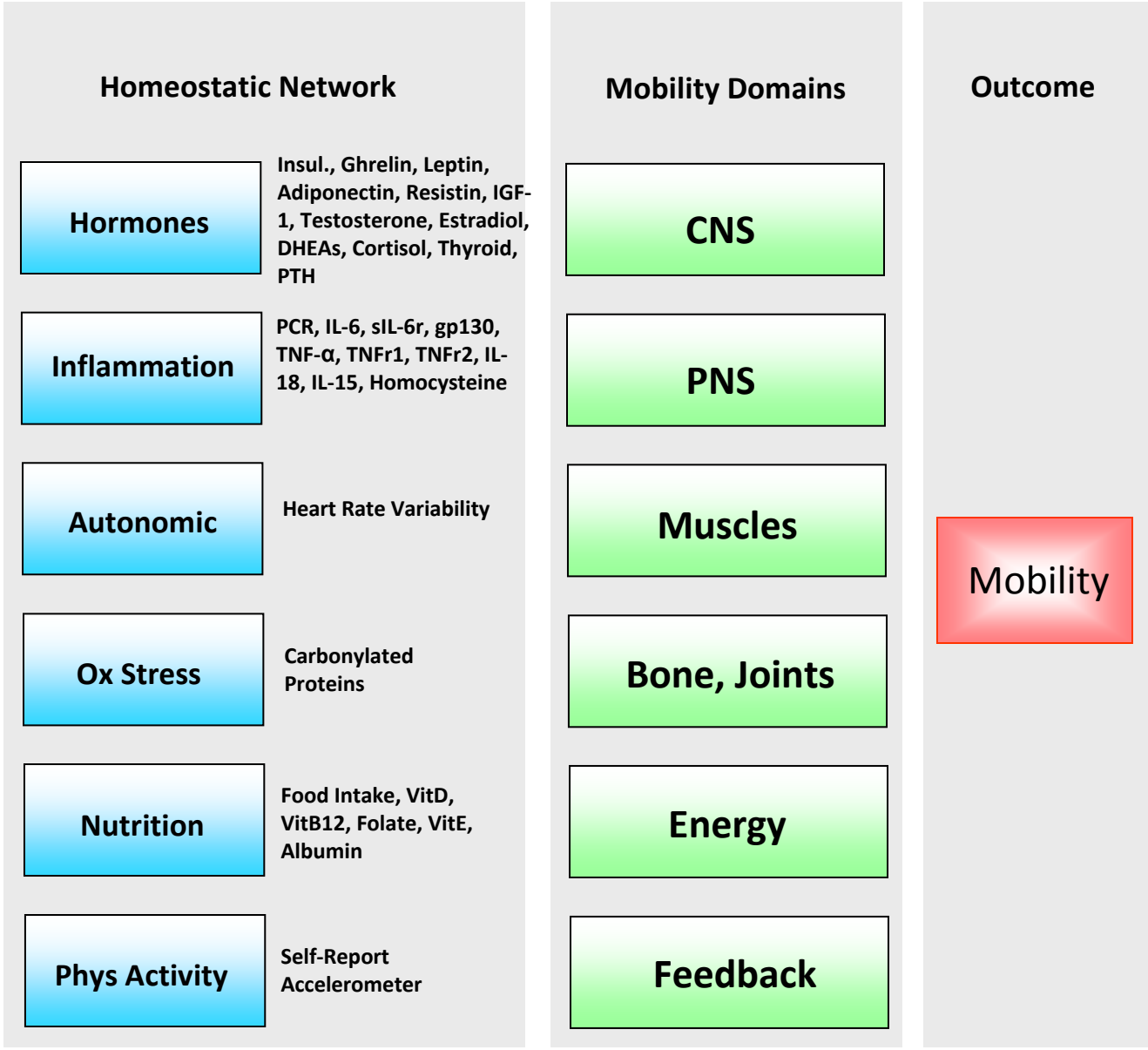
Skeletal muscle fibre

Mitochondrial protein encoded in nuclear DNA

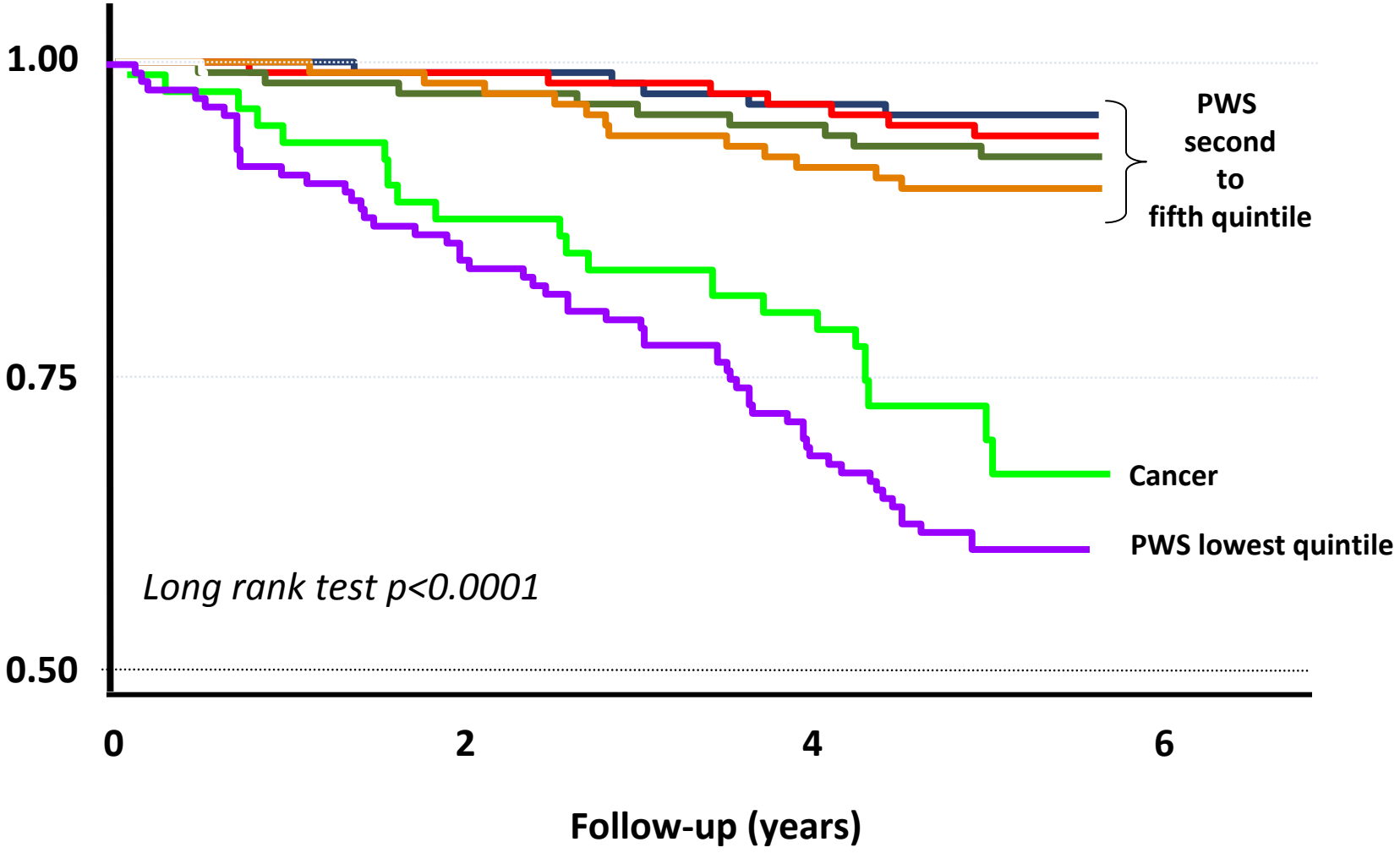
mtTFA and mtTFB

Mitochondrial protein encoded in mitochondrial DNA


input
Food Intake
Oxygen Consumption
Hormones
Inflammation
Autonomic
Ox Stress/
Antioxidants
output
Physical Activity
Cognitive Activity
Resting Metabolic Rate


Homeostatic Network
Hormones
Insul., Ghrelin, Leptin, Adiponectin, Resistin, IGF-1, Testosterone, Estradiol, DHEAs, Cortisol, Thyroid, PTH
Inflammation
PCR, IL-6, sIL-6r, gp130, TNF-α, TNFr1, TNFr2, IL-18, IL-15, Homocysteine
Autonomic
Heart Rate Variability
Ox Stress
Carbonylated Proteins
Nutrition
Food Intake, VitD, VitB12, Folate, VitE, Albumin
Phys Activity
Self-Report Accelerometer
Mobility Domains
CNS
PNS
Muscles
Bone, Joints
Energy
Feedback
Outcome
Mobility

Preferred Walking Speed Predicts Mortality



Exercise promotes healthy aging

Normal Aging

- Ameliorates decline: Canadian researchers[1] examined active lifestyle for "elderly" individuals over 2-5 years, showed stability in cognitive functioning for individuals who were active, greater change if sedentary.
- 90% of individuals with greatest daily energy scored consistently on tests each year
- Activities included walking, cooking, cleaning

1. Archives of Internal Medicine, 2011

Exercise promotes healthy aging

Normal Aging

•More specifically, women in 70's with vascular disease showed a slower rate of cognitive decline than the active group. Editorial (Dr. Eric Larson) noted the goal was to slow the onset of dementia.

Exercise promotes healthy aging

Normal Aging

- A second study[2] showed that light duty weight training has neurological effects.

- After one year, older women who lifted 2x per week showed changes on both functional MRIs and cognitive tests.

2. Neurobiology of Aging, 2011

Exercise promotes healthy aging

Normal Aging: start early!

- Mayo clinic study of 1,126 individuals with "normal cognition" (as opposed to Mild cognitive impairment)[3]
- Individuals with Moderate exercise during midlife were less likely to develop impairment in later life

3. Archives of Neurology, 2011

Exercise promotes healthy aging

- Exercise prevents onset of dementia
- Meta analysis of 1600 research papers examining role of exercise in perserving cognitive abilities
- Conclusion: Important therapy *against* dementia

Exercise promotes healthy aging

"…you can make a very compelling argument for exercise as a disease-modifying strategy to prevent dementia and mild cognitive impairment, and for favorably modifying these processes once they have developed."

