

Conquering Alzheimer's Disease: A Progress Report

Howard Fillit, MD

**Founding Executive Director and Chief Science
Officer**

**Alzheimer's Drug Discovery Foundation
Clinical Professor of Geriatric Medicine, Palliative Care and
Neurosciences, The Icahn School of Medicine at Mount Sinai**



Facts About Alzheimer's Disease

A chronic progressive, uniformly fatal disease

Effects 1 in 3 persons at age 80;
a most feared disease

Leading cause of disability,
5th leading cause of death in elderly

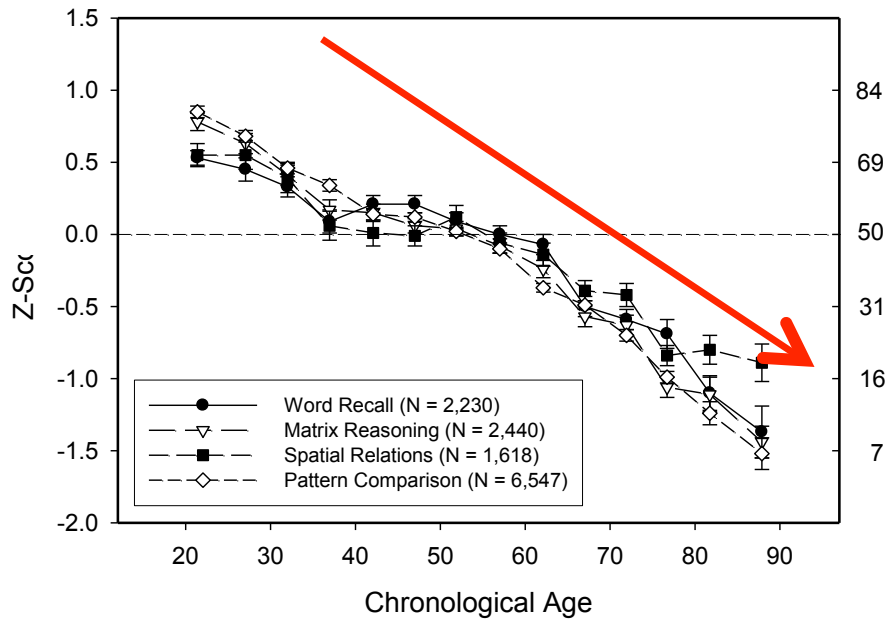
Most costly disease (>\$200B/year),
more than heart disease and cancer

No drugs to effectively treat



What is “Normal” Cognitive Aging?

~30-50% Loss of Some Cognitive Functions



~0.4% Loss of Brain Volume Per Year

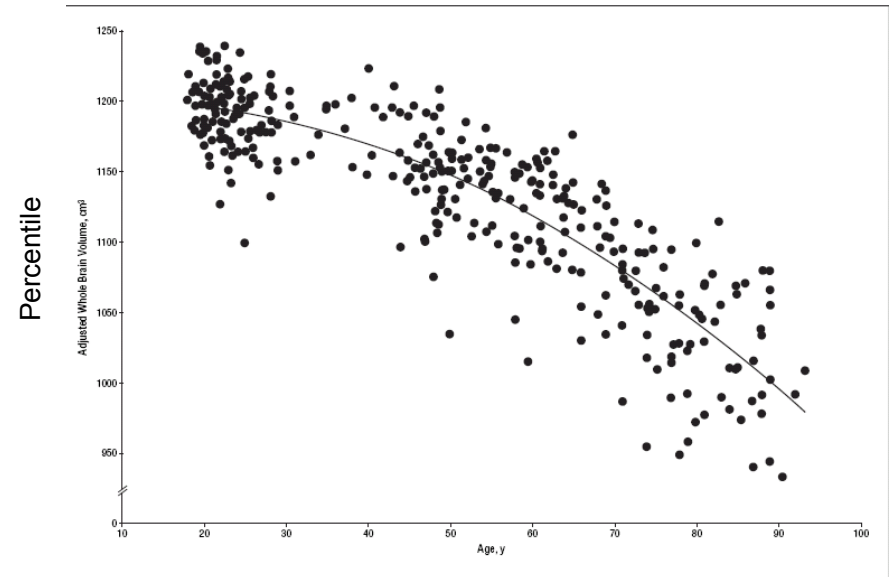


Figure 1. Cross-sectional plot of brain volume in nondemented adults over the adult life span.

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117

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If Cognitive Aging Affects Us All, When Is It *Dementia*?

Agnosia



*“I remember the face,
but I’ve forgotten your name”*



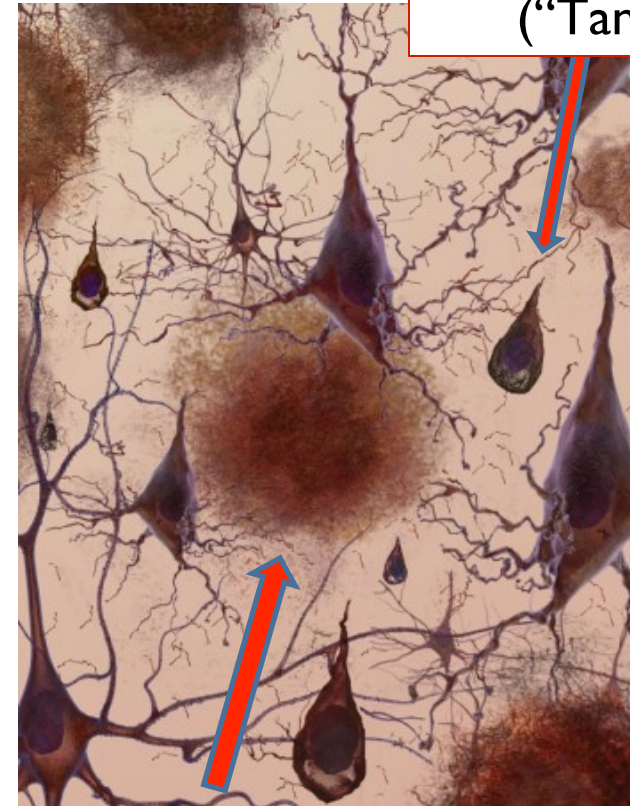
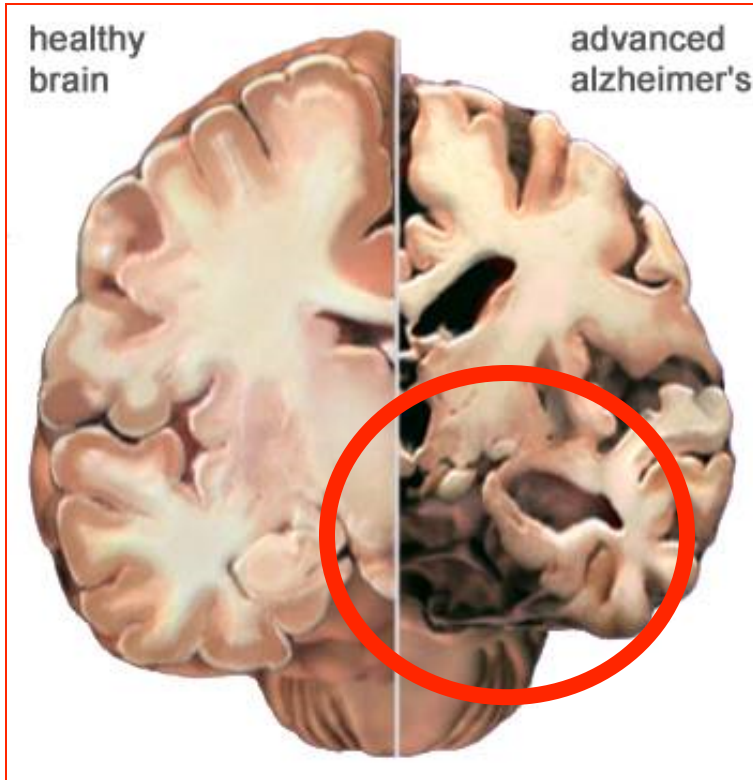
Why is Alzheimer's Fatal?

Apraxia and the Need for Long Term Care



So What is Alzheimer's Disease?

The Most Common Cause of Dementia



Cognitive health begins at conception: addressing dementia as a lifelong and preventable condition

Jennifer H Barnett^{1,2*}, Vladimir Hachinski³ and Andrew D Blackwell^{1,2}



Figure 2 Preventing dementia throughout life.



Preventing Alzheimer's Disease: Managing Lifelong Risk May Delay the Onset of Dementia

Genetics and Gender

Physical Exercise

Psychological factors

- *education, social engagement*
- *distress and depression*

Dietary factors

- *Mediterranean diet*
- *omega-3 fatty acids/DHA*
- *vitamin deficiency*
 - *folate, B₁, B₁₂, D*

Medical Risk Factors

- *hypertension, diabetes,*
- *heart disease, others*

Head trauma

Major Surgery

Substance Abuse

- *alcohol, drugs, smoking*

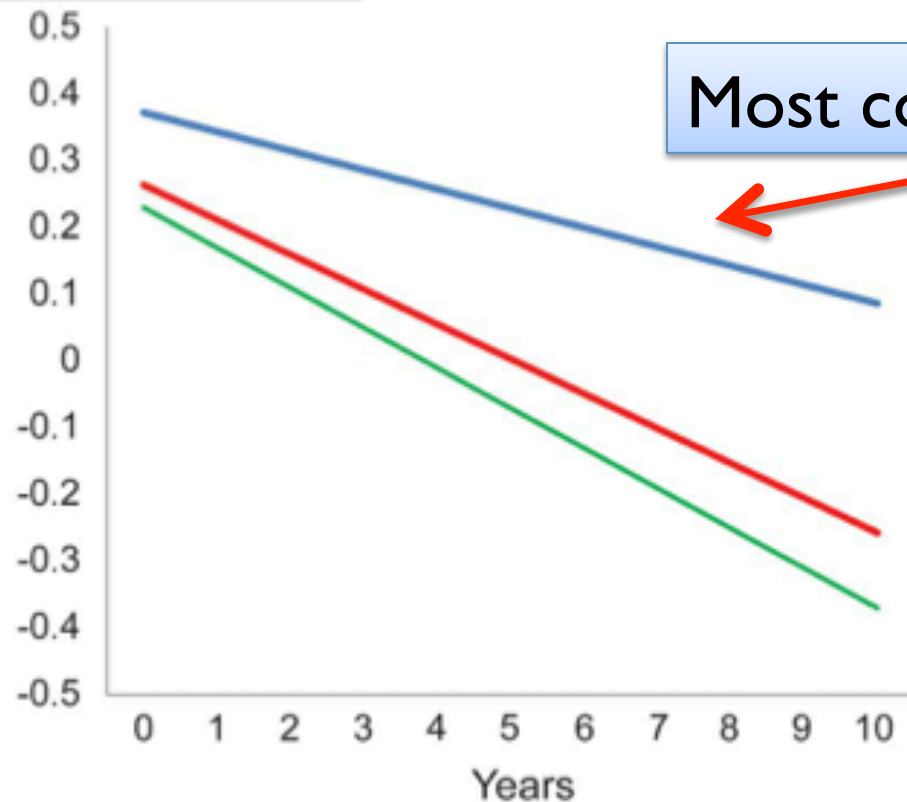
Environmental Factors

- *pesticides, lead*



Mediterranean Diet and Cognitive Decline: Olive Oil, Fatty Fish, Nuts, Vegetables and Fruits