-- J. Eric Ahlskog, M.D., Ph.D., neurologist, Mayo Clinic

Exercise promotes healthy aging

Other Neurologic Disease

- Parkinson's Disease
  - Researchers[4] followed 140,000 people with avg. age of 63 for 10 years.
  - Moderate to vigorous activity levels were related to a 40% less chance to develop Parkinsons than those with light or no activity levels.
  - Not clear if the relationship is focused on short term or long term (i.e., do you need to start exercising at 40?)

4. American Academy of Neurology, 2007

Exercise promotes healthy aging

Other Neurologic Disease

- Mild cognitive impairment (MCI): each year, 10-15% of individuals with mild cognitive impairment will develop dementia[5].
- Study: 33 adults with MCI. 23 assigned randomly to aerobic group and exercised at high intensity levels for 45-60 minutes per day, 4 days per week, with a trainer. Control group: 10 individuals performed supervised stretching with low heart rate.

5. Archives of Neurology, 2011

Exercise promotes healthy aging

Other Neurologic Disease

- Found improved fitness (body fat analysis, metabolic markers) and improved cognition.

- Cognitive improvements were more marked in women than men. This may be related to body's use of insulin, glucose, and cortisol, which differed between the sexes.

Exercise and Stress

- Chronic cortisol release leads to detrimental effects:
  - Chronically high cortisol reduces dopamine
- Exercise initially mimics this effect
- Regular exercise training helps to reduce cortisol levels (e.g., a 20 minute walk ceases to be "stressful" to the body).

Mood Benefits

Exercise improves stress tolerance:

- Exercise causes a drop in stress hormones
- Improves "resilience" to stress
- Brain-derived neurotrophic factors (BDNF)
  - "fertilizer" of the brain's neurons
  - Grow more quickly, develop stronger connections
  - Associated with improved cognition, mood

Mood Benefits

Exercise improves stress tolerance:

- Rats assigned to 4 groups[6]:
  - Engaged in "voluntary running"
  - Given antidepressants
  - Both
  - Neither
- Rats then underwent a 2-day "forced swimming" procedure

6. California State University, 2001

Mood Benefits

Exercise improves stress tolerance:

- Results:
  - BDNF levels in untreated animals were depressed
  - Animals that were given physical training or antidepressants had BDNF restored to baseline
  - Animals with both showed increase in hippocampal BDNF well above baseline.

Mood Benefits

Improved mood improves cognition:

- Exercise has an "antidepressant effect"
- Antidepressant effect of running was associate with more cell growth in hippocampus[9]

9. Proceedings of the Academy of Natural Sciences, 2010

Does exercise foster neuroplasticity?

- Exercise increased growth factors in brain making it easier to grow new connections[10]
- Mice that ran on a wheel had twice as many new brain cells as mice housed in standard cages[11]. As a comparison, provided mice with other "enriched" environments (e.g., "free swim")- only running produced the effect.
    - Growth was in the hippocampus (learning and memory)

10. UCLA, 2011

11. Nature Neuroscience, 1999

Does exercise foster neuroplasticity?

- Illinois researchers scanned brains of 55 individuals aged 55-79, measured maximal O2 during exercise[12]
- Used MRIs and functional imaging to examine age-related brain shrinkage
- Results: fit subjects had less shrinkage in temporal, parietal, and frontal areas- crucial for learning and memory

12. Journal of Gerontology, 2003

Does exercise foster neuroplasticity?

- Meta-analysis of 18 controlled studies of cognitive function and aerobic fitness for individuals aged 55-80[13]

13. Psychological Sciences, 2003

Does exercise foster neuroplasticity?

Results:

- Exercise had clear, selective cognitive benefits for attention, organization, planning
- Frontal skills
- Strength training combined with aerobic fitness was most effective
- Exercise sessions of less than 30 minutes per session had little impact

Does exercise foster neuroplasticity?

- Brain-derived neurotrophic factors (BDNF)
- "fertilizer" of the brain's neurons
    - Grow more quickly, develop stronger connections
- Associated with improved cognition, mood

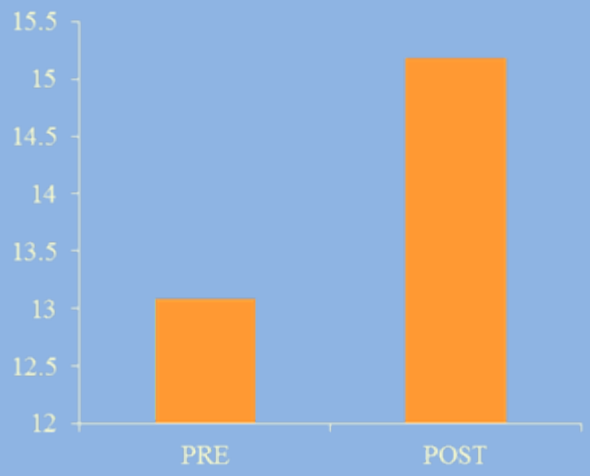
Does exercise foster neuroplasticity?