Cognitive Function

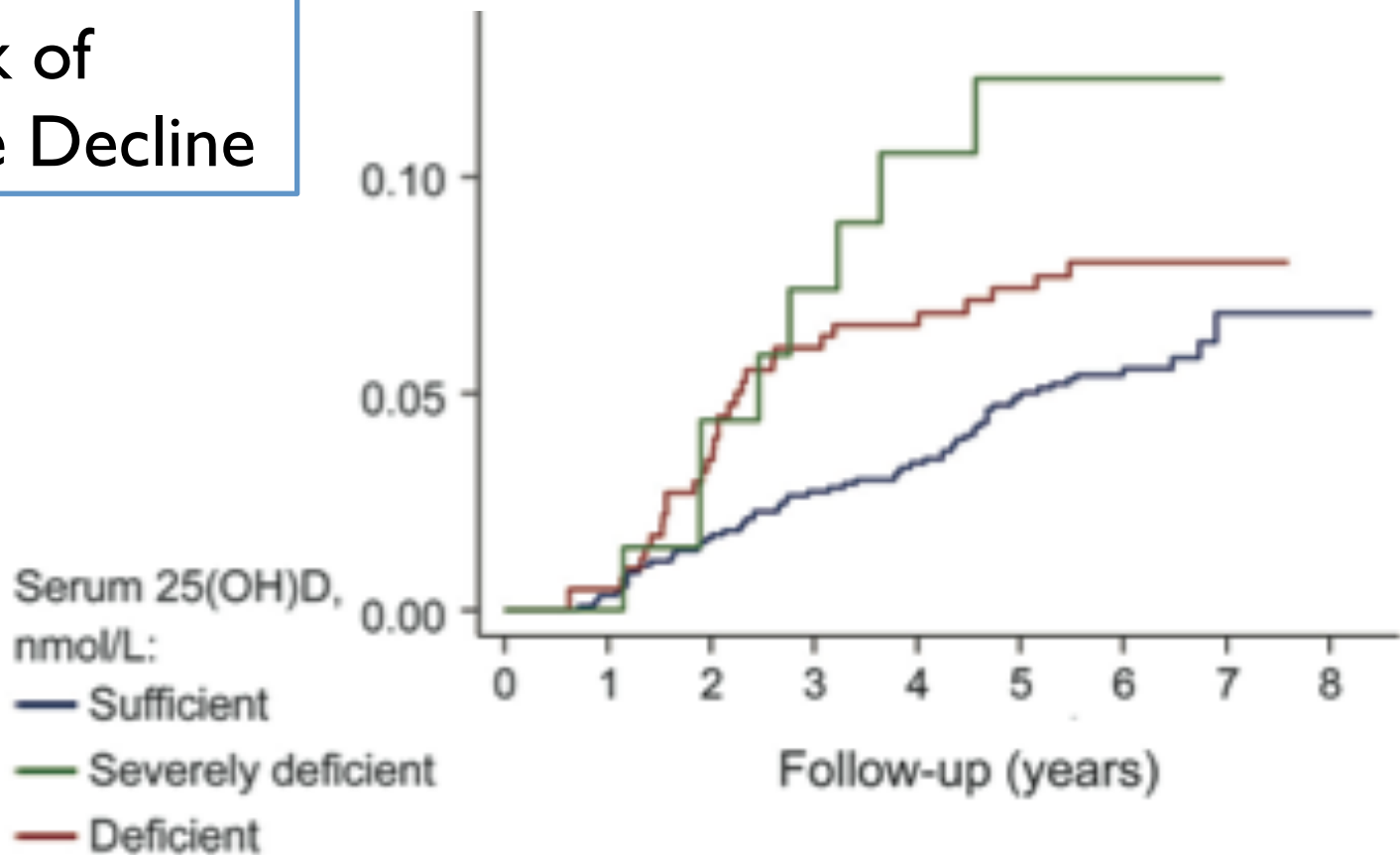


Most compliance to diet



Vitamin D and the Risk of Alzheimer's

Risk of Cognitive Decline



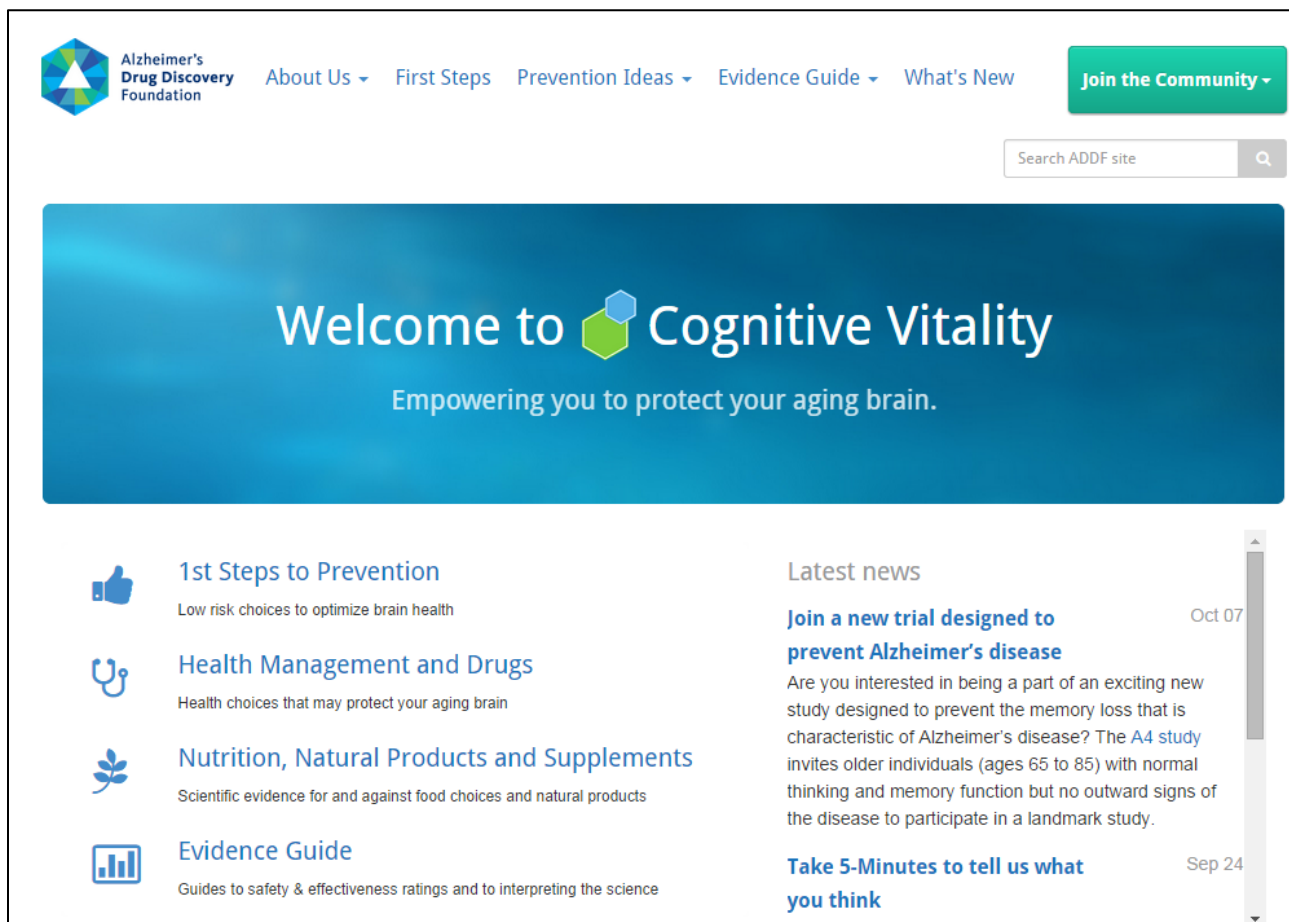
Physical Exercise & the Prevention of Alzheimer's: Multiple Levels of Evidence

- *Epidemiologic data:* Lack of exercise is a risk factor for Alzheimer's disease
- *Animal and human clinical trial data:* Exercise improves cognitive function and slows brain atrophy in animals and in the elderly
- *Understanding mechanism of action:* Exercise acts by several mechanisms, including ***production of neuroprotective factors***
- ***Translating the data into new drugs***



Making Better, More Informed Decisions for Prevention

www.CognitiveVitality.org



The screenshot shows the Alzheimer's Drug Discovery Foundation website. At the top left is the logo and name. The navigation menu includes 'About Us', 'First Steps', 'Prevention Ideas', 'Evidence Guide', and 'What's New'. A green button for 'Join the Community' is on the right. A search bar is located below the navigation. The main banner features the text 'Welcome to Cognitive Vitality' with a logo of three overlapping hexagons (green, blue, and yellow) and the tagline 'Empowering you to protect your aging brain.' Below the banner are four categories: '1st Steps to Prevention' (Low risk choices to optimize brain health), 'Health Management and Drugs' (Health choices that may protect your aging brain), 'Nutrition, Natural Products and Supplements' (Scientific evidence for and against food choices and natural products), and 'Evidence Guide' (Guides to safety & effectiveness ratings and to interpreting the science). On the right side, there is a 'Latest news' section with two articles: 'Join a new trial designed to prevent Alzheimer's disease' (dated Oct 07) and 'Take 5-Minutes to tell us what you think' (dated Sep 24).

Alzheimer's Drug Discovery Foundation





About Us ▾ First Steps Prevention Ideas ▾ Evidence Guide ▾ What's New

Join the Community ▾

Search ADDF site

Welcome to Cognitive Vitality

Empowering you to protect your aging brain.

-  **1st Steps to Prevention**
Low risk choices to optimize brain health
-  **Health Management and Drugs**
Health choices that may protect your aging brain
-  **Nutrition, Natural Products and Supplements**
Scientific evidence for and against food choices and natural products
-  **Evidence Guide**
Guides to safety & effectiveness ratings and to interpreting the science

Latest news

Join a new trial designed to prevent Alzheimer's disease Oct 07
Are you interested in being a part of an exciting new study designed to prevent the memory loss that is characteristic of Alzheimer's disease? The *A4 study* invites older individuals (ages 65 to 85) with normal thinking and memory function but no outward signs of the disease to participate in a landmark study.

Take 5-Minutes to tell us what you think Sep 24

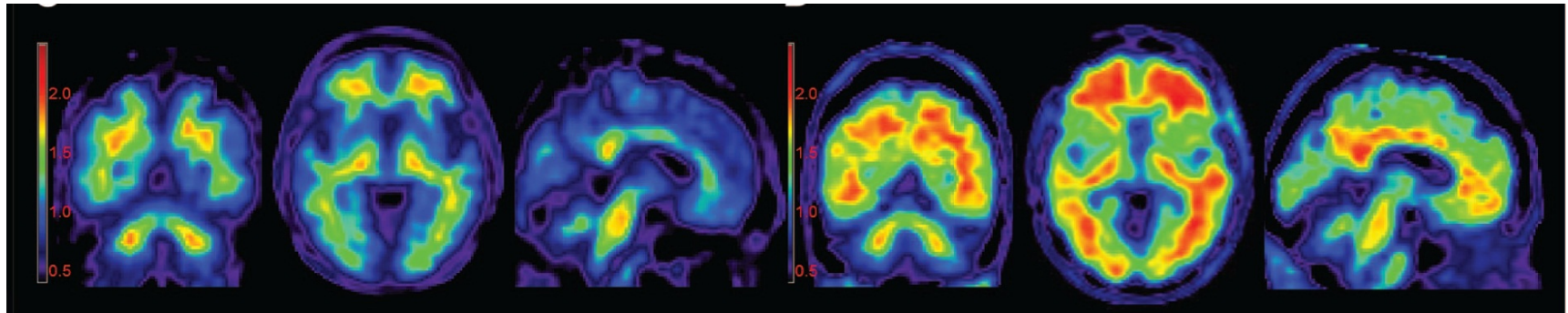


PET Amyloid Imaging (Amyvid™) has Enabled Prevention Clinical Trials with Drugs for Alzheimer's