- Brain-derived neurotrophic factors (BDNF)
- produced in the brain during endurance training
- produced peripherally in resistance training, circulates to the brain
- University of Florida study: 20 college aged men[14]
    - Increased neurotrophic factors at 1, 30 and 60 minutes after endurance training

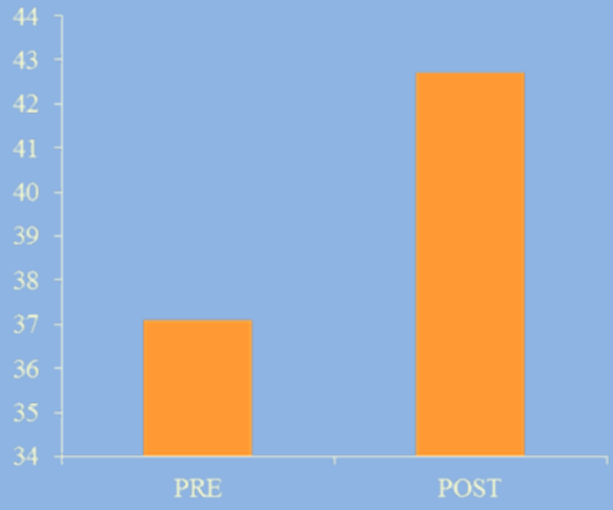
14. American College of Sports Medicine, 2010