Mild Cognitive Impairment

Patient Improved

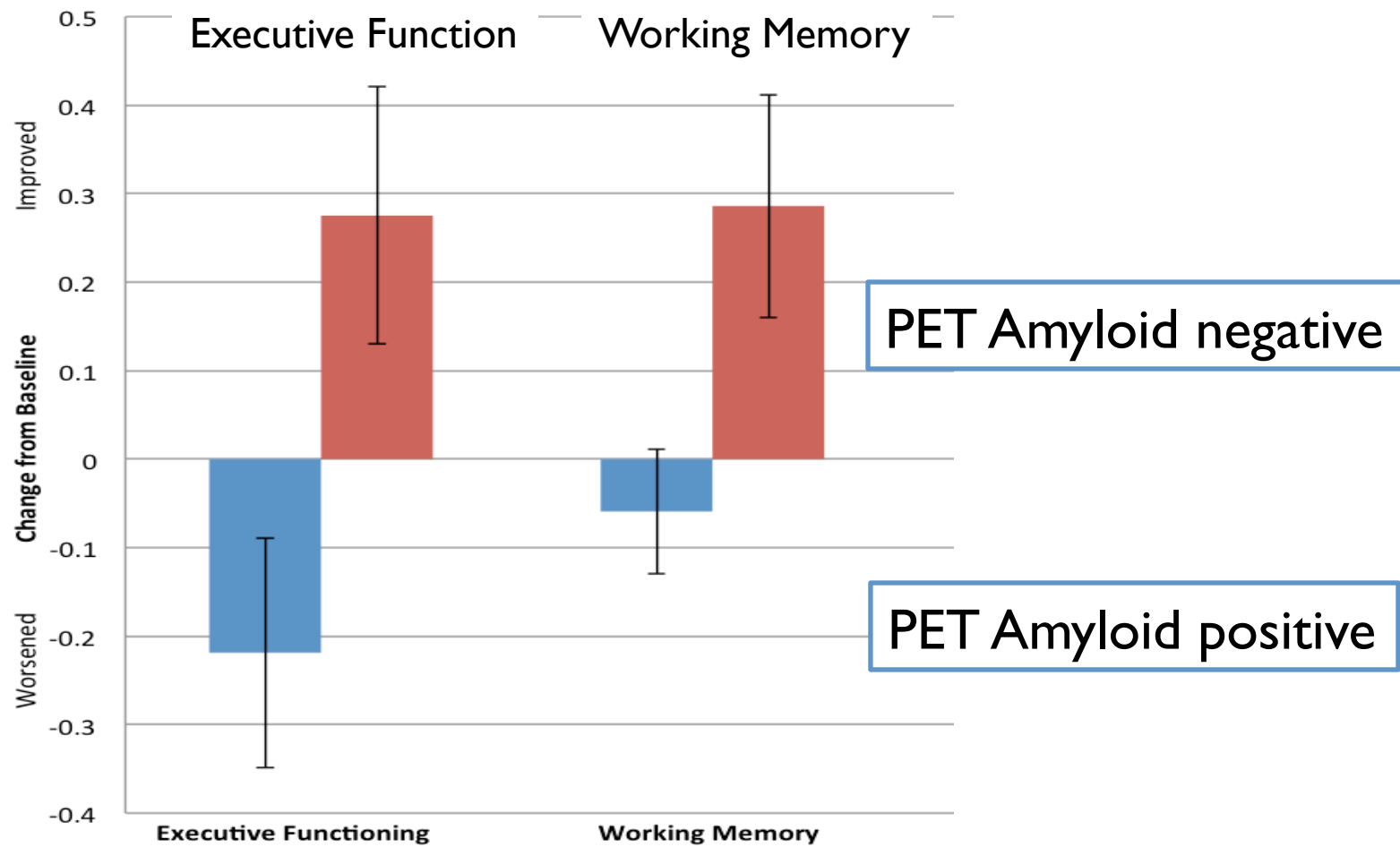
Progressed to Dementia



- Disease starts ~20 years before symptoms begin
- *Large anti-amyloid prevention clinical trials in normal elderly with positive amyloid PET scans are underway*

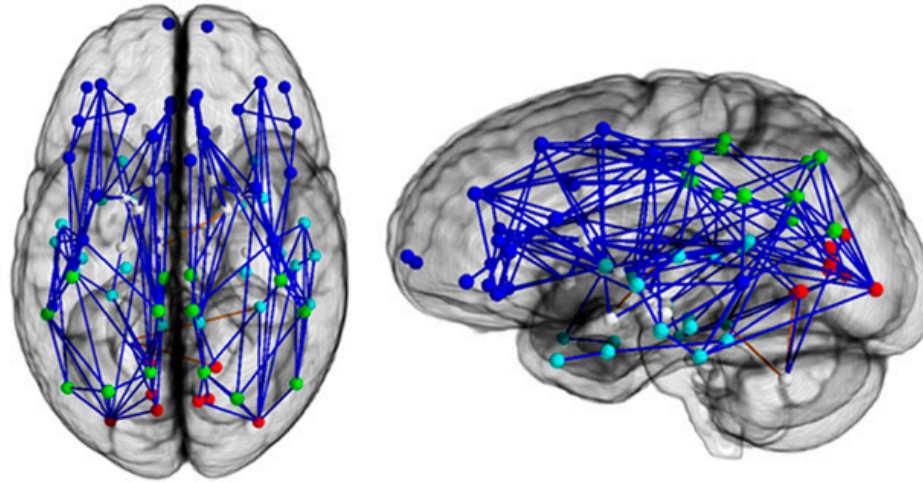


Predicting Risk for Cognitive Decline After Major Surgery in “Normal Elderly”

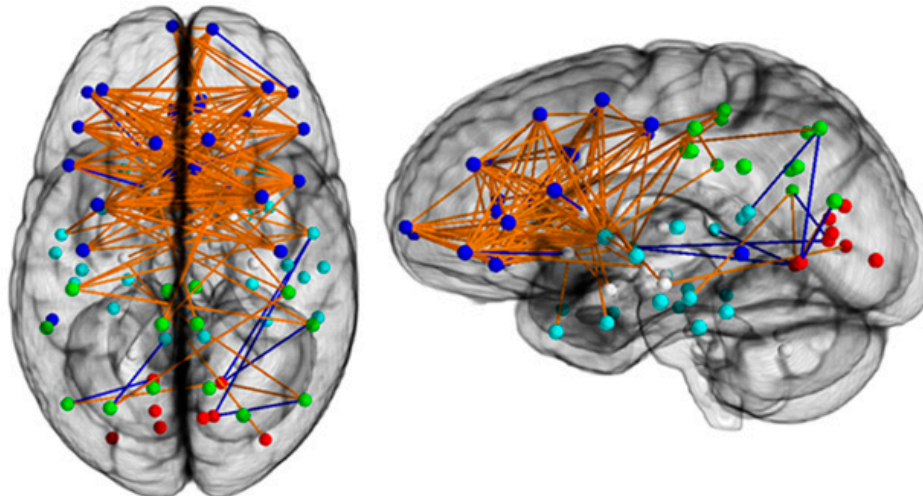


The Neurobiology of Gender: Men and Women Are Really Different!

Men



Women



Why Alzheimer's Disease is a Women's Issue

- More women get Alzheimer's than men
- Most caregivers are women
- Many women caregivers end up in poverty
- Most people in nursing homes (up to 90%) are women with Alzheimer's disease



Female Gender and the Risk for Alzheimer's: Implications for Drug Treatment

Psychoneuroendocrinology, Vol. 11, No. 3, pp. 337–345, 1986.
Printed in Great Britain.

0306–4530/86 \$3.00 + 0.00
Pergamon Journals Ltd.

OBSERVATIONS IN A PRELIMINARY OPEN TRIAL OF ESTRADIOL THERAPY FOR SENILE DEMENTIA-ALZHEIMER'S TYPE

HOWARD FILLIT,* HERMAN WEINREB, INA CHOLST,† VICTOR
BRUCE MCEWEN, ROBERTO AMADOR‡ and JOHN ZABRINSKY

The Rockefeller University, New York, U.S.A.; †Department of Obstetrics and Gynecology, Cornell Medical Center, U.S.A.; and ‡Universidad Nacional, Bogotá, Colombia

(Received 27 March, 1985; in final form 29 October 1985)

REVIEW ARTICLE

The Role of Hormone Replacement Therapy in the Prevention of Alzheimer Disease

Howard M. Fillit, MD

JAMA Neurology 2002

Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women Women's Health Initiative Memory Study

JAMA 2004

Sally A. Shumaker, PhD

Claudine Legault, PhD

Lewis Kuller, MD, DrPH

Stephen R. Rapp, PhD

Leon Thal, MD

Dorothy S. Lane, MD, MPH

Howard Fillit, MD

Marie C. Serlin, PhD

Context The Women's Health Initiative Memory Study (WHIMS) previously found increased risk for dementia and no effect on mild cognitive impairment (MCI) in women treated with conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA).

Objective To determine the effects of CEE alone and CEE plus MPA on incidence of probable dementia and MCI in older women.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled clinical trials of CEE (estrogen-alone trial) or CEE plus MPA (estrogen plus progestin trial) in community-dwelling women aged 65 to 79 years, conducted from June 1995 to July 8, 2002 (estrogen plus progestin; n=4532), or to February 29, 2004 (estrogen-alone trial; n=4532).