Cognitive Changes with Exercise at 12 weeks

Working Memory
p=0.01



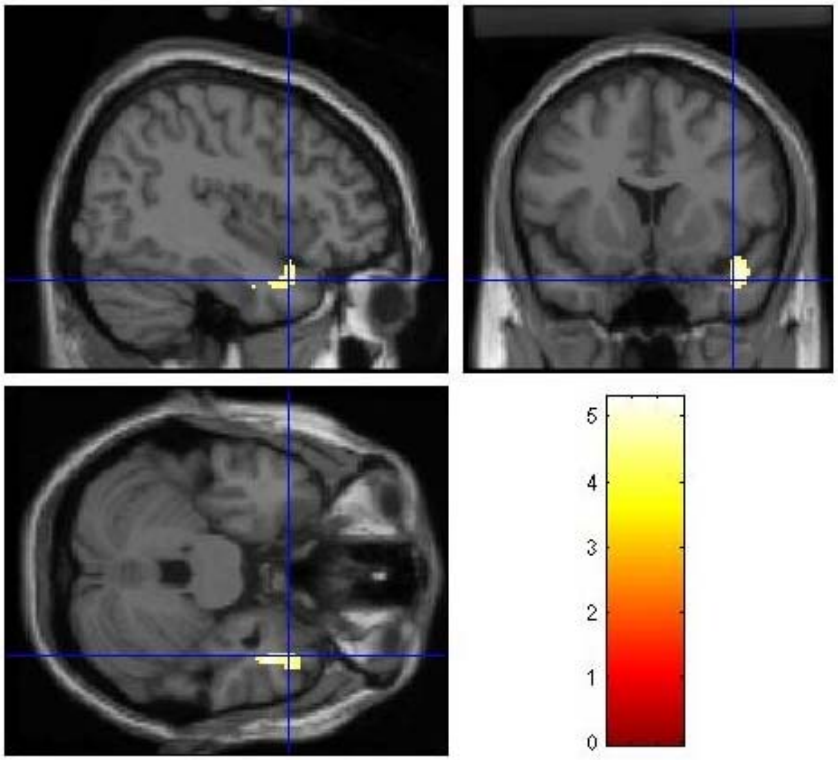
Episodic Memory
p=0.009



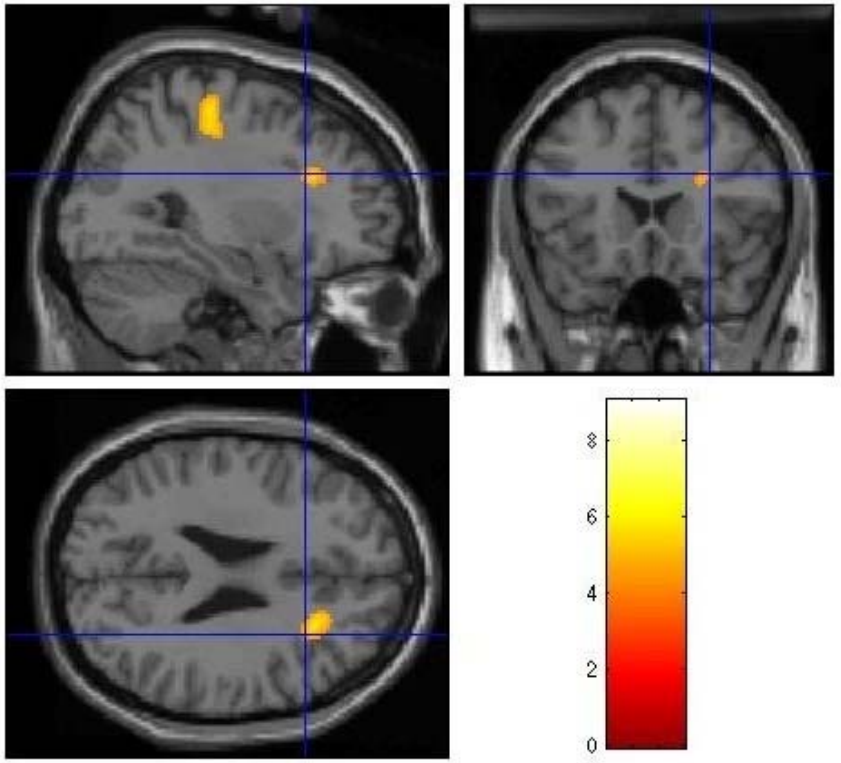
Verbal Fluency
p=0.02

Cerebral Blood Flow Changes with Exercise at 12 weeks

Increased brain blood flow to temporal lobe

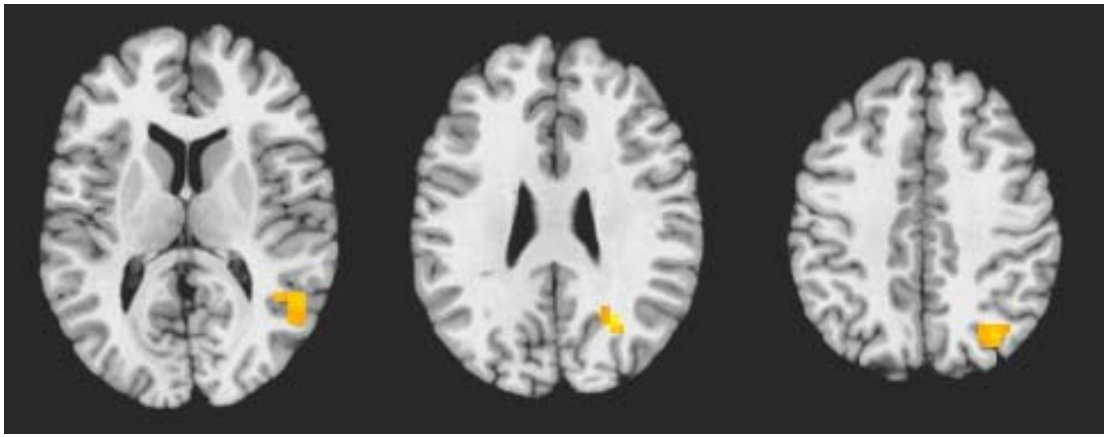


Decreased in frontal & parietal lobes

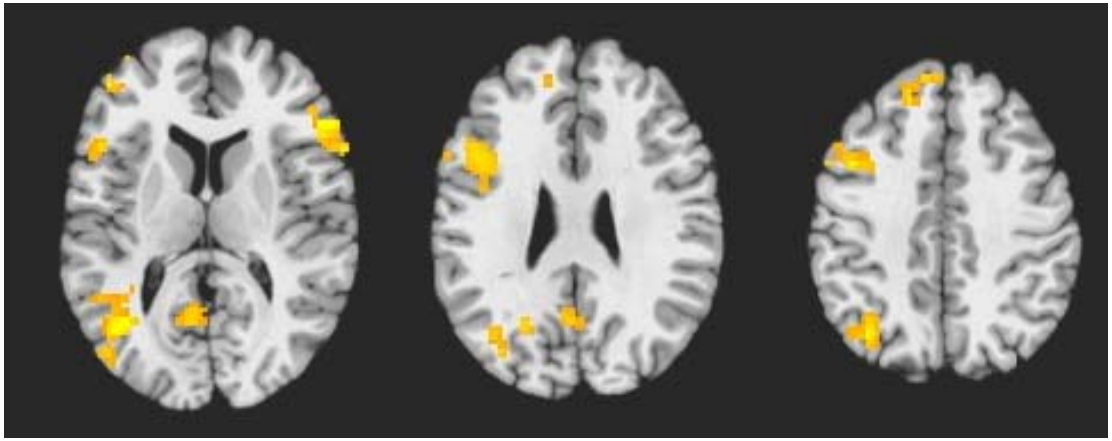


* Whole brain ASL changes

fMRI: Gist activation study
Exercise Group vs. Control Group



Pre-Training
n=9



Post-Training
n=9

Practical Advice

The Basics:

- Do something
- Stick with what you stick with
- Every bit counts: even 20 minutes of exercise facilitates brain function

Practical Advice

The Details:

- Exercise has short term effects of mood, concentration, memory and stress that last for several hours after exercise

- Moderate exercise for a six month time frame is beneficial to begin to see long term benefits

Practical Advice

The Details:

- Exercise should continue with age
- Exercise that encourages cognitive focus has additional benefits : find something that challenges you (ballroom dancing, a new class, yoga, etc.)
- Exercise that is interesting is also good (vary your walk!)