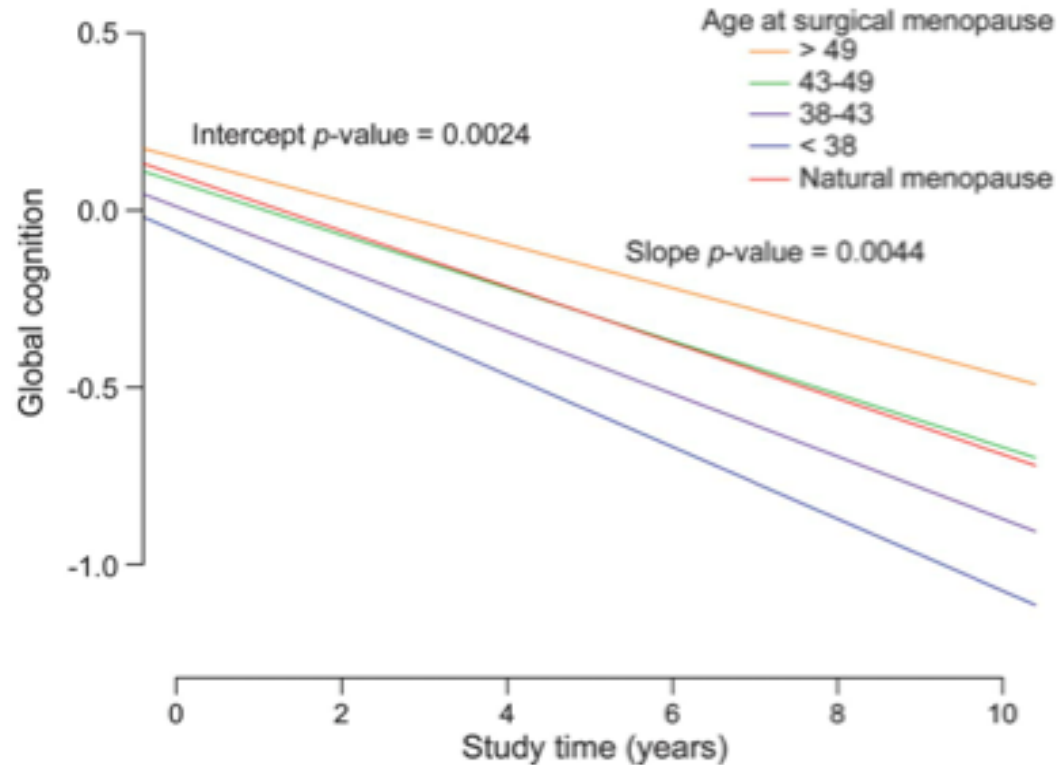


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Conquering Alzheimer's
Through Drug Discovery

Female Gender and the Risk for Alzheimer's: Implications for Drug Treatment

Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women



Neurology® 2014;82:222–229



Some Good News: Prevention of Alzheimer's is Possible

- Recent studies indicate the incidence of dementia is declining, primarily due to healthier lifestyles
 - An American 60 years old today has a 44% lower chance of developing Alzheimer's than 30 years ago
 - Average age of onset went from 80 to 85
- Recent intervention studies are showing comprehensive lifestyle interventions can delay the onset of dementia



Aging is the Leading Risk Factor for Alzheimer's: Implications for Developing New Drugs



Some Causes of Aging: “Wear and Tear” And “Living on Earth”



Epigenetics: Linking lifelong risk factors to genetic changes that cause disease

FROM THE NOVEMBER 2006 ISSUE

DNA Is Not Destiny: The New Science of Epigenetics

Discoveries in epigenetics are rewriting the rules of disease, heredity, and identity.

By Ethan Watters | Wednesday, November 22, 2006



Audrey Hepburn, who spent her childhood in the Netherlands during the Dutch Hongerwinter, attributed her clinical depression later in life to the malnutrition in her formative years (Credit: Hulton Archive)

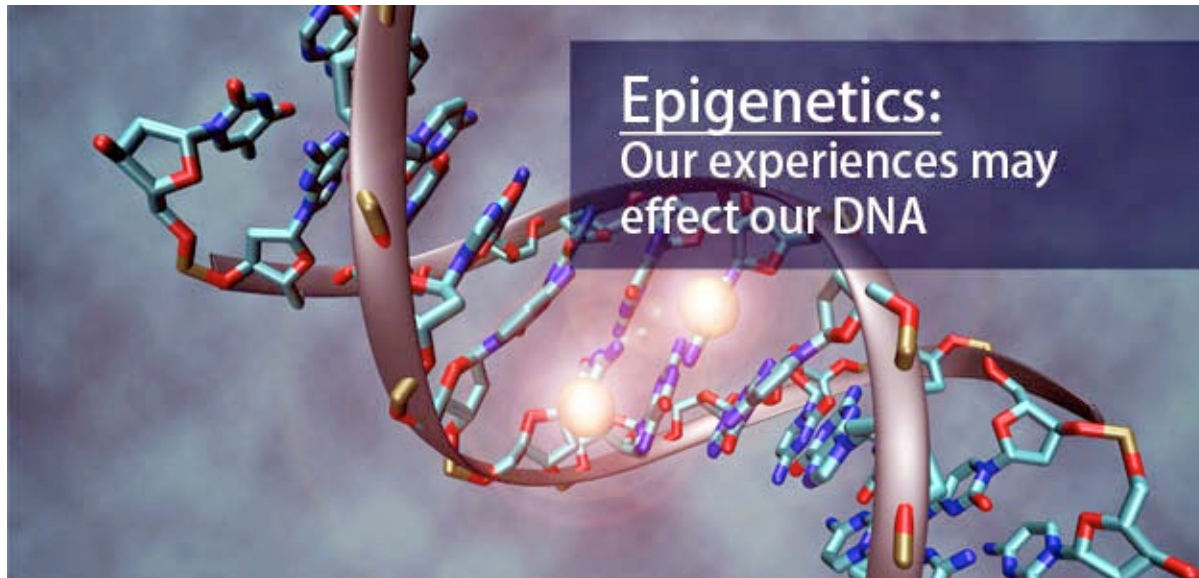


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**Conquering Alzheimer's
Through Drug Discovery**

Epigenetics: Linking lifelong risk factors to genes that cause disease

- Lifelong risk factors cause cellular stress, resulting in the chemical modification of genes *and their expression*
- Epigenetics plays a role in cancer; some chemotherapy drugs treat epigenetic changes



With aging, epigenetic changes in genes
may cause neurodegeneration

LETTER

doi:10.1038/nature10849

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff^{1,2,3}, Damien Rei^{1,2}, Ji-Song Guan^{1,2,3}, Wen-Yuan Wang^{1,2,3}, Jinsoo Seo^{1,2}, Krista M. Hennig^{3,4}, Thomas J. F. Nieland³, Daniel M. Fass^{3,4}, Patricia F. Kao⁵, Martin Kahn¹, Susan C. Su^{1,2}, Alireza Samiei¹, Nadine Joseph^{1,2,3}, Stephen J. Haggarty^{3,4}, Ivana Delalle⁵ & Li-Huei Tsai^{1,2,3}

NATURE | VOL 483 | 8 MARCH 2012

Drugs are in development to
treat Alzheimer's based on epigenetics



ADDF-Funded Companies Developing Epigenetic Therapies for Alzheimer's



ABOUT

TEAM

INVESTORS AND PARTNERS

PRESS

CONTACT

“Applying Insights of Epigenetics to Neurological Disorders”



About Atlas Venture

Atlas Venture is a leading early-stage international venture capital firm that invests in technology and life sciences businesses. Since inception in 1980, its partners have helped build over 350 companies in more than 16 different countries. Atlas Venture is currently investing from its ninth fund which closed in May 2013. For more information, visit www.atlasventure.com.



About Proteros

Proteros, Martinsried/Munich, is a privately held company, which provides a leading platform to support protein structure accelerated drug discovery. Proteros has established unique and best in class technologies for protein crystallography, kinetic and thermodynamic profiling and tailor made protein production. Proteros provides services to more than 80 pharmaceutical and biotechnology clients in North America, Europe and Asia. For more information visit www.proteros.com.



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About Alzheimer's Drug Discovery Foundation

Founded in 1998 by co-chairmen Leonard A. and Ronald S. Lauder of the Estée Lauder cosmetics family, the Alzheimer's Drug Discovery Foundation (ADDF) provides funding to leading scientists who are conducting the most promising, innovative Alzheimer's drug research worldwide. Our goal is to provide seed



About Johnson & Johnson

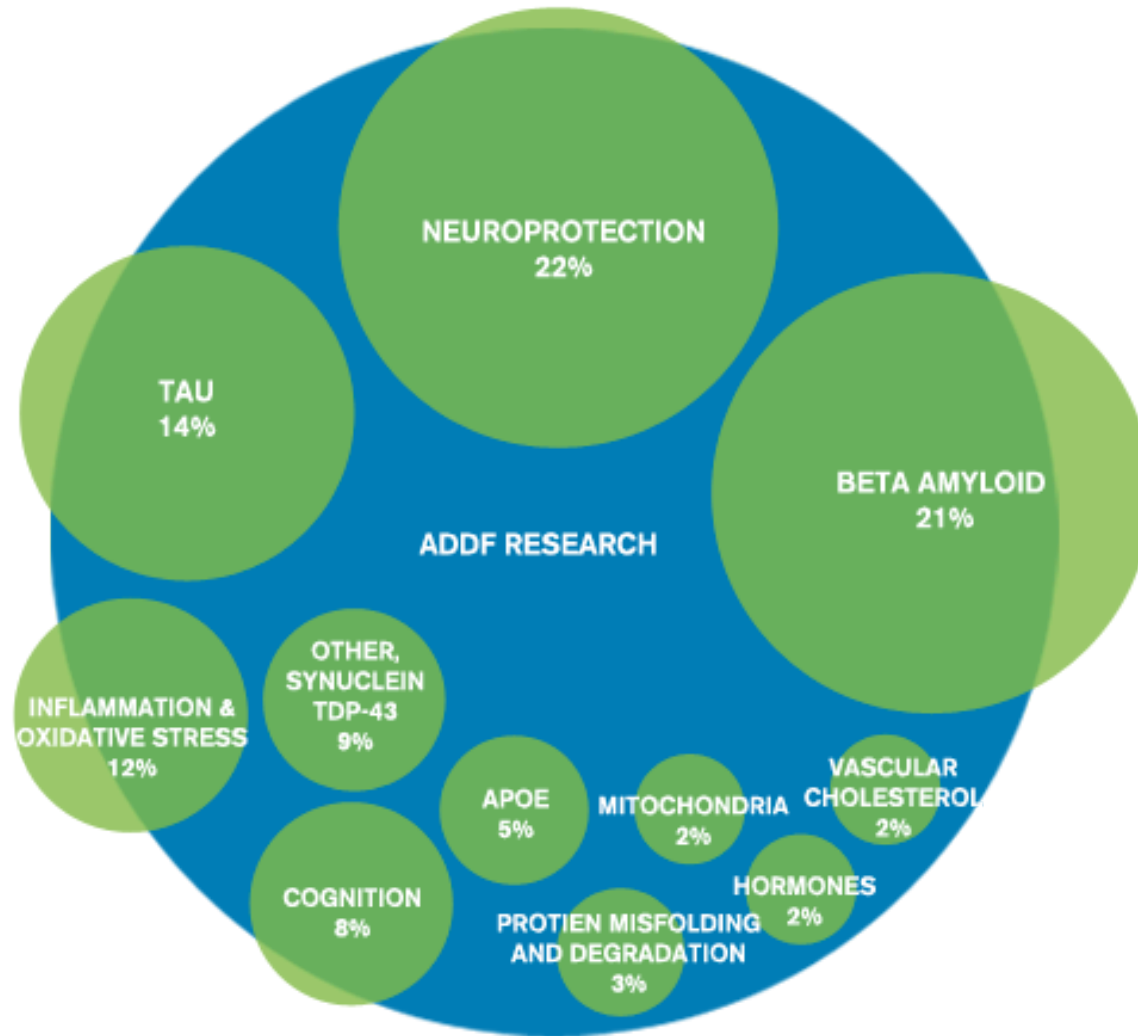
The Johnson & Johnson Innovation Centers bring together resources from across the Johnson & Johnson Family of Companies to rapidly meet the needs of entrepreneurs and innovators. The team consists of veteran R&D and product development leaders, experienced investors, transactions and



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Conquering Alzheimer's
Through Drug Discovery

Our Diverse Drug Portfolio



Today, Conquering Alzheimer's is an Achievable Goal

- Today, *early diagnosis* of Alzheimer's disease is possible
- Today, *delaying the onset* of Alzheimer's disease is possible
- Today, *disease modifying drugs* to prevent and treat Alzheimer's disease are being tested in human clinical trials

Our Mission:
Accelerate The Discovery of New Drugs For Alzheimer's Disease

Basic Science

Understanding the underlying causes of disease

Preclinical Drug Discovery

Research focused on translating knowledge into drugs

Clinical Trials

Human trials of potential new drugs

ADD FUNDING

www.AlzDiscovery.org

www.CognitiveVitality.org