Cognitive exercise

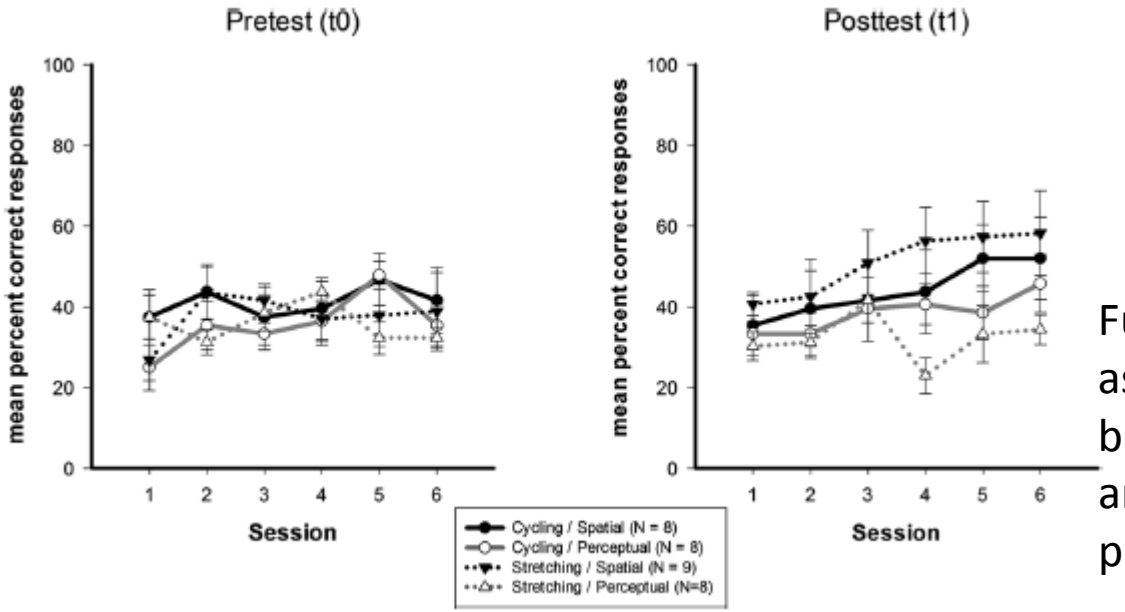
- Cognitive exercise has similar effects
- Two together have strongest effects
- Visualizing exercise improves neuroplasticity as well
- Best exercise is novel tasks: at any level

BMC Neuroscience 2013, 14:73

Effects of a cognitive training on spatial learning and associated functional brain activations

Kirsten Hötting[1*†], Kathrin Holzschneider[1†], Anna Stenzel[1], Thomas Wolbers[2] and Brigitte Röder[1]

The present study assessed the effects of cognitive training (spatial vs. perceptual training) and physical training (endurance training vs. non-endurance training) on spatial learning and associated brain activation in 33 adults (40–55 years). Spatial learning was assessed with a virtual maze task, and at the same time neural correlates were measured with functional magnetic resonance imaging (fMRI).



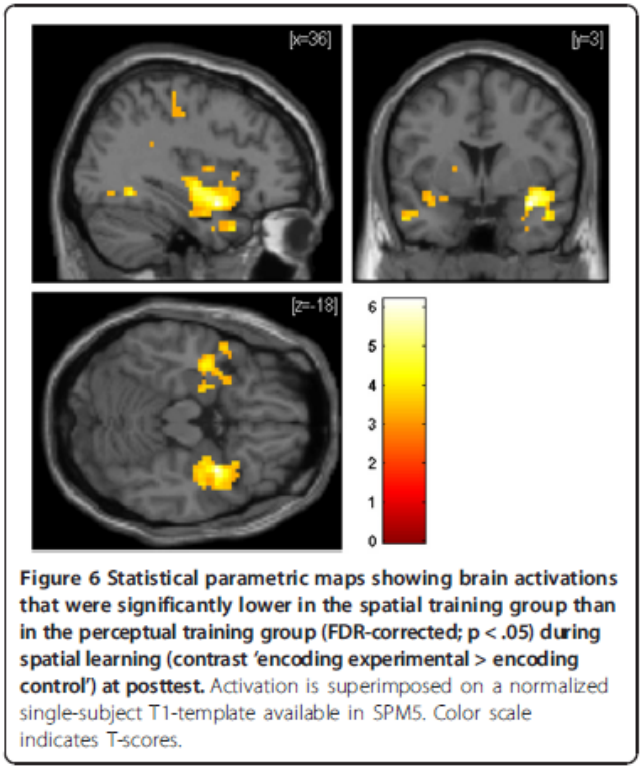
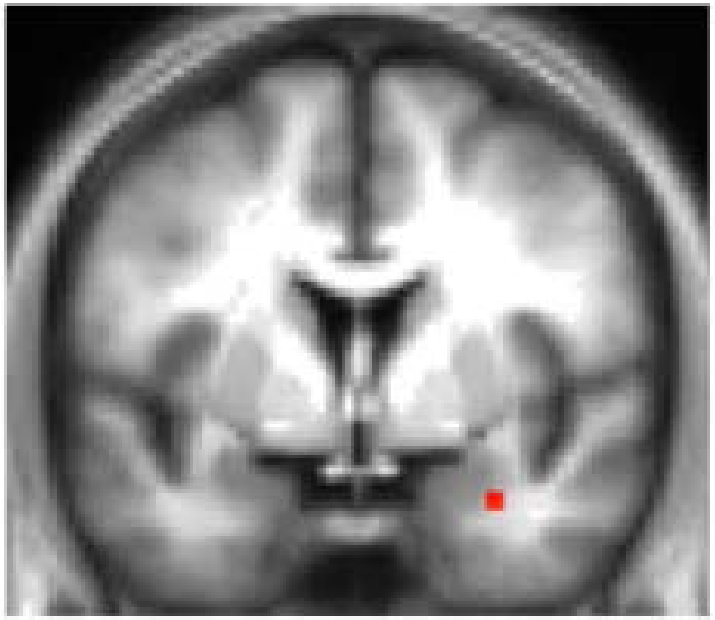


Figure 6 Statistical parametric maps showing brain activations that were significantly lower in the spatial training group than in the perceptual training group (FDR-corrected; $p < .05$) during spatial learning (contrast 'encoding experimental > encoding control') at posttest. Activation is superimposed on a normalized single-subject T1-template available in SPM5. Color scale indicates T-scores.

Functional changes in neural systems associated with spatial navigation can be induced by cognitive interventions and seem to be stronger than effects of physical exercise in middle-aged adults.

B



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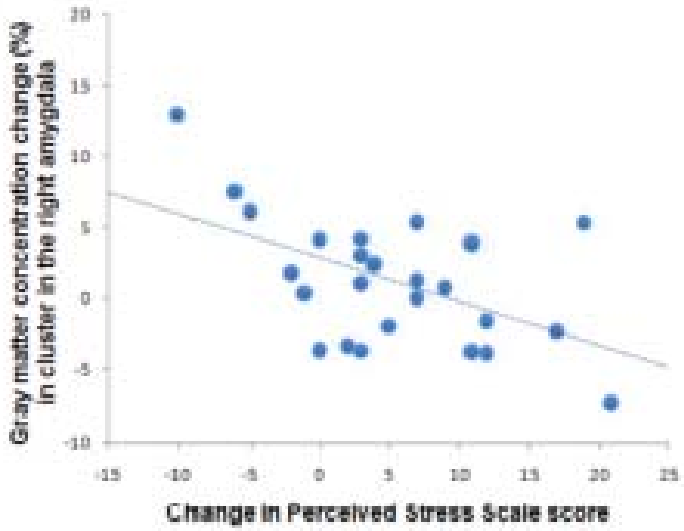


Change in gray matter volume in the right basolateral amygdala from pre to post eight weeks of mindfulness-based stress reduction (MBSR) was associated with decreases in perceived stress over this same time period. Individuals undergoing MBSR who showed the largest decreases in perceived stress also showed the largest decreases in basolateral amygdala gray matter volume

Table 4.1 Cognitive domains influenced by *Synapse* productive engagement tasks

Task	Speed	Visual–spatial working memory	Verbal working memory	Long-term memory	Reasoning	Mental control
Quilting						
Using sewing machine	x	x		x	x	
Planning		x	x	x	x	x
Preparation		x		x	x	x
Creating quilt		x		x	x	x
Photography						
Using digital camera	x	x		x	x	
Computer skills		x	x	x	x	x
Artistic skills		x	x	x	x	x
Creating final products		x	x	x	x	x

Note: x's indicate cognitive domains that are thought to be facilitated by the listed skill

Learn something new - Sudoku

9	6	3	1	7	4	2	5	8
1	7	8	3	2	5	6	4	9
2	5	4	6	8	9	7	3	1
8	2	1	4	3	7	5	9	6
4	9	6	8	5	2	3	1	7
7	3	5	9	6	1	8	2	4
5	8	9	7	1	3	4	6	2
3	1	7	2	4	6	9	8	5
6	4	2	5	9	8	1	7	3

Designing a Program to “Really Use It”

- Brain Plasticity-Based Workouts
  - Learn to play the violin
  - Learn Japanese
  - Learn to juggle
  - Learn to tango
  - Learn to use your “other” hand
  - Become an air traffic controller

Use Programs Designed to Target the Root Causes of Brain Function Decline

IMPACT Shows that the Right Kind of Cognitive Exercise Can Rejuvenate the Brain

The researchers found that people using the Posit Science program:

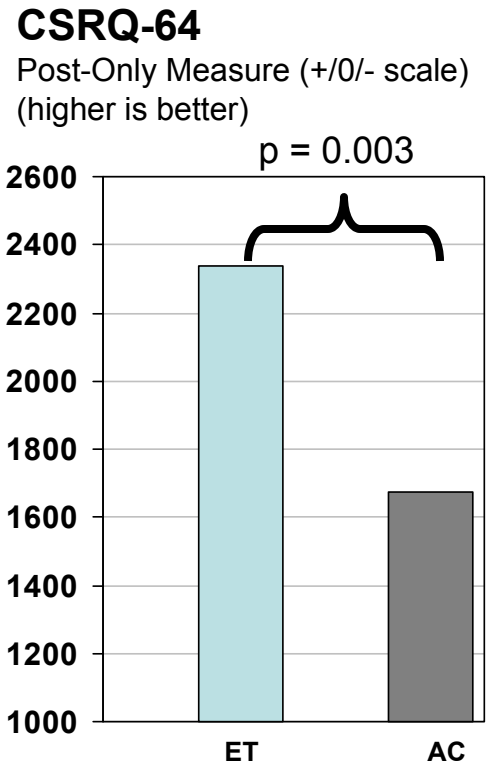
Best >

Noticed benefits in their everyday lives

Findings:

- **3 out of 4 people** self-reported positive changes in their everyday lives

- Benefits ranged from remembering shopping lists, being more independent, feeling more self-confident and hearing conversations more clearly



How is this research helping?

The Benefits of DriveSharp Brain Fitness Training

- Decades of research show the technology in DriveSharp:
- Speeds up visual processing and increases "useful field of view" so drivers see more of the road with each glance
- Decreases reaction time, so drivers can stop 22 feet sooner at 55 mph
- Cuts at-fault crash risk by 50%

http://www.positscience.com/testlets/jeweldiver/index.php?session=cbomppsn4i8ijpp1o50o9bfcp0

Brainer

- Comprehensive software program for brain fitness
- Targets six areas of brain functioning
  - Short-term memory
  - Long-term memory
  - Critical thinking
  - Visuospatial orientation
  - Computation
  - Language
- Fun, easy to use touch system with five levels of challenge

Serious Question and Issue

- Two decades of medical research
- Can reduce risk of decline of brain functioning by 63%
- Studies show: If you don’t use it, you will lose it!

Games vs. Fitness?

	Brain Games	Brain Fitness
What They Are	Individual games that target one skill	Structured system to work 6 areas of brain
Commitment	Almost none	Greater investment= greater rewards
Appeal	Fun past-time within busy lifestyle	Staying sharp and fighting memory loss
Benefit	Offer amusement	Potential tool against memory loss and decline in thinking abilities
Who Uses Them	People who want enjoy brain teasers	People who are serious about brain health

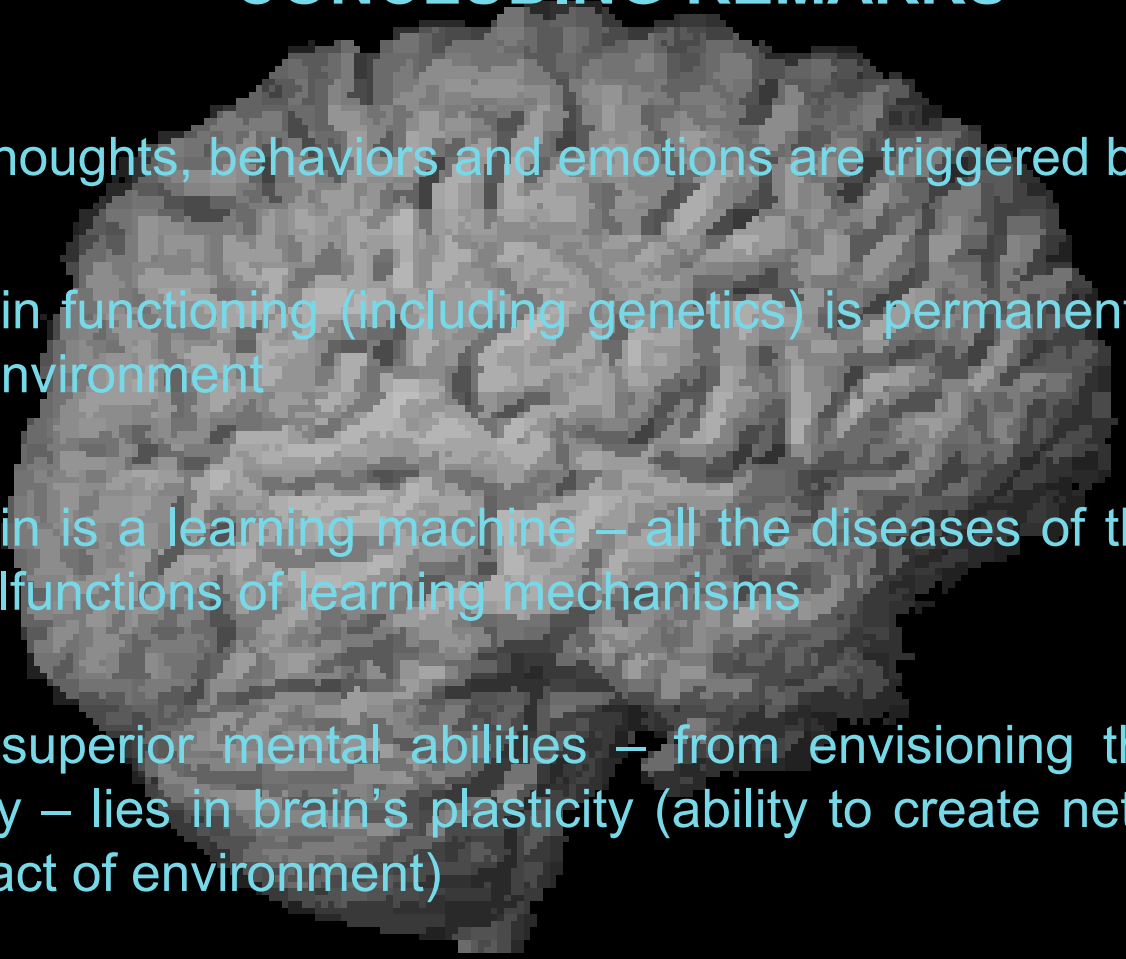
References

- Free sample of BrainFitness software at www.brainer.it

- Journal of the American Medical AssociationLong-term effects of cognitive training on everyday functional outcomes in older adults (2006)Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, Morris JN, Rebok GW, Unverzagt FW, Stoddard AM, Wright E. Journal of the American Medical Association, 296: 2805-2814.

- The New England Journal of MedicineLeisure activities and the risk of dementia in the elderly (2003)Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslanksy G, Ambrose A, Sliwinski M, Buschke H. The New England Journal of Medicine, 348: 2508-2516.

CONCLUDING REMARKS



All the thoughts, behaviors and emotions are triggered by the brain

The brain functioning (including genetics) is permanently impacted by the environment

The brain is a learning machine – all the diseases of the brain are also malfunctions of learning mechanisms

All the superior mental abilities – from envisioning the future to creativity – lies in brain's plasticity (ability to create networks upon the impact of environment)

Mental health, superior performance and healthy longevity could be achieved by knowing how to control brain's mechanisms

Welcome to

AACL 2013